Genetic, Metabolic and Environmental Contributions to Intraocular Pressure in the Canadian Longitudinal Study on Aging

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Preface

The research outlined here was approved to be conducted by the School of Epidemiology and Public Health. This thesis contains original research and work undertaken by Rebecca Lelievre. Dr. Marie-Hélène Roy-Gagnon, Dr. Ellen Freeman and Dr. Julian Little oversaw the completion of the thesis and provided feedback and guidance. Other co-authors: Mohan Rakesh and Pirro Hysi were involved in project conception, validation and revision of the final manuscript. Author contributions will be provided in more detail as a preface to each manuscript.

Manuscript 1

Title: Effect modification by sex of genetic associations of vitamin C related metabolites in the Canadian Longitudinal Study on Aging

Authors: Rebecca Lelievre, Mohan Rakesh, Dr. Pirro G Hysi, Dr. Julian Little, Dr. Ellen E Freeman, Dr. Marie-Hélène Roy-Gagnon

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Manuscript 2

Title: Evaluating vitamin C-related gene-environment and metabolite-environment interaction effects on intraocular pressure in the Canadian Longitudinal Study on Aging

Authors: Rebecca Lelievre, Mohan Rakesh, Dr. Pirro G Hysi, Dr. Julian Little, Dr. Ellen E Freeman, Dr. Marie-Hélène Roy-Gagnon

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Abstract

Several genetic factors have been associated with glaucoma, and its endophenotype intraocular pressure (IOP), but do not explain all the variance. Metabolites are intermediates in metabolic pathways as substrates or products which can offer a bridge between the internal and the external environment. By investigating gene-environment interactions and metabolite measurements, we can better understand factors that contribute to IOP and glaucoma variation. We used data from the Canadian Longitudinal Study on Aging to investigate: 1) how sex modifies the association of genetic factors with metabolite measurements of two vitamin C related metabolites, and 2) interactions between metabolites, genetic factors and dietary environmental variables. We found some evidence of biological sex influencing genetic associations with vitamin C related metabolites and of an interaction between genetic variants and alcohol consumption influencing IOP levels. Our findings support the use of metabolites to better understand glaucoma risk factors to improve treatment and prevention.

(149/150 words)

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1. Introduction

1.1. Glaucoma and Intraocular Pressure

Glaucoma is one of the leading causes of blindless globally (Jonas et al., 2017). Previous projections have estimated that there will be over 100 million people affected by glaucoma globally in 2040 (Tham et al., 2014). Other reports indicate that glaucoma caused 11% of all global blindness in 2020 (Blindness et al., 2021). Glaucoma is a universal term for different conditions with some similarities. A common feature of glaucoma is the loss of retinal ganglion cells, which in turn leads to optic disk cupping and eventual vision loss (Jonas et al., 2017). Often, the condition progresses without any noticeable symptoms until the onset of vision loss, which makes it difficult to have early intervention (Jonas et al., 2017).

The pathophysiology of glaucoma is still not fully understood, but one known modifiable causal risk factor is elevated intraocular pressure (IOP) (Nouri-Mahdavi et al., 2004; Leske et al., 2007). When fluid is not able to drain properly from the eye, there is an increase of IOP (Jonas et al., 2017). While not all cases of glaucoma are associated with elevated IOP (Fox and Fingert, 2023), it is still the case in many situations and has become a common endophenotype used to study glaucoma progression and susceptibility (Xu et al., 2021). All current treatments for glaucoma involve lowering IOP through different methods such as medication, laser therapy and surgery (Heijl et al., 2002; Schuster et al., 2020).

There are many different subtypes of glaucoma, with the most common being open angle glaucoma (OAG). In OAG, the drainage pathway from the eye is not obstructed, but usually the ability for the eye to drain fluid is reduced in some way, leading to an increase in eye pressure (Weinreb et al., 2014). This can be further classified into primary open-angle glaucoma (POAG) and secondary open-angle glaucoma. POAG refers to when the primary disease is glaucoma, whereas secondary open-angle glaucoma refers to when the glaucoma is occurring due to another condition or factor (Weinreb et al., 2014). Another form of glaucoma is angle-closure glaucoma, in which there is a physical block in the drainage pathway leading to increased eye pressure (Sun et al., 2017).

1.2. Genetic Risk Factors of Glaucoma and IOP

There has been extensive research done on the genetic factors which contribute to both glaucoma and elevated IOP risk. IOP is a known heritable factor (Freeman et al., 2013). Estimates of heritability across multiple studies appear to be between 0.4 and 0.7 (Xu et al., 2021) with one systematic review finding a pooled heritability for IOP to be 0.43 (Asefa et al., 2019). Most of the genetic factors that have been investigated in association with glaucoma and IOP are single nucleotide polymorphisms (SNP). A SNP refers to a one-base change in the genetic code (Shastry, 2009). Disease research using genetics often studies how a change at a specific point in the genome influences specific disease phenotypes. Several genome-wide association studies (GWAS) have been conducted to try and find genetic factors associated with IOP and glaucoma (Abu-Amero et al., 2015; Wiggs and Pasquale, 2017; Khawaja et al., 2018). In a GWAS analysis, all possible measured or imputed genetic variants, often SNPs, are simultaneously analyzed to see if they are associated with the outcome of interest, in this case, glaucoma and IOP (Chang et al., 2018). One of the largest GWAS on IOP to date was conducted by Khawaja et al, 2018 where over 100 genetic regions were found to be significantly associated with IOP (Khawaja et al., 2018). In 2023, Han et al., conducted a multi-ancestry and multi-trait analysis GWAS where they were able to identify over 300 genetic regions which were associated with

POAG (Han et al., 2023). These regions point to a wide range of potential cellular functions, but often these variants are common with small effects (Xu et al., 2021).

One of the tools that has been developed in genetic epidemiology is the creation of polygenic risk scores (PRS) to try and quantify an individual's genetic risk to a specific disease phenotype based on the sum of individual genetic variants (Lewis and Vassos, 2020). This concept has also been applied to glaucoma. Craig et al., created a PRS using results from GWAS on glaucoma and some of its key endophenotypes, including IOP (Craig et al., 2020). When tested in independent cohorts, those in the higher PRS percentiles were at a higher risk for glaucoma than in lower percentiles (Craig et al., 2020). Overall, there have been major advances in both finding variants associated with glaucoma and IOP and in their application. However, despite these advances, there is still a considerable percentage of variation unexplained (Stuart et al., 2023b).

1.3. Using Metabolites in Disease Research

While genetic factors are essential in understanding the pathophysiology and risk factors associated with glaucoma, they do not explain all the variance seen in the population. Another concept for disease etiology is the exposome (Wild, 2005; Zhang et al., 2021). In essence, the exposome is the totality of environmental exposures that an individual is exposed to over time, which include both the internal and external environment (Wild, 2005). Understanding and quantifying the exposome can help to explain disease progression and risk, but it is difficult to capture. One emerging field to try and quantify the effect of the environment on internal biological processes is by quantifying the levels of metabolites, or the metabolome (Walker et al., 2019).

Metabolites are compounds which play a role in metabolic pathways as either products or substrates. Metabolites offer an intermediate between molecular factors such as genetics and external factors such as diet (Aderemi et al., 2021). There are hundreds of thousands of known metabolites within the body, all of which can be used as biomarkers to study human disease (Wishart et al., 2022). Metabolomics technologies continue to improve, and often metabolite levels are quantified using mass spectrometry (Walker et al., 2019). In general, mass spectrometry tells us the molecular mass and profile of compounds within a sample. This information can then be used to match this profile with known metabolite profiles to identify which compounds are present and quantify the amount in a sample (Zhou et al., 2012).

Several epidemiological studies have begun to apply the idea of using metabolite measurements in disease research (Playdon et al., 2019). For example, this concept has been applied by analyzing whether the concentrations of any metabolites are associated with disease phenotypes in an untargeted, metabolome-wide association study (MWAS), similar to a GWAS (Nicholson et al., 2008).

1.4. Metabolites Associated with Glaucoma and IOP

In the context of glaucoma and IOP, there have been a few studies which have explored the connection to metabolites. Most studies have focused on metabolic profiling of patients with glaucoma to identify any dysregulated metabolites. One systematic review of 18 articles, 13 of which focused on OAG, noted 17 metabolites identified as altered in at least 2 studies (Wang et al., 2021). The most prominent pathway from this analysis was amino acid dysregulation (Wang et al., 2021).

A handful of studies have done more large-scale association tests to identify potential metabolite biomarkers for IOP. For example, Pasquale et al. looked at the association of 168 metabolites with IOP using UK Biobank participants (Pasquale et al., 2023). Another study looked at the association of selected metabolites with IOP in a multi-ethnic Asian population (Qian et al., 2023). Both studies found evidence of increased albumin, increased lactate and lower glutamine associations.

Hysi et al., conducted an MWAS with IOP using a random forest machine learning approach and found that O-methylascorbate was the most highly ranked metabolite (Hysi et al., 2019). The researchers repeated the study in the Canadian Longitudinal Study on Aging and found that the most highly ranked metabolite was sex dependent. In females, O-methylascorbate was still a highly ranked metabolite, but not in males (Hysi, personal communication, 2022). O-methylascorbate is involved in ascorbic acid (vitamin C) metabolism as a by-product of ascorbic acid methylation (Blaschke and Hertting, 1971). Researchers found that in males, a different metabolite associated with ascorbic acid metabolism was highly ranked, ascorbic acid 2-sulfate (Hysi, personal communication, 2022). Ascorbic acid 2-sulfate is an end product once ascorbic acid is metabolized (Tolbert et al., 1975).

Vitamin C has many implications in disease research, including glaucoma (Age-Related Eye Disease Study Research Group, 2001; Villagran et al., 2021). In general, ascorbic acid works as an antioxidant and is implicated in many processes including immune modulation (Arrigoni and De Tullio, 2002; Carr and Maggini, 2017). Oxidative stress has been evaluated in the context of glaucoma and is thought to be involved in disease pathogenesis (Dziedziak et al., 2021; Jabbehdari et al., 2021; Mlynarczyk et al., 2022). One systematic review concluded that there was evidence that oxidative stress markers were higher in glaucoma (Benoist d'Azy et al., 2016).

Recently, a Mendelian Randomization (MR) analysis found a causal relationship between oxidative stress and glaucoma (Shi et al., 2024).

Vitamin C also cannot be synthesized by humans and needs to be ingested externally through sources such as citrus fruits (Santos et al., 2021). Interestingly, there have been noted sex differences in serum vitamin C concentrations (Schleicher et al., 2009; Carr and Lykkesfeldt, 2023). There are several theories for this, including body size, lifestyle factors and sex hormones, but the full reason is not understood (Travica et al., 2020).

1.5. Genetic Factors Which Influence Metabolites

Another facet to metabolomics research is to understand the genetic factors which influence metabolite levels, as it has been found that many metabolite levels are heritable (Hagenbeek et al., 2020). In addition, determining genetic factors that are associated with metabolite levels allow for them to be used as instrumental variables in causal association analyses such as Mendelian Randomization (Chen et al., 2023). There have been several studies which have investigated the genetic factors associated with metabolites in a large-scale analysis (Yin et al., 2022; Chen et al., 2023). One recent study by Chen et al., conducted several GWAS using data from the Canadian Longitudinal Study on Aging (CLSA), including on O-methylascorbate and ascorbic acid 2-sulfate (Chen et al., 2023). Significant genetic variants were found associated with both metabolites in this analysis. Chen et al. also investigated the causal role of these metabolites on 12 diseases or traits using MR analysis but did not look at glaucoma or vitamin C metabolism specifically (Chen et al., 2023).

1.6. Dietary Environmental Factors Associated with Glaucoma and IOP

Alongside advances in genetic and metabolic risk factor associations, several epidemiological studies have investigated environmental factors related to glaucoma and IOP. Some of the evaluated risk factors include alcohol consumption, smoking, and diet which may also be associated with vitamin C metabolism. In addition, researchers have used MR analyses to assess causality of these environmental variables. MR refers to an analysis method where genetic factors linked to exposures of interest are used as instrumental variables in analysis to help better assess causality between an exposure and an outcome. In theory, by using genetic factors instead of more traditional measures of exposure, we can remove the bias from unobserved confounding (Sanderson et al., 2022).

1.6.1. Alcohol

Several observational studies have investigated the link between glaucoma, IOP and alcohol consumption. Recent studies include a retrospective cohort study which found that current alcohol consumption was associated with an increased risk of glaucoma development and that this association was higher in men when considering a sex modification effect (Mahmoudinezhad et al., 2023). In a recent cross-sectional study using CLSA data, higher weekly alcohol consumption was associated with higher IOP (Grant et al., 2023). One systematic review from 2022 on alcohol and IOP and OAG found that there was a positive, but small pooled (odds ratios and rate ratios) effect size association (1.18: 95% CI 1.02-1.36) between OAG and alcohol consumption when compared to no alcohol consumption. The authors noted that there was some uncertainty of the conclusions based on potential biases and heterogeneity of the studies (Stuart et al., 2022). To assess causality between alcohol and glaucoma and alcohol and IOP, Stuart et al. 2023, undertook a MR analysis, but did not find evidence for a causal relationship (Stuart et al., 2023a). Overall, there is some evidence of an association between alcohol and glaucoma/IOP, but there is still a need for further evidence to increase certainty.

1.6.2. Smoking

The evidence for the association between smoking and glaucoma/IOP has many conflicting results. Some studies show an association between glaucoma and increased smoking (Perez-de-Arcelus et al., 2017; Law et al., 2018). Other studies have shown a protective effect of smoking on POAG risk (Chiam et al., 2018). There have also been systematic reviews evaluating smoking as a risk factor (Zhou et al., 2016; Jain et al., 2017). Jain et al., did not conduct a meta-analysis but qualitative evaluation of the literature pointed to very limited evidence for a causal association, although there were hints of a potential association between heavy smoking and POAG (Jain et al., 2017). Zhou et al. conducted a meta-analysis of six studies looking at smoking and POAG and found that current smokers (RR: 0.97, CI: 0.81-1.16) and past smokers (RR: 0.97, CI: 0.83-1.13) did not have a significantly increased risk of POAG (Zhou et al., 2016). Looking at intraocular pressure, some studies have reported a positive association between smoking and IOP (Yoshida et al., 2014; Lee et al., 2020a). To assess causality, one MR study looked at the association between genetically predicted smoking initiation and IOP and OAG risk and found an inverse relationship (Tran et al., 2023).

1.6.3. Fruit and Vegetable Consumption

A few studies have investigated the effect of dietary patterns on glaucoma (Francisco et al., 2020). Some studies point to a protective effect of green leafy vegetables such as kale (Coleman et al., 2008; Giaconi et al., 2012; Kang et al., 2016; Ramdas, 2018). Other studies have pointed to the potential associations with vitamin C (Yuki et al., 2010; Lee et al., 2020b; Moreno-Montanes et al., 2022). One cross-sectional study of Korean participants indicated an association between lower vitamin C intake and POAG in participants with a low body mass index (Lee et al., 2020b). One prospective cohort study found that individuals with a higher ACE index (vitamin A, C and E consumption) had a lower risk for glaucoma, but this pattern was not seen with the vitamins individually (Moreno-Montanes et al., 2022). One study found that there was a protective effect against glaucoma in those who consumed more fruit/fruit juices, fresh oranges, and vitamin C specifically (Giaconi et al., 2012). Some studies have found no significant association between OAG and vitamin C (Kang et al., 2003; Ramdas et al., 2012). A systematic review from 2018 which evaluated the effect of vitamins on glaucoma suggested that there was a probable protective effect for vitamin C on glaucoma after addressing heterogeneity and when combining studies using serum levels or dietary intake exposures (Ramdas, 2018). A more recent systematic review from 2022 looked at several vitamins, and concluded that there was a probable protective effect of vitamin A and B on glaucoma, a tentative relationship with vitamin C and vitamin D, and no indication of a relationship with vitamin E. The researchers also indicated that many of the studies available had small sample sizes and potential concerns for bias (Han and Fu, 2022).

Other researchers have explored the utility of dietary interventions in glaucoma in randomized controlled trials (RCTs). One study gave patients a food supplement intervention with a mixture of several vitamins and minerals (not including vitamin C) and found a decrease of IOP at 6, 9, 12 months of follow up (Mutolo et al., 2016). Another RCT with a supplement rich in docosahexaenoic acid, vitamins (including vitamin C) and minerals found better IOP and oxidative stress marker outcomes in the treatment group (Romeo Villadoniga et al., 2018). In patients with POAG with controlled IOP, antioxidant supplementations did not improve other visual field indices in a 2-year RCT (Garcia-Medina et al., 2015). Dietary environmental exposures offer a unique opportunity for prevention and treatment as supplements but still require further research.

1.7. Gene-Environment Interactions

As can be seen previously, environmental exposures, especially dietary exposures, show some associations with glaucoma and IOP but are inconsistent or with low certainty. Another avenue to look at these factors is how they interact with genetic factors to get more precise risk estimates.

1.7.1. Alcohol

Grant et al., evaluated the interaction between the polygenic risk score for glaucoma created by Craig et al. and alcohol with regards to IOP in CLSA participants (Grant et al., 2023). They found that higher alcohol intake was more strongly associated with IOP in higher genetic risk quartiles (Grant et al., 2023). Stuart et al., also found that those in individuals belonging to the higher genetic risk quartiles for glaucoma, alcohol intake was more strongly associated with IOP when looking at UK Biobank participants (Stuart et al., 2023a).

1.7.2. Fruit/Vegetable Consumption

A handful of studies have evaluated genetic and environmental dietary factors concurrently, while not being strictly gene-environment interaction studies. Zanon-Moreno et al., constructed a genetic risk score for POAG risk based on past GWAS. They found that this genetic risk score was significantly associated with both POAG risk and plasma vitamin C and E concentrations (Zanon-Moreno et al., 2017). Another study specifically looked at genetic factors associated with the *SLC23A2* gene which encodes ascorbic acid transporters (Zanon-Moreno et al., 2011). Researchers found one SNP which was associated with an increased risk of POAG and lower plasma vitamin C concentrations. When the logistic regression model was adjusted for plasma vitamin C concentrations, the SNP was no longer associated with POAG risk, which could suggest mediation (Zanon-Moreno et al., 2011). Finally, Jee et al., constructed a polygenic risk score for glaucoma risk and looked at the interaction with several dietary measures (Jee et al., 2020). They found that the PRS association with glaucoma was modified by low blood pressure, low serum glucose and high carbohydrate intake (Jee et al., 2020). Overall, there is still a lack of studies which evaluate fruit and vegetable consumption and other dietary factors using gene-environment interactions.

1.8. Canadian Longitudinal Study on Aging

The Canadian Longitudinal Study on Aging (CLSA) is an ongoing, prospective, longitudinal study which recruited 51 338 participants between 2010 and 2015 aged 45-85 at baseline (Raina et al., 2019). The goal of the CLSA was to collect information on, and better understand, the needs of an older population. Participants were divided into a Comprehensive and Tracking cohort. The Comprehensive Cohort consists of 30 097 participants who were interviewed in person and of which 27 170 participants provided blood samples. From those that provided blood samples, 26 622 individuals were genotyped, and 9992 individuals had their metabolite measurements quantified (Forgetta et al., 2022; Michelotti et al., 2023). Information for the Comprehensive Cohort was collected from participants living within 25-50 km of 11 different sites in 7 provinces: Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, and St. John’s. Participants were recruited from a subset of Canadian Community Health Survey participants, health registries and random digit dialing using stratified random sampling. The CLSA excluded individuals from Federal First Nations reserves, provincial First Nations settlements, residents of the three territories and some remote regions, full-time members of the Canadian Armed Forces, those in a long-term care institution, those who were not able to respond in either English or French and those who had cognitive impairments at baseline.

1.9. Rationale

There is a large amount of evidence for genetic factors and environmental factors influencing glaucoma and IOP, but there is still a lack of understanding of the variation of glaucoma and IOP in the population and of glaucoma etiology. Metabolomics is an emerging field which can be used to better understand disease etiology, and which has begun to be applied to glaucoma research. In addition, studies which investigate gene-environment interactions can add valuable knowledge for both prevention and treatment strategies. There is still a lack of studies which investigate genetic, metabolic and environmental factors concurrently to understand glaucoma risk. The following study aims to fill this knowledge gap by investigating factors which can be linked to ascorbic acid metabolism. One of the benefits of this research is to understand more of the variation of IOP in the population, which, in turn, will provide information on the etiology of glaucoma.

The majority of glaucoma cases are in those over the age of 40, and symptoms are not apparent until disease progression is significant (Cohen and Pasquale, 2014; Allison et al., 2020). Having earlier diagnoses of patients can improve disease outcomes through earlier intervention, which can also decrease healthcare costs and utilization. In addition, having a clearer picture of modifiable risk factors can lead to public health interventions in susceptible populations. A second application of these gene, metabolite and environment studies is to increase the capacity of personalized medicine. By understanding how an individual's genes can predict disease risk and how they modify the way in which environmental factors influence risk, this can allow for more specific prevention and treatment plans.

1.10. Objectives

Aim 1- Perform a genome-wide association study to detect significant genetic polymorphisms associated with plasma metabolite levels of previously identified metabolites for IOP as well as investigate whether sex modifies these associations.

Aim 2- Investigate how interactions among genetic factors, environmental factors, and metabolite levels affect IOP.

1.11. Structure of Thesis

This thesis will be presented in a thesis-by-manuscript format. Each objective is evaluated in a separate manuscript/chapter of the thesis. A brief overview of each chapter is presented below, but prior to each chapter, an overview of the chapter will explain each manuscript's significance in the overall thesis.

Chapter 2 presents the results from aim 1. This manuscript details the results from a genome-wide association study to identify lead genetic variants associated with metabolite levels of both O-methylascorbate and ascorbic acid 2-sulfate and to investigate potential sex modification in these genetic associations.

Chapter 3 presents the results from aim 2. This manuscript details the results from several cross-sectional associations between the genetic factors identified in Chapter 2 which are associated with O-methylascorbate and ascorbic acid 2-sulfate, O-methylascorbate and ascorbic acid 2 sulfate levels and dietary environmental factors (smoking, alcohol, and fruit and vegetable consumption).

Chapter 4 details an overall discussion of the findings from both manuscripts and how they fit into the overall objective of the thesis, as well as future research directions and strengths and limitations.

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2. **Effect modification by sex of genetic associations of vitamin C related metabolites in the Canadian Longitudinal Study on Aging**

Objective: Perform a genome-wide association study to detect significant genetic polymorphisms associated with plasma metabolite levels of previously identified metabolites for IOP as well as investigate whether sex modifies these associations.

Author Contributions: Rebecca Lelievre was responsible for conceptualizing the project, preparing the dataset, conducting data analysis, visualizing the results, and preparing the manuscript. Mohan Rakesh helped with results validation and support with data analysis. Julian Little, Pirro Hysi, Marie-Helene Roy-Gagnon and Ellen Freeman helped with securing funding for the project and project conceptualization. Marie-Helene Roy-Gagnon, with the support of Ellen Freeman, supervised the project completion, including providing feedback on the methodology, analysis and results interpretation, and provided resources to aid in project completion. All authors aided in reviewing the manuscript and providing final approval.

Ethics: This research was approved by the University of Ottawa Research Ethics Board

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Title Page

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Abstract

Introduction: Vitamin C is an essential nutrient. Sex differences in serum vitamin C concentrations have been observed but are not fully known. Investigation of levels of metabolites may help shed light on how dietary and other environmental exposures interact with molecular processes. O-methylascorbate and ascorbic acid 2-sulfate are two metabolites in the Vitamin C metabolic pathway. Past research has found genetic factors that influence the levels of these two metabolites. Therefore, we investigated possible effect modification by sex of genetic variant-metabolite associations and characterized the biological function of these interactions.

Methods: We included individuals of European descent from the Canadian Longitudinal Study on Aging with available genetic and metabolic data (n= 9004). We used linear mixed models to tests for genome-wide associations with O-methylascorbate and ascorbic acid 2-sulfate, with and without a sex interaction. We also investigated the biological function of the important genetic variant-sex interactions found for each metabolite.

Results: Two genome-wide statistically significant (P value $< 5x10^{-8}$) interaction effects and several suggestive (P value $< 10^{-5}$) interaction effects were found. These suggestive interaction effects were mapped to several genes including *HSD11B2*, associated with sex hormones, and *AGRP*, associated with hunger drive. The genes mapped to O-methylascorbate were differently expressed in the testis tissues, and the genes mapped to ascorbic acid 2-sulfate were differently expressed in stomach tissues.

Discussion: By understanding the genetic factors that impact metabolites associated with vitamin C, we can better understand its function in disease risk and the mechanisms behind sex differences in vitamin C concentrations.

2.1. Introduction

Vitamin C consumption and its effects on aging have been extensively studied (Balboa-Castillo et al., 2018; Carr and Zawari, 2023). There has been evidence to suggest that older adults do not consume a high enough concentration, and this may lead to increased risk of frailty and other conditions due to the immune effects of the vitamin (Carr and Maggini, 2017; Carr and Zawari, 2023). Past research has also found differences between serum vitamin C concentrations in males and females, with males more likely to have lower concentrations (Schleicher et al., 2009; Carr and Lykkesfeldt, 2023). Several theories have been proposed to account for this difference, including external factors such as body size and lifestyle factors and internal or molecular factors such as sex hormones (Travica et al., 2020). Some studies which have noted the influence of sex hormones on vitamin C concentrations have relied on cellular and animal models (Nathani and Nath, 1972; Kume-Kick and Rice, 1998; Travica et al., 2020). One recent cross-sectional study in infertile men found there was an inverse association between serum ascorbic acid and luteinizing hormone levels, however, the relationship between vitamin C and sex hormones in humans needs to be further explored (Rastegar Panah et al., 2023).

The exposome is the totality of all environmental exposures in someone's lifetime and how they influence disease (Wild, 2005). One way to quantify a portion of the exposome is through the levels of metabolites. A metabolite refers to a substance that is produced or consumed during metabolism. Metabolites are intermediates in a metabolic pathway and can be substrates or products. Quantifying metabolites can bring insight into mechanisms by which the environment affects biological/metabolic processes (Walker et al., 2019). For example, a study by Hysi et al., 2019 used this strategy to look at the metabolic associations of intraocular pressure (IOP) which is an endophenotype for glaucoma (Hysi et al., 2019).

Genetic factors can influence the levels of metabolites and there have been recently conducted large-scale genome-wide association studies (GWAS) to identify genetic associations (Lotta et al., 2021; Hysi et al., 2022; Yin et al., 2022; Chen et al., 2023). Chen et al., 2023 recently conducted a GWAS to identify genetic factors associated with all metabolites measured in participants of the Canadian Longitudinal Study on Aging (CLSA) (Raina et al., 2019; Michelotti et al., 2023). Among the metabolites investigated were O-methylascorbate and ascorbic acid 2-sulfate, both of which are involved in vitamin C metabolism (Blaschke and Hertting, 1971; Tolbert et al., 1975). A few single nucleotide polymorphisms (SNPs) were found to be significantly associated with these two metabolites (Chen et al., 2023). Yin et al. 2022, conducted a similar analysis which included both metabolites in a Finnish population and found significant associations (Yin et al., 2022). However, it is not known whether these genetic associations are affected by sex, which may explain some of the sex differences in vitamin C concentrations seen between males and females.

In this paper we aimed to investigate how sex affects the genetic association of variants across the genome with O-methylascorbate and ascorbic acid 2-sulfate in the CLSA data. In addition, using the comprehensive functional annotation platform FUMA (Watanabe et al., 2017), we aimed to uncover the functional consequences of these genetic associations. This would help to investigate potential molecular mechanisms for sex-differences in vitamin C concentrations such as through an association with sex hormones. Understanding how genetic factors affect vitamin C-related metabolites can aid in understanding the influence of vitamin C on metabolic processes, and in turn how vitamin C influences disease phenotypes.

2.2. Methods

2.2.1. Study Population

We used baseline data from the Comprehensive Cohort of the Canadian Longitudinal Study on Aging (CLSA) (Raina et al., 2019). The CLSA recruited participants between 2010 and 2015 who were between the ages of 45-85 years to investigate social, environmental, and other factors that affect aging and disease. The Comprehensive Cohort included 30,097 participants with baseline data collected between 2012 and 2015 via in-home interviews and in-person physical examinations and biospecimen sample collections at CLSA data collection sites located in Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, and St. John's, Canada. Inclusion criteria required participants to be community dwelling, be cognitively unimpaired, and to speak English or French. Not included were full-time members of the Canadian Armed Forces, those residing on a federal First Nations reserve or settlement, those living in a long-term care institution, and non-residents or citizens of Canada.

Of the Comprehensive Cohort, 9,992 participants had metabolite levels quantified and 26,622 individuals were genotyped (Forgetta et al., 2022; Michelotti et al., 2023). In this study we focused on ~9,000 CLSA participants of European ancestry with genetic and metabolic information (n= 9052) and without any missing covariate information (n = 9004). Written informed consent was obtained for all participants, and research ethics board approval was obtained for all CLSA affiliated sites. The analysis presented here was approved by the University of Ottawa research ethics board.

2.2.2. Genomic Data Quality Control

Blood samples were collected from consenting participants of the CLSA Comprehensive Cohort, and samples were moved to -80°C storage before shipment to the genomics facility where they were stored at -20°C. The Affymetrix Axiom array was used to perform genome-wide genotyping, resulting in 794,409 variants from 26,622 participants (Forgetta et al., 2022). We followed the genetic ancestry procedures performed by the CLSA to identify participants of European descent (Forgetta et al., 2022). The CLSA genomic data release included genotype data imputed using the TOPMed reference panel, resulting in ~308 million variants imputed (Taliun et al., 2021). Prior to GWAS, we filtered out variants from the imputed data that had a minor allele frequency (MAF) <0.01, an imputation quality score <0.3 and missingness >0.1. After these filters, 8,836,359 variants remained for analysis. Both single nucleotide polymorphisms (SNPs) and insertions/deletions (INDELs) were included. All genomic positions are according to the human reference genome assembly GRCh38/hg38.

2.2.3. Metabolite Processing

Metabolite levels were quantified using mass spectrometry and then identified using the Metabolon Discovery HD4TM LC-MS platform (Michelotti et al., 2023). Metabolite values underwent quality control measures and 1,314 metabolites were included in the final dataset. We were interested in 2 metabolites: O-methylascorbate and ascorbic acid 2-sulfate. In this GWAS we used the CLSA data with batch normalized values and where missing values were imputed with the lowest value recorded. Other researchers have reported using this imputation approach for missing values, and we assumed missing values were due to the limit of detection of the Metabolon platform (Playdon et al., 2019). For O-methyl ascorbate, there were no missing values, and for ascorbic acid 2-sulfate, there were 113 missing values. Prior to analysis, metabolites levels were log-transformed and extreme outliers (more than 3 SD away) removed followed by normalization to a mean of 0 and an SD of 1 which was done in prior studies (Chen et al., 2023).

2.2.4. Overall Genome-Wide Association Study

We first performed a GWAS on the complete dataset using mixed linear models as implemented in the GCTA/fastGWA program (Jiang et al., 2019). Briefly, the model fit by GCTA/fastGWA is:

$$\boldsymbol{y} = \boldsymbol{x}_{snp}\beta_{snp} + \boldsymbol{X}_c\boldsymbol{\beta}_c + \boldsymbol{g} + \boldsymbol{e}$$

where **y** is the vector of metabolite levels, $\boldsymbol{x}_{snp}$ is the vector of genotypes of a specific genetic variant, β_{snp} is the coefficient of the genetic variant, $\boldsymbol{X}_c$ is the matrix of fixed covariates with their respective coefficients $\boldsymbol{\beta}_c$, $\boldsymbol{g}$ captures the total genetic effects with $\boldsymbol{g} \sim N(0, \boldsymbol{\pi}\sigma_g^2)$ and relatedness matrix $\boldsymbol{\pi}$, and $\boldsymbol{e}$ is the residual effect with $\boldsymbol{e} \sim N(0, \boldsymbol{I}\sigma_e^2)$. We used a sparse SNP-derived genetic relatedness matrix (GRM) as a covariance structure to control for population stratification and relatedness. The covariates included in the model were age, sex, batch number, the first ten genetic principal components, province, and hours since the last meal or drink.

After removing individuals with missing covariate values and outlier metabolites, there were 8,916 participants for the O-methylascorbate GWAS and 8,835 participants for the ascorbic acid 2-sulfate GWAS. Manhattan plots and qqplots were made using the qqman (Turner, 2018) package in R to visualize for any statistically significant variants. We only followed up genome-wide significant genetic variants (p-value < 5 x 10^{-8}). In our Supplementary Tables, we also provide our results for variants meeting the suggestive level of significance (p-value < 1 x 10^{-5}) (Duggal et al., 2008) for ease of replication in future studies.

Independent (i.e. in linkage equilibrium) genetic variants were obtained using the GCTA/COJO program (Yang et al., 2012) which implements a stepwise selection procedure to identify variants within significantly associated genomic regions that remain independently associated with the trait after conditioning on most statistically significant variants. The program also incorporates linkage disequilibrium (LD) structure information from an input population, which was set as the same individuals as those used in the GWAS analysis. Significant variant threshold was based on the genome-wide significance level of 5 x 10^{-8}.

We investigated functional significance using the platform FUMA (Watanabe et al., 2017) for lead variants identified by COJO analysis. To identify associated genes, positional mapping, quantitative expression quantitative trait loci (eQTL) mapping, and chromatin interaction mapping were used. FUMA identifies all variants in LD (based on 1000 Genomes LD structure) with lead variants to use for mapping. Variants were filtered prior to mapping to only those with a Combined Annotation Dependent Depletion (CADD) (Rentzsch et al., 2019) score above a threshold established as associated with variants with deleterious effects (Amendola et al., 2015; Watanabe et al., 2017) that based on research classifying the pathogenicity of genetic variants was set at the suggested level of >12.37 (Amendola et al., 2015). For positional mapping, we additionally only used exonic or splicing variants. For eQTL mapping, a false discovery rate (FDR) threshold of <0.05 was adopted. For chromatin interaction mapping the threshold was an FDR of <1 x 10^{-06}, in line with the default FUMA parameters (Watanabe et al., 2017). All tissues were used for mapping.

2.2.5. Genetic Variant-Sex Interaction GWAS

We performed a GWAS to test whether genetic effects were modified by chromosomal sex. To achieve this, we used the GCTA program fastGWA-GE (Zhong et al., 2023), which fits the following model:

$$\boldsymbol{y} = \boldsymbol{G}\beta_G + (\boldsymbol{G} \circ \boldsymbol{E})\beta_{GEI} + \boldsymbol{X}_c\boldsymbol{\beta}_c + \boldsymbol{g}_\rho + \boldsymbol{\epsilon}$$

where $\circ$ is the Hadamard element-wise product. In this model, $\boldsymbol{y}$ is the $n \times 1$ vector of phenotypes, $\boldsymbol{G}$ is the vector of genotypes of a specific genetic variant, $\boldsymbol{E}$ is the vector of standardized environmental variable (here chromosomal sex) and β_{GEI} is the gene-environment interaction (GEI) effect while $\boldsymbol{X}_c$ is the matrix of covariates with effects $\boldsymbol{\beta}_c$. The vector of residuals $\boldsymbol{\epsilon} \sim N(\boldsymbol{0}, \boldsymbol{I}_n\sigma_\epsilon^2)$ where $\boldsymbol{I}_n$ is an $n \times n$ identity matrix. The vector $\boldsymbol{g}_\rho$ is an $n \times 1$ vector of all combined genetic main and GEI effects with $\boldsymbol{g}_\rho \sim N(\boldsymbol{0}, \boldsymbol{K}_\rho\sigma_g^2)$, where $\boldsymbol{K}_\rho = \rho\boldsymbol{K} + (1-\rho)\boldsymbol{DKD}$, $\boldsymbol{K}$ is the kinship matrix (or a sparse GRM), $\boldsymbol{D}$ is an $n\ x\ n$ matrix where the jth diagonal entry is E_j, $\rho = \frac{\sigma_{\text{main}}^2}{\sigma_g^2}$, and $\sigma_g^2 = \sigma_{\text{main}}^2 + \sigma_{GEI}^2$. In fastGWA-GE, the variance components σ_g^2 and σ_ϵ^2, and ρ are estimated under the null hypothesis of no genetic or GEI effects. These estimates are then used to obtain a residualized phenotype, $\boldsymbol{y}_{\text{resid}} = \boldsymbol{y}_{\text{adj}} - \widehat{\boldsymbol{g}}_\rho$, by removing the predicted genetic effects $\widehat{\boldsymbol{g}}_\rho = \hat{\sigma}_\epsilon^2\boldsymbol{V}^{-1}\boldsymbol{y}_{\text{adj}}$, where $\boldsymbol{y}_{\text{adj}} = \boldsymbol{y} - \boldsymbol{X}_c(\boldsymbol{X}_c^T\boldsymbol{X}_c)^{-1}\boldsymbol{X}_c^T\boldsymbol{y}$ and $\boldsymbol{V}^{-1}$is obtained from the estimates of σ_g^2, σ_ϵ^2, and ρ. The test of $\beta_{GEI} = 0$ after adjusting for genetic main effects is then performed by a Wald test with sandwich correction from the linear regression: $\boldsymbol{y}_{\text{resid}} = \boldsymbol{G}\beta_G + (\boldsymbol{G} \circ \boldsymbol{E})\beta_{GEI} + \boldsymbol{\epsilon}$.

We adjusted for the covariates age, batch number, province, hours since last meal and the first 10 principal components. We used the same sparse GRM as for the main GWAS above and filtered for MAF 0.01 using the GCTA program, leading to 8,580,042 variants.

2.2.6. Finding Significant Signals of Interaction and their Functional Consequences

We followed up all suggestive interaction signals based on a p-value threshold commonly used for suggestive significance in GWASs (p-value of interaction test < 1 x 10^{-05}) (Duggal et al., 2008). We used the FUMA application to select lead variants and define loci of interest. The same parameters were used as before, such as filtering by CADD score; however, lead variants were not provided to FUMA externally. In this case, the application selects lead variants and independent significant variants based on LD (r^2) information (Watanabe et al., 2017). In brief, all variants with p-values below the suggestive threshold and independent from each other (r^2 <0.6) were identified. Variants that were in r^2 > 0.6 with these variants and had a p-value less than 0.05 were equally considered for gene mapping. Lead variants were chosen from the identified suggestive variants if they had r^2 <0.1 with other shortlisted variants.

In a small number of cases (8), variants that were suggestive were not recognized in the FUMA application, and required an alternative investigation. These variant regions were visualized using LD Link (Machiela and Chanock, 2015) and lead variants and any additional annotated variants were selected based on similar criteria to FUMA. The CADD score of resulting variants was determined to filter variants that could be used for mapping. None of the identified variants were above the CADD threshold for deleteriousness and therefore were not mapped to genes. To annotate the functions of the lead variants and variants that met FUMA criteria, but which were not recognized in the platform, the Variant Effect Predictor (VEP) platform from Ensembl was used (McLaren et al., 2016).

To follow-up on interaction results, we estimated the effect sizes for each lead variant in linear mixed models using fastGWA after stratifying the sample by sex. The models were the same as for the overall GWAS described above and were adjusted for the same covariates. For O-methylascorbate, the number of participants was 4,580 and 4,329 for males and females, respectively. For ascorbic acid 2-sulfate, the number of participants was 4,310 and 4,518 for males and females, respectively.

To illustrate the direction of effect for each lead identified variant stratified by sex, we plotted interaction graphs using the results from the GWAS stratified by sex. We plotted the effect size of each lead variant by sex with a 95% confidence interval using R/ggplot.

To report the results of this study, we were informed by Strengthening the Reporting of Genetic Associations (STREGA) guidelines (Little et al., 2009).

2.3. Results

2.3.1. Overall GWAS Results

Using the GCTA-fastGWA program we found 592 statistically significantly associated variants (p value $< 5 \times 10^{-8}$) with O-methylascorbate. For ascorbic acid 2-sulfate, we found 56 statistically significantly associated variants (p value $<5 \times 10^{-8}$). The Manhattan plot of these results is displayed in Figure S1 and Figure S2. The full list of suggestive variants and p-values for O-methylascorbate and ascorbic acid 2-sulfate are found in Table S1 and Table S2 respectively.

Using the GCTA-COJO software to follow-up significantly associated variants (p value $<5 \times 10^{-8}$), we identified 3 independent lead variants for O-methylascorbate, all of which were on chromosome 22. For ascorbic acid 2-sulfate, we identified 2 lead variants on chromosome 16 and 1 lead variant at chromosome 10. The variant positions, effect allele frequencies, GWAS p-value and COJO-adjusted p-value are summarized in Table 1.

2.3.2. Functional Consequences of Genes

Using the FUMA platform, we determined the functional consequences of the lead variants found in the COJO analysis and variants in LD with those variants which met FUMA criteria. Variants associated with O-methylascorbate were mapped to 13 genes, which included both known and novel gene associations (Table S5). We subsequently used the FUMA platform to identify the functional consequences of the mapped genes, such as their expression levels in different tissue types and whether the set of genes was enriched in any functional pathways. The mapped genes were not significantly differentially expressed in any tissue types (Table S6). The functional gene sets linked to some processes such as genes which are involved in a cancer cell-death evasion mechanism (Jinesh and Kamat, 2017). No gene sets could be directly related to vitamin C functions (Table S7).

Variants associated with ascorbic acid 2-sulfate were mapped to 71 genes (Table S8). Using the same process as before, we found that the mapped genes were not significantly differentially expressed in any tissue types (Table S9). The mapped genes were linked to gene sets for chromosomal and proximal deletions syndromes; however, they did not link to any vitamin C functions (Table S10). Several novel genes were mapped to ascorbic acid 2-sulfate as well.

2.3.3. Genetic Variant-Sex Interaction GWAS

We conducted a genetic variant-by-sex GWAS and found that, for O-methylascorbate, there were no statistically significant interactions while there were 69 suggestive interaction variants. For ascorbic acid 2-sulfate, we found 2 statistically significant interaction variants and 83 suggestive interaction variants. The significant variants were rs1296721356 (chr1:13354706) and rs1301173408 (chr1:13341668). Manhattan plots visualizing the associations are shown in Figure 1. The full list of suggestive interaction variants and p-values for O-methylascorbate and ascorbic acid 2-sulfate are found in Table S3 and Table S4 respectively.

We investigated all the signals at statistically significant and suggestive levels. Using the default parameters of FUMA, we identified 25 lead variants for O-methylascorbate and 23 lead variants for ascorbic acid 2-sulfate (Table S11, Table S12). After conducting separate sex stratified GWAS analyses for comparison, we saw that all interactions were qualitative in nature, meaning that the variants had opposite effects in males and females in the sex-stratified analyses (Figure 2).

In Table 2 and Table 3, we summarized the lead variants for each suggestive interaction loci, nearest genes, annotated functions, and number of genes mapped at each suggestive genomic loci for O-methylascorbate and ascorbic acid 2-sulfate respectively. Overall, most of the genomic loci included variants in intronic or intergenic regions, which were not mapped to any genes. However, some regions had variants of likely functional importance which were mapped to more than one gene.

Variants rs1470819913 and rs1296721356 were not available in FUMA and were annotated separately. No genes were mapped to these regions, and the summary of their functions is included in Table 2 and Table 3.

2.3.4. Functional Consequences of Interaction Signals

The variants that interacting with sex were significantly associated with O-methylascorbate levels, were mapped to 23 different genes (Table S13). Looking at tissue expression data, the set of genes is statistically significantly differentially expressed (corrected p-value <0.05) in testis (Table S14).

The variants that interacted with sex for ascorbic acid 2-sulfate were mapped to 59 genes (Table S15). Looking at tissue expression data, the set of genes is statistically significantly differentially expressed (correct p-value <0.05) in the stomach (Table S16). One of the mapped genes was *AGRP* which is a neuropeptide which controls feeding behavior as a stimulating hormone antagonist (Deem et al., 2022). Another gene mapped was *HSD11B2*, which is an enzyme involved in cortisol metabolism, and which has been shown to be controlled by sex hormones (Garbrecht et al., 2007). The significant genomic loci identified on chromosome 1 was not mapped to any genes and we did not find evidence of a potential functional consequence of this region based on our criteria. For both O-methylascorbate and ascorbic acid 2-sulfate, no gene-sets related to vitamin C metabolism or sex hormones were identified (Table S17, Table S18).

2.4. Discussion

In the present study, we investigated associations and the functional consequences of genetic variant-metabolite associations for two specific metabolites related to vitamin C: O-methylascorbate and ascorbic acid 2-sulfate. In addition, our study is the first to investigate potential genetic variant-sex interactions influencing these two metabolites by conducting a gene by sex GWAS. We also examined the functionality of these variants of interest and found some associations with hormone-related genes.

Past research has studied the genomic associations of these metabolite levels, and Chen et al. 2023, conducted their study using the CLSA metabolite and genomic data. We aimed to have a more focused analysis with a less stringent threshold to gain a deeper understanding of the two vitamin C-related metabolites specifically. We report the same associations, with rs144009214 for ascorbic acid 2-sulfate and rs61484427 and rs4680 for O-methylascorbate (Chen et al., 2023). We also examined additional lead variants than was previously reported due to our less stringent significance threshold of 5×10^{-8} (not corrected for examining all measured metabolites). Chen et al. also identified *COMT* as the closest protein coding genes to the O-methylascorbate variants, which we also identified using FUMA. Using this platform, we were able to find several novel genes that were mapped to our GWAS results and should be investigated more thoroughly. Yin et al., 2022 also identified variant rs4680 as significant with O-methylascorbate in their analysis (Yin et al., 2022).

Chen et al., identified *CD2BP2* as the closest protein coding genes to the ascorbic acid-2 sulfate associated variant, which we also identified in FUMA, among several other genes (Chen et al., 2023). Schlosser et al., 2023 conducted a GWAS on plasma and urine metabolite levels with individuals with chronic kidney disease. In their analysis, ascorbic acid-2 sulfate was associated with rs111894927 which is in the genetic region of the *MAPK3* gene, which we also identified in FUMA (Schlosser et al., 2023). Yin et al. found some genetic associations with ascorbic acid-2 sulfate, however none of their identified putative causal genes were found in our analysis (Yin et al., 2022).

The FUMA analysis from the initial GWAS identified several new genes that were associated with metabolite levels. However, this comprehensive evaluation did not provide any new evidence of mechanisms or pathways through which these gene associations influence metabolite levels. In addition, none of the novel genes associated could be connected to vitamin C metabolism.

Of the mapped genes, *COMT* is a known factor in vitamin C metabolism. O-methylascorbate is a product of O-methylation by the *COMT* gene (Krumsiek et al., 2012). Therefore, this work strengthens an existing connection and further emphasizes the potential importance of this gene in vitamin C metabolism.

Our analysis of a potential sex effect on the gene associations seen for each metabolite found two significant interactions and several suggestive interactions. The effect of sex is an important factor to consider in disease etiology, and in this case, the sex differences of vitamin C concentrations between males and females are not completely understood. One of the proposed theories for the sex differences seen between vitamin C concentrations in males and females is due to influence by sex hormones (Travica et al., 2020). We explored all suggestive interactions to determine their functional significance as well as if there are any connections to genes related to hormone signaling or sex hormones.

For both ascorbic acid 2-sulfate and O-methylascorbate, there were no gene-sets which are enriched and may be related to vitamin C metabolism or sex hormones. Interestingly, the set of genes mapped for ascorbic acid 2-sulfate was significantly differentially expressed in stomach tissues while the set of genes mapped for O-methylascorbate was differentially expressed in testis tissues.

The variants that interacted with sex for ascorbic acid 2-sulfate were mapped to several genes, one of which was *AGRP*, which produces a peptide agonist molecule important for initiating hunger cues. In general, the *AGRP* neurons signal for increased food intake (Deem et al., 2022). In one animal study using a bird model, researchers found that this protein was differentially expressed between male and female chickens (Caughey et al., 2018). Since vitamin C intake is heavily influenced by dietary exposures, this association with a hunger-driving signal protein may be something of further consideration.

Other variants that interacted with sex for ascorbic acid 2-sulfate were mapped to *HSD11B2*. The role of 11-β hydroxysteroid dehydrogenase type 2, the enzyme encoded by the *HSD11B2* gene, is to oxidize cortisol, a glucocorticoid, into its inactive version cortisone (Chapman et al., 2013). Several animal and in vivo studies have shown that the activity of this enzyme is regulated by various sex hormones (Darnel et al., 1999; Garbrecht et al., 2007; Wang et al., 2009). In addition, cortisol may potentially affect vitamin C concentrations in the body; however, it is unclear whether this acts in a sex dependent manner (Travica et al., 2020). Overall, this may point to an important mechanism for future research.

This study has several strengths, including the use of high quality genetic and metabolic datasets. In addition, the use of such a comprehensive tool to annotate variant functions allowed us to use several bioinformatics tools to identify novel associations and areas for future research.

This study also had some limitations to consider. One limitation is the sample size, which may have hindered the ability to find more statistically significant associations, especially in the interaction analysis. However, these findings showed several associations at the suggestive level, which could be followed up by other researchers. Future studies should replicate these findings ideally with a larger sample size. Another limitation is that this study was only conducted using participants of European descent to avoid problems with population stratification. The CLSA had a very high percentage of participants of European descent so using populations from other ancestries would not provide enough power for an accurate analysis in those groups. Finally, because we decided to use the suggestive threshold for the interaction signals to follow up with for functional annotation and mapping, there is a possibility that some of these associations represent type I error. As this represents the first analysis of a potential sex interaction, future studies should evaluate these regions with larger sample sizes to determine if they are true associations.

In conclusion, our study found potential evidence for an effect modification by sex of genetic associations with two vitamin C related metabolites. In addition, a comprehensive analysis of the functions of genomic regions showing suggestive evidence of genetic variant-sex interactions led to some insight into potential mechanisms for these differences. Future studies are needed to expand on this analysis and further understand the different mechanisms which influence vitamin C concentrations in the body. Mechanisms influencing vitamin C concentrations have several implications for different disease phenotypes (Age-Related Eye Disease Study Research Group, 2001; Villagran et al., 2021) and are an especially important consideration for older adults.

2.5. Conflict of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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2.8. Data and Code Availability

The data analyzed in this study is subject to the following licenses/restrictions: Data are available from the Canadian Longitudinal Study on Aging for researchers who meet the criteria for access to de-identified CLSA data. Requests to access these datasets should be directed to www.clsa-elcv.ca. Summary statistics from the genetic variant-sex GWAS are deposited in the GWAS catalogue (https://www.ebi.ac.uk/gwas/home), accession numbers GCST90399837 and GCST90399838. Code is made available on GitHub (https://github.com/Roy-Gagnon-lab).

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2.10. Figures

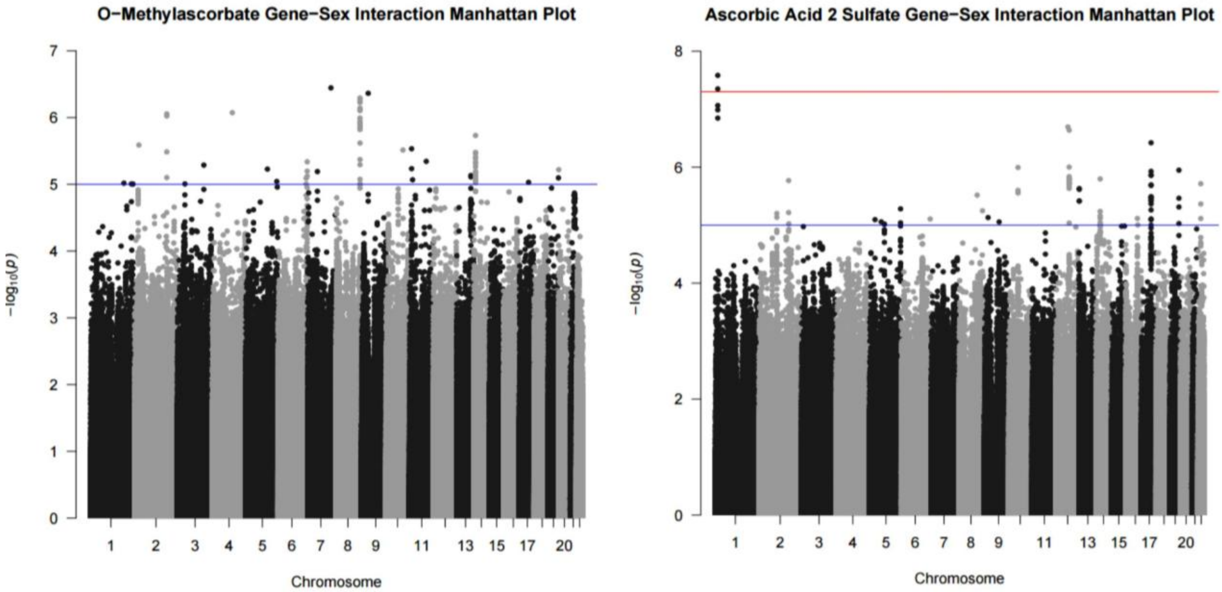

Figure 1. O-methylascorbate and ascorbic acid 2-sulfate interaction with sex results. Results from the GWAS analysis using the FastGWA-GE program from GCTA in the form of a Manhattan plot. GWAS conducted using a mixed linear model adjusted for age, batch number, province, 10 principal components, and hours since last meal or drink which incorporated a genetic relatedness matrix to account for population stratification. The models also included an interaction term for sex. Each point represents the p-value of the interaction between sex and the variant on the associated chromosome. The red line is the significant (5×10^{-8}) threshold and the blue line is the suggestive (1×10^{-5}) threshold.

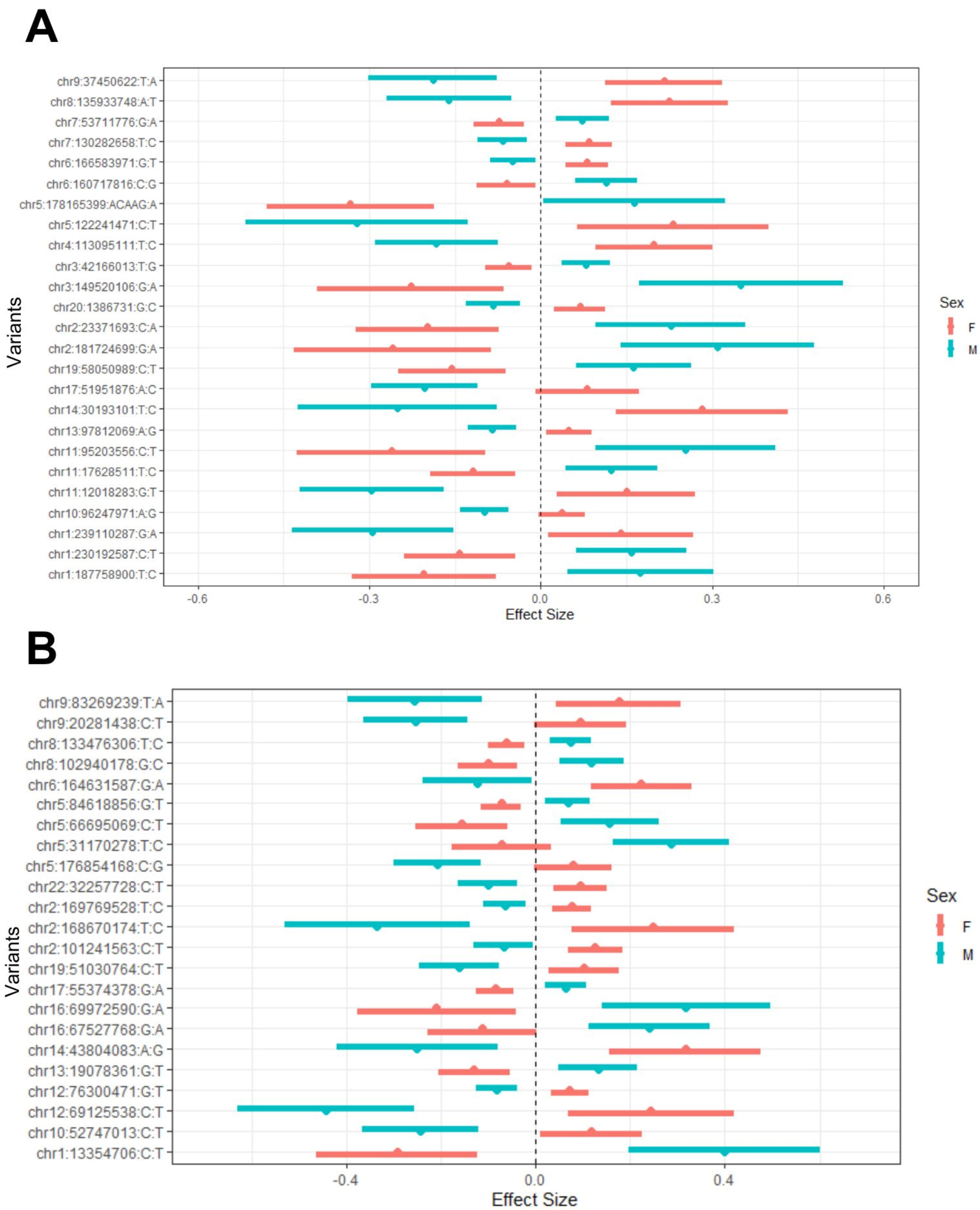

Figure 2. O-methylascorbate (A) and ascorbic acid 2-sulfate (B) effect sizes of lead interacting variant by sex. Effect sizes and 95% confidence intervals from the GWAS stratified by sex. GWAS conducted using a mixed linear model adjusted for age, batch number, province, 10 principal components, and hours since last meal or drink which incorporated a genetic relatedness matrix to account for population stratification. The list of variants are the lead variants for each suggestive locus found in the interaction GWAS analysis. Red represents female values and blue represents male values.

2.11. Tables

Table 1. Lead variants from overall **GWAS analysis selected using GCTA-COJO.** Details of chromosome, position, effect allele frequency, p-value from GWAS, and COJO-adjusted p-value. Variants were selected using the GCTA-COJO program.

O-methylascorbate

Chr	Variant	Effect Allele Frequency	p-value	COJO-adjusted p-value
22	chr22:19953481:A:G	0.95	4.62×10^{-22}	8.24×10^{-09}
22	chr22:19959676:CTCT:C	0.15	4.35×10^{-11}	1.13×10^{-29}
22	chr22:19963748:G:A	0.52	5.20×10^{-214}	3.24×10^{-204}

Ascorbic Acid 2-sulfate

Chr	Variant	Effect Allele Frequency	p-value	COJO-adjusted p-value
10	chr10:87718088:G:A	0.38	3.42×10^{-08}	3.61×10^{-08}
16	chr16:30343759:C:T	0.02	1.31×10^{-12}	2.94×10^{-11}
16	chr16:30374516:T:C	0.73	2.12×10^{-11}	4.70×10^{-10}

Table 2. O-methylascorbate suggestive interaction loci functions. Lead variants for each suggestive interaction locus were selected based on FUMA criteria. For each locus, variants in LD of the lead variant were analyzed to note down the nearest gene and function. The number of genes mapped to each locus is based on FUMA criteria. Loci that did not register in FUMA, and whose functions and nearest gene information were retrieved using VEP are marked.

Locus	Locus Lead Variant RSID	Locus Lead Variant Position	Nearest Gene	Function	# Genes mapped	Interaction p-value
1	rs561458908	chr1:187758900:T:C	RP5-925F19.1	Intergenic	0	9.61×10^{-6}
2	rs6673444	chr1:230192587:C:T	GALNT2	Intronic/Exonic	0	9.86×10^{-6}
3	rs74527587	chr1:239110287:G:A	RP11-307O1.1	Intergenic	0	9.91×10^{-6}
4	rs13427429	chr2:23371693:C:A	AC012506.4	Intergenic	0	2.58×10^{-6}
5	rs183979544	chr2:181724699:G:A	CERKL/AC013733.5/RUN6AT AC19)/PDE1A	Intronic/UTR5/Intergenic	0	8.81×10^{-7}
6	rs6775014	chr3:42166013:T:G	TRAK1	Intronic	0	9.86×10^{-6}
7	rs139707525	chr3:149520106:G:A	WWTR1	UTR3	0	5.15×10^{-6}
8	rs74597555	chr4:113095111:T:C	ANK2	Intronic	0	8.44×10^{-7}
9	rs2656901	chr5:175120419:G:A	CTC-281M20.1/ARL2BPP6	Intergenic	0	9.06×10^{-6}
10	rs783146	chr6:160717816:C:G	PLG	Intronic/Intergenic	0	8.10×10^{-6}
11	rs3823198	chr6:166583971:G:T	RPS6KA2	Intronic	0	4.60×10^{-6}
12	rs11764886	chr7:53711776:G:A	GS1-179L18.1	Intergnic/ncRNA_intronic/	3	6.43×10^{-6}
13	rs6952090	chr7:130282658:T:C	RP11-190G13.4/CPA2	NcRNA_intronic/Intergenic/Downstream/Intronic/Upstream	13	3.59×10^{-7}
14	rs2922384	chr8:135933748:A:T	Several	NcRNA_intronic/Intergenic/NcRNA_exonic/Intronic/Upstream	2	5.08×10^{-7}
15	rs116934390	chr9:37450622:T:A	ZBTB5	Intronic	0	4.33×10^{-7}
16	rs10882762	chr10:96247971:A:G	BLNK	Intronic	0	3.07×10^{-6}
17	rs79414703	chr11:12018283:G:T	RP13-631K18.2/DKK3	Intergenic/Intronic	0	2.93×10^{-6}
18	rs79157408	chr11:17628511:T:C	OTOG	Intronic	0	8.56×10^{-6}
19	rs80136724	chr11:95203556:C:T	RP11-712B9.2:SESN3	NcRNA_Intronic	0	4.53×10^{-6}
20	rs7331036	chr13:97812069:A:G	snoU13	Intergenic	1	7.38×10^{-6}
21	rs75638828	chr14:30193101:T:C	PRKD1:CTD-2251F13.1	NcRNA_intronic	2	1.85×10^{-6}
22	rs74665914	chr17:51951876:A:C	CA10	Intronic	2	9.33×10^{-6}

23	rs76958646	chr19:58050989:C:T	ZNF135/ ZSCAN1	Intronic	0	8.00×10^{-6}
24	rs6041909	chr20:1386731:G:C	FKBP1A	Intronic	0	6.03×10^{-6}
25[a]	rs1470819913	chr5:122241471:C:T	ZNF474	Intergenic	0	5.92×10^{-6}

[a]Features annotated using VEP platform, genetic region not available in FUMA.

Table 3. Ascorbic acid 2-sulfate suggestive interaction loci functions. Lead variants for each suggestive interaction locus were selected based on FUMA criteria. For each locus, variants in LD of the lead variant here analyzed to note down the nearest gene and function. The number of genes mapped to each locus is based on FUMA criteria. Loci that did not register in FUMA, and whose functions and nearest gene information were retrieved using VEP are marked.

Locus	Locus Lead Variant RSID	Locus Lead Variant Position	Nearest Gene	Function	# genes mapped	Interaction p-value
1	rs1192803	chr2:101241563:C:T	Several	Intergenic/Intronic/Downstream/Exonic	0	6.29×10^{-6}
2	rs142867333	chr2:168670174:T:C	CERS6	Intronic	0	1.70×10^{-6}
3	rs12692923	chr2:169769528:T:C	KLHL23/ KLHL23:PTCHD3P2	Intronic/ncRNA_exonic/UTR3	0	9.45×10^{-6}
4	rs7720392	chr5:31170278:T:C	RP11-152K4.2	NcRNA_intronic	1	8.03×10^{-6}
5	rs114959781	chr5:66695069:C:T	MAST4	Intronic	0	8.76×10^{-6}
6	rs28579435	chr5:84618856:G:T	CTD-2269F5.1	Intergenic	3	9.58×10^{-6}
7	rs4976655	chr5:176854168:C:G	UNC5A/HK3	Intronic/UTR3	3	5.23×10^{-6}
8	rs13204324	chr6:164631587:G:A	RP11-300M24.1	Intergenic	0	7.83×10^{-6}
9	rs62526542	chr8:102940178:G:C	AZIN1:KB-1507C5.2/ KB-1507C5.2	Intronic/Intergenic/Upstream	0	3.03×10^{-6}
10	rs1048471	chr8:133476306:T:C	ST3GAL1	Intronic/Exonic/UTR5	0	5.64×10^{-6}
11	rs11792574	chr9:20281438:C:T	AL512635.1	Intergenic	0	7.38×10^{-6}
12	rs117196678	chr9:83269239:T:A	RP11-439K3.1/FRMD3	NcRNA_intronic/Intronic	0	8.81×10^{-6}
13	rs117271698	chr10:52697952:C:T	RP11-556E13.1/MBL2	ncRNA_intronic/Intergenic	0	1.01×10^{-6}
14	rs117414281	chr12:69125538:C:T	AC139931.1	Intergenic	0	2.03×10^{-7}
15	rs10859572	chr12:76300471:G:T	RP11-54A9.1	ncRNA_intronic/ncRNA_exonic	0	2.31×10^{-7}

16	rs10162161	chr13:19078361:G:T	RNA5SP24	Intergenic/Downstream	0	2.34×10^{-6}
17	rs76250049	chr14:43804083:A:G	RP11-305B6.3	Intergenic	0	1.59×10^{-6}
18	rs35031569	chr16:67527768:G:A	Several	Exonic/Intronic/Upstream/Downstream/ Intergenic/UTR3/ncRNA_exonic/ ncRNA_Intronic	49	7.65×10^{-6}
19	rs148001569	chr16:69972590:G:A	NFAT5/PDXDC2P/ST3GAL 2	Intronic/Intergenic	0	9.92×10^{-6}
20	rs4334353	chr17:55374378:G:A	RP11-515O17.3/MMD	Intergenic	3	3.79×10^{-7}
21	rs75565227	chr19:51030764:C:T	KLK/CTC-518B2.10	NcRNA_Intronic/Upstream/Intergenic	0	1.13×10^{-6}
22	rs9609471	chr22:32257728:C:T	RFPL2/ RP1- 90G24.10:SLC5A4	Intergenic/Downstream/Intronic/ncRNA _intronic	0	1.93×10^{-6}
23[a]	rs129672135 6	chr1:13354706:C:T	Several	Upstream/Downstream/Intron/Intergeni c/UTR	0	2.61×10^{-8}

[a]Features annotated using VEP platform, genetic region not available in FUMA.Appendices

2.11.1. Supplementary Information

2.11.1.1. Supplementary Figures

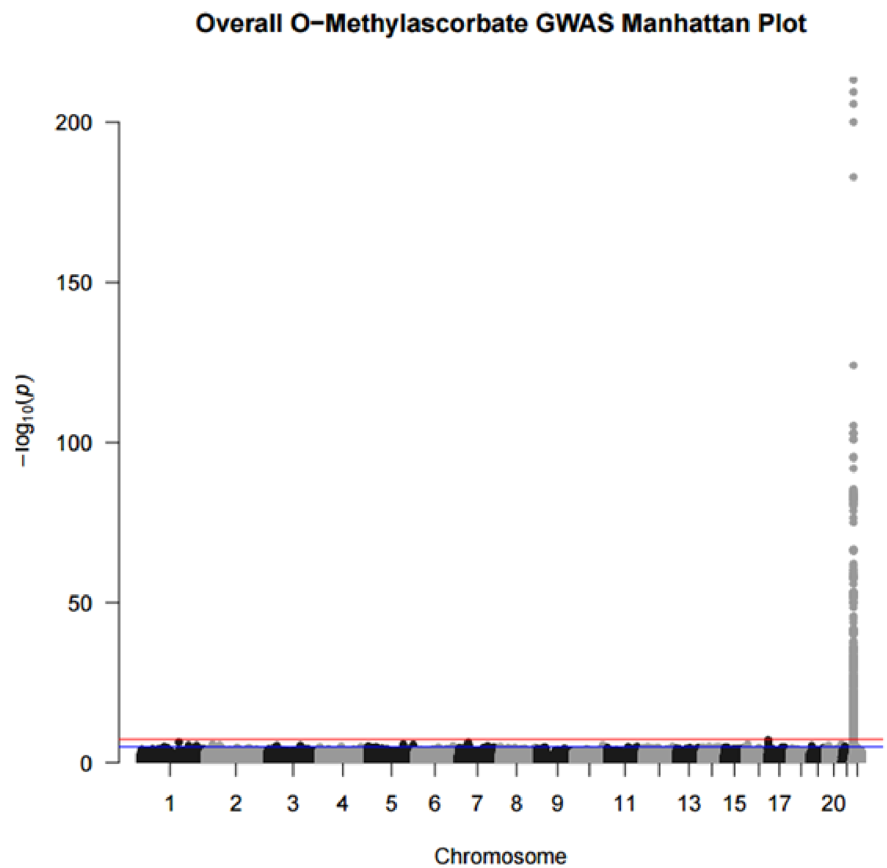

Figure S1. O-methylascorbate overall **results**. Results from the GWAS analysis using the FastGWA program from GCTA in the form of a Manhattan plot. GWAS conducted using a mixed linear model adjusted for age, sex, batch number, province, 10 principal components, and hours since last meal or drink which incorporated a genetic relatedness matrix to account for population stratification. Each point represents the p-value of a variant on the associated chromosome. The red line is the significant (5×10^{-8}) threshold and the blue line is the suggestive (1×10^{-5}) threshold.

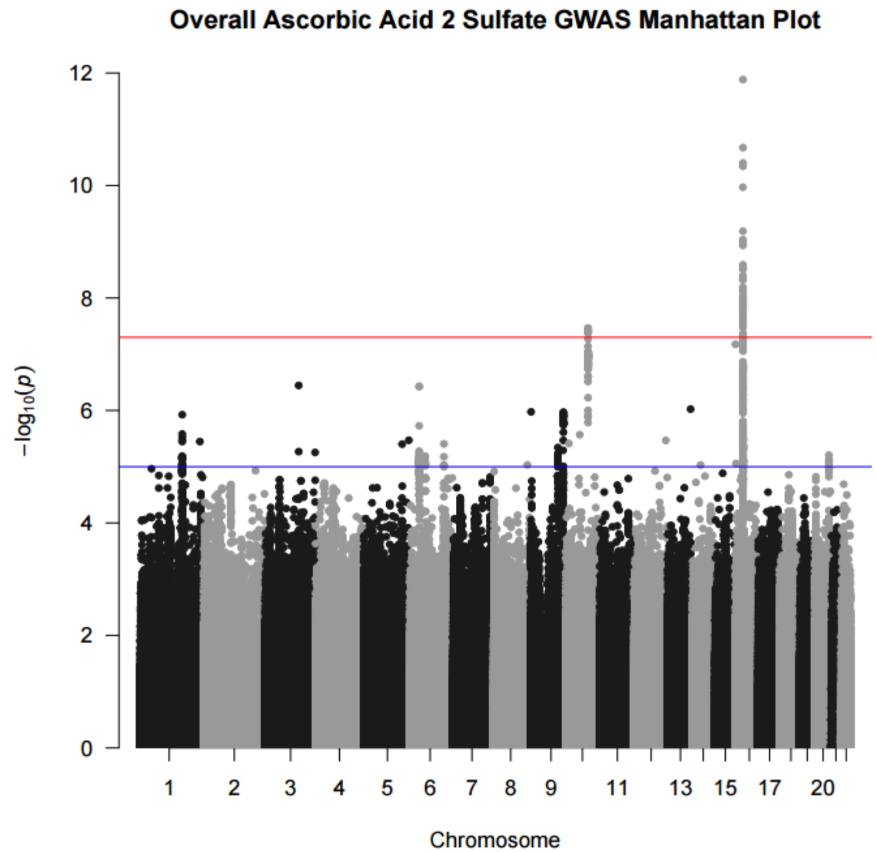

Figure S2. Ascorbic acid 2-sulfate overall **results**. Results from the GWAS analysis using the FastGWA program from GCTA in the form of a Manhattan plot. GWAS conducted using a mixed linear model adjusted for age, sex, batch number, province, 10 principal components, and hours since last meal or drink which incorporated a genetic relatedness matrix to account for population stratification. Each point represents the p-value of a variant on the associated chromosome. The red line is the significant (5×10^{-8}) threshold and the blue line is the suggestive (1×10^{-5}) threshold.

2.11.1.2. Supplementary Tables

Table S1. List of suggestive (1e-5) SNPs and p-value for overall o-methylascorbate GWAS.

CHR	SNP	POS	A1	A2	N	AF1	BETA	SE	P
1	chr1:148463834:A:C	148463834	C	A	8575	0.00530612	0.503529	0.0990033	3.7E-07
1	chr1:185949368:G:A	185949368	A	G	8881	0.00968359	-0.335312	0.0719245	3.1E-06
1	chr1:216904465:C:A	216904465	A	C	8893	0.059485	-0.138147	0.0298316	3.6E-06
2	chr2:29644733:A:C	29644733	C	A	8882	0.0372664	-0.163979	0.0370118	9.4E-06
2	chr2:29655859:A:T	29655859	T	A	8901	0.0310639	-0.18265	0.0405646	6.7E-06
2	chr2:29656951:T:C	29656951	C	T	8901	0.0311201	-0.180138	0.0405327	8.8E-06
2	chr2:29657341:C:T	29657341	T	C	8901	0.0311201	-0.180138	0.0405327	8.8E-06
2	chr2:29658011:C:T	29658011	T	C	8890	0.0303712	-0.189094	0.0410803	4.2E-06
2	chr2:29661950:G:A	29661950	A	G	8877	0.0301341	-0.185581	0.0412581	6.9E-06
2	chr2:29662748:C:T	29662748	T	C	8879	0.0301836	-0.184524	0.0412233	7.6E-06
2	chr2:29668280:C:T	29668280	T	C	8902	0.0282521	-0.188669	0.0424275	8.7E-06
2	chr2:29668965:C:T	29668965	T	C	8895	0.027656	-0.191532	0.0429465	8.2E-06
2	chr2:29671736:T:C	29671736	C	T	8879	0.030803	-0.187665	0.0407659	4.2E-06
2	chr2:29682471:C:T	29682471	T	C	8877	0.03081	-0.187443	0.0407663	4.3E-06
2	chr2:29704576:G:T	29704576	T	G	8890	0.0262655	-0.19582	0.0441785	9.3E-06
2	chr2:29708099:G:A	29708099	A	G	8893	0.0281682	-0.188889	0.0425058	8.8E-06
2	chr2:29709220:T:G	29709220	G	T	8888	0.0312781	-0.192708	0.0405376	2E-06
2	chr2:29709701:T:C	29709701	C	T	8891	0.0280058	-0.189368	0.0427105	9.3E-06
2	chr2:29722688:C:T	29722688	T	C	8890	0.0275028	-0.195123	0.0430659	5.9E-06
2	chr2:29734208:C:T	29734208	T	C	8887	0.0270057	-0.193272	0.0435287	9E-06
2	chr2:29746524:A:G	29746524	G	A	8876	0.0271519	-0.193316	0.043447	8.6E-06
2	chr2:29750915:C:T	29750915	T	C	8886	0.0267274	-0.203287	0.0437341	3.3E-06
2	chr2:57212734:G:C	57212734	C	G	8867	0.0217097	-0.223874	0.0479321	3E-06
3	chr3:37355300:T:A	37355300	A	T	8852	0.0970402	0.110746	0.0240181	4E-06
3	chr3:128201859:A:C	128201859	C	A	8847	0.0134509	0.283757	0.0614796	3.9E-06
3	chr3:128231412:G:GTAACTCT	128231412	GTAACTCT	G	8850	0.0135028	0.281474	0.061356	4.5E-06
4	chr4:5640885:C:G	5640885	G	C	8626	0.0761071	0.119725	0.0269581	8.9E-06
4	chr4:88391891:C:T	88391891	T	C	8865	0.233785	0.0756622	0.0167778	6.5E-06
5	chr5:3501414:T:A	3501414	A	T	8825	0.494278	0.0621694	0.0140591	9.8E-06
5	chr5:3501425:G:A	3501425	A	G	8825	0.494278	0.0621694	0.0140591	9.8E-06
5	chr5:3523017:C:T	3523017	T	C	8888	0.505063	-0.0628352	0.0140035	7.2E-06
5	chr5:3524790:A:C	3524790	C	A	8890	0.505793	-0.0622853	0.0139934	8.5E-06
5	chr5:3525326:A:G	3525326	G	A	8888	0.505794	-0.0620598	0.0139997	9.3E-06
5	chr5:3529546:T:C	3529546	C	T	8895	0.505902	-0.061992	0.0139905	9.4E-06
5	chr5:3529869:C:T	3529869	T	C	8907	0.506063	-0.0623998	0.0139795	8.1E-06
5	chr5:3530360:A:G	3530360	G	A	8897	0.505901	-0.0619902	0.0139905	9.4E-06
5	chr5:3530361:A:C	3530361	C	A	8906	0.506288	-0.0623376	0.0139797	8.2E-06
5	chr5:139151542:T:C	139151542	C	T	8905	0.0370578	-0.16495	0.0371728	9.1E-06
5	chr5:139163527:G:A	139163527	A	G	8907	0.0372741	-0.164462	0.0370738	9.2E-06

5	chr5:139170250:C:A	139170250	A	C	8907	0.0372741	-0.164562	0.0370738	9E-06
5	chr5:139201866:G:A	139201866	A	G	8899	0.0367457	-0.1717	0.0373203	4.2E-06
5	chr5:139205800:A:G	139205800	G	A	8891	0.036835	-0.171784	0.0372964	4.1E-06
5	chr5:139215809:A:C	139215809	C	A	8894	0.0362042	-0.180508	0.037571	1.6E-06
5	chr5:139220909:G:A	139220909	A	G	8893	0.0360396	-0.177872	0.0376501	2.3E-06
5	chr5:177361621:A:C	177361621	C	A	8782	0.340469	0.0690739	0.0150505	4.4E-06
5	chr5:177365490:A:G	177365490	G	A	8786	0.339688	0.0675636	0.015071	7.4E-06
5	chr5:177365556:T:C	177365556	C	T	8785	0.338589	0.0717257	0.0150792	2E-06
5	chr5:177365742:G:A	177365742	A	G	8837	0.270227	0.0707784	0.0159742	9.4E-06
5	chr5:177367190:G:A	177367190	A	G	8737	0.351837	0.0663614	0.0149983	9.7E-06
5	chr5:177371305:G:A	177371305	A	G	8904	0.270272	0.0709827	0.0159358	8.4E-06
6	chr6:150091067:T:C	150091067	C	T	8486	0.0950978	0.11277	0.0247883	5.4E-06
7	chr7:38769390:G:A	38769390	A	G	8885	0.900113	-0.119513	0.0236759	4.5E-07
7	chr7:38825594:C:T	38825594	T	C	8863	0.900542	-0.112502	0.0237867	2.2E-06
7	chr7:38827133:A:T	38827133	T	A	8861	0.900632	-0.111608	0.0237969	2.7E-06
7	chr7:38828311:CA:C	38828311	C	CA	8851	0.898543	-0.111337	0.0235966	2.4E-06
7	chr7:38851690:A:C	38851690	C	A	8840	0.896437	-0.105455	0.0233776	6.5E-06
7	chr7:38868309:C:A	38868309	A	C	8838	0.896583	-0.104965	0.0233913	7.2E-06
7	chr7:38874334:A:G	38874334	G	A	8842	0.896686	-0.109488	0.023392	2.9E-06
7	chr7:38895799:C:T	38895799	T	C	8858	0.896534	-0.107874	0.0233623	3.9E-06
7	chr7:38898378:A:G	38898378	G	A	8860	0.896896	-0.109117	0.0234011	3.1E-06
7	chr7:38898454:A:G	38898454	G	A	8860	0.896896	-0.109117	0.0234011	3.1E-06
7	chr7:38898994:C:T	38898994	T	C	8860	0.896896	-0.109117	0.0234011	3.1E-06
7	chr7:38903950:A:C	38903950	C	A	8856	0.897075	-0.108174	0.0234054	3.8E-06
7	chr7:38904046:C:T	38904046	T	C	8856	0.89685	-0.107161	0.0233888	4.6E-06
7	chr7:38913487:C:G	38913487	G	C	8839	0.897104	-0.106971	0.0234284	5E-06
7	chr7:38926596:TA:T	38926596	T	TA	8580	0.0888695	0.11994	0.0254603	2.5E-06
7	chr7:113702070:G:A	113702070	A	G	8905	0.983156	-0.250116	0.0548127	5E-06
8	chr8:3237574:AT:A	3237574	A	AT	8894	0.163481	0.0845825	0.0189806	8.3E-06
10	chr10:116969286:C:G	116969286	G	C	8889	0.0110249	-0.315879	0.0678687	3.3E-06
10	chr10:122365153:T:C	122365153	C	T	8877	0.0571139	-0.135976	0.0301692	6.6E-06
11	chr11:81462848:G:A	81462848	A	G	8909	0.0230666	0.207285	0.0467512	9.3E-06
11	chr11:116025015:G:A	116025015	A	G	8817	0.0272769	-0.195191	0.0434957	7.2E-06
12	chr12:22849848:A:C	22849848	C	A	8906	0.0398046	0.159716	0.0360224	9.3E-06
12	chr12:118064662:A:G	118064662	G	A	8844	0.177069	-0.0822603	0.0186139	9.9E-06
12	chr12:118064870:A:G	118064870	G	A	8901	0.179306	-0.0822787	0.0184319	8E-06
14	chr14:51357163:C:G	51357163	G	C	8821	0.0730643	0.121733	0.0270972	7E-06
14	chr14:78170839:G:C	78170839	C	G	8647	0.195386	0.0796119	0.0179837	9.6E-06
14	chr14:88468842:T:C	88468842	C	T	8909	0.0168369	0.243951	0.0548154	8.6E-06
16	chr16:10693337:C:T	10693337	T	C	8848	0.00977622	0.324706	0.0717305	6E-06
16	chr16:11783568:G:A	11783568	A	G	8735	0.981511	0.249705	0.0524374	1.9E-06
17	chr17:899017:G:C	899017	C	G	8671	0.620459	-0.0709687	0.0146664	1.3E-06
17	chr17:900770:A:G	900770	G	A	8891	0.623439	-0.0739933	0.014535	3.6E-07
17	chr17:901308:T:C	901308	C	T	8826	0.659075	-0.0802385	0.0148905	7.1E-08
19	chr19:6278205:T:C	6278205	C	T	8832	0.0131907	0.283754	0.061578	4.1E-06
20	chr20:13494123:G:A	13494123	A	G	8907	0.0103851	0.320515	0.0694308	3.9E-06
20	chr20:62670503:G:A	62670503	A	G	8455	0.07055	-0.134682	0.0282437	1.9E-06
21	chr21:22416907:G:A	22416907	A	G	8902	0.0108964	-0.305494	0.0675055	6E-06

22	chr22:19745162:C:T	19745162	T	C	8904	0.0293688	-0.186888	0.0418468	8E-06
22	chr22:19809211:G:A	19809211	A	G	8677	0.16538	-0.0882029	0.0192421	4.6E-06
22	chr22:19818192:G:A	19818192	A	G	8855	0.0103331	0.325718	0.0694166	2.7E-06
22	chr22:19822762:G:A	19822762	A	G	8749	0.15859	0.0906037	0.0195299	3.5E-06
22	chr22:19823010:C:T	19823010	T	C	8748	0.158436	0.0918465	0.0195598	2.7E-06
22	chr22:19827686:T:G	19827686	G	T	8909	0.162196	0.0962361	0.0191743	5.2E-07
22	chr22:19829842:G:T	19829842	T	G	8897	0.161628	0.0926219	0.0192253	1.5E-06
22	chr22:19831221:G:A	19831221	A	G	8888	0.163535	0.0922284	0.0191377	1.4E-06
22	chr22:19832932:C:T	19832932	T	C	8887	0.161247	0.0943836	0.019259	9.5E-07
22	chr22:19834649:TTAAG:T	19834649	T	TTA AG	8888	0.161172	0.0938665	0.0192603	1.1E-06
22	chr22:19837186:T:C	19837186	C	T	8888	0.161172	0.0940511	0.0192602	1E-06
22	chr22:19852673:C:G	19852673	G	C	8792	0.209679	0.0891512	0.0175758	3.9E-07
22	chr22:19866608:AC:A	19866608	A	AC	8799	0.00971701	0.353804	0.0717026	8E-07
22	chr22:19868949:G:A	19868949	A	G	8757	0.109455	0.12281	0.0229612	8.9E-08
22	chr22:19870544:A:G	19870544	G	A	8905	0.916227	0.112752	0.0255008	9.8E-06
22	chr22:19871558:G:T	19871558	T	G	8905	0.0254913	-0.258087	0.0442218	5.3E-09
22	chr22:19886083:C:T	19886083	T	C	8902	0.0220737	-0.327824	0.0481576	9.9E-12
22	chr22:19886686:T:C	19886686	C	T	8705	0.0831706	0.205117	0.0254823	8.3E-16
22	chr22:19886962:G:A	19886962	A	G	8813	0.0451606	0.170929	0.0338523	4.4E-07
22	chr22:19890839:T:C	19890839	C	T	8871	0.291173	0.116519	0.0154429	4.5E-14
22	chr22:19890991:G:A	19890991	A	G	8845	0.290107	0.116936	0.0154663	4E-14
22	chr22:19891229:A:T	19891229	T	A	8842	0.290262	0.116382	0.015465	5.3E-14
22	chr22:19892114:A:G	19892114	G	A	8837	0.290031	0.11505	0.0154928	1.1E-13
22	chr22:19892817:G:A	19892817	A	G	8827	0.0847966	0.227531	0.0250533	1.1E-19
22	chr22:19897134:C:T	19897134	T	C	8860	0.0889955	0.230779	0.0245307	5.1E-21
22	chr22:19898920:G:A	19898920	A	G	8897	0.0522648	-0.181993	0.0317492	9.9E-09
22	chr22:19899827:A:T	19899827	T	A	8867	0.0890944	0.230683	0.0245295	5.2E-21
22	chr22:19899853:A:G	19899853	G	A	8901	0.052466	-0.184296	0.0316895	6E-09
22	chr22:19901338:A:G	19901338	G	A	8891	0.0114723	0.390184	0.0655248	2.6E-09
22	chr22:19901900:G:A	19901900	A	G	8702	0.471443	0.0736028	0.0142317	2.3E-07
22	chr22:19901968:G:A	19901968	A	G	8761	0.0712818	-0.237953	0.0275915	6.5E-18
22	chr22:19902112:A:G	19902112	G	A	8863	0.111418	0.189998	0.0223926	2.2E-17
22	chr22:19904175:C:T	19904175	T	C	8909	0.0879448	0.233339	0.0245188	1.8E-21
22	chr22:19904799:G:C	19904799	C	G	8902	0.108009	0.191454	0.0225167	1.9E-17
22	chr22:19905557:A:G	19905557	G	A	8900	0.108876	0.190358	0.0224629	2.4E-17
22	chr22:19906500:T:G	19906500	G	T	8904	0.0892296	0.227919	0.0243894	9.2E-21
22	chr22:19908986:C:A	19908986	A	C	8903	0.0896327	0.229789	0.0243502	3.8E-21
22	chr22:19911363:C:T	19911363	T	C	8891	0.0900911	0.230468	0.0243207	2.6E-21
22	chr22:19912363:A:G	19912363	G	A	8900	0.109551	0.189025	0.0223945	3.2E-17
22	chr22:19912552:A:G	19912552	G	A	8900	0.109551	0.189025	0.0223945	3.2E-17
22	chr22:19915003:T:C	19915003	C	T	8904	0.0587938	0.232062	0.0297096	5.7E-15
22	chr22:19918032:C:T	19918032	T	C	8749	0.0537776	0.18774	0.0314756	2.5E-09
22	chr22:19918847:G:A	19918847	A	G	8893	0.0290678	0.221417	0.0417175	1.1E-07
22	chr22:19920397:G:T	19920397	T	G	8704	0.157169	0.123678	0.0195813	2.7E-10
22	chr22:19920454:A:G	19920454	G	A	8803	0.0832671	0.11837	0.0255941	3.7E-06
22	chr22:19921056:G:A	19921056	A	G	8787	0.0617958	0.250022	0.0293405	1.6E-17
22	chr22:19921366:G:C	19921366	C	G	8841	0.0310485	0.253223	0.0403612	3.5E-10

22	chr22:19924308:A:G	19924308	G	A	8808	0.0808924	0.215374	0.0259275	9.8E-17
22	chr22:19924835:G:A	19924835	A	G	8821	0.0384877	0.199185	0.0366497	5.5E-08
22	chr22:19925011:A:G	19925011	G	A	8747	0.0572196	-0.193315	0.0306415	2.8E-10
22	chr22:19925060:G:A	19925060	A	G	8689	0.0313615	0.22804	0.0406846	2.1E-08
22	chr22:19925104:G:A	19925104	A	G	8782	0.0206103	0.23334	0.0495849	2.5E-06
22	chr22:19925107:G:A	19925107	A	G	8773	0.0210304	0.219806	0.0491547	7.8E-06
22	chr22:19925570:A:G	19925570	G	A	8636	0.268759	0.206743	0.0160549	6E-38
22	chr22:19925575:A:C	19925575	C	A	8645	0.269346	0.20685	0.0160126	3.6E-38
22	chr22:19925965:A:G	19925965	G	A	8682	0.546648	0.209794	0.0142167	2.8E-49
22	chr22:19926203:G:A	19926203	A	G	8790	0.562969	0.272278	0.0140884	3.2E-83
22	chr22:19926382:T:C	19926382	C	T	8758	0.523293	0.229458	0.0140602	7.2E-60
22	chr22:19926507:C:T	19926507	T	C	8868	0.0240189	0.298549	0.0457118	6.5E-11
22	chr22:19926713:C:G	19926713	G	C	8744	0.523387	0.229575	0.0140685	7.3E-60
22	chr22:19926788:A:C	19926788	C	A	8723	0.328843	0.258441	0.0149249	3.6E-67
22	chr22:19926985:A:AT	19926985	AT	A	8878	0.064091	0.254217	0.0286862	7.9E-19
22	chr22:19927331:T:C	19927331	C	T	8901	0.0645995	0.258917	0.0285027	1E-19
22	chr22:19927803:A:G	19927803	G	A	8901	0.565835	0.271813	0.0140009	5.9E-84
22	chr22:19929295:C:G	19929295	G	C	8734	0.329116	0.257409	0.0149049	7.9E-67
22	chr22:19929490:C:T	19929490	T	C	8808	0.563862	0.272665	0.0140744	1.3E-83
22	chr22:19929817:T:TC	19929817	TC	T	8769	0.523093	0.231287	0.0140547	7.6E-61
22	chr22:19930333:C:T	19930333	T	C	8716	0.139628	0.16582	0.0204525	5.2E-16
22	chr22:19931710:C:G	19931710	G	C	8889	0.0471369	0.287868	0.0329348	2.3E-18
22	chr22:19931945:G:A	19931945	A	G	8695	0.13801	0.167528	0.0206034	4.3E-16
22	chr22:19932078:G:A	19932078	A	G	8722	0.327448	0.259118	0.014961	3.4E-67
22	chr22:19932836:C:G	19932836	G	C	8745	0.562493	0.272191	0.0141286	1.1E-82
22	chr22:19933123:C:G	19933123	G	C	8728	0.521712	0.227386	0.0141217	2.5E-58
22	chr22:19933224:C:T	19933224	T	C	8907	0.0176827	-0.24956	0.0532069	2.7E-06
22	chr22:19933426:G:A	19933426	A	G	8891	0.0478574	0.286079	0.0326819	2.1E-18
22	chr22:19933480:T:C	19933480	C	T	8751	0.563764	0.272681	0.0141322	5.9E-83
22	chr22:19933614:C:T	19933614	T	C	8680	0.133929	0.19798	0.0209091	2.8E-21
22	chr22:19933855:C:T	19933855	T	C	8751	0.279454	0.212482	0.0156838	8.2E-42
22	chr22:19933993:CAG:C	19933993	C	CAG	8704	0.0240119	0.232995	0.0461745	4.5E-07
22	chr22:19934118:G:A	19934118	A	G	8748	0.279664	0.212435	0.0156865	8.8E-42
22	chr22:19934302:A:G	19934302	G	A	8735	0.473097	0.172685	0.0141981	4.9E-34
22	chr22:19934455:A:G	19934455	G	A	8738	0.473106	0.173274	0.0141939	2.8E-34
22	chr22:19934820:T:A	19934820	A	T	8751	0.279397	0.212794	0.015683	6.2E-42
22	chr22:19934851:C:T	19934851	T	C	8748	0.279492	0.212187	0.0156861	1.1E-41
22	chr22:19934923:A:G	19934923	G	A	8752	0.563357	0.272945	0.0141268	3.6E-83
22	chr22:19935020:C:T	19935020	T	C	8885	0.0478334	0.284036	0.0327012	3.8E-18
22	chr22:19935062:C:T	19935062	T	C	8752	0.279422	0.212639	0.0156828	7E-42
22	chr22:19935630:T:C	19935630	C	T	8730	0.521879	0.228564	0.0141217	6.4E-59
22	chr22:19935883:T:C	19935883	C	T	8718	0.52145	0.226983	0.0141301	4.6E-58
22	chr22:19935892:A:G	19935892	G	A	8748	0.563729	0.273815	0.0141346	1.3E-83
22	chr22:19935918:C:G	19935918	G	C	8749	0.563607	0.273534	0.0141343	1.9E-83
22	chr22:19936209:G:A	19936209	A	G	8890	0.0472441	0.287531	0.0329017	2.4E-18
22	chr22:19936605:C:T	19936605	T	C	8841	0.00967085	-0.35225	0.0721226	1E-06
22	chr22:19937015:T:G	19937015	G	T	8725	0.521662	0.227797	0.0141225	1.6E-58
22	chr22:19937089:G:C	19937089	C	G	8753	0.279447	0.212729	0.0156823	6.5E-42

22	chr22:19937643:G:A	19937643	A	G	8872	0.0389427	0.250853	0.0363796	5.4E-12
22	chr22:19937749:C:T	19937749	T	C	8875	0.0240563	0.29495	0.0456644	1.1E-10
22	chr22:19937891:A:G	19937891	G	A	8824	0.279692	0.210374	0.015607	2.1E-41
22	chr22:19938481:T:C	19938481	C	T	8826	0.279685	0.210507	0.0156057	1.8E-41
22	chr22:19938808:G:A	19938808	A	G	8865	0.0470389	0.289217	0.0330047	1.9E-18
22	chr22:19939623:A:C	19939623	C	A	8730	0.563517	0.274717	0.0141443	5E-84
22	chr22:19940170:G:A	19940170	A	G	8824	0.279918	0.209778	0.0156	3.2E-41
22	chr22:19940499:G:A	19940499	A	G	8823	0.279893	0.209997	0.0155957	2.5E-41
22	chr22:19940569:G:A	19940569	A	G	8726	0.562801	0.275721	0.0141452	1.3E-84
22	chr22:19941361:C:T	19941361	T	C	8831	0.279753	0.209947	0.0155862	2.3E-41
22	chr22:19941504:C:T	19941504	T	C	8728	0.13852	0.158614	0.0204598	9E-15
22	chr22:19941996:G:A	19941996	A	G	8895	0.0392917	0.254473	0.0361888	2E-12
22	chr22:19942028:A:G	19942028	G	A	8752	0.516168	0.219292	0.0141439	3.2E-54
22	chr22:19942586:T:C	19942586	C	T	8848	0.282776	0.211885	0.0155004	1.5E-42
22	chr22:19942598:A:G	19942598	G	A	8847	0.282751	0.211894	0.0155008	1.5E-42
22	chr22:19942636:C:T	19942636	T	C	8900	0.285112	0.20832	0.0154078	1.2E-41
22	chr22:19942664:GC:G	19942664	G	GC	8711	0.136092	0.195743	0.020717	3.4E-21
22	chr22:19943287:T:C	19943287	C	T	8906	0.0391309	0.258413	0.0362296	9.8E-13
22	chr22:19943573:C:T	19943573	T	C	8752	0.564157	0.275909	0.0141196	4.9E-85
22	chr22:19943650:A:T	19943650	T	A	8611	0.42527	0.29031	0.0142211	1.3E-92
22	chr22:19943884:T:C	19943884	C	T	8775	0.276809	0.115309	0.0156966	2E-13
22	chr22:19943901:AG:A	19943901	A	AG	8724	0.563675	0.274758	0.0141349	3.7E-84
22	chr22:19944145:A:G	19944145	G	A	8754	0.564599	0.276969	0.0141138	9.7E-86
22	chr22:19944330:C:T	19944330	T	C	8750	0.562743	0.274689	0.0141131	2.2E-84
22	chr22:19944453:T:C	19944453	C	T	8777	0.276062	0.115391	0.0157145	2.1E-13
22	chr22:19944572:C:T	19944572	T	C	8838	0.282813	0.209066	0.0155103	2.1E-41
22	chr22:19945525:T:G	19945525	G	T	8838	0.2827	0.209238	0.0155094	1.8E-41
22	chr22:19945573:GAA:G	19945573	G	GAA	8838	0.2827	0.209238	0.0155094	1.8E-41
22	chr22:19945888:C:A	19945888	A	C	8834	0.283903	0.210633	0.0154806	3.7E-42
22	chr22:19946164:C:T	19946164	T	C	8774	0.275872	0.116038	0.0157238	1.6E-13
22	chr22:19946255:C:G	19946255	G	C	8695	0.953076	-0.307943	0.0333667	2.7E-20
22	chr22:19946502:A:G	19946502	G	A	8671	0.719352	-0.114588	0.0157268	3.2E-13
22	chr22:19946528:T:C	19946528	C	T	8672	0.719384	-0.114536	0.0157262	3.3E-13
22	chr22:19946947:A:G	19946947	G	A	8663	0.719266	-0.114146	0.015732	4E-13
22	chr22:19947113:G:A	19947113	A	G	8638	0.420873	-0.265563	0.0142788	3.3E-77
22	chr22:19947347:T:G	19947347	G	T	8835	0.0110922	0.331222	0.067166	8.2E-07
22	chr22:19947476:T:C	19947476	C	T	8669	0.720671	-0.112647	0.0157635	8.9E-13
22	chr22:19947548:G:A	19947548	A	G	8832	0.282212	0.209936	0.015518	1.1E-41
22	chr22:19947625:T:C	19947625	C	T	8897	0.0397887	0.263564	0.0359777	2.4E-13
22	chr22:19947732:T:TA	19947732	TA	T	8890	0.0244657	0.299129	0.0452722	3.9E-11
22	chr22:19948084:G:T	19948084	T	G	8731	0.433398	-0.272286	0.0141358	1.1E-82
22	chr22:19948433:C:T	19948433	T	C	8693	0.953123	-0.306527	0.0333859	4.3E-20
22	chr22:19948502:G:A	19948502	A	G	8693	0.953123	-0.306527	0.0333859	4.3E-20
22	chr22:19948686:G:A	19948686	A	G	8809	0.288341	0.208549	0.0154046	9.3E-42
22	chr22:19948785:C:T	19948785	T	C	8693	0.953123	-0.306527	0.0333859	4.3E-20
22	chr22:19950115:T:G	19950115	G	T	8904	0.522799	0.213808	0.0139656	6.6E-53
22	chr22:19951186:C:T	19951186	T	C	8607	0.319217	0.226418	0.0151189	1.1E-50
22	chr22:19951236:A:G	19951236	G	A	8883	0.0413712	0.276034	0.0352807	5.1E-15

22	chr22:19951314:A:G	19951314	G	A	8691	0.95317	-0.303858	0.0334495	1E-19
22	chr22:19951830:A:G	19951830	G	A	8727	0.954795	-0.318393	0.0338757	5.5E-21
22	chr22:19951909:G:A	19951909	A	G	8689	0.421683	-0.293331	0.014082	2.3E-96
22	chr22:19952116:A:G	19952116	G	A	8668	0.784033	-0.136948	0.0172282	1.9E-15
22	chr22:19952377:T:C	19952377	C	T	8837	0.0512052	-0.236087	0.0320514	1.8E-13
22	chr22:19952395:T:A	19952395	A	T	8862	0.0273076	0.341376	0.0431711	2.6E-15
22	chr22:19952504:G:C	19952504	C	G	8642	0.461988	-0.300164	0.0140187	1E-101
22	chr22:19952659:C:A	19952659	A	C	8356	0.245871	0.201498	0.0166621	1.1E-33
22	chr22:19953120:T:C	19953120	C	T	8833	0.0210008	0.230617	0.0491533	2.7E-06
22	chr22:19953138:C:T	19953138	T	C	8747	0.512804	0.264422	0.0140158	2.2E-79
22	chr22:19953481:A:G	19953481	G	A	8725	0.955415	-0.329418	0.034114	4.6E-22
22	chr22:19953984:A:G	19953984	G	A	8783	0.515371	0.266435	0.0139823	5.9E-81
22	chr22:19954180:C:T	19954180	T	C	8904	0.0639039	-0.23432	0.0288634	4.7E-16
22	chr22:19954251:G:T	19954251	T	G	8770	0.514196	0.267797	0.0139856	1E-81
22	chr22:19955121:C:T	19955121	T	C	8857	0.0090324	-0.338843	0.0740308	4.7E-06
22	chr22:19955157:C:G	19955157	G	C	8844	0.514756	0.267018	0.0139417	9.2E-82
22	chr22:19955474:A:G	19955474	G	A	8896	0.516637	0.26569	0.0139035	2.1E-81
22	chr22:19956621:C:T	19956621	T	C	8880	0.0106419	0.505137	0.067865	9.8E-14
22	chr22:19956800:G:A	19956800	A	G	8870	0.0271139	0.350991	0.0432851	5.1E-16
22	chr22:19957037:G:A	19957037	A	G	8785	0.43523	-0.33175	0.0139602	8E-125
22	chr22:19957200:C:T	19957200	T	C	8812	0.527179	0.270252	0.0139988	4.8E-83
22	chr22:19957654:A:G	19957654	G	A	8803	0.527547	0.273841	0.0140123	4.7E-85
22	chr22:19959676:CTCT:C	19959676	C	CTCT	8625	0.153159	0.130741	0.0198348	4.4E-11
22	chr22:19959946:C:T	19959946	T	C	8467	0.451163	-0.402733	0.0139364	1E-183
22	chr22:19960250:C:T	19960250	T	C	8871	0.0444144	0.371509	0.0338974	6E-28
22	chr22:19960419:C:A	19960419	A	C	8901	0.0680261	-0.284842	0.027996	2.6E-24
22	chr22:19960814:T:C	19960814	C	T	8660	0.396132	0.296082	0.0142531	7.6E-96
22	chr22:19961340:G:C	19961340	C	G	8677	0.522243	-0.411995	0.0136265	8E-201
22	chr22:19961469:C:T	19961469	T	C	8890	0.0127672	-0.283387	0.0631826	7.3E-06
22	chr22:19961490:C:T	19961490	T	C	8674	0.518677	-0.418052	0.0136353	2E-206
22	chr22:19961580:G:A	19961580	A	G	8874	0.0276651	0.363018	0.0429558	2.9E-17
22	chr22:19962121:G:C	19962121	C	G	8762	0.402591	0.305329	0.0141152	9E-104
22	chr22:19962429:A:G	19962429	G	A	8760	0.402797	0.304893	0.0141136	2E-103
22	chr22:19962712:C:T	19962712	T	C	8786	0.516219	-0.418211	0.0135173	4E-210
22	chr22:19962905:A:G	19962905	G	A	8761	0.402694	0.305105	0.0141144	1E-103
22	chr22:19963240:T:G	19963240	G	T	8836	0.404595	0.306766	0.0140281	5E-106
22	chr22:19963684:C:G	19963684	G	C	8836	0.39854	0.301112	0.0140612	1E-101
22	chr22:19963748:G:A	19963748	A	G	8896	0.516805	-0.419037	0.0134208	5E-214
22	chr22:19964374:G:C	19964374	C	G	8621	0.175502	-0.339758	0.0184453	9.1E-76
22	chr22:19964609:C:T	19964609	T	C	8877	0.238707	0.205742	0.016501	1.1E-35
22	chr22:19964645:G:A	19964645	A	G	8780	0.416173	0.278275	0.0141346	2.8E-86
22	chr22:19964701:T:C	19964701	C	T	8907	0.0460312	0.375414	0.0333949	2.5E-29
22	chr22:19964978:C:T	19964978	T	C	8570	0.312135	-0.229629	0.0153243	9.3E-51
22	chr22:19965038:G:A	19965038	A	G	8571	0.311807	-0.229059	0.0153218	1.6E-50
22	chr22:19965536:T:C	19965536	C	T	8187	0.340296	-0.242108	0.0152694	1.3E-56
22	chr22:19965665:A:C	19965665	C	A	8664	0.428324	0.278268	0.0141927	1.4E-85
22	chr22:19966309:A:G	19966309	G	A	8828	0.952594	-0.381302	0.0330644	9.1E-31

22	chr22:19966359:T:C	19966359	C	T	8864	0.16505	0.173275	0.0187707	2.7E-20
22	chr22:19966376:C:T	19966376	T	C	8873	0.0427702	-0.179392	0.0347658	2.5E-07
22	chr22:19966935:C:T	19966935	T	C	8836	0.949751	-0.366229	0.0320577	3.2E-30
22	chr22:19967634:G:A	19967634	A	G	8572	0.0648623	0.273182	0.0290599	5.4E-21
22	chr22:19968169:C:T	19968169	T	C	8902	0.159571	0.170879	0.0189735	2.1E-19
22	chr22:19968491:G:C	19968491	C	G	8823	0.0632438	-0.265548	0.0291374	8E-20
22	chr22:19968739:G:GC	19968739	GC	G	8593	0.733271	-0.17653	0.0161739	9.8E-28
22	chr22:19969030:C:G	19969030	G	C	8883	0.0440167	-0.179749	0.0343186	1.6E-07
22	chr22:19969258:G:A	19969258	A	G	8803	0.693002	-0.232985	0.0152883	1.9E-52
22	chr22:19969362:T:C	19969362	C	T	8883	0.0433975	-0.175453	0.0345315	3.8E-07
22	chr22:19969500:C:T	19969500	T	C	8839	0.951069	-0.380262	0.032679	2.7E-31
22	chr22:19970108:C:A	19970108	A	C	8807	0.693653	-0.233111	0.0152891	1.7E-52
22	chr22:19970110:A:T	19970110	T	A	8885	0.0431626	-0.174146	0.0346567	5E-07
22	chr22:19970240:G:A	19970240	A	G	8805	0.69364	-0.232716	0.0152909	2.6E-52
22	chr22:19970264:C:T	19970264	T	C	8829	0.907068	-0.124085	0.0244023	3.7E-07
22	chr22:19970499:G:A	19970499	A	G	8883	0.163965	0.169896	0.0187832	1.5E-19
22	chr22:19971089:G:A	19971089	A	G	8890	0.0274466	0.348116	0.0430894	6.5E-16
22	chr22:19971146:G:A	19971146	A	G	8831	0.69307	-0.232765	0.0152698	1.8E-52
22	chr22:19971288:C:T	19971288	T	C	8890	0.0264904	0.354776	0.0437961	5.5E-16
22	chr22:19971306:G:A	19971306	A	G	8900	0.0466292	0.309083	0.0332978	1.7E-20
22	chr22:19971375:GGTTA:G	19971375	G	GGT TA	8725	0.025616	-0.228083	0.0449847	4E-07
22	chr22:19971488:G:A	19971488	A	G	8750	0.147886	-0.342326	0.0197333	2.1E-67
22	chr22:19971510:G:A	19971510	A	G	8883	0.163852	0.172341	0.0187605	4.1E-20
22	chr22:19971704:G:A	19971704	A	G	8661	0.088327	-0.218985	0.0250745	2.5E-18
22	chr22:19971843:G:A	19971843	A	G	8860	0.906546	-0.120039	0.0243021	7.8E-07
22	chr22:19971950:C:T	19971950	T	C	8903	0.85971	-0.197828	0.0202997	1.9E-22
22	chr22:19972223:C:T	19972223	T	C	8900	0.0473596	0.29928	0.0330441	1.3E-19
22	chr22:19972432:A:G	19972432	G	A	8864	0.906588	-0.118202	0.024302	1.2E-06
22	chr22:19972617:G:A	19972617	A	G	8886	0.164866	0.172485	0.0187269	3.2E-20
22	chr22:19972661:C:G	19972661	G	C	8777	0.285006	-0.239557	0.0154965	6.6E-54
22	chr22:19972665:T:C	19972665	C	T	8864	0.90687	-0.117542	0.0243443	1.4E-06
22	chr22:19972675:G:C	19972675	C	G	8781	0.285047	-0.239407	0.0154948	7.5E-54
22	chr22:19972871:G:A	19972871	A	G	8897	0.0474317	0.296321	0.0329895	2.7E-19
22	chr22:19973083:G:C	19973083	C	G	8865	0.30564	0.229956	0.0152425	2E-51
22	chr22:19973484:G:C	19973484	C	G	8883	0.164753	0.172111	0.0187248	3.9E-20
22	chr22:19973487:C:CG	19973487	CG	C	8863	0.163432	0.17591	0.0188063	8.5E-21
22	chr22:19973487:C:T	19973487	T	C	8905	0.0468276	0.308647	0.0332284	1.6E-20
22	chr22:19973578:C:T	19973578	T	C	8905	0.0441325	0.323212	0.0341207	2.7E-21
22	chr22:19973910:C:T	19973910	T	C	8892	0.0432973	-0.176447	0.0345487	3.3E-07
22	chr22:19974403:G:A	19974403	A	G	8901	0.0472419	0.30158	0.033117	8.5E-20
22	chr22:19974432:A:G	19974432	G	A	8858	0.860296	-0.198086	0.0204145	2.9E-22
22	chr22:19974680:T:G	19974680	G	T	8908	0.0457454	0.309466	0.033559	2.9E-20
22	chr22:19974857:C:T	19974857	T	C	8907	0.950039	-0.350093	0.0320338	8.4E-28
22	chr22:19975246:C:T	19975246	T	C	8867	0.882993	-0.256989	0.0218381	5.7E-32
22	chr22:19975264:T:C	19975264	C	T	8858	0.949706	-0.352257	0.0320253	3.8E-28
22	chr22:19975440:G:T	19975440	T	G	8843	0.716047	-0.257608	0.015498	4.8E-62
22	chr22:19975900:C:T	19975900	T	C	8901	0.0439276	0.310415	0.0342104	1.2E-19

22	chr22:19976143:C:T	19976143	T	C	8867	0.883049	-0.256874	0.0218414	6.2E-32
22	chr22:19976628:G:T	19976628	T	G	8893	0.0274373	0.323362	0.0431106	6.3E-14
22	chr22:19976895:T:G	19976895	G	T	8850	0.949209	-0.349455	0.0319093	6.5E-28
22	chr22:19976926:G:A	19976926	A	G	8872	0.0095807	-0.344827	0.0723299	1.9E-06
22	chr22:19977034:TG:T	19977034	T	TG	8846	0.883224	-0.254583	0.0218773	2.7E-31
22	chr22:19977247:G:A	19977247	A	G	8833	0.0103589	0.373314	0.0701641	1E-07
22	chr22:19979226:C:T	19979226	T	C	8892	0.0651147	0.153155	0.0285384	8E-08
22	chr22:19979545:G:A	19979545	A	G	8830	0.716365	-0.255908	0.0155335	5.6E-61
22	chr22:19979703:C:T	19979703	T	C	8901	0.0435344	0.309415	0.034392	2.3E-19
22	chr22:19979725:T:C	19979725	C	T	8900	0.0435393	0.309495	0.0343921	2.3E-19
22	chr22:19980285:G:T	19980285	T	G	8862	0.085703	0.148061	0.0251607	4E-09
22	chr22:19980457:C:T	19980457	T	C	8882	0.308489	-0.243005	0.0150081	5.8E-59
22	chr22:19981074:C:T	19981074	T	C	8907	0.166161	0.172711	0.0186051	1.6E-20
22	chr22:19981448:G:A	19981448	A	G	8889	0.352683	-0.168288	0.0145346	5.3E-31
22	chr22:19981552:A:G	19981552	G	A	8853	0.783294	-0.241399	0.0168529	1.6E-46
22	chr22:19981583:A:G	19981583	G	A	8902	0.354134	-0.167771	0.0145067	6.2E-31
22	chr22:19981877:G:A	19981877	A	G	8577	0.0638918	0.272532	0.0292865	1.3E-20
22	chr22:19982173:C:T	19982173	T	C	8889	0.308696	-0.243275	0.01501	4.5E-59
22	chr22:19982202:G:A	19982202	A	G	8902	0.0436419	0.309287	0.0343534	2.2E-19
22	chr22:19982424:C:A	19982424	A	C	8901	0.043703	0.310376	0.0343799	1.8E-19
22	chr22:19982491:C:G	19982491	G	C	8857	0.950265	-0.347332	0.032185	3.8E-27
22	chr22:19983024:G:T	19983024	T	G	8893	0.353143	-0.168683	0.0145315	3.7E-31
22	chr22:19983060:A:G	19983060	G	A	8892	0.353914	-0.168714	0.014517	3.2E-31
22	chr22:19983868:C:T	19983868	T	C	8899	0.165861	0.17371	0.0186248	1.1E-20
22	chr22:19984029:T:C	19984029	C	T	8891	0.308795	-0.242943	0.0150065	6E-59
22	chr22:19984595:C:A	19984595	A	C	8893	0.28826	-0.237276	0.0153563	7.4E-54
22	chr22:19984842:T:C	19984842	C	T	8902	0.0436419	0.309287	0.0343534	2.2E-19
22	chr22:19984929:C:G	19984929	G	C	8890	0.353543	-0.168194	0.0145135	4.7E-31
22	chr22:19985021:G:T	19985021	T	G	8672	0.113584	-0.202043	0.0223835	1.8E-19
22	chr22:19985036:G:A	19985036	A	G	8889	0.288221	-0.23704	0.0153585	9.7E-54
22	chr22:19985107:C:T	19985107	T	C	8672	0.113526	-0.202543	0.0223865	1.5E-19
22	chr22:19985301:T:C	19985301	C	T	8892	0.353745	-0.168474	0.0145151	3.8E-31
22	chr22:19985682:T:G	19985682	G	T	8892	0.353745	-0.168474	0.0145151	3.8E-31
22	chr22:19985718:C:CACA	19985718	CA CA	C	8839	0.351454	-0.168724	0.0145871	6.1E-31
22	chr22:19986074:C:T	19986074	T	C	8891	0.165336	0.175217	0.018664	6.1E-21
22	chr22:19986509:T:C	19986509	C	T	8888	0.333765	-0.159126	0.0147705	4.6E-27
22	chr22:19986551:T:C	19986551	C	T	8861	0.0856562	0.148319	0.0251667	3.8E-09
22	chr22:19986821:A:G	19986821	G	A	8865	0.333503	-0.159864	0.0147837	3E-27
22	chr22:19987060:A:G	19987060	G	A	8864	0.333371	-0.159581	0.0147905	3.9E-27
22	chr22:19987131:G:A	19987131	A	G	8864	0.333427	-0.159019	0.0147881	5.7E-27
22	chr22:19987382:T:C	19987382	C	T	8823	0.332937	-0.15875	0.0148189	8.9E-27
22	chr22:19987921:A:G	19987921	G	A	8889	0.288615	-0.236925	0.0153611	1.1E-53
22	chr22:19988169:G:A	19988169	A	G	8883	0.0126646	-0.28857	0.063166	4.9E-06
22	chr22:19988883:G:A	19988883	A	G	8889	0.288559	-0.236549	0.0153657	1.8E-53
22	chr22:19988987:C:A	19988987	A	C	8889	0.288503	-0.236368	0.01537	2.3E-53
22	chr22:19989311:C:G	19989311	G	C	8843	0.950582	-0.339084	0.032385	1.2E-25
22	chr22:19989322:G:A	19989322	A	G	8888	0.288591	-0.23661	0.0153663	1.7E-53

22	chr22:19989387:C:T	19989387	T	C	8889	0.0270559	0.324504	0.0434928	8.6E-14
22	chr22:19990124:C:T	19990124	T	C	8864	0.332638	-0.159202	0.014813	6.1E-27
22	chr22:19990183:A:C	19990183	C	A	8886	0.0432703	0.309476	0.0345112	3E-19
22	chr22:19990317:C:T	19990317	T	C	8873	0.165558	0.174147	0.0186526	1E-20
22	chr22:19990467:C:T	19990467	T	C	8885	0.0432189	0.307817	0.0345326	4.9E-19
22	chr22:19990499:C:T	19990499	T	C	8864	0.333371	-0.158971	0.0147913	6.1E-27
22	chr22:19990551:A:T	19990551	T	A	8886	0.0432703	0.309476	0.0345112	3E-19
22	chr22:19991035:T:C	19991035	C	T	8818	0.784362	-0.24004	0.0169152	1E-45
22	chr22:19991518:A:G	19991518	G	A	8883	0.0126646	-0.28857	0.063166	4.9E-06
22	chr22:19991743:A:G	19991743	G	A	8881	0.0428443	0.307282	0.0347199	8.7E-19
22	chr22:19992190:G:A	19992190	A	G	8906	0.066865	0.154882	0.0283731	4.8E-08
22	chr22:19992410:C:A	19992410	A	C	8885	0.0431064	0.307718	0.034572	5.5E-19
22	chr22:19993025:A:G	19993025	G	A	8845	0.95065	-0.343649	0.0323557	2.4E-26
22	chr22:19993184:C:T	19993184	T	C	8893	0.0118633	0.429382	0.0647607	3.4E-11
22	chr22:19994143:G:A	19994143	A	G	8871	0.0478526	0.179072	0.0332541	7.2E-08
22	chr22:19994171:C:T	19994171	T	C	8881	0.0428443	0.31394	0.0347615	1.7E-19
22	chr22:19994955:G:A	19994955	A	G	8894	0.0489656	0.341786	0.0324195	5.5E-26
22	chr22:19995171:A:G	19995171	G	A	8881	0.0429006	0.312268	0.0347432	2.5E-19
22	chr22:19995491:G:A	19995491	A	G	8839	0.661161	0.14615	0.0149215	1.2E-22
22	chr22:19995690:C:T	19995690	T	C	8893	0.287811	-0.237059	0.0153583	9.5E-54
22	chr22:19995780:C:T	19995780	T	C	8864	0.166573	0.173352	0.0186309	1.3E-20
22	chr22:19996490:C:T	19996490	T	C	8891	0.2881	-0.236104	0.0153541	2.3E-53
22	chr22:19996504:T:A	19996504	A	T	8882	0.0428957	0.315143	0.0347401	1.2E-19
22	chr22:19996677:C:T	19996677	T	C	8574	0.0642057	0.267077	0.0291818	5.6E-20
22	chr22:19996680:G:A	19996680	A	G	8882	0.0428957	0.315143	0.0347401	1.2E-19
22	chr22:19996688:C:T	19996688	T	C	8891	0.28557	-0.236004	0.0154092	6E-53
22	chr22:19996754:C:T	19996754	T	C	8894	0.285305	-0.235474	0.0154071	9.9E-53
22	chr22:19996778:C:T	19996778	T	C	8882	0.0428957	0.315143	0.0347401	1.2E-19
22	chr22:19997651:T:G	19997651	G	T	8875	0.0434366	0.316983	0.0345137	4.1E-20
22	chr22:19997826:G:A	19997826	A	G	8622	0.185398	0.238065	0.0182783	8.9E-39
22	chr22:19998221:G:A	19998221	A	G	8875	0.0429296	0.312837	0.0347437	2.2E-19
22	chr22:19998786:G:A	19998786	A	G	8874	0.0427654	0.311927	0.0348049	3.2E-19
22	chr22:19999679:G:T	19999679	T	G	8897	0.284703	-0.235855	0.0154103	7.1E-53
22	chr22:20000241:A:C	20000241	C	A	8792	0.950011	-0.333503	0.0322838	5.1E-25
22	chr22:20000499:GCTCCCACCGC:G	20000499	G	GCT CCC ACC GC	8808	0.213045	0.216032	0.0170637	9.8E-37
22	chr22:20000644:G:A	20000644	A	G	8908	0.2848	-0.235458	0.0153969	8.6E-53
22	chr22:20000694:G:C	20000694	C	G	8875	0.00969014	-0.329267	0.0719282	4.7E-06
22	chr22:20000735:G:T	20000735	T	G	8875	0.0428732	0.317808	0.0347586	6.1E-20
22	chr22:20000994:G:C	20000994	C	G	8757	0.952381	-0.359664	0.0332839	3.2E-27
22	chr22:20001153:T:C	20001153	C	T	8792	0.950011	-0.33381	0.0322835	4.6E-25
22	chr22:20002089:C:G	20002089	G	C	8900	0.285169	-0.236466	0.0154058	3.6E-53
22	chr22:20002119:A:G	20002119	G	A	8807	0.212899	0.216085	0.0170713	1E-36
22	chr22:20002367:C:T	20002367	T	C	8809	0.213021	0.216292	0.0170628	8E-37
22	chr22:20003266:G:T	20003266	T	G	8823	0.169047	0.165253	0.01859	6.1E-19
22	chr22:20003460:A:G	20003460	G	A	8679	0.0685563	-0.173501	0.0280906	6.6E-10

22	chr22:20003544:T:C	20003544	C	T	8823	0.16916	0.164741	0.0185881	7.8E-19
22	chr22:20003597:G:A	20003597	A	G	8650	0.0343353	0.192321	0.0391727	9.1E-07
22	chr22:20003865:CAG:C	20003865	C	CAG	8809	0.213021	0.216292	0.0170628	8E-37
22	chr22:20003940:C:T	20003940	T	C	8872	0.0428877	0.317723	0.0347592	6.2E-20
22	chr22:20004427:G:A	20004427	A	G	8810	0.212997	0.216455	0.0170621	7E-37
22	chr22:20005776:G:A	20005776	A	G	8808	0.212931	0.216091	0.0170645	9.5E-37
22	chr22:20006562:G:C	20006562	C	G	8886	0.0230137	-0.21172	0.0466256	5.6E-06
22	chr22:20006657:G:C	20006657	C	G	8823	0.153236	0.174531	0.0193378	1.8E-19
22	chr22:20007310:G:A	20007310	A	G	8869	0.0426767	0.324415	0.0348332	1.2E-20
22	chr22:20007991:CAG:C	20007991	C	CAG	8584	0.23171	0.209321	0.017002	7.8E-35
22	chr22:20008355:C:T	20008355	T	C	8670	0.0959631	-0.190864	0.0241364	2.6E-15
22	chr22:20008717:A:G	20008717	G	A	8791	0.949437	-0.328245	0.0321357	1.7E-24
22	chr22:20008732:A:G	20008732	G	A	8791	0.949437	-0.328245	0.0321357	1.7E-24
22	chr22:20009047:C:T	20009047	T	C	8705	0.597817	0.121462	0.0144734	4.8E-17
22	chr22:20009306:G:A	20009306	A	G	8668	0.598812	0.120754	0.0145184	9E-17
22	chr22:20009355:G:C	20009355	C	G	8744	0.326452	-0.188149	0.0150073	4.7E-36
22	chr22:20009637:C:T	20009637	T	C	8889	0.0122061	0.406794	0.0639102	2E-10
22	chr22:20010681:C:T	20010681	T	C	8812	0.152746	0.174635	0.0193531	1.8E-19
22	chr22:20010858:T:TC	20010858	TC	T	8846	0.0405268	0.324209	0.0358363	1.5E-19
22	chr22:20010863:T:C	20010863	C	T	8655	0.504391	-0.0861807	0.014332	1.8E-09
22	chr22:20011132:G:C	20011132	C	G	8737	0.789974	-0.231381	0.017241	4.6E-41
22	chr22:20011440:T:G	20011440	G	T	8847	0.0405787	0.325368	0.0358128	1E-19
22	chr22:20011641:C:T	20011641	T	C	8791	0.946479	-0.299816	0.0313694	1.2E-21
22	chr22:20011657:AGT:A	20011657	A	AGT	8773	0.0308902	-0.242223	0.040919	3.2E-09
22	chr22:20011748:C:T	20011748	T	C	8847	0.0405787	0.325368	0.0358128	1E-19
22	chr22:20011969:T:C	20011969	C	T	8796	0.949636	-0.327031	0.0321821	2.9E-24
22	chr22:20012090:C:A	20012090	A	C	8818	0.0410524	0.314822	0.0356965	1.2E-18
22	chr22:20012237:A:G	20012237	G	A	8731	0.346638	-0.197558	0.0147786	9.3E-41
22	chr22:20012905:G:T	20012905	T	G	8800	0.153466	0.173752	0.0193441	2.7E-19
22	chr22:20013427:T:G	20013427	G	T	8785	0.973705	-0.384587	0.0442748	3.7E-18
22	chr22:20013483:G:A	20013483	A	G	8800	0.952102	-0.349644	0.0331331	4.9E-26
22	chr22:20013911:C:T	20013911	T	C	8862	0.025615	0.36694	0.0448482	2.8E-16
22	chr22:20014299:A:G	20014299	G	A	8849	0.0406826	0.32349	0.0357702	1.5E-19
22	chr22:20014708:C:T	20014708	T	C	8849	0.0406826	0.32349	0.0357702	1.5E-19
22	chr22:20015325:G:T	20015325	T	G	8736	0.326179	-0.187753	0.0150046	6.3E-36
22	chr22:20015536:C:T	20015536	T	C	8807	0.152436	0.175943	0.0193567	9.9E-20
22	chr22:20015629:C:T	20015629	T	C	8846	0.0364572	0.325769	0.0378101	6.9E-18
22	chr22:20016182:C:T	20016182	T	C	8823	0.022158	0.268372	0.0481975	2.6E-08
22	chr22:20016208:C:T	20016208	T	C	8745	0.781018	-0.228606	0.0169853	2.7E-41
22	chr22:20016640:C:A	20016640	A	C	8844	0.036635	0.31969	0.037737	2.4E-17
22	chr22:20016788:C:T	20016788	T	C	8735	0.326045	-0.187795	0.0150155	6.9E-36
22	chr22:20016907:G:T	20016907	T	G	8820	0.0614512	-0.258929	0.0294928	1.6E-18
22	chr22:20016908:C:T	20016908	T	C	8820	0.0614512	-0.258929	0.0294928	1.6E-18
22	chr22:20017181:C:T	20017181	T	C	8754	0.738805	-0.267541	0.015985	7E-63
22	chr22:20017735:G:T	20017735	T	G	8896	0.747752	-0.195971	0.0161606	7.6E-34
22	chr22:20017736:C:T	20017736	T	C	8908	0.0291311	-0.342492	0.0419681	3.3E-16
22	chr22:20018621:T:C	20018621	C	T	8772	0.650992	0.0922459	0.0148632	5.4E-10
22	chr22:20020076:G:A	20020076	A	G	8814	0.241434	0.190904	0.0164268	3.2E-31

22	chr22:20021365:C:T	20021365	T	C	8809	0.23493	0.179383	0.0165841	2.9E-27
22	chr22:20022405:T:C	20022405	C	T	8883	0.261286	-0.190655	0.0159732	7.7E-33
22	chr22:20023207:A:G	20023207	G	A	8831	0.911505	-0.192628	0.0249317	1.1E-14
22	chr22:20023296:T:C	20023296	C	T	8796	0.241928	0.191186	0.0164321	2.7E-31
22	chr22:20023327:G:A	20023327	A	G	8852	0.258642	-0.195238	0.0160433	4.5E-34
22	chr22:20023335:C:T	20023335	T	C	8788	0.0892126	-0.226072	0.0247255	6.1E-20
22	chr22:20023400:G:A	20023400	A	G	8814	0.241377	0.191296	0.0164315	2.5E-31
22	chr22:20023636:C:T	20023636	T	C	8840	0.259106	-0.189284	0.0160399	3.9E-32
22	chr22:20024466:G:A	20024466	A	G	8908	0.911933	-0.191444	0.0248772	1.4E-14
22	chr22:20024763:A:G	20024763	G	A	8833	0.648364	0.0906397	0.0147712	8.4E-10
22	chr22:20025439:G:A	20025439	A	G	8895	0.0339517	-0.230956	0.0392254	3.9E-09
22	chr22:20025445:T:C	20025445	C	T	8905	0.649691	0.0912329	0.0147113	5.6E-10
22	chr22:20025468:T:C	20025468	C	T	8869	0.0141504	-0.288294	0.0596733	1.4E-06
22	chr22:20025699:A:G	20025699	G	A	8846	0.648203	0.0906593	0.0147537	8E-10
22	chr22:20026187:C:T	20026187	T	C	8889	0.0119811	0.401376	0.0644881	4.8E-10
22	chr22:20026280:G:C	20026280	C	G	8839	0.911302	-0.191032	0.0249023	1.7E-14
22	chr22:20026290:T:C	20026290	C	T	8837	0.647505	0.0894263	0.0147562	1.4E-09
22	chr22:20026950:T:C	20026950	C	T	8824	0.416534	-0.0759002	0.0142624	1E-07
22	chr22:20027493:C:T	20027493	T	C	8849	0.39496	-0.0718853	0.0143423	5.4E-07
22	chr22:20027868:G:A	20027868	A	G	8847	0.39471	-0.0726373	0.0143449	4.1E-07
22	chr22:20028092:C:A	20028092	A	C	8752	0.0873515	-0.175032	0.0250398	2.7E-12
22	chr22:20028218:C:T	20028218	T	C	8840	0.393156	-0.0758479	0.0143621	1.3E-07
22	chr22:20028451:T:C	20028451	C	T	8826	0.905563	-0.17136	0.0241729	1.4E-12
22	chr22:20028969:G:A	20028969	A	G	8846	0.394189	-0.0728545	0.0143495	3.8E-07
22	chr22:20029745:A:G	20029745	G	A	8783	0.906467	-0.174182	0.0243213	8E-13
22	chr22:20030580:C:T	20030580	T	C	8766	0.393452	-0.0726316	0.0144239	4.8E-07
22	chr22:20032268:C:T	20032268	T	C	8908	0.014762	-0.459167	0.0582272	3.1E-15
22	chr22:20032550:A:G	20032550	G	A	8748	0.411065	-0.0734145	0.0143637	3.2E-07
22	chr22:20032706:C:T	20032706	T	C	8765	0.39344	-0.0727576	0.0144274	4.6E-07
22	chr22:20034209:A:C	20034209	C	A	8715	0.410327	-0.0730442	0.014402	3.9E-07
22	chr22:20034340:C:T	20034340	T	C	8727	0.392575	-0.0721494	0.0144684	6.1E-07
22	chr22:20034415:G:T	20034415	T	G	8724	0.391735	-0.0739628	0.014478	3.2E-07
22	chr22:20034975:C:G	20034975	G	C	8785	0.910302	-0.190085	0.0248027	1.8E-14
22	chr22:20035223:C:T	20035223	T	C	8740	0.1127	-0.160208	0.0223224	7.1E-13
22	chr22:20035780:T:G	20035780	G	T	8773	0.906588	-0.171243	0.0243636	2.1E-12
22	chr22:20036022:A:C	20036022	C	A	8883	0.0119892	0.394905	0.0644931	9.2E-10
22	chr22:20036651:A:G	20036651	G	A	8793	0.974639	-0.368696	0.0450216	2.6E-16
22	chr22:20038129:C:T	20038129	T	C	8847	0.0816661	0.16178	0.025691	3E-10
22	chr22:20038244:C:T	20038244	T	C	8770	0.233922	0.190081	0.0166154	2.6E-30
22	chr22:20038684:G:A	20038684	A	G	8878	0.0411692	-0.202923	0.0352208	8.3E-09
22	chr22:20039002:A:G	20039002	G	A	8812	0.313039	0.113342	0.0153799	1.7E-13
22	chr22:20039154:G:A	20039154	A	G	8857	0.0473072	-0.152589	0.0330012	3.8E-06
22	chr22:20039394:T:C	20039394	C	T	8755	0.376185	0.0700279	0.0147293	2E-06
22	chr22:20041018:C:A	20041018	A	C	8853	0.0621823	-0.131798	0.0291375	6.1E-06
22	chr22:20041737:T:C	20041737	C	T	8758	0.376741	0.0717788	0.0146965	1E-06
22	chr22:20042355:T:C	20042355	C	T	8768	0.376026	0.0693959	0.014701	2.4E-06
22	chr22:20042518:G:A	20042518	A	G	8880	0.188682	0.127563	0.0180665	1.7E-12
22	chr22:20043226:C:A	20043226	A	C	8854	0.0622318	-0.130667	0.0291274	7.3E-06

22	chr22:20043457:C:T	20043457	T	C	8853	0.0621823	-0.129509	0.0291387	8.8E-06
22	chr22:20043493:G:C	20043493	C	G	8869	0.0432969	-0.165664	0.0343647	1.4E-06
22	chr22:20043579:G:A	20043579	A	G	8880	0.188626	0.128413	0.0180667	1.2E-12
22	chr22:20044441:G:T	20044441	T	G	8854	0.0622318	-0.130667	0.0291274	7.3E-06
22	chr22:20044531:ATCAG:A	20044531	A	ATC AG	8849	0.0466154	-0.150532	0.0332629	6E-06
22	chr22:20044804:T:C	20044804	C	T	8734	0.382528	0.0717437	0.0146872	1E-06
22	chr22:20045059:G:A	20045059	A	G	8854	0.0624012	-0.129186	0.0290687	8.8E-06
22	chr22:20046664:C:T	20046664	T	C	8830	0.0324462	-0.27787	0.0397953	2.9E-12
22	chr22:20047232:G:T	20047232	T	G	8671	0.298812	-0.177508	0.0154254	1.2E-30
22	chr22:20051632:G:A	20051632	A	G	8858	0.0793633	-0.172731	0.0259795	3E-11
22	chr22:20054553:TG:T	20054553	T	TG	8858	0.0804922	-0.175109	0.0258034	1.2E-11
22	chr22:20055847:C:T	20055847	T	C	8860	0.0808691	-0.171938	0.0257589	2.5E-11
22	chr22:20056107:C:T	20056107	T	C	8908	0.0167827	-0.249476	0.0547133	5.1E-06
22	chr22:20057888:A:G	20057888	G	A	8899	0.377739	0.0688046	0.0145926	2.4E-06
22	chr22:20057896:T:C	20057896	C	T	8777	0.708955	0.175268	0.0154668	9.1E-30
22	chr22:20058519:A:G	20058519	G	A	8887	0.157083	0.170502	0.0193023	1E-18
22	chr22:20058821:A:G	20058821	G	A	8903	0.239751	0.183567	0.0163312	2.6E-29
22	chr22:20059164:G:A	20059164	A	G	8810	0.569353	0.177659	0.0142352	9.6E-36
22	chr22:20060924:G:A	20060924	A	G	8904	0.0393643	0.191524	0.0362935	1.3E-07
22	chr22:20061762:G:A	20061762	A	G	8902	0.157156	0.17091	0.0192618	7.1E-19
22	chr22:20061817:T:C	20061817	C	T	8870	0.376776	0.0689099	0.0146255	2.5E-06
22	chr22:20061931:A:G	20061931	G	A	8869	0.376424	0.06831	0.0146277	3E-06
22	chr22:20062412:A:C	20062412	C	A	8870	0.376888	0.0683986	0.0146241	2.9E-06
22	chr22:20062496:C:T	20062496	T	C	8907	0.157404	0.17082	0.0192508	7.1E-19
22	chr22:20062878:T:C	20062878	C	T	8877	0.345387	0.0867712	0.0148201	4.8E-09
22	chr22:20063943:G:A	20063943	A	G	8857	0.376821	0.0684109	0.0146344	2.9E-06
22	chr22:20064897:G:A	20064897	A	G	8882	0.157172	0.171397	0.0192786	6.1E-19
22	chr22:20064958:C:A	20064958	A	C	8873	0.278485	0.13293	0.0157862	3.7E-17
22	chr22:20065009:C:G	20065009	G	C	8862	0.376608	0.0682105	0.014633	3.1E-06
22	chr22:20065043:G:A	20065043	A	G	8860	0.37658	0.0681629	0.0146332	3.2E-06
22	chr22:20065259:C:T	20065259	T	C	8852	0.376299	0.0670333	0.0146427	4.7E-06
22	chr22:20066685:AG:A	20066685	A	AG	8885	0.155824	0.167521	0.0193251	4.4E-18
22	chr22:20067559:G:T	20067559	T	G	8869	0.375691	0.0681733	0.0146446	3.2E-06
22	chr22:20067577:A:G	20067577	G	A	8868	0.37562	0.0682056	0.0146473	3.2E-06
22	chr22:20069555:C:T	20069555	T	C	8887	0.278384	0.0797855	0.0157245	3.9E-07
22	chr22:20069620:A:G	20069620	G	A	8887	0.278665	0.0804495	0.015721	3.1E-07
22	chr22:20070283:C:T	20070283	T	C	8908	0.247081	0.103203	0.0162301	2E-10
22	chr22:20071340:T:A	20071340	A	T	8846	0.246609	0.106173	0.0163154	7.6E-11
22	chr22:20072457:C:T	20072457	T	C	8866	0.276506	0.0790767	0.015795	5.5E-07
22	chr22:20072500:T:A	20072500	A	T	8868	0.276669	0.0790904	0.0157901	5.5E-07
22	chr22:20072613:T:C	20072613	C	T	8866	0.276957	0.0796027	0.0157877	4.6E-07
22	chr22:20072614:G:A	20072614	A	G	8906	0.0398046	0.188813	0.0360598	1.6E-07
22	chr22:20073201:G:A	20073201	A	G	8849	0.270765	0.0797139	0.0159275	5.6E-07
22	chr22:20073892:G:C	20073892	C	G	8861	0.275138	0.0794231	0.0158414	5.3E-07
22	chr22:20074524:C:G	20074524	G	C	8851	0.0654163	-0.128569	0.0284822	6.4E-06
22	chr22:20074771:C:T	20074771	T	C	8882	0.180308	0.179266	0.0182321	8.2E-23
22	chr22:20075756:CA:C	20075756	C	CA	8839	0.0623939	-0.129899	0.0291486	8.3E-06

22	chr22:20076204:C:G	20076204	G	C	8798	0.300921	-0.173845	0.0153053	6.7E-30
22	chr22:20076620:C:CAGGAG	20076620	CA GG AG	C	8818	0.271604	0.0740735	0.0159742	3.5E-06
22	chr22:20076861:G:C	20076861	C	G	8876	0.0619649	-0.129136	0.0291726	9.6E-06
22	chr22:20077228:T:C	20077228	C	T	8881	0.179822	0.179396	0.0182482	8.3E-23
22	chr22:20077257:G:A	20077257	A	G	8884	0.17993	0.179316	0.018244	8.5E-23
22	chr22:20077753:T:C	20077753	C	T	8887	0.180038	0.178886	0.0182331	1E-22
22	chr22:20077847:G:A	20077847	A	G	8867	0.242303	0.102569	0.0164242	4.2E-10
22	chr22:20078228:A:G	20078228	G	A	8858	0.274554	0.0784029	0.0158685	7.8E-07
22	chr22:20078459:C:CACA	20078459	CA CA	C	8866	0.242274	0.10197	0.0164253	5.4E-10
22	chr22:20078737:C:T	20078737	T	C	8876	0.0619649	-0.129136	0.0291726	9.6E-06
22	chr22:20078899:T:C	20078899	C	T	8876	0.0619649	-0.129136	0.0291726	9.6E-06
22	chr22:20079088:G:C	20079088	C	G	8841	0.399898	0.0859619	0.0145267	3.3E-09
22	chr22:20079142:G:A	20079142	A	G	8874	0.0618098	-0.130181	0.0292044	8.3E-06
22	chr22:20079275:T:G	20079275	G	T	8874	0.0618661	-0.12974	0.029194	8.8E-06
22	chr22:20079994:T:G	20079994	G	T	8885	0.17991	0.179515	0.0182503	7.9E-23
22	chr22:20080563:G:C	20080563	C	G	8859	0.242465	0.104877	0.0164274	1.7E-10
22	chr22:20080588:CG:C	20080588	C	CG	8860	0.0655756	-0.126192	0.0284167	9E-06
22	chr22:20080973:C:T	20080973	T	C	8878	0.179939	0.179736	0.0182412	6.6E-23
22	chr22:20080980:G:T	20080980	T	G	8878	0.179939	0.179736	0.0182412	6.6E-23
22	chr22:20081591:C:T	20081591	T	C	8886	0.0410196	-0.203984	0.0353104	7.6E-09
22	chr22:20081649:A:G	20081649	G	A	8878	0.179939	0.179736	0.0182412	6.6E-23
22	chr22:20082202:G:A	20082202	A	G	8678	0.18328	-0.10769	0.0183195	4.1E-09
22	chr22:20082321:G:A	20082321	A	G	8832	0.399796	0.0853598	0.0145347	4.3E-09
22	chr22:20082390:A:G	20082390	G	A	8851	0.275393	0.0811533	0.0158516	3.1E-07
22	chr22:20082648:T:C	20082648	C	T	8878	0.179995	0.179547	0.0182334	7.1E-23
22	chr22:20082762:G:A	20082762	A	G	8877	0.179903	0.179761	0.0182426	6.6E-23
22	chr22:20083828:A:G	20083828	G	A	8874	0.180358	0.180462	0.0182223	4E-23
22	chr22:20083900:T:C	20083900	C	T	8877	0.180297	0.180052	0.0182214	5E-23
22	chr22:20084129:T:G	20084129	G	T	8878	0.179939	0.18017	0.0182477	5.4E-23
22	chr22:20084214:T:C	20084214	C	T	8874	0.233491	0.116067	0.0166616	3.3E-12
22	chr22:20084376:C:T	20084376	T	C	8876	0.17998	0.179508	0.0182494	7.8E-23
22	chr22:20087525:G:A	20087525	A	G	8874	0.179288	0.179197	0.0182846	1.1E-22
22	chr22:20088335:A:G	20088335	G	A	8862	0.265516	0.0887436	0.0160618	3.3E-08
22	chr22:20089119:G:A	20089119	A	G	8893	0.0121444	0.357228	0.0640851	2.5E-08
22	chr22:20089240:GT:G	20089240	G	GT	8877	0.179847	0.179401	0.018244	8.1E-23
22	chr22:20092080:A:G	20092080	G	A	8844	0.389699	0.0915361	0.014627	3.9E-10
22	chr22:20092165:T:C	20092165	C	T	8886	0.180059	0.179261	0.0182332	8.2E-23
22	chr22:20092450:G:A	20092450	A	G	8886	0.180002	0.179404	0.018234	7.6E-23
22	chr22:20093288:T:C	20093288	C	T	8872	0.265555	0.0900232	0.0160458	2E-08
22	chr22:20093316:A:C	20093316	C	A	8833	0.0112646	0.311447	0.0673728	3.8E-06
22	chr22:20093404:A:G	20093404	G	A	8875	0.179437	0.178251	0.0182893	1.9E-22
22	chr22:20094329:T:C	20094329	C	T	8842	0.495759	0.174229	0.0140679	3.2E-35
22	chr22:20095043:C:T	20095043	T	C	8886	0.180002	0.179404	0.018234	7.6E-23
22	chr22:20095358:C:T	20095358	T	C	8886	0.180002	0.179404	0.018234	7.6E-23
22	chr22:20095438:T:C	20095438	C	T	8872	0.265498	0.090117	0.0160456	2E-08

22	chr22:20095977:CAGG:C	20095977	C	CAG G	8887	0.179926	0.178681	0.0182423	1.2E-22
22	chr22:20096845:C:T	20096845	T	C	8903	0.0220151	0.222085	0.0484117	4.5E-06
22	chr22:20097158:G:A	20097158	A	G	8876	0.265435	0.0898613	0.0160432	2.1E-08
22	chr22:20097298:T:C	20097298	C	T	8903	0.261934	0.115952	0.0159216	3.3E-13
22	chr22:20098050:C:G	20098050	G	C	8885	0.179854	0.179411	0.0182374	7.8E-23
22	chr22:20099048:G:T	20099048	T	G	8889	0.180054	0.179432	0.0182307	7.4E-23
22	chr22:20099214:T:C	20099214	C	T	8889	0.18011	0.179289	0.0182298	8E-23
22	chr22:20099950:T:A	20099950	A	T	8888	0.180018	0.179561	0.018232	6.9E-23
22	chr22:20100016:A:G	20100016	G	A	8889	0.180054	0.179432	0.0182307	7.4E-23
22	chr22:20100122:A:G	20100122	G	A	8867	0.247773	0.124519	0.016199	1.5E-14
22	chr22:20100227:C:T	20100227	T	C	8888	0.180018	0.179492	0.018232	7.2E-23
22	chr22:20101140:C:G	20101140	G	C	8846	0.0706534	-0.240722	0.0274876	2E-18
22	chr22:20101560:G:A	20101560	A	G	8889	0.233378	0.115169	0.0166423	4.5E-12
22	chr22:20101748:A:G	20101748	G	A	8900	0.180225	0.179738	0.0182115	5.6E-23
22	chr22:20102357:T:C	20102357	C	T	8885	0.265729	0.089136	0.0160251	2.7E-08
22	chr22:20102515:G:T	20102515	T	G	8900	0.180225	0.179738	0.0182115	5.6E-23
22	chr22:20102669:A:T	20102669	T	A	8895	0.233671	0.115227	0.0166374	4.3E-12
22	chr22:20104105:C:T	20104105	T	C	8898	0.180153	0.180135	0.0182139	4.6E-23
22	chr22:20104233:T:C	20104233	C	T	8794	0.606948	0.202291	0.0144478	1.5E-44
22	chr22:20104310:G:A	20104310	A	G	8899	0.180133	0.179467	0.0182142	6.6E-23
22	chr22:20104889:G:A	20104889	A	G	8861	0.389516	0.0902098	0.0146124	6.7E-10
22	chr22:20105254:C:A	20105254	A	C	8900	0.180225	0.179738	0.0182115	5.6E-23
22	chr22:20105440:A:G	20105440	G	A	8863	0.38971	0.0905935	0.0146043	5.5E-10
22	chr22:20105473:C:T	20105473	T	C	8899	0.180189	0.179557	0.0182131	6.3E-23
22	chr22:20105603:T:C	20105603	C	T	8777	0.696309	0.174518	0.0152778	3.2E-30
22	chr22:20105765:C:T	20105765	T	C	8898	0.180097	0.180573	0.0182144	3.6E-23
22	chr22:20105794:A:G	20105794	G	A	8908	0.180624	0.177112	0.0181872	2.1E-22
22	chr22:20105999:C:T	20105999	T	C	8898	0.180097	0.179313	0.0182158	7.3E-23
22	chr22:20106444:G:A	20106444	A	G	8904	0.029425	-0.263878	0.0416807	2.4E-10
22	chr22:20108645:T:TG	20108645	TG	T	8832	0.24615	0.125228	0.0162647	1.4E-14
22	chr22:20110207:C:T	20110207	T	C	8887	0.180038	0.1784	0.0182267	1.3E-22
22	chr22:20110836:T:G	20110836	G	T	8779	0.481091	0.175031	0.0140715	1.6E-35
22	chr22:20111021:G:A	20111021	A	G	8905	0.0871982	-0.139301	0.0249203	2.3E-08
22	chr22:20111359:T:C	20111359	C	T	8802	0.245456	0.126234	0.0163126	1E-14
22	chr22:20111808:G:A	20111808	A	G	8794	0.242609	0.121661	0.0163895	1.1E-13
22	chr22:20112131:C:T	20112131	T	C	8886	0.180059	0.178898	0.0182266	9.7E-23
22	chr22:20112886:C:T	20112886	T	C	8886	0.180171	0.178894	0.0182177	9.3E-23
22	chr22:20113073:T:C	20113073	C	T	8802	0.245683	0.123846	0.0163046	3.1E-14
22	chr22:20114567:T:C	20114567	C	T	8848	0.389862	0.0876333	0.0146135	2E-09
22	chr22:20115740:G:T	20115740	T	G	8905	0.0372824	-0.18643	0.0373552	6E-07
22	chr22:20115741:C:T	20115741	T	C	8905	0.0372824	-0.18643	0.0373552	6E-07
22	chr22:20116712:C:T	20116712	T	C	8872	0.179385	0.178227	0.0182574	1.6E-22
22	chr22:20116778:T:C	20116778	C	T	8698	0.69378	0.16708	0.0152924	8.7E-28
22	chr22:20117296:A:C	20117296	C	A	8719	0.785182	-0.153942	0.0172364	4.2E-19
22	chr22:20117330:T:G	20117330	G	T	8846	0.390346	0.0879822	0.0146153	1.7E-09
22	chr22:20120977:G:A	20120977	A	G	8853	0.180617	0.179896	0.0182355	5.9E-23
22	chr22:20121213:A:G	20121213	G	A	8800	0.0688636	-0.144135	0.0278572	2.3E-07

22	chr22:20121802:A:G	20121802	G	A	8848	0.390088	0.0879571	0.0146209	1.8E-09
22	chr22:20122154:G:A	20122154	A	G	8631	0.18196	-0.113267	0.0184041	7.5E-10
22	chr22:20124206:G:T	20124206	T	G	8884	0.0860536	-0.137176	0.0251929	5.2E-08
22	chr22:20125730:T:G	20125730	G	T	8848	0.265597	0.0898987	0.0160648	2.2E-08
22	chr22:20126254:T:C	20126254	C	T	8849	0.26568	0.0887066	0.0160604	3.3E-08
22	chr22:20128039:C:T	20128039	T	C	8825	0.264986	0.0890691	0.0160914	3.1E-08
22	chr22:20128492:T:G	20128492	G	T	8835	0.389983	0.0884116	0.0146262	1.5E-09
22	chr22:20128659:T:G	20128659	G	T	8827	0.265039	0.0891676	0.0160903	3E-08
22	chr22:20129070:C:T	20129070	T	C	8856	0.0325203	-0.264801	0.0397795	2.8E-11
22	chr22:20129822:T:G	20129822	G	T	8835	0.390153	0.0879254	0.0146189	1.8E-09
22	chr22:20130787:G:A	20130787	A	G	8703	0.036654	0.180131	0.0381297	2.3E-06
22	chr22:20131098:TG:T	20131098	T	TG	8553	0.184906	0.171027	0.0184135	1.6E-20
22	chr22:20132189:A:G	20132189	G	A	8822	0.180401	0.175747	0.0182548	6.1E-22
22	chr22:20132407:A:G	20132407	G	A	8661	0.298868	-0.171357	0.0154344	1.2E-28
22	chr22:20134319:C:T	20134319	T	C	8827	0.08474	-0.137529	0.0254268	6.3E-08
22	chr22:20140031:A:G	20140031	G	A	8898	0.373904	0.0785831	0.0146578	8.3E-08
22	chr22:20141128:T:G	20141128	G	T	8607	0.67782	0.150964	0.0152048	3.1E-23
22	chr22:20142219:G:C	20142219	C	G	8851	0.162637	0.16844	0.0190861	1.1E-18
22	chr22:20143592:C:T	20143592	T	C	8851	0.162806	0.168323	0.019066	1.1E-18
22	chr22:20145115:T:A	20145115	A	T	8863	0.37177	0.075568	0.0147245	2.9E-07
22	chr22:20145449:A:G	20145449	G	A	8858	0.371529	0.0748919	0.0147338	3.7E-07
22	chr22:20145767:T:C	20145767	C	T	8850	0.216102	0.100153	0.017213	5.9E-09
22	chr22:20146624:A:G	20146624	G	A	8730	0.243929	0.0746926	0.0166766	7.5E-06
22	chr22:20146827:C:A	20146827	A	C	8761	0.21356	0.0992212	0.0173788	1.1E-08
22	chr22:20146919:T:C	20146919	C	T	8761	0.21356	0.0992212	0.0173788	1.1E-08
22	chr22:20147002:C:T	20147002	T	C	8796	0.16121	0.164931	0.0192061	8.9E-18
22	chr22:20147216:C:T	20147216	T	C	8759	0.213552	0.0992117	0.0173684	1.1E-08
22	chr22:20147688:T:C	20147688	C	T	8731	0.244245	0.0754126	0.01667	6.1E-06
22	chr22:20147860:C:T	20147860	T	C	8797	0.161305	0.16501	0.0192027	8.5E-18
22	chr22:20148062:T:C	20148062	C	T	8798	0.161287	0.165151	0.0192022	7.9E-18
22	chr22:20148438:T:C	20148438	C	T	8760	0.21347	0.0990291	0.0173803	1.2E-08
22	chr22:20148740:G:A	20148740	A	G	8522	0.314363	-0.149428	0.0154032	3E-22
22	chr22:20148856:C:A	20148856	A	C	8690	0.284522	0.127343	0.0158285	8.6E-16
22	chr22:20149083:T:C	20149083	C	T	8812	0.0806287	-0.12554	0.0260197	1.4E-06
22	chr22:20149128:A:T	20149128	T	A	8794	0.161587	0.164626	0.0191905	9.6E-18
22	chr22:20149523:C:A	20149523	A	C	8790	0.161661	0.164054	0.0191927	1.3E-17
22	chr22:20149524:C:T	20149524	T	C	8792	0.161738	0.164678	0.0191884	9.3E-18
22	chr22:20150299:C:G	20150299	G	C	8652	0.357143	0.0739698	0.0150022	8.2E-07
22	chr22:20150582:T:C	20150582	C	T	8647	0.357407	0.0724093	0.0150087	1.4E-06
22	chr22:20151370:G:A	20151370	A	G	8653	0.357564	0.0692715	0.0150064	3.9E-06
22	chr22:20151776:C:T	20151776	T	C	8518	0.633012	-0.0742623	0.0150299	7.8E-07
22	chr22:20151817:C:T	20151817	T	C	8496	0.632533	-0.074168	0.0150495	8.3E-07
22	chr22:20152711:G:GC	20152711	GC	G	8652	0.306461	0.109188	0.0155273	2E-12
22	chr22:20153539:C:A	20153539	A	C	8650	0.306647	0.108848	0.0155258	2.4E-12
22	chr22:20154469:C:G	20154469	G	C	8475	0.68767	-0.114322	0.0156304	2.6E-13
22	chr22:20154990:C:A	20154990	A	C	8606	0.153498	0.15885	0.0198825	1.4E-15
22	chr22:20155409:C:T	20155409	T	C	8194	0.693312	-0.108132	0.0160056	1.4E-11
22	chr22:20155876:C:T	20155876	T	C	8786	0.0571933	-0.186508	0.0304579	9.2E-10

22	chr22:20156103:C:T	20156103	T	C	8271	0.457139	-0.173	0.0145483	1.3E-32
22	chr22:20156108:G:A	20156108	A	G	8258	0.740131	-0.124629	0.0164818	4E-14
22	chr22:20156259:C:T	20156259	T	C	8382	0.80476	-0.104266	0.0181834	9.8E-09
22	chr22:20157037:C:T	20157037	T	C	8312	0.447666	-0.0930314	0.0147299	2.7E-10
22	chr22:20157140:T:G	20157140	G	T	8898	0.825635	-0.0975021	0.018475	1.3E-07
22	chr22:20157230:G:A	20157230	A	G	8357	0.31686	0.110503	0.0157465	2.3E-12
22	chr22:20157273:G:A	20157273	A	G	8601	0.158005	0.146618	0.0197234	1.1E-13
22	chr22:20157334:G:A	20157334	A	G	8784	0.168773	0.0943367	0.0188335	5.5E-07
22	chr22:20157735:C:T	20157735	T	C	8775	0.173162	0.0872928	0.0186565	2.9E-06
22	chr22:20159272:G:C	20159272	C	G	8403	0.328633	-0.132819	0.0153375	4.7E-18
22	chr22:20160844:G:T	20160844	T	G	8352	0.526461	-0.171074	0.0144227	1.9E-32
22	chr22:20160845:G:T	20160845	T	G	8352	0.526461	-0.171074	0.0144227	1.9E-32
22	chr22:20161160:T:C	20161160	C	T	8272	0.719959	-0.156238	0.0163275	1.1E-21
22	chr22:20161218:C:T	20161218	T	C	8410	0.326159	-0.133207	0.0153362	3.8E-18
22	chr22:20161662:C:A	20161662	A	C	8796	0.0613347	-0.188904	0.0294083	1.3E-10
22	chr22:20165036:T:C	20165036	C	T	8468	0.271434	0.152497	0.0163232	9.4E-21
22	chr22:20166101:T:C	20166101	C	T	8442	0.250652	0.15785	0.0167471	4.3E-21
22	chr22:20166216:C:A	20166216	A	C	8584	0.164958	0.153552	0.0193895	2.4E-15
22	chr22:20167204:A:G	20167204	G	A	8474	0.262745	0.156975	0.016503	1.9E-21
22	chr22:20167669:T:C	20167669	C	T	8303	0.518367	-0.0800251	0.014697	5.2E-08
22	chr22:20167775:G:A	20167775	A	G	8490	0.262191	0.156367	0.0164921	2.5E-21
22	chr22:20168460:T:C	20168460	C	T	8249	0.722391	-0.159202	0.0164079	2.9E-22
22	chr22:20168535:C:T	20168535	T	C	8907	0.0208263	0.239355	0.0492752	1.2E-06
22	chr22:20168588:A:G	20168588	G	A	8247	0.717352	-0.149629	0.0163233	4.9E-20
22	chr22:20168892:T:C	20168892	C	T	8251	0.714519	-0.1523	0.0162493	7.1E-21
22	chr22:20169221:G:A	20169221	A	G	8367	0.461515	0.170492	0.0144624	4.5E-32
22	chr22:20169330:T:C	20169330	C	T	8797	0.0695692	-0.152866	0.027674	3.3E-08
22	chr22:20169695:G:T	20169695	T	G	8798	0.0693339	-0.151622	0.0277337	4.6E-08
22	chr22:20169776:C:T	20169776	T	C	8814	0.183628	0.0814096	0.0182266	7.9E-06
22	chr22:20170823:C:T	20170823	T	C	8820	0.070068	-0.146661	0.027545	1E-07
22	chr22:20171526:A:G	20171526	G	A	8386	0.596053	-0.11358	0.0148871	2.4E-14
22	chr22:20171787:G:A	20171787	A	G	8561	0.258206	0.151029	0.0164553	4.4E-20
22	chr22:20171824:C:T	20171824	T	C	8457	0.40635	-0.158443	0.0145901	1.8E-27
22	chr22:20171899:T:C	20171899	C	T	8652	0.141412	0.164027	0.020451	1.1E-15
22	chr22:20172558:G:A	20172558	A	G	8818	0.0703107	-0.143923	0.0275129	1.7E-07
22	chr22:20172682:C:T	20172682	T	C	8503	0.332059	-0.127053	0.0151762	5.7E-17
22	chr22:20173149:C:T	20173149	T	C	8819	0.0701894	-0.147509	0.0275276	8.4E-08
22	chr22:20173248:G:T	20173248	T	G	8574	0.258397	0.152215	0.0164409	2.1E-20
22	chr22:20173449:T:C	20173449	C	T	8389	0.596197	-0.113875	0.0148794	2E-14
22	chr22:20173794:G:C	20173794	C	G	8389	0.596019	-0.114648	0.0148784	1.3E-14
22	chr22:20173901:T:C	20173901	C	T	8461	0.406394	-0.158685	0.0145788	1.4E-27
22	chr22:20174082:G:A	20174082	A	G	8652	0.142048	0.164589	0.0204174	7.6E-16
22	chr22:20175200:T:C	20175200	C	T	8450	0.728402	-0.145747	0.016287	3.6E-19
22	chr22:20175547:G:A	20175547	A	G	8408	0.592412	-0.109218	0.0148583	2E-13
22	chr22:20176837:T:C	20176837	C	T	8571	0.543694	-0.156992	0.0143115	5.3E-28
22	chr22:20177066:G:A	20177066	A	G	8606	0.520974	-0.150374	0.0142615	5.4E-26
22	chr22:20177173:C:T	20177173	T	C	8569	0.335045	-0.1224	0.0150977	5.2E-16
22	chr22:20177279:G:T	20177279	T	G	8608	0.520853	-0.149928	0.0142651	7.8E-26

22	chr22:20177426:G:A	20177426	A	G	8589	0.519793	-0.149214	0.0142886	1.6E-25
22	chr22:20177916:C:A	20177916	A	C	8621	0.460735	-0.170849	0.0142965	6.5E-33
22	chr22:20178109:C:T	20178109	T	C	8623	0.398411	-0.138265	0.0145157	1.6E-21
22	chr22:20178308:G:A	20178308	A	G	8623	0.398469	-0.138043	0.014517	1.9E-21
22	chr22:20178490:C:T	20178490	T	C	8624	0.398423	-0.138274	0.0145156	1.6E-21
22	chr22:20178679:T:C	20178679	C	T	8630	0.519293	-0.150093	0.0142546	6.3E-26
22	chr22:20178699:C:T	20178699	T	C	8651	0.459022	-0.171033	0.0142843	4.9E-33
22	chr22:20179178:T:G	20179178	G	T	8599	0.515641	-0.14838	0.0142861	2.9E-25
22	chr22:20179181:G:C	20179181	C	G	8599	0.515641	-0.14838	0.0142861	2.9E-25
22	chr22:20179200:T:G	20179200	G	T	8650	0.45896	-0.170686	0.0142867	6.7E-33
22	chr22:20179388:G:A	20179388	A	G	8638	0.458555	-0.171324	0.0142979	4.4E-33
22	chr22:20179487:G:T	20179487	T	G	8907	0.0607387	-0.152919	0.0294619	2.1E-07
22	chr22:20179883:C:T	20179883	T	C	8893	0.0598786	-0.159421	0.0297098	8.1E-08
22	chr22:20180262:G:A	20180262	A	G	8895	0.0600337	-0.158583	0.029676	9.1E-08
22	chr22:20180772:G:T	20180772	T	G	8715	0.458979	-0.171916	0.0142232	1.2E-33
22	chr22:20180986:G:A	20180986	A	G	8716	0.459098	-0.171779	0.0142195	1.3E-33
22	chr22:20181081:C:T	20181081	T	C	8703	0.397219	-0.138137	0.0144437	1.1E-21
22	chr22:20181102:T:C	20181102	C	T	8636	0.0558129	-0.148829	0.031243	1.9E-06
22	chr22:20181118:T:G	20181118	G	T	8717	0.459332	-0.171579	0.014222	1.6E-33
22	chr22:20181459:CCCCGGCTGG:C	20181459	C	CCC CGG CTG G	8712	0.459137	-0.170603	0.0142225	3.8E-33
22	chr22:20181514:T:C	20181514	C	T	8719	0.459342	-0.171409	0.0142188	1.8E-33
22	chr22:20181571:G:T	20181571	T	G	8718	0.459394	-0.171156	0.0142206	2.3E-33
22	chr22:20181844:G:T	20181844	T	G	8716	0.459385	-0.171674	0.0142166	1.4E-33
22	chr22:20181899:G:A	20181899	A	G	8680	0.163306	0.126856	0.0194389	6.8E-11
22	chr22:20181976:A:G	20181976	G	A	8883	0.464539	-0.169564	0.0140695	1.9E-33
22	chr22:20182373:C:T	20182373	T	C	8868	0.0592016	-0.163617	0.0299454	4.7E-08
22	chr22:20182390:A:G	20182390	G	A	8492	0.711493	-0.12549	0.0160161	4.7E-15
22	chr22:20183750:G:A	20183750	A	G	8890	0.0123172	-0.295825	0.0631188	2.8E-06
22	chr22:20183845:C:T	20183845	T	C	8632	0.26952	0.0962049	0.0162443	3.2E-09
22	chr22:20184525:G:A	20184525	A	G	8851	0.0651904	-0.164939	0.0287402	9.5E-09
22	chr22:20184790:C:T	20184790	T	C	8553	0.460248	-0.0673519	0.0144064	2.9E-06
22	chr22:20186577:A:G	20186577	G	A	8863	0.0649893	-0.168639	0.028755	4.5E-09
22	chr22:20186747:G:C	20186747	C	G	8862	0.0649402	-0.168817	0.0287652	4.4E-09
22	chr22:20187038:TG:T	20187038	T	TG	8773	0.2608	0.0940844	0.0162694	7.3E-09
22	chr22:20188996:C:A	20188996	A	C	8892	0.0652834	-0.166463	0.0286334	6.1E-09
22	chr22:20189182:C:T	20189182	T	C	8822	0.135003	0.103666	0.0209716	7.7E-07
22	chr22:20189538:C:T	20189538	T	C	8906	0.545756	-0.104269	0.0141356	1.6E-13
22	chr22:20189696:G:A	20189696	A	G	8709	0.65771	-0.0784765	0.0150404	1.8E-07
22	chr22:20189797:A:T	20189797	T	A	8757	0.47522	-0.0649002	0.0142008	4.9E-06
22	chr22:20190072:C:G	20190072	G	C	8709	0.657883	-0.079924	0.0150529	1.1E-07
22	chr22:20190122:G:T	20190122	T	G	8792	0.314206	0.072631	0.015325	2.1E-06
22	chr22:20190146:A:G	20190146	G	A	8709	0.657997	-0.0800871	0.0150513	1E-07
22	chr22:20190325:A:G	20190325	G	A	8707	0.657861	-0.0813601	0.0150492	6.4E-08
22	chr22:20190420:G:A	20190420	A	G	8708	0.657384	-0.0804145	0.0150476	9.1E-08
22	chr22:20190500:T:C	20190500	C	T	8708	0.657499	-0.0801375	0.0150502	1E-07

22	chr22:20190572:G:A	20190572	A	G	8711	0.657502	-0.0802641	0.0150449	9.6E-08
22	chr22:20190624:A:G	20190624	G	A	8709	0.657481	-0.0802779	0.015046	9.5E-08
22	chr22:20190652:A:G	20190652	G	A	8715	0.657487	-0.0809621	0.015043	7.4E-08
22	chr22:20190663:G:A	20190663	A	G	8717	0.657623	-0.0810838	0.0150404	7E-08
22	chr22:20190682:A:G	20190682	G	A	8717	0.657508	-0.0812375	0.0150418	6.6E-08
22	chr22:20190685:C:T	20190685	T	C	8718	0.657548	-0.081017	0.015041	7.2E-08
22	chr22:20191276:T:G	20191276	G	T	8717	0.657508	-0.0811454	0.0150418	6.9E-08
22	chr22:20191278:G:A	20191278	A	G	8717	0.657508	-0.0811454	0.0150418	6.9E-08
22	chr22:20191406:A:G	20191406	G	A	8719	0.657415	-0.0805745	0.0150386	8.4E-08
22	chr22:20191466:C:T	20191466	T	C	8717	0.657451	-0.0803344	0.0150469	9.3E-08
22	chr22:20191516:T:C	20191516	C	T	8714	0.65762	-0.080143	0.01505	1E-07
22	chr22:20191518:G:A	20191518	A	G	8714	0.65762	-0.080143	0.01505	1E-07
22	chr22:20191523:T:C	20191523	C	T	8718	0.657376	-0.0803854	0.0150435	9.1E-08
22	chr22:20191573:A:C	20191573	C	A	8898	0.661441	-0.0803857	0.0149305	7.3E-08
22	chr22:20191650:G:A	20191650	A	G	8900	0.0655056	-0.161081	0.0285593	1.7E-08
22	chr22:20191700:A:T	20191700	T	A	8714	0.657563	-0.0797796	0.015051	1.2E-07
22	chr22:20191763:G:A	20191763	A	G	8765	0.475642	-0.0627182	0.0141861	9.8E-06
22	chr22:20191782:T:C	20191782	C	T	8683	0.652539	-0.0812596	0.0150536	6.7E-08
22	chr22:20191816:G:A	20191816	A	G	8683	0.652712	-0.0810353	0.0150554	7.3E-08
22	chr22:20191856:G:A	20191856	A	G	8693	0.653054	-0.0814395	0.0150504	6.3E-08
22	chr22:20191980:T:C	20191980	C	T	8700	0.656494	-0.0775336	0.0150367	2.5E-07
22	chr22:20192548:C:T	20192548	T	C	8894	0.064313	-0.15922	0.0287261	3E-08
22	chr22:20192594:G:A	20192594	A	G	8820	0.153968	0.102582	0.0197172	2E-07
22	chr22:20193613:G:T	20193613	T	G	8626	0.416763	-0.0644761	0.0145125	8.9E-06
22	chr22:20193688:G:A	20193688	A	G	8906	0.0663598	-0.159377	0.028249	1.7E-08
22	chr22:20194546:G:T	20194546	T	G	8908	0.156657	0.102429	0.0194321	1.4E-07
22	chr22:20195507:G:A	20195507	A	G	8612	0.834707	-0.102044	0.019336	1.3E-07
22	chr22:20195516:G:C	20195516	C	G	8625	0.835015	-0.101757	0.0193317	1.4E-07
22	chr22:20196479:G:A	20196479	A	G	8830	0.160532	0.0990624	0.0193092	2.9E-07
22	chr22:20199027:T:C	20199027	C	T	8831	0.161307	0.099686	0.0192717	2.3E-07
22	chr22:20200400:A:G	20200400	G	A	8835	0.161517	0.0993227	0.0192549	2.5E-07
22	chr22:20201223:A:T	20201223	T	A	8869	0.0616191	-0.169063	0.0293978	8.9E-09
22	chr22:20204624:C:G	20204624	G	C	8852	0.0619069	-0.171182	0.0293387	5.4E-09
22	chr22:20205576:C:T	20205576	T	C	8847	0.0536905	-0.17954	0.0311972	8.7E-09
22	chr22:20208207:C:T	20208207	T	C	8886	0.14506	-0.124365	0.019959	4.6E-10
22	chr22:20208255:T:C	20208255	C	T	8886	0.145116	-0.122762	0.0199582	7.7E-10
22	chr22:20208476:G:C	20208476	C	G	8886	0.145116	-0.122762	0.0199582	7.7E-10
22	chr22:20208523:C:A	20208523	A	C	8899	0.145747	-0.122029	0.0199074	8.8E-10
22	chr22:20208927:G:A	20208927	A	G	8886	0.145116	-0.122762	0.0199582	7.7E-10
22	chr22:20209043:C:A	20209043	A	C	8886	0.145116	-0.122762	0.0199582	7.7E-10
22	chr22:20209153:C:G	20209153	G	C	8886	0.145116	-0.122762	0.0199582	7.7E-10
22	chr22:20209249:A:G	20209249	G	A	8886	0.145116	-0.122762	0.0199582	7.7E-10
22	chr22:20210681:C:T	20210681	T	C	8885	0.145132	-0.123397	0.0199582	6.3E-10
22	chr22:20210688:C:T	20210688	T	C	8844	0.0999548	-0.107568	0.0234875	4.7E-06
22	chr22:20210716:T:G	20210716	G	T	8885	0.145132	-0.123397	0.0199582	6.3E-10
22	chr22:20210818:G:C	20210818	C	G	8845	0.1	-0.107317	0.0234829	4.9E-06
22	chr22:20211061:G:T	20211061	T	G	8886	0.145285	-0.122736	0.0199435	7.5E-10
22	chr22:20212056:C:A	20212056	A	C	8803	0.142111	-0.124301	0.0202801	8.8E-10

22	chr22:20212990:T:G	20212990	G	T	8824	0.143982	-0.124156	0.0201094	6.7E-10
22	chr22:20213131:G:A	20213131	A	G	8817	0.141772	-0.124577	0.0202882	8.2E-10
22	chr22:20213907:C:T	20213907	T	C	8817	0.140467	-0.126556	0.0203442	4.9E-10
22	chr22:20214214:G:A	20214214	A	G	8825	0.142266	-0.125445	0.0201865	5.2E-10
22	chr22:20214591:T:C	20214591	C	T	8826	0.142817	-0.124735	0.0201572	6.1E-10
22	chr22:20214637:G:A	20214637	A	G	8826	0.142647	-0.124772	0.0201725	6.2E-10
22	chr22:20214899:G:T	20214899	T	G	8821	0.142784	-0.126123	0.0201528	3.9E-10
22	chr22:20214982:A:G	20214982	G	A	8820	0.1428	-0.126728	0.0201528	3.2E-10
22	chr22:20215189:G:C	20215189	C	G	8824	0.142679	-0.124844	0.0201732	6.07E-10
22	chr22:20215635:T:C	20215635	C	T	8806	0.142005	-0.13036	0.0201917	1.07E-10
22	chr22:20215842:G:C	20215842	C	G	8795	0.143718	-0.12359	0.0200725	7.41E-10
22	chr22:20215867:C:T	20215867	T	C	8798	0.141396	-0.123991	0.0202636	9.42E-10
22	chr22:20215926:A:G	20215926	G	A	8795	0.143718	-0.123549	0.0200725	7.50E-10
22	chr22:20216145:C:T	20216145	T	C	8783	0.141353	-0.123845	0.0202797	1.02E-09
22	chr22:20216414:C:T	20216414	T	C	8798	0.141566	-0.122897	0.0202392	1.26E-09
22	chr22:32122048:C:T	32122048	T	C	8863	0.0208733	-0.222067	0.0494889	7.22E-06

Table S2. List of suggestive (1e-5) SNPs and p-value for overall ascorbic acid 2-sulfate GWAS.

CHR	SNP	POS	A1	A2	N	AF1	BETA	SE	P
1	chr1:164868256:T:C	164868256	C	T	8746	0.584096	-0.0713338	0.0146845	1.2E-06
1	chr1:164869857:G:A	164869857	A	G	8759	0.429672	0.0657225	0.0146348	7.1E-06
1	chr1:164877039:G:A	164877039	A	G	8711	0.454598	0.0649811	0.0146243	8.9E-06
1	chr1:164882064:C:G	164882064	G	C	8738	0.45634	0.0647789	0.0146023	9.2E-06
1	chr1:164884985:A:G	164884985	G	A	8739	0.456288	0.0648174	0.0146009	9E-06
1	chr1:164888013:G:A	164888013	A	G	8735	0.456096	0.0658491	0.0146029	6.5E-06
1	chr1:164888620:AACTG:A	164888620	A	AAC TG	8735	0.455238	0.0656822	0.0145891	6.7E-06
1	chr1:164891658:C:T	164891658	T	C	8735	0.455638	0.065475	0.0146021	7.3E-06
1	chr1:164892171:A:T	164892171	T	A	8730	0.455613	0.0654814	0.0146022	7.3E-06
1	chr1:164895704:G:A	164895704	A	G	8736	0.455643	0.0647189	0.0146193	9.6E-06
1	chr1:164904138:G:A	164904138	A	G	8792	0.481745	0.0678386	0.0145992	3.4E-06
1	chr1:164905471:A:C	164905471	C	A	8791	0.481572	0.0676609	0.014598	3.6E-06
1	chr1:164908824:C:T	164908824	T	C	8825	0.482436	0.0680456	0.0145627	3E-06
1	chr1:164909643:C:T	164909643	T	C	8807	0.481889	0.0685099	0.0145819	2.6E-06
1	chr1:164910090:G:A	164910090	A	G	8746	0.500629	0.0656316	0.0145708	6.7E-06
1	chr1:164913647:G:A	164913647	A	G	8790	0.477474	0.0655959	0.0146056	7.1E-06
1	chr1:234476613:A:T	234476613	T	A	8664	0.0201408	0.241054	0.0520069	3.6E-06
3	chr3:132049425:T:C	132049425	C	T	8791	0.0360596	0.198299	0.0389622	3.6E-07
3	chr3:132102320:C:T	132102320	T	C	8778	0.034746	0.180344	0.0396463	5.4E-06
3	chr3:196689403:A:G	196689403	G	A	8750	0.0153714	0.269628	0.059368	5.6E-06
5	chr5:151105328:G:A	151105328	A	G	8361	0.202009	0.0865707	0.0187663	4E-06
5	chr5:177241818:C:T	177241818	T	C	8827	0.0252068	-0.216772	0.0466576	3.4E-06
6	chr6:36575279:C:T	36575279	T	C	8775	0.0466667	-0.154786	0.0345753	7.6E-06
6	chr6:36593299:A:G	36593299	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36594398:G:C	36594398	C	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06

6	chr6:36595217:A:G	36595217	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36595383:T:C	36595383	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36595546:C:T	36595546	T	C	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36595637:A:G	36595637	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36595852:A:G	36595852	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36595932:G:T	36595932	T	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36596237:T:A	36596237	A	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36596308:G:A	36596308	A	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36596693:T:C	36596693	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36597295:G:C	36597295	C	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36597682:T:C	36597682	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36598053:A:G	36598053	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36599347:T:C	36599347	C	T	8827	0.0259431	-0.205982	0.0459346	7.3E-06
6	chr6:36601902:TA:T	36601902	T	TA	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36602304:GT:G	36602304	G	GT	8821	0.0260741	-0.204466	0.0458432	8.2E-06
6	chr6:36602425:G:A	36602425	A	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36604030:T:C	36604030	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36604132:T:C	36604132	C	T	8828	0.0260535	-0.203158	0.0458429	9.4E-06
6	chr6:36604232:C:T	36604232	T	C	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36604567:A:T	36604567	T	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36604830:C:G	36604830	G	C	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36605243:G:A	36605243	A	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36605872:G:T	36605872	T	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36605976:A:G	36605976	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36606628:G:T	36606628	T	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36606740:A:G	36606740	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36606826:T:C	36606826	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36607520:C:T	36607520	T	C	8827	0.0259998	-0.204267	0.0458889	8.5E-06
6	chr6:36607831:G:GT	36607831	GT	G	8823	0.0272583	-0.198807	0.0447116	8.7E-06
6	chr6:36608067:CAA:C	36608067	C	CAA	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36608265:G:A	36608265	A	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36609600:C:T	36609600	T	C	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36610123:C:A	36610123	A	C	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36610214:T:C	36610214	C	T	8827	0.0259998	-0.204239	0.0458889	8.6E-06
6	chr6:36610265:G:T	36610265	T	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36610408:A:G	36610408	G	A	8822	0.0554863	-0.15077	0.0316309	1.9E-06
6	chr6:36610729:T:C	36610729	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36611276:C:A	36611276	A	C	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36611329:G:A	36611329	A	G	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36611636:T:C	36611636	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36612443:T:C	36612443	C	T	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36612458:A:G	36612458	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36612602:G:C	36612602	C	G	8827	0.0259431	-0.203575	0.0459358	9.3E-06
6	chr6:36613448:A:G	36613448	G	A	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36613612:TGAAA:T	36613612	T	TGAAA	8828	0.0259968	-0.204102	0.0458889	8.7E-06
6	chr6:36614372:A:G	36614372	G	A	8808	0.0262262	-0.204899	0.0457525	7.5E-06
6	chr6:36614474:C:A	36614474	A	C	8809	0.0262232	-0.205134	0.0457522	7.3E-06

6	chr6:36614486:A:G	36614486	G	A	8808	0.0262829	-0.20481	0.0457065	7.4E-06
6	chr6:36614532:TGTGCTAA:T	36614532	T	TGT GCT AA	8808	0.0261126	-0.208704	0.0458429	5.3E-06
6	chr6:36614861:G:A	36614861	A	G	8826	0.0259461	-0.206773	0.0459344	6.7E-06
6	chr6:36615150:A:C	36615150	C	A	8827	0.0258298	-0.206183	0.0460281	7.5E-06
6	chr6:36615508:A:G	36615508	G	A	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36615962:C:T	36615962	T	C	8825	0.025949	-0.205587	0.0459351	7.6E-06
6	chr6:36616285:C:T	36616285	T	C	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36616308:A:G	36616308	G	A	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36616368:G:A	36616368	A	G	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36618218:C:T	36618218	T	C	8827	0.0261697	-0.206734	0.0457488	6.2E-06
6	chr6:36618317:C:T	36618317	T	C	8824	0.0259519	-0.205286	0.0459354	7.9E-06
6	chr6:36618546:A:G	36618546	G	A	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36618633:C:A	36618633	A	C	8826	0.0258894	-0.208636	0.0459801	5.7E-06
6	chr6:36618656:G:A	36618656	A	G	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36618855:A:G	36618855	G	A	8826	0.0258894	-0.205228	0.0459819	8.1E-06
6	chr6:36619983:T:C	36619983	C	T	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36620217:G:A	36620217	A	G	8827	0.0259431	-0.205438	0.0459349	7.7E-06
6	chr6:36621232:G:A	36621232	A	G	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36623582:C:T	36623582	T	C	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36624542:C:T	36624542	T	C	8825	0.0248725	-0.21118	0.0469582	6.9E-06
6	chr6:36624885:T:C	36624885	C	T	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36625407:G:T	36625407	T	G	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36625810:G:A	36625810	A	G	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36625831:A:G	36625831	G	A	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36626153:T:C	36626153	C	T	8827	0.0248669	-0.211039	0.046958	7E-06
6	chr6:36626286:C:T	36626286	T	C	8827	0.0225445	-0.24972	0.0491477	3.8E-07
6	chr6:36626302:C:G	36626302	G	C	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36626509:A:G	36626509	G	A	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36626891:G:A	36626891	A	G	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36627508:G:C	36627508	C	G	8826	0.0247564	-0.210367	0.0470589	7.8E-06
6	chr6:36628071:C:A	36628071	A	C	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36628073:G:T	36628073	T	G	8827	0.0248102	-0.210059	0.0470086	7.9E-06
6	chr6:36630989:G:T	36630989	T	G	8827	0.0248102	-0.209899	0.0470087	8E-06
6	chr6:36631992:C:CT	36631992	CT	C	8824	0.0244787	-0.211286	0.0473131	8E-06
6	chr6:36634645:A:T	36634645	T	A	8821	0.0556626	-0.141119	0.0316305	8.1E-06
6	chr6:36634902:A:G	36634902	G	A	8828	0.0225419	-0.249769	0.0491475	3.7E-07
6	chr6:61015285:A:T	61015285	T	A	8768	0.0105497	-0.317605	0.0717836	9.7E-06
6	chr6:61021249:T:A	61021249	A	T	8770	0.0106613	-0.318715	0.0714054	8.1E-06
6	chr6:61027016:G:A	61027016	A	G	8772	0.0107729	-0.320238	0.0710331	6.5E-06
6	chr6:61049658:A:G	61049658	G	A	8773	0.0108287	-0.314551	0.0708524	9E-06
6	chr6:61050680:G:C	61050680	C	G	8773	0.0108287	-0.314551	0.0708524	9E-06
6	chr6:134019122:C:G	134019122	G	C	8798	0.193283	-0.0816801	0.0184604	9.7E-06
6	chr6:134019363:T:C	134019363	C	T	8801	0.193728	-0.0830257	0.0184311	6.6E-06
6	chr6:134019598:C:A	134019598	A	C	8824	0.195093	-0.0813111	0.0183424	9.3E-06
6	chr6:134023325:C:G	134023325	G	C	8789	0.193936	-0.0850902	0.0184369	3.9E-06
8	chr8:132335691:T:C	132335691	C	T	8550	0.766433	-0.0772644	0.0174281	9.3E-06

9	chr9:2029392:G:A	2029392	A	G	8820	0.0150227	-0.291728	0.0597757	1.1E-06
9	chr9:107175136:T:C	107175136	C	T	8401	0.567254	0.0680291	0.0150969	6.6E-06
9	chr9:107176815:C:T	107176815	T	C	8402	0.56558	0.0691897	0.0150936	4.6E-06
9	chr9:107177990:A:G	107177990	G	A	8415	0.567083	0.0671338	0.0150872	8.6E-06
9	chr9:107178070:G:T	107178070	T	G	8413	0.56698	0.0671044	0.01509	8.7E-06
9	chr9:107178228:A:G	107178228	G	A	8414	0.567328	0.067391	0.0150928	8E-06
9	chr9:107178649:A:G	107178649	G	A	8414	0.567209	0.0672237	0.0150918	8.4E-06
9	chr9:107179107:A:C	107179107	C	A	8408	0.567852	0.0670637	0.0151045	9E-06
9	chr9:107180148:C:T	107180148	T	C	8418	0.566762	0.0671858	0.0150864	8.5E-06
9	chr9:107180273:G:T	107180273	T	G	8409	0.566714	0.0670185	0.0150895	8.9E-06
9	chr9:107180489:A:G	107180489	G	A	8419	0.566694	0.0673878	0.015084	7.9E-06
9	chr9:107180622:G:A	107180622	A	G	8419	0.566694	0.0673878	0.015084	7.9E-06
9	chr9:107180780:T:G	107180780	G	T	8418	0.566821	0.0670761	0.0150888	8.8E-06
9	chr9:107180893:G:A	107180893	A	G	8418	0.566702	0.0673239	0.015084	8.1E-06
9	chr9:107180916:T:C	107180916	C	T	8419	0.566991	0.0667911	0.0150849	9.5E-06
9	chr9:107183067:G:T	107183067	T	G	8419	0.566991	0.0668675	0.0150848	9.3E-06
9	chr9:107183569:C:T	107183569	T	C	8419	0.566635	0.0679354	0.015085	6.7E-06
9	chr9:107185510:C:T	107185510	T	C	8416	0.567075	0.0684023	0.0150939	5.8E-06
9	chr9:127738666:C:T	127738666	T	C	8822	0.0149059	-0.272573	0.059772	5.1E-06
9	chr9:129038856:C:T	129038856	T	C	8822	0.00895489	0.336377	0.0760919	9.8E-06
9	chr9:129056141:A:C	129056141	C	A	8822	0.00906824	0.368751	0.0756228	1.1E-06
9	chr9:129056542:G:A	129056542	A	G	8822	0.00912492	0.365434	0.0754016	1.3E-06
9	chr9:129057363:G:A	129057363	A	G	8822	0.00912492	0.365434	0.0754016	1.3E-06
9	chr9:129057754:C:T	129057754	T	C	8822	0.00912492	0.365434	0.0754016	1.3E-06
9	chr9:129058125:G:A	129058125	A	G	8822	0.00912492	0.365434	0.0754016	1.3E-06
9	chr9:129060021:G:C	129060021	C	G	8821	0.00906927	0.367518	0.0756235	1.2E-06
9	chr9:129061070:A:G	129061070	G	A	8821	0.00889922	0.367525	0.076787	1.7E-06
9	chr9:129061332:T:C	129061332	C	T	8821	0.00889922	0.367525	0.076787	1.7E-06
9	chr9:129062713:A:G	129062713	G	A	8820	0.00884354	0.370721	0.0770211	1.5E-06
9	chr9:129063392:T:C	129063392	C	T	8820	0.00895692	0.373317	0.0765503	1.1E-06
9	chr9:129064238:G:A	129064238	A	G	8821	0.00906927	0.358631	0.0760976	2.4E-06
9	chr9:129064268:A:G	129064268	G	A	8821	0.0089559	0.369703	0.0765522	1.4E-06
9	chr9:129064818:C:T	129064818	T	C	8820	0.00890023	0.367578	0.076787	1.7E-06
9	chr9:129064983:A:C	129064983	C	A	8821	0.00889922	0.367525	0.076787	1.7E-06
9	chr9:129065011:G:A	129065011	A	G	8821	0.00889922	0.367525	0.076787	1.7E-06
9	chr9:129065825:C:A	129065825	A	C	8821	0.00889922	0.367525	0.076787	1.7E-06
9	chr9:129065867:C:T	129065867	T	C	8821	0.0089559	0.365371	0.0765546	1.8E-06
9	chr9:129065872:C:T	129065872	T	C	8821	0.00912595	0.363966	0.0758675	1.6E-06
9	chr9:129066546:C:T	129066546	T	C	8819	0.00952489	0.361792	0.074335	1.1E-06
9	chr9:129066735:A:G	129066735	G	A	8821	0.00889922	0.367525	0.076787	1.7E-06
9	chr9:129067528:C:T	129067528	T	C	8822	0.00889821	0.367661	0.0767868	1.7E-06
9	chr9:129070821:A:G	129070821	G	A	8823	0.00912388	0.350251	0.0754097	3.4E-06
9	chr9:129072939:C:T	129072939	T	C	8821	0.0086158	0.373995	0.0779849	1.6E-06
10	chr10:12435301:C:G	12435301	G	C	8805	0.0113004	0.319874	0.0692588	3.9E-06
10	chr10:55111495:T:C	55111495	C	T	8730	0.0211913	-0.240116	0.0511683	2.7E-06
10	chr10:87709326:CATAT:C	87709326	C	CATAT	8249	0.405504	-0.0748303	0.0154684	1.3E-06
10	chr10:87709832:C:T	87709832	T	C	8313	0.404427	-0.0738846	0.0154157	1.6E-06

10	chr10:87709877:T:C	87709877	C	T	8315	0.406554	-0.0748021	0.0154146	1.2E-06
10	chr10:87710262:T:C	87710262	C	T	8314	0.406423	-0.0753951	0.0154118	1E-06
10	chr10:87712964:CT:C	87712964	C	CT	8457	0.367979	-0.0774416	0.0155088	5.9E-07
10	chr10:87713720:A:G	87713720	G	A	8675	0.409856	-0.080552	0.0150788	9.2E-08
10	chr10:87714531:A:G	87714531	G	A	8670	0.410784	-0.0795694	0.015074	1.3E-07
10	chr10:87715883:GA:G	87715883	G	GA	8640	0.409722	-0.0804115	0.0151116	1E-07
10	chr10:87715935:A:G	87715935	G	A	8673	0.410181	-0.0793652	0.015083	1.4E-07
10	chr10:87715960:G:A	87715960	A	G	8679	0.409552	-0.0803677	0.015079	9.8E-08
10	chr10:87716432:A:G	87716432	G	A	8677	0.409877	-0.0804311	0.0150788	9.6E-08
10	chr10:87716863:T:C	87716863	C	T	8677	0.409819	-0.0798871	0.0150816	1.2E-07
10	chr10:87717124:G:A	87717124	A	G	8659	0.375505	-0.083818	0.0152702	4E-08
10	chr10:87717153:T:G	87717153	G	T	8676	0.409463	-0.0802846	0.0150854	1E-07
10	chr10:87717352:C:T	87717352	T	C	8679	0.409609	-0.0811931	0.0150797	7.3E-08
10	chr10:87717464:T:C	87717464	C	T	8679	0.409552	-0.0798957	0.015083	1.2E-07
10	chr10:87718088:G:A	87718088	A	G	8661	0.375649	-0.0842302	0.015264	3.4E-08
10	chr10:87718631:A:G	87718631	G	A	8677	0.409992	-0.0789255	0.015082	1.7E-07
10	chr10:87718632:T:A	87718632	A	T	8677	0.409992	-0.0789255	0.015082	1.7E-07
10	chr10:87718759:C:T	87718759	T	C	8676	0.409866	-0.0787592	0.0150835	1.8E-07
10	chr10:87718872:G:A	87718872	A	G	8679	0.409552	-0.0798957	0.015083	1.2E-07
10	chr10:87718952:A:G	87718952	G	A	8672	0.409709	-0.0799458	0.0150881	1.2E-07
10	chr10:87719257:C:T	87719257	T	C	8660	0.376039	-0.0839713	0.0152595	3.7E-08
10	chr10:87719322:T:C	87719322	C	T	8673	0.409662	-0.080025	0.0150868	1.1E-07
10	chr10:87719493:C:T	87719493	T	C	8672	0.409536	-0.0799472	0.0150919	1.2E-07
10	chr10:87719618:C:T	87719618	T	C	8678	0.409541	-0.0802602	0.0150791	1E-07
10	chr10:87719794:T:C	87719794	C	T	8671	0.41016	-0.0792423	0.0150832	1.5E-07
10	chr10:87719943:T:G	87719943	G	T	8680	0.409274	-0.080217	0.0150768	1E-07
10	chr10:87720743:CA:C	87720743	C	CA	8635	0.40747	-0.0780347	0.0151392	2.5E-07
10	chr10:87722022:G:A	87722022	A	G	8669	0.37611	-0.0841009	0.0152459	3.5E-08
10	chr10:87722114:G:T	87722114	T	G	8684	0.409661	-0.0803197	0.0150725	9.9E-08
10	chr10:87723076:C:T	87723076	T	C	8685	0.409729	-0.0801751	0.0150737	1E-07
10	chr10:87723117:C:T	87723117	T	C	8671	0.376081	-0.083718	0.015245	4E-08
10	chr10:87723313:C:G	87723313	G	C	8671	0.376081	-0.083718	0.015245	4E-08
10	chr10:87723437:C:CT	87723437	CT	C	8655	0.375505	-0.0829878	0.0152607	5.4E-08
10	chr10:87723678:GCTGT:G	87723678	G	GCT GT	8683	0.409939	-0.0801033	0.0150786	1.1E-07
10	chr10:87725133:C:T	87725133	T	C	8685	0.409672	-0.0801997	0.0150762	1E-07
10	chr10:87725205:C:T	87725205	T	C	8670	0.376125	-0.083577	0.0152462	4.2E-08
10	chr10:87725314:A:C	87725314	C	A	8685	0.409787	-0.0800486	0.015075	1.1E-07
10	chr10:87725334:A:G	87725334	G	A	8686	0.40974	-0.0801907	0.0150736	1E-07
10	chr10:87725473:A:G	87725473	G	A	8686	0.40974	-0.0801907	0.0150736	1E-07
10	chr10:87725505:G:T	87725505	T	G	8686	0.40974	-0.0801907	0.0150736	1E-07
10	chr10:87725538:T:C	87725538	C	T	8681	0.40963	-0.0805053	0.0150763	9.3E-08
10	chr10:87725638:T:C	87725638	C	T	8685	0.409672	-0.0798882	0.0150764	1.2E-07
10	chr10:87725943:T:C	87725943	C	T	8684	0.410064	-0.0795459	0.0150739	1.3E-07
10	chr10:87725944:G:A	87725944	A	G	8686	0.40974	-0.0801907	0.0150736	1E-07
10	chr10:87726447:A:G	87726447	G	A	8686	0.40974	-0.0801907	0.0150736	1E-07
10	chr10:87726676:G:A	87726676	A	G	8808	0.413545	-0.0797634	0.0149309	9.2E-08
10	chr10:87726750:T:A	87726750	A	T	8685	0.409729	-0.0801751	0.0150737	1E-07

10	chr10:87727843:C:T	87727843	T	C	8725	0.411175	-0.079378	0.015027	1.3E-07
10	chr10:87728375:C:T	87728375	T	C	8716	0.377467	-0.0835096	0.0151917	3.9E-08
10	chr10:87728921:G:A	87728921	A	G	8725	0.411289	-0.0788459	0.0150333	1.6E-07
10	chr10:87729067:A:G	87729067	G	A	8724	0.411222	-0.0796437	0.0150317	1.2E-07
10	chr10:87729132:T:C	87729132	C	T	8723	0.411384	-0.0788699	0.0150394	1.6E-07
10	chr10:87729819:G:A	87729819	A	G	8691	0.41054	-0.0791321	0.0150746	1.5E-07
10	chr10:87729938:C:T	87729938	T	C	8691	0.410597	-0.0792935	0.015072	1.4E-07
10	chr10:87729944:C:T	87729944	T	C	8691	0.410597	-0.0792935	0.015072	1.4E-07
10	chr10:87731951:A:G	87731951	G	A	8689	0.410174	-0.0778247	0.0150721	2.4E-07
10	chr10:87732687:G:A	87732687	A	G	8685	0.410593	-0.0785635	0.0150666	1.8E-07
10	chr10:87733482:C:T	87733482	T	C	8679	0.408976	-0.0771671	0.0150728	3.1E-07
12	chr12:124867120:C:T	124867120	T	C	8800	0.00414773	-0.52727	0.113522	3.4E-06
13	chr13:107368585:G:T	107368585	T	G	8710	0.82853	-0.0951414	0.0194061	9.5E-07
14	chr14:52365323:A:G	52365323	G	A	8769	0.0100924	0.325119	0.0733533	9.3E-06
16	chr16:810258:A:G	810258	G	A	8817	0.0179199	0.293913	0.054427	6.7E-08
16	chr16:2840858:A:G	2840858	G	A	8703	0.00247041	-0.656485	0.147678	8.8E-06
16	chr16:29747337:T:G	29747337	G	T	8723	0.0218388	-0.262247	0.050174	1.7E-07
16	chr16:29771895:G:C	29771895	C	G	8732	0.0218163	-0.26022	0.0501741	2.1E-07
16	chr16:29780254:C:G	29780254	G	C	8748	0.0225194	-0.266137	0.0493823	7.1E-08
16	chr16:29797540:G:A	29797540	A	G	8760	0.0182648	-0.281067	0.0546409	2.7E-07
16	chr16:29912189:G:A	29912189	A	G	8518	0.610531	0.0708298	0.0151498	2.9E-06
16	chr16:29913584:A:G	29913584	G	A	8776	0.540793	0.0642004	0.0145308	1E-05
16	chr16:29916794:A:G	29916794	G	A	8702	0.620834	0.0789624	0.0150858	1.7E-07
16	chr16:29920272:T:C	29920272	C	T	8705	0.61189	0.0763627	0.0150408	3.8E-07
16	chr16:29923731:G:C	29923731	C	G	8697	0.612165	0.076729	0.0150529	3.4E-07
16	chr16:29923745:G:C	29923745	C	G	8767	0.537983	0.0643551	0.0145443	9.7E-06
16	chr16:29925333:A:G	29925333	G	A	8827	0.542257	0.0642367	0.0144892	9.3E-06
16	chr16:29928987:G:A	29928987	A	G	8758	0.0106189	-0.336032	0.0711945	2.4E-06
16	chr16:29954115:C:T	29954115	T	C	8815	0.019966	-0.333946	0.051723	1.1E-10
16	chr16:29967484:A:G	29967484	G	A	8497	0.845887	0.125402	0.0205573	1.1E-09
16	chr16:30003654:G:T	30003654	T	G	8828	0.0206162	-0.33537	0.050916	4.5E-11
16	chr16:30003655:G:T	30003655	T	G	8828	0.0206162	-0.33537	0.050916	4.5E-11
16	chr16:30005499:A:C	30005499	C	A	8825	0.0206232	-0.335766	0.0509161	4.3E-11
16	chr16:30024485:C:T	30024485	T	C	8786	0.0346574	-0.215409	0.0398569	6.5E-08
16	chr16:30051535:A:G	30051535	G	A	8776	0.0348678	-0.209138	0.0397071	1.4E-07
16	chr16:30070046:G:T	30070046	T	G	8577	0.155066	-0.119784	0.0204069	4.4E-09
16	chr16:30079930:C:T	30079930	T	C	8798	0.0335872	-0.229154	0.0403867	1.4E-08
16	chr16:30086309:C:T	30086309	T	C	8702	0.337394	-0.0870318	0.0155793	2.3E-08
16	chr16:30091070:G:A	30091070	A	G	8804	0.0345866	-0.210051	0.0398572	1.4E-07
16	chr16:30091481:T:C	30091481	C	T	8706	0.325637	-0.080252	0.0157287	3.4E-07
16	chr16:30099674:T:TC	30099674	TC	T	8781	0.0112743	-0.323911	0.069073	2.7E-06
16	chr16:30106908:A:G	30106908	G	A	8814	0.0103245	-0.364035	0.071929	4.2E-07
16	chr16:30108204:C:A	30108204	A	C	8819	0.869203	-0.0975094	0.0215699	6.2E-06
16	chr16:30109051:C:T	30109051	T	C	7986	0.3215	-0.077318	0.0166257	3.3E-06
16	chr16:30116567:T:C	30116567	C	T	8824	0.0330916	-0.234541	0.040596	7.6E-09
16	chr16:30123335:T:C	30123335	C	T	8609	0.415902	-0.0741894	0.0149113	6.5E-07
16	chr16:30123358:C:T	30123358	T	C	8616	0.327994	-0.0822957	0.0157462	1.7E-07
16	chr16:30128579:T:G	30128579	G	T	8624	0.3343	-0.0786265	0.015664	5.2E-07

16	chr16:30128971:T:C	30128971	C	T	8654	0.330136	-0.0799252	0.0156998	3.6E-07
16	chr16:30129937:A:C	30129937	C	A	8622	0.334841	-0.076779	0.01566	9.4E-07
16	chr16:30130526:C:T	30130526	T	C	8656	0.329251	-0.0813409	0.0157129	2.3E-07
16	chr16:30130592:G:A	30130592	A	G	8652	0.329866	-0.0796024	0.0157062	4E-07
16	chr16:30130664:T:C	30130664	C	T	8646	0.41684	-0.0737541	0.0148718	7.1E-07
16	chr16:30130700:G:C	30130700	C	G	8648	0.416166	-0.0749834	0.0148781	4.7E-07
16	chr16:30133058:C:G	30133058	G	C	8687	0.415276	-0.0745565	0.0148471	5.1E-07
16	chr16:30135944:C:T	30135944	T	C	8795	0.463786	-0.0689663	0.0146396	2.5E-06
16	chr16:30141147:T:C	30141147	C	T	8803	0.514711	-0.0811285	0.0144691	2.1E-08
16	chr16:30142519:C:CCT	30142519	CCT	C	8740	0.51167	-0.0842798	0.0145198	6.5E-09
16	chr16:30143419:A:G	30143419	G	A	8825	0.520963	-0.0837557	0.0144721	7.1E-09
16	chr16:30143710:T:C	30143710	C	T	8809	0.52049	-0.0818553	0.0144869	1.6E-08
16	chr16:30143969:C:A	30143969	A	C	8803	0.514313	-0.0819389	0.0144696	1.5E-08
16	chr16:30145642:C:T	30145642	T	C	8804	0.514255	-0.0821004	0.0144677	1.4E-08
16	chr16:30146201:C:CA	30146201	CA	C	8798	0.513924	-0.0822921	0.0144703	1.3E-08
16	chr16:30146380:G:C	30146380	C	G	8802	0.514201	-0.082067	0.0144628	1.4E-08
16	chr16:30147436:T:G	30147436	G	T	8802	0.514372	-0.0817197	0.0144682	1.6E-08
16	chr16:30147786:G:A	30147786	A	G	8800	0.514318	-0.0822333	0.0144661	1.3E-08
16	chr16:30149961:G:T	30149961	T	G	8754	0.335104	-0.0737206	0.0155039	2E-06
16	chr16:30150984:G:A	30150984	A	G	8801	0.514203	-0.0823725	0.0144724	1.3E-08
16	chr16:30151161:G:A	30151161	A	G	8802	0.514201	-0.0823738	0.0144724	1.3E-08
16	chr16:30151836:A:G	30151836	G	A	8802	0.515565	-0.082701	0.014481	1.1E-08
16	chr16:30151845:C:T	30151845	T	C	8802	0.515281	-0.0826974	0.0144789	1.1E-08
16	chr16:30152512:G:A	30152512	A	G	8805	0.473027	-0.0892763	0.0144506	6.5E-10
16	chr16:30153167:A:G	30153167	G	A	8807	0.522369	-0.0815712	0.0144934	1.8E-08
16	chr16:30153430:C:A	30153430	A	C	8798	0.472948	-0.0884673	0.0144498	9.2E-10
16	chr16:30153437:G:A	30153437	A	G	8802	0.473245	-0.0881625	0.0144475	1E-09
16	chr16:30153818:T:C	30153818	C	T	8805	0.481317	-0.08492	0.0144352	4E-09
16	chr16:30153879:G:A	30153879	A	G	8791	0.480662	-0.0856946	0.0144572	3.1E-09
16	chr16:30154183:A:AC	30154183	AC	A	8700	0.527414	-0.0811967	0.0146022	2.7E-08
16	chr16:30154404:T:C	30154404	C	T	8825	0.48153	-0.0859512	0.0144293	2.6E-09
16	chr16:30154862:C:T	30154862	T	C	8809	0.485526	-0.0817495	0.0144326	1.5E-08
16	chr16:30155305:A:T	30155305	T	A	8808	0.48104	-0.0856621	0.014437	3E-09
16	chr16:30158072:C:G	30158072	G	C	8812	0.530186	-0.0790346	0.0145287	5.3E-08
16	chr16:30158440:G:C	30158440	C	G	8811	0.530076	-0.0792221	0.0145216	4.9E-08
16	chr16:30159694:GT:G	30159694	G	GT	8808	0.480643	-0.0845087	0.0144337	4.8E-09
16	chr16:30161306:A:G	30161306	G	A	8805	0.530153	-0.0786767	0.0145271	6.1E-08
16	chr16:30163605:T:C	30163605	C	T	8826	0.530308	-0.080066	0.0145006	3.4E-08
16	chr16:30164188:C:T	30164188	T	C	8800	0.480511	-0.0856993	0.0144397	2.9E-09
16	chr16:30166486:C:T	30166486	T	C	8814	0.346097	-0.0678843	0.0153355	9.6E-06
16	chr16:30167195:A:C	30167195	C	A	8805	0.537422	-0.0789242	0.0145291	5.6E-08
16	chr16:30168729:A:C	30168729	C	A	8582	0.951585	-0.168313	0.0340903	7.9E-07
16	chr16:30171220:T:C	30171220	C	T	8802	0.537435	-0.0792091	0.0145322	5E-08
16	chr16:30172965:A:G	30172965	G	A	8798	0.537338	-0.0788776	0.0145386	5.8E-08
16	chr16:30176192:C:T	30176192	T	C	8718	0.487956	-0.083804	0.0144877	7.3E-09
16	chr16:30176355:T:G	30176355	G	T	8717	0.487955	-0.0832928	0.0144913	9E-09
16	chr16:30183519:A:G	30183519	G	A	8675	0.538963	-0.0765196	0.0146278	1.7E-07
16	chr16:30186830:A:G	30186830	G	A	8634	0.537352	-0.0767894	0.0146657	1.6E-07

16	chr16:30281179:A:T	30281179	T	A	8487	0.47667	0.0698058	0.0147956	2.4E-06
16	chr16:30308986:G:T	30308986	T	G	8598	0.472668	0.0697944	0.0147423	2.2E-06
16	chr16:30309954:T:A	30309954	A	T	8791	0.0212718	-0.307771	0.0505765	1.2E-09
16	chr16:30311847:G:C	30311847	C	G	8681	0.116288	0.108775	0.0228835	2E-06
16	chr16:30311987:C:T	30311987	T	C	8598	0.472494	0.0686763	0.0147452	3.2E-06
16	chr16:30312059:G:A	30312059	A	G	8598	0.472494	0.0686763	0.0147452	3.2E-06
16	chr16:30312489:C:T	30312489	T	C	8586	0.472339	0.0688388	0.0147593	3.1E-06
16	chr16:30315250:G:C	30315250	C	G	8596	0.472953	0.0684798	0.0147472	3.4E-06
16	chr16:30316996:T:C	30316996	C	T	8595	0.473008	0.0689755	0.0147485	2.9E-06
16	chr16:30319150:CT:C	30319150	C	CT	8397	0.469334	0.0683689	0.014927	4.6E-06
16	chr16:30320807:T:G	30320807	G	T	8803	0.0103942	-0.39704	0.0717191	3.1E-08
16	chr16:30323602:G:A	30323602	A	G	8600	0.47314	0.0685928	0.0147414	3.3E-06
16	chr16:30324709:A:T	30324709	T	A	8599	0.473427	0.0691797	0.0147385	2.7E-06
16	chr16:30325887:T:A	30325887	A	T	8396	0.469748	0.0675066	0.0149744	6.5E-06
16	chr16:30326165:GAGCC:G	30326165	G	GAG CC	8520	0.470012	0.0672177	0.0148304	5.8E-06
16	chr16:30327682:T:C	30327682	C	T	8599	0.473427	0.0691603	0.0147385	2.7E-06
16	chr16:30328432:G:A	30328432	A	G	8587	0.472284	0.0685585	0.0147579	3.4E-06
16	chr16:30329353:A:G	30329353	G	A	8583	0.473145	0.0680723	0.0147537	4E-06
16	chr16:30331915:G:A	30331915	A	G	8629	0.472998	0.0695727	0.0147106	2.3E-06
16	chr16:30335371:A:G	30335371	G	A	8602	0.345617	0.0775385	0.015548	6.1E-07
16	chr16:30336410:A:G	30336410	G	A	8598	0.356187	0.0699641	0.0154051	5.6E-06
16	chr16:30340303:T:C	30340303	C	T	8582	0.339839	0.0819209	0.0155972	1.5E-07
16	chr16:30340504:G:T	30340504	T	G	8791	0.0212149	-0.289923	0.0506524	1E-08
16	chr16:30340521:T:C	30340521	C	T	8582	0.337917	0.0838351	0.0156294	8.1E-08
16	chr16:30341282:T:C	30341282	C	T	8604	0.349431	0.0741266	0.0154284	1.6E-06
16	chr16:30341316:G:A	30341316	A	G	8606	0.348826	0.0752421	0.0154465	1.1E-06
16	chr16:30343759:C:T	30343759	T	C	8787	0.0176966	-0.39105	0.0551279	1.3E-12
16	chr16:30348087:T:C	30348087	C	T	8689	0.338877	0.0807272	0.0155023	1.9E-07
16	chr16:30348198:CA:C	30348198	C	CA	8682	0.337883	0.0787007	0.0155304	4E-07
16	chr16:30348690:A:G	30348690	G	A	8680	0.349136	0.0707164	0.0153635	4.2E-06
16	chr16:30350020:G:T	30350020	T	G	8682	0.349343	0.0713397	0.0153573	3.4E-06
16	chr16:30350153:ATATC:A	30350153	A	ATA TC	8620	0.0488399	0.16611	0.033855	9.3E-07
16	chr16:30352750:A:G	30352750	G	A	8718	0.35031	0.0731743	0.0153082	1.8E-06
16	chr16:30354718:G:A	30354718	A	G	8721	0.338665	0.0805655	0.0154858	2E-07
16	chr16:30360334:C:G	30360334	G	C	8804	0.342344	0.0800999	0.0153235	1.7E-07
16	chr16:30363060:C:T	30363060	T	C	8804	0.34189	0.0795313	0.0153336	2.1E-07
16	chr16:30365165:T:C	30365165	C	T	8827	0.353914	0.0723211	0.0151327	1.8E-06
16	chr16:30365638:T:C	30365638	C	T	8803	0.342099	0.0800478	0.0153286	1.8E-07
16	chr16:30369982:C:G	30369982	G	C	8787	0.342665	0.0802691	0.0153306	1.6E-07
16	chr16:30371434:T:C	30371434	C	T	8767	0.353257	0.0723468	0.0151995	1.9E-06
16	chr16:30374182:G:A	30374182	A	G	8691	0.643827	-0.0719372	0.0152471	2.4E-06
16	chr16:30374516:T:C	30374516	C	T	8480	0.732311	-0.111792	0.0166927	2.1E-11
16	chr16:30374941:C:T	30374941	T	C	8696	0.646217	-0.0690154	0.0152898	6.4E-06
16	chr16:30377388:A:G	30377388	G	A	8701	0.646535	-0.0687537	0.0152874	6.9E-06
16	chr16:30378993:T:C	30378993	C	T	8712	0.658632	-0.0786858	0.0154291	3.4E-07
16	chr16:30379356:A:G	30379356	G	A	8787	0.0211676	-0.300671	0.05071	3E-09

16	chr16:30380611:ATTT:A	30380611	A	ATTT	8750	0.657829	-0.0800009	0.0153751	2E-07
16	chr16:30380778:A:G	30380778	G	A	8745	0.657862	-0.0797564	0.0153809	2.2E-07
16	chr16:30382339:G:A	30382339	A	G	8827	0.659964	-0.0819282	0.015315	8.8E-08
16	chr16:30382450:G:A	30382450	A	G	8754	0.658213	-0.0803989	0.0153723	1.7E-07
16	chr16:30383220:G:A	30383220	A	G	8756	0.65812	-0.0800952	0.0153689	1.9E-07
16	chr16:30385484:A:G	30385484	G	A	8753	0.658574	-0.0807958	0.0153836	1.5E-07
16	chr16:30385494:G:A	30385494	A	G	8754	0.658213	-0.0801993	0.0153724	1.8E-07
16	chr16:30385580:A:AC	30385580	AC	A	8726	0.646631	-0.0708253	0.0152597	3.5E-06
16	chr16:30387087:T:C	30387087	C	T	8745	0.658205	-0.0788153	0.0153771	3E-07
16	chr16:30387356:G:A	30387356	A	G	8735	0.658729	-0.0791866	0.0153942	2.7E-07
16	chr16:30388807:T:C	30388807	C	T	8681	0.667319	-0.0743122	0.0154916	1.6E-06
16	chr16:30388986:T:C	30388986	C	T	8750	0.658171	-0.0790509	0.0153714	2.7E-07
16	chr16:30392537:A:G	30392537	G	A	8817	0.658784	-0.0788924	0.0153124	2.6E-07
16	chr16:30393163:G:C	30393163	C	G	8745	0.619268	-0.0753152	0.0150043	5.2E-07
16	chr16:30395948:C:A	30395948	A	C	8724	0.618925	-0.0745555	0.0150137	6.8E-07
16	chr16:30396658:G:C	30396658	C	G	8697	0.618547	-0.0762648	0.0150463	4E-07
16	chr16:30397444:C:T	30397444	T	C	8691	0.618111	-0.075462	0.0150414	5.2E-07
16	chr16:30399124:C:T	30399124	T	C	8694	0.65666	-0.0786501	0.0154224	3.4E-07
16	chr16:30400061:C:G	30400061	G	C	8697	0.618547	-0.0762648	0.0150463	4E-07
16	chr16:30409530:T:C	30409530	C	T	8522	0.621216	-0.0765057	0.0151948	4.8E-07
16	chr16:30412430:G:A	30412430	A	G	8819	0.847035	-0.0923503	0.0200946	4.3E-06
16	chr16:30413567:GT:G	30413567	G	GT	8670	0.881142	-0.10442	0.0226722	4.1E-06
16	chr16:30420782:C:T	30420782	T	C	8300	0.637651	-0.0892666	0.0155855	1E-08
16	chr16:30420953:C:T	30420953	T	C	8246	0.328159	-0.0871585	0.0160111	5.2E-08
16	chr16:30422409:A:G	30422409	G	A	8650	0.879538	-0.105194	0.0225301	3E-06
16	chr16:30422839:G:T	30422839	T	G	8439	0.655172	-0.0773721	0.015666	7.86E-07
16	chr16:30426817:A:G	30426817	G	A	8431	0.656031	-0.0766102	0.0156794	1.03E-06
16	chr16:30439251:T:C	30439251	C	T	8808	0.010218	-0.396149	0.0722973	4.27E-08
16	chr16:30446984:G:A	30446984	A	G	8697	0.022709	-0.262418	0.0486989	7.10E-08
16	chr16:30467744:C:T	30467744	T	C	8822	0.0193834	-0.348255	0.0527273	3.98E-11
16	chr16:30495875:A:G	30495875	G	A	8818	0.0233046	-0.238027	0.048541	9.41E-07
16	chr16:30988048:C:T	30988048	T	C	8785	0.0134889	-0.286114	0.0620137	3.96E-06
16	chr16:31490477:A:G	31490477	G	A	8825	0.010085	-0.32418	0.0727297	8.30E-06
16	chr16:31712803:C:T	31712803	T	C	8828	0.0155188	-0.261911	0.0590636	9.23E-06
16	chr16:31772168:T:C	31772168	C	T	8824	0.0154125	-0.264853	0.0592712	7.88E-06
16	chr16:31795158:A:T	31795158	T	A	8825	0.0154674	-0.265047	0.0591664	7.48E-06
16	chr16:31806475:A:G	31806475	G	A	8826	0.0155223	-0.263589	0.0590629	8.09E-06
16	chr16:31847141:C:T	31847141	T	C	8825	0.0155241	-0.263623	0.059063	8.07E-06
16	chr16:31882565:C:A	31882565	A	C	8827	0.0147842	-0.278365	0.0606934	4.51E-06
16	chr16:31902402:A:G	31902402	G	A	8823	0.0145075	-0.280405	0.0612661	4.72E-06
16	chr16:31985827:G:A	31985827	A	G	8809	0.0142468	-0.28259	0.061857	4.91E-06
16	chr16:32007384:C:G	32007384	G	C	8802	0.0129516	-0.286772	0.0648204	9.68E-06
16	chr16:32026299:C:G	32026299	G	C	8796	0.0123352	-0.304817	0.0663954	4.41E-06
20	chr20:56280636:G:T	56280636	T	G	8826	0.0237933	0.214852	0.0479399	7.41E-06
20	chr20:56284607:C:T	56284607	T	C	8827	0.0236774	0.213753	0.0480478	8.64E-06
20	chr20:56291568:G:T	56291568	T	G	8824	0.0237421	0.214496	0.047994	7.85E-06
20	chr20:56292449:A:G	56292449	G	A	8787	0.975475	-0.214034	0.0473681	6.23E-06

20	chr20:56292853:G:C	56292853	C	G	8824	0.0237421	0.214496	0.047994	7.85E-06
20	chr20:56293309:CT:C	56293309	C	CT	8824	0.0237421	0.214496	0.047994	7.85E-06
20	chr20:56293439:T:C	56293439	C	T	8824	0.0237421	0.214496	0.047994	7.85E-06
20	chr20:56298401:A:G	56298401	G	A	8823	0.0239148	0.212396	0.0478349	8.99E-06

Table S3. List of suggestive (1e-5) SNPs and p-value for interaction O-methylascorbate GWAS.

CHR	SNP	POS	A1	A2	N	AF1	BETA_G	BETA_G_by_E	SE_G	SE_G_by_E	P_G	P_G_by_E
1	chr1:187758900:T:C	187758900	C	T	8859	0.0247206	-0.0192394	-0.188066	0.0425018	0.042493	0.650785	9.61E-06
1	chr1:230192587:C:T	230192587	T	C	8907	0.0428315	0.010012	-0.149034	0.0337374	0.0337155	0.766647	9.86E-06
1	chr1:239110287:G:A	239110287	A	G	8903	0.0218466	-0.0680294	0.220943	0.0498463	0.0499968	0.172321	9.91E-06
2	chr2:23371693:C:A	23371693	A	C	8905	0.0235261	0.0106918	-0.214784	0.0457253	0.0456812	0.815119	2.58E-06
2	chr2:181680483:G:A	181680483	A	G	8868	0.0115584	0.0135338	-0.277376	0.0625814	0.0620919	0.828785	7.93E-06
2	chr2:181703482:C:T	181703482	T	C	8859	0.0133762	0.0347171	-0.281441	0.0576569	0.0574058	0.547086	9.45E-07
2	chr2:181724699:G:A	181724699	A	G	8862	0.0134281	0.0247821	-0.280992	0.0574083	0.0571519	0.665973	8.81E-07
2	chr2:181756224:G:C	181756224	C	G	8868	0.0135882	0.0363986	-0.271707	0.0587509	0.0583899	0.535559	3.27E-06
3	chr3:42166013:T:G	42166013	G	T	8626	0.651577	0.00981995	-0.0669605	0.015132	0.0151485	0.516368	9.86E-06
3	chr3:149520106:G:A	149520106	A	G	8711	0.0136609	0.0546298	-0.288873	0.0633368	0.0633717	0.388397	5.15E-06
4	chr4:113095111:T:C	113095111	C	T	8907	0.0362075	0.0105454	0.190253	0.0385762	0.0386311	0.784572	8.44E-07
5	chr5:122241471:C:T	122241471	T	C	8330	0.0126651	-0.0369426	0.27321	0.0599604	0.060321	0.537818	5.92E-06
5	chr5:175120419:G:A	175120419	A	G	8672	0.368888	0.0146797	0.0659528	0.0148426	0.014859	0.322654	9.06E-06
6	chr6:160717816:C:G	160717816	G	C	8894	0.162076	0.0269348	-0.0855342	0.0191745	0.0191671	0.160105	8.10E-06
6	chr6:160732958:G:A	160732958	A	G	8882	0.162069	0.0263675	-0.0846664	0.019162	0.0191548	0.168812	9.87E-06
6	chr6:166583240:T:C	166583240	C	T	8832	0.472656	0.0191236	0.0635149	0.0140484	0.0140682	0.17343	6.34E-06
6	chr6:166583503:C:A	166583503	A	C	8896	0.474089	0.0188687	0.0625044	0.013944	0.0139615	0.175999	7.57E-06
6	chr6:166583971:G:T	166583971	T	G	8821	0.467917	0.0178898	0.0644091	0.0140373	0.0140568	0.202506	4.60E-06
7	chr7:53711776:G:A	53711776	A	G	8862	0.248364	-0.00163167	-0.0721618	0.0159871	0.0159948	0.918708	6.43E-06
7	chr7:130282658:T:C	130282658	C	T	8723	0.335779	0.0116343	0.0771846	0.015142	0.0151653	0.44228	3.59E-07
8	chr8:135924342:A:C	135924342	C	A	8878	0.0348051	0.0410135	0.191074	0.0393027	0.0393696	0.296703	1.21E-06
8	chr8:135926782:G:A	135926782	A	G	8878	0.0351431	0.0375854	0.189888	0.0390052	0.0390695	0.335247	1.17E-06
8	chr8:135929229:C:A	135929229	A	C	8879	0.0353643	0.0362654	0.187427	0.0388998	0.0389656	0.351193	1.51E-06
8	chr8:135931037:A:T	135931037	T	A	8866	0.0356982	0.0332721	0.18715	0.0386209	0.0386995	0.38896	1.32E-06
8	chr8:135931895:C:A	135931895	A	C	8870	0.0354566	0.0391608	0.189067	0.0387995	0.0388621	0.312825	1.14E-06
8	chr8:135932216:T:TATC	135932216	TATC	T	8899	0.0363524	0.0359688	0.186132	0.0382943	0.0383659	0.34759	1.23E-06
8	chr8:135932453:A:G	135932453	G	A	8899	0.0364648	0.0348142	0.185283	0.0381997	0.0382701	0.362099	1.29E-06
8	chr8:135933748:A:T	135933748	T	A	8900	0.0358427	0.0373733	0.194462	0.0386407	0.0387133	0.333445	5.08E-07
8	chr8:135935805:G:A	135935805	A	G	8908	0.0359228	0.0413486	0.188845	0.0385636	0.0386313	0.283622	1.02E-06
8	chr8:135936671:G:A	135936671	A	G	8902	0.0355538	0.0409207	0.194628	0.0387949	0.0388633	0.291519	5.50E-07
8	chr8:135937564:C:G	135937564	G	C	8901	0.0358387	0.0345114	0.191137	0.0386253	0.0387029	0.371594	7.87E-07
8	chr8:135939062:C:T	135939062	T	C	8900	0.0355056	0.0405476	0.194265	0.0388455	0.0389108	0.29657	5.96E-07
8	chr8:135939992:T:A	135939992	A	T	8890	0.0352643	0.0371681	0.194099	0.0391596	0.0392275	0.342547	7.50E-07
8	chr8:135940960:A:G	135940960	G	A	8887	0.0353888	0.039185	0.194047	0.0390898	0.0391631	0.316134	7.24E-07
8	chr8:135941002:C:A	135941002	A	C	8887	0.0353325	0.039038	0.194197	0.0391512	0.0392283	0.318711	7.40E-07
8	chr8:135947134:C:G	135947134	G	C	8810	0.0334847	0.0547961	0.192003	0.0406545	0.0407158	0.177707	2.41E-06
8	chr8:135948309:C:T	135948309	T	C	8851	0.0315219	0.0552514	0.189068	0.0410749	0.041112	0.178581	4.25E-06

8	chr8:135985795:G:T	135985795	T	G	8826	0.0399388	0.0126407	0.166657	0.0364329	0.0365374	0.728622	5.08E-06
8	chr8:136003885:T:C	136003885	C	T	8861	0.032502	0.0415078	0.195185	0.0404333	0.0404618	0.304622	1.41E-06
8	chr8:136015051:C:A	136015051	A	C	8892	0.0332321	0.0478001	0.178062	0.0399746	0.0399727	0.231789	8.41E-06
8	chr8:136033928:G:A	136033928	A	G	8897	0.0337192	0.0430539	0.174486	0.0394797	0.0394661	0.275478	9.82E-06
9	chr9:37450622:T:A	37450622	A	T	8863	0.0344127	0.0190117	0.200409	0.0395332	0.0396541	0.630583	4.33E-07
10	chr10:96247971:A:G	96247971	G	A	8319	0.572605	-0.030215	0.0681099	0.0145826	0.0145958	0.0382664	3.07E-06
11	chr11:12003703:C:T	12003703	T	C	8863	0.0248787	-0.0622746	0.218125	0.0481218	0.0481227	0.19563	5.82E-06
11	chr11:12018283:G:T	12018283	T	G	8860	0.0248307	-0.0677994	0.224363	0.0479936	0.0479869	0.157751	2.93E-06
11	chr11:17628511:T:C	17628511	C	T	8768	0.0697422	-0.000437693	-0.121953	0.0273983	0.0274004	0.987254	8.56E-06
11	chr11:95203556:C:T	95203556	T	C	8813	0.0147509	-0.0103542	-0.260883	0.0569078	0.0568912	0.855624	4.53E-06
13	chr13:97810928:T:C	97810928	C	T	8727	0.364272	-0.0158894	0.0669354	0.0149569	0.0149666	0.28808	7.74E-06
13	chr13:97812069:A:G	97812069	G	A	8610	0.363647	-0.0157443	0.0676543	0.0150878	0.0150933	0.296711	7.38E-06
14	chr14:30140830:T:C	30140830	C	T	8897	0.0136001	0.0212517	0.257122	0.0575783	0.057418	0.712059	7.53E-06
14	chr14:30145028:C:T	30145028	T	C	8899	0.0138218	0.0191471	0.25719	0.0567415	0.0565768	0.735782	5.47E-06
14	chr14:30147224:A:C	30147224	C	A	8899	0.0137656	0.0186772	0.256093	0.0569646	0.0568121	0.743008	6.55E-06
14	chr14:30149090:C:T	30149090	T	C	8899	0.0137094	0.0192973	0.256697	0.0571698	0.0570068	0.735708	6.70E-06
14	chr14:30153259:G:A	30153259	A	G	8905	0.0139809	0.0290056	0.253456	0.0563579	0.0561812	0.606785	6.44E-06
14	chr14:30157939:G:T	30157939	T	G	8905	0.0140371	0.0275956	0.25238	0.0561711	0.0560037	0.62323	6.59E-06
14	chr14:30160467:G:T	30160467	T	G	8906	0.0140355	0.0277429	0.252229	0.0561712	0.0560039	0.621378	6.68E-06
14	chr14:30161960:G:C	30161960	C	G	8904	0.0142071	0.0303984	0.248094	0.0558065	0.0556412	0.585952	8.24E-06
14	chr14:30168311:G:A	30168311	A	G	8890	0.0141732	0.0182624	0.260408	0.0561811	0.0560022	0.745133	3.32E-06
14	chr14:30173926:A:G	30173926	G	A	8902	0.0138171	0.0249119	0.249864	0.0565888	0.0564148	0.659774	9.46E-06
14	chr14:30174600:A:C	30174600	C	A	8904	0.0139825	0.018174	0.250954	0.056663	0.0564736	0.748408	8.84E-06
14	chr14:30175996:AT:A	30175996	A	AT	8906	0.0140355	0.0253164	0.257899	0.0561512	0.0559895	0.652089	4.10E-06
14	chr14:30178577:G:A	30178577	A	G	8890	0.014342	0.0283053	0.256004	0.0556131	0.0554638	0.610774	3.92E-06
14	chr14:30178833:T:G	30178833	G	T	8883	0.0145784	0.0174467	0.254281	0.055709	0.055541	0.754147	4.69E-06
14	chr14:30184459:G:A	30184459	A	G	8905	0.0141494	0.012958	0.257265	0.0564498	0.0562785	0.818442	4.85E-06
14	chr14:30187955:T:A	30187955	A	T	8907	0.0142023	0.0163433	0.260733	0.0563318	0.0561658	0.771719	3.45E-06
14	chr14:30193101:T:C	30193101	C	T	8909	0.0141991	0.0217222	0.265964	0.0559143	0.0557725	0.697653	1.85E-06
17	chr17:51951876:A:C	51951876	C	A	8842	0.048575	-0.0610028	0.145526	0.0328784	0.0328342	0.0635382	9.33E-06
19	chr19:58050989:C:T	58050989	T	C	8906	0.0416573	0.000374093	-0.160685	0.0358224	0.0359871	0.991668	8.00E-06
20	chr20:1386731:G:C	1386731	C	G	8780	0.232403	-0.00525427	0.076223	0.0168031	0.0168441	0.754511	6.03E-06

Table S4. List of suggestive (1e-5) SNPs and p-value for interaction ascorbic acid 2 sulfate GWAS.

CHR	SNP	POS	A1	A2	N	AF1	BETA_G	BETA_G_by_E	SE_G	SE_G_by_E	P_G	P_G_by_E
1	chr1:13316425:C:T	13316425	T	C	8474	0.0123318	0.036235	-0.324591	0.0614696	0.061685	0.55554	1.42E-07
1	chr1:13341668:C:A	13341668	A	C	8463	0.0124069	0.0505379	-0.341904	0.0621678	0.0624897	0.41626	4.47E-08
1	chr1:13348372:A:G	13348372	G	A	8414	0.0121821	0.0486469	-0.31988	0.0598962	0.060106	0.416685	1.03E-07
1	chr1:13354706:C:T	13354706	T	C	8461	0.012469	0.0460258	-0.349149	0.0624139	0.0627325	0.460862	2.61E-08
1	chr1:13364727:G:A	13364727	A	G	8433	0.012629	0.044273	-0.330195	0.0613742	0.061676	0.470688	8.62E-08
2	chr2:101229410:A:C	101229410	C	A	8625	0.86858	0.0282212	0.0956758	0.0213342	0.0213382	0.185897	7.33E-06
2	chr2:101241563:C:T	101241563	T	C	8628	0.868452	0.0286725	0.0962228	0.0213	0.0213051	0.178262	6.29E-06
2	chr2:168670174:T:C	168670174	C	T	8809	0.0121467	-0.0383846	0.294078	0.0610847	0.0614463	0.529753	1.70E-06
2	chr2:168710847:G:A	168710847	A	G	8823	0.0147342	-0.0322123	0.257547	0.0566572	0.056929	0.569663	6.07E-06
2	chr2:169769528:T:C	169769528	C	T	8744	0.320849	0.00591376	0.0689513	0.0155374	0.0155668	0.70349	9.45E-06

5	chr5:31170278:T:C	31170278	C	T	8792	0.0329845	0.104333	-0.17766	0.0395948	0.0397938	0.0084131	8.03E-06
5	chr5:66695069:C:T	66695069	T	C	8766	0.0427219	-0.00356685	-0.155174	0.0348158	0.0349047	0.9184	8.76E-06
5	chr5:84618856:G:T	84618856	T	G	8792	0.278662	-0.00637354	-0.0718182	0.0161968	0.0162245	0.693945	9.58E-06
5	chr5:84619158:C:T	84619158	T	C	8790	0.278555	-0.00578748	-0.0717546	0.0161964	0.0162236	0.720844	9.74E-06
5	chr5:176853584:T:C	176853584	C	T	8822	0.0695421	-0.0377393	0.127792	0.0287298	0.0287995	0.188983	9.11E-06
5	chr5:176854168:C:G	176854168	G	C	8793	0.057887	-0.0578328	0.145572	0.0318806	0.0319566	0.0696709	5.23E-06
6	chr6:164631587:G:A	164631587	A	G	8823	0.0347387	0.0514412	0.173776	0.0388245	0.0388768	0.185182	7.83E-06
8	chr8:102940178:G:C	102940178	C	G	8694	0.108293	0.00458994	-0.109348	0.0234344	0.0234226	0.844717	3.03E-06
8	chr8:133476306:T:C	133476306	C	T	8813	0.563145	0.00350673	-0.0679427	0.0149349	0.014967	0.814363	5.64E-06
9	chr9:20281438:C:T	20281438	T	C	8794	0.0395724	-0.0794289	0.17349	0.0385651	0.0387057	0.0394365	7.38E-06
9	chr9:83269239:T:A	83269239	A	T	8799	0.0221616	-0.0353636	0.215943	0.0483648	0.0485854	0.464667	8.81E-06
10	chr10:52687125:T:C	52687125	C	T	8825	0.0337677	-0.0933096	0.182978	0.039097	0.0390472	0.0170043	2.79E-06
10	chr10:52697952:C:T	52697952	T	C	8813	0.0331329	-0.0574687	0.187948	0.0384495	0.0384383	0.135005	1.01E-06
10	chr10:52747013:C:T	52747013	T	C	8779	0.032236	-0.0597754	0.185442	0.039344	0.0393963	0.128686	2.51E-06
12	chr12:69125538:C:T	69125538	T	C	8804	0.0122672	-0.0924701	0.346017	0.0663961	0.0665813	0.163709	2.03E-07
12	chr12:76293904:C:T	76293904	T	C	8717	0.347769	0.00836288	-0.0676952	0.0152397	0.0152646	0.583172	9.22E-06
12	chr12:76295389:G:C	76295389	C	G	8780	0.395103	0.00102765	-0.070274	0.0147064	0.0147316	0.944291	1.84E-06
12	chr12:76295668:G:GC	76295668	GC	G	8726	0.601192	-0.00107873	0.0702454	0.014742	0.0147659	0.941668	1.96E-06
12	chr12:76295965:AAGGG:A	76295965	A	AAG GG	8784	0.603484	-0.000624299	0.0698191	0.0146789	0.014703	0.966076	2.05E-06
12	chr12:76296114:T:C	76296114	C	T	8781	0.395001	0.00109343	-0.0702576	0.0147085	0.0147334	0.94074	1.86E-06
12	chr12:76296296:C:T	76296296	T	C	8760	0.60234	-0.000867043	0.0708686	0.0146878	0.0147119	0.952927	1.46E-06
12	chr12:76296531:T:C	76296531	C	T	8780	0.39533	0.00146553	-0.070269	0.0147072	0.0147322	0.920624	1.84E-06
12	chr12:76297218:T:C	76297218	C	T	8782	0.395183	0.000881857	-0.0702156	0.0147081	0.0147334	0.95219	1.88E-06
12	chr12:76297237:G:A	76297237	A	G	8780	0.395387	-4.43E-05	-0.0695632	0.0147018	0.0147271	0.997595	2.32E-06
12	chr12:76297564:C:T	76297564	T	C	8780	0.603417	-3.23E-05	0.0704362	0.0146839	0.0147082	0.998246	1.68E-06
12	chr12:76297631:C:T	76297631	T	C	8788	0.60355	-0.000137724	0.0704461	0.0146751	0.0146996	0.992512	1.65E-06
12	chr12:76298187:C:G	76298187	G	C	8793	0.602752	-0.00050307	0.0704404	0.0146594	0.0146829	0.972624	1.61E-06
12	chr12:76298193:A:G	76298193	G	A	8793	0.602809	-0.000545075	0.0703995	0.0146639	0.0146872	0.970349	1.64E-06
12	chr12:76298228:G:A	76298228	A	G	8805	0.396593	0.000836665	-0.0694784	0.0146744	0.0146984	0.954533	2.28E-06
12	chr12:76298610:C:T	76298610	T	C	8789	0.602401	-0.000883522	0.0701429	0.0146551	0.0146788	0.951926	1.77E-06
12	chr12:76298690:G:A	76298690	A	G	8788	0.602583	-0.000442977	0.0706416	0.0146677	0.0146912	0.975907	1.52E-06
12	chr12:76298776:G:A	76298776	A	G	8789	0.602515	-0.000912639	0.0704694	0.014657	0.0146804	0.950351	1.58E-06
12	chr12:76298855:T:C	76298855	C	T	8779	0.395888	0.00169423	-0.0706231	0.0147057	0.0147307	0.90828	1.63E-06
12	chr12:76298887:A:G	76298887	G	A	8789	0.602685	-0.000550365	0.0704259	0.0146642	0.0146877	0.970062	1.63E-06
12	chr12:76298977:G:A	76298977	A	G	8785	0.60239	1.05E-05	0.0698296	0.0146619	0.0146856	0.999429	1.98E-06
12	chr12:76299930:C:T	76299930	T	C	8768	0.397525	-0.000602402	-0.0721256	0.0147167	0.0147426	0.967349	9.97E-07
12	chr12:76300471:G:T	76300471	T	G	8598	0.59508	-0.00500932	0.0766147	0.0147827	0.0148111	0.734712	2.31E-07
13	chr13:19077920:C:T	19077920	T	C	8724	0.0699221	-0.0035809	-0.135529	0.0286837	0.0287432	0.90065	2.42E-06
13	chr13:19078361:G:T	19078361	T	G	8726	0.0698487	-0.00384376	-0.135784	0.0286974	0.0287562	0.893449	2.34E-06
13	chr13:19079756:C:A	19079756	A	C	8733	0.0692202	-0.00245938	-0.133187	0.0287645	0.0288276	0.931864	3.84E-06
13	chr13:19079757:G:A	19079757	A	G	8733	0.0692202	-0.00245938	-0.133187	0.0287645	0.0288276	0.931864	3.84E-06
14	chr14:43804083:A:G	43804083	G	A	8804	0.0149364	0.0403716	0.290221	0.0603075	0.0604712	0.503221	1.59E-06
14	chr14:43815643:T:C	43815643	C	T	8827	0.0156905	0.0711324	0.258946	0.0584448	0.0585798	0.223571	9.85E-06
14	chr14:43817833:C:T	43817833	T	C	8827	0.0156905	0.0711324	0.258946	0.0584448	0.0585798	0.223571	9.85E-06
14	chr14:43818105:TG:T	43818105	T	TG	8826	0.0159189	0.0774923	0.259409	0.0578142	0.0579451	0.180126	7.58E-06
14	chr14:43821452:C:T	43821452	T	C	8827	0.0161436	0.0671146	0.262156	0.057677	0.057824	0.244575	5.80E-06
14	chr14:43823305:C:G	43823305	G	C	8827	0.0159737	0.0775617	0.259626	0.0576119	0.0577333	0.178212	6.89E-06

14	chr14:43823492:T:C	43823492	C	T	8827	0.0156905	0.0711324	0.258946	0.0584448	0.0585798	0.223571	9.85E-06
14	chr14:43832209:C:T	43832209	T	C	8817	0.0166723	0.0949741	0.250313	0.0562924	0.0563868	0.0915733	9.03E-06
16	chr16:67527768:G:A	67527768	A	G	8823	0.0283917	0.0588425	-0.176038	0.039342	0.0393403	0.13474	7.65E-06
16	chr16:69972590:G:A	69972590	A	G	8620	0.0137471	0.0512512	-0.262958	0.0595307	0.0595072	0.389283	9.92E-06
17	chr17:55357605:T:C	55357605	C	T	8672	0.601937	-0.0178845	-0.0659926	0.0147697	0.0147834	0.225936	8.05E-06
17	chr17:55358373:T:C	55358373	C	T	8663	0.522683	-0.00983875	-0.0673705	0.0145406	0.0145464	0.498634	3.63E-06
17	chr17:55361548:G:T	55361548	T	G	8590	0.520431	-0.0111296	-0.069544	0.0146299	0.0146361	0.44681	2.02E-06
17	chr17:55362078:G:A	55362078	A	G	8603	0.52162	-0.0111075	-0.0711632	0.0146394	0.0146459	0.448009	1.18E-06
17	chr17:55363034:T:C	55363034	C	T	8825	0.528725	-0.0136842	-0.0662315	0.0144037	0.0144104	0.342086	4.30E-06
17	chr17:55363934:T:C	55363934	C	T	8600	0.52186	-0.0111435	-0.0706774	0.0146307	0.0146374	0.446267	1.38E-06
17	chr17:55364153:G:C	55364153	C	G	8590	0.521653	-0.0117414	-0.0706983	0.014637	0.0146437	0.422452	1.38E-06
17	chr17:55365495:GA:G	55365495	G	GA	8514	0.514447	-0.00950214	-0.0697678	0.0146868	0.0146978	0.517643	2.07E-06
17	chr17:55367769:C:T	55367769	T	C	8560	0.515187	-0.00784704	-0.0683003	0.0146617	0.0146707	0.592507	3.23E-06
17	chr17:55368347:G:T	55368347	T	G	8564	0.516172	-0.00913053	-0.0677274	0.0146551	0.0146638	0.533265	3.86E-06
17	chr17:55368638:C:T	55368638	T	C	8561	0.515244	-0.00800538	-0.068164	0.0146646	0.0146737	0.585136	3.40E-06
17	chr17:55368655:C:T	55368655	T	C	8559	0.51513	-0.00741016	-0.0683017	0.0146649	0.0146739	0.61335	3.25E-06
17	chr17:55369426:T:C	55369426	C	T	8554	0.517769	-0.00971576	-0.0667531	0.0146732	0.0146828	0.50788	5.46E-06
17	chr17:55373954:G:T	55373954	T	G	8410	0.515755	-0.00718079	-0.0664173	0.0148447	0.0148559	0.628578	7.79E-06
17	chr17:55374378:G:A	55374378	A	G	8365	0.525643	-0.0119955	-0.0744919	0.0146491	0.0146663	0.412868	3.79E-07
19	chr19:51030764:C:T	51030764	T	C	8259	0.0741615	-0.0289152	0.133768	0.0273485	0.0274774	0.290381	1.13E-06
19	chr19:51036204:A:G	51036204	G	A	8310	0.0770156	-0.0229053	0.125254	0.0269064	0.0269763	0.394604	3.43E-06
19	chr19:51038932:G:T	51038932	T	G	8233	0.103243	-0.027162	0.10549	0.0237685	0.0238081	0.253133	9.39E-06
19	chr19:51041286:C:T	51041286	T	C	8325	0.0715916	-0.0360615	0.127276	0.0277901	0.027845	0.194412	4.86E-06
22	chr22:32225482:G:A	32225482	A	G	8794	0.231465	0.000228055	0.0788897	0.0175912	0.017632	0.989656	7.67E-06
22	chr22:32226552:A:G	32226552	G	A	8799	0.235765	-0.00247526	0.0800428	0.0173748	0.0174156	0.886714	4.31E-06
22	chr22:32257728:C:T	32257728	T	C	8253	0.149643	-0.000588523	0.0992546	0.0208253	0.0208472	0.977455	1.93E-06

Table S5. List of Mapped Genes to O-Methylascorbate using the FUMA software

ensg	entrezID	symbol	hgnc_symbol	OMIM	uniprotID	DrugBank
ENSG00000100075	6576	SLC25A1	SLC25A1	190315	P53007	NA
ENSG00000070010	7353	UFD1L	UFD1L	601754	Q92890	NA
ENSG00000093009	8318	CDC45	CDC45	603465	O75419	NA
ENSG00000184058	6899	TBX1	TBX1	602054	O43435	NA
ENSG00000185838	54584	GNB1L	GNB1L	610778	Q9BYB4	NA
ENSG00000215012	79680	C22orf29	C22orf29	610778	Q7L3V2	NA
ENSG00000093010	1312	COMT	COMT	116790	P21964	DB00118:DB00323:DB00494:DB02105:DB02342:DB03336:DB03907:DB04820:DB07462:DB08049:DB11632
ENSG00000099889	421	ARVCF	ARVCF	602269	O00192	NA
ENSG00000183597	128989	TANGO2	TANGO2	NA	Q6ICL3	NA
ENSG00000099899	27037	TRMT2A	TRMT2A	611151	Q8IZ69	NA
ENSG00000099901	5902	RANBP1	RANBP1	601180	P43487	DB09130:DB12695
ENSG00000099904	29801	ZDHHC8	ZDHHC8	608784	Q9ULC8	NA
ENSG00000234409	388849	AC006547.14	NA	NA	NA	NA

Table S6. Expression levels of the genes mapped to O-methylascorbate levels in different tissues using FUMA.

Category	GeneSet	N_genes	N_overlap	p	adjP	genes
DEG.up	Adipose_Tissue	1554	0	1	1	
DEG.up	Adrenal_Gland	1204	0	1	1	
DEG.up	Bladder	728	0	1	1	
DEG.up	Blood	1477	2	0.289697	1	ENSG00000093009:ENSG00000183597
DEG.up	Blood_Vessel	2139	2	0.468543	1	ENSG00000099889:ENSG00000183597
DEG.up	Brain	2348	0	1	1	
DEG.up	Breast	1428	1	0.658738	1	ENSG00000184058
DEG.up	Cervix_Uteri	2514	3	0.269205	1	ENSG00000184058:ENSG00000099899:ENSG00000099904
DEG.up	Colon	1107	0	1	1	
DEG.up	Esophagus	1008	0	1	1	
DEG.up	Fallopian_Tube	451	0	1	1	
DEG.up	Heart	458	0	1	1	
DEG.up	Kidney	963	0	1	1	
DEG.up	Liver	1090	0	1	1	
DEG.up	Lung	3029	0	1	1	
DEG.up	Muscle	879	1	0.478576	1	ENSG00000184058
DEG.up	Nerve	4157	4	0.352169	1	ENSG00000099889:ENSG00000099899:ENSG00000099904:ENSG00000234409
DEG.up	Ovary	3674	1	0.948672	1	ENSG00000099904
DEG.up	Pancreas	549	0	1	1	
DEG.up	Pituitary	3253	4	0.195905	1	ENSG00000099889:ENSG00000099899:ENSG00000099904:ENSG00000234409
DEG.up	Prostate	2019	2	0.437397	1	ENSG00000215012:ENSG00000099899
DEG.up	Salivary_Gland	1285	0	1	1	
DEG.up	Skin	2568	4	0.102156	1	ENSG00000093009:ENSG00000184058:ENSG00000185838:ENSG00000215012
DEG.up	Small_Intestine	1855	0	1	1	
DEG.up	Spleen	2666	3	0.300938	1	ENSG00000099889:ENSG00000183597:ENSG00000099899
DEG.up	Stomach	780	0	1	1	
DEG.up	Testis	5947	5	0.439003	1	ENSG00000093009:ENSG00000184058:ENSG00000099899:ENSG00000099901:ENSG00000234409
DEG.up	Thyroid	3732	6	0.035383	1	ENSG00000184058:ENSG00000215012:ENSG00000099889:ENSG00000183597:ENSG00000099899:ENSG00000099904
DEG.up	Uterus	3999	1	0.961918	1	ENSG00000099904
DEG.up	Vagina	2013	1	0.786168	1	ENSG00000184058
DEG.down	Adipose_Tissue	1360	1	0.640069	1	ENSG00000099889
DEG.down	Adrenal_Gland	2994	2	0.662557	1	ENSG00000099889:ENSG00000234409
DEG.down	Bladder	103	0	1	1	
DEG.down	Blood	5553	6	0.183435	1	ENSG00000100075:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000099901:ENSG00000099904
DEG.down	Blood_Vessel	1485	1	0.673694	1	ENSG00000234409
DEG.down	Brain	4950	2	0.909454	1	ENSG00000070010:ENSG00000183597
DEG.down	Breast	912	0	1	1	
DEG.down	Cervix_Uteri	44	0	1	1	
DEG.down	Colon	1245	2	0.225725	1	ENSG00000184058:ENSG00000234409
DEG.down	Esophagus	1465	1	0.668517	1	ENSG00000234409
DEG.down	Fallopian_Tube	1	0	1	1	

DEG.down	Heart	8251	8	0.195518	1	ENSG00000100075:ENSG00000070010:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000099899:ENSG00000099901:ENSG00000099904
DEG.down	Kidney	4932	2	0.9082	1	ENSG00000070010:ENSG00000215012
DEG.down	Liver	7196	5	0.646589	1	ENSG00000070010:ENSG00000215012:ENSG00000099889:ENSG00000183597:ENSG00000099904
DEG.down	Lung	820	0	1	1	
DEG.down	Muscle	6093	7	0.111191	1	ENSG00000100075:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000099899:ENSG00000099901:ENSG00000099904
DEG.down	Nerve	784	0	1	1	
DEG.down	Ovary	1429	2	0.276386	1	ENSG00000183597:ENSG00000234409
DEG.down	Pancreas	8671	8	0.246446	1	ENSG00000070010:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000183597:ENSG00000099899:ENSG00000099901:ENSG00000099904
DEG.down	Pituitary	1752	1	0.736032	1	ENSG00000184058
DEG.down	Prostate	698	1	0.402146	1	ENSG00000234409
DEG.down	Salivary_Gland	1666	1	0.71727	1	ENSG00000234409
DEG.down	Skin	1775	1	0.740851	1	ENSG00000099889
DEG.down	Small_Intestine	1257	1	0.609988	1	ENSG00000099889
DEG.down	Spleen	1930	1	0.771269	1	ENSG00000184058
DEG.down	Stomach	2290	2	0.50654	1	ENSG00000184058:ENSG00000234409
DEG.down	Testis	2599	1	0.868442	1	ENSG00000183597
DEG.down	Thyroid	976	0	1	1	
DEG.down	Uterus	788	0	1	1	
DEG.down	Vagina	598	0	1	1	
DEG.twoside	Adipose_Tissue	2914	1	0.899452	1	ENSG00000099889
DEG.twoside	Adrenal_Gland	4198	2	0.843259	1	ENSG00000099889:ENSG00000234409
DEG.twoside	Bladder	831	0	1	1	
DEG.twoside	Blood	7030	8	0.085814	1	ENSG00000100075:ENSG00000093009:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000183597:ENSG00000099901:ENSG00000099904
DEG.twoside	Blood_Vessel	3624	3	0.503419	1	ENSG00000099889:ENSG00000183597:ENSG00000234409
DEG.twoside	Brain	7298	2	0.988592	1	ENSG00000070010:ENSG00000183597
DEG.twoside	Breast	2340	1	0.836571	1	ENSG00000184058
DEG.twoside	Cervix_Uteri	2558	3	0.278328	1	ENSG00000184058:ENSG00000099899:ENSG00000099904
DEG.twoside	Colon	2352	2	0.52172	1	ENSG00000184058:ENSG00000234409
DEG.twoside	Esophagus	2473	1	0.853733	1	ENSG00000234409
DEG.twoside	Fallopian_Tube	452	0	1	1	
DEG.twoside	Heart	8709	8	0.251368	1	ENSG00000100075:ENSG00000070010:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000099899:ENSG00000099901:ENSG00000099904
DEG.twoside	Kidney	5895	2	0.957904	1	ENSG00000070010:ENSG00000215012
DEG.twoside	Liver	8286	5	0.794459	1	ENSG00000070010:ENSG00000215012:ENSG00000099889:ENSG00000183597:ENSG00000099904
DEG.twoside	Lung	3849	0	1	1	
DEG.twoside	Muscle	6972	8	0.082007	1	ENSG00000100075:ENSG00000184058:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000099899:ENSG00000099901:ENSG00000099904
DEG.twoside	Nerve	4941	4	0.497624	1	ENSG00000099889:ENSG00000099899:ENSG00000099904:ENSG00000234409
DEG.twoside	Ovary	5103	3	0.75946	1	ENSG00000183597:ENSG00000099904:ENSG00000234409
DEG.twoside	Pancreas	9220	8	0.322138	1	ENSG00000070010:ENSG00000215012:ENSG00000093010:ENSG00000099889:ENSG00000183597:ENSG00000099899:ENSG00000099901:ENSG00000099904

DEG.twoside	Pituitary	5005	5	0.281503	1	ENSG00000184058:ENSG00000099889:ENSG00000099899:ENSG00000099904:ENSG00000234409
DEG.twoside	Prostate	2717	3	0.311704	1	ENSG00000215012:ENSG00000099899:ENSG00000234409
DEG.twoside	Salivary_Gland	2951	1	0.902613	1	ENSG00000234409
DEG.twoside	Skin	4343	5	0.184635	1	ENSG00000093009:ENSG00000184058:ENSG00000185838:ENSG00000215012:ENSG00000099889
DEG.twoside	Small_Intestine	3112	1	0.915328	1	ENSG00000099889
DEG.twoside	Spleen	4596	4	0.433786	1	ENSG00000184058:ENSG00000099889:ENSG00000183597:ENSG00000099899
DEG.twoside	Stomach	3070	2	0.677144	1	ENSG00000184058:ENSG00000234409
DEG.twoside	Testis	8546	6	0.643379	1	ENSG00000093009:ENSG00000184058:ENSG00000183597:ENSG00000099899:ENSG00000099901:ENSG00000234409
DEG.twoside	Thyroid	4708	6	0.096672	1	ENSG00000184058:ENSG00000215012:ENSG00000099889:ENSG00000183597:ENSG00000099899:ENSG00000099904
DEG.twoside	Uterus	4787	1	0.982075	1	ENSG00000099904
DEG.twoside	Vagina	2611	1	0.869769	1	ENSG00000184058

Table S7. Functional gene sets related to the genes mapped to O-methylascorbate levels using FUMA.

Category	**GeneSet**	**N_genes**	**N_overlap**	**p**	**adjP**	**genes**	**link**
Curated_gene_sets	WP_22Q112_COPY_NUMBER_VARIATION_SYNDROME	116	13	1.08E-29	6.98E-26	SLC25A1:UFD1L:CDC45:TBX1:GNB1L:C22orf29:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8:AC006547.14	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_22Q112_COPY_NUMBER_VARIATION_SYNDROME
Curated_gene_sets	STARK_HYPPOCAMPUS_22Q11_DELETION_DN	20	8	4.55E-22	1.48E-18	SLC25A1:UFD1L:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/STARK_HYPPOCAMPUS_22Q11_DELETION_DN
Curated_gene_sets	STARK_PREFRONTAL_CORTEX_22Q11_DELETION_DN	497	8	2.81E-10	6.08E-07	SLC25A1:UFD1L:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/STARK_PREFRONTAL_CORTEX_22Q11_DELETION_DN
Curated_gene_sets	JINESH_BLEBBISHIELD_TO_IMMUNE_CELL_FUSION_PBSHMS_UP	358	5	2.91E-06	0.004722	C22orf29:COMT:TANGO2:RANBP1:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/JINESH_BLEBBISHIELD_TO_IMMUNE_CELL_FUSION_PBSHMS_UP
Canonical_Pathways	WP_22Q112_COPY_NUMBER_VARIATION_SYNDROME	116	13	1.08E-29	3.32E-26	SLC25A1:UFD1L:CDC45:TBX1:GNB1L:C22orf29:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8:AC006547.14	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_22Q112_COPY_NUMBER_VARIATION_SYNDROME
TF_targets	SAFB2_TARGET_GENES	640	7	7.9E-08	8.81E-05	SLC25A1:GNB1L:C22orf29:COMT:ARVCF:TANGO2:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/SAFB2_TARGET_GENES
TF_targets	E2F1_Q6_01	231	5	3.35E-07	0.000187	SLC25A1:UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F1_Q6_01

TF_targets	FOXR2_TARGET_GENES	171	4	4.62E-06	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/FOXR2_TARGET_GENES
TF_targets	NPAT_TARGET_GENES	217	4	1.19E-05	0.001536	GNB1L:C22orf29:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/NPAT_TARGET_GENES
TF_targets	E2F_Q3	217	4	1.19E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_Q3
TF_targets	E2F1_Q4_01	222	4	1.3E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F1_Q4_01
TF_targets	E2F_Q4_01	229	4	1.47E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_Q4_01
TF_targets	E2F_Q3_01	229	4	1.47E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_Q3_01
TF_targets	E2F_Q6_01	231	4	1.52E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_Q6_01
TF_targets	E2F_Q6	231	4	1.52E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_Q6
TF_targets	E2F_Q4	234	4	1.6E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_Q4
TF_targets	E2F_03	239	4	1.73E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_03
TF_targets	E2F1_Q4	241	4	1.79E-05	0.001536	UFD1L:CDC45:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F1_Q4
TF_targets	SNRNP70_TARGET_GENES	710	5	7.96E-05	0.006336	CDC45:COMT:TRMT2A:RANBP1:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/SNRNP70_TARGET_GENES
TF_targets	CCAWYNNGAAR_UNKNOWN	137	3	0.000106	0.007867	UFD1L:CDC45:ARVCF	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/CCAWYNNGAAR_UNKNOWN
TF_targets	RBM34_TARGET_GENES	879	5	0.000218	0.015191	SLC25A1:ARVCF:TANGO2:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/RBM34_TARGET_GENES
TF_targets	MCRS1_TARGET_GENES	33	2	0.000235	0.015418	UFD1L:CDC45	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/MCRS1_TARGET_GENES
TF_targets	KAT2A_TARGET_GENES	919	5	0.000268	0.016441	UFD1L:CDC45:COMT:TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KAT2A_TARGET_GENES

TF_targets	SOX11_TARGET_GENES	36	2	0.00028	0.016441	TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/SOX11_TARGET_GENES
TF_targets	ER_Q6_01	269	3	0.000768	0.042806	SLC25A1:GNB1L:C22orf29	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/ER_Q6_01
TF_targets	TGANNYRGCA_TCF11MAFG_01	287	3	0.000926	0.045699	UFD1L:CDC45:TANGO2	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/TGANNYRGCA_TCF11MAFG_01
TF_targets	GGCKCATGS_UNKNOWN	66	2	0.000943	0.045699	TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/GGCKCATGS_UNKNOWN
TF_targets	E2F_01	66	2	0.000943	0.045699	TRMT2A:RANBP1	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/E2F_01
Wikipathways	WP_22Q112_COPY_NUMBER_VARIATION_SYNDROME	116	13	1.08E-29	7.88E-27	SLC25A1:UFD1L:CDC45:TBX1:GNB1L:C22orf29:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8:AC006547.14	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_22Q112_COPY_NUMBER_VARIATION_SYNDROME
Positional_gene_sets	chr22q11	116	13	1.08E-29	3.23E-27	SLC25A1:UFD1L:CDC45:TBX1:GNB1L:C22orf29:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8:AC006547.14	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/chr22q11
Chemical_and_Genetic_pertubation	STARK_HYPPOCAMPUS_22Q11_DELETION_DN	20	8	4.55E-22	1.55E-18	SLC25A1:UFD1L:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/STARK_HYPPOCAMPUS_22Q11_DELETION_DN
Chemical_and_Genetic_pertubation	STARK_PREFRONTAL_CORTEX_22Q11_DELETION_DN	497	8	2.81E-10	4.78E-07	SLC25A1:UFD1L:COMT:ARVCF:TANGO2:TRMT2A:RANBP1:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/STARK_PREFRONTAL_CORTEX_22Q11_DELETION_DN
Chemical_and_Genetic_pertubation	JINESH_BLEBBISHIELD_TO_IMMUNE_CELL_FUSION_PBSHMS_UP	358	5	2.91E-06	0.003301	C22orf29:COMT:TANGO2:RANBP1:ZDHHC8	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/JINESH_BLEBBISHIELD_TO_IMMUNE_CELL_FUSION_PBSHMS_UP

Table S8. List of Mapped Genes to ascorbic acid 2 sulfate using the FUMA software.

ensg	entrezID	symbol	hgnc_symbol	OMIM	uniprotID	DrugBank
ENSG00000198682	9060	PAPSS2	PAPSS2	603005	O95340	NA
ENSG00000138138	84896	ATAD1	ATAD1	614452	Q8NBU5	NA
ENSG00000227268	100144748	KLLN	KLLN	612105	B2CW77	NA
ENSG00000171862	5728	PTEN	PTEN	601728	P60484	DB04327
ENSG00000184719	55328	RNLS	RNLS	609360	Q5VYX0	NA
ENSG00000204022	142910	LIPJ	LIPJ	613921	Q5W064	NA
ENSG00000204021	643414	LIPK	LIPK	613922	Q5VXJ0	NA
ENSG00000204020	643418	LIPN	LIPN	613924	Q5VXI9	NA
ENSG00000168488	11273	ATXN2L	ATXN2L	607931	Q8WWM7	NA

ENSG00000176953	84901	NFATC2IP	NFATC2IP	614525	Q8NCF5	NA
ENSG00000169682	83985	SPNS1	SPNS1	612583	Q9H2V7	NA
ENSG00000213658	27040	LAT	LAT	602354	O43561	NA
ENSG00000254206	728888	NPIPB11	NPIPB11	NA	E5RHQ5	NA
ENSG00000261740	552900	RP11-345J4.5	NA	613182	NA	NA
ENSG00000183336	654483	BOLA2	BOLA2	613182	Q9H3K6	NA
ENSG00000181625	548593	SLX1B	SLX1B	NA	Q9BQ83	NA
ENSG00000258150	NA	RP11-345J4.3	NA	NA	NA	NA
ENSG00000169203	NA	RP11-231C14.4	NA	NA	NA	NA
ENSG00000185905	101929877	C16orf54	C16orf54	NA	Q6UWD8	NA
ENSG00000079616	3835	KIF22	KIF22	603213	Q14807	NA
ENSG00000103495	4150	MAZ	MAZ	600999	P56270	NA
ENSG00000167371	112476	PRRT2	PRRT2	614386	Q7Z6L0	NA
ENSG00000185928	79447	PAGR1	PAGR1	612033	Q9BTK6	NA
ENSG00000263136	79447	PAGR1	NA	612033	NA	NA
ENSG00000013364	9961	MVP	MVP	605088	Q14764	NA
ENSG00000103502	10423	CDIPT	CDIPT	605893	O14735	DB03106
ENSG00000174938	26470	SEZ6L2	SEZ6L2	NA	Q6UXD5	NA
ENSG00000174939	253982	ASPHD1	ASPHD1	NA	Q5U4P2	NA
ENSG00000174943	253980	KCTD13	KCTD13	608947	Q8WZ19	NA
ENSG00000149930	9344	TAOK2	TAOK2	613199	Q9UL54	DB04522:DB12010
ENSG00000149929	8479	HIRIP3	HIRIP3	603365	Q9BW71	NA
ENSG00000169592	283899	INO80E	INO80E	NA	Q8NBZ0	NA
ENSG00000149926	100996332	FAM57B	FAM57B	615175	Q71RH2	NA
ENSG00000149925	226	ALDOA	ALDOA	103850	P04075	DB01593:DB02512:DB04326:DB04733:DB08240:DB11638:DB14487:DB14533
ENSG00000149923	5531	PPP4C	PPP4C	602035	P60510	NA
ENSG00000149922	6911	TBX6	TBX6	602427	O95947	NA
ENSG00000090238	83719	YPEL3	YPEL3	609724	P61236	NA
ENSG00000102886	79153	GDPD3	GDPD3	NA	Q7L5L3	NA
ENSG00000102882	5595	MAPK3	MAPK3	601795	P27361	DB00605:DB01169:DB02733:DB04604:DB06195:DB08862:DB13930
ENSG00000102879	11151	CORO1A	CORO1A	605000	P31146	NA
ENSG00000198064	101929910	RP11-347C12.1	NA	NA	A6NJU9	NA
ENSG00000169217	10421	CD2BP2	CD2BP2	604470	O95400	NA
ENSG00000169221	26000	TBC1D10B	TBC1D10B	613620	Q4KMP7	NA
ENSG00000180209	29895	MYLPF	MYLPF	NA	Q96A32	NA
ENSG00000180035	197407	ZNF48	ZNF48	NA	Q96MX3	NA
ENSG00000180096	1731	SEPT1	SEPT1	612897	Q8WYJ6	NA
ENSG00000270466	NA	SEPT1	NA	612897	NA	NA
ENSG00000179965	51333	ZNF771	ZNF771	NA	Q7L3S4	NA
ENSG00000179958	79077	DCTPP1	DCTPP1	NA	Q9H773	NA
ENSG00000179918	22928	SEPHS2	SEPHS2	606218	Q99611	NA
ENSG00000005844	3683	ITGAL	ITGAL	153370	P20701	DB00095:DB00098:DB00227:DB00641:DB02177:DB03932:DB04724:DB06972:DB07486:DB11611
ENSG00000169957	79724	ZNF768	ZNF768	NA	Q9H5H4	NA
ENSG00000169955	65988	ZNF747	ZNF747	NA	Q9BV97	NA
ENSG00000261459	65988	ZNF747	NA	NA	NA	NA
ENSG00000260869	NA	AC002310.13	NA	NA	NA	NA

ENSG00000169951	92595	ZNF764	ZNF764	NA	Q96H86	NA
ENSG00000229809	146542	ZNF688	ZNF688	NA	P0C7X2	NA
ENSG00000197162	146540	ZNF785	ZNF785	NA	A8K8V0	NA
ENSG00000156853	115509	ZNF689	ZNF689	NA	Q96CS4	NA
ENSG00000156858	78994	PRR14	PRR14	NA	Q9BWN1	NA
ENSG00000156860	64319	FBRS	FBRS	608601	Q9HAH7	NA
ENSG00000080603	10847	SRCAP	SRCAP	611421	Q6ZRS2	NA
ENSG00000156873	5261	PHKG2	PHKG2	172471	P15735	NA
ENSG00000196118	90835	C16orf93	C16orf93	NA	A1A4V9	NA
ENSG00000103549	9810	RNF40	RNF40	607700	O75150	NA
ENSG00000102870	23361	ZNF629	ZNF629	NA	Q9UEG4	NA
ENSG00000099385	9274	BCL7C	BCL7C	605847	Q8WUZ0	NA
ENSG00000150281	1489	CTF1	CTF1	600435	Q16619	NA
ENSG00000099364	54620	FBXL19	FBXL19	609085	Q6PCT2	NA
ENSG00000167394	79759	ZNF668	ZNF668	NA	Q96K58	NA
ENSG00000167395	9726	ZNF646	ZNF646	NA	O15015	NA

Table S9. Expression levels of the genes mapped to ascorbic acid 2 sulfate levels in different tissues using FUMA.

Category	**GeneSet**	**N_genes**	**N_overlap**	**p**	**adjP**	**genes**
DEG.up	Adipose_Tissue	1554	2	0.987456	1	ENSG00000198682:ENSG00000171862
DEG.up	Adrenal_Gland	1204	3	0.862306	1	ENSG00000198682:ENSG00000184719:ENSG00000174938
DEG.up	Bladder	728	2	0.787743	1	ENSG00000213658:ENSG00000150281
DEG.up	Blood	1477	7	0.364521	1	ENSG00000227268:ENSG00000171862:ENSG00000204020:ENSG00000185905:ENSG00000102879:ENSG00000180096:ENSG00000005844
DEG.up	Blood_Vessel	2139	5	0.935432	1	ENSG00000171862:ENSG00000213658:ENSG00000167371:ENSG00000099385:ENSG00000150281
DEG.up	Brain	2348	7	0.835363	1	ENSG00000167371:ENSG00000174938:ENSG00000174939:ENSG00000174943:ENSG00000149926:ENSG00000179965:ENSG00000099364
DEG.up	Breast	1428	2	0.980063	1	ENSG00000198682:ENSG00000156853
DEG.up	Cervix_Uteri	2514	10	0.540767	1	ENSG00000171862:ENSG00000176953:ENSG00000213658:ENSG00000167371:ENSG00000102886:ENSG00000169955:ENSG00000169951:ENSG00000197162:ENSG00000099385:ENSG00000150281
DEG.up	Colon	1107	3	0.820486	1	ENSG00000213658:ENSG00000102886:ENSG00000180035
DEG.up	Esophagus	1008	3	0.767433	1	ENSG00000149922:ENSG00000102886:ENSG00000150281
DEG.up	Fallopian_Tube	451	2	0.534382	1	ENSG00000167371:ENSG00000169592
DEG.up	Heart	458	0	1	1	
DEG.up	Kidney	963	0	1	1	
DEG.up	Liver	1090	1	0.988261	1	ENSG00000198682
DEG.up	Lung	3029	7	0.96604	1	ENSG00000198682:ENSG00000213658:ENSG00000149930:ENSG00000102879:ENSG00000180096:ENSG00000005844:ENSG00000196118
DEG.up	Muscle	879	1	0.971629	1	ENSG00000180209
DEG.up	Nerve	4157	11	0.957372	1	ENSG00000227268:ENSG00000171862:ENSG00000167371:ENSG00000174943:ENSG00000149930:ENSG00000102886:ENSG00000169955:ENSG00000169951:ENSG00000197162:ENSG00000099385:ENSG00000150281
DEG.up	Ovary	3674	9	0.967734	1	ENSG00000198682:ENSG00000167371:ENSG00000149929:ENSG00000102886:ENSG00000179965:ENSG00000169951:ENSG00000197162:ENSG00000099385:ENSG00000150281
DEG.up	Pancreas	549	0	1	1	

DEG.up	Pituitary	3253	9	0.915008	1	ENSG00000167371:ENSG00000174938:ENSG00000174939:ENSG00000174943:ENSG00000149926:ENSG00000169951:ENSG00000197162:ENSG00000156873:ENSG00000196118
DEG.up	Prostate	2019	6	0.822261	1	ENSG00000213658:ENSG00000167371:ENSG00000149922:ENSG00000197162:ENSG00000156873:ENSG00000150281
DEG.up	Salivary_Gland	1285	2	0.966664	1	ENSG00000174938:ENSG00000180209
DEG.up	Skin	2568	6	0.951033	1	ENSG00000204021:ENSG00000204020:ENSG00000183336:ENSG00000079616:ENSG00000102870:ENSG00000167394
DEG.up	Small_Intestine	1855	7	0.607129	1	ENSG00000198682:ENSG00000176953:ENSG00000213658:ENSG00000185905:ENSG00000102879:ENSG00000180096:ENSG00000005844
DEG.up	Spleen	2666	10	0.619779	1	ENSG00000176953:ENSG00000213658:ENSG00000254206:ENSG00000185905:ENSG00000149930:ENSG00000102886:ENSG00000102879:ENSG00000180096:ENSG00000005844:ENSG00000156873
DEG.up	Stomach	780	1	0.957239	1	ENSG00000174939
DEG.up	Testis	5947	27	0.219545	1	ENSG00000138138:ENSG00000227268:ENSG00000184719:ENSG00000204022:ENSG00000176953:ENSG00000254206:ENSG00000183336:ENSG00000079616:ENSG00000103495:ENSG00000174938:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149926:ENSG00000180209:ENSG00000169951:ENSG00000229809:ENSG00000156853:ENSG00000080603:ENSG00000156873:ENSG00000196118:ENSG00000103549:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.up	Thyroid	3732	13	0.737281	1	ENSG00000198682:ENSG00000184719:ENSG00000213658:ENSG00000254206:ENSG00000169203:ENSG00000079616:ENSG00000149922:ENSG00000198064:ENSG00000197162:ENSG00000080603:ENSG00000156873:ENSG00000196118:ENSG00000150281
DEG.up	Uterus	3999	20	0.143894	1	ENSG00000171862:ENSG00000184719:ENSG00000176953:ENSG00000213658:ENSG00000103495:ENSG00000167371:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000102886:ENSG00000180035:ENSG00000179965:ENSG00000169955:ENSG00000169951:ENSG00000197162:ENSG00000156853:ENSG00000080603:ENSG00000102870:ENSG00000099385:ENSG00000150281
DEG.up	Vagina	2013	5	0.910678	1	ENSG00000204021:ENSG00000167371:ENSG00000149922:ENSG00000102886:ENSG00000150281
DEG.down	Adipose_Tissue	1360	7	0.288697	1	ENSG00000185905:ENSG00000079616:ENSG00000174938:ENSG00000174939:ENSG00000180209:ENSG00000196118:ENSG00000099364
DEG.down	Adrenal_Gland	2994	9	0.856356	1	ENSG00000213658:ENSG00000079616:ENSG00000167371:ENSG00000174939:ENSG00000102886:ENSG00000180096:ENSG00000005844:ENSG00000099385:ENSG00000167395
DEG.down	Bladder	103	0	1	1	
DEG.down	Blood	5553	19	0.808737	1	ENSG00000198682:ENSG00000138138:ENSG00000184719:ENSG00000254206:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149922:ENSG00000180035:ENSG00000169957:ENSG00000169955:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000080603:ENSG00000196118:ENSG00000102870:ENSG00000099385
DEG.down	Blood_Vessel	1485	3	0.939585	1	ENSG00000174938:ENSG00000005844:ENSG00000196118
DEG.down	Brain	4950	21	0.390874	1	ENSG00000198682:ENSG00000171862:ENSG00000184719:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000079616:ENSG00000013364:ENSG00000169592:ENSG00000149923:ENSG00000149922:ENSG00000102886:ENSG00000180096:ENSG00000005844:ENSG00000169951:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000099385:ENSG00000150281:ENSG00000167395
DEG.down	Breast	912	3	0.704794	1	ENSG00000174939:ENSG00000180209:ENSG00000005844
DEG.down	Cervix_Uteri	44	0	1	1	
DEG.down	Colon	1245	3	0.877297	1	ENSG00000174938:ENSG00000174939:ENSG00000196118
DEG.down	Esophagus	1465	6	0.524048	1	ENSG00000174938:ENSG00000102879:ENSG00000180209:ENSG00000180096:ENSG00000005844:ENSG00000196118
DEG.down	Fallopian_Tube	1	0	1	1	
DEG.down	Heart	8251	37	0.172925	1	ENSG00000198682:ENSG00000171862:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174938:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149923:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000169217:ENSG00000169221:ENSG00000180035:ENSG00000180096:ENSG00000179965:ENSG0000017991

						8:ENSG00000005844:ENSG00000169955:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000156873:ENSG00000103549:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.down	Kidney	4932	16	0.854994	1	ENSG00000138138:ENSG00000171862:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000102882:ENSG00000102879:ENSG00000169221:ENSG00000156853:ENSG00000080603:ENSG00000103549:ENSG00000167394:ENSG00000167395
DEG.down	Liver	7196	36	0.043209	1	ENSG00000138138:ENSG00000171862:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000183336:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000090238:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000169217:ENSG00000169221:ENSG00000180035:ENSG00000180096:ENSG00000179958:ENSG00000169957:ENSG00000169955:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000103549:ENSG00000102870:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.down	Lung	820	3	0.633779	1	ENSG00000174939:ENSG00000180209:ENSG00000179965
DEG.down	Muscle	6093	30	0.086457	1	ENSG00000198682:ENSG00000171862:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000079616:ENSG00000167371:ENSG00000013364:ENSG00000103502:ENSG00000174943:ENSG00000149930:ENSG00000169592:ENSG00000149926:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000180035:ENSG00000169951:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000156873:ENSG00000103549:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.down	Nerve	784	3	0.603059	1	ENSG00000174938:ENSG00000174939:ENSG00000005844
DEG.down	Ovary	1429	3	0.928377	1	ENSG00000102879:ENSG00000180209:ENSG00000005844
DEG.down	Pancreas	8671	43	0.024084	0.72253	ENSG00000138138:ENSG00000171862:ENSG00000184719:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000183336:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174939:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149923:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000169217:ENSG00000169221:ENSG00000180035:ENSG00000179965:ENSG00000179958:ENSG00000179918:ENSG00000169957:ENSG00000169955:ENSG00000169951:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000156873:ENSG00000196118:ENSG00000103549:ENSG00000102870:ENSG00000099385:ENSG00000150281:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.down	Pituitary	1752	3	0.974106	1	ENSG00000198682:ENSG00000180096:ENSG00000179958
DEG.down	Prostate	698	1	0.940041	1	ENSG00000174939
DEG.down	Salivary_Gland	1666	5	0.798349	1	ENSG00000171862:ENSG00000213658:ENSG00000185905:ENSG00000167371:ENSG00000179965
DEG.down	Skin	1775	9	0.2639	1	ENSG00000213658:ENSG00000167371:ENSG00000174939:ENSG00000102879:ENSG00000180209:ENSG00000180096:ENSG00000005844:ENSG00000196118:ENSG00000150281
DEG.down	Small_Intestine	1257	1	0.994207	1	ENSG00000174939
DEG.down	Spleen	1930	5	0.890271	1	ENSG00000138138:ENSG00000167371:ENSG00000174938:ENSG00000179965:ENSG00000150281
DEG.down	Stomach	2290	7	0.815251	1	ENSG00000198682:ENSG00000185905:ENSG00000079616:ENSG00000167371:ENSG00000174943:ENSG00000005844:ENSG00000196118
DEG.down	Testis	2599	6	0.954829	1	ENSG00000198682:ENSG00000213658:ENSG00000102886:ENSG00000102879:ENSG00000180096:ENSG00000005844
DEG.down	Thyroid	976	1	0.981064	1	ENSG00000174938
DEG.down	Uterus	788	0	1	1	
DEG.down	Vagina	598	2	0.688267	1	ENSG00000174938:ENSG00000174939
DEG.twoside	Adipose_Tissue	2914	9	0.833021	1	ENSG00000198682:ENSG00000171862:ENSG00000185905:ENSG00000079616:ENSG00000174938:ENSG00000174939:ENSG00000180209:ENSG00000196118:ENSG00000099364
DEG.twoside	Adrenal_Gland	4198	12	0.927134	1	ENSG00000198682:ENSG00000184719:ENSG00000213658:ENSG00000079616:ENSG00000167371:ENSG00000174938:ENSG00000174939:ENSG00000102886:ENSG00000180096:ENSG00000005844:ENSG00000099385:ENSG00000167395

DEG.twoside	Bladder	831	2	0.845879	1	ENSG00000213658:ENSG00000150281
DEG.twoside	Blood	7030	26	0.704631	1	ENSG00000198682:ENSG00000138138:ENSG00000227268:ENSG00000171862:ENSG00000184719:ENSG00000204020:ENSG00000254206:ENSG00000185905:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149922:ENSG00000102879:ENSG00000180035:ENSG00000180096:ENSG00000005844:ENSG00000169957:ENSG00000169955:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000080603:ENSG00000196118:ENSG00000102870:ENSG00000099385
DEG.twoside	Blood_Vessel	3624	8	0.983691	1	ENSG00000171862:ENSG00000213658:ENSG00000167371:ENSG00000174938:ENSG00000005844:ENSG00000196118:ENSG00000099385:ENSG00000150281
DEG.twoside	Brain	7298	28	0.620016	1	ENSG00000198682:ENSG00000171862:ENSG00000184719:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000079616:ENSG00000167371:ENSG00000013364:ENSG00000174938:ENSG00000174939:ENSG00000174943:ENSG00000169592:ENSG00000149926:ENSG00000149923:ENSG00000149922:ENSG00000102886:ENSG00000180096:ENSG00000179965:ENSG00000005844:ENSG00000169951:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000099385:ENSG00000150281:ENSG00000099364:ENSG00000167395
DEG.twoside	Breast	2340	5	0.962606	1	ENSG00000198682:ENSG00000174939:ENSG00000180209:ENSG00000005844:ENSG00000156853
DEG.twoside	Cervix_Uteri	2558	10	0.56422	1	ENSG00000171862:ENSG00000176953:ENSG00000213658:ENSG00000167371:ENSG00000102886:ENSG00000169955:ENSG00000169951:ENSG00000197162:ENSG00000099385:ENSG00000150281
DEG.twoside	Colon	2352	6	0.915987	1	ENSG00000213658:ENSG00000174938:ENSG00000174939:ENSG00000102886:ENSG00000180035:ENSG00000196118
DEG.twoside	Esophagus	2473	9	0.654964	1	ENSG00000174938:ENSG00000149922:ENSG00000102886:ENSG00000102879:ENSG00000180209:ENSG00000180096:ENSG00000005844:ENSG00000196118:ENSG00000150281
DEG.twoside	Fallopian_Tube	452	2	0.535584	1	ENSG00000167371:ENSG00000169592
DEG.twoside	Heart	8709	37	0.304954	1	ENSG00000198682:ENSG00000171862:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174938:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149923:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000169217:ENSG00000169221:ENSG00000180035:ENSG00000180096:ENSG00000179965:ENSG00000179918:ENSG00000005844:ENSG00000169955:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000156873:ENSG00000103549:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.twoside	Kidney	5895	16	0.978242	1	ENSG00000138138:ENSG00000171862:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000102882:ENSG00000102879:ENSG00000169221:ENSG00000156853:ENSG00000080603:ENSG00000103549:ENSG00000167394:ENSG00000167395
DEG.twoside	Liver	8286	37	0.181532	1	ENSG00000198682:ENSG00000138138:ENSG00000171862:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000183336:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000090238:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000169217:ENSG00000169221:ENSG00000180035:ENSG00000180096:ENSG00000179958:ENSG00000169957:ENSG00000169955:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000103549:ENSG00000102870:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.twoside	Lung	3849	10	0.956261	1	ENSG00000198682:ENSG00000213658:ENSG00000174939:ENSG00000149930:ENSG00000102879:ENSG00000180209:ENSG00000180096:ENSG00000179965:ENSG00000005844:ENSG00000196118
DEG.twoside	Muscle	6972	31	0.231199	1	ENSG00000198682:ENSG00000171862:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000079616:ENSG00000167371:ENSG00000013364:ENSG00000103502:ENSG00000174943:ENSG00000149930:ENSG00000169592:ENSG00000149926:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000180209:ENSG00000180035:ENSG00000169951:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000156873:ENSG00000103549:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.twoside	Nerve	4941	14	0.948972	1	ENSG00000227268:ENSG00000171862:ENSG00000167371:ENSG00000174938:ENSG00000174939:ENSG00000174943:ENSG00000149930:ENSG00000102886:ENSG00000005844:ENSG00000169955:ENSG00000169951:ENSG00000197162:ENSG00000099385:ENSG00000150281

DEG.twoside	Ovary	5103	12	0.991428	1	ENSG00000198682:ENSG00000167371:ENSG00000149929:ENSG00000102886:ENSG00000102879:ENSG00000180209:ENSG00000179965:ENSG00000005844:ENSG00000169951:ENSG00000197162:ENSG00000099385:ENSG00000150281
DEG.twoside	Pancreas	9220	43	0.072088	1	ENSG00000138138:ENSG00000171862:ENSG00000184719:ENSG00000176953:ENSG00000169682:ENSG00000213658:ENSG00000183336:ENSG00000079616:ENSG00000103495:ENSG00000167371:ENSG00000174939:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149923:ENSG00000102886:ENSG00000102882:ENSG00000102879:ENSG00000169217:ENSG00000169221:ENSG00000180035:ENSG00000179965:ENSG00000179958:ENSG00000179918:ENSG00000169957:ENSG00000169955:ENSG00000169951:ENSG00000229809:ENSG00000197162:ENSG00000156853:ENSG00000156858:ENSG00000156860:ENSG00000080603:ENSG00000156873:ENSG00000196118:ENSG00000103549:ENSG00000102870:ENSG00000099385:ENSG00000150281:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.twoside	Pituitary	5005	12	0.988883	1	ENSG00000198682:ENSG00000167371:ENSG00000174938:ENSG00000174939:ENSG00000174943:ENSG00000149926:ENSG00000180096:ENSG00000179958:ENSG00000169951:ENSG00000197162:ENSG00000156873:ENSG00000196118
DEG.twoside	Prostate	2717	7	0.926478	1	ENSG00000213658:ENSG00000167371:ENSG00000174939:ENSG00000149922:ENSG00000197162:ENSG00000156873:ENSG00000150281
DEG.twoside	Salivary_Gland	2951	7	0.958503	1	ENSG00000171862:ENSG00000213658:ENSG00000185905:ENSG00000167371:ENSG00000174938:ENSG00000180209:ENSG00000179965
DEG.twoside	Skin	4343	15	0.764345	1	ENSG00000204021:ENSG00000204020:ENSG00000213658:ENSG00000183336:ENSG00000079616:ENSG00000167371:ENSG00000174939:ENSG00000102879:ENSG00000180209:ENSG00000180096:ENSG00000005844:ENSG00000196118:ENSG00000102870:ENSG00000150281:ENSG00000167394
DEG.twoside	Small_Intestine	3112	8	0.940343	1	ENSG00000198682:ENSG00000176953:ENSG00000213658:ENSG00000185905:ENSG00000174939:ENSG00000102879:ENSG00000180096:ENSG00000005844
DEG.twoside	Spleen	4596	15	0.839028	1	ENSG00000138138:ENSG00000176953:ENSG00000213658:ENSG00000254206:ENSG00000185905:ENSG00000167371:ENSG00000174938:ENSG00000149930:ENSG00000102886:ENSG00000102879:ENSG00000180096:ENSG00000179965:ENSG00000005844:ENSG00000156873:ENSG00000150281
DEG.twoside	Stomach	3070	8	0.934244	1	ENSG00000198682:ENSG00000185905:ENSG00000079616:ENSG00000167371:ENSG00000174939:ENSG00000174943:ENSG00000005844:ENSG00000196118
DEG.twoside	Testis	8546	33	0.612999	1	ENSG00000198682:ENSG00000138138:ENSG00000227268:ENSG00000184719:ENSG00000204022:ENSG00000176953:ENSG00000213658:ENSG00000254206:ENSG00000183336:ENSG00000079616:ENSG00000103495:ENSG00000174938:ENSG00000174943:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000149926:ENSG00000102886:ENSG00000102879:ENSG00000180209:ENSG00000180096:ENSG00000005844:ENSG00000169951:ENSG00000229809:ENSG00000156853:ENSG00000080603:ENSG00000156873:ENSG00000196118:ENSG00000103549:ENSG00000099385:ENSG00000099364:ENSG00000167394:ENSG00000167395
DEG.twoside	Thyroid	4708	14	0.918612	1	ENSG00000198682:ENSG00000184719:ENSG00000213658:ENSG00000254206:ENSG00000169203:ENSG00000079616:ENSG00000174938:ENSG00000149922:ENSG00000198064:ENSG00000197162:ENSG00000080603:ENSG00000156873:ENSG00000196118:ENSG00000150281
DEG.twoside	Uterus	4787	20	0.426372	1	ENSG00000171862:ENSG00000184719:ENSG00000176953:ENSG00000213658:ENSG00000103495:ENSG00000167371:ENSG00000149930:ENSG00000149929:ENSG00000169592:ENSG00000102886:ENSG00000180035:ENSG00000179965:ENSG00000169955:ENSG00000169951:ENSG00000197162:ENSG00000156853:ENSG00000080603:ENSG00000102870:ENSG00000099385:ENSG00000150281
DEG.twoside	Vagina	2611	7	0.906159	1	ENSG00000204021:ENSG00000167371:ENSG00000174938:ENSG00000174939:ENSG00000149922:ENSG00000102886:ENSG00000150281

Table S10. Functional gene sets related to the genes mapped to ascorbic acid 2 sulfate levels using FUMA.

Category	GeneSet	N_genes	N_overlap	p	adjP	genes	link
Curated_gene_sets	WP_16P112_PROXIMAL_DELETION_SYNDROME	66	20	1.03E-34	6.7E-31	PTEN:KIF22:MAZ:PRRT2:PAGR1:PAGR1:MVP:CDIPT:SEZ6L2:ASPHD1:KCTD13:TAOK2:HIRIP3:INO80E:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:CORO1A	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_16P112_PROXIMAL_DELETION_SYNDROME
Curated_gene_sets	WP_16P112_DISTAL_DELETION_SYNDROME	30	4	3.47E-06	0.011277	ATXN2L:NFATC2IP:SPNS1:LAT	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_16P112_DISTAL_DELETION_SYNDROME
Canonical_Pathways	WP_16P112_PROXIMAL_DELETION_SYNDROME	66	20	1.03E-34	3.19E-31	PTEN:KIF22:MAZ:PRRT2:PAGR1:PAGR1:MVP:CDIPT:SEZ6L2:ASPHD1:KCTD13:TAOK2:HIRIP3:INO80E:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:CORO1A	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_16P112_PROXIMAL_DELETION_SYNDROME
Canonical_Pathways	WP_16P112_DISTAL_DELETION_SYNDROME	30	4	3.47E-06	0.005365	ATXN2L:NFATC2IP:SPNS1:LAT	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_16P112_DISTAL_DELETION_SYNDROME
TF_targets	FXR1_TARGET_GENES	1036	18	9.44E-09	1.05E-05	PTEN:ATXN2L:MAZ:MVP:SEZ6L2:ASPHD1:TAOK2:INO80E:ALDOA:PPP4C:TBX6:SEPT1:ZNF768:ZNF764:FBRS:SRCAP:C16orf93:RNF40	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/FXR1_TARGET_GENES
TF_targets	VDR_Q3	226	7	1.36E-05	0.006691	MAZ:PRRT2:PAGR1:PAGR1:TAOK2:ZNF688:FBRS:FBXL19	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/VDR_Q3
TF_targets	TEL2_Q6	236	7	1.8E-05	0.006691	HIRIP3:INO80E:PPP4C:CD2BP2:ZNF768:ZNF668:ZNF646	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/TEL2_Q6
TF_targets	ELF2_TARGET_GENES	1296	14	0.000125	0.025611	ATXN2L:NFATC2IP:SPNS1:CDIPT:PPP4C:CD2BP2:ZNF48:SEPT1:ZNF747:ZNF747:ZNF688:ZNF689:PRR14:FBRS:PHKG2	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/ELF2_TARGET_GENES
TF_targets	SALL4_TARGET_GENES	1497	15	0.000158	0.025611	KLLN:PTEN:ATXN2L:NFATC2IP:MAZ:KCTD13:TAOK2:TBC1D10B:MYLPF:ZNF764:ZNF689:C16orf93:RNF40:BCL7C:FBXL19	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/SALL4_TARGET_GENES
TF_targets	ZF5_B	235	6	0.000169	0.025611	MAZ:TAOK2:PRR14:FBXL19:ZNF668:ZNF646	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/ZF5_B
TF_targets	SP1_Q6_01	239	6	0.000185	0.025611	MAZ:ASPHD1:TAOK2:ZNF48:ZNF768:BCL7C	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/SP1_Q6_01
TF_targets	YY1_01	242	6	0.000198	0.025611	TAOK2:YPEL3:ZNF747:ZNF747:ZNF688:ZNF668:ZNF646	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/YY1_01
TF_targets	SF1_Q6	244	6	0.000207	0.025611	TAOK2:ALDOA:TBX6:ZNF768:FBRS:FBXL19	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/SF1_Q6
TF_targets	DLX6_TARGET_GENES	472	8	0.00023	0.025611	ATXN2L:HIRIP3:INO80E:TBX6:MYLPF:ZNF48:SEPHS2:FBXL19	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/DLX6_TARGET_GENES

Wikipathways	WP_16P112_PROXIMAL_DELETION_SYNDROME	66	20	1.03E-34	7.56E-32	PTEN:KIF22:MAZ:PRRT2:PAGR1:PAGR1:MVP:CDIPT:SEZ6L2:ASPHD1:KCTD13:TAOK2:HIRIP3:INO80E:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:CORO1A	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_16P112_PROXIMAL_DELETION_SYNDROME
Wikipathways	WP_16P112_DISTAL_DELETION_SYNDROME	30	4	3.47E-06	0.001273	ATXN2L:NFATC2IP:SPNS1:LAT	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_16P112_DISTAL_DELETION_SYNDROME
GWAScatalog	Body fat distribution (arm fat ratio)	104	13	3.1E-17	1.37E-13	ATXN2L:SEZ6L2:ASPHD1:KCTD13:TAOK2:HIRIP3:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:ZNF668:ZNF646	
GWAScatalog	Immunoglobulin light chain (AL) amyloidosis	12	5	3.46E-10	7.65E-07	PRR14:FBRS:SRCAP:RNF40:BCL7C	
GWAScatalog	Brain morphology (MOSTest)	1049	19	1.65E-09	2.43E-06	ATXN2L:RP11-345J4.5:BOLA2:SLX1B:ASPHD1:KCTD13:TAOK2:HIRIP3:INO80E:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:CORO1A:BOLA2B:CD2BP2:TBC1D10B:ZNF48	
GWAScatalog	Autism spectrum disorder or schizophrenia	355	12	3.14E-09	3.48E-06	SEZ6L2:ASPHD1:KCTD13:TAOK2:HIRIP3:INO80E:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3	
GWAScatalog	Schizophrenia	613	12	1.2E-06	0.001062	SEZ6L2:ASPHD1:KCTD13:TAOK2:HIRIP3:INO80E:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3	
GWAScatalog	Chronic obstructive pulmonary disease or high blood pressure (pleiotropy)	63	5	2.68E-06	0.001973	TAOK2:HIRIP3:INO80E:ALDOA:PPP4C	
GWAScatalog	Educational attainment	59	4	5.34E-05	0.033788	ATXN2L:NFATC2IP:SPNS1:LAT	
Positional_gene_sets	chr16p11	97	54	4.1E-120	1.2E-117	ATXN2L:NFATC2IP:SPNS1:LAT:NPIPB11:RP11-345J4.5:BOLA2:SLX1B:KIF22:MAZ:PRRT2:PAGR1:PAGR1:MVP:CDIPT:SEZ6L2:ASPHD1:KCTD13:TAOK2:HIRIP3:INO80E:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:CORO1A:BOLA2B:CD2BP2:TBC1D10B:MYLPF:ZNF48:SEPT1:ZNF771:DCTPP1:SEPHS2:ITGAL:ZNF768:ZNF747:ZNF747:ZNF764:ZNF688:ZNF785:ZNF689:PRR14:FBRS:SRCAP:PHKG2:C16orf93:RNF40:ZNF629:BCL7C:CTF1:FBXL19:ZNF668:ZNF646	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/chr16p11
Positional_gene_sets	chr10q23	84	8	5.03E-10	7.54E-08	PAPSS2:ATAD1:KLLN:PTEN:RNLS:LIPJ:LIPK:LIPN	http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/chr10q23

Table S11. List of lead variants of O-methylascorbate gene-sex GWAS provided by FUMA.

No	GenomicLocus	uniqID	rsID	chr	pos	p	nIndSigSNPs	IndSigSNPs
1	1	1:187728031:C:T	rs561458908	1	1.88E+08	9.61E-06	1	rs561458908
2	2	1:230328333:C:T	rs6673444	1	2.3E+08	9.86E-06	1	rs6673444

3	3	1:239273587:A:G	rs74527587	1	2.39E+08	9.91E-06	1	rs74527587
4	4	2:23594564:A:C	rs13427429	2	23594564	2.58E-06	1	rs13427429
5	5	2:182589426:A:G	rs183979544	2	1.83E+08	8.81E-07	1	rs183979544
6	6	3:42207505:G:T	rs6775014	3	42207505	9.86E-06	1	rs6775014
7	7	3:149237893:A:G	rs139707525	3	1.49E+08	5.15E-06	1	rs139707525
8	8	4:114016267:C:T	rs74597555	4	1.14E+08	8.44E-07	1	rs74597555
9	9	5:174547422:A:G	rs2656901	5	1.75E+08	9.06E-06	1	rs2656901
10	10	6:161138848:C:G	rs783146	6	1.61E+08	8.1E-06	1	rs783146
11	11	6:166997459:G:T	rs3823198	6	1.67E+08	4.6E-06	1	rs3823198
12	12	7:53779469:A:G	rs11764886	7	53779469	6.43E-06	1	rs11764886
13	13	7:129922498:C:T	rs6952090	7	1.3E+08	3.59E-07	1	rs6952090
14	14	8:136945991:A:T	rs2922384	8	1.37E+08	5.08E-07	2	rs2922384;rs67358231
15	15	9:37450619:A:T	rs116934390	9	37450619	4.33E-07	1	rs116934390
16	16	10:98007727:A:G	rs10882762	10	98007727	3.07E-06	1	rs10882762
17	17	11:12039830:G:T	rs79414703	11	12039830	2.93E-06	1	rs79414703
18	18	11:17650058:C:T	rs79157408	11	17650058	8.56E-06	1	rs79157408
19	19	11:94936720:C:T	rs80136724	11	94936720	4.53E-06	1	rs80136724
20	20	13:98464323:A:G	rs7331036	13	98464323	7.38E-06	1	rs7331036
21	21	14:30662307:C:T	rs75638828	14	30662307	1.85E-06	1	rs75638828
22	22	17:50029236:A:C	rs74665914	17	50029236	9.33E-06	1	rs74665914
23	23	19:58562357:C:T	rs76958646	19	58562357	8E-06	1	rs76958646
24	24	20:1367375:C:G	rs6041909	20	1367375	6.03E-06	1	rs6041909

Table S12. List of lead variants of ascorbic acid 2 sulfate gene-sex GWAS provided by FUMA.

No	GenomicLocus	uniqID	rsID	chr	pos	p	nIndSigSNPs	IndSigSNPs
1	1	2:101858025:C:T	rs1192803	2	1.02E+08	6.29E-06	1	rs1192803
2	2	2:169526684:C:T	rs142867333	2	1.7E+08	1.7E-06	1	rs142867333
3	3	2:170626038:C:T	rs12692923	2	1.71E+08	9.45E-06	1	rs12692923
4	4	5:31170385:C:T	rs7720392	5	31170385	8.03E-06	1	rs7720392
5	5	5:65990897:C:T	rs114959781	5	65990897	8.76E-06	1	rs114959781
6	6	5:83914674:G:T	rs28579435	5	83914674	9.58E-06	1	rs28579435
7	7	5:176281169:C:G	rs4976655	5	1.76E+08	5.23E-06	1	rs4976655
8	8	6:165052620:A:G	rs13204324	6	1.65E+08	7.83E-06	1	rs13204324
9	9	8:103952406:C:G	rs62526542	8	1.04E+08	3.03E-06	1	rs62526542
10	10	8:134488549:C:T	rs1048471	8	1.34E+08	5.64E-06	1	rs1048471
11	11	9:20281436:C:T	rs11792574	9	20281436	7.38E-06	1	rs11792574
12	12	9:85884154:A:T	rs117196678	9	85884154	8.81E-06	1	rs117196678
13	13	10:54457712:C:T	rs117271698	10	54457712	1.01E-06	1	rs117271698
14	14	12:69519318:C:T	rs117414281	12	69519318	2.03E-07	1	rs117414281
15	15	12:76694251:G:T	rs10859572	12	76694251	2.31E-07	1	rs10859572
16	16	13:19652501:G:T	rs10162161	13	19652501	2.34E-06	1	rs10162161
17	17	14:44273286:A:G	rs76250049	14	44273286	1.59E-06	1	rs76250049
18	18	16:67561671:A:G	rs35031569	16	67561671	7.65E-06	1	rs35031569
19	19	16:70006493:A:G	rs148001569	16	70006493	9.92E-06	1	rs148001569
20	20	17:53451739:A:G	rs4334353	17	53451739	3.79E-07	2	rs4334353;rs7212518

21	21	19:51534020:C:T	rs75565227	19	51534020	1.13E-06	1	rs75565227
22	22	22:32653715:C:T	rs9609471	22	32653715	1.93E-06	2	rs9609471;rs8137034

Table S13. List of Mapped Genes to O-methylascorbate gene-sex interaction regions using FUMA.

ensg	entrezID	symbol	hgnc_symbol	OMIM	uniprotID	DrugBank
ENSG00000221900	285877	POM121L12	POM121L12	NA	Q8N7R1	NA
ENSG00000170419	222008	VSTM2A	VSTM2A	NA	Q8TAG5	NA
ENSG00000132432	23480	SEC61G	SEC61G	609215	P60059	NA
ENSG00000091732	51530	ZC3HC1	ZC3HC1	NA	Q86WB0	NA
ENSG00000128607	23008	KLHDC10	KLHDC10	615152	Q6PID8	NA
ENSG00000146842	84928	TMEM209	TMEM209	NA	Q96SK2	NA
ENSG00000165120	136263	SSMEM1	SSMEM1	NA	Q8WWF3	NA
ENSG00000158516	1358	CPA2	CPA2	600688	P48052	NA
ENSG00000128510	51200	CPA4	CPA4	607635	Q9UI42	NA
ENSG00000158525	93979	CPA5	CPA5	609561	Q8WXQ8	NA
ENSG00000091704	1357	CPA1	CPA1	114850	P15085	DB02494:DB02652:DB03012:DB03201:DB03441:DB04058:DB04316:DB06924:DB07351:DB07484:DB07506:DB08368:DB08762
ENSG00000106477	95681	CEP41	CEP41	610523	Q9BYV8	NA
ENSG00000106484	4232	MEST	MEST	601029	Q5EB52	NA
ENSG00000158623	26958	COPG2	COPG2	604355	NA	NA
ENSG00000213265	114960	TSGA13	TSGA13	NA	Q96PP4	NA
ENSG00000174595	136259	KLF14	KLF14	609393	Q8TD94	NA
ENSG00000066827	57623	ZFAT	ZFAT	610931	Q9P243	NA
ENSG00000131773	10656	KHDRBS3	KHDRBS3	610421	O75525	NA
ENSG00000125249	5911	RAP2A	RAP2A	179540	P10114	DB04137:DB04315
ENSG00000176165	2290	FOXG1	FOXG1	164874	P55316	NA
ENSG00000186960	NA	C14orf23	C14orf23	NA	Q86U37	NA
ENSG00000141200	84643	KIF2B	KIF2B	615142	Q8N4N8	NA
ENSG00000141198	10040	TOM1L1	TOM1L1	604701	O75674	NA

Table S14. Expression levels of the genes mapped to O-methylascorbate gene-sex interaction regions in different tissues using FUMA.

Category	GeneSet	N_genes	N_overlap	p	adjP	genes
DEG.up	Adipose_Tissue	1554	1	0.874863	1	ENSG00000106484
DEG.up	Adrenal_Gland	1204	3	0.196582	1	ENSG00000146842:ENSG00000106484:ENSG00000158623
DEG.up	Bladder	728	0	1	1	
DEG.up	Blood	1477	0	1	1	
DEG.up	Blood_Vessel	2139	3	0.52597	1	ENSG00000131773:ENSG00000125249:ENSG00000141198
DEG.up	Brain	2348	5	0.172308	1	ENSG00000170419:ENSG00000131773:ENSG00000125249:ENSG00000176165:ENSG00000186960
DEG.up	Breast	1428	1	0.850829	1	ENSG00000106484

DEG.up	Cervix_Uteri	2514	1	0.968662	1	ENSG00000158623
DEG.up	Colon	1107	0	1	1	
DEG.up	Esophagus	1008	1	0.734604	1	ENSG00000128510
DEG.up	Fallopian_Tube	451	0	1	1	
DEG.up	Heart	458	0	1	1	
DEG.up	Kidney	963	1	0.717944	1	ENSG00000141198
DEG.up	Liver	1090	0	1	1	
DEG.up	Lung	3029	1	0.985614	1	ENSG00000106484
DEG.up	Muscle	879	1	0.684134	1	ENSG00000091732
DEG.up	Nerve	4157	4	0.812832	1	ENSG00000146842:ENSG00000106484:ENSG00000131773:ENSG00000125249
DEG.up	Ovary	3674	2	0.963941	1	ENSG00000106484:ENSG00000158623
DEG.up	Pancreas	549	3	0.031774	0.953216	ENSG00000158516:ENSG00000128510:ENSG00000091704
DEG.up	Pituitary	3253	4	0.618582	1	ENSG00000128607:ENSG00000106477:ENSG00000106484:ENSG00000176165
DEG.up	Prostate	2019	1	0.935339	1	ENSG00000141198
DEG.up	Salivary_Gland	1285	2	0.496279	1	ENSG00000106477:ENSG00000141198
DEG.up	Skin	2568	2	0.860229	1	ENSG00000128510:ENSG00000158623
DEG.up	Small_Intestine	1855	0	1	1	
DEG.up	Spleen	2666	3	0.683487	1	ENSG00000091732:ENSG00000091704:ENSG00000106484
DEG.up	Stomach	780	2	0.262978	1	ENSG00000158516:ENSG00000141198
DEG.up	Testis	5947	18	1.13E-05	0.000338	ENSG00000221900:ENSG00000091732:ENSG00000128607:ENSG00000146842:ENSG00000165120:ENSG00000158516:ENSG00000158525:ENSG00000091704:ENSG00000106477:ENSG00000106484:ENSG00000158623:ENSG00000213265:ENSG00000066827:ENSG00000131773:ENSG00000176165:ENSG00000186960:ENSG00000141200:ENSG00000141198
DEG.up	Thyroid	3732	2	0.966597	1	ENSG00000146842:ENSG00000141198
DEG.up	Uterus	3999	2	0.976671	1	ENSG00000091732:ENSG00000158623
DEG.up	Vagina	2013	1	0.934778	1	ENSG00000128510
DEG.down	Adipose_Tissue	1360	1	0.836083	1	ENSG00000141198
DEG.down	Adrenal_Gland	2994	3	0.761707	1	ENSG00000066827:ENSG00000131773:ENSG00000125249
DEG.down	Bladder	103	0	1	1	
DEG.down	Blood	5553	7	0.595222	1	ENSG00000091732:ENSG00000128607:ENSG00000091704:ENSG00000106477:ENSG00000106484:ENSG00000158623:ENSG00000125249
DEG.down	Blood_Vessel	1485	2	0.57679	1	ENSG00000158516:ENSG00000106484
DEG.down	Brain	4950	6	0.638196	1	ENSG00000091732:ENSG00000158516:ENSG00000091704:ENSG00000106484:ENSG00000066827:ENSG00000141198
DEG.down	Breast	912	0	1	1	
DEG.down	Cervix_Uteri	44	0	1	1	
DEG.down	Colon	1245	0	1	1	
DEG.down	Esophagus	1465	4	0.112162	1	ENSG00000158516:ENSG00000106477:ENSG00000106484:ENSG00000176165
DEG.down	Fallopian_Tube	1	0	1	1	
DEG.down	Heart	8251	9	0.803326	1	ENSG00000128607:ENSG00000146842:ENSG00000091704:ENSG00000106484:ENSG00000158623:ENSG00000066827:ENSG00000131773:ENSG00000125249:ENSG00000141198
DEG.down	Kidney	4932	5	0.797312	1	ENSG00000146842:ENSG00000158516:ENSG00000106477:ENSG00000158623:ENSG00000125249
DEG.down	Liver	7196	5	0.981016	1	ENSG00000146842:ENSG00000158623:ENSG00000066827:ENSG00000131773:ENSG00000125249
DEG.down	Lung	820	1	0.658104	1	ENSG00000158516
DEG.down	Muscle	6093	4	0.976528	1	ENSG00000146842:ENSG00000091704:ENSG00000106484:ENSG00000125249
DEG.down	Nerve	784	2	0.264902	1	ENSG00000158516:ENSG00000141198
DEG.down	Ovary	1429	3	0.274233	1	ENSG00000131773:ENSG00000176165:ENSG00000141198

DEG.down	Pancreas	8671	7	0.973795	1	ENSG00000091732:ENSG00000128607:ENSG00000146842:ENSG00000158623:ENSG00000066827:ENSG00000131773:ENSG00000125249
DEG.down	Pituitary	1752	1	0.905313	1	ENSG00000128510
DEG.down	Prostate	698	1	0.597622	1	ENSG00000125249
DEG.down	Salivary_Gland	1666	1	0.893078	1	ENSG00000125249
DEG.down	Skin	1775	3	0.399196	1	ENSG00000158516:ENSG00000106484:ENSG00000131773
DEG.down	Small_Intestine	1257	1	0.811064	1	ENSG00000131773
DEG.down	Spleen	1930	1	0.926521	1	ENSG00000131773
DEG.down	Stomach	2290	5	0.159825	1	ENSG00000106477:ENSG00000106484:ENSG00000158623:ENSG00000131773:ENSG00000125249
DEG.down	Testis	2599	1	0.972391	1	ENSG00000125249
DEG.down	Thyroid	976	2	0.356877	1	ENSG00000158516:ENSG00000131773
DEG.down	Uterus	788	1	0.643141	1	ENSG00000131773
DEG.down	Vagina	598	1	0.540542	1	ENSG00000106484
DEG.twoside	Adipose_Tissue	2914	2	0.906495	1	ENSG00000106484:ENSG00000141198
DEG.twoside	Adrenal_Gland	4198	6	0.45584	1	ENSG00000146842:ENSG00000106484:ENSG00000158623:ENSG00000066827:ENSG00000131773:ENSG00000125249
DEG.twoside	Bladder	831	0	1	1	
DEG.twoside	Blood	7030	7	0.856571	1	ENSG00000091732:ENSG00000128607:ENSG00000091704:ENSG00000106477:ENSG00000106484:ENSG00000158623:ENSG00000125249
DEG.twoside	Blood_Vessel	3624	5	0.505961	1	ENSG00000158516:ENSG00000106484:ENSG00000131773:ENSG00000125249:ENSG00000141198
DEG.twoside	Brain	7298	11	0.305948	1	ENSG00000170419:ENSG00000091732:ENSG00000158516:ENSG00000091704:ENSG00000106484:ENSG00000066827:ENSG00000131773:ENSG00000125249:ENSG00000176165:ENSG00000186960:ENSG00000141198
DEG.twoside	Breast	2340	1	0.95947	1	ENSG00000106484
DEG.twoside	Cervix_Uteri	2558	1	0.970649	1	ENSG00000158623
DEG.twoside	Colon	2352	0	1	1	
DEG.twoside	Esophagus	2473	5	0.200567	1	ENSG00000158516:ENSG00000128510:ENSG00000106477:ENSG00000106484:ENSG00000176165
DEG.twoside	Fallopian_Tube	452	0	1	1	
DEG.twoside	Heart	8709	9	0.864145	1	ENSG00000128607:ENSG00000146842:ENSG00000091704:ENSG00000106484:ENSG00000158623:ENSG00000066827:ENSG00000131773:ENSG00000125249:ENSG00000141198
DEG.twoside	Kidney	5895	6	0.815614	1	ENSG00000146842:ENSG00000158516:ENSG00000106477:ENSG00000158623:ENSG00000125249:ENSG00000141198
DEG.twoside	Liver	8286	5	0.995893	1	ENSG00000146842:ENSG00000158623:ENSG00000066827:ENSG00000131773:ENSG00000125249
DEG.twoside	Lung	3849	2	0.971419	1	ENSG00000158516:ENSG00000106484
DEG.twoside	Muscle	6972	5	0.97484	1	ENSG00000091732:ENSG00000146842:ENSG00000091704:ENSG00000106484:ENSG00000125249
DEG.twoside	Nerve	4941	6	0.636181	1	ENSG00000146842:ENSG00000158516:ENSG00000106484:ENSG00000131773:ENSG00000125249:ENSG00000141198
DEG.twoside	Ovary	5103	5	0.824225	1	ENSG00000106484:ENSG00000158623:ENSG00000131773:ENSG00000176165:ENSG00000141198
DEG.twoside	Pancreas	9220	10	0.829621	1	ENSG00000091732:ENSG00000128607:ENSG00000146842:ENSG00000158516:ENSG00000128510:ENSG00000091704:ENSG00000158623:ENSG00000066827:ENSG00000131773:ENSG00000125249
DEG.twoside	Pituitary	5005	5	0.809134	1	ENSG00000128607:ENSG00000128510:ENSG00000106477:ENSG00000106484:ENSG00000176165
DEG.twoside	Prostate	2717	2	0.882146	1	ENSG00000125249:ENSG00000141198
DEG.twoside	Salivary_Gland	2951	3	0.752343	1	ENSG00000106477:ENSG00000125249:ENSG00000141198
DEG.twoside	Skin	4343	5	0.683661	1	ENSG00000158516:ENSG00000128510:ENSG00000106484:ENSG00000158623:ENSG00000131773
DEG.twoside	Small_Intestine	3112	1	0.987343	1	ENSG00000131773
DEG.twoside	Spleen	4596	4	0.875337	1	ENSG00000091732:ENSG00000091704:ENSG00000106484:ENSG00000131773
DEG.twoside	Stomach	3070	7	0.082836	1	ENSG00000158516:ENSG00000106477:ENSG00000106484:ENSG00000158623:ENSG00000131773:ENSG00000125249:ENSG00000141198

DEG.twoside	Testis	8546	19	0.000577	0.017318	ENSG00000221900:ENSG00000091732:ENSG00000128607:ENSG00000146842:ENSG00000165120:ENSG00000158516:ENSG00000158525:ENSG00000091704:ENSG00000106477:ENSG00000106484:ENSG00000158623:ENSG00000213265:ENSG00000066827:ENSG00000131773:ENSG00000125249:ENSG00000176165:ENSG00000186960:ENSG00000141200:ENSG00000141198
DEG.twoside	Thyroid	4708	4	0.8883	1	ENSG00000146842:ENSG00000158516:ENSG00000131773:ENSG00000141198
DEG.twoside	Uterus	4787	3	0.965398	1	ENSG00000091732:ENSG00000158623:ENSG00000131773
DEG.twoside	Vagina	2611	2	0.866888	1	ENSG00000128510:ENSG00000106484

Table S15. List of Mapped Genes to ascorbic acid 2 sulfate gene-sex interaction regions using FUMA.

ensg	entrezID	symbol	hgnc_symbol	OMIM	uniprotID	DrugBank
ENSG00000113407	6897	TARS	TARS	187790	P26639	DB00156
ENSG00000127184	1350	COX7C	COX7C	603774	P15954	DB02659:DB04464
ENSG00000233828	NA	AC008394.1	NA	NA	NA	NA
ENSG00000145715	5921	RASA1	RASA1	139150	P20936	NA
ENSG00000175414	285598	ARL10	ARL10	NA	Q8N8L6	NA
ENSG00000113763	90249	UNC5A	UNC5A	607869	Q6ZN44	NA
ENSG00000160867	2264	FGFR4	FGFR4	134935	P22455	DB00039:DB01109:DB08901:DB09078:DB12147
ENSG00000166548	7084	TK2	TK2	188250	O00142	DB02452:DB02594:DB04485
ENSG00000217555	51192	CKLF	CKLF	NA	Q9UBR5	NA
ENSG00000140932	146225	CMTM2	CMTM2	607885	Q8TAZ6	NA
ENSG00000140931	123920	CMTM3	CMTM3	607886	Q96MX0	NA
ENSG00000166595	51647	FAM96B	FAM96B	614778	Q9Y3D0	NA
ENSG00000172831	8824	CES2	CES2	605278	O00748	NA
ENSG00000172828	23491	CES3	CES3	605279	Q6UWW8	NA
ENSG00000067955	865	CBFB	CBFB	121360	Q13951	NA
ENSG00000125149	80262	C16orf70	C16orf70	NA	Q9BSU1	NA
ENSG00000237172	84752	B3GNT9	B3GNT9	NA	Q6UX72	NA
ENSG00000102871	8717	TRADD	TRADD	603500	Q15628	NA
ENSG00000135722	55336	FBXL8	FBXL8	609077	Q96CD0	NA
ENSG00000102878	3299	HSF4	HSF4	602438	Q9ULV5	NA
ENSG00000265690	NA	RP11-5A19.5	NA	NA	NA	NA
ENSG00000140939	8996	NOL3	NOL3	605235	O60936	NA
ENSG00000196123	653319	KIAA0895L	KIAA0895L	NA	Q68EN5	NA
ENSG00000179044	283849	EXOC3L1	EXOC3L1	614117	Q86VI1	NA
ENSG00000205250	1874	E2F4	E2F4	600659	Q16254	NA
ENSG00000102890	79767	ELMO3	ELMO3	606422	Q96BJ8	NA
ENSG00000125122	26231	LRRC29	LRRC29	NA	Q8WV35	NA
ENSG00000237102	NA	AC040160.1	NA	NA	NA	NA
ENSG00000168701	29100	TMEM208	TMEM208	NA	Q9BTX3	NA
ENSG00000135723	29109	FHOD1	FHOD1	606881	Q9Y613	NA
ENSG00000135740	6553	SLC9A5	SLC9A5	600477	Q14940	NA
ENSG00000196155	25894	PLEKHG4	PLEKHG4	609526	Q58EX7	NA
ENSG00000168676	146212	KCTD19	KCTD19	NA	Q17RG1	NA
ENSG00000159708	55282	LRRC36	LRRC36	NA	Q1X8D7	NA
ENSG00000159713	51673	TPPP3	TPPP3	NA	Q9BW30	NA

ENSG00000159714	29800	ZDHHC1	ZDHHC1	NA	Q8WTX9	NA
ENSG00000176387	3291	HSD11B2	HSD11B2	614232	P80365	DB00157:DB00741:DB01185:DB01569:DB14538:DB14539:DB14540:DB14541:DB14542:DB14543:DB14544
ENSG00000159720	9114	ATP6V0D1	ATP6V0D1	607028	P61421	NA
ENSG00000159723	181	AGRP	AGRP	602311	O00253	NA
ENSG00000039523	79567	FAM65A	FAM65A	NA	Q6ZS17	NA
ENSG00000159753	146206	RLTPR	RLTPR	610859	Q6F5E8	NA
ENSG00000102977	65057	ACD	ACD	609377	Q96AP0	NA
ENSG00000102981	50855	PARD6A	PARD6A	607484	Q9NPB6	NA
ENSG00000124074	84080	ENKD1	ENKD1	NA	Q9H0I2	NA
ENSG00000159761	388284	C16orf86	C16orf86	NA	Q6ZW13	NA
ENSG00000141098	81577	GFOD2	GFOD2	NA	Q3B7J2	NA
ENSG00000102901	80152	CENPT	CENPT	611510	Q96BT3	NA
ENSG00000159792	5681	PSKH1	PSKH1	177015	P11801	NA
ENSG00000213398	3931	LCAT	LCAT	606967	P04180	NA
ENSG00000124067	6560	SLC12A4	SLC12A4	604119	Q9UP95	DB00761:DB00887
ENSG00000141096	64180	DPEP3	DPEP3	609926	Q9H4B8	NA
ENSG00000167261	64174	DPEP2	DPEP2	609925	Q9H4A9	NA
ENSG00000167264	54920	DUS2	DUS2	609707	Q9NX74	NA
ENSG00000072736	4775	NFATC3	NFATC3	602698	Q12968	NA
ENSG00000103066	23659	PLA2G15	PLA2G15	609362	Q8NCC3	NA
ENSG00000132600	54496	PRMT7	PRMT7	610087	Q9NVM4	NA
ENSG00000166260	1353	COX11	COX11	603648	Q9Y6N1	NA
ENSG00000166263	252983	STXBP4	STXBP4	610415	Q6ZWJ1	NA
ENSG00000108960	23531	MMD	MMD	604467	Q15546	NA

Table S16. Expression levels of the genes mapped to ascorbic acid 2 sulfate gene-sex interaction regions in different tissues using FUMA.

Category	GeneSet	N_genes	N_overlap	p	adjP	genes
DEG.up	Adipose_Tissue	1554	5	0.584775	1	ENSG00000166548:ENSG00000140931:ENSG00000179044:ENSG00000135723:ENSG00000108960
DEG.up	Adrenal_Gland	1204	4	0.562932	1	ENSG00000160867:ENSG00000172831:ENSG00000196123:ENSG00000159723
DEG.up	Bladder	728	0	1	1	
DEG.up	Blood	1477	6	0.354962	1	ENSG00000217555:ENSG00000140932:ENSG00000159753:ENSG00000141096:ENSG00000167261:ENSG00000167264
DEG.up	Blood_Vessel	2139	6	0.717521	1	ENSG00000237172:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000166260:ENSG00000166263
DEG.up	Brain	2348	6	0.799007	1	ENSG00000113763:ENSG00000135740:ENSG00000159713:ENSG00000159753:ENSG00000102981:ENSG00000108960
DEG.up	Breast	1428	7	0.184968	1	ENSG00000140931:ENSG00000135722:ENSG00000179044:ENSG00000196155:ENSG00000159714:ENSG00000176387:ENSG00000108960

DEG.up	Cervix_Uteri	2514	13	0.060794	1	ENSG00000175414:ENSG00000140931:ENSG00000067955:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000159714:ENSG00000176387:ENSG00000102977:ENSG00000124074:ENSG00000213398:ENSG00000166263
DEG.up	Colon	1107	4	0.495376	1	ENSG00000113407:ENSG00000160867:ENSG00000172828:ENSG00000176387
DEG.up	Esophagus	1008	0	1	1	
DEG.up	Fallopian_Tube	451	5	0.015972	0.479173	ENSG00000140931:ENSG00000237172:ENSG00000102878:ENSG00000196123:ENSG00000124074
DEG.up	Heart	458	0	1	1	
DEG.up	Kidney	963	5	0.207325	1	ENSG00000160867:ENSG00000172828:ENSG00000102890:ENSG00000176387:ENSG00000103066
DEG.up	Liver	1090	5	0.285671	1	ENSG00000160867:ENSG00000172831:ENSG00000172828:ENSG00000125149:ENSG00000213398
DEG.up	Lung	3029	15	0.060949	1	ENSG00000160867:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000102871:ENSG00000179044:ENSG00000135723:ENSG00000159708:ENSG00000159713:ENSG00000159723:ENSG00000213398:ENSG00000124067:ENSG00000167261:ENSG00000103066:ENSG00000166263
DEG.up	Muscle	879	4	0.325491	1	ENSG00000172828:ENSG00000135723:ENSG00000072736:ENSG00000103066
DEG.up	Nerve	4157	18	0.117258	1	ENSG00000145715:ENSG00000175414:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000067955:ENSG00000196155:ENSG00000159714:ENSG00000102977:ENSG00000124074:ENSG00000159761:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000072736:ENSG00000132600:ENSG00000166260:ENSG00000166263
DEG.up	Ovary	3674	18	0.043459	1	ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000140931:ENSG00000237172:ENSG00000135722:ENSG00000196123:ENSG00000179044:ENSG00000135723:ENSG00000196155:ENSG00000159714:ENSG00000176387:ENSG00000102977:ENSG00000124074:ENSG00000159792:ENSG00000132600:ENSG00000166263
DEG.up	Pancreas	549	5	0.033689	1	ENSG00000160867:ENSG00000135722:ENSG00000102890:ENSG00000102981:ENSG00000124074
DEG.up	Pituitary	3253	13	0.25985	1	ENSG00000113763:ENSG00000237172:ENSG00000135722:ENSG00000102878:ENSG00000196123:ENSG00000102890:ENSG00000125122:ENSG00000159714:ENSG00000159753:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000132600
DEG.up	Prostate	2019	10	0.11976	1	ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000102890:ENSG00000125122:ENSG00000159714:ENSG00000176387:ENSG00000124074:ENSG00000213398
DEG.up	Salivary_Gland	1285	5	0.414152	1	ENSG00000172828:ENSG00000102871:ENSG00000135722:ENSG00000102890:ENSG00000176387
DEG.up	Skin	2568	6	0.864536	1	ENSG00000125149:ENSG00000135722:ENSG00000102890:ENSG00000196155:ENSG00000176387:ENSG00000167264
DEG.up	Small_Intestine	1855	7	0.407319	1	ENSG00000160867:ENSG00000172831:ENSG00000172828:ENSG00000102890:ENSG00000176387:ENSG00000159753:ENSG00000167261
DEG.up	Spleen	2666	15	0.022598	0.677936	ENSG00000160867:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000102871:ENSG00000179044:ENSG00000135723:ENSG00000135740:ENSG00000196155:ENSG00000159753:ENSG00000141098:ENSG00000141096:ENSG00000167261:ENSG00000167264:ENSG00000103066
DEG.up	Stomach	780	1	0.927086	1	ENSG00000102890
DEG.up	Testis	5947	23	0.201188	1	ENSG00000145715:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000196123:ENSG00000179044:ENSG00000102890:ENSG00000125122:ENSG00000135740:ENSG00000196155:ENSG00000168676:ENSG00000159708:ENSG00000159714:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000159792:ENSG00000141096:ENSG00000167264:ENSG00000072736

DEG.up	Thyroid	3732	15	0.228666	1	ENSG00000145715:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000179044:ENSG00000102890:ENSG00000125122:ENSG00000135723:ENSG00000159714:ENSG00000176387:ENSG00000124074:ENSG00000213398:ENSG00000124067:ENSG00000103066
DEG.up	Uterus	3999	14	0.440071	1	ENSG00000145715:ENSG00000175414:ENSG00000140931:ENSG00000237172:ENSG00000196123:ENSG00000159714:ENSG00000176387:ENSG00000102977:ENSG00000124074:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000132600:ENSG00000166263
DEG.up	Vagina	2013	5	0.804086	1	ENSG00000175414:ENSG00000067955:ENSG00000102890:ENSG00000176387:ENSG00000141098
DEG.down	Adipose_Tissue	1360	7	0.155511	1	ENSG00000160867:ENSG00000140932:ENSG00000172828:ENSG00000102890:ENSG00000176387:ENSG00000159753:ENSG00000102981
DEG.down	Adrenal_Gland	2994	7	0.880894	1	ENSG00000175414:ENSG00000067955:ENSG00000102890:ENSG00000135740:ENSG00000159713:ENSG00000072736:ENSG00000108960
DEG.down	Bladder	103	0	1	1	
DEG.down	Blood	5553	25	0.040345	1	ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000172831:ENSG00000237172:ENSG00000135722:ENSG00000102878:ENSG00000140939:ENSG00000196123:ENSG00000102890:ENSG00000196155:ENSG00000159713:ENSG00000039523:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000102901:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000103066:ENSG00000132600:ENSG00000166260:ENSG00000108960
DEG.down	Blood_Vessel	1485	6	0.359755	1	ENSG00000179044:ENSG00000102890:ENSG00000135740:ENSG00000196155:ENSG00000167261:ENSG00000108960
DEG.down	Brain	4950	23	0.036653	1	ENSG00000113407:ENSG00000160867:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000067955:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000140939:ENSG00000179044:ENSG00000205250:ENSG00000102890:ENSG00000135723:ENSG00000196155:ENSG00000159714:ENSG00000176387:ENSG00000124074:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000167264:ENSG00000072736
DEG.down	Breast	912	3	0.580678	1	ENSG00000140932:ENSG00000159753:ENSG00000102981
DEG.down	Cervix_Uteri	44	1	0.13468	1	ENSG00000102981
DEG.down	Colon	1245	3	0.784486	1	ENSG00000179044:ENSG00000135740:ENSG00000159753
DEG.down	Esophagus	1465	7	0.201946	1	ENSG00000160867:ENSG00000179044:ENSG00000135723:ENSG00000135740:ENSG00000159753:ENSG00000167261:ENSG00000103066
DEG.down	Fallopian_Tube	1	0	1	1	
DEG.down	Heart	8251	35	0.025741	0.772218	ENSG00000113407:ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000067955:ENSG00000125149:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000102878:ENSG00000196123:ENSG00000179044:ENSG00000102890:ENSG00000125122:ENSG00000168701:ENSG00000135723:ENSG00000135740:ENSG00000159714:ENSG00000176387:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000141098:ENSG00000102901:ENSG00000159792:ENSG00000213398:ENSG00000167264:ENSG00000072736:ENSG00000132600:ENSG00000166260:ENSG00000108960
DEG.down	Kidney	4932	17	0.452814	1	ENSG00000113407:ENSG00000145715:ENSG00000175414:ENSG00000217555:ENSG00000140931:ENSG00000067955:ENSG00000140939:ENSG00000135740:ENSG00000196155:ENSG00000159753:ENSG00000102977:ENSG00000124067:ENSG00000167261:ENSG00000167264:ENSG00000072736:ENSG00000132600:ENSG00000108960
DEG.down	Liver	7196	30	0.058956	1	ENSG00000145715:ENSG00000217555:ENSG00000140931:ENSG00000067955:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000102878:ENSG00000140939:ENSG00000196123:ENSG00000179044:ENSG00000205250:ENSG00000102890:ENSG00000125122:ENSG00000135723:ENSG00000159714:ENSG00000039523:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000102901:ENSG00000159792:ENSG00000124067:ENSG00000167264:ENSG00000072736:ENSG00000103066:ENSG00000132600:ENSG00000166260:ENSG00000108960
DEG.down	Lung	820	1	0.936451	1	ENSG00000102981

DEG.down	Muscle	6093	25	0.107412	1	ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000168701:ENSG00000135740:ENSG00000159714:ENSG00000039523:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000141098:ENSG00000102901:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000167264:ENSG00000108960
DEG.down	Nerve	784	3	0.477495	1	ENSG00000179044:ENSG00000176387:ENSG00000159753
DEG.down	Ovary	1429	4	0.699368	1	ENSG00000172828:ENSG00000102890:ENSG00000159713:ENSG00000108960
DEG.down	Pancreas	8671	32	0.211189	1	ENSG00000113407:ENSG00000145715:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000172831:ENSG00000067955:ENSG00000125149:ENSG00000237172:ENSG00000102871:ENSG00000196123:ENSG00000179044:ENSG00000205250:ENSG00000125122:ENSG00000135723:ENSG00000196155:ENSG00000159713:ENSG00000159714:ENSG00000176387:ENSG00000159720:ENSG00000039523:ENSG00000102977:ENSG00000159761:ENSG00000141098:ENSG00000213398:ENSG00000124067:ENSG00000167264:ENSG00000072736:ENSG00000103066:ENSG00000132600:ENSG00000166260:ENSG00000108960
DEG.down	Pituitary	1752	4	0.83884	1	ENSG00000140931:ENSG00000176387:ENSG00000072736:ENSG00000108960
DEG.down	Prostate	698	4	0.195109	1	ENSG00000172828:ENSG00000159753:ENSG00000102981:ENSG00000108960
DEG.down	Salivary_Gland	1666	7	0.303459	1	ENSG00000175414:ENSG00000135740:ENSG00000159713:ENSG00000159753:ENSG00000102981:ENSG00000159761:ENSG00000108960
DEG.down	Skin	1775	5	0.703832	1	ENSG00000160867:ENSG00000172828:ENSG00000179044:ENSG00000102981:ENSG00000159761
DEG.down	Small_Intestine	1257	6	0.228493	1	ENSG00000102878:ENSG00000140939:ENSG00000135740:ENSG00000159714:ENSG00000102981:ENSG00000103066
DEG.down	Spleen	1930	4	0.889899	1	ENSG00000102878:ENSG00000140939:ENSG00000159713:ENSG00000166260
DEG.down	Stomach	2290	20	2.24E-05	0.000673	ENSG00000145715:ENSG00000175414:ENSG00000113763:ENSG00000217555:ENSG00000140931:ENSG00000172828:ENSG00000067955:ENSG00000125149:ENSG00000179044:ENSG00000135723:ENSG00000135740:ENSG00000196155:ENSG00000159713:ENSG00000159753:ENSG00000159761:ENSG00000141098:ENSG00000167261:ENSG00000072736:ENSG00000103066:ENSG00000108960
DEG.down	Testis	2599	8	0.632823	1	ENSG00000175414:ENSG00000113763:ENSG00000067955:ENSG00000102871:ENSG00000135722:ENSG00000140939:ENSG00000176387:ENSG00000159753
DEG.down	Thyroid	976	4	0.398658	1	ENSG00000160867:ENSG00000172828:ENSG00000102981:ENSG00000108960
DEG.down	Uterus	788	4	0.258118	1	ENSG00000102890:ENSG00000159753:ENSG00000102981:ENSG00000108960
DEG.down	Vagina	598	4	0.13235	1	ENSG00000135740:ENSG00000159753:ENSG00000102981:ENSG00000108960
DEG.twoside	Adipose_Tissue	2914	12	0.238817	1	ENSG00000160867:ENSG00000166548:ENSG00000140932:ENSG00000140931:ENSG00000172828:ENSG00000179044:ENSG00000102890:ENSG00000135723:ENSG00000176387:ENSG00000159753:ENSG00000102981:ENSG00000108960
DEG.twoside	Adrenal_Gland	4198	11	0.843102	1	ENSG00000175414:ENSG00000160867:ENSG00000172831:ENSG00000067955:ENSG00000196123:ENSG00000102890:ENSG00000135740:ENSG00000159713:ENSG00000159723:ENSG00000072736:ENSG00000108960
DEG.twoside	Bladder	831	0	1	1	
DEG.twoside	Blood	7030	31	0.024281	0.728441	ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140932:ENSG00000172831:ENSG00000237172:ENSG00000135722:ENSG00000102878:ENSG00000140939:ENSG00000196123:ENSG00000102890:ENSG00000196155:ENSG00000159713:ENSG00000039523:ENSG00000159753:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000102901:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000141096:ENSG00000167261:ENSG00000167264:ENSG00000103066:ENSG00000132600:ENSG00000166260:ENSG00000108960

DEG.twoside	Blood_Vessel	3624	12	0.536417	1	ENSG00000237172:ENSG00000179044:ENSG00000102890:ENSG00000135740:ENSG00000196155:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000167261:ENSG00000166260:ENSG00000166263:ENSG00000108960
DEG.twoside	Brain	7298	29	0.11275	1	ENSG00000113407:ENSG00000113763:ENSG00000160867:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000067955:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000140939:ENSG00000179044:ENSG00000205250:ENSG00000102890:ENSG00000135723:ENSG00000135740:ENSG00000196155:ENSG00000159713:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102981:ENSG00000124074:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000167264:ENSG00000072736:ENSG00000108960
DEG.twoside	Breast	2340	10	0.231747	1	ENSG00000140932:ENSG00000140931:ENSG00000135722:ENSG00000179044:ENSG00000196155:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102981:ENSG00000108960
DEG.twoside	Cervix_Uteri	2558	14	0.034302	1	ENSG00000175414:ENSG00000140931:ENSG00000067955:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000159714:ENSG00000176387:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000213398:ENSG00000166263
DEG.twoside	Colon	2352	7	0.666178	1	ENSG00000113407:ENSG00000160867:ENSG00000172828:ENSG00000179044:ENSG00000135740:ENSG00000176387:ENSG00000159753
DEG.twoside	Esophagus	2473	7	0.718549	1	ENSG00000160867:ENSG00000179044:ENSG00000135723:ENSG00000135740:ENSG00000159753:ENSG00000167261:ENSG00000103066
DEG.twoside	Fallopian_Tube	452	5	0.016111	0.483341	ENSG00000140931:ENSG00000237172:ENSG00000102878:ENSG00000196123:ENSG00000124074
DEG.twoside	Heart	8709	35	0.060159	1	ENSG00000113407:ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000067955:ENSG00000125149:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000102878:ENSG00000196123:ENSG00000179044:ENSG00000102890:ENSG00000125122:ENSG00000168701:ENSG00000135723:ENSG00000135740:ENSG00000159714:ENSG00000176387:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000141098:ENSG00000102901:ENSG00000159792:ENSG00000213398:ENSG00000167264:ENSG00000072736:ENSG00000132600:ENSG00000166260:ENSG00000108960
DEG.twoside	Kidney	5895	22	0.269684	1	ENSG00000113407:ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000217555:ENSG00000140931:ENSG00000172828:ENSG00000067955:ENSG00000140939:ENSG00000102890:ENSG00000135740:ENSG00000196155:ENSG00000176387:ENSG00000159753:ENSG00000102977:ENSG00000124067:ENSG00000167261:ENSG00000167264:ENSG00000072736:ENSG00000103066:ENSG00000132600:ENSG00000108960
DEG.twoside	Liver	8286	35	0.027603	0.828098	ENSG00000145715:ENSG00000160867:ENSG00000217555:ENSG00000140931:ENSG00000172831:ENSG00000172828:ENSG00000067955:ENSG00000125149:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000102878:ENSG00000140939:ENSG00000196123:ENSG00000179044:ENSG00000205250:ENSG00000102890:ENSG00000125122:ENSG00000135723:ENSG00000159714:ENSG00000039523:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000102901:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000167264:ENSG00000072736:ENSG00000103066:ENSG00000132600:ENSG00000166260:ENSG00000108960
DEG.twoside	Lung	3849	16	0.178238	1	ENSG00000160867:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000102871:ENSG00000179044:ENSG00000135723:ENSG00000159708:ENSG00000159713:ENSG00000159723:ENSG00000102981:ENSG00000213398:ENSG00000124067:ENSG00000167261:ENSG00000103066:ENSG00000166263
DEG.twoside	Muscle	6972	29	0.066677	1	ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000172828:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000168701:ENSG00000135723:ENSG00000135740:ENSG00000159714:ENSG00000039523:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000141098:ENSG00000102901:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000167264:ENSG00000072736:ENSG00000103066:ENSG00000108960
DEG.twoside	Nerve	4941	21	0.106232	1	ENSG00000145715:ENSG00000175414:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000067955:ENSG00000179044:ENSG00000196155:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102977:ENSG00000124074:ENSG00000159761:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000072736:ENSG00000132600:ENSG00000166260:ENSG00000166263
DEG.twoside	Ovary	5103	22	0.086124	1	ENSG00000145715:ENSG00000175414:ENSG00000160867:ENSG00000166548:ENSG00000140931:ENSG00000172828:ENSG00000237172:ENSG00000135722:ENSG00000196123:ENSG00000179044:ENSG00000102890:ENSG00000135723:ENSG0000019

						6155:ENSG00000159713:ENSG00000159714:ENSG00000176387:ENSG00000102977:ENSG00000124074:ENSG00000159792:ENSG00000132600:ENSG00000166263:ENSG00000108960
DEG.twoside	Pancreas	9220	37	0.050246	1	ENSG00000113407:ENSG00000145715:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140931:ENSG00000172831:ENSG00000067955:ENSG00000125149:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000179044:ENSG00000205250:ENSG00000102890:ENSG00000125122:ENSG00000135723:ENSG00000196155:ENSG00000159713:ENSG00000159714:ENSG00000176387:ENSG00000159720:ENSG00000039523:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000141098:ENSG00000213398:ENSG00000124067:ENSG00000167264:ENSG00000072736:ENSG00000103066:ENSG00000132600:ENSG00000166260:ENSG00000108960
DEG.twoside	Pituitary	5005	17	0.480741	1	ENSG00000113763:ENSG00000140931:ENSG00000237172:ENSG00000135722:ENSG00000102878:ENSG00000196123:ENSG00000102890:ENSG00000125122:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000072736:ENSG00000132600:ENSG00000108960
DEG.twoside	Prostate	2717	14	0.053209	1	ENSG00000172828:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000102890:ENSG00000125122:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102981:ENSG00000124074:ENSG00000213398:ENSG00000108960
DEG.twoside	Salivary_Gland	2951	12	0.252734	1	ENSG00000175414:ENSG00000172828:ENSG00000102871:ENSG00000135722:ENSG00000102890:ENSG00000135740:ENSG00000159713:ENSG00000176387:ENSG00000159753:ENSG00000102981:ENSG00000159761:ENSG00000108960
DEG.twoside	Skin	4343	11	0.874764	1	ENSG00000160867:ENSG00000172828:ENSG00000125149:ENSG00000135722:ENSG00000179044:ENSG00000102890:ENSG00000196155:ENSG00000176387:ENSG00000102981:ENSG00000159761:ENSG00000167264
DEG.twoside	Small_Intestine	3112	13	0.209909	1	ENSG00000160867:ENSG00000172831:ENSG00000172828:ENSG00000102878:ENSG00000140939:ENSG00000102890:ENSG00000135740:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102981:ENSG00000167261:ENSG00000103066
DEG.twoside	Spleen	4596	19	0.152377	1	ENSG00000160867:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000102871:ENSG00000102878:ENSG00000140939:ENSG00000179044:ENSG00000135723:ENSG00000135740:ENSG00000196155:ENSG00000159713:ENSG00000159753:ENSG00000141098:ENSG00000141096:ENSG00000167261:ENSG00000167264:ENSG00000103066:ENSG00000166260
DEG.twoside	Stomach	3070	21	0.00047	0.014099	ENSG00000145715:ENSG00000175414:ENSG00000113763:ENSG00000217555:ENSG00000140931:ENSG00000172828:ENSG00000067955:ENSG00000125149:ENSG00000179044:ENSG00000102890:ENSG00000135723:ENSG00000135740:ENSG00000196155:ENSG00000159713:ENSG00000159753:ENSG00000159761:ENSG00000141098:ENSG00000167261:ENSG00000072736:ENSG00000103066:ENSG00000108960
DEG.twoside	Testis	8546	31	0.25809	1	ENSG00000145715:ENSG00000175414:ENSG00000113763:ENSG00000160867:ENSG00000166548:ENSG00000217555:ENSG00000140932:ENSG00000140931:ENSG00000067955:ENSG00000102871:ENSG00000135722:ENSG00000140939:ENSG00000196123:ENSG00000179044:ENSG00000102890:ENSG00000125122:ENSG00000135740:ENSG00000196155:ENSG00000168676:ENSG00000159708:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159761:ENSG00000159792:ENSG00000141096:ENSG00000167264:ENSG00000072736
DEG.twoside	Thyroid	4708	19	0.180352	1	ENSG00000145715:ENSG00000160867:ENSG00000172828:ENSG00000237172:ENSG00000102871:ENSG00000135722:ENSG00000196123:ENSG00000179044:ENSG00000102890:ENSG00000125122:ENSG00000135723:ENSG00000159714:ENSG00000176387:ENSG00000102981:ENSG00000124074:ENSG00000213398:ENSG00000124067:ENSG00000103066:ENSG00000108960
DEG.twoside	Uterus	4787	18	0.291456	1	ENSG00000145715:ENSG00000175414:ENSG00000140931:ENSG00000237172:ENSG00000196123:ENSG00000102890:ENSG00000159714:ENSG00000176387:ENSG00000159753:ENSG00000102977:ENSG00000102981:ENSG00000124074:ENSG00000159792:ENSG00000213398:ENSG00000124067:ENSG00000132600:ENSG00000166263:ENSG00000108960
DEG.twoside	Vagina	2611	9	0.491167	1	ENSG00000175414:ENSG00000067955:ENSG00000102890:ENSG00000135740:ENSG00000176387:ENSG00000159753:ENSG00000102981:ENSG00000141098:ENSG00000108960

Table S17. Functional gene sets related to the genes mapped to O-methylascorbate gene-sex interactions regions using FUMA.

Category	GeneSet	N_genes	N_overlap	p	adjP	genes

GWAScatalog	Waist-to-hip ratio adjusted for BMI (age >50)	178	8	1.71E-11	7.57E-08	CPA4:CPA5:CPA1:CEP41:MEST:COPG2:TSGA13:KLF14
GWAScatalog	Waist-to-hip ratio adjusted for BMI x sex x age interaction (4df test)	299	8	1.07E-09	2.36E-06	CPA4:CPA5:CPA1:CEP41:MEST:COPG2:TSGA13:KLF14
GWAScatalog	Hip index	222	5	5.16E-06	0.007611	CPA4:CPA5:CPA1:CEP41:KLF14
Chemical_and_Genetic_pertubation	LIN_MELANOMA_COPY_NUMBER_UP	69	5	1.52E-08	5.17E-05	CPA1:CEP41:MEST:COPG2:KLF14
Cancer_modules	MODULE_402	11	2	7.29E-05	0.031437	CPA2:CPA1
Positional_gene_sets	chr7q32	44	13	4.98E-30	1.49E-27	ZC3HC1:KLHDC10:TMEM209:SSMEM1:CPA2:CPA4:CPA5:CPA1:CEP41:MEST:COPG2:TSGA13:KLF14
Positional_gene_sets	chr7p11	17	2	0.00018	0.026938	VSTM2A:SEC61G
GO_mf	GOMF_METALLOCARBOXYPEPTIDASE_ACTIVITY	30	4	3.94E-08	6.98E-05	CPA2:CPA4:CPA5:CPA1
GO_mf	GOMF_CARBOXYPEPTIDASE_ACTIVITY	46	4	2.32E-07	0.000205	CPA2:CPA4:CPA5:CPA1
GO_mf	GOMF_METALLOEXOPEPTIDASE_ACTIVITY	64	4	8.89E-07	0.000525	CPA2:CPA4:CPA5:CPA1
GO_mf	GOMF_EXOPEPTIDASE_ACTIVITY	99	4	5.13E-06	0.002271	CPA2:CPA4:CPA5:CPA1
GO_mf	GOMF_METALLOPEPTIDASE_ACTIVITY	191	4	6.81E-05	0.024142	CPA2:CPA4:CPA5:CPA1
Curated_gene_sets	LIN_MELANOMA_COPY_NUMBER_UP	69	5	1.52E-08	9.86E-05	CPA1:CEP41:MEST:COPG2:KLF14

Table S18. Functional gene sets related to the genes mapped to ascorbic acid 2 sulfate gene-sex interactions regions using FUMA.

Category	GeneSet	N_genes	N_overlap	p	adjP	genes
GWAScatalog	Refractive error	1381	22	2.22E-11	9.83E-08	SLC9A5:PLEKHG4:KCTD19:LRRC36:TPPP3:ZDHHC1:HSD11B2:ATP6V0D1:AGRP:ACD:PARD6A:ENKD1:GFOD2:CENPT:PSKH1:LCAT:SLC12A4:DPEP3:DPEP2:NFATC3:PLA2G15:PRMT7
GWAScatalog	Schizophrenia	613	15	2.3E-10	5.09E-07	ACD:PARD6A:ENKD1:C16orf86:GFOD2:CENPT:PSKH1:LCAT:SLC12A4:DPEP3:DPEP2:DUS2:NFATC3:PLA2G15:PRMT7
GWAScatalog	Empathy quotient	13	4	5.16E-08	7.61E-05	ZDHHC1:HSD11B2:ATP6V0D1:GFOD2
Chemical_and_Genetic_pertubation	PROVENZANI_METASTASIS_UP	187	7	1.42E-06	0.004825	TARS:FAM96B:CES2:CBFB:TMEM208:ATP6V0D1:ACD
Positional_gene_sets	chr16q22	117	44	6.82E-90	2.05E-87	CMTM3:FAM96B:CES2:CES3:CBFB:C16orf70:B3GNT9:TRADD:FBXL8:HSF4:NOL3:KIAA0895L:EXOC3L1:E2F4:ELMO3:LRRC29:TMEM208:FHOD1:SLC9A5:PLEKHG4:KCTD19:LRRC36:TPPP3:ZDHHC1:HSD11B2:ATP6V0D1:AGRP:FAM65A:RLTPR:ACD:PARD6A:ENKD1:C16orf86:GFOD2:CENPT:PSKH1:LCAT:SLC12A4:DPEP3:DPEP2:DUS2:NFATC3:PLA2G15:PRMT7
Positional_gene_sets	chr16q21	39	3	0.000219	0.032789	TK2:CKLF:CMTM2
Positional_gene_sets	chr17q22	45	3	0.000335	0.03351	COX11:STXBP4:MMD
Curated_gene_sets	PROVENZANI_METASTASIS_UP	187	7	1.42E-06	0.009204	TARS:FAM96B:CES2:CBFB:TMEM208:ATP6V0D1:ACD
TF_targets	FOXN3_TARGET_GENES	1198	16	2.83E-07	0.000316	TK2:CKLF:KIAA0895L:E2F4:FHOD1:SLC9A5:PLEKHG4:ZDHHC1:AGRP:RLTPR:ACD:PARD6A:LCAT:NFATC3:COX11:STXBP4

TF_targets	AP2ALPHA_01	228	6	6.17E-05	0.034415	LRRC29:TMEM208:HSD11B2:FAM65A:SLC12A4:NFATC3
TF_targets	ZNF776_TARGET_GENES	6	2	0.000132	0.049226	LRRC29:TMEM208

3. Evaluating vitamin C-related gene-environment and metabolite-environment interaction effects on intraocular pressure in the Canadian Longitudinal Study on Aging

Objective: The aim of this study was to evaluate how genetic, metabolic and environmental factors are associated with intraocular pressure levels, and how they interact together to modify these associations.

Author Contributions: Rebecca Lelievre was responsible for conceptualizing the project, preparing the dataset, conducting data analysis, visualizing the results, and preparing the manuscript. Mohan Rakesh helped with results validation and support with data analysis. Julian Little, Pirro Hysi, Marie-Helene Roy-Gagnon and Ellen Freeman helped with securing funding for the project and project conceptualization. Marie-Helene Roy-Gagnon, with the support of Ellen Freeman, supervised the project completion, including providing feedback on the methodology, analysis and results interpretation, and provided resources to aid in project completion. All authors aided in reviewing the manuscript and providing final approval.

Ethics: This research was approved by the University of Ottawa Research Ethics Board

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Title Page

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Keywords: CLSA, gene-environment interaction, intraocular pressure, metabolites

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Conflict of Interests: None declared.

Abstract

Background: High intraocular pressure (IOP) is an important risk factor for glaucoma, which is influenced by genetic and environmental factors. However, the etiology of high IOP remains uncertain. Metabolites are compounds involved in metabolism which provide a link between the internal (genetic) and external environments. O-methylascorbate has been reported to be associated with IOP. In addition, researchers have identified several genetic variants which are associated with metabolite concentrations, including O-methylascorbate and another vitamin C related metabolite, ascorbic acid 2-sulfate. We aimed to understand how O-methylascorbate and ascorbic acid 2-sulfate, or genetic variants associated with these metabolites, modify the associations between dietary environmental variables and IOP.

Results: We used data from 8060 participants of the Canadian Longitudinal Study on Aging. Using linear models adjusted for relevant covariates, we tested for interactions between six genetic variants previously found to be associated with O-methylascorbate and ascorbic acid 2-sulfate and four environmental variables related to diet (alcohol consumption frequency, smoking status, fruit consumption, and vegetable consumption). We also tested for interactions between serum concentrations of O-methylascorbate and ascorbic acid 2-sulfate and these environmental factors. We used a False Discovery Rate approach to correct for the 32 interaction tests performed. One interaction was suggestively significant after multiple testing correction (adjusted P-value < 0.1): rs8050812 and alcohol consumption frequency.

Conclusions: Understanding how genetic variants and metabolites interact with the environment could shed light on biological pathways controlling IOP and lead to improved prevention and treatment of glaucoma.

Keywords: CLSA, gene-environment, intraocular pressure, metabolites

3.1. Introduction

Glaucoma is one of the leading causes of irreversible blindness in the world (Sun et al., 2022). While there is global concern about vitamin C status (Rowe and Carr, 2020), there is conflicting evidence about the association between glaucoma and vitamin C (Ramdas, 2018; Han and Fu, 2022). One of the most important risk factors for glaucoma is elevated intraocular pressure (IOP)(Nouri-Mahdavi et al., 2004; Leske et al., 2007), which is heritable(Freeman et al., 2013; Asefa et al., 2019). Investigation of the etiology of elevated IOP may be key to preventing glaucoma(Heijl et al., 2002). Several studies have investigated the genetic and environmental components that contribute to variation in IOP (Stuart et al., 2023b). A recent genome-wide association study identified over 300 genetic loci associated with IOP (Han et al., 2023). However, there is still a large proportion of IOP variance which is unexplained (Han et al., 2023; Stuart et al., 2023b).

The exposome represents the totality of environmental exposures over the lifetime (Wild, 2005; Zhang et al., 2021). One way to quantify a component of the exposome is through measured metabolite levels (Walker et al., 2019). Metabolites are compounds involved in metabolism as intermediates or end-products. They can also help provide a link between the molecular/genetic environment and the external environment (Walker et al., 2019). Past research by Hysi et al. investigated the influence of metabolites on IOP and found that O-methylascorbate, a vitamin C metabolite, was most associated (Hysi et al., 2019).

Other studies have identified genetic factors that are associated with metabolite levels (Yin et al., 2022; Chen et al., 2023). These genetic factors can be used when assessing the effect of metabolites on phenotypes in certain study designs, such as Mendelian Randomization(Chen et al., 2023) and could be helpful to detect interactions with environmental factors acting on metabolic pathways. We previously investigated genetic factors associated with O-methylascorbate and ascorbic acid 2-sulfate, which are both vitamin C related, and found several associations which had also been found in previous research (Chen et al., 2023; Lelievre et al., 2024). We identified three genetic variants which were independently significantly associated with each metabolite at the genome-wide significance level (P-value <5 x 10-8). The variants identified were rs144009214, rs12414734 and rs8050812 for ascorbic acid 2-sulfate, and rs165879, rs4680, and rs61484427 for O-methylascorbate (Lelievre et al., 2024).

Furthermore, several environmental risk factors may interact with vitamin C in their effect on IOP and glaucoma. Some environmental risk factors relevant to vitamin C that were previously found to be associated with glaucoma include diet (including vitamin consumption)(Coleman et al., 2008; Giaconi et al., 2012; Moreno-Montanes et al., 2022), smoking (Jain et al., 2017; Tran et al., 2023) and alcohol (Stuart et al., 2022; Stuart et al., 2023a). Smoking and alcohol are also associated with IOP (Song et al., 2020; Stuart et al., 2022; Grant et al., 2023b; Stuart et al., 2023a; Tran et al., 2023; Stuart et al., 2024).

There is still a large proportion of IOP variance which is not explained by genetic or environmental factors alone. By investigating the interplay between genetic variants, the metabolome, and the environment we can better understand IOP variation and glaucoma etiology. In this study, we investigated interactions between environmental risk factors relevant to vitamin C and metabolic/genetic factors affecting IOP in the Canadian Longitudinal Study on Aging (CLSA).

3.2. Materials and Methods

3.2.1. Study population and design

We carried out a cross-sectional analysis using data from the Comprehensive Cohort of the Canadian Longitudinal Study on Aging (CLSA)(Raina et al., 2019). The Comprehensive Cohort includes 30 097 Canadians between 45 to 85 years at recruitment with baseline data collected between 2012 and 2015. Participants in the Comprehensive Cohort underwent in-home interviews, in-depth clinical examinations and some provided biological samples at CLSA data collection sites located in Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, and St. John's, Canada. Participants were included if they were community dwelling at baseline, not cognitively impaired at baseline, and able to respond in English or French. Full-time members of the Canadian Armed Forces, those residing on a federal First Nations reserve or settlement, residents in the three territories and some remote regions, those living in a long-term care institution at baseline, were excluded.

Of those in the Comprehensive Cohort, 26 622 individuals were genotyped (Forgetta et al., 2022), 9992 participants had their metabolite levels quantified,(Michelotti et al., 2023) and around 9000 participants had both. Participants were then further excluded if they were not of European ancestry, were related to other participants, had missing or outlier IOP values or had missing confounder covariate information, leading to a final sample of 8060 individuals. Reporting of this research was informed by the Strengthening the Reporting of Genetic

Associations (STREGA) guideline (Little et al., 2009). Written informed consent was obtained for all participants, and research ethics board approval was obtained for all CLSA affiliated sites. The analysis presented here was approved by the University of Ottawa research ethics board.

3.2.2. Genetic data

Consenting individuals from the Comprehensive Cohort provided blood samples which were stored at -80°C before being shipped to a genomics facility and stored at -20°C. 26 622 individuals in the CLSA were genotyped from the Comprehensive Cohort using the Affymetrix Axiom Array, leading to 794 409 variants genotyped (Forgetta et al., 2022). We genetic ancestry inferred from genomic data by the CLSA to restrict the sample to European ancestry(Forgetta et al., 2022). Genotyped data was used for imputation using the TOPMED reference panel, resulting in ~308 million imputed variants. For this analysis, we used the imputed genetic data from six genetic variants of interest (rs144009214, rs12414734, rs8050812, rs165879, rs4680, and rs61484427) which were found in our previous research to be associated with either ascorbic acid 2 sulfate or O-methylascorbate. Genetic data were coded based on the number of minor alleles in an individual's genotype.

3.2.3. Metabolic data

Ten thousand participants were selected for metabolomics quantification. Among those, 3000 were selected from a group of participants who had fasted for over 5 hours while 7000 were selected from the rest of the cohort. Sample selection was made to reflect the distribution of the Comprehensive Cohort by data collection site, age and sex. This process resulted in 9992 consenting participants from the Comprehensive Cohort having their metabolite levels quantified by an untargeted approach (Michelotti et al., 2023). Metabolite levels were measured using mass spectrometry, followed by identification using the Metabolon Discovery HD4TM LC-MS platform. After quality control checks, 1314 identified metabolites were included in the final dataset. For our analysis, we focused on two metabolites: 2-O-methylascorbate and ascorbic acid-2-sulfate. We used measurements provided by the CLSA which were batch normalized. Metabolite values were log-transformed, extreme outliers (more than 3 SD away) were removed, and then the values were normalized to a mean of 0 and SD of 1, as done in previous research (Chen et al., 2023).

3.2.4. Outcome variable (IOP)

The outcome of interest for this analysis was intraocular pressure (IOP). IOP was measured in mmHg using a Reichart Ocular Response Analyzer in the baseline examination in the Comprehensive Cohort. Participants with an eye infection, who reported that they had eye surgery in the three months prior to examination, or who reported a detached retina in the three months prior to examination. Participants with measurements in both eyes had their IOP levels averaged. For participants with only one eye measurement, that value was used. We used IOP measurements that were adjusted for corneal mechanic properties, i.e. corneal compensated IOP (IOPcc). Instead of using current IOP, we estimated pre-treatment IOP. In those who reported taking IOP lowering medications (van der Valk et al., 2005) at the time of baseline examination, IOPcc was divided by 0.7 to account for the average medication effect, as done previously (Khawaja et al., 2018; Grant et al., 2023b). Three participants with outlier IOP levels, defined as >60 mmHg (Grant et al., 2023b), were removed, as these most likely represented measurement error based on expert opinion.

3.2.5. Alcohol consumption

Participants were asked “Have you ever drunk alcohol?” and if they said yes were asked “About how often during the past twelve months did you drink alcohol?”. Respondents were categorized as “Never”, “Occasional”, “Weekly” and “Daily” drinkers based on these responses.

3.2.6. Cigarette smoking

The smoking variable was coded using the questions “Have you smoked at least 100 cigarettes in your life?” and “At the present time, do you smoke cigarettes daily, occasionally or not at all?”. Based on the responses, the participants were categorized as “Never” “Former” or “Current” smokers. If participants said no to smoking at least 100 cigarettes, they were considered as never smokers. Those who said they smoke cigarettes daily or occasionally were considered as current smokers. Those who said they had smoked 100 cigarettes, but currently not at all were considered former smokers.

3.2.7. Dietary variables

Participants were asked to fill in the validated 36-item Short Diet Questionnaire (Shatenstein and Payette, 2015; Gilsing et al., 2018). For fruit consumption, participants were asked “How often do you eat fruit (fresh, frozen, canned)?” and “How often do you drink 100% fruit juices?”. These responses were standardized to the number of reported servings per day and added together total fruit consumption per day. One participant was excluded from this analysis based on having an outlier value of 20.

For vegetable consumption, the frequency of the consumption of the following foods were added together: “How often do you usually eat green salad (lettuce, with or without other ingredients)?", "How often do you usually eat carrots (fresh, frozen, canned, eaten on their own or with other food, cooked or raw)?", and "How often do you usually eat other vegetables (except carrots, potatoes or salad)?". These responses were standardized to the number of reported servings per day.

To calculate total daily caloric intake, responses from the Short Diet Questionnaire were used with methods described previously(Shatenstein and Payette, 2015; Grant et al., 2023b). Briefly, we used the reported frequencies of each food item from the SDQ, using portion sizes from a full food frequency questionnaire(Shatenstein et al., 2005) used previously in the NuAge Study(Gaudreau et al., 2007), and a nutrient database from the 2015 Canadian Nutrient File.

3.2.8. Other covariates

Sex was determined based on chromosomal sex using the genetic data. Other demographic variables included age, province of residence, highest level of education and income and were based on the responses given in in-home interviews. Highest level of education was based on the questions: "What is the highest degree, certificate, or diploma you have obtained?" and "Have you received any other education that could be counted towards a degree, certificate, or diploma from an educational institution?". Participants were coded as: Less than a Bachelor's, a Bachelor's degree or higher than a Bachelor's. Total household income was categorized as follows: <$20 000, $20 000-50 000, $50 000-100 000, $100 000-150 000,>$150 000, Don't know/Missing/Refused.

Participants were also asked "In the last 24 hours, have you had any food or (excluding water) drink?" and respondents who said yes stated the last time they did so. This variable was included as the time since last meal or drink in order to determine fasting status which is relevant to interpreting metabolite data. Participants were also asked if they had received a physician's diagnosis of diabetes or high blood pressure. Blood pressure was measured six times in a single session for each participant, and the average of the last five readings was used as the blood pressure measurement. We defined hypertension as self-reported physician diagnosis of high blood pressure or an average systolic blood pressure > 130 mmHg or a diastolic blood pressure > 80 mmHg. BMI was categorized as underweight (<20 kg/m2), normal (20-24.9 kg/m2), overweight (25-29.9 kg/m2) and obese (> 30.0 kg/m2) similar to past studies (Grant et al., 2023a).

3.2.9. Statistical analysis

First, we used descriptive statistics and graphs to understand the distribution of the variables and check necessary assumptions such as normality and linearity. Next, we assessed the association of each environmental, genetic, and metabolic variable individually with IOP using linear models adjusted for age, sex, income, province, education level, BMI, alcohol frequency, hypertension, diabetes, smoking status, total daily caloric intake, first ten genetic principal components (genetic models only), and hours since last meal or drink (metabolite models only). Environmental variables included: total fruit consumption, total vegetable consumption, alcohol consumption, and smoking status. Genetic variables included the six genetic variants associated with metabolites (rs144009214, rs12414734 and rs8050812 for ascorbic acid 2-sulfate and rs165879, rs4680, and rs61484427 for O-methylascorbate). Metabolic factors included O-methylascorbate and ascorbic acid 2-sulfate measured levels.

To assess the gene-environment and metabolite-environment interactions, we first fit linear models with and without gene-environment or metabolite-environment interaction terms. Each model was adjusted for the following potential confounders: age, sex, income, province, education level, hypertension, diabetes, total daily caloric intake, BMI, alcohol frequency, and smoking status. The gene-environment models were additionally adjusted for the first 10 principal components or genetic variation to account for confounding by ancestry. The metabolite-environment models were additionally adjusted for the hours since last meal or drink to reduce metabolite measurement bias. We conducted a likelihood ratio test for each gene/metabolite environment pair to assess the significance of the interaction term(s) in the model. We performed a complete case analysis, resulting in each model using slightly different sample sizes based on the number of missing values for the included genetic variables, metabolite levels, and fruit and vegetable consumption values. The total number of participants for each model is stated in Table S1 and ranged from 7722 to 8050. We ran a total of 32 interaction tests and adjusted for multiple testing using a False Discovery Rate approach (Benjamini and Hochberg, 1995) using the p.adjust function in R. Suggestive interactions were visualized by creating interaction plots using the R package sjPlot v. 2.8.15(Ludecke, 2023). All analyses were performed in R v.4.3.1(R Core Team, 2023).

3.3. Results

3.3.1. Study sample description

The genetic and environmental variables of the 8060 participants from the CLSA Comprehensive Cohort are described in Table 1. The mean age of the cohort was 63 years (SD: 10.1) and 51.1% of the cohort were females. The mean IOP for the sample was 16.32 mmHg (SD: 3.95). The average number of servings of fruit consumed per day was 1.81 (SD: 1.14) and of vegetables was 1.91 (SD: 1.07). In the cohort, 46.3% of participants were never smokers, 44.7% were former smokers and 9.1% were current smokers. For alcohol consumption, 1.8% of participants were never drinkers, 39% were occasional drinkers, 42.7% were weekly drinkers and 16.5% were daily drinkers.

3.3.2. Single factor models

We examined each genetic, metabolic, and environmental factor in single factor models without interaction. Of the factors, total vegetable consumption, O-methylascorbate, and ascorbic acid 2-sulfate were statistically significantly associated with IOP. None of the genetic factors were significantly associated with IOP. The coefficient estimates and 95% confidence intervals for each model are shown in Figure 1.

3.3.3. Interaction results

Next, we examined the interactions between the metabolic/genetic factors and the environmental variables. Results from all the models are detailed in Additional File 1. Of the interactions evaluated, one was suggestively significant (P-value <0.1) after correction for multiple testing, visualized in Figure 2. This interaction was between alcohol consumption frequency and a genetic variant associated with ascorbic acid 2-sulfate: rs8050812.

The suggestive interaction between rs8050812 and alcohol consumption frequency (adjusted P-value=0.094) is displayed in Figure 2. The trend in Figure 2 suggests that predicted values of

IOP do not differ greatly by genotype in those that consume alcohol but are different among non-drinkers. In those that have the TT genotype, the predicted IOP value is lower.

3.4. Discussion

In the present analysis, we identified one gene-environment interaction associated with IOP that was suggestive after correcting for multiple testing. This interaction was between a genetic variant associated with ascorbic acid 2-sulfate (rs8050812) and alcohol consumption frequency.

To better understand how environmental variables are influenced by the genome and metabolome, we also looked more closely at the gene-environment interactions themselves using interaction plots. For the interaction between rs8050812 and alcohol consumption, those in the never drinker category had lower IOP predicted levels with an increasing number of minor alleles. This could suggest a protective effect of that genotype which could be inhibited by alcohol consumption.

While we were able to identify a suggestive gene-environment interaction, and while both metabolites were associated with IOP in the single factor models, none of the metabolite-environment interactions were statistically significant. This casts doubt on whether the identified effect of the genetic variant on IOP is acting through the metabolite or whether the variant is acting through another pathway. Metabolite levels are influenced by many factors, which could make the identification of an interaction more difficult.

We considered other pathways through which the genetic variant may be interacting with the environmental variable outside of the metabolite. In our previous research, we identified genes which were mapped to genetic variants associated with ascorbic acid 2-sulfate using the platform FUMA(Lelievre et al., 2024). Some of the genes mapped included MAPK3 and PTEN. MAPK3, also known as extracellular signal-regulated kinase 1 (ERK1) is involved in the MAPK signaling pathway which has several functions (Busca et al., 2016). Some research has also investigated the effect of alcohol on this signaling pathway (Aroor and Shukla, 2004). For example, one study noted that alcohol inhibited the MAPK signaling pathway during the differentiation of liver cells(Gao et al., 2014). Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene which has been implicated in glaucoma pathogenesis and other markers such as visual acuity(Tellios et al., 2017; Shabanzadeh et al., 2019; Tan et al., 2020). Other research has discussed the effects of alcohol on PTEN activity in the context of other diseases such as alcoholic liver disorder and ostopenia(Shearn and Petersen, 2015; Chen et al., 2019). These genes identified may suggest other pathways for impacting IOP that are not directly through the ascorbic acid 2-sulfate metabolic pathway.

The current analysis has many strengths, including the use of a large, high quality data sample of environmental, genetic, and metabolic data. There are also some limitations. One limitation is that only European-descent participants were included in the analysis due to the small percentage of participants of non-European ancestry in the sample. Therefore, our findings would need to be investigated in other ancestry groups. Another limitation is that for some of the genetic variables, the number of participants with certain genotypes were very low. For example, the number of homozygotes for the minor alleles were three and 19 for the rs144009214 and rs165879 variants, respectively. No significant gene-environment interactions were detected with these variants, which could be due to a lack of power in these analyses. Finally, due to the cross-sectional nature of the analysis, it may be difficult to establish temporality between the exposure and outcome variables, since they vary over time, unlike the genetic variables. Future research should conduct a longitudinal analysis of these associations to get more precise measurements and better understand the relationship between the dietary variables and IOP levels.

3.5. Conclusions

In conclusion, we found suggestive evidence of gene-alcohol consumption interaction effect on IOP involving a metabolite-associated variant. This analysis would need to be reproduced in other samples with larger sample sizes to confirm these findings and to better understand the effect of the interactions. As well, future studies are needed to understand the role that metabolites play in these interactions.

3.6. Declarations

3.6.1. Acknowledgements

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The development, testing and validation of the Short Diet Questionnaire (SDQ) were carried out among NuAge study participants as part of the Canadian Longitudinal Study on Aging (CLSA) Phase II validation studies, CIHR 2006-2008. The NuAge study was supported by the Canadian Institutes for Health Research (CIHR), Grant number MOP-62842, and the Quebec Network for Research on Aging, a network funded by the Fonds de Recherche du Québec-Santé.

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3.6.3. Competing interests

The authors declare that they have no competing interests.

3.6.4. Availability of data and materials

Data are available from the Canadian Longitudinal Study on Aging (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data. Code is made available on GitHub (https://github.com/Roy-Gagnon-lab).

3.6.5. Ethics approval and consent to participate

The analysis presented here was approved by the University of Ottawa research ethics board.

3.6.6. Consent for publication

Not applicable.

3.6.7. Authors' Contributions

RL was responsible for preparing the dataset, conducting data analysis, interpreting and visualizing the results, and preparing the manuscript. MR helped with results validation and support with data analysis. JL, PH, MHRG and EF helped with securing funding for the project and project conceptualization. MHRG and EF supervised the project completion and provided resources to aid in project completion. MHRG also helped with feedback on the methodology, analysis and results interpretation. All authors aided in reviewing the manuscript and providing final approval.

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3.8. Figures

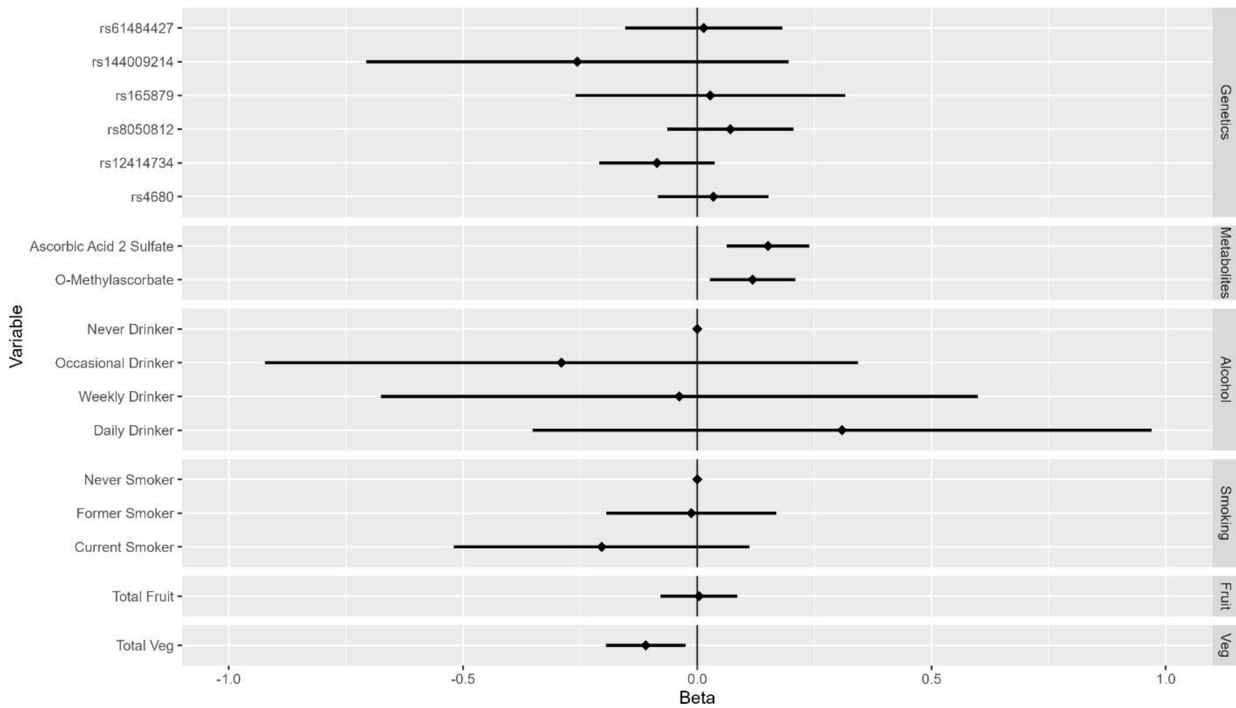

Figure 1. Simple linear regression coefficient estimates (beta) and 95% confidence intervals for each individual genetic, metabolic, and environmental variable.

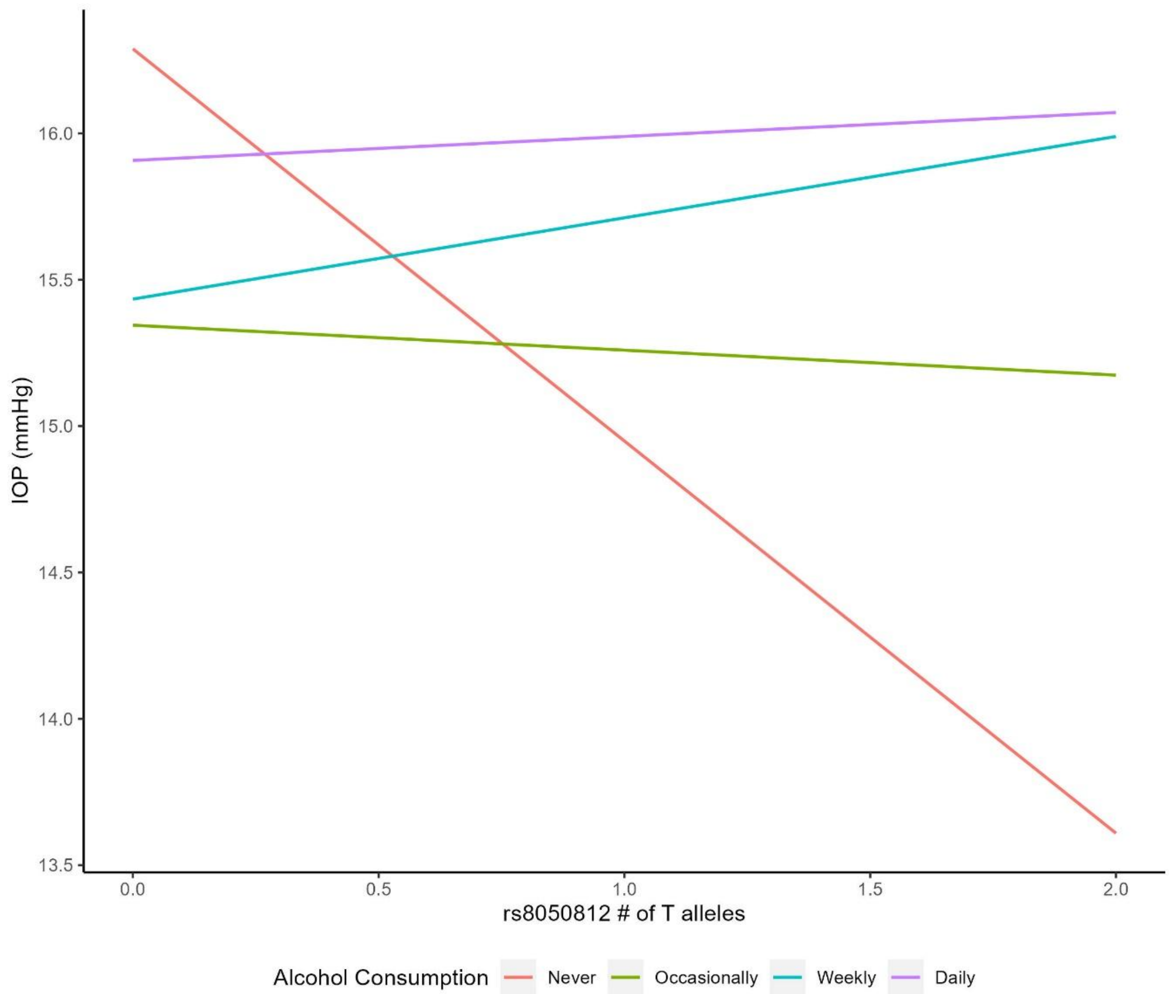

Figure 2. Interaction plot for the suggestive interaction between rs8050812 and alcohol consumption frequency.

3.9. Table

Table 1. Descriptive characteristics of sample (N=8060).

Variable		N (%) or Mean (SD)
Intraocular Pressure		16.32 (3.95)
Female Sex		4120 (51.1%)
Age, Years		63 (10.1)
Low education	Less than a Bachelor’s	1678 (20.8%)
	Bachelor’s Degree	1855 (23.0%)
	University Degree above Bachelor’s	4527 (56.2%)
Smoking Status	Never Smoker	3728 (46.3%)
	Former Smoker	3599 (44.7%)
	Current Smoker	733 (9.1%)
Alcohol Frequency	Never	147 (1.8%)
	Occasionally	3141 (39.0%)
	Weekly	3442 (42.7%)
	Daily	1330 (16.5%)
Fruit Consumption, # servings per day		1.81 (1.14)
Vegetable Consumption, # servings per day		1.91 (1.07)
Province	Alberta	801 (9.9%)
	British Columbia	1650 (20.5%)
	Manitoba	837 (10.4%)
	Newfoundland and Labrador	585 (7.3%)
	Nova Scotia	834 (10.3%)
	Ontario	1758 (21.8%)
	Quebec	1595 (19.8%)
Income	<$20 000	385 (4.8%)
	$20 000-$50 000	1718 (21.3%)
	$50 000-$100 000	2680 (33.3%)
	$100 000-$150 000	1546 (19.2%)
	>$150 000	1256 (15.6%)
	Missing/Refused/Don’t Know	475 (5.9%)
Hypertension		4530 (56.2%)
Diabetes		1368 (17.0%)
Daily Caloric Intake		1516.5 (466.3)
BMI	Underweight	219 (2.7%)
	Normal Weight	2165 (26.9%)
	Overweight	3289 (40.8%)
	Obese	2387 (29.6%)
rs4680	AA	2143 (26.6%)
	AG	4036 (50.1%)

	GG	1871 (23.2%)
rs8050812	CC	4141 (53.5%)
	CT	3033 (39.2%)
	TT	570 (7.4%)
rs165879	GG	7212 (91.3%)
	GA	664 (8.4%)
	AA	19 (0.2%)
rs144009214	CC	7744 (96.6%)
	CT	272 (3.4%)
	TT	3 (0.0%)
rs61484427	$(TCT)_2$	5622 (72.0%)
	$(TCT)_2$/delTCT	2007 (25.7%)
	delTCT/delTCT	179 (2.3%)
rs12414734	GG	3043 (38.5%)
	GA	3776 (47.7%)
	AA	1093 (13.8%)

3.10. Appendices

3.10.1. Supplementary Information

Table S1. Adjusted linear regression models for each metabolite-environment or SNP-environment interaction.

Metabolite or Variant	Environmental Factor	Genetic Variant/Metabolite Beta (SE)	Environmental Variable Beta (SE)	Interaction Beta (SE)	Interaction p-value	LRT p-value	Adjusted LRT p-value	N
O-Methyl Ascorbate	Total Fruit	0.167 (0.0785)	-0.00792 (0.0421)	-0.0309 (0.0384)	0.422	0.422	0.618	7960
	Total Veg	0.188 (0.0862)	-0.115 (0.0436)	-0.0389 (0.0410)	0.342	0.342	0.618	7974
	Alcohol	-0.205 (0.303)	-	-	-	0.344	0.618	7984
	Never (Ref)	-	-	-	-	-	-	-
	Occasional	-	-0.281 (0.330)	0.378 (0.309)	0.221	-	-	-
	Weekly	-	-0.0417 (0.331)	0.250 (0.310)	0.420	-	-	-
	Daily	-	0.289 (0.343)	0.385 (0.320)	0.229	-	-	-
	Smoking	0.0909 (0.0680)				0.344	0.618	7984
	Never (Ref)	-	-	-	-	-	-	-
	Former	-	-0.0270 (0.0929)	0.0886 (0.0915)	0.333	-	-	-
	Current	-	-0.190 (0.165)	-0.0999 (0.140)	0.476	-	-	-
Ascorbic Acid	Total Fruit	0.204 (0.0770)	-0.0140 (0.0424)	-0.0318 (0.0385)	0.409	0.409	0.618	7841
	Total Veg	0.288 (0.0834)	-0.116 (0.0441)	-0.0754 (0.0397)	0.0575	0.0575	0.335	7854
	Alcohol	-0.408 (0.264)	-	-	-	0.144	0.384	7863
	Never (Ref)	-	-	-	-	-	-	-
	Occasional	-	-0.299 (0.329)	0.615 (0.271)	0.0233	-	-	-
	Weekly	-	-0.0415 (0.330)	0.532 (0.272)	0.0511	-	-	-
	Daily	-	0.354 (0.342)	0.566 (0.284)	0.0464	-	-	-
	Smoking	0.0571 (0.0667)	-	-	-	0.0806	0.368	7863
	Never (Ref)	-	-	-	-	-	-	-

	Former	-	-0.00863 (0.0936)	0.202 (0.0923)	0.0283	-	-	-
	Current	-	-0.141 (0.168)	0.0399 (0.139)	0.774	-	-	-
rs4680	Total Fruit	0.216 (0.115)	0.100 (0.0660)	-0.100 (0.0539)	0.0628	0.0627	0.335	8028
	Total Veg	0.111 (0.125)	-0.0710 (0.0715)	-0.0388 (0.0569)	0.496	0.496	0.618	8040
	Alcohol	-0.123 (0.459)	-	-	-	0.898	0.927	8050
	Never (Ref)	-	-	-	-	-	-	-
	Occasional	-	-0.441 (0.539)	0.162 (0.469)	0.729	-	-	-
	Weekly	-	-0.222 (0.540)	0.192 (0.468)	0.681	-	-	-
	Daily	-	0.241 (0.559)	0.0730 (0.481)	0.880	-	-	-
	Smoking	0.161 (0.0881)	-	-	-	0.1366	0.385	8050
	Never (Ref)	-	-	-	-	-	-	-
	Former	-	0.204 (0.154)	-0.226 (0.126)	0.0738	-	-	-
	Current	-	0.0761 (0.263)	-0.298 (0.221)	0.178	-	-	-
rs12414734	Total Fruit	-0.150 (0.117)	-0.00853 (0.0591)	0.0341 (0.0551)	0.536	0.536	0.618	7890
	Total Veg	-0.171 (0.131)	-0.141 (0.0617)	0.0430 (0.0610)	0.481	0.481	0.618	7902
	Alcohol	-0.816 (0.444)	-	-	-	0.0154	0.245	7912
	Never (Ref)	-	-	-	-	-	-	-
	Occasional	-	-1.035 (0.488)	0.848 (0.455)	0.0626	-	-	-
	Weekly	-	-0.733 (0.488)	0.801 (0.454)	0.0777	-	-	-
	Daily	-	-0.719 (0.504)	0.356 (0.470)	0.449	-	-	-
	Smoking	-0.152 (0.0922)	-	-	-	0.541	0.618	7912
	Never (Ref)	-	-	-	-	-	-	-
	Former	-	-0.108 (0.136)	0.102 (0.132)	0.441	-	-	-
	Current	-	-0.382 (0.235)	0.222 (0.226)	0.325	-	-	-
rs8050812	Total Fruit	0.239 (0.129)	0.0548 (0.0529)	-0.0917 (0.0600)	0.126	0.126	0.385	7722
	Total Veg	0.265 (0.141)	-0.0503 (0.0558)	-0.0998 (0.0636)	0.117	0.117	0.385	7734
	Alcohol	-1.340 (0.497)	-	-	-	0.00294	0.094	7744
	Never (Ref)	-	-	-	-	-	-	-

	Occasional	-	-0.944 (0.417)	1.254 (0.509)	0.0137	-	-	-
	Weekly	-	-0.855 (0.418)	1.617 (0.508)	0.00146	-	-	-
	Daily	-	-0.381 (0.433)	1.42 (0.526)	0.00692	-	-	-
	Smoking	0.00494 (0.101)	-	-	-	0.168	0.414	7744
	Never (Ref)	-	-	-	-	-	-	-
	Former	-	-0.0234 (0.122)	0.0523 (0.144)	0.717	-	-	-
	Current	-	-0.426 (0.212)	0.468 (0.249)	0.0601	-	-	-
rs165879	Total Fruit	-0.325 (0.280)	-0.00986 (0.0438)	0.210 (0.141)	0.137	0.137	0.385	7873
	Total Veg	-0.513 (0.292)	-0.140 (0.0458)	0.290 (0.134)	0.0306	0.0306	0.245	7886
	Alcohol	1.888 (1.251)	-	-	-	0.441	0.618	7895
	Never (Ref)	-	-	-	-	-	-	-
	Occasional	-	-0.121 (0.341)	-2.000 (1.274)	0.116	-	-	-
	Weekly	-	0.112 (0.342)	-1.778 (1.271)	0.162	-	-	-
	Daily	-	0.451 (0.355)	-1.901 (1.298)	0.143	-	-	-
	Smoking	0.235 (0.220)	-	-	-	0.449	0.618	7895
	Never (Ref)	-	-	-	-	-	-	-
	Former	-	0.0288 (0.0975)	-0.0360 (0.0312)	0.248	-	-	-
	Current	-	-0.182 (0.170)	-0.421 (0.490)	0.391	-	-	-
rs144009214	Total Fruit	-0.249 (0.438)	0.00953 (0.0425)	-0.00559 (0.199)	0.978	0.978	0.978	7997
	Total Veg	-0.530 (0.448)	-0.110 (0.0441)	0.140 (0.205)	0.496	0.496	0.618	8009
	Alcohol	2.595 (1.929)	-	-	-	0.475	0.618	8019
	Never (Ref)	-	-	-	-	-	-	-
	Occasional	-	-0.168 (0.329)	-2.788 (1.964)	0.156	-	-	-
	Weekly	-	0.101 (0.330)	-2.894 (1.960)	0.140	-	-	-
	Daily	-	0.451 (0.342)	-3.16 (2.018)	0.118	-	-	-
	Smoking	-0.278 (0.336)	-	-	-	0.191	0.437	8019
	Never (Ref)	-	-	-	-	-	-	-
	Former	-	-0.0153 (0.0942)	-0.244 (0.487)	0.616	-	-	-

	Current	-	-0.257 (0.164)	1.19 (0.784)	0.129	-	-	-
	Total Fruit	-0.0424 (0.163)	-0.000968 (0.0480)	0.0333 (0.0773)	0.667	0.667	0.711	7786
	Total Veg	-0.0893 (0.179)	-0.130 (0.0493)	0.0519 (0.0841)	0.537	0.537	0.618	7798
	Alcohol	-0.421 (0.607)	-	-	-	0.644	0.711	7808
	Never (Ref)	-	-	-	-	-	-	-
	Occasional	-	-0.466 (0.397)	0.482 (0.622)	0.438	-	-	-
rs61484427	Weekly	-	-0.202 (0.398)	0.487 (0.620)	0.433	-	-	-
	Daily	-	0.183 (0.411)	0.237 (0.642)	0.712			
	Smoking	0.115 (0.125)	-	-	-	0.0268	0.245	7808
	Never (Ref)	-	-	-	-	-	-	-
	Former	-	0.0160 (0.0108)	-0.0543 (0.180)	0.763	-	-	-
	Current	-	0.0505 (0.191)	-0.798 (0.302)	0.008109	-	-	-

Coefficient estimates and standard errors (SE) are shown from models adjusted for age, sex, income, province, education level, hypertension, diabetes, total daily caloric intake, BMI, alcohol frequency, smoking status, first 10 genetic principal components (genetic models only) and hours since last meal or drink (metabolite models only). LRT p-value = p-value of likelihood ratio test comparing models with and without interaction terms for each interaction tested. Adjusted LRT p-value = p-value adjusted for multiple testing of all 32 LRT tests performed using a False Discovery Rate approach. N = number of participants with complete data for each model.

3.10.2. Confirmation of Publication Submission

Email confirmation of submission to *BMC Genomic Data*.

BD

BMC Genomic Data<sankara.narayanan@springernature.com>

To: Rebecca Lelievre

Fri 9/27/2024 12:05 PM

Attention : courriel externe | external email

Ref: Submission ID efbd49a9-f772-4a1a-8be9-f81a50f96cf9

Dear Dr Lelievre,

Please note that you are listed as a co-author on the manuscript "Evaluating vitamin C-related gene-environment and metabolite-environment interaction effects on intraocular pressure in the Canadian Longitudinal Study on Aging", which was submitted to BMC Genomic Data on 27 September 2024 UTC.

If you have any queries related to this manuscript please contact the corresponding author, who is solely responsible for communicating with the journal.

Kind regards,

Editorial Assistant
BMC Genomic Data

4. Discussion

4.1. Overview of Results/Summary of Findings

In the present thesis, we investigated the genetic, metabolic and environmental contributions to intraocular pressure using data from the Canadian Longitudinal Study on Aging. We first investigated genetic factors associated with the serum concentrations of two metabolites associated with vitamin C which have been linked to IOP. In addition, we investigated whether these genetic associations were modified by sex, since vitamin C concentrations have been found to differ by sex. We identified some statistically significant and several suggestive variants whose associations with O-methylascorbate and ascorbic acid 2-sulfate were modified by sex. Next, we investigated how the genetic variants we identified previously and serum metabolite concentrations modify the association between dietary environmental variables and IOP. We identified two statistically significant gene-environment interactions between genetic variants associated with ascorbic acid 2-sulfate and alcohol consumption frequency.

4.2. Findings in the Context of Metabolites

Metabolites can be the missing link in understanding the functionality of the genome and can represent a better measure of environmental contributions to changes in molecular pathways (Walker et al., 2019). Many of the studies which have utilized metabolites in the past have been more targeted studies, with smaller sample sizes (van Roekel et al., 2019; Wang et al., 2021; Tang et al., 2022). Here, we wanted to build on previous research and further assess how metabolite measurements can be utilized on the population scale in the context of glaucoma and IOP.

Previous studies have investigated the genetic determinants of metabolite levels, since many of them have been shown to be heritable (Hagenbeek et al., 2020) and have found several genetic variants associated with metabolites in large scale analyses (Chen et al., 2023). Here we furthered this research by focusing on vitamin C-related metabolites specifically and looking at them more comprehensively. In addition, for these metabolites, it has not been previously investigated whether biological sex modifies the associations between the genetic variants and metabolite measurements. Here, we were able to identify several genetic loci which appear to be modified by biological sex and can be of future interest. These genes were also functionally annotated to several genes which can help to clarify what may be some of underlying molecular reasons for why vitamin C differs between sexes. Some of the genes discovered could be linked to sex hormones, which follows a proposed theory that sex hormones could contribute to the sex differences in vitamin C concentrations (Travica et al., 2020).

4.3. Findings in the Context of IOP

Glaucoma is a complex disease, with a disease etiology that is not fully understood, but where early diagnosis is crucial for later outcomes (Jonas et al., 2017). As such, researchers have investigated both genetic and environmental factors associated with glaucoma and its endophenotype intraocular pressure (IOP). While identifying genetic variants is important, it can be difficult to translate these findings into actual function, and much of the variance in IOP is still not understood (Xu et al., 2021). By leveraging the power of metabolites and looking at gene-environment interactions, we can understand both better. Here, we report interactions between genetic variants associated with ascorbic acid 2-sulfate and alcohol consumption. Previous research has found the genetic variants related to glaucoma can modify the association between alcohol and IOP (Grant et al., 2023; Stuart et al., 2023). Our research built on this and found evidence that genetic factors related to metabolites can also modify the association between alcohol and IOP. Overall, by first conducting a genome-wide association study and using these results to comprehensively investigate risk factors for IOP, this research utilized several levels of evidence to evaluate disease risk.

4.4. Strengths and Limitations

One of this research's strengths is using a large population sample with detailed survey responses that also included genetic, metabolic and environmental data. Resources like the CLSA allow a more comprehensive investigation of risk factors affecting disease-related traits. In addition, in the present thesis we used several state-of-the-art analytical methods and software programs to aid in our analysis, including software such as FUMA and GCTA which have been used extensively in previous research. Finally, we were able to control for several potential confounders in our analyses.

There were also some limitations for this thesis. One limitation is that this was a cross-sectional analysis, so it is not possible to account for the change in environmental variables over time. In addition, it is difficult to assess the temporality between our environmental variables of interest and IOP. Since there has been little research which has investigated the metabolic contributions to IOP, the scope of our study was to identify any associations which should be investigated more thoroughly in future studies, including the use of longitudinal analysis.

Another limitation is the potential lack of generalizability of these findings, since the population used in this study were only those of European ancestry. The CLSA dataset includes over 90% of participants from European ancestry, and therefore we would not have enough power to conduct our analyses in other populations. While our results should be replicated in different ancestries in the future, they provide important information for future research on the effect of metabolite levels on IOP variation.

Finally, many of the variables, including the dietary exposures and metabolite measurements may be subject to measurement error. In our study, we do not believe that the measurement error would be differential for those with higher or lower IOP, but instead would be non-differential. Essentially, the less precise measurements would introduce more variability into the analysis which would dilute the effect, and lead to a bias towards the null. For example, there is also a large amount of within-individual variability of metabolite measurements, and this can reduce the power of these analyses (Sampson et al., 2013), however, in our case, our sample size was reasonably large to still detect an effect.

4.5. Significance

As mentioned previously, we cannot understand the variance of IOP and the mechanisms of glaucoma using genetics or environmental variables alone. Utilizing metabolites allows us to gain a more functional understanding of glaucoma and elevated IOP risk. Currently, the treatments for glaucoma involve lowering IOP, and there is a need for better diagnostics and treatments (Jonas et al., 2017). Finding better predictors of risk, whether that be genetic, environmental, metabolic, will allow better identification of high-risk patients for earlier treatment. In addition, by understanding the biological pathways which contribute to glaucoma and elevated IOP, we can develop more targeted treatments. Finally, using gene-environment interaction analysis helps to better understand how our environment modifies our inherent risk, so that physicians can give more personalized advice on lowering risks, and reducing glaucoma progression. While there is still more research needed to translate findings into prevention and treatment strategies, the results presented here can build towards better healthcare options for glaucoma patients and those at risk for developing glaucoma.

4.6. Conclusion & Future Steps

In conclusion, we investigated genetic factors associated with O-methylascorbate and ascorbic acid 2-sulfate, as well as how they are modified by sex. In addition, we investigated how these metabolites interact with environment variables in their association with intraocular pressure. These findings help better understand vitamin C's activity at the molecular level, the disease pathogenesis of glaucoma and the factors associated with IOP variation. There are many next steps for the work presented here. Firstly, these results should be replicated in an independent cohort, and should be analyzed looking at more diverse ancestries, since our research focused on European ancestry. A larger cohort could also give more power to detect gene-environment interactions, whether that be the gene-sex associations in GWAS, or gene-environment interactions when studying IOP. In addition, since we found evidence of gene-sex interactions in our GWAS, the gene-alcohol interaction effects on IOP that we identified could be analyzed in a sex-stratified manner to see if biological sex plays an important role in these interactions. Finally, this study utilized only one round of data from the CLSA, but future studies should conduct longitudinal analyses to investigate changes over time and lead to more robust conclusions.

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