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Population-specific genetic variants and related health outcomes in a cohort of Inuit children in Nunavut

Jimena Gonzalez-Lema[1], Jean Allen[2], Ekua Agyemang[3], Michael Patterson[4], Amber Miners[3], Holden Sheffield[4], Amy Caughey[5], Anne Pham-Huy[6], Tom Kovesi[7], Adam J. Shapiro[8], Kristin Kernohan[9], Edward Yeh[9], Adam Yeh[9], Alan Mears[9], Melanie Lacaria[9], Sorcha Collins[10], Melissa Braschel[11], Julien Marcadier[12], Anthony Otley[13], Gwen Healey Akearok[14], Michelle Doucette[3], Cheryl Rockman-Greenberg[15], Pranesh Chakraborty[9], Nadine Caron[16,17], Anna Lehman[1] and Laura Arbour[1,11*]

Abstract

Introduction Like all populations, Inuit children experience rare genetic conditions. Awareness of the unique Inuit genetic architecture allows the identification of specific variants associated with autosomal recessive conditions affecting child health across the Arctic. As a priority, the impact of the *IFNAR2* c.157T>C variant causing IFNAR2 Deficiency, *DNAH11* c.4095+2C>A causing Primary Ciliary Dyskinesia, and *SI* c.273_274delAG causing Congenital Sucrase-Isomaltase Deficiency (CSID), along with other disease-causing variants were assessed to determine the potential health outcomes on infant and child health in Nunavut.

Methods With the direction of Nunavut Tunngavik Incorporated and the Government of Nunavut Department of Health a research group was established utilizing local and national expertise. Newborn dried screening blood spots of a 4-year cohort of infants born to residents of Nunavut between January 1st, 2010, and December 31st, 2013, were genotyped (*n*=2947) followed by linkage of a subset of the cohort to a database with demographic and health information collected from records spanning from birth to 5 years (*n*=2206 Inuit children). Live birth prevalence (LBP) of cases and carrier frequencies were first estimated for the full cohort and recalculated for the subset with linked data. Health visit information was reviewed for phenotype features consistent with the conditions of interest. In addition, baseline characteristics, and health visits for CSID cases were compared to those without the variant.

Results LBP of cases due to homozygosity of the *DNAH11*, *IFNAR2* and *SI* variants were 1/1474, 1/737 and 1/28; carrier frequency was 1/13, 1/18 and 1/4, respectively. Four children with *IFNAR2*, one with *DNAH11*, and 83 with *SI* homozygosity were linked to health data, confirming phenotypes consistent with the conditions. CSID was associated with significant increased health care utilization for gastrointestinal illness visits before age two (OR=1.9, 95% CI 1.2–3.0). However, breastfeeding for up to six months was found to be protective, with a reduced number of health care visits (OR=0.80, 95% CI 0.63–1.0).

*Correspondence:
Laura Arbour
larbour@uvic.ca

Full list of author information is available at the end of the article

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Conclusion We describe the presence and health impact of three autosomal recessive conditions in a Canadian Inuit population. Genetic testing, practitioner education, and Inuit-informed management strategies are urgently needed to address these conditions and improve outcomes.

Keywords IFNAR2 deficiency (*IFNAR2*), Primary ciliary dyskinesia (*DNAH11*), Congenital sucrase-isomaltase deficiency, Inuit, Child health

Introduction

Rare genetic disease, most often presenting in childhood, occurs in every population [1] and Indigenous populations are no exception [2]. In the current era of 'precision medicine', a concept that takes individual genetic variability into account for diagnosis, prevention, and treatment strategies [3], knowledge of the genetic basis of disease is considered alongside the social determinants of health, which also contribute greatly to health outcomes throughout the life course [4]. In some populations, certain rare genetic conditions become common because of historic population structures that increased the frequency of disease-causing genetic variants, including autosomal recessive conditions [5, 6], providing a unique opportunity for precision medicine to be integrated into public health strategies.

The Inuit are Indigenous people inhabiting the Arctic regions of Russia, United States (Alaska), Canada, and Greenland. Inuit Nunangat (Inuit homelands) within Canada comprises four regions: Nunatsiavut (northern Labrador), Inuvialuit Settlement Region (northern Northwest Territories), Nunavik (northern Quebec), and the territory of Nunavut. Nunavut, the largest of the four regions, is home to over 30,895 people, (about 44% of the Canadian Inuit population) living in 25 communities, within three regions, Qikiqtani/Qikiqtaaluk, Kitikmeot, and Kivalliq within the territory [7, 8].

Recent genomic studies of Greenlandic Inuit suggest that modern Inuit can trace ancestral lineage to a small population of about 300 individuals (sometimes referred to as 'founders') who traversed the Arctic less than 1000 years ago [9], settling along the way in various locations including what is now Canada. In addition to this small group of ancestors, a series of 'bottlenecks' (events that reduce population size) contributed to a unique genetic architecture, where certain autosomal recessive conditions affecting health may become more common, but also may be efficiently recognized and managed [9, 10]. Although certain autosomal recessive conditions may be more common among Inuit, the overall impact of genetic disease is not increased compared to other populations [9, 10], corroborating other studies of unique populations with recognizable autosomal recessive conditions due to founder variants [5].

Most Inuit children are born healthy, however much attention has been directed to higher rates of infant mortality [11], congenital anomalies [12, 13], and hospitalizations for respiratory tract and other infections [14, 15] than their non-Indigenous counterparts. In recent years clinicians have speculated that in addition to underlying social determinants of health, genetic factors could be influencing outcomes. Conditions such as inborn errors of immunity [16], primary ciliary dyskinesia (PCD) (a rare condition leading to recurrent respiratory tract infection and bronchiectasis) [17], as well as congenital sucrase-isomaltase deficiency (CSID) (causing malabsorption of certain sugars and starches leading to diarrhea, abdominal pain, and bloating), have been documented to impact Inuit infant and child health disproportionate to other populations. Notably, the first published report of patients in Nunavut affected by disaccharide malabsorption was nearly 50 years ago [18], and more than a decade has passed since the Inuit specific gene variant causing CSID (*SI* c.273_274delAG p.Gly92Leufs*8) was delineated [19].

In 2022, Duncan et al. identified an Inuit specific genetic variant in *IFNAR2* associated with increased susceptibility to serious viral illness as well as life-threatening events following vaccination with live-attenuated viral vaccines [20]. Inuit Children from Alaska, Nunavik and Greenland were identified with *IFNAR2* c.157T>C p.(Ser53Pro), suggesting Inuit children throughout the Canadian Arctic were at risk. This publication prompted discussions between Nunavut Tunngavik Incorporated (NTI) (the organization that represents Nunavut Inuit and oversees the adherence to obligations in the Nunavut (land claim) Agreement) and the Government of Nunavut Department of Health (DoH)—both seeking to determine the impact on Inuit children in Nunavut.

The awareness of the potential impact of the *IFNAR2* variant and other disease-causing variants in Inuit children from Alaska to Greenland, compelled the initiative to understand the impact of these variants on infant and child health in Nunavut. With leadership from NTI and the Department of Health, health care providers serving all three regions of Nunavut were consulted, and an agreed-upon assessment was implemented of six pathogenic genetic variants potentially contributing to serious genetic conditions in Inuit infants and children, all amenable to treatment. A previously established database of health and demographic information for a four-year cohort of Inuit births to residents of Nunavut, with linked newborn dried blood spots and followed to 5 years of age, was utilized [21–23] with the goal of determining

the birth prevalence of cases and the spectrum of presentation for each condition of interest. Here we present the results of that assessment.

Methods

Partnership and ethics

The current study was initiated by Nunavut Tunngavik Incorporated (NTI) [24], the Nunavut Department of Health (DoH) [25] and implemented by the UBC Community Genetics Research Program [26]. A core study group was established (Allen, Patterson, Doucette, Arbour, Chakraborty). In addition, epidemiologists, nutritionists, primary care physicians, pediatricians, specialists in immunology, respirology, genetics, and gastroenterology were consulted, most of whom were serving the Nunavut population. Multiple virtual meetings with the core study group, and numerous additional virtual meetings with the extended study team took place between May 2022 and October 2025. The University of British Columbia (UBC), University of Manitoba, and the Children's Hospital of Eastern Ontario (CHEO) Research Ethics Boards approved the original study [21, 22] and amendments for the current study. The Nunavut Research Institute granted a research license.

Data sources

This study used a previously developed database and linked newborn blood spots [21, 22] established in partnership with NTI, DoH, Qaujigiartiit Health Research Centre (QHRC) and the UBC Community Genetics Research Program. In summary, maternal and child health data were collected for consecutive births between January 1, 2010, and December 31, 2013, for 18 of Nunavut's 25 communities (about 85% of births). Health data were collected within communities from paper charts, and electronic health records when available. The final collection of health data included demographic and health information on Inuit children (determined by at least one parent self-reported as Inuk) including 2206 with linked dried blood spots born during the stated period and followed until age 5 years. A wide range of variables and outcome data documenting gestational age, breastfeeding practices, food insecurity, country food use as documented at well baby visits (traditional Inuit foods obtained through hunting, fishing, and gathering from the local environment), community health care provider visits for health concerns, diagnoses, congenital anomalies, hospitalizations (local and tertiary), and mortality (up to five years of age) were collected. Food insecurity was obtained from well-baby records collected at 2, 6, 12, 24, and 48 months of age, and breastfeeding status at 6 months was collected at 6, 12 and 24 months, using caregiver-reported information. Missing data arose when children did not attend the relevant visits or when responses were recorded as "refused to answer" or "don't know" for food insecurity, and "unknown" for breastfeeding at 6 months. These responses were treated as missing for the purposes of the analysis [23, 27].

Genetic variant testing

In consultation with the DoH, and NTI, clinicians providing healthcare across Nunavut including in the relevant specialties, were invited to contribute their expertise and experience regarding which genetic variants characterized as pathogenic and present in Inuit children should be studied. Selected variants were evaluated for their relevance to infant and child health. Known variants impacting adult health such as for susceptibility to chronic illness were not considered for this study. The six pathogenic variants selected for this study were *IFNAR2* c.157T>C p.(Ser53Pro), *ADA* c.424C>T p.(Arg142*)/c.956_960del p.(Glu319Glyfs*3), *CYBB* c.54_79del p.(Trp18Cysfs*8), *DNAH11* c.4095+2C>A p.(?), and *SI* c.273_274delAG p.(Gly92Leufs*8). One additional research candidate was also included and will be reported separately. (See Supplementary Table 1 for descriptions of each variant and relevance for inclusion).

Dried newborn screening blood spots were stored in the CHEO newborn screening laboratory (Newborn Screening Ontario) for those infants from Qikiqtaaluk and the Kitikmeot regions at the time of the original study, and the Cadham Provincial Laboratory (CPL) for those from the Kivalliq region. Unique identifiers for each record were matched to the dried newborn screening blood spot card associated with that record. Guthrie card blood spots were transferred from CPL to the CHEO lab to enable genotyping of the complete set of the samples within the same laboratory.

A BSD300 puncher (BSD Robotics) was used to obtain a single 3 mm punch from each patient's card. Genotyping was performed using a MassARRAY® system (equipped with a 384-chip platform module [CPM]) and iPLEX ® chemistry (Agena Bioscience) using an in-house designed genotyping panel. Regions of interest were amplified through a multiplex PCR reaction. Oligos were designed such that the masses of each oligo, as well as all predicted extended oligos, were unique. Raw data analysis and genotype calling were done using Typer software (Agena Bioscience). All reaction conditions were as per vendor protocol. To confirm our assay's specificity and sensitivity, two synthetic positive DNA molecules were designed and manufactured (Integrated DNA Technologies) to mimic genomic regions containing the variants of interest. These synthetic positive quality control molecules possess all the variants of interest and were used as positive quality control material for every experiment performed. Please see supplementary data providing details.

Statistical analysis

Overall variant statistics: For each variant studied, the minor allele frequency (MAF), live birth prevalence for homozygosity, and heterozygote carrier frequency were estimated for Nunavut overall ($n = 2947$) and stratified by region using data from participants with linked health records ($n = 2206$).

Homozygous cases of *IFNAR2*, *DNAH11* and *SI* deficiency were assessed with linked health data. Phenotypic features consistent with known phenotypes described in the literature (Table 1) were documented. As well, health impact as documented through health care visits and mortality until age 5 were noted.

To assess the clinical impact of the *SI* c.273_274delAG variant causing CSID, a case-cohort study compared outcomes (reports of diarrhea, healthcare visits for gastrointestinal illness (GI) at various ages, and multiple (≥ 3 GI visits) for homozygous cases versus cohort participants who tested negative for the variant. Heterozygotes were excluded for outcome analysis because previous reports have suggested that heterozygotes for CSID may present with mild features [28, 29]. To evaluate whether the exclusion of heterozygous individuals influenced the findings, we also conducted a sensitivity analysis using a combined reference group consisting of both heterozygous and wild-type individuals (Supplementary Table 2). Descriptive statistics were used to summarize the characteristics of all children in the cohort according to genotype. Associations with the outcomes were estimated using logistic regression, with multivariable models adjusting for sex and preterm birth. Additionally, a mixed effects model adjusted for the same covariates and included home community as a random effect. Association between breastfeeding at 6 months and the outcomes were estimated with logistic regression models adjusted for variant status. As a sensitivity analysis, Fisher's exact test was used to evaluate the association between breastfeeding at 6 months and genotype, considering homozygous and wild type separately. Odds ratios (OR) with 95% confidence intervals (CI) are reported. Differences in the number of healthcare visits among wild type, heterozygous and homozygous individuals were evaluated using Kruskal-Wallis test. Pairwise comparisons were performed using Dunn's post hoc test. Statistical significance was defined as $p < 0.05$. GraphPad Prism was used for all statistical analysis, except for mixed-effects models, which were performed with R Software (version 4.3.3).

Communication and knowledge translation

For the conditions requiring in depth evaluation working groups were established consisting of pediatricians

Table 1 Key features of variants of interest with identified cases in our cohort

	IFNAR2 Deficiency	DNAH11 Deficiency (PCD)	SI Deficiency
Pathophysiology	■ Defective type I IFN signaling leading to → impaired innate antiviral host response	■ Abnormal ciliary motion (normal structure) → reduced mucociliary clearance	■ Reduced or lack of sucrase-isomaltase enzyme activity → Maldigestion of sucrose/starch
Presentation	■ Life-threatening complications following LAVV (MMRV) ■ Narrow infectious spectrum with severe infections described with select viruses (SARS CoV-2, Varicella, Influenza, HSV) ■ Viral induced hyperinflammation and HLH ■ Possible increased susceptibility to viral and other infections	■ Neonatal respiratory distress syndrome at term birth ■ Chronic wet cough, recurrent LRTI ■ Severe, recurrent otitis media with effusion ■ Chronic rhinosinusitis ■ Progressive bronchiectasis ■ Male and Female subfertility ■ Laterality defects, heterotaxy; congenital heart defects	■ Chronic osmotic diarrhea ■ Bloating ■ Flatulence ■ Abdominal pain ■ Severe cases: failure to thrive and malnutrition
Diagnosis	■ Genetic testing (*IFNAR2* c.157T > C)	■ Genetic testing (*DNAH11* c.4095+2C>A) ■ Low nasal nitric oxide ■ Abnormal ciliary beat pattern on HSVA. ■ Normal ciliary EM	■ Genetic testing (*SI* c.273_274delAG) ■ Low sucrase-isomaltase activity in small intestinal biopsy ■ Sucrose hydrogen breath test
Management	■ Prevention of viral infections. ■ Avoidance LAVV ■ Select antiviral prophylaxis ■ Optimization of inactivated and passive immunization ■ Consideration of immunoglobulin replacement therapy (IVIG or SCIG)	■ Daily airway clearance +/- inhaled mucolytics ■ Anti-inflammatories ■ Aggressive use of antibiotics ■ Frequent otolaryngology cares/surgeries	■ Dietary sucrose restriction ■ Enzyme replacement
Prevalence	■ Extremely rare	■ 1/7,600–20,000	■ ~1/ 5,000 in European populations

EM Electron microscopy, *HLH* Hemophagocytic lymphohistiocytosis, *HSVA* High speed videomicroscopy analysis, *INF* Interferon, *LAVV* Live attenuated viral vaccines, *LRTI* Lower respiratory tract infection, *MMVR* Measles Mumps Rubella Varicella, *SCIG* Subcutaneous immunoglobulin

Table 2 Genetic variants tested, cases and carrier rates for the full cohort ($n = 2947$)

Variant	MAF	Homozygous Cases	Heterozygous Carriers	Carrier Rate (Freq)
IFNAR2 c.157T>C	2.9%	4 (BP 1/737)	163	5.5% (1/18)
DNAH11 c.4095+2C>A	3.9%	2 (BP 1/1474)	225	7.6% (1/13)
SI c.273_274delAG	17.8%	107 (BP 1/28)	832	35.6% (~1/4)
ADA c.424C>T	0.4%	0	25	0.8% (1/118)
ADA c.956_960del	0.3%	0	18	0.6% (1/163)
CYBB c.54_79del	0	0	0	0

MAF Minor allele frequency, *BP* Birth prevalence, *Freq* Frequency

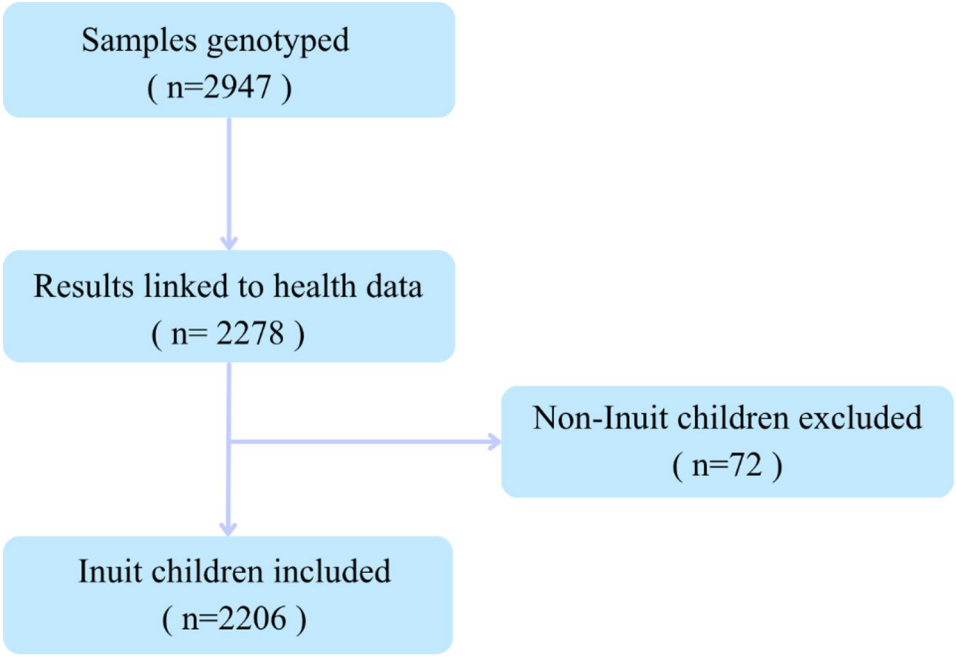

Fig. 1 Flowchart for final dataset

in all three regions, specialists delivering care to affected patients, external consultants in Medical Genetics, Respirology, Immunology, and Gastroenterology. The Chief Public Health Officer and representatives of NTI were members of each group. Results were reviewed, optimum genetic testing and management strategies discussed. Communications were planned for local health care providers.

Results

Birth prevalence and carrier frequency based on total Nunavut sample of dried blood spots

From the 2947 samples genotyped for the *IFNAR2*, *ADA*, *CYBB*, *DNAH11*, and *SI* variants, we documented four homozygous cases with the *IFNAR2* variant, two homozygous cases with the *DNAH11* variant, and 107 homozygous cases with the *SI* variant. The *CYBB* variant was not detected, and there were no homozygous cases or compound heterozygous cases due to the *ADA* variants. See Table 2 for details on birth prevalence of cases, minor allele frequency, and total carrier frequency (includes Inuit and non-Inuit samples).

Linkage of genetic results and health data

In total, 2278 genotyping results were successfully linked to health data. After excluding 72 non-Inuit children, the final sample size of health data linked to genetic variants was 2206 Inuit children (Fig. 1). Supplementary Table 3 shows carrier frequency within the three regions of Nunavut for *IFNAR2*, *DNAH11*, and *SI* variants linked to health data, thereby identifying the regional frequencies.

Genetic results linked to health data

ADA deficiency

We identified 25 heterozygous carriers of the *ADA* c.424C>T variant, and 18 for the second variant found within the *ADA* gene, c.956_960del. Given these results, the chance in our cohort of being a carrier for either *ADA* variant is 1/69.

Table 3 Clinical summary of four *IFNAR2* homozygous c.157T>C cases linked to the health database

Case number	1	2	3	4
Age at first infection	2 months	4 months	5 months	15 days
Otitis media	4	4	7	6
LRTI	2	5	3	4
Other infections	2	5	5	5
Infection related admissions	1	4	13	4
Admitted to ICU				Yes
Outcome	Died in infancy†	Records until 4.6 years.	Records until 4 years.	Records until 5 years.
Vaccination status		Unknown administration of LAV.	Unknown administration of LAV.	Unknown administration of LAV.

LRTI Lower respiratory tract infections, *LAV* Live attenuated vaccines (including BCG, rotavirus, measles-mumps-rubella and varicella vaccines)

†Cause of death: disseminated viral infection

Table 4 Descriptive infant characteristics by c.273_274del *SI* variant, numerators and denominators with proportions

Variable	Total Cohort *n* = 2206	*SI* Hom *n* = 83	*SI* Het *n* = 650	WT *n* = 1473	Hom vs. Het	Hom vs. WT	Missing
	n/N (%)	*n/N* (%)	*n/N* (%)	*n/N* (%)	OR (95%CI) *p* value	OR (95%CI) *p* value	*n* (%)
Male	1099/2205 (49.8)	39/83 (47.0)	316/650 (48.6)	744/1472 (50.5)	0.9 (0.6–1.5) 0.81	0.9 (0.6–1.3) 0.57	1 (0.04)
BF started at birth	1528/2054 (74.3)	59/80 (73.8)	431/601 (71.5)	1038/1373 (75.6)	1.1 (0.6–1.9) 0.79	0.9 (0.5–1.5) 0.68	152 (6.9)
BF at 6 months	720/1756 (41.0)	20/68 (29.4)	210/524 (40.1)	490/1164 (42.1)	0.6 (0.4–1.1) 0.11	0.6 (0.3–0.96) 0.04 *	450 (20.4)
Preterm birth (< 37 weeks)	249/2170 (11.5)	3/83 (3.6)	85/637 (13.3)	161/1450 (11.1)	0.2 (0.1–0.7) 0.007 *	0.3 (0.1–0.9) 0.027 *	36 (1.6)
Food insecurity	729/1729 (42.2)	34/66 (51.5)	240/516 (46.5)	455/1147 (39.7)	1.2 (0.7–2.1) 0.51	1.6 (1.0–2.7) 0.07	477 (21.6)

The extent of missing data was comparable across genotype groups, with missing breastfeeding data ranging from 18.1% to 21.0%, and for food insecurity ranging from 20.5% to 22.1%

BF Breastfeeding, *CI* Confidence intervals, *N* number of charts with data for category, *OR* Odds ratio, *SI SI* c.273_274delAG mutation

* Denotes statistical significance ($p<0.05$)

IFNAR2 deficiency

Four homozygous cases were identified (Table 2). Health data were available for all cases, enabling phenotypic characterization (Table 3). All four children were documented to have recurrent episodes of otitis media, infections of the lower respiratory tract, and other infections. One child died during infancy with a documented severe disseminated viral infection, consistent with the known phenotype for IFNAR2 deficiency. The remaining three had health visit records for the next 4–5 years. No severe life-threatening illness associated with live-attenuated vaccination was documented among the cases identified in the study; however, vaccination status could not be ascertained because vaccine administration data were unavailable in the data sources used for the original study.

Primary ciliary dyskinesia (DNAH11)

There were two homozygous *DNAH11* (c.4095+2C>A) cases identified within the total Nunavut sample with a birth prevalence of 1/1474 cases. There were 225 heterozygotes (1/13), with an overall allele frequency of 3.9%. We successfully linked one homozygous case to health data. This case had an atrial septal defect, 4 documented infections of the lower respiratory tract, 2 episodes of otitis media and one hospital admission for pertussis. The first presentation was at 1 month of age.

Congenital sucrase-isomaltase deficiency

We identified 107 homozygous *SI* c.273_274delAG cases, (birth prevalence of 1/28) and 832 heterozygotes for a minor allele frequency of 17.8%. We were able to link 83 homozygous cases and 650 heterozygotes to health information. Among the 83 cases, only one had a documented diagnosis of CSID during follow-up. Notably the carrier frequency within the linked health data varied between regions with a case frequency of 1/12 in the Kitikmeot region, and 1/55 in the Qikiqtaaluk region.

Table 4 summarizes the descriptive characteristics stratified by those homozygous and heterozygous for the *SI* variant and those homozygous for the wild-type allele (non-carriers). Of note, the proportion of preterm births (3.6%) was significantly lower among homozygous births compared with heterozygous ($p = 0.007$), and wild type ($p = 0.027$). Although there was no difference in initiation of breastfeeding those homozygous were breastfed significantly ($p = 0.04$) less often at 6 months (29.4%) compared with children without the variant (42.1%).

Figure 2 presents results from mixed effects models for diarrhea and GI visits by the *SI* c.273_274delAG variant. We found homozygosity of the variant to be associated with diarrhea (OR 1.6, 95% CI 1.0–2.6) GI (≥ 1) visits in infants (OR 1.6, 95% CI 1.0–2.6), and from 0 to 2 years (OR 1.9, 95% CI 1.2–3.0), and multiple (≥ 3) GI visits in

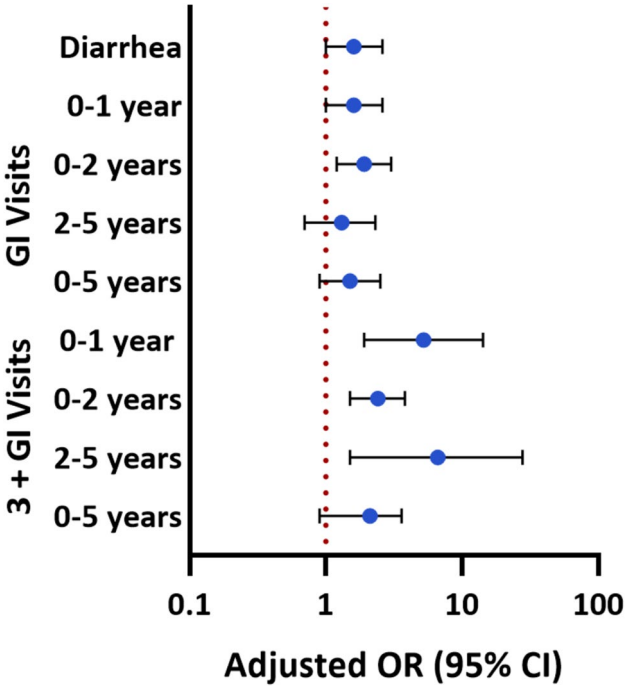

Fig. 2 Forest plot showing adjusted odds ratios and 95% confidence intervals for the association between *SI* c.273_274delAG homozygosity and gastrointestinal outcomes (diarrhea, GI visits, more than three GI visits), estimated using mixed effects logistic regression models adjusted for preterm birth (< 37 weeks), sex, and a random effect for home community. Non-carriers (homozygous wild type) used as reference. CI: confidence interval; GI visits: related to gastrointestinal symptoms, including visits and admissions to health centres, emergency departments, and regional or tertiary hospitals; OR: odds ratio

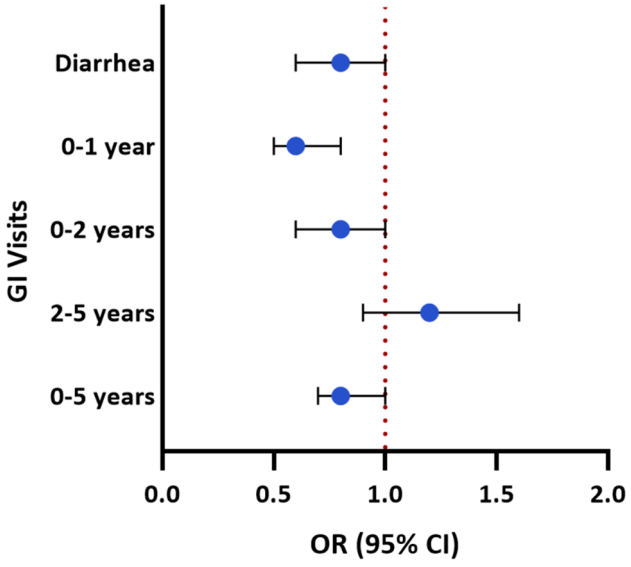

Fig. 3 Forest plot showing odds ratios and 95% confidence intervals for the association between breastfeeding at 6 months and the outcomes diarrhea and GI visits, estimated using logistic regression models adjusted for *SI* c.273_274delAG variant status. CI: confidence interval; GI visits: related to gastrointestinal symptoms, including visits and admissions to health centres, emergency departments, and regional or tertiary hospitals; OR: odds ratio

both infants (OR 5.2, 95% CI 1.9–14.2), and children aged 0–2 years (OR 2.4, CI 1.5–3.8). Overall, just 22 children had multiple GI visits in the 2–5-year group, with 3.6% of the homozygous for the variant and 0.9% of heterozygous documented for this outcome (OR 6.6, 95% CI 1.5–27.7).

Figure 3 shows adjusted odds ratios for the effect of breastfeeding at 6 months on outcomes, derived from multiple logistic regression analyses adjusted for variant status. Breastfeeding at 6 months was associated with lower odds of diarrhea (OR 0.80, 95% CI 0.63–1.0), and GI visits in infants (OR 0.59, 95% CI 0.45–0.76), as well as GI visits from 0 to 2 years (OR 0.80, 95% CI 0.63–1.0), and 0–5 years (OR 0.83, 95% CI 0.66–1.0), but no statistical association was observed for ≥ 3 GI visits in any age group. Sensitivity analysis for the 68 homozygous CSID cases with breastfeeding information demonstrated consistent lower odds for visits for diarrhea, and GI visits for infants and less than 2 years of age (0.46, 0.69, and 0.54 respectively), but no result was statistically significant (see Supplementary Table 4).

Homozygous cases had significantly higher total health visits than heterozygous individuals ($p = 0.009$), and wild-type individuals ($p < 0.0001$) (see Fig. 4).

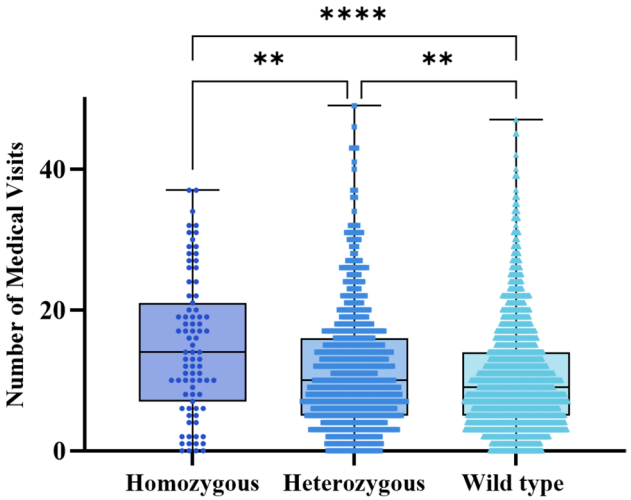

Fig. 4 Median medical visits were 14 (IQR 7–21) in homozygous, 10 (IQR 5–16) in heterozygous, and 9 (IQR 5–14) in wild-type participants, with significant pairwise differences for homozygous vs heterozygous ($p = 0.009$), homozygous vs wild-type ($p < 0.0001$), and heterozygous vs wild-type ($p = 0.006$). Line represents median, boxplot represent interquartile range (IQR), whiskers cover the remaining data points. Overall group differences were assessed using Kruskal-Wallis test, with pairwise comparisons performed using Dunn's post hoc test

Discussion

By utilizing our previously developed infant/early childhood database with health information from birth to 5 years of age with linked dried newborn blood spots we

were able to explore the health outcomes of 6 known disease-causing genetic variants for Inuit children of Nunavut. Of the 6 variants, one was shown not to have a population impact (*CYBB* c.54_79del contributing to X-linked chronic granulomatous disease), likely affecting a single family. Although the condition due to other variants in *CYBB* has been observed in at least seven First Nations children elsewhere in Canada, it has only been observed once in Nunavut [16].

Two unique variants in *ADA* (c.424C>T and c.956_960del) did not result in autosomal recessive disease in this cohort, with respective carrier rates of 1/118 and 1/163. The chance of inheriting either variant is 1/69 which, depending on population structure, could result in a homozygous or compound heterozygous case of ADA deficiency about every 5–6 years. ADA deficiency causes severe combined immunodeficiency syndrome (SCID) accounting for ~ 15% of all SCID cases. However, newborn screening for SCID is available in Nunavut through TRECs (T cell receptor excision circles) with subsequent genetic sequencing confirming the diagnoses and genetic cause. Although not all cases of ADA deficiency are detected by TRECs (about 15–20% have late onset disease which is less likely to screen positive) [30], the cases in Nunavut described with these variants presented as classic SCID and were detected by newborn screening.

Three genetic variants were identified to have a greater impact on early Inuit health in Nunavut (*IFNAR2* c.157T>C, *DNAH11* c.4095+2C>A, and *SI* c.273_274delAG) and are discussed in more detail below.

IFNAR2 deficiency caused by the *IFNAR2* c.157T>C variant

IFNAR2 deficiency has been only recently recognized as a serious condition affecting viral immunity in children [31], and specifically from Alaska, Canada (Nunavik) and Greenland due to the Inuit founder variant *IFNAR2* c.157T>C [20]. Our data supported the seriousness of the condition, identifying four children homozygous for the variant, each with recurrent infections, all cases presenting initially before age 5 months, one required an intensive care unit admission, and another died during infancy with a documented severe viral infection, consistent with the known phenotype of IFNAR2 deficiency; however, causality cannot be definitely established from these data alone. Children from Nunavut with diagnosed severe immunodeficiencies, such as IFNAR2 deficiency, are evaluated and followed by pediatric specialists at the three referral centres in Edmonton, Winnipeg, and Ottawa. During the study period, no formal diagnoses of IFNAR2 deficiency were made. In addition, immunoglobulin replacement therapy is also prescribed and managed by pediatric subspecialists and no patients received this treatment during that time period. Although there is concern that live attenuated virus vaccine (LAVV) such as that included in the measles-mumps-rubella-varicella (MMRV) vaccine administered at 12 months may lead to disseminated disease for those with IFNAR2 deficiency, we could not confirm such an association because vaccination administration was not collected in our dataset. Although recurrent viral infection is not uncommon in Inuit children in Nunavut, those with IFNAR2 deficiency have impaired innate antiviral defense leading to life-threatening and severe disease following certain viral infections [31]. Immunoglobulin replacement therapy has been suggested as preventive treatment and used successfully in identified cases in Nunavut and elsewhere. Given the baseline high rate of respiratory and other infection in Inuit children [32], local health care providers will be challenged to discern those children at higher risk of severe disease. Knowledge of the condition and genetic confirmation allows for prompt delivery of medical care, including anti-viral therapy, avoidance of live-attenuated vaccines and other measures when cases are known.

Primary ciliary dyskinesia, caused by the *DNAH11* c.4095+ 2C> A variant

More than a decade ago, a study of bronchiectasis in Nunavut demonstrated that approximately 1/500 children are affected, suggesting Nunavut has one of the highest bronchiectasis rates in the world [15]. Genetic contributors were suspected, including primary ciliary dyskinesia. In 2023, Hunter-Schouela et al. described that the c.4095+2C>A splice site variant in the *DNAH11* gene was found in seven Inuit individuals from four different families, from Nunavik and Nunavut [17], confirming a genetic cause for at least some cases of bronchiectasis caused by PCD in Nunavut. The condition due to this variant has now been reported in Alaska and Greenland, confirming it as a pan-Arctic, Inuit variant [33, 34]. PCD is characterized by recurrent infections of the upper and lower respiratory tract, persistent otitis media with effusion, neonatal respiratory distress with lobar atelectasis in term newborns, and congenital heart malformations or other organ laterality defects [35]. It is a rare, autosomal recessive, genetically heterogenous disorder of cilia dysfunction, affecting what is essentially the first line of defense for upper and lower respiratory tract infection. Cilia are motile hair-like structures required to move fluids and particles within the body, including the respiratory tract, where they clear inhaled microbes and other particles. Recent population estimates suggest the condition affects approximately 1:7600 people worldwide and more than 50 genes have been identified to contribute [36]. Unfortunately, the condition is largely underdiagnosed [35], partly due to widespread reliance on outdated diagnostic methods, including the assessment of

ciliary ultrastructure on electron microscopy, which can be normal in 30% of PCD, including cases caused by variants in *DNAH11*. The current study has suggested the birth prevalence of the condition in Nunavut due to the *DNAH11* c.4095+2C>A variant is 1/1474, however given the known high rate of bronchiectasis in the region, it is likely other etiologies, including other gene variants that cause PCD, may have not yet been delineated [15]. Of note, the carrier frequency for the condition is higher than the carrier frequency of the *IFNAR2* variant, suggesting population structure may impact the case rate.

Congenital sucrase-isomaltase deficiency caused by the *SI* c.273_274delAG variant

In 1978, clinicians serving patients in communities that are now part of Nunavut flagged that disaccharide malabsorption was leading to gastrointestinal disturbance, with an impact on quality of life for Inuit of all ages [18]. A severe presentation in an infant led to the delineation of the *SI* c.273_274delAG variant in 2015 [19] confirming that congenital sucrase-isomaltase deficiency in the Inuit population of Nunavut was due to a common genetic variant, which has since been confirmed in Inuit of Alaska, and Greenland. Although the variant likely arose some 10,000 years ago, accompanying the Inuit on their journey from the Bering Strait to Greenland [9], it is possible that the historical Arctic diet high in protein and fat, and low in carbohydrate may have mitigated the clinical expression of this variant in the past [10].

From a research perspective, the common variant has garnered much attention in Greenland, as clinicians and researchers establish both beneficial effects [37], as well as the impact on health care services [38], and quality of life [39]. Furthermore, although community health programs have been put in place in Alaska to guide testing and dietary management for all age groups [40], the population impact of CSID based on the *SI* c.273_274delAG variant has not been studied in Inuit children across the Arctic. Our data support a health impact for infants and children, with statistically significantly increased need for health care attention. We demonstrated significantly higher odds of health centre visits for diarrhea, GI visits, and multiple GI visits for those infants under the age of two, homozygous for the variant. Although the outcome counts were small, in the 2–5-year age group, the odds of having multiple visits for GI complaints were 6-fold. Only one case had a diagnosis of CSID within the cohort timelines, and it is unclear whether any dietary modifications were implemented. Given that a single case was diagnosed, any impact of dietary intervention on the study outcomes would have been negligible.

We were interested to see a trend towards significance between homozygous and wild type for food insecurity. It is not likely that there is a biological etiology in this case, but other factors may play a role. We also noted that those born prematurely were less likely to be homozygous, potentially a reflection on maternal health and the positive metabolic health benefits this variant confers [37]. But of concern, although the rate of initiation of breastfeeding was not different between CSID cases and those who were wild type, breastfeeding until 6 months of age was significantly less for CSID cases, suggesting GI symptoms may have prompted a feeding regime change. This is especially a concern in that fewer health visits for GI complaints were recorded before 2 years of age for those breastfeeding until 6 months, for all in the cohort, including CSID cases. Early recognition of variant status should prompt health care education on the merits of continued breastfeeding and encouragement of country foods as the infant grows older, while avoiding sugars and carbohydrates present in market foods with an overall aim to improve early child health, quality of life and reduce health care visits. Consisting with previous reports, our data does not rule out a milder heterozygote effect, as shown in Fig. 4, one that might benefit from the avoidance of dietary triggers, however the merits of genetic testing for this possibility would need further study.

Genetic testing options

The provision of genetic diagnosis is challenging for those living in remote areas, and interpretation is especially challenging for Indigenous populations where genomic reference data are absent or limited. Genetic testing is indicated for those symptomatic with the conditions described above, and currently for residents of Nunavut, multi-gene panel testing is available through commercial laboratories such as Invitae (https://www.invitae.com/) or Blueprint Genetics (https://www.blueprintgenetics.com/), if any of the three conditions are suspected. The cost of such testing is >$1000 CDN/per panel. Although becoming increasingly available to practitioners within Nunavut, the complexity of results generally requires specialized clinical knowledge to determine the implications for the individual patient. Furthermore, given the lack of Indigenous reference data in public databases, multi-gene panels are likely to yield an increased number of variants of uncertain significance, resulting in ambiguity as to whether a patient harbours a disease-causing variant and uncertainty as to the relevance for family members. Because frequency (rarity) is a key factor in characterizing variants for the potential of pathogenesis, variants that are not present in typical population reference databases may be reported as uncertain based on rarity alone, contributing to ambiguity in results. Although efforts are being made to remedy the paucity of Indigenous reference data in Canada through the Silent Genomes Project, Indigenous Background Variant Library (IBVL) (https://

www.bcchr.ca/silent-genomes-project/ibvl), practitioners should be aware that variants rare in mainstream population reference databases may not be rare in populations that are poorly represented, for a number of reasons, in current population databases. Of note and relevant to this discussion, Inuit genomic reference data are lacking in current population databases. In the case that panel testing is utilized, genetic counselling should be provided prior to testing, preparing the patient for the likelihood of variants of uncertain significance. Clinicians should interpret the variants of uncertain significance with caution.

One potential low-cost remedy, although not yet available for the Inuit specific variants in Canada, is targeted variant testing allowing for a definitive positive, or negative, reducing complexity and allowing for primary care clinicians to initiate testing upon early suspicion of the condition. Although there is risk for missing other variants or genes contributing to the patient's condition, consideration to a 'staged approach' where targeted variant testing can be the first line, and if negative in those with a high clinical suspicion of diagnosis, a referral to the appropriate specialty for initiation of a sequencing panel could be considered. A successful example of this approach is carried out in British Columbia where there is a high rate of Long QT syndrome due to two disease causing variants occurring disproportionately in the First Nations population [41]. For that population targeted sequencing of the *KCNQ1* gene is carried out within the provincial laboratory as a first-tier test, followed by panel sequencing if negative and suspicion is high for disease.

Targeted genotyping for newborn screening for conditions having a health impact in infancy is a third option (see Table 5). For founder populations with well delineated pathogenic variants increasing risk for serious genetic conditions, targeted genotyping has been successfully implemented. For example, in Manitoba newborn screening is carried out for a specific variant (p. G710E) in the Hutterite population at risk for classic CPT1A deficiency [42]. Additionally, in Manitoba and Ontario, newborn screening (NBS) includes two founder pathogenic variants associated with SCID (*IKBKB* and *ZAP70*) which affect First Nations of Northern Cree ancestry and Mennonites populations, respectively [43]. A recent article out of Puerto Rico demonstrated the effectiveness of NBS utilizing targeted genotyping for a population with a high rate of primary ciliary dyskinesia due to the *RSPH4A* founder variant [44].

The main purpose of NBS is to identify serious conditions before symptoms appear allowing early initiation of

Table 5 Pros and Cons of different methods of genetic testing to consider for population specific variants

Testing Type	Indication	Pros	Cons
Panel Testing	Symptomatic patients with features of above three conditions.	■ Sequencing of many genes and multiple conditions ■ Will identify pathogenic variants contributing to the condition ■ Early identification of conditions, allowing early treatment ■ Improved health outcomes ■ Available to specialists and some primary care clinicians in Nunavut	■ Expect a high rate of variants of uncertain significance (VUS) in populations without adequate reference data, with risk of increasing uncertainty and raising anxiety ■ Greater interpretive complexity often requiring specialist ■ High overall cost ■ Used only in selective cases which may miss those affected because of limited specificity of presentation features
Targeted Variant Testing	First-tier rapid test for symptomatic patients with features of above three conditions.	■ Definitive positive or negative test result for well characterized Inuit specific variants ■ Reduces complexity in interpretation ■ Eliminates risk for VUS allowing for streamlined post-screening care and counselling if positive ■ Cost-effective for testing specific variants	■ Scope limited to specific variants in genes known to be prevalent in Inuit populations ■ If negative panel testing may be indicated ■ When utilized as first-tier may delay diagnosis achievable by panel testing ■ Acceptable turn around time may be difficult to achieve given low volume of testing ■ Not yet available/under discussion
Newborn Screening using targeted variant testing assay	Population level testing for conditions that are common, well characterized and with evidence that early management or treatment improves outcomes.	■ Early identification of conditions affecting newborn and infant health in Inuit populations ■ When using targeted genotype testing for specific variants, eliminates chance of false positive results ■ Enables early intervention and preventative education strategies. ■ Informed medical care ■ Potential to reduce long-term health-care costs because of prevention ■ For those who are symptomatic, but negative for NBS screening, clarifies indication for panel testing	■ If other methods of newborn screening used (biochemical screening), false negative results delaying early intervention ■ If sequencing methods used, expect high rates of VUS because of lack of reference data for Inuit population ■ Resources need to be available to provide results and support for newly diagnosed conditions ■ Unexpected genetic findings may cause parental anxiety if public education is not in place ■ Not yet available/under discussion/ possible that Nunavut regions will be asynchronous in implementation.

Proposed for the diagnosis of IFNAR2 deficiency, SI deficiency and Primary Ciliary dyskinesia due to variants common in the Inuit

VUS Variants of Uncertain Significance, *NBS* Newborn Screening

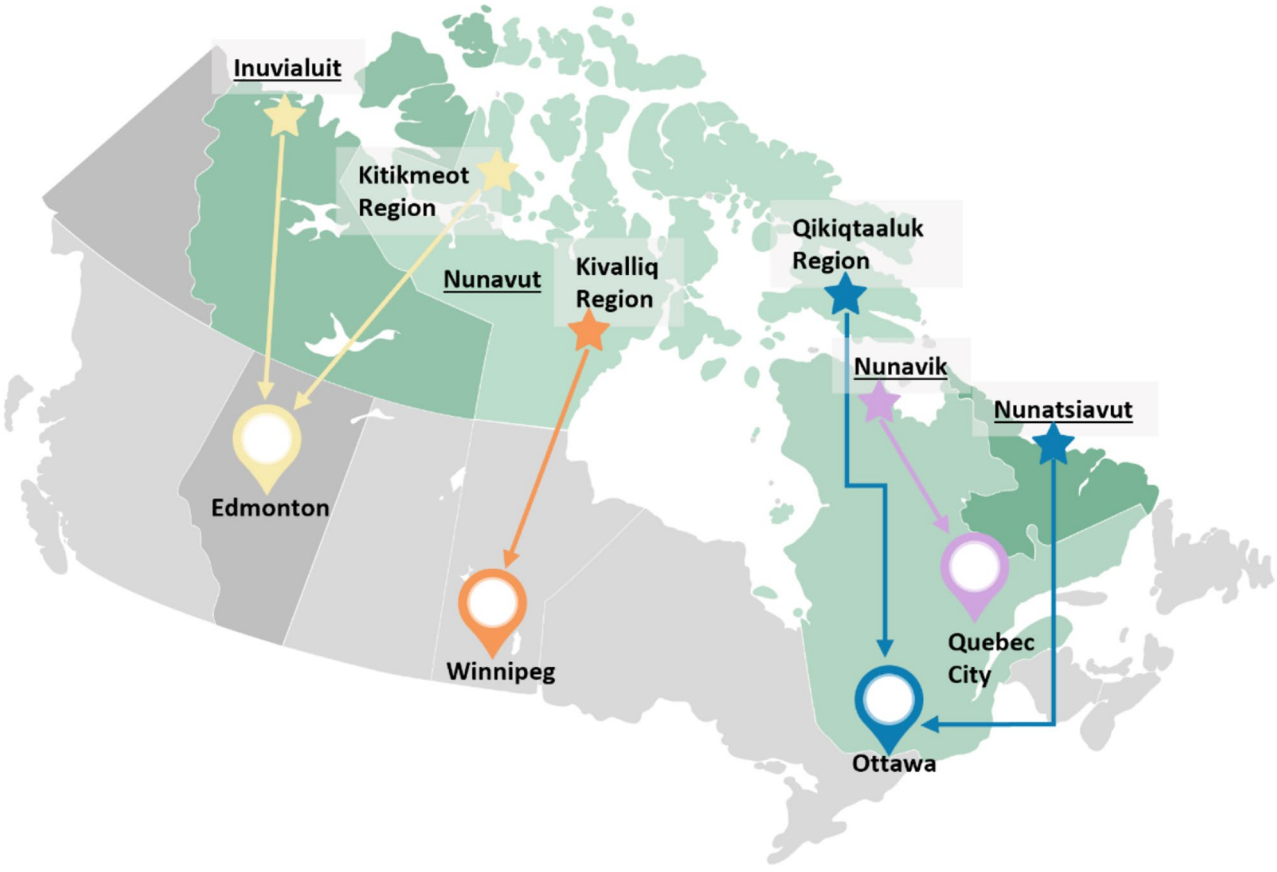

Fig. 5 Newborn screening service jurisdictions across Inuit Nunangat. Adapted from '*Canada editable PowerPoint map*' by presentationgo.com

treatment and avoidance of complications. The natural history in childhood should be known, there should be a reliable and cost-effective test, and treatment or other strategies to prevent serious manifestations should be available [45]. Each NBS program evaluates which conditions are to be included in their test menu to best serve the population at hand.

NBS programs in Canada are administered provincially, not nationally [45]. The number of conditions screened in the different provinces varies and there are only 9 conditions in common across the country. For those regions without their own programs such as Nunavut, laboratory services including newborn screening is contracted out. The Kitikmeot region NBS depends on Edmonton through the Alberta Newborn Screening Program, for the Kivalliq region Manitoba provides services at Cadham Provincial Laboratory, and finally the Children's Hospital of Eastern Ontario (CHEO) provides services to the Qikiqtani region through Newborn Screening Ontario. The number of tests delivered for residents of each region ranges from 22 to 40, and only 21 tests are in common for residents of all three regions. Please see Supplementary Table 5. Although it could be argued that rare disease occurs in all populations, and infants in Nunavut could be at risk for the numerous conditions where tests are available, our study underscores the importance of an Inuit focused lens given the increased risk for specific autosomal recessive conditions known to impact infants and children of Nunavut, and other regions within Inuit Nunangat. Please see Fig. 5 illustrating the various jurisdictions that deliver newborn screening for Inuit Nunangat.

It is not clear how much education on newborn screening is currently provided to Inuit families, however any expansion of newborn screening, or any genetic testing strategy will require community education to address benefits and risks of being identified with a genetic condition. Strategies to ensure follow-up care, counselling and public health education initiatives to reduce potential stigma associated with genetic disease are needed.

Limitations

Although we had a unique opportunity to explore health data of Inuit children linked to genotyping results for five rare genetic conditions, there are important limitations. Our chart review included more than 85% of Inuit children born within a defined four-year time frame residing within Nunavut. However, communities with less than 20 deliveries a year were not included, and important case information was likely missed. Additionally, in rare

occasions charts were unavailable when data extraction was conducted in the communities. (This was especially noted for SI deficiency, where 24 cases were not linked). We restricted the analysis to Inuit children based on self-reported Inuit identity (at least one parent was Inuit as recorded in prenatal records); however, some individuals may have preferred not to self-identify. Retrospective clinical chart reviews are subject to inherent limitations, including the potential for human error and incomplete or missing data. Intrinsic healthcare service delivery challenges in Nunavut, such as frequent personnel changes and shortages of health providers, can limit access to medical care and may affect the accuracy of medical chart entry. Additionally, given our cohort includes births from 2010 to 2013, differences in clinical documentation practices relative to current standards may have impacted the availability of certain data (e.g., vaccination status). Our database contained health and mortality information only to 5 years of age. In addition, outcome data after age 2 years became less robust. For example, those with multiple GI visits in the 2–5-year group appeared strongly associated with the *SI* variant in the regression analysis, but the estimate lacks precision due to the small number of outcome events. Although breastfeeding at 6 months was associated with lower odds of diarrhea and healthcare utilization for GI related complaints, the small number of cases that were breastfed at 6 months (20) limited our ability to confirm the benefit for CSID cases.

Conclusion

With the knowledge of an Inuit specific variant contributing to a severe immune deficiency in Inuit children across the Arctic (IFNAR2 deficiency), NTI and the Department of Health sought to understand the impact of this and other disease-causing population specific variants on the children of Nunavut. Multi-disciplinary expertise and input was pursued, and a previously developed database of Inuit children linked to dried newborn blood spots was utilized for this study. Six disease causing variants were identified as relevant for Inuit and child health, were genotyped, and linked to health data. Three conditions (IFNAR2 deficiency, *DNAH11* mediated PCD, and congenital sucrase-isomaltase deficiency) emerged as requiring urgent attention to deliver health care including diagnosis, Inuit informed management strategies, as well as practitioner and community education. Efforts are underway to establish optimal genetic testing strategies, and to support efforts for management. This study illustrates the importance of understanding population genetic underpinnings in the delivery of relevant and optimal health care.

Abbreviations

CHEO	Children's Hospital of Eastern Ontario
CI	Confidence Interval
CPL	Cadham Provincial Laboratory
CPM	Chip Platform Module
CSID	Congenital Sucrase-isomaltase Deficiency
DoH	Department of Health
GI	Gastrointestinal Illness
IBVL	Indigenous Background Variant Library
LAVV	Live Attenuated Viral Vaccines
LBP	Live Birth Prevalence
MAF	Minor Allele Frequency
MMRV	Measles Mumps Rubella Varicella
NBS	Newborn Screening
NTI	Nunavut Tunngavik Incorporated
OR	Odds Ratio
PCD	Primary Ciliary Dyskinesia
QHRC	Qaujigiartiit Health Research Centre
SCID	Severe Combined Immunodeficiency Syndrome
TREC	T Cell Receptor Excision Circles
UBC	University of British Columbia

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

J.A., M.P., M.D., L.A., P.C. designed the study; P.C., and K.K. led the genotyping in the CHEO lab and provided allele frequencies; E.Y., A.Y., A.M. and M.L. were on the team that provided the genotyping; A.M. and H.S. provided local pediatric perspectives; A.P.H. provided expertise on inborn errors of immunity including IFNAR2 deficiency; T.K., and A.S., provided expertise on primary ciliary dyskinesia; J.M. and A.O. provided expertise on CSID; A.C. contributed nutritional expertise; M.B. provided statistical support; J.GL. carried out the analysis, and wrote the first draft of the manuscript under the supervision of L.A.; S.C. developed the original database for a previous study. All authors reviewed the results at various stages and contributed to editing of the manuscript.

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Data availability

The data used in this study are subject to the following licenses and restrictions: UBC-UVic-Government of Nunavut Research Disclosure Agreement M17-00229. To obtain access to these datasets, contact the corresponding author, Dr. Laura Arbour, larbour@uvic.ca. Accession Number: Not applicable.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. For the original study, an ethical waiver for consent was received by all ethics boards which approved the retrospective data collection without the need for individual informed consent due to the de-identified nature of the data collected and the public health implications for the results. That dataset was utilized for the current study. The University of British Columbia (H13-02699), University of Manitoba (HS17732), and the Children's Hospital of Eastern Ontario (22/130X) Research Ethics Boards approved the original study and amendments for the current study. The Nunavut Research Institute granted a research license (07 006 26R-M).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada
[2]Department of Research, Monitoring, and Evaluation, Nunavut Tunngavik Inc, Iqaluit, NU, Canada
[3]Department of Health, Government of Nunavut, Iqaluit, NU, Canada
[4]Qikiqtani General Hospital, Iqaluit, NU, Canada
[5]University of Alberta School of Public Health, Iqaluit, NU, Canada
[6]Division of Infectious Diseases, Immunology and Allergy, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada
[7]Department of Pediatrics, University of Ottawa, Ottawa, ON, Canada
[8]Montreal Children's Hospital, Research Institute of the McGill University Health Centre, Montreal, QC, Canada
[9]Newborn Screening Ontario, Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, ON, Canada
[10]School of Public Health and Social Policy, Faculty of Health, University of Victoria, Victoria, BC, Canada
[11]BC Children's Hospital Research Institute, Vancouver, BC, Canada
[12]Department of Medical Genetics, University of Calgary, Calgary, AB, Canada
[13]Department of Pediatrics, IWK Health Centre, Dalhousie University, Halifax, NS, Canada
[14]Qaujigiartiit Health Research Centre, Iqaluit, NU, Canada
[15]Department of Pediatrics and Child Health, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada
[16]Department of Surgery, University of British Columbia, Vancouver, BC, Canada
[17]Centre for Excellence in Indigenous Health, University of British Columbia, Vancouver, BC, Canada

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References

1. Frederiksen SD, Avramović V, Maroilley T, Lehman A, Arbour L, Tarailo-Graovac M. Rare disorders have many faces: in silico characterization of rare disorder spectrum. Orphanet J Rare Dis. 2022;17:76. https://doi.org/10.1186/s13023-022-02217-9.
2. Baynam G, Julkowska D, Bowdin S, Hermes A, McMaster CR, Prichep E, et al. Advancing diagnosis and research for rare genetic diseases in Indigenous peoples. Nat Genet. 2024;56:189–93. https://doi.org/10.1038/s41588-023-01642-1.
3. Collins FS, Varmus H. A New Initiative on Precision Medicine. N Engl J Med. 2015;372:793–5. https://doi.org/10.1056/NEJMp1500523.
4. Amjad S, Tromburg C, Adesunkanmi M, Mawa J, Mahbub N, Campbell S, et al. Social Determinants of Health and Pediatric Emergency Department Outcomes: A Systematic Review and Meta-Analysis of Observational Studies. Ann Emerg Med. 2024;83:291–313. https://doi.org/10.1016/j.annemergmed.2023.10.010.
5. Chong JX, Ouwenga R, Anderson RL, Waggoner DJ, Ober C. A Population-Based Study of Autosomal-Recessive Disease-Causing Mutations in a Founder Population. Am J Hum Genet. 2012;91:608–20. https://doi.org/10.1016/j.ajhg.2012.08.007.
6. Béziat V, Casanova J-L. Monogenic disorders of immunity: Common variants are not so rare. Cell Genomics. 2026;6:101129. https://doi.org/10.1016/j.xgen.2025.101129.
7. About Inuit. Inuit Tapiriit Kanatami. https://www.itk.ca/about-canadian-inuit/. Accessed 4 Nov 2025.
8. Government of Canada SC. Profile table, Census Profile. 2021 Census of Population - Nunavut [Territory]. 2022. https://www12.statcan.gc.ca/census-recensement/2021/dp-pd/prof/index.cfm?Lang=E. Accessed 4 Nov 2025.
9. Stæger FF, Andersen MK, Li Z, Hjerresen JP, He S, Santander CG, et al. Genetic architecture in Greenland is shaped by demography, structure and selection. Nature. 2025;639:404–10. https://doi.org/10.1038/s41586-024-08516-4.
10. Arbour L. Greenland genetic data can narrow health-care gaps. Nature. 2025;639:307–9. https://doi.org/10.1038/d41586-025-00091-6.
11. Collins SA, Surmala P, Osborne G, Greenberg C, Bathory LW, Edmunds-Potvin S, et al. Causes and risk factors for infant mortality in Nunavut, Canada 1999–2011. BMC Pediatr. 2012;12:190. https://doi.org/10.1186/1471-2431-12-190.
12. Arbour L, Gilpin C, Millor-Roy V, Platt R, Pekeles G, Egeland GM, et al. Heart defects and other malformations in the Inuit in Canada: a baseline study. Int J Circumpolar Health. 2004;63:251–66. https://doi.org/10.3402/ijch.v63i3.17720.
13. Arbour L, Melnikov V, McIntosh S, Olsen B, Osborne G, Vaktskjold A. The current state of birth outcome and birth defect surveillance in northern regions of the world. Int J Circumpolar Health. 2009;68:443–58. https://doi.org/10.3402/ijch.v68i5.17376.
14. Kovesi TA, Cao Z, Osborne G, Egeland GM. Severe Early Lower Respiratory Tract Infection is Associated with Subsequent Respiratory Morbidity in Preschool Inuit Children in Nunavut, Canada. J Asthma. 2011;48:241–7. https://doi.org/10.3109/02770903.2011.560320.
15. Das L, Kovesi TA. Bronchiectasis in children from Qikiqtani (Baffin) Region, Nunavut, Canada. Ann Am Thorac Soc. 2015;12:96–100. https://doi.org/10.1513/AnnalsATS.201406-257OC.
16. Pham-Huy A, Murguia-Favela L, Rubin T, Suresh S, Wright NAM, Derfalvi B, et al. Inborn errors of immunity in Canadian First Nations and Nunavut Inuit Children: the tip of the iceberg. Paediatr Child Health. 2025;30:40–7. https://doi.org/10.1093/pch/pxae026.
17. Hunter-Schouela J, Geraghty MT, Hegele RA, Dyment DA, St Pierre D, Richer J, et al. First reports of primary ciliary dyskinesia caused by a shared DNAH11 allele in Canadian Inuit. Pediatr Pulmonol. 2023;58:1942–9. https://doi.org/10.1002/ppul.26414.
18. Ellestad-Sayed J, Haword J, Hildes J. Disaccharide Malabsorption And Dietary Patterns In Two Canadian Eskimo-communities. Am J Clin Nutr. 1978;31:1473–8. https://doi.org/10.1093/ajcn/31.8.1473.
19. Marcadier JL, Boland M, Scott CR, Issa K, Wu Z, McIntyre AD, et al. Congenital sucrase–isomaltase deficiency: identification of a common Inuit founder mutation. Can Med Assoc J. 2015;187:102–7. https://doi.org/10.1503/cmaj.140657.
20. Duncan CJA, Skouboe MK, Howarth S, Hollensen AK, Chen R, Børresen ML, et al. Life-threatening viral disease in a novel form of autosomal recessive *IFNAR2* deficiency in the Arctic. J Exp Med. 2022;219:e20212427. https://doi.org/10.1084/jem.20212427.
21. Collins SA, Hildes-Ripstein GE, Thompson JR, Edmunds S, Miners A, Rockman-Greenberg C, et al. Neonatal hypoglycemia and the CPT1A P479L variant in term newborns: A retrospective cohort study of Inuit newborns from Kivalliq Nunavut. Paediatr Child Health. 2021;26:218–27. https://doi.org/10.1093/pch/pxaa039.
22. Collins SA, Edmunds S, Akearok GH, Thompson JR, Erickson AC, Hildes-Ripstein E, et al. Association of the CPT1A p.P479L Metabolic Gene Variant With Childhood Respiratory and Other Infectious Illness in Nunavut. Front Pediatr. 2021;9. https://doi.org/10.3389/fped.2021.678553.
23. Joyal KM, Collins S, Miners A, Barrowman N, Sucha E, Allen J, et al. Head circumference values among Inuit children in Nunavut, Canada: a retrospective cohort study. Can Med Assoc J. 2024;196:E1189–200. https://doi.org/10.1503/cmaj.230905.
24. Nunavut Tunngavik Inc. | Inuit economic, social and cultural well-being through the implementation of the Nunavut Land Claims Agreement. https://www.tunngavik.com/. Accessed 23 June 2026.
25. Health | Government of Nunavut. https://www.gov.nu.ca/en/health. Accessed 23 June 2026.

26. Laura Arbour - Medical Sciences. - University of Victoria. UVic.ca. https://www.uvic.ca/health/medsci/faculty-staff/faculty/adjunct/arbour-laura.php. Accessed 9 July 2026.
27. Caughey A, Harper SL, Sanguya I, Sargeant JM, Miners A, Doucette M, et al. Early life nutrition in Nunavut, Canada: a retrospective descriptive study of food security, vitamin D and rickets. Int J Circumpolar Health. 2025;84:2580100. https://doi.org/10.1080/22423982.2025.2580100.
28. Husein DM, Wanes D, Marten LM, Zimmer K-P, Naim HY. Heterozygotes Are a Potential New Entity among Homozygotes and Compound Heterozygotes in Congenital Sucrase-Isomaltase Deficiency. Nutrients. 2019;11:2290. https://doi.org/10.3390/nu11102290.
29. Danialifar TF, Chumpitazi BP, Mehta DI, Di Lorenzo C. Genetic and acquired sucrase-isomaltase deficiency: A clinical review. J Pediatr Gastroenterol Nutr. 2024;78:774–82. https://doi.org/10.1002/jpn3.12151.
30. Jeganathan K, Byrne A, White G, Grunebaum E, Haddad E, Hershfield MS, et al. Early identification of delayed-onset ADA deficiency: The case for expanded first-tier newborn screening. J Hum Immun. 2025;2:e20250102. https://doi.org/10.70962/jhi.20250102.
31. Duncan CJA, Mohamad SMB, Young DF, Skelton AJ, Leahy TR, Munday DC, et al. Human IFNAR2 deficiency: Lessons for antiviral immunity. Sci Transl Med. 2015;7:307ra154. https://doi.org/10.1126/scitranslmed.aac4227.
32. Banerji A, Bell A, Mills EL, McDonald J, Subbarao K, Stark G, et al. Lower respiratory tract infections in Inuit infants on Baffin Island. CMAJ. 2001;164:1847–50.
33. Nygaard C, Dunø M, Heilmann CJ, Marthin JK, Nygaard S, Qvist T, et al. First Case of Primary Ciliary Dyskinesia in Greenland. Pediatr Pulmonol. 2025;60:e27485. https://doi.org/10.1002/ppul.27485.
34. Hirschfeld M, Kovesi TA. First case of primary ciliary dyskinesia in an Alaska Native individual: Evidence supporting the presence of a founder effect. Pediatr Pulmonol. 2024;59:3024–5. https://doi.org/10.1002/ppul.27124.
35. Lavoie V, Zysman-Colman Z, Shapiro AJ. Primary ciliary dyskinesia. Paediatr Child Health. 2025;30:203–11. https://doi.org/10.1093/pch/pxae102.
36. Zariwala MA, Despotes KA, Davis SD, Primary Ciliary D. 2007 Jan 24 Updat 2025 May 22 Adam MP Bick Mirzaa GM Al Ed GeneReviews® Internet Seattle WA Univ Wash Seattle 1993–2026. https://www.ncbi.nlm.nih.gov/books/NBK1122/.
37. Andersen MK, Skotte L, Jørsboe E, Polito R, Stæger FF, Aldiss P, et al. Loss of Sucrase-Isomaltase Function Increases Acetate Levels and Improves Metabolic Health in Greenlandic Cohorts. Gastroenterology. 2022;162:1171–e11823. https://doi.org/10.1053/j.gastro.2021.12.236.
38. Andersen K, Hansen T, Jørgensen M, Senftleber N. Healthcare Burden in Greenland of Gastrointestinal Symptoms in Adults with Inherited Loss of Sucrase-Isomaltase Function. Appl Clin Genet. 2024;17:15–21. https://doi.org/10.2147/TACG.S437484.
39. Isidor S, Senftleber N, Schnoor C, Pedersen KS, Seibæk L, Jørgensen ME, et al. Personal experiences of living with sucrose intolerance and attitudes towards genetic research in Greenland - a user study. Int J Circumpolar Health. 2024;83:2383023. https://doi.org/10.1080/22423982.2024.2383023.
40. Congenital Sucrase-Isomaltase Deficiency (CSID). - Guide to YKHC Medical Practices. https://yk-health.org/wiki/Congenital_Sucrase-Isomaltase_Deficiency_(CSID). Accessed 29 Apr 2026.
41. Jackson H, Huisman L-A, Sanatani S, Arbour LT. Long QT syndrome. Can Med Assoc J CMAJ. 2011;183:1272–5. https://doi.org/10.1503/cmaj.100138.
42. Prasad C, Johnson JP, Bonnefont JP, Dilling LA, Innes AM, Haworth JC, et al. Hepatic Carnitine Palmitoyl Transferase 1 (CPT1 A) Deficiency in North American Hutterites (Canadian and American): Evidence for a Founder Effect and Results of a Pilot Study on a DNA-Based Newborn Screening Program. Mol Genet Metab. 2001;73:55–63. https://doi.org/10.1006/mgme.2001.3149.
43. Thompson J, Rockman- Greenberg C, Dick A, Jilkina O, Kwan L, Rubin T, et al. Development of a Population-Based Newborn Screening Method for Severe Combined Immunodeficiency in Manitoba, Canada. Int J Neonatal Screen. 2018;4:19. https://doi.org/10.3390/ijns4020019.
44. De Jesús-Rojas W, Guerra-Torres KP, Rosado-Ayala AJ, Acevedo-Soto EL, Ramos-Benitez MJ, Mosquera RA. Identification of an *RSPH4A* Founder Variant and Newborn Screening for Primary Ciliary Dyskinesia. JAMA Netw Open. 2025;8:e2530551. https://doi.org/10.1001/jamanetworkopen.2025.30551.
45. Groulx-Boivin E, Osman H, Chakraborty P, Lintern S, Oskoui M, Selby K, et al. Variability in Newborn Screening Across Canada: Spinal Muscular Atrophy and Beyond. Can J Neurol Sci J Can Sci Neurol. 2024;51:203–9. https://doi.org/10.1017/cjn.2023.34.

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