ESTABLISHING THE MUTATION SPECTRUM FOR FLOATING-HARBOR SYNDROME

Lloyd Mai[1], Rebecca L. Hood[2,3], Kym M. Boycott[3,4], Dennis E. Bulman[2,3,5]

(1)Department of Science, University of Ottawa; (2) Department of Biochemistry, Microbiology and Immunology, University of Ottawa; (3) CHEO Research Institute, Children's Hospital of Eastern Ontario; (4) Department of Genetics, Children's Hospital of Eastern Ontario; (5) Department of Pediatrics, University of Ottawa

Background

Floating-Harbor syndrome (FHS) is a rare condition characterized by short stature with delayed bone maturation, deficits in expressive language and a unique facial appearance.[1] These symptoms were first described in 1973 at Boston Floating Hospital and Harbor General Hospital, the two hospitals after which the syndrome was named.[2,3]

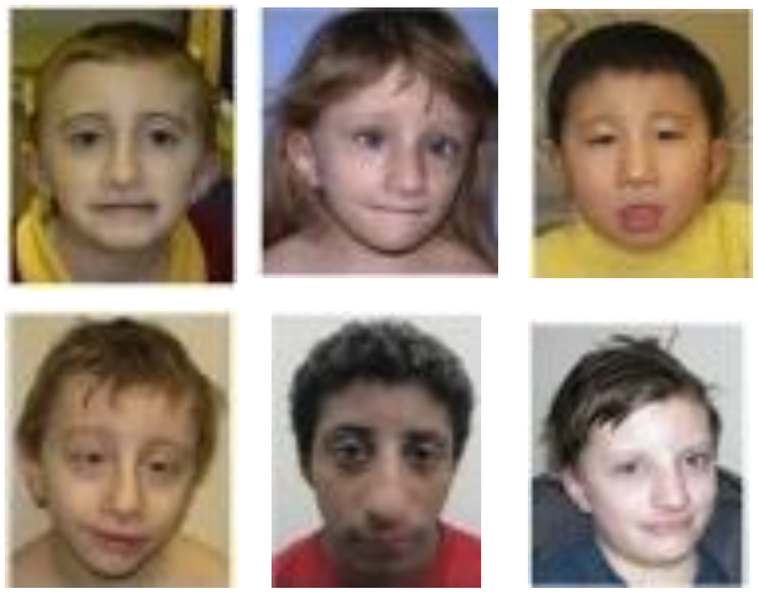

Figure 1. Characteristics of Floating-Harbor syndrome[4]
Clinical photos of FHS patients with a confirmed *SRCAP* mutation displaying unique facial characteristics: triangular face, distinguishing nose(long and narrow nasal bridge, broad base, full tip, and low-hanging columella), wide mouth, thin upper vermilion border, short chin.

FHS has a genetic basis with the large majority of the cases being the result of *de novo* mutations, however the few cases that did turn out to be parent-child transmitted were consistent with being an autosomal dominant disorder. Until recently, no causative gene was identified.

Recently, our lab demonstrated that heterozygous truncating mutations of Snf2-related CREBBP activator protein (*SRCAP*) as the cause underlying FHS.[4] The *SRCAP* gene is located on chromosome 16 and mutations causing FSH appear to be clustered in a very small region of this gene.

Of importance is the need for the establishment of a genotype-phenotype correlation to determine the range of the disease spectrum for the disorder.

Objective

In order to establish the genotype-phenotype correlation, a database of mutations for the disease must first be constructed. The objective of my project is to screen additional FHS patients for mutations in *SRCAP*. All the data obtained can then be compiled into a database for analysis.

The database is of great significance as it will be used in conjunction with clinical data to compare phenotypic manifestations of FSH and determine whether particular mutations in *SRCAP* are associated with these manifestations.

Genetic Pathway

The *SRCAP* gene encodes the SRCAP protein . SRCAP is a coactivator of the *CREBBP* gene responsible for producing CREP-binding protein, which plays an important role in the regulation of cell growth and division.[5] The SRCAP protein also mediates the ATP-dependent exchange of H2A.Z for H2A which transcriptionally regulates other genes via chromatin remodelling.[6]

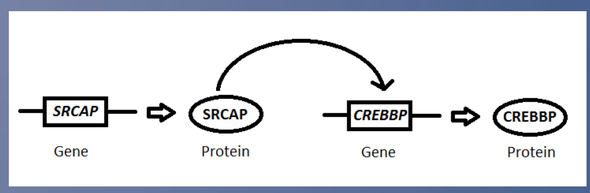

Figure 3. Coactivation of CREBBP with SRCAP
The *SRCAP* gene encodes for SRCAP protein . SRCAP protein is a coactivator of the *CREBBP* gene which encodes for CREBBP protein

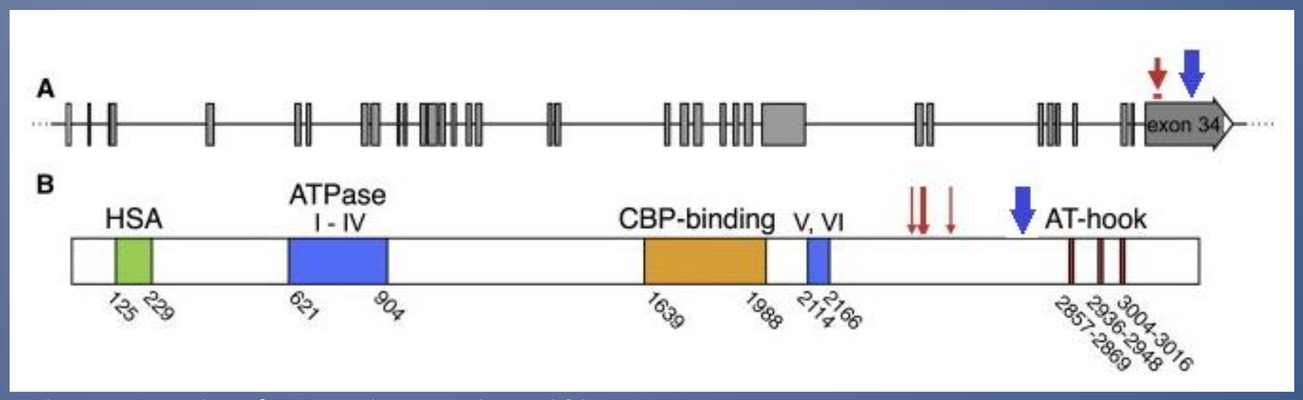

Figure 2. Location of FHS-causing mutations within *SRCAP*[4]
Arrows indicate where heterozygous truncating mutations were recently and previously detected
A Intron-exon structure of *SRCAP.*
B Domain architecture of SRCAP. Helicase-SANT-associated domain is abbreviated as HSA and the ATPase is domain is divided into two sections, one containing motifs I-IV and the other containing V-VI.

Methods and Results

PCR amplification of patient DNA was done for the clustered region of *SRCAP* on exon 34. The PCR products were then sequenced and screened for mutations. If no mutation was found, the screening process would be repeated moving outwards from the clustered region until a mutation was found or the whole gene was covered.

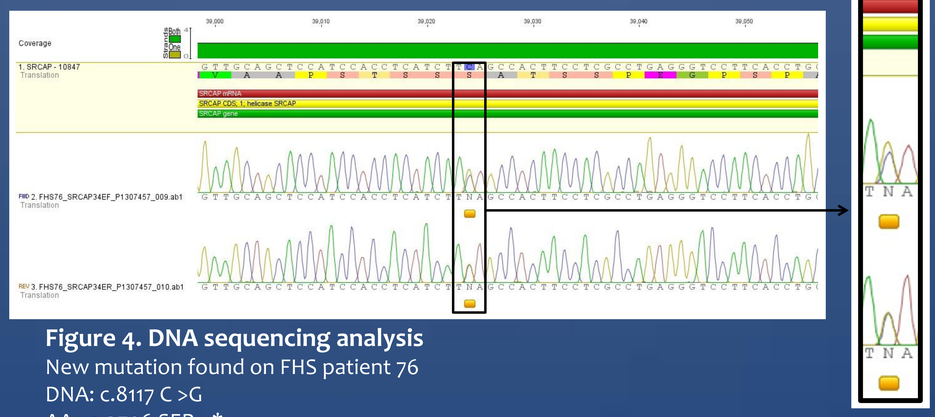

Figure 4. DNA sequencing analysis
New mutation found on FHS patient 76
DNA: c.8117 C >G
AA: p.2706 SER >*

Discussion and Conclusion

The new mutation discovered is interesting in that it is located downstream from the cluster of mutations found in the original study. Although *SRCAP* mutations still appear clustered in FHS, the region of mutations has expanded.

Previous studies have shown that mutations in the *SRCAP* gene cause Floating-Harbor syndrome, however, the mechanism underlying these mutations and how they cause FHS is currently unknown and will remain the focus of our future work.

Acknowledgements

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