ESTABLISHING THE MUTATION SPECTRUM FOR FLOATING-HARBOR SYNDROME

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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.²³

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 gene (SRCAP) is the cause underlying FHS.¹ 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.

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.

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.

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References