

October 1, 2014

The following document describes findings from genetic research performed at the HudsonAlpha Institute for Biotechnology through the Genomic Diagnosis in Children with Developmental Delay project (protocol no. 20130675). **These results were verified by a CLIA-certified laboratory, but the DNA isolation was carried out in a research setting (at HudsonAlpha) and therefore the results cannot be considered CLIA-certified.**

Family study ID#: 000XX-C

Affected child, year of birth: XXXX

Affected child, gender: Male

Relationship to affected child: Self

Indication for testing: Based on the information provided to the research laboratory, the affected child has a history of developmental delay, pulmonary stenosis, growth hormone deficiency, and dysmorphic features. Prior genetic testing has included Noonan syndrome (PTPN11 gene sequencing).

Primary Result: Causative (pathogenic) variant found

Gene	Variant	Zygoty	Classification ⁱ	Disease	Inheritance
SHOC2	chromosome 10 pos 112724120 c.4A>G,p.S2G	Heterozygous (one copy)	5 = Pathogenic	Noonan-like syndrome with loose anagen hair	Autosomal dominant (de novo)

The genetic variant listed above was detected in one copy of this your son's SHOC2 gene. This variant is thought to be pathogenic (the likely cause of symptoms).

Variations in the SHOC2 gene are known to be associated with a subtype of Noonan syndrome, characterized by typical Noonan syndrome features in addition to sparse, slow growing hair. Classic Noonan syndrome is caused by a genetic change in a set of other genes including PTPN11, SOS1 and RAF1. Your son has previously been tested for genetic changes in one ore more of these more commonly associated genes.

Among individuals with SHOC gene changes, facial features were typical of classic Noonan syndrome and short stature was often due to a documented growth hormone deficiency. Cognitive deficits were common as well as hyperactive behavior. Distinctive features of this subtype of the disorder among some patients are sparse and slow growing hair and areas of darkly pigmented skin with accompanying eczema or ichthyosis. Several cases also reported a

hypernasal voice. Cardiac defects were common as with classic Noonan syndrome. It is important to keep in mind that patients with a particular condition can vary in specific symptoms and their severity.

See accompanying resources for more details about the common signs and symptoms of Noonan syndrome.

Genetics

The specific variant identified in your child is a substitution of a DNA nucleotide within the SHOC2 gene. This change (c.4A>G, p.S2G) results in a change in the resulting protein sequence. This specific genetic change in SHOC2 has been identified in at least 25 unrelated patients with Noonan-like syndrome with loose anagen hair.

People have two copies of every gene, one inherited from each parent. The change was found in one of your son's two copies of SHOC2, known as being heterozygous.

Given the clear association between this specific genetic change and Noonan-like syndrome and the overlap between your child's symptoms and the symptoms of Noonan syndrome we have classified this variant as pathogenic, meaning we believe this variant is the cause of your child's developmental delay and other symptoms.

Inheritance

SHOC2 associated Noonan syndrome with loose anagen hair is inherited in a dominant pattern, meaning that the loss of one copy of the gene is sufficient to cause symptoms (despite a second working copy).

The SHOC2 variant detected in your child was not found in the DNA from blood of either parent. Therefore we believe it is a new mutation (also called "de novo"). This indicates that the probability of having another affected child would be very low. There is a very small possibility (<1%) that this new mutation is present in a parent's germ cells (egg or sperm) and could be passed on to another child. This situation is referred to as "germline mosaicism."

Any siblings of the affected child, along with other family members, would not be expected to have an increased risk of having a child with the SHOC2 variant or Noonan syndrome. Despite this, some family members may still be interested in having prenatal genetic testing for the condition.

Were an individual with the condition to have children, they would have a 50% chance of passing the variant (and the condition) on to each child.

Management

Your child should continue to be managed based on his specific symptoms. When a diagnosis of Noonan syndrome is made, evaluations should be considered to determine the extent and severity of symptoms among various body systems (growth, cardiac, ophthalmologic, hearing, coagulation). Treatment of symptoms are typically similar to treatment of similar symptoms in the general population. We encourage your family to stay in touch with your neurology and

genetics healthcare teams to help guide medical management and to stay up to date on new findings.

This document pertains only to the diagnostic result for the affected child. **Any parental secondary results that were identified and reported are discussed in a separate document.**

If you have questions about the interpretation of these results and medical recommendations you may contact either Dr. Edward Lose, pediatric geneticist at UAB, or myself. It has been a pleasure working with this family through this research study.

Sincerely,

Kelly East, MS, CGC
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Resources:

Noonan Syndrome Foundation (Advocacy and Support Group): <http://www.teamnoonan.org/>

Allanson JE and Roberts AE. (Updated 2011) Noonan syndrome. *GeneReviews*. Available online at <http://www.ncbi.nlm.nih.gov/books/NBK1124/>.

National Library of Medicine. Noonan Syndrome. *Genetics Home Reference*. Available online at <http://ghr.nlm.nih.gov/condition/noonan-syndrome>

References:

Cordeddu V, et al (2009). Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. *Nature Genetics*, 41, 1022-1026. [PubMed: 19684605]

*Please Note that exome sequencing cannot detect all genetic variations and does not provide complete coverage of all coding exons. A negative exome sequencing test does not preclude the need for additional genetic testing. Interpretation of genetic data may change over time and the results reported here are based on current knowledge. Only variants in genes associated with the affected child's symptoms are reported here. These results must be interpreted in the context of this individual's clinical profile.

Technical Information:

Exome sequencing was performed on genomic DNA using Nimblegen v3.0 targeted sequence capture method to enrich for exon sequences. Targeted regions were sequenced using the Illumina HiSeq 2000 sequencing system with 100 basepair paired-end reads at an average coverage of 65x per base in the target region. DNA sequence is mapped to and analyzed in comparison with the published human genome build UCSC hg19 reference sequence. Targeted coding exons and splice junctions of known protein-coding RefSeq genes are assessed for depth of coverage and data quality threshold values (80% of bases within the target region must be covered at 20X). All reported sequence variants are confirmed by Sanger sequencing at Emory Genetics.

ⁱ HudsonAlpha variant classification system: 1 = benign, 2 = likely benign, 3 = variant of uncertain significance, 4 = likely pathogenic, 5 = pathogenic