Diagnostic Testing Report

Confirmatory Testing of Whole Exome Sequencing Analysis

Subject Name:	[redacted]
Date of Birth:	**06/26/2001**
Specimen Type:	**Peripheral Blood**
Ordering Clinician:	**Yael Shiloh-Malawsky**
Other Clinician:	**James P. Evans**
Date of Report:	**5/1/2013**
Study ID	[redacted]

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INDICATION FOR TESTING:
The UNC Hospitals Clinical Molecular Genetics Laboratory performed Sanger DNA sequencing analysis to confirm the presence of a mutation in this patient that was identified as part of the NCGENES project at the University of North Carolina by massively parallel exome sequencing and analysis of a subset of genes known to be associated with neuropathy, leukodystrophy, or myopathy.

RESULT:
Homozygous for a *FAM126A* c.125_126insA [p.Tyr42fs] mutation.

INTERPRETATION:
This result is consistent with a diagnosis of hypomyelination and congenital cataract (HCC, OMIM 610532).

Mutation in the *FAM126A* (family with sequence similarity 126, member A) gene has been associated with HCC, a rare autosomal disorder characterized by congenital cataract, neurologic impairment with peripheral neuropathy, and hypomyelination (1,2). The *FAM126A* c.125_126insA mutation found in this patient is a frameshift mutation predicted to result in premature truncation of the hyccin protein (3). To our knowledge, this mutation has not been previously reported in the literature; however there are multiple reports of other similar *FAM126A* truncating frameshift mutations in affected individuals with HCC.

The *FAM126A* c.125_126insA mutation is apparently homozygous in this individual, indicating that both of this patient's parents are likely carriers of this mutation. However, we cannot rule out the possibility that this mutation is on one allele and the other allele harbors a deletion in the *FAM126A* gene. Either of these possibilities is consistent with the diagnosis of HCC. Targeted genetic testing of this patient's parents may be helpful in differentiating these possibilities and confirming carrier status.

REFERENCES:

1. Zara et al. Deficiency of hyccin, a newly identified membrane protein, causes hypomyelination and congenital cataract Nat Genet. 2006 Oct;38(10):1111-3.
2. Biancheri et al. Hypomyelination and congenital cataract: broadening the clinical phenotype. Arch Neurol. 2011 Sep;68(9):1191-4.
3. SIFT Indel: http://sift.bii.a-star.edu.sg/www/SIFT_indels2.html
4. Online Mendelian Inheritance in Man: www.omim.org

COMMENT:
The nucleotide and protein numbering for human *FAM126A* are NM_032581.3 and NP_115970.2 according to the current entries for this gene in the NCBI RefSeq database. The genomic coordinate for this mutation is NC_000007.13:g23023590_23023591insT.

METHOD:
Bi-directional Sanger sequencing of approximately 200 base pairs centered around the locus of the relevant mutation reported by NCGENES was performed on genomic DNA extracted from peripheral blood.

This test was developed and its performance characteristics determined by the UNC Hospitals Molecular Genetics Laboratory. It has not been approved by the US Food and Drug Administration. However, such approval is not required for clinical implementation, and test results have been shown to be clinically useful. This laboratory is CAP accredited and CLIA certified to perform high-complexity testing.