Rady Children's Institute Genomic Medicine

Rady Children's Institute for Genomic Medicine
Clinical Genome Center
7910 Frost Street, Suite 240, San Diego, CA 92123
Phone: 858-966-8127, Fax: 858-966-8092
Email: RCIGM_results@rchsd.org
CLIA ID# 05D2129627
CAP# 9487427

RCIGM Genome Report

Patient's Name	**Ordering Physician**	**Specimen**
Sex	**Ordering Provider**	**Collected**
Date of Birth	**Hospital**	**Received**
Indication for Testing	**Telephone**	**Report Date**
Case ID	**Email**	
Test Type		

TEST RESULT: PRIMARY FINDING IDENTIFIED
A pathogenic, apparently de novo, heterozygous c.489C>A (p.His163Gln) variant in the ACTA1 gene was detected in this individual. Pathogenic variation in ACTA1 is associated with autosomal dominant and autosomal recessive ACTA1-related myopathy (OMIM #161800). This variant was confirmed by Sanger sequencing. Analysis of the parental samples showed the mother is negative and the father is negative for this variant.

PATIENT PHENOTYPE

hypotonia, encephalopathy, respiratory distress, smooth philtrum, long fingers, short chin

PRIMARY FINDINGS - Variants in genes associated with patient's reported phenotype

CONFIRMATION STATUS	GENE (TRANSCRIPT)	CONDITION	CHROMOSOME: GENOMIC COORDINATES	VARIANT	ZYGOSITY (INHERITANCE)	CLASSIFICATION
Confirmed	ACTA1 (ENST00000366684)	NEMALINE MYOPATHY 3	1:229568144	c.489C>A p.His163Gln	Heterozygous (De Novo)	Pathogenic

INTERPRETATION

Variant Information

A heterozygous c.489C>A (p.His163Gln) variant in ACTA1 was detected in this individual. This variant has not been previously reported or functionally characterized in the literature to our knowledge. Another variant at the same amino acid position (p.His163Asp) has been previously reported in an affected individual with autosomal dominant nemaline myopathy (PMID: 28780987). The c.489C>A (p.His163Gln) is absent from the ExAC and gnomAD population databases and thus is presumed to be rare. This variant affects a highly conserved amino acid and is predicted by multiple in silico tools to have a deleterious effect on protein function. This result was confirmed by Sanger sequencing. Analysis of the parental samples was negative for the variant, indicating this variant likely occurred as a de novo event. However, low-level parental mosaicism cannot be excluded. Based on the available evidence, the c.489C>A p.His163Gln variant is classified as pathogenic.

Gene Information

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The ACTA1 gene is located on chromosome 1q42.13 and encodes skeletal muscle actin, alpha 1 which is involved in cell movement, muscle contraction, and maintenance of the cellular cytoskeleton. Pathogenic alterations in the ACTA1 gene are associated with several types of hereditary myopathies which may be autosomal dominant or autosomal recessive with variable penetrance and expressivity and a range in severity and age of onset (OMIM: 102610) (PMID 10508519, 11333380). Nemaline myopathy 3 (OMIM: 161800) is associated with limited spontaneous movement, severe hypotonia, respiratory insufficiency, difficulty swallowing and sucking, respiratory infections, and abnormal muscle biopsy. Pathogenic variants in the ACTA1 gene can alter the structure or function of the skeletal muscle actin protein, causing it to cluster together and form aggregates, which interfere with the normal functioning of muscle cells (PMID 15198992). Management of Nemaline Myopathy 3 is dependent on its clinical manifestations and has been reviewed (https://www.ncbi.nlm.nih.gov/books/NBK1288/, PMID 20301465). Clinical correlation and genetic counseling is strongly recommended.

REFERENCES

Adam MP, Ardinger HH, Pagon RA, Wallace SE, et al. None. 1993. Nemaline Myopathy (PMID: 20301465)

Ilkovski B, Cooper ST, Nowak K, Ryan MM, et al. American journal of human genetics. 2001, Jun. Nemaline myopathy caused by mutations in the muscle alpha-skeletal-actin gene. (PMID: 11333380)

Ilkovski B, Nowak KJ, Domazetovska A, Maxwell AL, et al. Human molecular genetics. 2004, Aug 15. Evidence for a dominant-negative effect in ACTA1 nemaline myopathy caused by abnormal folding, aggregation and altered polymerization of mutant actin isoforms. (PMID: 15198992)

Moreno CAM, Abath Neto O, Donkervoort S, Hu Y, et al. Pediatric neurology. 2017, Oct. Clinical and Histologic Findings in ACTA1-Related Nemaline Myopathy: Case Series and Review of the Literature. (PMID: 28780987)

Nowak KJ, Wattanasirichaigoon D, Goebel HH, Wilce M, et al. Nature genetics. 1999, Oct. Mutations in the skeletal muscle alpha-actin gene in patients with actin myopathy and nemaline myopathy. (PMID: 10508519)

RECOMMENDATIONS

- Clinical correlation is recommended.
- Clinical molecular testing should be interpreted in the context of the patient's clinical presentation and the prior probability of the clinical signs and symptoms being associated with known single gene disorders (defects in the identified gene).
- Genetic counseling is recommended to assess the specific implications of these results relative to an individual's clinical context.
- Additional testing may be appropriate to evaluate for other types of variants not detected in this test.
- As knowledge increases, periodic re-evaluation of the clinical implications of variants is appropriate.

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TEST METHODOLOGY

Sequence via next generation sequencing (NGS) technology is generated from genomic DNA. PCR-free library preparation is performed prior to whole genome sequencing (WGS). An average genomic coverage of at least 35x is obtained for each proband genome. Alignment and variant calling are performed using the Edico DRAGEN pipeline using the official reference build 37.1. The current version of this test assesses single nucleotide variants (SNVs), small deletions and insertions, and larger deletions and duplications. The sensitivity and specificity for SNVs (single nucleotide variants) and small insertions and deletions is greater than 99%. The sensitivity for larger deletions and duplications from WGS is estimated to be greater than 80%, although reliable reference data for these types of events are not well established. All likely pathogenic and pathogenic reported variants are confirmed using orthogonal technologies.

Variants are curated and classifed in accordance with the American College of Medical Genetics and Genomics Guidelines (Richards et al. 2015; PMID: 25741868).

TEST LIMITATIONS

Full coverage of the genome is not currently possible due to technical challenging repetitive elements and duplicated regions within the genome. Thus, not all regions of the genome are sequenced or uniquely aligned to the reference genome. Certain genomic alterations may not be covered with the current version of this test. This test only interprets single nucleotide variants, small insertions and deletions, and larger deletions and duplications for the phenotypes indicated. Thus, genomic alterations such as trinucleotide repeat expansions and translocations will not be analyzed with the current version of the test.

This test is set up to evaluate the potential contribution of rare disease causing variants in known disease genes. It is not designed to evaluate for common variants in genes that might contribute to disease risk or for disorders that have a multigenic inheritance. Based on current knowledge, potential disease causing variants may not always be recognized at the time of testing.

REGULATORY DISCLOSURES

This test was developed and its performance characteristics determined by the Rady Children's Institute for Genomic Medicine. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. RCIGM has established and verified the test's accuracy and precision as outlined in the requirements of CLIA '88.

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LAB CONTACT

For any questions regarding results, please contact the RCIGM staff at RCIGM_results@rchsd.org or 858-966-8127.

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