Rady Children's Institute for Genomic Medicine
Clinical Genome Center
7910 Frost Street, Suite 330, San Diego, CA 92123
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Email: RCIGM_clinicallab@rchsd.org
CLIA ID# 05D2129627
CAP# 9487427

# RCIGM Final Report

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|---|---|---|---|---|---|
| **Patient's Name** | John Smith | **Ordering Physician** | Dr. David Dimmock | **Specimen** | Peripheral blood |
| **Sex** | Male | **Account#** | RCH | **Collected** | 08/28/2018 |
| **Date of Birth** | 01/01/2018 | **Hospital** | RCH | **Received** | 08/29/2018 |
| **Indication for Testing** | Suspected Genetic Disease | | | **Reported** | 08/30/2018 |
| **Case ID** | CSXXXX_INXXXX | | | | |

**TEST RESULT:** A pathogenic, apparently de novo, heterozygous variant in ATAD3A (c.1726C>T, p.Arg576Trp) was detected in this individual. Pathogenic variants in ATAD3A are associated with Harel-Yoon syndrome [MIM: 612316], a disorder characterized by developmental delay, feeding difficulties, truncal hypotonia, axonal neuropathy, and hypertrophic cardiomyopathy. These results were confirmed by Sanger sequencing.

## PATIENT PHENOTYPE

Developmental delay, hypotonia, feeding difficulties, cardiomyopathy

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

| CONFIRMATION STATUS | GENE & TRANSCRIPT | CONDITION | CHROMOSOME: GENOMIC COORDINATES | VARIANT | ZYGOSITY | INHERITANCE | CLASSIFICATION |
|---|---|---|---|---|---|---|---|
| Confirmed | ATAD3A ENST00000378755 | HAREEL-YOON SYNDROME | 1:1464679 | c.1726C>T p.Arg576Trp | Heterozygous | De novo | Pathogenic |

## INTERPRETATION

Variant Information

An apparently de novo missense variant in the ATAD3A gene (c.1726C>T, p.Arg576Trp) was detected in this individual. This variant has been previously reported as a de novo change in multiple unrelated individuals with developmental delay and additional features (PMID 27640307). An analysis of fibroblasts derived from a patient with this variant and the features of Harel-Yoon syndrome showed increased mitochondrial degradation (PMID 27640307). Similarly, a dramatic reduction in mitochondrial content and highly aberrant mitochondrial morphology were observed in Drosophila harboring this mutation (PMID 27640307). This variant is absent from the ExAC and gnomAD population databases. Algorithms developed to predict the effect of missense changes on protein function suggest this variant is likely to be deleterious. This variant was confirmed by Sanger sequencing. Sanger sequencing of the parental samples was negative for the variant, indicating the variant likely occurred as a de novo event. However, low-level parental mosaicism cannot be excluded. Based on the available evidence, the p.Arg576Trp variant in ATAD3A is classified as a pathogenic change.

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Gene Information

ATAD3A encodes a ubiquitously expressed mitochondrial membrane protein that contributes to mitochondrial dynamics, mitochondrial DNA maintenance and replication, and cholesterol metabolism (PMID 27640307). Pathogenic variants in ATAD3A cause Harel-Yoon syndrome [MIM: 612316], a recently described neurological disorder characterized by developmental delay, hypotonia, spasticity, peripheral neuropathy, feeding difficulties, and hypertrophic cardiomyopathy (PMID 27640307). Additional phenotypes reported in association with ATAD3A variants include hereditary spastic paraplegia (PMID 28158749) and pontocerebellar hypoplasia/cerebellar atrophy (PMID 28549128).

## REFERENCES

Cooper HM, Yang Y, Ylikallio E, Khairullin R, et al. Human molecular genetics. 2017, 04 15. ATPase-deficient mitochondrial inner membrane protein ATAD3A disturbs mitochondrial dynamics in dominant hereditary spastic paraplegia. (PMID: 28158749)

Desai R, Frazier AE, Durigon R, Patel H, et al. Brain : a journal of neurology. 2017, Jun 01. ATAD3 gene cluster deletions cause cerebellar dysfunction associated with altered mitochondrial DNA and cholesterol metabolism. (PMID: 28549128)

Harel T, Yoon WH, Garone C, Gu S, et al. American journal of human genetics. 2016, Oct 06. Recurrent De Novo and Biallelic Variation of ATAD3A, Encoding a Mitochondrial Membrane Protein, Results in Distinct Neurological Syndromes. (PMID: 27640307)

## RECOMMENDATIONS

- Clinical correlation is recommended.
- Clinical molecular testing should be interpreted in the context of the child'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.

## 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

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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.

## 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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Test results reviewed and approved by:
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