Rady Children's Institute
Genomic Medicine

Clinical Genome Center
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CLIA ID# 05D2129627
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RCIGM Genome Report

PATIENT'S NAME	**ORDERING PHYSICIAN**	**SPECIMEN**
SEX	**HOSPITAL**	**COLLECTED**
DATE OF BIRTH	**TELEPHONE**	**RECEIVED**
INDICATION FOR TESTING	**EMAIL**	**REPORT DATE**
CASE ID		
TEST TYPE		
MOTHER ID		
FATHER ID		

PATIENT PHENOTYPE

Abnormality of brain morphology; Abnormality of vision; Abnormality of the immune system

TEST RESULT:

No diagnostic findings associated with the patient's phenotype were identified. Please see the subsequent sections of the report that describe the methodology and limitations of the assay. For further information, please contact the Rady Children's Institute for Genomic Medicine staff at (858) 966-8127 or RCIGM_results@rchsd.org.

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 (i.e. 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 by this test.
- As knowledge increases, periodic re-evaluation of the clinical implications of variants is appropriate.

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. Copy number variation (CNV) calling is performed using a combination of CNV callers. Interpretation of CNVs is focused on variants that overlap or have a boundary that lies within 1 kb of an exon in one of approximately 8000 genes known to have a gene-disease association. The current version of this test assesses single nucleotide variants (SNVs), small deletions and insertions, and larger deletions and duplications. All likely pathogenic and pathogenic reported variants are confirmed using orthogonal technologies.

The sensitivity and specificity for SNVs (single nucleotide variants) and small insertions and deletions up to 50 base pairs is greater than 99%. The analytical validity of SNVs was assessed using reference samples provided through the Genome in a Bottle (Zook et al. 2019, PMID: 30936564).

The sensitivity for larger deletions and duplications from WGS is estimated to be greater than 85%, although reliable reference data for these types of events are not well established. Deletions and duplications from 1 Kb to whole chromosomal abnormalities are detected with this test.

This test is validated for copy number analysis of exons 7 and 8 of the SMN1 and SMN2 genes. Over 95% of pathogenic variation for SMA involves biallelic loss of exon 7 of the SMN1 gene (Prior et al. 2010, PMID: 20057317). Other variation within the SMN1 gene is not detected with this assay. Results will only be reported in the proband if 0 copies of SMN1 are detected. Parental carrier status will be reported for affected patients if samples are available. Results are orthogonally confirmed by Multiplex Ligation-dependent Probe Amplification (MLPA). Whole genome sequencing is unable to determine the phase of SMN1 variants in the absence of parental testing. Therefore, in the absence of phasing this assay does not exclude the possibility than an individual harbors two copies of SMN1 on the same allele and no copies on the other allele (silent carriers), two pathogenic sequence variants on the same SMN1 allele, two pathogenic sequence variants on opposite SMN1 alleles, and one pathogenic sequence variant and the loss of exon 8 on the opposite SMN1 allele.

A phenotype-driven analysis is performed. Therefore, only variants related to the indication for testing are reported. Incidentally ascertained medically-actionable findings are also reported unless the individual has opted out of receiving incidental results. Likely pathogenic and pathogenic variants that may explain the patient's phenotype will be reported. Selected variants of uncertain significance may be reported as well. Reported variants are curated and classified in accordance with the American College of Medical Genetics and Genomics Guidelines (Richards et al. 2015, PMID: 25741868; Kearney et al. 2011, PMID 21681106; South et al. 2013, PMID 24071793).

LIMITATIONS

Full coverage of the genome is not currently possible due to technically challenging repetitive elements and duplicated regions within the genome. Thus, not all regions of the genome are sequenced and/or uniquely aligned to the reference genome. Certain genomic alterations may not be detected with the current version of this test. For example, genomic alterations such as trinucleotide repeat expansions and translocations will not be identified 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 Hospital and 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. The test is used for clinical purposes. It should not be regarded as investigational or for research. The Rady Children’s Institute for Genomic Medicine is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing.

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