Shwachman-Diamond Syndrome (SBDS) Sequencing

Patient: [redacted]
DOB: [redacted] Age: 68 Sex: M
Patient Identifiers: [redacted]

Visit Number (FIN): [redacted]

Client: ARUP Physician Services
321 TESTING ANSR EXTRACT
Salt Lake City, NY 84108

Physician: TEST TEST

ARUP Test Code: 2006240

Collection Date: 09/05/2023
Received in lab: 09/05/2023
Completion Date: 09/12/2023

Test Information

Test performed at GeneDx.

For clinical utility and genes tested, visit:
https://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_shw.pdf

Patient Report

Patient's results from GeneDx continue on following page(s).

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Jonathan R. Genzen, MD, PhD, Laboratory Director

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[redacted]

GeneDx

DOB [redacted]

Accession [redacted]

Submitter Patient ID(s) [redacted]

Sample	Testing	Provider
Source: Blood in EDTA Date Collected: 12-SEP-2023 Date Received: 12-SEP-2023	Date Started: 12-SEP-2023 Date Reported: 12-SEP-2023	Account #: A.R.U.P Laboratories

Test(s) Requested

SBDS Gene / Shwachman-Diamond Syndrome (SDS)

Clinical Indications

Result: Positive

Gene	Mode of Inheritance	Variant	Zygosity	Classification
SBDS	Autosomal recessive	c.258+2 T>C p.?	ABSENT	Pathogenic Variant
SBDS	Autosomal recessive	c.171dup p.(V58Cfs*5)	Heterozygous	Likely Pathogenic Variant

Interpretation

Recommendation(s)

Resources

MyGene2 is a portal through which families with rare genetic conditions who are interested in sharing their health and genetic information can connect with other families, clinicians, and researchers. If you are interested in learning more and/or participating, please visit www.mygene2.org.

GenomeConnect is an NIH initiative created to enable individuals and families with the same genetic variant or medical history to connect and share de-identified information. If you are interested in participating, please visit www.genomeconnect.org.

SBDS

GENE SUMMARY

The SBDS gene encodes a highly-conserved protein thought to play a role in RNA and tRNA metabolism, ribosome production, and translation initiation (PMID: 12496757, 22997148, 22046100). Homozygous or compound heterozygous pathogenic variants in SBDS cause Shwachman-Diamond syndrome (SDS), an autosomal recessive disorder with a broad clinical spectrum characterized by pancreatic exocrine insufficiency, hematologic dysfunction, and skeletal abnormalities (PMID: 20301722). Other clinical features of SDS may include short stature, liver dysfunction, and increased risk of malignancy, such as acute myeloid leukemia (PMID: 20301722). Additionally, heterozygous pathogenic SBDS variants have been associated with susceptibility to aplastic anemia (PMID: 17478638). Most variants in the SBDS gene result from the occurrence of gene conversion between SBDS and a nearby pseudogene, although some variants may occur independently (PMID: 12496757, 15769891, 14749921). To date, no genotype-phenotype correlations have been identified in patients with genetically-confirmed SDS (PMID: 15769891).

[redacted]

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c.171dup:p.(Val58Cysfs*5) in exon 2 of the SBDS gene (NM_016038.2) The sequence with the altered base(s) in brackets is: TGTT[dupT]GTAA

- Frameshift variant predicted to result in protein truncation or nonsense mediated decay in a gene for which loss of function is a known mechanism of disease
- Not observed at significant frequency in large population cohorts (gnomAD)
- Has not been previously published as pathogenic or benign to our knowledge

We interpret this as a Likely Pathogenic Variant.

Additional Comments

Genes Evaluated

SBDS

Methods

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene were PCR amplified and capillary sequencing was performed. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method was used to confirm all potentially pathogenic variants. If present, apparently homozygous variants were confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence alterations were reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants are not routinely reported but are available upon request. The methods used by GeneDx are expected to be greater than 99% sensitive in detecting variants identifiable by sequencing. Available evidence for variant classification may change over time and reported variant(s) may be reclassified according to the ACMG/AMP Standards and Guidelines (PMID: 25741868), which may lead to issuing a revised report.

Disclaimer

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test. The methods used cannot reliably detect deletions of 20bp to 500bp in size, or insertions of 10bp to 500bp in size. Sequencing cannot detect low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results. Inaccurate results may occur in the setting of allogeneic bone marrow/stem cell transplantation, active or chronic hematologic conditions, recent blood transfusion, suboptimal DNA quality, or in other rare circumstances. Rarely, incidental findings of large chromosomal rearrangements outside the gene of interest may be identified. As the ability to detect genetic variants and naming conventions can differ among laboratories, rare false negative results may occur when no positive control is provided for testing of a specific variant identified at another laboratory. In addition, the chance of an erroneous result due to laboratory errors incurred during any phase of testing cannot be completely excluded. Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. Consultation with a genetics professional is recommended for interpretation of results.

This test was developed and its performance characteristics determined by GeneDx. This test 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. The test is used for clinical purposes and should not be regarded as investigational or for research. The laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

References

Lek et al. (2016) Nature 536 (7616):285-91 (PMID: 27535533);Stenson et al. (2014) Human genetics 133 (1):1-9 (PMID: 24077912);Landrum et al. (2016) Nucleic Acids Res. 44 (D1):D862-8 (PMID: 26582918);Lott et al. (2013) Curr Protoc Bioinformatics 44 :1.23.1-26 (PMID: 25489354);Richards et al. (2015) Genetics In Medicine: 17 (5):405-24 (PMID: 25741868);Boocock GR et al. (2003) Nat Genet. 33 (1):97-101 (PMID: 12496757);Nakashima E et al. (2004) Hum Genet. 114 (4):345-8 (PMID: 14749921);Kuijpers TW et al. (2005) Blood. 105 (1):356-61 (PMID: 15769891);Calado RT et al. (2007) Blood. 110 (4):1141-6 (PMID: 17478638);Nelson A and Myers K. (2018) GeneReviews. Shwachman-Diamond Syndrome (PMID: 20301722);Vasieva O. (2011) Adv Appl Bioinform Chem. 4 :43-50 (PMID: 22046100);Sezgin G et al. (2013) Pediatr Blood Cancer. 60 (2):281-6 (PMID: 22997148);

Report Electronically Signed By

LIMS Cardiology

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GeneDx

DOB [redacted] Accession [redacted]

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Variant Table

Gene: Coding DNA	SBDS: c.171dup
Variant (Protein)	p.(Val58Cysfs*5) ((V58Cfs*5))
Classification	Likely Pathogenic Variant
Zygosity	Heterozygous
Chr: Position	7: 66459285
dbSNP	
gnomAD_Freq	
gnomAD_AMR	
gnomAD_NFE	
gnomAD_AFR	
gnomAD_EAS	
gnomAD_FIN	
gnomAD_Other	
gnomAD_SAS	
gnomAD_ASJ	
gnomAD_Hom	
Provean	
ClinVar	

This supplement provides evidence to support the classification of each reportable variant in the attached result report. This information is provided as a resource. It is not inclusive of all available information used by GeneDx for variant classification, and individual data elements may be weighted differently to derive at the classification. This information is subject to change and may differ from what is currently available. Results should always be interpreted in the context of the patient's clinical presentation. Blank fields indicate that no data were available at time of analysis.

- dbSNP - NCBI repository for single base nucleotide substitutions and short deletion and insertion polymorphisms https://www.ncbi.nlm.nih.gov/snp/
- The Genome Aggregation Database (gnomAD) combines exome and genome sequencing data from a variety of large-scale sequencing projects, including approximately 15,000 genomes and 123,000 exomes, including individuals recruited for disease-specific studies such as cancer and cardiovascular diseases. (PMID 32461654).
- gnomAD_Freq - variant allele frequency (in percent) from approximately 15,000 genomes and 123,000 exomes in the Genome Aggregation Database. Select ancestries include: gnomAD_AMR (Admixed American/Latino); gnomAD_AFR (African); gnomAD_EAS (East Asian); gnomAD_FIN (Finnish of European ancestry); gnomAD_NFE (non-Finnish of European ancestry); gnomAD_SAS (South Asian); gnomAD_ASJ (Ashkenazi Jewish). gnomAD_Hom - number of individuals homozygous for the variant.
- gnomAD_AMR- variant frequency (in percent) for individuals of Latino ancestry
- PROVEAN (Protein Variation Effect Analyzer) - predicts whether an amino acid substitution or indel affects the biological function of a protein using a delta alignment score from -14 to +14 (< or = -2.5, predicted deleterious; >-2.5, predicted neutral).
- Other published in silico algorithms, including those that predict splicing impact, may be considered for variant analysis. In silico scores may change. In silico models use algorithms that predict the effect a variant may have on the protein. Thus, predictions should be interpreted with caution and only be used in combination with other available evidence to support the classification of any variant (PMID 23056405).
- ClinVar - Classification of variant in ClinVar database, an NCBI archive of human variants with supporting evidence of phenotypic association. https://www.ncbi.nlm.nih.gov/clinvar/ (PMID 26582918).

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