Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/10/1954
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Shwachman-Diamond Syndrome (SBDS) Sequencing

ARUP test code 2006240

EER Shwachman-Diamond Syndrome (SBDS)

See Note

Authorized individuals can access the ARUP Enhanced Report using the following link:

[redacted]

Shwachman-Diamond Syndrome (SBDS)

Positive *

Date Test(s) Started: 12-SEP-2023 10:33:33
Sample Source: Blood in EDTA Date Collected: 12-SEP-2023 Date Received:
12-SEP-2023 Testing Date Started: 12-SEP-2023 Date Reported: 12-SEP-2023
Provider Account #: A.R.U.P Laboratories Additional Provider:
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

H=High, L=Low, *=Abnormal, C=Critical

(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). 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. 106
(1): 356-61 (PMID: 15769891);Calado RT et al. (2007) Blood. 110 (4): 1141-6
(PMID: 17478638);Nelson A and Myers K. (2018) GeneReviews.

H=High, L=Low, *=Abnormal, C=Critical

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);
###
Variant Table
Gene: Coding DNASBDS: c.171dup
Variant (Protein)p.(Val58Cysfs*5) ((V58Cfs*5))
ClassificationLikely Pathogenic Variant
ZygosityHeterozygous
Chr: Position7: 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 ancestryPROVEAN (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).

Report electronically signed by: LIMS Cardiology
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
EER Shwachman-Diamond Syndrome (SBDS)	23-248-106350	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Shwachman-Diamond Syndrome (SBDS)	23-248-106350	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical