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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/28/2019
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Shwachman-Diamond Syndrome (SBDS) Sequencing

ARUP test code 2006240

Ordering Physician Name

[redacted]
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

Ordering Physician Phone Number

[redacted]
Performed by: GeneDx
207 Perry Parkway
Gaithersburg, MD 20877

Anne Maddalena, Ph.D.,FACMG,

Shwachman-Diamond Syndrome (SBDS)

POSITIVE *

Date Test(s) Started: [redacted]
Test(s) Requested SBDS Gene / Shwachman-Diamond Syndrome (SDS)
Clinical Indication None provided.
Result(s): POSITIVE
Gene Mode of Inheritance Variant Zygosity Classification
SBDS Autosomal Recessive c.258+2 T>C Heterozygous Pathogenic Variant
SBDS Autosomal Recessive c.183_184delTAinsCT p.K62X Heterozygous Pathogenic Variant
No additional reportable variants were identified in the SBDS gene by
sequencing analysis.
Interpretation This individual is heterozygous for two pathogenic variants in
the SBDS gene, which is consistent with a diagnosis of autosomal recessive
Schwachman-Diamond syndrome in this individual if these variants were inherited
on different alleles (in trans).
Recommendation(s) Genetic counseling is recommended to discuss the implications
of these results.Correlation of these findings with the clinical features of
this individual is recommended.Targeted carrier testing is available to family
members, and molecular prenatal diagnosis is available for the parents of this
individual, if desired, for the variants in the SBDS gene.

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

However, targeted
carrier testing of both parents is necessary prior to or concurrently with any
carrier testing or predictive testing in this family to determine whether the
two variants were inherited on separate alleles (in trans) or inherited on one
allele with a normal copy of the gene on the second allele (in cis).
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 (Boocock et al., 2003; Sezgin et al., 2013; Vasieva, 2011).
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 (Nelson and Myers, 2018).
Other clinical features of SDS may include short stature, liver dysfunction,
and increased risk of malignancy, such as acute myeloid leukemia (Nelson and
Myers, 2018). Additionally, heterozygous pathogenic SBDS variants have been
associated with susceptibility to aplastic anemia (Calado et al., 2007). 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
(Boocock et al., 2003; Kuijpers et al., 2005; Nakashima et al., 2004). To date,
no genotype-phenotype correlations have been identified in patients with
genetically-confirmed SDS (Kuijpers et al., 2005). c.258+2 T>C: IVS2+2 T>C in
intron 2 of the SBDS gene (NM_016038.2) Has been published previously in
association with Shwachman-Diamond syndrome in multiple unrelated patients
(Boocock et al., 2003; Nakashima et al., 2004; Andolina et al., 2013) Observed
multiple times with a pathogenic variant on the opposite allele (in trans) in
unrelated patients referred for genetic testing at GeneDx Canonical splice site
variant in a gene for which loss-of-function is a known mechanism of disease
Results from a conversion event with a nearby SBDS pseudogene, an inactive gene
with numerous pathogenic variants (Boocock et al., 2003) Published functional

studies demonstrate that truncating variants, including c.258+2 T>C, may affect the protein's cellular localization and motility (Austin et al., 2005; Orelio et al., 2011)
We interpret this as a Pathogenic Variant. c.183_184delTAinsCT: p.Lys62Ter (K62X) in exon 2 of the SBDS gene (NM_016038.2) Observed multiple times with a pathogenic variant on the opposite allele (in trans) in unrelated patients referred for genetic testing at GeneDx and in the published literature (Boocock et al., 2003) Nonsense 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 Results from a conversion event with a nearby SBDS pseudogene, an inactive gene with numerous pathogenic variants (Boocock et al., 2003) Observed in 0.02476% (70/282670 alleles) in large population cohorts (Lek et al., 2016)
We interpret this as a Pathogenic Variant.
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 the reported variant(s) may be re-classified according to the AMP/ACMG guidelines for variant classification (Richards et al. 2015), which may lead to re-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 with this test.
This test cannot reliably detect mosaicism. Capillary sequencing cannot reliably detect exon-level deletion/duplications, if present, nor will it detect variants deep within the introns or in the regulatory regions unless

specifically indicated in the methods. If performed, copy number assessment may not reliably detect chromosomal aberrations and deletions/insertions of less than 500 bp, and may incidentally reveal large chromosome rearrangements outside the gene of interest. Some genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that may result in suboptimal data, potentially impairing accuracy of the results. False negative results may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. 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. The chance of a false positive or false negative 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);Nakashima et al. (2004) Hum. Genet. 114 (4): 345-8 (PMID: 14749921);Boocock et al. (2003) Nat. Genet. 33 (1): 97-101 (PMID: 12496757);Kuijpers et al. (2005) Blood 106 (1): 356-61 (PMID: 15769891);Calado et al. (2007) Blood 110 (4): 1141-6 (PMID: 17478638);Vasieva et al. (2011) Adv Appl Bioinform Chem 4 : 43-50 (PMID: 22046100);Sezgin et al. (2013) Pediatr Blood Cancer 60 (2): 281-6 (PMID: 22997148);Nelson et al. Shwachman-Diamond Syndrome. 2008 Jul 17 [Updated 2018 Oct 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.

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

(Available from: https: //www.ncbi.nlm.nih.gov/books/NBK1756/): (PMID:
20301722); Boocock et al. (2003) Nat. Genet. 33 (1): 97-101 (PMID:
12496757);Nakashima et al. (2004) Hum. Genet. 114 (4): 345-8 (PMID:
14749921);Andolina et al. (2013) J. Pediatr. Hematol. Oncol. 35 (6): 486-9
(PMID: 22935661);Austin et al. (2005) Blood 106 (4): 1253-8 (PMID:
15860664);Orelio et al. (2011) PLoS ONE 6 (6): e20727 (PMID: 21695142)
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Gene: Coding DNASBDS: c.258+2 T>CSBDS: c.183_184delTAinsCT
Variant (Protein)IVS2+2 T>Cp.Lys62Ter (K62X)
ClassificationPathogenic VariantPathogenic Variant
ZygosityHeterozygousHeterozygous
Chr: Position7: 664591977: 66459273
dbSNPrs113993993rs113993991
gnomAD_Freq0.0039
gnomAD_AMR0.00265417
gnomAD_NFE0.00366542
gnomAD_AFR0.00140213
gnomAD_EAS0.00517536
gnomAD_FIN0.00941214
gnomAD_Other0.00457190
gnomAD_SAS0.00320429
gnomAD_ASJ0.00231481
gnomAD_Hom2
Provean
ClinVarPathogenicPathogenic
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 the classification. This information is subject to change
over time 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 was available at time of
analysis.dbSNP - NCBI repository for single base nucleotide substitutions and
short deletion and insertion polymorphismsThe 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 (Lek et al., 2016).The gnomAD set integrates data from the 1000
Genomes project as well as individuals recruited for disease-specific studies,
including cancer and cardiovascular diseases. Genotype quality metrics and site
quality metrics for a specific variant are available at http: //gnomad.broadinstitute.org/.gnomAD_Freq - variant allele frequency (in
percent) from approximately 15,000 genomes and 123,000 exomes in the Genome
Aggregation DatabasegnomAD_AMR- variant frequency (in percent) for individuals
of Latino ancestrygnomAD_NFE - variant frequency (in percent) for non-Finnish
individuals of European ancestrygnomAD_AFR - variant frequency (in percent) for
individuals of African ancestrygnomAD_EAS - variant frequency

(in percent) for
individuals of East Asian ancestrygnomAD_FIN - variant frequency (in percent)
for Finnish individuals of European ancestrygnomAD_Other - variant frequency
(in percent) for individuals of other ancestrygnomAD_SAS - variant frequency
(in percent) for individuals of South Asian ancestrygnomAD_ASJ- variant
frequency (in percent) for individuals of Ashkenazi Jewish ancestrygnomAD_Hom -
The number of individuals who are homozygous for the variantPROVEAN (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 (more negative=more damaging) with a predefined threshold
of -2.5. If the PROVEAN score is equal to or below -2.5, the variant is
predicted to have a deleterious effect. If the PROVEAN score is greater than
-2.5, the variant is predicted to have a neutral effect.Note that other
published in silico algorithms, including those that predict splicing impact,
may be considered for variant analysis. In silico scores used by GeneDx are
precomputed and may change over time. In silico models use algorithms that
predict the effect a variant may have on the protein, but they do not provide
direct evidence regarding the actual impact on protein structure or function.
In silico models should be interpreted with caution and only be used in
combination with other available evidence to support the classification of any
variant.ClinVar - Classification of variant in ClinVar database, an NCBI
archive of human variants with supporting evidence of phenotypic association.REFERENCES:
1. gnomAD: Lek et al. (2016) Nature 536 (7616): 285-91 (PMID: 27535533). 2.
PROVEAN: Choi et al. (2012) PLoS ONE 7 (10): e46688 (PMID: 23056405). 3.
ClinVar: Landrum et al. (2014) Nucleic Acids Res. 42 (1): D980-5 (PMID:
24234437).
S S S
Report electronically signed by: Patricia Celestino Soper PhD, FACMG
Performed by: GeneDx
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Anne Maddalena, Ph.D.,FACMG,

EER Shwachman-Diamond Syndrome (SBDS)

See Note

Access ARUP Enhanced Report using the link below:

-Direct access:
[redacted]

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Ordering Physician Name	21-008-401384	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Ordering Physician Phone Number	21-008-401384	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Shwachman-Diamond Syndrome (SBDS)	21-008-401384	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
EER Shwachman-Diamond Syndrome (SBDS)	21-008-401384	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