Golden Labs
Precision Medicine

Golden Labs
Enterprise Blvd. Bozeman, MT
Phone: (406) 867-3309 / Fax: (406) 555-6666
http://goldenlabs.org/tests

Name: Smith, John D.

Accession ID: GL-26-104812

DOB: **08/14/1987**
Sex: **Male**
Family #: **F-2026-1124**

MRN: **04812379**
Referring Facility: **Cascade Medical Center, Genetics Clinic**
Referring physician: **Sarah J. Martinez, MD**
Copies to: **Michael Chen, MD (PCP)**

Panel Coverage: **98.7% at ≥30X**
Avg. Read Depth: **142X**
Type: **Whole Blood (EDTA)**

Date of Collection: **04/22/2026**
Date of Receipt: **04/24/2026**
Date of Report: **05/11/2026**

Test(s) Performed: **Oxford Nanopore Panel Sequencing**

RESULT: Positive
Findings explain patient phenotype

APPROACH

Sequencing of select genes was done using Oxford Nanopore and the data was analyzed to identify both previously classified and novel variants in targeted genes. A total of 287 genes with previous implications in various mendelian disorders (see Supplement for a list of genes and coverage information) were covered with minimum read depth of 30X. Note that this test cannot exclude the possibility of variants in genes not analyzed or assayed with incomplete coverage.

VARIANTS RELEVANT TO INDICATION FOR TESTING

One pathogenic variant in XPC was identified in this individual. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

Gene & Transcript	Variant	Allele State	Location	Disorder	Inheritance	Classification
XPC NM_004628.5	p.Cys670Ter	Heterozygous	Exon 10	Unspecified / All Highly Penetrant Disorders	Recessive	Pathogenic

OTHER VARIANTS OF MEDICAL SIGNIFICANCE (INCIDENTAL FINDINGS)

Incidental findings are variants of medical significance that are not associated with the individual's reported indication. Please note that the presence of pathogenic variants in genes with incomplete coverage or in genes not examined cannot be fully excluded.

Carrier Status

This individual is a carrier of one heterozygous pathogenic variant in a gene associated with a recessive disorder that is unrelated to this individual's reported phenotype. In the heterozygous state, this variant is not known to play a role in disease. Please see below for more detailed variant information.

Name	Type	Size	Classification
SDHA ex14-15 del	Het Deletion	4.0 Kb	Uncertain significance

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RECOMMENDATIONS

The interpretation of these results should be done in the context of a patient's medical record and family history. Please note that interpretation and classification of the variants reported here may change over time. Please see a genetic counselor for services regarding the implications of these results in the context of understanding the implications of incidental findings, family planning and the informing of family members of potentially shared genetic outcomes.

DETAILED VARIANT INFORMATION (VARIANTS RELEVANT TO INDICATION FOR TESTING)

Gene & Transcript	Variant	Inheritance	Disorder	Criteria	Classification
XPC NM_004628.5	p.Cys670Ter	Recessive	Unspecified / All Highly Penetrant Disorders	PM2, PVS1, PP5	Pathogenic

Location	Allele State	gnomAD v4 All (Novel) Allele Frequency
Exon 10	Heterozygous	Novel

Genomic Position	NGS Reads Supporting Change
g.14156358A>T	40.00% (8 of 20)

VARIANT INTERPRETATION: The stop gained NM_004628.5(XPC):c.2010T>A (p.Cys670Ter) has been reported to ClinVar as Pathogenic/Likely pathogenic with a status of (2 stars) criteria provided, multiple submitters, no conflicts (Variation ID 1454617 as of 2025-11-06). The p.Cys670Ter variant is novel (not in any individuals) in gnomAD v4 All. The p.Cys670Ter variant is novel (not in any individuals) in 1kG All. This variant is predicted to cause loss of normal protein function through protein truncation. This variant is a stop gained variant which occurs in an exon of XPC upstream of where nonsense mediated decay is predicted to occur. This variant has been previously classified as pathogenic, indicating that the region is critical to protein function. There are 57 downstream pathogenic loss of function variants, with the furthest variant being 195 residues downstream of this variant. This indicates that the region is critical to protein function. The p.Cys670Ter variant is a loss of function variant in the gene XPC, which is intolerant of Loss of Function variants, as indicated by the presence of existing pathogenic loss of function variant NP_004619.3:p.M1V and 133 others. For these reasons, this variant has been classified as Pathogenic.

DETAILED VARIANT INFORMATION (INCIDENTAL FINDINGS)

Monogenic Disease Risk

There were NO monogenic disease risk variants identified in this individual in genes unrelated to this individual's clinical presentation. Please see limitations for more detail.

Carrier Status

This individual is a carrier of one heterozygous pathogenic variant in a gene associated with a recessive disorder that is unrelated to this individual's reported phenotype. In the heterozygous state, this variant is not known to play a role in disease. Please see below for more detailed variant information.

Copy Number Variation (CNV): SDHA ex14-15 del 4.0 Kb Het Deletion

ISCN	Type	Criteria	Score	Classification
5p15.33 (5:253745-257711)x1	Het Deletion	1A, 3B, 2B	0.45	Uncertain significance

Inheritance	Size
Unknown	4.0 Kb

Z-score	Ratio	Flags

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		PRECISE
Genomic Position		**Primary Gene**
NC_000005:g.(240476_253745)_(257711_?)del		SDHA

VARIANT INTERPRETATION: This variant results in deletion of the genomic region encompassing exons 14-15 of SDHA, a gene that has previously not been evaluated for dosage sensitivity by ClinGen. The variant overlaps with the 3' end of the SDHA gene, including 2 exons, and is anticipated to result in nonsense mediated decay. This is expected to result in an absent or disrupted protein product. While this particular variant has not been reported in the literature, loss-of-function variants in SDHA are known to be pathogenic. The variant overlaps the ISCA-37390 known haploinsufficient region.
The SDHA gene is in the OMIM Morbid Map. The gene contains 285 pathogenic loss of function variants. The gene overlaps 107 pathogenic copy number losses in ClinVar. The gene's coding region partially overlaps a high frequency GnomAD CNV region with an average frequency of 0.01. The gene's coding region partially overlaps a high frequency DGV CNV with an average frequency of 0.06.

Relevant Genomic Content:

This deletion includes 1 protein coding genes, including the following, which are relevant to this report:

Gene	%CDS	Disease	Mode of Inheritance	Relevance Category
SDHA	10.08	Mitochondrial complex ii deficiency nuclear type 1	Unknown	Reason for referral

More detailed gene information:

SDHA

Evidence for Haploinsufficiency: Zhang, et al. (2005) characterize the 5p deletions using CGH array for 94 patients with Cri du Chat syndrome. Their results confirm that deletion of the distal 11.3 Mb of 5p are associated with speech delay, a cat-like cry and high pitched voice, distinctive facial features, and variable intellectual disability that is described in patients with Cri du Chat syndrome. In addition, they provide genotype-phenotype data regarding genomic regions associated with variable degrees of intellectual disability in patients with larger deletions. Cerruti Mainardi, et al. (2001) provide genotype-phenotype data for 80 patients with Cri du Chat syndrome and deletions on 5p using FISH. Their results are consistent with those of Zhang et al.

Variants of Unknown Significance

The following table includes detected variants that do not, at the time of this report, have enough clinical evidence to be reported as actionable biomarkers. Generally, there exists some in-silico and functional evidence that these variants may be damaging or activating mutations. In the future, new clinical evidence may become available to further classify these variants.

This report does not list variants meeting criteria to be classified as Benign or Likely Benign, including common polymorphism and mutations with no impact or predicted impact on their gene product.

Structural Variations

Name	Effect	Supporting Reads	WT Reads	Classification
RTEL1-TNFRSF6B::FOXN3 e30-e1	Transcript ablation	4	-	Not classified

METHODOLOGY

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The individual's DNA was extracted and fragmented, with fragments from the coding regions of the select gene panel targeted for amplification and sequencing. Reads from the sequence output were aligned to the human reference genome (GRCh37) using the Burrows-Wheeler Aligner (BWA). Variants to the reference were called using the Genomic Analysis Tool Kit (GATK). The variants were annotated and filtered using the Golden Helix VarSeq analysis workflow implementing the ACMG guidelines for interpretation of sequence variants. This includes comparison against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium's publication of 2,500 genomes, the NCBI ClinVar database of clinical assertions on variant's pathogenicity and multiple lines of computational evidence on conservation and functional impact. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

VARIANT ASSESSMENT PROCESS

The following databases and in-silico algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB RefSeq Genes, ExAC Gene Constraints, VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, GeneSplicer, MaxEntScan, NNSplice, PWM Splice Predictor. Analysis was reported using the to HGVS nomenclature (www.hgvs.org/mutnomen) as implemented by the VarSeq transcript annotation algorithm. The reported transcript matches that used most frequently by the clinical labs submitting to ClinVar.

LIMITATIONS

It should be noted that this test is limited to a limited number of genes and does not include all intronic and non-coding regions. This report only includes variants that meets a level of evidence threshold for cause or contribute to disease. Certain classes of genomic variants are also not covered using the NGS testing technology, including triplet repeat expansions, copy number alterations, translocations and gene fusions or other complex structural rearrangements. More evidence for disease association of genes and causal pathogenic variants are discovered every year, and it is recommended that genetic variants are re-interpreted with updated software and annotations periodically.

CLASSIFICATION SYSTEM AND FREQUENCY THRESHOLDS

This interpretation was preformed using the ACMG variant classification guidelines. The following recessive gene thresholds were used:

- Common Allele Frequency: 0.01
- High for Disorder Allele Frequency: 0.0015
- Extremely Rare Allele Frequency: 0.0002

The following dominant gene thresholds were used:

- Common Allele Frequency: 0.005
- High for Disorder Allele Frequency: 0.0005
- Extremely Rare Allele Frequency: 0.0001

Sub-populations were excluded from consideration if the total allele number failed to exceed 2000.

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ANNOTATION SOURCES

This interpretation was preformed using the following annotation sources:

Name	Version	Type
gnomAD Joint Variant Frequencies 4.1, BROAD	v4.1	Frequency
1kG Phase3 - Variant Frequencies 5a with Genotype Counts, GHI	2015-05-26	Frequency
Multiple Sequence Alignments of 100 Vertebrates, UCSC	2015-05-06	Annotation
CADD Scores InDels v1.7, UW	1.7	Annotation
ClinVar CNVs and Large Variants 2025-09-04, NCBI	2025-09-04	Annotation
dbSNP 155, NCBI	2021-05-25	Annotation
Haploinsufficiency Predictions Version 3, DECIPHER	v3	Annotation
DECIPHER Population CNV v9.2	2015-09-15	Annotation
Genomic Super Dups 2014-10-19, UCSC	2014-10-19	Annotation
gnomAD High Frequency CNV Regions 2024-02-20, GHI	2024-02-20	Annotation
gnomAD Structural Variants 4.0 v2, BROAD	2024-04-11	Annotation
DGV CNVs - Gold Standard Variants 2016-05-15 v3, DGV	2016-05-15 v3	Annotation
1kG Phase3 CNVs and Large Variants 5b V2, GHI	2015-08-18v2	Annotation
gnomAD Joint Variant Frequencies 4.0 v2, BROAD	v4.0v2	Annotation
Reference Sequence GRCH37g1k V2, 1000Genomes	2022-10-17	Annotation
Reference Sequence GRCh38 V2, NCBI	2022-10-17	Annotation
ClinGen Gene Dosage Sensitivity 2025-10-01, NCBI	2025-10-01	Annotation
ClinGen Region Dosage Sensitivity 2025-10-01, NCBI	2025-10-01	Annotation
ClinVar Assessments 2025-10-02, NCBI	2025-10-02	Annotation
ClinVarCNVsandLargeVariant Assessments 2025-09-04, NCBI	2025-09-04	Annotation
ClinVar 2025-11-06, NCBI	2025-11-06	Annotation
ClinVar Transcript Counts 2025-10-02, NCBI	2025-10-02	Annotation
Conservation Scores Exonic, GHI	2020-10-02	Annotation
DECIPHER Developmental Disorders 2025-10-02, GHI	2025-10-02	Annotation
gnomAD - Gene Constraint 4.0 v2, BROAD	2024-05-07	Annotation
Gene Identifiers and Descriptions 2022-12-19, GHI	2022-12-19	Annotation
gnomAD Exomes Variant Frequencies 2.0.1, BROAD	2017-05-09	Annotation
Human Phenotype Ontology 2025-09-04	2025-09-04	Annotation
SIFT and PolyPHen2 Missense Predictions 2021-04-21, GHI	2021-02-11	Annotation
MONDO 2025-09-04, GHI	2025-09-04	Annotation
Mondo Gene Disease Association 2023-11-21, MI	2023-11-21	Annotation
OMIM Genes 2025-10-01, GHI	2025-10-01	Annotation
Orphanet Gene Associations 2025-08-01, GHI	2025-08-01	Annotation
Cytobands 2014-06-11, UCSC		Annotation
RefSeq Genes 110 v2, NCBI	2022-04-12	Annotation
InterPro Regions 2025-08-19	2025-08-19	Annotation
ClinGen Gene Disease Validity 2025-08-01, NCBI	2025-08-01	Annotation
Clinical Genomic Database 2025-02-21, GHI	2025-05-02	Annotation
Genetics Home Reference 2025-10-01, GHI	2025-10-01	Annotation
Missense Badness and MPC, BROAD	2017-07-14	Annotation
Low Complexity Regions and Universal Mask-GHI	2015-03-29	Annotation

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Repeating Elements by RepeatMasker, UCSC	2014-04-06	Annotation

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