

Patient Information:
Sample report

Accession:
Sample report

Physician:
Sample report

Laboratory:
Fulgent Therapeutics LLC
CAP#: 8042697
CLIA#: 05D2043189
Laboratory Director:
Dr. Amar Jariwala
Report Date: **Aug 15, 2025**

Final Report

TEST PERFORMED

23andMe Gene Panel - 104 Genes

(104 Gene Panel; gene sequencing with deletion and duplication analysis)

RESULTS:



A heterozygous likely pathogenic variant consistent with a molecular diagnosis of a *DSG2*-related condition was identified. Additionally, one variant of potential clinical relevance is reported.

Clinically Significant Variants

Gene	Variant	Condition/Inheritance	Zygosity	Classification
DSG2 NM_001943.5	c.210del p.Ile70Metfs*42	arrhythmogenic right ventricular cardiomyopathy (AD)	Heterozygous	Likely Pathogenic

Additional Variants of Potential Clinical Relevance

Gene	Variant	Condition/Inheritance	Zygosity	Classification
MUTYH NM_001128425.1	c.1187G>A p.Gly396Asp	MUTYH-associated polyposis (AR)	Heterozygous	Pathogenic

INTERPRETATION:

Notes and Recommendations:

- As requested, this report only includes variants classified as Pathogenic, Likely Pathogenic, or Risk Allele at the time of analysis. If detected, this report does not include variants classified as of uncertain significance.
- Children, siblings, and each parent of this individual are at risk of harboring the pathogenic variant reported. Testing of at risk family members for this variant is available.
- Gene specific notes and limitations may be present. See below.
- These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National Society of Genetic Counselors (NSGC; <https://www.nsgc.org>)
- Guide to Interpreting Genomic Reports: A Genomics Toolkit (CSER Consortium; February 2017) (<https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources#hep>)

About *DSG2*

Autosomal dominant mutations in *DSG2* are associated with dilated cardiomyopathy-1BB and arrhythmogenic right ventricular dysplasia-10 (ARVD10) (PubMed: [20301486](#), [20301310](#); OMIM: [125671](#)). Limited studies have suggested that biallelic mutations in the *DSG2* gene have been associated with dilated cardiomyopathy 1BB (PubMed: [33949662](#), [18678517](#); OMIM: [612877](#)).

See OMIM gene entry for *DSG2* (OMIM: [125671](#)) for further information.

***DSG2* NM_001943.5:c.210del (p.Ile70Metfs*42)**

Classification: **Likely Pathogenic**

Zygosity and Inheritance 	This heterozygous Likely Pathogenic variant is consistent with autosomal dominant inheritance of a <i>DSG2</i>-related condition.
Variant Type 	- Genomic change: Chr18(GRCh37):g.29099894del. - This variant is predicted to result in a frame-shift in exon 3 of the <i>DSG2</i> gene. - This variant is predicted to introduce a premature stop codon at least 50 nucleotides upstream of the canonical donor splice site of the penultimate exon and to result in the loss of function of the protein product due to nonsense-mediated mRNA decay (PubMed: 25741868, 30192042, 27618451, 11532962, 18066079). There's sufficient evidence that loss of function in this gene is a known disease mechanism for dilated cardiomyopathy-1BB and arrhythmogenic right ventricular dysplasia-10 (ARVD10) (PubMed: 20301486, 20301310).
Variant in Cases 	This variant has not been reported as associated with a clinical condition in the Human Gene Mutation Database (HGMD).
Variant in Controls 	- This variant is absent from the general population. - The Broad Institute gnomAD database (>120,000 Individuals with no known severe, pediatric onset disease) was used for this analysis.
Other Variant Information 	- Computational predictions for p.Ile70Metfs*42 (gnomAD: pLI = [Exp: , Obs:]) (granthamDist =). - No other information is available for this variant.

About *MUTYH*

Biallelic germline mutations in *MUTYH* can result in *MUTYH*-associated polyposis (MAP), a colorectal cancer predisposition syndrome inherited in an autosomal recessive manner. Heterozygous carriers may also be at increased risk for polyposis, particularly with a family history of MAP (PubMed: [23035301](#); OMIM: [604933](#)).

See OMIM gene entry for *MUTYH* (OMIM: [604933](#)) for further information.

100% of the coding sequence of the NM_001128425.1 transcript of *MUTYH* gene was sequenced to a minimum depth of 20x in the submitted specimen. A second sequencing mutation was not detected in this gene, nor were copy number variants observed, however, the presence of mutations in the deep intronic or regulatory regions cannot be ruled out. As the clinical condition(s) associated with mutations in the *MUTYH* gene are recessive and only a single heterozygous variant has been detected, this result is interpreted as carrier status only. Further clinical evaluation may be warranted to clarify these findings.

MUTYH NM_001128425.1:c.1187G>A (p.Gly396Asp)

Classification: **Pathogenic**

Zygosity and Inheritance 	This heterozygous Pathogenic variant is consistent with this individual being a carrier for an autosomal recessive <i>MUTYH</i>-related condition.
Variant Type 	- Genomic change: Chr1 (GRCh37):g.45797228C>T. - This variant is in the dbSNP database: rs36053993 - This variant is predicted to result in a single amino acid substitution (missense) of Gly to Asp at codon 396 in exon 13 of the <i>MUTYH</i> gene. - This variant is located near an intron-exon boundary.
Variant in Cases 	- This variant, p.Gly396Asp, also known as p.Gly382Asp, has been reported to be commonly found in the homozygous or compound heterozygous state in affected individuals (PubMed: 19032956, 16557584, 17489848, 19793053, 12606733). - This variant is classified as "Pathogenic" or "Likely Pathogenic" in ClinVar, with multiple submitters in agreement (ClinVar: 5294). - This variant is classified as a "Disease Mutation" (DM) in the Human Gene Mutation Database (HGMD). - This variant has one or more entries in ClinVar: RCV000005614.26, RCV000005615.4, RCV000079501.14, RCV000515320.1, RCV000115748.17, RCV000121598.3, RCV000144637.1, RCV001262769.1, RCV000501239.1, RCV000493920.1, RCV000477907.1, RCV001282788.1
Variant in Controls 	- This variant has been observed at a frequency of 0.31% (860/281146 alleles). - The highest allele frequency that this variant has been observed at in any sub-population with available data is 0.49% in the European (Non-Finnish) population. - There are three homozygous control individuals for this variant. - The Broad Institute gnomAD database (>120,000 Individuals with no known severe, pediatric onset disease) was used for this analysis.



Other Variant Information



- In vitro studies suggest that this variant will impair the function of the protein product encoded by this gene (PubMed: [18534194](#), [15987719](#), [19836313](#)).
- Analysis of amino acid conservation indicates that the wild-type amino acid Gly is completely conserved across vertebrate species, suggesting that a change at this position may not be tolerated and could adversely affect the structure and/or function of the protein.
- Amino acid conservation data:
 - Primates: 12 out of 12 match the wild type.
 - Mammals: 62 out of 62 match the wild type.
 - Vertebrates: 93 out of 93 match the wild type.
- The physiochemical difference between Gly and Asp as measured by Grantham's Distance is 94. This score is considered a "moderate" change. (PubMed: [4843792](#), [6442359](#)).
- Computational predictions for p.Gly396Asp (2P/0B AGVGD, SIFT/) (REVEL = 0.95) (gnomAD: Z = -0.21 [Exp: 311.7, Obs: 322]) (granthamDist = 94).



GENES TESTED:

23andMe Gene Panel - 104 Genes

104 genes tested (99.89% at >20x).

ABCD1, ACTA2, ACTC1, ACVRL1, APC, APOB, APOE, APOL1, ATM, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTBD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, CHEK2, COL3A1, COL5A1, COL5A2, CYP27A1, DES, DSC2, DSG2, DSP, ENG, F2, F5, FBN1, FLNC, G6PD, GAA, GBA, GLA, HFE, HNF1A, HOXB13, KCNH2, KCNQ1, LDLR, LDLRAP1, LMNA, LRRK2, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKD1, PKD2, PKP2, PLN, PMS2, POLD1, POLE, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SERPINA1, SMAD3, SMAD4, STK11, TGFB2, TGFB3, TGFB3R1, TGFB3R2, TMEM127, TMEM43, TNNC1, TNNT3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1

Gene Specific Notes and Limitations

GBA: Significant pseudogene interference and/or reciprocal exchanges between the GBA gene and its pseudogene, GBAP1, have been known to occur and may impact results. As such, the relevance of variants reported in this gene must be interpreted clinically in the context of this individual's clinical findings, biochemical profile, and family history. The current testing method cannot detect copy-neutral rearrangements between the pseudogene and the functional gene, which have been reported in very rare cases of Gaucher disease (PubMed: [21704274](#)). Variants described as 'Possible Heterozygote' indicate that the variant occurs either in the GBA gene or in the GBAP1 pseudogene. Confirmatory testing by LR-PCR and/or MLPA is required to resolve the genomic location of these variants. **MSH2:** Inversion of MSH2 exons 1-7 ("Boland" inversion) is not assessed. **NF2:** The ordered testing method does not guarantee the detection of potentially causative somatic changes in NF2. **PKD1:** Significant pseudogene interference and/or reciprocal exchanges between the PKD1 gene and its six pseudogenes have been known to occur and may impact results. As such, the relevance of variants reported in this gene must be interpreted clinically in the context of this individual's clinical findings, biochemical profile, and family history. **PMS2:** Significant pseudogene interference and/or reciprocal exchanges between the PMS2 gene and its pseudogene, PMS2CL, have been known to occur and may impact results. Variants located within exons 12-15 of transcript NM_000535.7 can not be detected by this test. **TP53:** Apparent heterozygous pathogenic variants reported in the TP53 gene may be somatic variants that are acquired through clonal hematopoiesis of indeterminate potential (CHIP) and are not of germline origin (PubMed: [28279308](#)). These patients do not carry hereditary cancer risk but are at risk for hematologic cancer, cardiovascular disease, and all-cause mortality (PubMed: [25426838](#); [27927582](#); [25426837](#); [28636844](#); [27923552](#)). Additional studies including testing additional family members or a fibroblast sample from the patient may be warranted based on the clinical presentation of this individual to determine whether the pathogenic variant is germline or somatic in origin. **TRDN:** Due to high GC content of certain exons (including exons 4-5), copy number analysis may have reduced sensitivity for partial gene deletions/duplications of *TRDN*. Confirmation of partial gene deletions/duplications are limited to individuals with a positive personal history of cardiac arrhythmia and/or individuals carrying a pathogenic/likely pathogenic sequence variant. **TTN:** Due to the interference of tandem repeats within the TTN gene, the variants (sequencing and del/dup) in the genomic regions between exons 153-155 of transcript NM_133378.4 are not detected by this test.

METHODS:

Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology (NGS). Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 99.92% and 99.89% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. High confidence copy number variants may be detectable by NGS, however, the sensitivity of copy number variant detection is dependent upon sample type and quality. All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications identified by NGS are confirmed by an orthogonal method (qPCR or MLPA), unless exceeding an internally specified and validated quality score, beyond which deletions and duplications are considered real without further confirmation. Bioinformatics: The FPLMv2.0 pipeline was used to analyze this specimen.

LIMITATIONS:



These test results and variant interpretation are based on the proper identification of the submitted specimen, accuracy of any stated familial relationships, and use of the correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributors, genetic or otherwise, to this individual's phenotype, and negative results do not rule out a genetic cause for the indication for testing. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (<https://www.genenames.org>) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the available clinical and family history information for this individual, collected published information, and Alamut annotation available at the time of reporting. This assay is designed and validated for detection of germline variants only. It is not designed or validated for the detection of low-level mosaicism or somatic mutations. This assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions (eg. trinucleotide or hexanucleotide repeat expansion). DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) may not be detected by this test. Unless otherwise indicated, no additional assays have been performed to evaluate genetic changes in this specimen. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm for copy number variants, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic alterations in both sequencing and deletion/duplication analyses. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not.

SIGNATURE:

Yan Meng, Ph.D., CGMB, FACMG on 08/15/2025
Laboratory Director, Fulgent

DISCLAIMER:

This test was developed, performed, and its performance characteristics determined by **Fulgent Therapeutics LLC** (CAP# 8042697, CLIA# 05D2043189), 4399 Santa Anita Ave., El Monte, CA 91731. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. For assistance with interpretation of these results, healthcare professionals may contact us directly at **(626) 350-0537** or info@fulgentgenetics.com. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.