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Patient Information:

Sex: M
MR#: BFA0207

Partner Information:
Not Tested

Physician:
Shaikly, Valerie
ATTN: Shaikly, Valerie
Fertility Genetics
1 Lanswood Park
Elmstead Market, Essex CO7 7FD GB
Phone: 7711197938

Laboratory:
Fulgent Therapeutics LLC
CAP#: 8042697
CLIA#: 05D2043189
Laboratory Director:
Dr. Amar Jariwala
Report Date: **Mar 20,2025**

N/A

Specimen Type: Saliva Swab
Collected: Feb 25,2025

FINAL RESULTS

Carrier for genetic conditions in **multiple** genes.
Genetic counseling is recommended.

TEST PERFORMED

176 Matched Fors Male with XL
(177 Gene Panel; gene sequencing with deletion and duplication analysis)

Condition and Gene	Inheritance		Partner
SLC26A2-related disorders *SLC26A2*	AR	Carrier c.1535_1536del (p.Thr512Serfs*16)	N/A
Alpha thalassemia *HBA2*	AR	Carrier Whole Gene Deletion (αα/α-)	N/A

INTERPRETATION:

Notes and Recommendations:

- Based on these results, this individual is positive for carrier mutations in 2 genes. Carrier screening for the reproductive partner is recommended to accurately assess the risk for any autosomal recessive conditions. A negative result reduces, but does not eliminate, the chance to be a carrier for any condition included in this screen. Please see the supplemental table for details.
- Testing for a 3 nucleotide (CGG) repeat sequence in the FMR1 gene was performed to screen for the carrier status for Fragile X Syndrome. The repeat size detected was: 30 repeats. These results are within the normal range. Therefore, this individual is not considered a carrier for Fragile X Syndrome.
- Testing for copy number changes in the SMN1 gene was performed to screen for the carrier status of Spinal Muscular Atrophy. The results for this individual are within the normal range for non-carriers. See Limitations section for more information.
- This carrier screening test does not screen for all possible genetic conditions, nor for all possible mutations in every gene tested. This report does not include variants of uncertain significance; only variants classified as pathogenic or likely pathogenic at the time of testing, and considered relevant for reproductive carrier screening, are reported. Please see the gene specific notes for details. Please note that the classification of variants can change over time.
- Patients may wish to discuss any carrier results with blood relatives, as there is an increased chance that they are also carriers. These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- Gene specific notes and limitations may be present. See below.
- Genetic counseling is recommended. Contact your physician about the available options for genetic counseling.

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SLC26A2-RELATED DISORDERS

Patient		Partner
Result	Carrier	N/A
Variant Details	***SLC26A2*** (NM_000112.4) c.1535_1536del (p.Thr512Serfs*16)	N/A

What is SLC26A2-related disorders?

The SLC26A2 gene is essential for the formation of healthy cartilage formation and bone development. Therefore, mutations in this gene tend to give rise to various forms of skeletal dysplasia. Several autosomal recessive conditions are associated with this gene including Achondrogenesis, type IB, Atelosteogenesis II, Diastrophic dysplasia, and Multiple epiphyseal dysplasia.

- Achondrogenesis type IB is characterized by very short limbs, a narrow chest that restricts lung development, and a prominent round abdomen. Due to abnormal bone development, the bones of the spine, skull, and pelvis are thin and soft. Clubfoot and hernias are also common features of this condition.
- Atelosteogenesis II is characterized by very short limbs, narrow chest that restricts lung development, and a prominent round abdomen. Cleft palate, clubfoot and hitchhiker-shaped thumbs are also common features of this condition. Because of the severity of this disorder, most affected children do not survive prenatally, and those that do, usually die in the newborn period from respiratory failure.
- Diastrophic dysplasia is characterized by very short arms and legs, early-onset osteoarthritis, and joint contractures that can restrict movement that can worsen with age. Additional features include progressive scoliosis, clubfoot, hitchhiker thumbs, and cleft palate.
- Multiple epiphyseal dysplasia primarily affects the end of the bones (epiphyses) and lead to joint pain, early-onset arthritis, and a waddling walk. Some affected individuals may be shorter than average, but most are normal height. Some individuals may have scoliosis, clubfoot at birth or cleft palate.

What is my risk of having an affected child?

SLC26A2-related disorders are inherited in an autosomal recessive manner. If the patient and the partner are both carriers, the risk for an affected child is 1 in 4 (25%).

What kind of medical management is available?

Each condition is managed differently based on its symptoms.

- The severity of Achondrogenesis, type IB and Atelosteogenesis II results in most affected children not surviving prenatally, and those that do, usually die in the newborn period from respiratory failure.
- Although some affected infants may have breathing issues, most people with diastrophic dysplasia live into adulthood and mental function is normal. Treatment is mainly based on orthopedic support and physical therapies to improve mobility. Surgical intervention may be necessary depending on the severity of cleft palate and scoliosis.
- Most people with multiple epiphyseal dysplasia live into adulthood and mental function is normal. Treatment is mainly based on physical therapies and anti-inflammatory medication to improve muscle strength and reduce joint pain. Surgical intervention may be necessary depending on the severity of cleft palate and scoliosis.

What mutation was detected?

The detected heterozygous variant was NM_000112.4:c.1535_1536del (p.Thr512Serfs*16). This variant is predicted to introduce a premature stop codon in the last exon or the last 50 nucleotides of the penultimate exon and result in a truncated protein. While this variant is not anticipated to cause nonsense-mediated mRNA decay (PubMed: 25741868, 30192042), it is expected to disrupt the last 228 (31%) amino acids of the original protein. There's sufficient evidence that loss of function in this gene is a known disease mechanism for SLC26A2-associated skeletal phenotypes (PubMed: 34529350, 20592910, 11241838). The laboratory

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classifies this variant as likely pathogenic.

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ALPHA THALASSEMIA

Patient		Partner
Result	Carrier	N/A
Variant Details	***HBA2*** (NM_000517.5) Whole Gene Deletion (αα/α-)	N/A

What is Alpha thalassemia?

Alpha thalassemia is a blood disorder that reduces the production of a protein called hemoglobin. This reduction in the amount of hemoglobin can prevent enough oxygen from reaching the body's tissues. Affected individuals may have anemia, which can cause pale skin, weakness, fatigue, and more serious complications. There are two distinct types of alpha thalassemia: the more severe type is known as Hb Bart syndrome, and the milder form is called HbH disease. Hb Bart syndrome is characterized by hydrops fetalis, a condition in which excess fluid builds up in the body before birth. Additional signs and symptoms can include severe anemia, hepatosplenomegaly (swollen liver and spleen), heart defects, and abnormalities of the urinary system or genitalia. As a result of these serious health problems, most babies with this condition are stillborn or die soon after birth. Hb Bart syndrome can also cause serious complications for women during pregnancy, including preeclampsia, premature delivery, and abnormal bleeding. HbH disease causes mild to moderate anemia, hepatosplenomegaly, and jaundice. Some affected individuals also have bone changes such as overgrowth of the upper jaw and an unusually prominent forehead.

See the table below for a description of the diseases associated with different combinations of HBA1 and HBA2 mutations.

Carrier Status of Partner 1	Carrier Status of Partner 2	Risk for a child with HbH disease (- -/-α)	Risk for a child with Hb Bart syndrome (- -/- -)
alpha thalassemia trait cis (αα/- -)	alpha thalassemia trait trans (α-/α-) or (-α/-α)	50%	No risk
	alpha thalassemia trait cis (αα/- -)	Residual Risk	25%
	silent carrier (αα/α-) or (αα/-α)	25%	Residual Risk
alpha thalassemia trait trans (α-/α-) or (-α/-α)	alpha thalassemia trait trans (α-/α-) or (-α/-α)	Residual Risk	Residual Risk
	silent carrier (αα/α-) or (αα/-α)	Residual Risk	Residual Risk
silent carrier (αα/α-) or (αα/-α)	silent carrier (αα/α-) or (αα/-α)	Residual Risk	Residual Risk

Note that carriers for single heterozygous deletions of HBA1 or HBA2 are commonly referred to as silent carriers (PubMed: 20301608).

What is my risk of having an affected child?

Generally, each person has two copies of the *HBA1* gene and two copies of the *HBA2* gene, or four copies (alleles) in total. The different forms of alpha thalassemia result from the loss of some or all of these alleles: Hb Bart syndrome results from the loss of all four alleles, while HbH disease results from the loss of three alleles. Alpha thalassemia is inherited in an autosomal recessive manner, which means that if one parent is a carrier for a loss of two alleles on one chromosome and a second parent is a carrier of a loss of one or more alleles on one chromosome, there is a 1 in 4 (25%) risk of having an affected child.

What kind of medical management is available?

There is currently no cure for alpha thalassemia. Medical management of Hb Bart syndrome is limited but may include blood transfusions or a stem cell transplant. For HbH disease, management can vary based on the severity of symptoms. Mild forms may have little effect on daily life, and management for such cases can include supplementation of iron or folic acid. Management for more severe cases usually requires regular transfusions. Untreated, the prognosis for HbH disease is poor, with a shortened lifespan of up to age 5 years. However, when treated, individuals with HbH disease may have a lifespan that approaches normal.

What mutation was detected?

The detected variant was a whole gene deletion (αα/α-) in the HBA2 gene (NM_000517.5). The detected mutation was a whole

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gene deletion in one of four alleles comprising the alpha globin locus. These results are consistent with having three functional copies of alpha-globin (αα/α-). If your partner is also a carrier for alpha thalassemia, there is an increased risk to have a child with HbH disease, but not hydrops fetalis. Genetic counseling is recommended. Individuals with a single alpha globin gene defect (αα/α-) are carriers and clinically asymptomatic. Deletions of HBA2 are common in many human populations (PubMed: 20301608, 25390741). The scope of the performed analysis is limited to the ordered genes and is not designed to determine the exact breakpoints or boundaries of copy number variants. This variant may or may not represent part of a larger event involving other potentially clinically relevant genes not assessed by this test. The laboratory classifies this variant as pathogenic.

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GENES TESTED:

176 Matched Fors Male with XL - 177 Genes

This analysis was run using the 176 Matched Fors Male with XL gene list. 177 genes were tested with 99.3% of targets sequenced at >20x coverage. For more gene-specific information and assistance with residual risk calculation, see the SUPPLEMENTAL TABLE.

ABCC8, ABCD1, ACADM, ACADS, ACADVL, ADA, AGA, AGL, AGXT, AIRE, ALDH3A2, ALDOB, ALG6, ALMS1, ALPL, AMT, ARG1, ARSA, ASL, ASPA, ASS1, ATM, ATP7A, ATP7B, BBS1, BBS10, BBS12, BBS2, BCKDHA, BCKDHB, BCS1L, BLM, BTD, CAPN3, CBS, CFTR, CLN3, CLN5, CLN6, CLN8, CLRN1, COL4A3, COL4A4, CPS1, CPT1A, CPT2, CRYL1, CTNS, CTSK, CYP11B1, CYP21A2, CYP27A1, DBT, DHCR7, DLD, DMD, DYSF, ELP1, ERCC6, ERCC8, EVC, EVC2, FAH, FANCA, FANCC, FKRP, FKTN, FMR1, G6PC, GAA, GALC, GALK1, GALT, GBA, GCDH, GJB2, GJB6, GLA, GLB1, GLDC, GNE, GNPTAB, GNPTG, GRHPR, HADHA, HBA1, HBA2, HBB, HEXA, HEXB, HGSNAT, HLCS, HMGCL, HOGA1, HSD17B4, HYLS1, IDS, IDUA, IL2RG, IVD, KCNJ11, LAMA2, LAMA3, LAMB3, LAMC2, LIPA, LRPPRC, MAN2B1, MCOLN1, MEFV, MESP2, MKS1, MLC1, MMAA, MMAB, MMACHC, MPI, MUT, MYO7A, NAGLU, NBN, NEB, NPC1, NPC2, NPHS1, NPHS2, NR0B1, OPA3, OTC, PAH, PC, PCCA, PCCB, PCDH15, PEX1, PEX10, PEX12, PEX2, PEX6, PEX7, PKHD1, PMM2, POMGNT1, PPT1, PROP1, PTS, RMRP, RS1, RTEL1, SACS, SGCA, SGCB, SGCD, SGCG, SGSH, SLC12A6, SLC17A5, SLC22A5, SLC26A2, SLC26A4, SLC37A4, SMN1, SMPD1, STAR, TAT, TCIRG1, TGM1, TH, TMEM216, TPP1, TTPA, USH1C, USH2A, VPS13B, XPA, XPC, ZFYVE26

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. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 99.37% and 99.26% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. 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. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). 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 are analyzed using Fulgent Germline proprietary pipeline for this specimen. Bioinformatics: The FPLMv2.0 pipeline was used to analyze this specimen.

LIMITATIONS:

General 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 future pregnancies, and negative results do not rule out the genetic risk to a pregnancy. 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 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 other than specified genes. 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, 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. Deletion/duplication analysis can identify alterations of genomic regions which include one whole

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gene (buccal swab specimens and whole blood specimens) and are two or more contiguous exons in size (whole b only); single exon deletions or duplications may occasionally be identified, but are not routinely detected by this test. 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. Unless otherwise indicated, deletion/duplication analysis has not been performed in regions that have been sequenced by Sanger.

Gene Specific Notes and Limitations

BTD: If detected, the variant NM_001370658.1:c.1270G>C (p.Asp424His) will not be reported as this variant is associated with low disease penetrance and is primarily associated with reduced enzyme activity when homozygous. *CFTR:* Analysis of the intron 8 polymorphic region (e.g. IVS8-5T allele) is only performed if the p.Arg117His (R117H) mutation is detected. Single exon deletion/duplication analysis is limited to deletions of previously reported exons: 1, 2, 3, 11, 19, 20, 21. CFTR variants primarily associated with CFTR-related isolated congenital bilateral absence of the vas deferens and CFTR-related pancreatitis are not included in this analysis. CFTR variants with insufficient evidence of being cystic fibrosis mutations will not be reported either. *CRYL1:* As mutations in the CRYL1 gene are not known to be associated with any clinical condition, sequence variants in this gene are not analyzed. However, to increase copy number detection sensitivity for large deletions, this gene was evaluated for copy number variation. *CYP11B1:* The current testing method is not able to reliably detect certain pathogenic variants in this gene due to the interference by highly homologous regions. This analysis is not designed to detect or rule-out copy-neutral chimeric CYP11B1/CYP11B2 gene. *CYP21A2:* Significant pseudogene interference and/or reciprocal exchanges between the CYP21A2 gene and its pseudogene, CYP21A1P, 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 the clinical findings, biochemical profile, and family history of each patient. CYP21A2 variants primarily associated with non-classic congenital adrenal hyperplasia (CAH) are not included in this analysis (PubMed: 23359698). The variants associated with non-classic disease, including but not limited to c.188A>T (p.His63Leu), c.844G>T (p.Val282Leu), c.1174G>A (p.Ala392Thr), and c.1360C>T (p.Pro454Ser) will not be reported. LR-PCR is not routinely ordered for NM_000500.9:c.955C>T (p.Gln319Ter). Individuals with c.955C>T (p.Gln319Ter) will be reported as a Possible Carrier indicating that the precise nature of the variant has not been determined by LR-PCR and that the variant may occur in the CYP21A2 wild-type gene or in the CYP21A1P pseudogene. The confirmation test is recommended if the second reproductive partner is tested positive for variants associated with classic CAH. *DMD:* Single exon deletion/duplication analysis is limited to exons with >1 patient reported in the UMD database (http://www.umd.be/DMD/W_DMD/index.html), accessed Dec 29,2020 and all out-of-frame exons after exon 3. This includes deletion of exon 1, and duplication of exon 2, and del/dup for exons 3,6~8,11,12,17~22,43~46,48,50~56,58~63,65~70,75,76 and 78. Single-exon detection is limited to blood samples. *FMR1:* The exact size of alleles >200 CGG repeats cannot be determined; these alleles are pathogenic for X-Linked Fragile X Syndrome. Alleles with <10 repeats may fail to amplify; these alleles are benign. The repeat length for this gene may vary by +/- 1 repeat unit. Methylation is not analyzed. RP-PCR analysis of the FMR1 promoter is not routinely performed in males. Small degrees of size mosaicism, including gonadal mosaicism, may not be detected. *GALT:* The D2 "Duarte" allele is not included in this analysis. While this allele can cause positive newborn screening results, it is not known to cause clinical symptoms in any state (PubMed: 25473725, 30593450). *GBA:* The current testing method may not be able to reliably detect certain pathogenic variants in the GBA gene due to homologous recombination between the pseudogene and the functional gene. *HBA1:* Significant interference from highly homologous regions in exons 1-2 of the HBA1 gene has been recognized to occur, potentially impeding the assay's technical capability to detect pathogenic alterations during sequencing analyses. *HBA2:* Significant interference from highly homologous regions in exons 1-2 of the HBA2 gene has been recognized to occur, potentially impeding the assay's technical capability to detect pathogenic alterations during sequencing analyses. *HSD17B4:* Copy number analysis for exons 4-6 may have reduced sensitivity in the HSD17B4 gene. Confirmation of these exons are limited to individuals with a positive personal history of D-bifunctional protein deficiency and Perrault syndrome and/or individuals carrying a pathogenic/likely pathogenic sequence variant. *NEB:* This gene contains a 32-kb triplicate region (exons 82-105) which is not amenable to sequencing and deletion/duplication analysis. *NPHS2:* If detected, the variant NM_014625.3:c.686G>A (p.Arg229Gln) will not be reported as this variant is not significantly associated with disease when homozygous or in the compound heterozygous state with variants in exons 1-6 of NPHS2. *SMN1:* The current testing method detects sequencing variants in exon 7 and copy number variations in exons 7-8 of the SMN1 gene (NM_022874.2). Sequencing and deletion/duplication analysis are not performed on any other region in this gene. About 5%-8% of the population have two copies of SMN1 on a single chromosome and a deletion on the other chromosome, known as a [2+0] configuration (PubMed: 20301526). The current testing method cannot directly detect carriers with a [2+0] SMN1 configuration, but can detect linkage between the silent carrier allele and certain population-specific single nucleotide changes. As a result, a negative result for carrier testing greatly reduces but does not eliminate the chance that a person is a carrier. Only abnormal results will be reported.

SIGNATURE:

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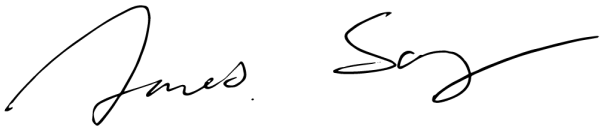

Jianbo Song, Ph.D., ABMGG, CGMB, CCS, FACMG on **3/20/2025**
Laboratory Director, Fulgent

DISCLAIMER:

This test was developed, performed and its performance characteristics determined by **Fulgent Therapeutics LLC**. 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.

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To view the supplemental table describing the carrier frequencies, detection rates, and residual risks associated with the genes tested on any Beacon panel, please visit the following link:
Beacon Expanded Carrier Screening Supplemental Table