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Patient Information:
20006, Donor
DOB: [redacted]
Sex: M
MR#:
Patient#: FT-PT8738081

Partner Information:
Not Tested

Physician:
Kuan, James
ATTN: Kuan, James
Las Vegas Sperm Bank
4915 25th Avenue NE, Ste 204W
Seattle, WA 98105
Phone: (206) 588-1484

Laboratory:
Fulgent Therapeutics LLC
CAP#: 8042697
CLIA#: 05D2043189
Laboratory Director:
Lawrence M. Weiss, MD
Report Date: **Jun 07,2024**

Accession:
FT-7040577
Test#: FT-TS14844865
Specimen Type: Blood (EDTA)
Collected: May 17,2024

Accession:
N/A

FINAL RESULTS

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

TEST PERFORMED

Beacon Preconception Carrier Screening - 515 Genes (without X-linked Disorders)
(515 Gene Panel; gene sequencing with deletion and duplication analysis)

Condition and Gene	Inheritance	20006, Donor	Partner
Severe combined immunodeficiency, JAK3-related *JAK3*	AR	⊕ Carrier c.507C>A (p.Asp169Glu)	N/A
EVC2-related bone growth disorders *EVC2*	AR	⊕ Carrier c.2263C>T (p.Gln755*)	N/A
USH1C-related disorders *USH1C*	AR	⊕ Carrier c.497-2del (p.?)	N/A
PMM2-glycosylation disorders *PMM2*	AR	⊕ Carrier c.422G>A (p.Arg141His)	N/A

INTERPRETATION:

Notes and Recommendations:

- **PLEASE NOTE: While some heterozygous variants in the EVC2 gene have been associated with autosomal dominant Weyers acrofacial dysostosis (WAD), the reported variant has not been associated with those findings.**
- Based on these results, this individual is positive for carrier mutations in 4 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 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.
- X-linked genes are not routinely analyzed for male carrier screening tests. Gene specific notes and limitations may be present. See below.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National

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Society of Genetic Counselors (NSGC; https://www.nsgc.org)

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SEVERE COMBINED IMMUNODEFICIENCY, JAK3-RELATED

Patient	20006, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***JAK3*** (NM_000215.4) c.507C>A (p.Asp169Glu)	N/A

What is Severe combined immunodeficiency, JAK3-related?

Severe combined immunodeficiency, JAK3-related is a disorder of the immune system characterized by the lack of the necessary immune cells to fight off certain bacteria, viruses, and fungi. Affected individuals are prone to repeated and persistent infections that can be very serious or life-threatening. Some signs and symptoms of the disorder include failure to thrive, recurrent upper respiratory tract infections, chronic diarrhea, inflammation of the brain and spinal cord membranes (meningitis), and skin rashes.

What is my risk of having an affected child?

Severe combined immunodeficiency, JAK3-related is inherited in an autosomal recessive manner. This means that when both parents are carriers for the same condition, there is a 25% (1 in 4) risk of having an affected child.

What kind of medical management is available?

Lifestyle modifications can be undertaken to avoid exposure to radiation and transmission of infections to the patient. Bone marrow hematopoietic cell transplantation may be curative. Immunoglobulin replacement therapy can be considered to replace missing antibodies that help affected individuals to fight infections.

What mutation was detected?

The detected heterozygous variant was NM_000215.4:c.507C>A (p.Asp169Glu). This variant has been previously reported in a compound heterozygous state with another pathogenic variant in 2 individuals with severe combined immunodeficiency. Functional analysis demonstrated that this variant is located in the N-terminal domain and these N-terminal domain mutations were found to inhibit the receptor binding and catalytic activity. (PubMed: 11741532, 14615376). The laboratory classifies this variant as likely pathogenic.

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EVC2-RELATED BONE GROWTH DISORDERS

Patient	20006, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***EVC2*** (NM_147127.5) c.2263C>T (p.Gln755*)	N/A

What is EVC2-related bone growth disorders?

There are two conditions associated with the EVC2 gene: Ellis-van Creveld syndrome and Weyers acrofacial dysostosis.

- Ellis-van Creveld syndrome affects the whole body. The main characteristic is short stature, (also referred to as “dwarfism”), present at birth that particularly affects the limbs and chest, but not the head. Cognitive development is considered normal. Other typical symptoms are the presence of additional fingers or toes, malformation of the nails and teeth, as well as heart defects, which may lead to life-threatening complications.
- A milder form of the disease, known as Weyers acrofacial dysostosis, typically does not involve heart defects and growth limitations are not as obvious as in individuals with Ellis-van Creveld syndrome. Weyers acrofacial dysostosis is a disorder mainly characterized by abnormal development of the teeth, which can include misshaped or fewer teeth as well as the presence of a single front tooth. The lower jaw may also be deformed. Affected individuals typically are of short stature and may have additional fingers.

What is my risk of having an affected child?

Ellis-van Creveld syndrome and Weyers acrofacial dysostosis 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.

- Many affected children with Ellis-van Creveld syndrome die in infancy due to complications from chest abnormalities or heart defects. However, for individuals without heart defects or severe chest anomalies, the prognosis is much better. Affected adults will routinely need monitoring of bone deformities and heart defects to avoid complications. They may also need special care with regard to their dental and oral manifestations. The intelligence of affected individuals is typically within the normal range.
- Although heart defects are not associated with Weyers acrofacial dysostosis, affected individuals should be assessed for possible involvement of the heart, to exclude a misdiagnosed Ellis-van Creveld syndrome. Affected individuals will need life-long special care to address their dental and oral manifestations. Skeletal manifestations might need specific treatments, if more severe malformations are present. Intelligence of affected individuals is typically within normal range.

What mutation was detected?

The detected heterozygous variant was NM_147127.5:c.2263C>T (p.Gln755*). 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 Ellis-Van Creveld syndrome (PubMed: 17024374, 26580685, 31645978). This variant has been found in the presumed compound heterozygous state in an individual with Ellis-van Creveld syndrome (PubMed: 17024374). The laboratory classifies this variant as pathogenic.

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USH1C-RELATED DISORDERS

Patient	20006, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***USH1C*** (NM_005709.4) c.497-2del (p.?)	N/A

What is USH1C-related disorders?

USH1C is a gene involved in the function of cells of the inner ear and retina, where it plays a role in hearing, balance, and vision. There are several conditions associated with this gene including Usher syndrome and non-syndromic hearing loss.

- Usher syndrome is a group of conditions characterized by partial or total hearing loss and vision loss that worsens over time. The different types are distinguished by the severity of hearing loss, balance issues and age of onset, which ranges from congenital hearing loss with vision loss beginning in childhood or adolescence to normal hearing and vision until late childhood or adolescence that gradually begins to dissipate. Some children also experience vestibular dysfunction that affects balance and may impact motor development.
- USH1C-related nonsyndromic hearing loss is characterized by prelingual, generally non-progressive sensorineural hearing loss. Vestibular function is not typically impacted. It is believed that different mutations in the USH1C gene contribute to the different conditions (Usher syndrome and hearing loss).

What is my risk of having an affected child?

USH1C-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.

- Currently, there is no cure for Usher syndrome. The best treatment involves early identification so that educational programs can begin as soon as possible. Typically, treatment will include hearing aids, assistive listening devices, cochlear implants, or other communication methods such as American Sign Language; orientation and mobility training; and communication services and independent-living training that may include Braille instruction, low-vision services, or auditory training.
- For non-syndromic hearing loss, affected individuals are healthy and lifespan is normal. Hearing aids are commonly used and individuals with this type of hearing loss may benefit from a cochlear implantation. Speech therapy and additional education tools may also aid in daily activities.

What mutation was detected?

The detected heterozygous variant was NM_005709.4:c.497-2del (p.?). This intronic variant, c.497-2del, alters the highly conserved splice acceptor site for exon 6 of this transcript and is predicted by all four splice site prediction tools queried to abolish canonical splice acceptor activity. This variant is expected to result in altered function of the USH1C gene product as a result of aberrant splicing. This splicing variant has previously been reported in association with Usher syndrome type 1C disease (PubMed: 10973247).There's sufficient evidence that loss of function in this gene is a known disease mechanism for Usher syndrome type 1C (PubMed: 31541171, 27957503, 27583663).This variant is classified as "Pathogenic" in ClinVar, with multiple submitters in agreement (Variation ID: 5140). The laboratory classifies this variant as pathogenic.

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PMM2-GLYCOSYLATION DISORDERS

Patient	20006, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***PMM2*** (NM_000303.3) c.422G>A (p.Arg141His)	N/A

What is PMM2-glycosylation disorders?

PMM2 glycosylation disorders occur due to variants in the PMM2 gene. There are disease phenotypes associated with variants in this gene: congenital disorder of glycosylation type 1a and polycystic kidney disease with hyperinsulinemic hypoglycemia.

- Congenital disorder of glycosylation, type 1a (CDG1a) is caused by the production of abnormally functioning proteins in many organs and tissues, which means that the disease affects many body systems. Infants with this disorder may have hypotonia, an abnormal distribution of fat, strabismus, developmental delay, and failure to thrive. Infants with CDG1a also frequently have an underdeveloped cerebellum that can lead to seizures and intellectual disability. About 20% of infants with CDG1a do not survive their first year of life due to complications of the disease. Occasionally the disease does not show signs until childhood or adulthood, in which case symptoms are often milder.
- Polycystic kidney disease with hyperinsulinemic hypoglycemia results from a promoter mutation c.-167G>T in the PMM2 gene, that occurs either as homozygous or as compound heterozygous with another PMM2 variant (PubMed: 28373276). Patients with this particular disease phenotype have enlarged kidneys with multiple cysts. The severity of kidney disease is variable and some patients may present with symptoms antenatally or during childhood. Some patients may have early-stage chronic kidney disease, and in severe cases may progress to end stage renal disease, requiring dialysis and/or kidney transplantation (PubMed: 28373276).

What is my risk of having an affected child?

PMM2 glycosylation disorders are inherited in an autosomal recessive manner. This means that if both parents are carriers of the disease, the risk of having an affected child is 1 in 4 (25%).

What kind of medical management is available?

For congenital disorder of glycosylation, type 1a, many affected babies die before birth or are stillborn. Affected individuals who survive infancy may have moderate intellectual disability, and some are unable to walk independently. Affected individuals may also experience stroke-like episodes. There is no specific treatment for the disorder itself, but management is mostly symptom-based and can include anti-epileptic drugs to prevent seizures, occupational therapy and physical therapy for developmental delay, and the use of a nasogastric tube or gastronomy tube to ensure appropriate caloric intake. For polycystic kidney disease with hyperinsulinemic hypoglycemia, symptoms can be managed with specific medications and in severe cases dialysis and/or kidney transplantation.

What mutation was detected?

The detected heterozygous variant was NM_000303.3:c.422G>A (p.Arg141His). This variant, p.Arg141His, has been identified in the compound heterozygous state in multiple unrelated individuals with CDG1a (Congenital Disorder Of Glycosylation, Type 1A) (PubMed: 9140401, 9781039, 10527672, 10922383, 11916319, 17166182, 9497260, 11517108, 25355454, 19357119). It is one of the most common mutations found in patients with CDG1a, with a carrier frequency of approximately 1 in 70 individuals in the Dutch and Danish populations (PubMed: 10854097). In vitro functional studies using protein expressed from bacteria showed that enzymatic activity was completely abolished in the presence of this variant (PubMed: 21541725). Furthermore, a mouse model demonstrated that mouse embryos compound heterozygous or homozygous for this variant (p.Arg137His) in the homologous mouse gene either died as embryos or were unable to survive postnatally and that supplementation with mannose did not reverse this effect (PubMed: 27053713). This variant is classified as "Pathogenic/Likely pathogenic" in ClinVar, with multiple submitters in agreement (ClinVar: 7706). The laboratory classifies this variant as pathogenic.

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GENES TESTED:

Beacon Preconception Carrier Screening - 515 Genes (without X-linked Disorders) - 515 Genes

This analysis was run using the Beacon Preconception Carrier Screening - 515 Genes (without X-linked Disorders) gene list. 515 genes were tested with 99.5% of targets sequenced at >20x coverage. For more gene-specific information and assistance with residual risk calculation, see the SUPPLEMENTAL TABLE.

AAAS, ABCA12, ABCA3, ABCA4, ABCB11, ABCB4, ABCC2, ABCC8, ACAD9, ACADM, ACADVL, ACAT1, ACOX1, ACSF3, ADA, ADAMTS2, ADAMTSL4, ADGRG1, ADGRV1, AGA, AGL, AGPS, AGXT, AHI1, AIPL1, AIRE, ALDH3A2, ALDH7A1, ALDOB, ALG1, ALG6, ALMS1, ALPL, AMN, AMT, ANO10, AP1S1, AQP2, ARG1, ARL6, ARSA, ARSB, ASL, ASNS, ASPA, ASS1, ATM, ATP6V1B1, ATP7B, ATP8B1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BCKDHA, BCKDHB, BCS1L, BLM, BLOC1S3, BLOC1S6, BMP1, BRIP1, BSND, CAD, CANT1, CAPN3, CASQ2, CBS, CC2D1A, CC2D2A, CCDC103, CCDC39, CCDC88C, CD3D, CD3E, CD40, CD59, CDH23, CEP152, CEP290, CERKL, CFTR, CHAT, CHRNE, CHRNG, CIITA, CLCN1, CLN3, CLN5, CLN6, CLN8, CLRN1, CNGB3, COL11A2, COL17A1, COL27A1, COL4A3, COL4A4, COL7A1, COX15, CPS1, CPT1A, CPT2, CRB1, CRTAP, CRYL1, CTNS, CTSA, CTSC, CTSD, CTSK, CYBA, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1B1, CYP21A2, CYP27A1, CYP27B1, CYP7B1, DBT, DCAF17, DCLRE1C, DDX11, DGAT1, DGUOK, DHCR7, DHDDS, DLD, DLL3, DNAH11, DNAH5, DNAI1, DNAI2, DNMT3B, DOK7, DUOX2, DYNC2H1, DYSF, EIF2AK3, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, ELP1, EPG5, ERCC2, ERCC6, ERCC8, ESCO2, ETFA, ETFB, ETFDH, ETHE1, EVC, EVC2, EXOSC3, EYS, FAH, FAM161A, FANCA, FANCC, FANCD2, FANCE, FANCG, FANCI, FANCL, FBP1, FBXO7, FH, FKBP10, FKRP, FKTN, FMO3, FOXN1, FOXRED1, FRAS1, FREM2, FUCA1, G6PC, G6PC3, GAA, GALC, GALE, GALK1, GALNS, GALNT3, GALT, GAMT, GATM, GBA, GBE1, GCDH, GCH1, GDF5, GFM1, GHR, GJB2, GJB6, GLB1, GLDC, GLE1, GNE, GNPAT, GNPTAB, GNPTG, GNS, GORAB, GRHPR, GRIP1, GSS, GUCY2D, GUSB, HADH, HADHA, HADHB, HAMP, HAX1, HBA1, HBA2, HBB, HEXA, HEXB, HGSNAT, HJV, HLCS, HMGCL, HMOX1, HOGA1, HPD, HPS1, HPS3, HPS4, HPS5, HPS6, HSD17B3, HSD17B4, HSD3B2, HYAL1, HYLS1, IDUA, IGHMBP2, IKBKB, IL7R, INVS, ITGA6, ITGB3, ITGB4, IVD, JAK3, KCNJ1, KCNJ11, LAMA2, LAMA3, LAMB3, LAMC2, LARGE1, LCA5, LDLR, LDLRAP1, LHX3, LIFR, LIG4, LIPA, LMBRD1, LOXHD1, LPL, LRAT, LRP2, LRPPRC, LYST, MAK, MAN2B1, MANBA, MCEE, MCOLN1, MCPH1, MECR, MED17, MESP2, MFSD8, MKKS, MKS1, MLC1, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MOCS1, MOCS2, MPI, MPL, MPV17, MRE11, MTHFR, MTR, MTRR, MTTP, MUSK, MUT, MVK, MYO15A, MYO7A, NAGA, NAGLU, NAGS, NBN, NCF2, NDRG1, NDUFAF2, NDUFAF5, NDUFS4, NDUFS6, NDUFS7, NDUFV1, NEB, NEU1, NGLY1, NPC1, NPC2, NPHP1, NPHS1, NPHS2, NR2E3, NSMCE3, NTRK1, OAT, OCA2, OPA3, OSTM1, OTOA, OTOF, P3H1, PAH, PANK2, PC, PCBD1, PCCA, PCCB, PCDH15, PCNT, PDHB, PEPD, PET100, PEX1, PEX10, PEX12, PEX13, PEX16, PEX2, PEX26, PEX5, PEX6, PEX7, PFKM, PGM3, PHGDH, PHKB, PHKG2, PHYH, PIGN, PJVK, PKHD1, PLA2G6, PLEKHG5, PLOD1, PMM2, PNPO, POLG, POLH, POMGNT1, POMT1, POMT2, POR, POU1F1, PPT1, PRCD, PRDM5, PRF1, PROP1, PSAP, PTPRC, PTS, PUS1, PYGM, QDPR, RAB23, RAG1, RAG2, RAPSN, RARS2, RDH12, RLBP1, RMRP, RNASEH2A, RNASEH2B, RNASEH2C, RPE65, RPGRIP1L, RTEL1, RXYLT1, RYR1, SACS, SAMD9, SAMHD1, SCO2, SEC23B, SEPSECS, SGCA, SGCB, SGCD, SGCG, SGSH, SKIV2L, SLC12A1, SLC12A3, SLC12A6, SLC17A5, SLC19A2, SLC19A3, SLC1A4, SLC22A5, SLC25A13, SLC25A15, SLC25A20, SLC26A2, SLC26A3, SLC26A4, SLC27A4, SLC35A3, SLC37A4, SLC38A8, SLC39A4, SLC45A2, SLC4A11, SLC5A5, SLC7A7, SMARCAL1, SMN1, SMPD1, SNAP29, SPG11, SPR, SRD5A2, ST3GAL5, STAR, STX11, STXBP2, SUMF1, SUOX, SURF1, SYNE4, TANGO2, TAT, TBCD, TBCE, TCIRG1, TCN2, TECPR2, TERT, TF, TFR2, TG, TGM1, TH, TK2, TMC1, TMEM216, TMEM67, TMPRSS3, TPO, TPP1, TREX1, TRIM32, TRIM37, TRMU, TSEN54, TSFM, TSHB, TSHR, TTC37, TTPA, TULP1, TYMP, TYR, TYRP1, UBR1, UNC13D, USH1C, USH2A, VDR, VLDLR, VPS11, VPS13A, VPS13B, VPS45, VPS53, VRK1, VSX2, WISP3, WNT10A, WRN, XPA, XPC, ZBTB24, ZFYVE26, ZNF469

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, 99.51% and 99.46% 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 Fulgent Germline v2019.2 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

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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 gene (buccal swab specimens and whole blood specimens) and are two or more contiguous exons in size (whole blood specimens 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

ALG1: Due to the interference by highly homologous regions, our current testing method has less sensitivity to detect variants in exons 6-13 of the ALG1 gene (NM_019109.4). *CEP290:* Copy number analysis for exons 8-13 and exons 39-42 may have reduced sensitivity in the CEP290 gene. Confirmation of these exons are limited to individuals with a positive personal history of CEP290-related conditions and/or individuals carrying a pathogenic/likely pathogenic sequence variant. *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. 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 including this gene and a neighboring on gene on the panel (GJB6, also known as connexin 30), 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. *CYP11B2:* 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. 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. *DDX11:* Due to the interference by highly homologous regions, our current testing method has less sensitivity to detect variants in the DDX11 gene. *DUOX2:* The current testing method is not able to reliably detect variants in exons 6-8 of the DUOX2 gene (NM_014080.5) due to significant interference by the highly homologous gene, DUOX1. *FANCD2:* Due to pseudogene interference, copy-number-variants within exon 14-17 of the FANCD2 gene (NM _033084.4) are not evaluated and detection of single-nucleotide variants and small insertions/deletions in this region is not guaranteed. *GALT:* In general, the D2 "Duarte" allele is not reported if detected, but can be reported upon request. While this allele can cause positive newborn screening results, it is not known to cause clinical symptoms in any state. See GeneReviews for more information: https://www.ncbi.nlm.nih.gov/books/NBK1518/ *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). *HBA1:* Significant interference

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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. *LMBRD1:* Copy number analysis for exons 9-12 may have reduced sensitivity in the LMBRD1 gene. Confirmation of these exons are limited to individuals with a positive personal history of combined methylmalonic aciduria and homocystinuria and/or individuals carrying a pathogenic/likely pathogenic sequence variant. *MTHFR:* As recommended by ACMG, the two common polymorphisms in the MTHFR gene - c.1286A>C (p.Glu429Ala, also known as c.1298A>C) and c.665C>T (p.Ala222Val, also known as c.677C>T) - are not reported in this test due to lack of sufficient clinical utility to merit testing (PubMed: 23288205). *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. *OTOA:* Due to pseudogene interference, our current testing method is not able to reliably detect variants in exons 20-28 (NM_144672.3) in the OTOA gene. *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. *TERT:* The TERT promoter region is analyzed for both sequencing and copy number variants. *TYR:* Due to the interference by highly homologous regions, our current testing method has less sensitivity to detect variants in exons 4-5 of the TYR gene (NM_000372.5). *VPS45:* LoF is not a known disease mechanism *WRN:* Due to the interference by highly homologous regions within the WRN gene, our current testing method has less sensitivity to detect variants in exons 10-11 of WRN (NM_000553.6).

SIGNATURE:

Geetu Mendiratta-Vij, PhD, FACMG, CGMBS on **6/7/2024**
Laboratory Director, Fulgent

DISCLAIMER:

This test was developed 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 by email at **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.

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

Patient Information	Specimen Information	Client Information
20006, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Fasting: U Phone: 725.257.0900 Patient ID: 20006	Specimen: LV752213W Requisition: 0000007 Collected: 05/17/2024 / 13:27 PDT Received: 05/17/2024 / 20:46 PDT Reported: 06/03/2024 / 10:59 PDT	Client #: 88807473 MAIL500 FOORD, DYLAN R LAS VEGAS SPERM BANK 2870 S MARYLAND PKWY STE 250 LAS VEGAS, NV 89109-1548

COMMENTS: FASTING:UNKNOWN

Cytogenetic Report

CHROMOSOME ANALYSIS, BLOOD - 14596 Lab:EZ

CHROMOSOME ANALYSIS, BLOOD

Order ID: 24-237278
Specimen Type: Blood
Clinical Indication: GAMETE DONOR

RESULT:
NORMAL MALE KARYOTYPE

INTERPRETATION:
Chromosome analysis revealed normal G-band patterns within the limits of standard cytogenetic analysis.

Please expect the results of any other concurrent study in a separate report.

NOMENCLATURE:
46,XY

ASSAY INFORMATION:

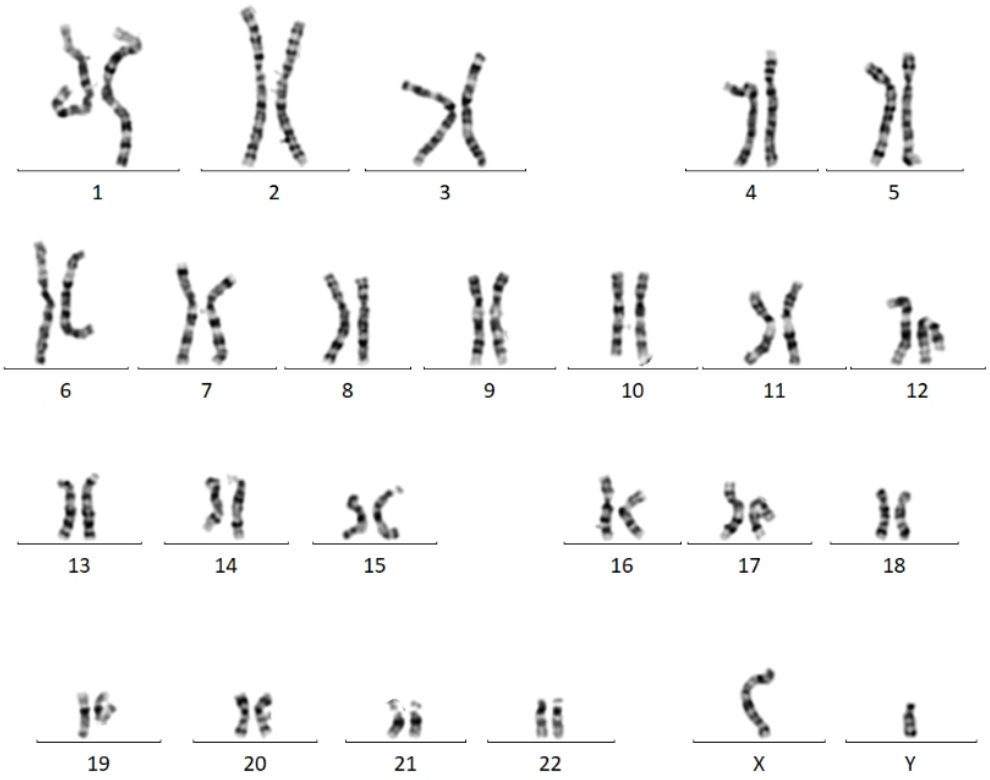
Method: G-Band (Digital Analysis: MetaSyst
Cells Counted: 20
Band Level: 450
Cells Analyzed: 5
Cells Karyotyped: 5

This test does not address genetic disorders that cannot be detected by standard cytogenetic methods or rare events such as low level mosaicism or subtle rearrangements.

Reha M. Toydemir, MD, PhD, FACMG, [site SJC5]

Electronic Signature: 6/3/2024 1:18 PM

Patient Information	Specimen Information	Client Information
20006, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Fasting: U Patient ID: 20006	Specimen: LV752213W Collected: 05/17/2024 / 13:27 PDT Received: 05/17/2024 / 20:46 PDT Reported: 06/03/2024 / 10:59 PDT	Client #: 88807473 FOORD, DYLAN R



PERFORMING SITE:
EZ QUEST DIAGNOSTICS/NICHOLS SJC, 33608 ORTEGA HWY, SAN JUAN CAPISTRANO, CA 92675-2042 Laboratory Director: IRINA MARAMICA,MD,PHD,MBA, CLIA: 05D0643352