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Lab Director: Arash Radfar M.D.
CLIA: 22D0957540



Patient Information:

13190, DONOR

DOB: [REDACTED]

Sex: M

MR#: 13190

Patient#: FT-PT8839819

Partner Information:

Not Tested

Physician:

Kuan, James

ATTN: SSB Genetics, Dept

Seattle 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: **Sep 30, 2024**

Accession:

FT-6948238

Test#: FT-TS14946879

Specimen Type: Blood (EDTA)

Collected: Sep 11, 2024

Accession:

N/A

FINAL RESULTS



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	13190, DONOR	Partner
Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration <i>TANGO2</i>	AR	⊕ Carrier c.418C>T (p.Arg140*)	N/A
Mucopolidosis II & III <i>GNPTAB</i>	AR	⊕ Carrier c.3503_3504del (p.Leu1168Glnfs*5)	N/A
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency <i>CYP21A2</i>	AR	⊕ Possible Carrier c.955C>T(;)*12C>T + CYP21A2 duplication p.(Gln319*)(;)(?)	N/A

INTERPRETATION:

Notes and Recommendations:

- Based on these results, this individual is positive for carrier mutations in 3 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 Society of Genetic Counselors (NSGC; <https://www.nsgc.org>)

Patient: 13190, DONOR; Sex: M;
DOB: [REDACTED] **MR#: 13190**

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METABOLIC ENCEPHALOMYOPATHIC CRISES, RECURRENT, WITH RHABDOMYOLYSIS, CARDIAC ARRHYTHMIAS, AND NEURODEGENERATION

Patient	13190, DONOR	Partner
Result	 Carrier	N/A
Variant Details	TANGO2 (NM_152906.7) c.418C>T (p.Arg140*)	N/A

What is Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration?

Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration is a medical condition that affects the skeletal muscle, cardiac muscle, and the nervous system. It is characterized by episodic metabolic degeneration. Individuals affected by this condition usually show acute encephalomyopathic symptoms, such as rhabdomyolysis, hypotonia, and neurologic regression during childhood, although most patients may have delayed psychomotor development before the acute onset. The disease's overall course is marked by progressive neurodegeneration leading to epilepsy, cognitive impairment, pyramidal and cerebellar signs, and loss of expressive language. Cardiac involvement with severe arrhythmias is a consistent and potentially life-threatening manifestation.

What is my risk of having an affected child?

Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration is 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?

Medical management depends on the specific combination of symptoms present in the patient. Targeted therapy has been shown to significantly reduce the risk of metabolic crises and arrhythmias in individuals with this condition. This therapy involves daily intake of a multivitamin that includes all eight B vitamins or a B-complex vitamin at the minimum recommended daily allowance for the individual's age. In the case of an acute metabolic crisis, early management is crucial to prevent the development of a cardiac crisis. Families and physicians should have an emergency treatment plan in place, which includes appropriate steps to suppress acute catabolism and promote hydration to minimize the risk of life-threatening rhabdomyolysis and cardiac tachyarrhythmias. For non-acute presentations, treatment options include developmental and educational support, anti-seizure medication for seizures, levothyroxine for hypothyroidism, feeding therapy and/or gastrostomy tube feeding as needed, and standard treatments for constipation. It is recommended that families and physicians work together to develop and implement a comprehensive treatment plan that addresses the unique needs of each individual with TANGO2 deficiency.

What mutation was detected?

The detected heterozygous variant was NM_152906.7:c.418C>T (p.Arg140*). 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 recurrent metabolic encephalomyopathic crises with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (PubMed: [26805781](#), [26805782](#)). This variant has been previously reported in the homozygous state in two unrelated individuals with recurrent metabolic encephalomyopathic crises with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (PubMed: [26805782](#), [37644014](#)). Functional studies, using fibroblasts derived from a patient who carried this variant in the homozygous state, resulted in impaired ER-Golgi trafficking as well as mitochondrial defects (PubMed: [32909282](#)). The laboratory classifies this variant as pathogenic.



MUCOLIPIDOSIS II & III

Patient	13190, DONOR	Partner
Result	 Carrier	N/A
Variant Details	GNPTAB (NM_024312.5) c.3503_3504del (p.Leu1168Glnfs*5)	N/A

What is Mucopolysaccharidosis II & III?

The GNPTAB gene is associated with two conditions: Mucopolysaccharidosis II and Mucopolysaccharidosis III. Mucopolysaccharidosis II and mucopolysaccharidosis III represent two ends of a spectrum of disease severity, with mucopolysaccharidosis II representing the most severe form of disease. These conditions are further divided into alpha and beta subtypes based on symptoms.

- Mucopolysaccharidosis II alpha/beta is a slowly progressive disorder characterized by severe joint stiffening and multiple skeletal abnormalities. Individuals with mucopolysaccharidosis II alpha/beta are slow growing from birth and often stop growing by the age of two. Skeletal abnormalities are severe and typically present at birth. They include deformations of the thorax, long bones, hips, and feet. Facial features are mildly deformed and gums are typically underdeveloped. Other characteristics are malformation of the heart valves and narrowing of the airways due to mucosal thickening and stiffening of the chest. Most affected children do not survive past childhood, due to heart or respiratory failure. Development of motor skills, including speech, is typically delayed. Affected children have lower than expected intellect but are capable of understanding and interacting with their environment.
- Mucopolysaccharidosis III alpha/beta is a slowly progressive disorder characterized by joint stiffening and multiple skeletal abnormalities. Individuals with mucopolysaccharidosis III alpha/beta typically are slow-growing during childhood and of short stature as adults. Symptoms commonly start manifesting at age of three. A characteristic symptom is a "squatting"-like posture and severe stiffness of all large joints. Other symptoms include heart defects, which may increase the risk of sudden cardiac arrest, as well as restricted breathing due to stiffening of tissue in the chest and lungs. Childhood bronchitis and pneumonia are common and for individuals with both impaired breathing and cardiac defects, life-threatening complications may arise. Developmental delay is also common, particularly with regard to motor skills. Intellect is typically not affected.

What is my risk of having an affected child?

Mucopolysaccharidosis II and III is 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.

- There is currently no cure for mucopolysaccharidosis II alpha/beta and affected individuals have not been reported to survive into adulthood. Treatment is mainly focused on managing symptoms and improving the quality of life for affected children.
- Progression of mucopolysaccharidosis III alpha/beta is not preventable and treatment is mainly focused on improving the quality of life for affected individuals. Due to the severe stiffness of joints, affected individuals typically experience frequent pain and need lifetime medical treatment. Other options such as surgery to improve mobility or relieve pain are often not available due to inefficient breathing. Heart failure and breathing impairment likely become more severe with age and may lead to life-threatening complications. Recent studies showed evidence that medical treatment might help with pain management and the severity of disease progression. However, the long-term outcome of this treatment is unknown at this point.

What mutation was detected?

The detected heterozygous variant was NM_024312.5:c.3503_3504del (p.Leu1168Glnfs*5). This frameshift variant, c.3503_3504del, is the result of the deletion of 2 base pairs, which leads to an out-of-frame transcript and the introduction of a premature stop codon. The introduced stop codon is predicted to be located at least 50 nucleotides upstream of the canonical

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donor splice site of the penultimate exon and is consistent with the resulting transcript being targeted for nonsense mediated decay (PubMed: [27618451](#), [11532962](#), [18066079](#)). There is sufficient evidence that loss of function in this gene is a known disease mechanism for mucopolipidosis II (PubMed: [32651481](#), [19617216](#), [19197337](#), [16116615](#)). This mutation has been previously reported in several studies as a founder mutation of mucopolipidosis II for the French Canadian population (PubMed: [18190596](#), [16465621](#), [19659762](#), [20880125](#)). This variant has also been found to co-segregate with stuttering in a family (PubMed: [29289611](#)). This variant is classified as "Pathogenic" in ClinVar, with multiple submitters in agreement (ClinVar: 2771). The laboratory classifies this variant as pathogenic.



CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY

Patient	13190, DONOR	Partner
Result	⊕ Possible Carrier	N/A
Variant Details	CYP21A2 (NM_000500.9) c.955C>T(;)*12C>T + CYP21A2 duplication p.(Gln319*)(;)(?)	N/A

What is Congenital adrenal hyperplasia due to 21-hydroxylase deficiency?

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an inherited disorder that affects the adrenal glands and hormone production. Approximately 75 percent of individuals with classic 21-hydroxylase deficiency have the salt-wasting type, whereby the body excretes too much salt in urine. Affected infants present with poor feeding, weight loss, dehydration, and vomiting, all of which can be life-threatening. Females with this condition typically have ambiguous genitalia, while males usually have normal genitalia, but with small testes. Individuals with the simple virilizing form and the non-classic form of the disease do not experience salt loss. Males and females with either the classic or non-classic forms of 21-hydroxylase deficiency tend to have an early growth spurt, but their final adult height is usually shorter than others in their family, and affected individuals may have reduced fertility. Additionally, individuals may have excessive body hair growth, hair loss, and irregular menstruation. Some individuals (male or female) with the non-classic form of the disease may have mild, non-life-threatening symptoms, while others may never develop symptoms of the disorder at all.

What is my risk of having an affected child?

CAH due to 21-hydroxylase deficiency is 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?

Treatment consists of early initiation of hormone replacement therapy and/or surgery for females. Prognosis is good for patients with appropriate medical management and psychological support.

What mutation was detected?

The heterozygous variants c.955C>T (p.Gln319*) and a whole gene duplication of CYP21A2 were detected in this sample. In addition, the benign polymorphism c.*12C>T was also detected. The phase of these variants is unknown but could be determined through parental testing.

The nonsense variant, p.Gln319*, introduces a premature stop codon and is expected to result in the loss of function of the protein product of the CYP21A2 gene, either as the result of protein truncation or of nonsense-mediated mRNA decay. This variant, also reported as Q318*, is a classic 21-hydroxylase-deficient congenital adrenal hyperplasia mutation and has been reported in multiple affected individuals (PubMed: [3267225](#), [12220458](#), [12915679](#)). The variant, p.Gln319*, and the polymorphism c.*12C>T are known to frequently occur in a duplicated copy of the CYP21A2 gene coexisting with a normal copy of CYP21A2 on the same chromosome. This haplotype was identified in approximately 2% of the general population and in ~80% of carriers of p.Gln319*, and such a configuration may represent a benign allele (PubMed: [28401898](#), [19773403](#)). Nonetheless, there is a possibility that p.Gln319* occurs on a chromosome with only a single copy of CYP21A2, in which case it results in a pathogenic allele. If multiple copies of CYP21A2 are present, we cannot be certain if this p.Gln319* variant occurs on a chromosome with one (i.e. pathogenic state) or two (i.e. benign state) copies of CYP21A2. While this combination of variants may represent a benign allele, the laboratory classifies the variant p.Gln319* as likely pathogenic.



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 99.6% 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, CHRNA, 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, FKBP, FKTN, FMO3, FOXN1, FOXRED1, FRAS1, FREM2, FUCA1, G6PC, G6PC3, GAA, GALT, GALE, GALK1, GALNS, GALNT3, GALT, GAMT, GATM, GBA, GBE1, GCDH, GCH1, GDF5, GFM1, GHR, GJB2, GJB6, GJB1, GLDC, GLE1, GNE, GNPAT, GNPTAB, GNPTG, GNS, GORAB, GRHR, 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, IKBK, 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, MECP, MED17, MESF2, MFSDB, MKKS, MKS1, MLC1, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MOCS1, MOCS2, MPI, MPL, MPV17, MRE11, MTHFR, MTR, MTRR, MTP, 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, PJK, 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, SMARCA1, 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, TMPPRS3, 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, 99.59% and 99.55% 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



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 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



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, CGMB on 9/30/2024
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](tel: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
13190, DONOR DOB: [REDACTED] AGE: [REDACTED] Gender: M Phone: 206.588.1484 Patient ID: 13190	Specimen: OW485376B Requisition: 0000707 Collected: 09/11/2024 / 12:42 PDT Received: 09/12/2024 / 04:27 PDT Reported: 09/24/2024 / 02:15 PDT	Client #: 98105026 VNLZR00 KUAN, JAMES K SEATTLE SPERM BANK 4915 25TH AVE NE STE 204W SEATTLE, WA 98105-5668

Cytogenetic Report

CHROMOSOME ANALYSIS, BLOOD - 14596

Lab:EZ

CHROMOSOME ANALYSIS, BLOOD

Order ID: 24-435965
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.

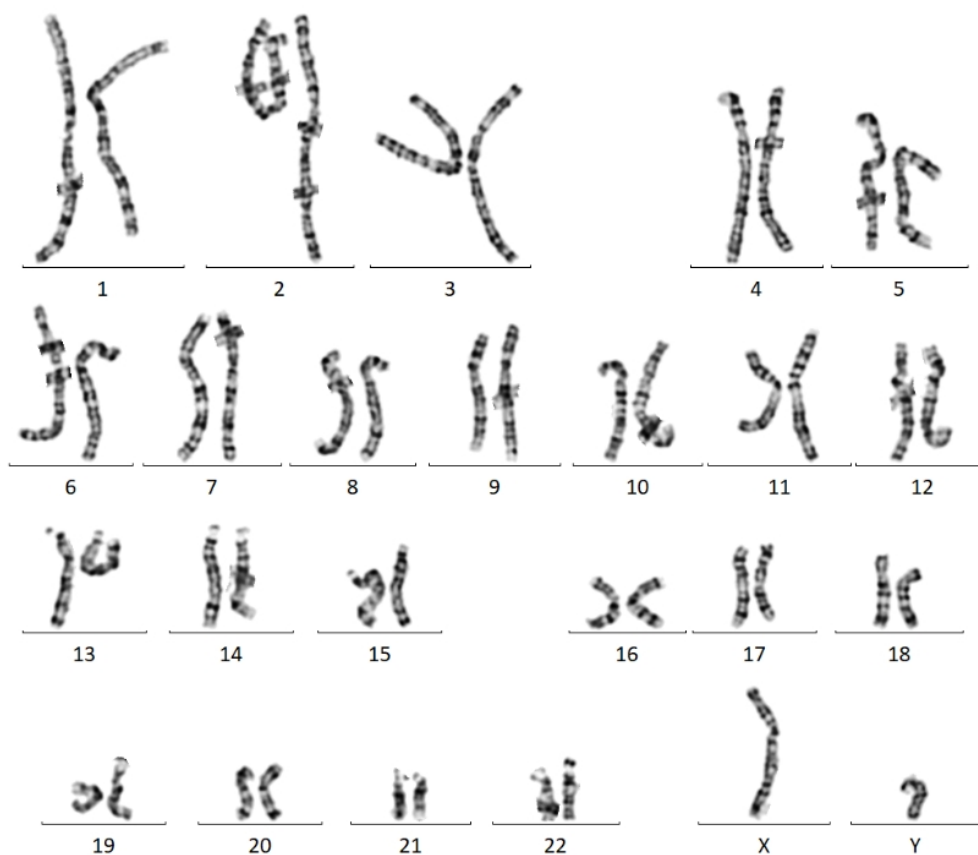
A portion of the testing was performed at SJC1

Guang Li, PhD, FACMG (800) NICHOLS-4307

Electronic Signature: 9/24/2024 4:24 AM



Patient Information	Specimen Information	Client Information
13190, DONOR DOB: [REDACTED] AGE: [REDACTED] Gender: M Patient ID: 13190	Specimen: OW485376B Collected: 09/11/2024 / 12:42 PDT Received: 09/12/2024 / 04:27 PDT Reported: 09/24/2024 / 02:15 PDT	Client #: 98105026 KUAN, JAMES K



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