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Patient Information:
18197, Donor
DOB: [redacted]
Sex: M
MR#:
Patient#: FT-PT8814578

Partner Information:
Not Tested

Physician:
Kuan, James
ATTN: Chogovadze, Avtandil
Denver 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 03,2024**

Accession:
FT-6995589
Test#: FT-TS14921563
Specimen Type: Blood (EDTA)
Collected: Aug 13,2024

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	18197, Donor	Partner
Oculocutaneous albinism, type IV *SLC45A2*	AR	⊕ Carrier c.1166_1167del (p.Lys389Serfs*55)	N/A
Citrin deficiency *SLC25A13*	AR	⊕ Carrier c.1591+2T>C (p.?)	N/A
Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency *HSD3B2*	AR	⊕ Carrier c.29C>T (p.Ala10Val)	N/A
Autosomal recessive spastic ataxia of Charlevoix-Saguenay *SACS*	AR	⊕ Carrier c.6434T>A (p.Leu2145*)	N/A

INTERPRETATION:

Notes and Recommendations:

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

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OCULOCUTANEOUS ALBINISM, TYPE IV

Patient	18197, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***SLC45A2*** (NM_016180.5) c.1166_1167del (p.Lys389Serfs*55)	N/A

What is Oculocutaneous albinism, type IV?

Oculocutaneous Albinism, Type IV (OCA4) is part of a group of genetic conditions that affect the pigmentation (color) in the skin, hair, and eyes. Affected individuals typically have very fair skin, white or light colored hair, and vision problems. Vision problems include reduced sharpness, rapid, involuntary movements of the eyes (nystagmus), and increased sensitivity to light. Additionally, those who have OCA4 are more sensitive to the sun and at an increased risk for skin damage and skin cancer (melanoma).

What is my risk of having an affected child?

Oculocutaneous albinism, type IV 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?

Prognosis is generally good for appropriately managed individuals with OCA4 and lifespan is normal. There is not a cure for OCA4, but management can include vision aids and measures to protect the skin. Regular visits to the opthamologist or dermatologist are recommended.

What mutation was detected?

The detected heterozygous variant was NM_016180.5:c.1166_1167del (p.Lys389Serfs*55). Truncating mutations in nearby codons (c.1164delAA, c.1121del) have previously been reported in patients with oculocutaneous albinism (OCA) (PubMed: 18463683, 16868655).This frameshift variant, p.Lys389Serfs*55, is the result of the deletion of two base pairs, which leads to an out-of-frame transcript and the introduction of a premature stop codon. This variant is predicted to result in loss of function of the protein product of the SLC45A2 gene, either as the result of protein truncation or of nonsense-mediated mRNA decay. There's sufficient evidence that loss of function in this gene is a known disease mechanism for oculocutaneous albinism type 4 (OCA4) (PubMed: 31630438, 14961451, 20301683, 29345414). The laboratory classifies this variant as pathogenic.

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CITRIN DEFICIENCY

Patient	18197, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***SLC25A13*** (NM_014251.3) c.1591+2T>C (p.?)	N/A

What is Citrin deficiency?

This disease occurs as a defect in the body's ability to break down urea and ammonia. Citrin deficiency can present in one of three ways according to age. The three forms of the disease can present in neonates (0 to 4 weeks old), in infancy/childhood (4 weeks to 11 years old), and in childhood to adulthood (11 years and older). Neonatal citrin deficiency presents as growth retardation with liver disease, anemia, blood coagulation disorder, and/or low blood sugar. In older children, this disease presents as failure to thrive with abnormal blood lipids, pancreatic disease, fatty liver, and/or liver cancer. Both of these sets of patients may go on to develop a different form of this disease later in life. The late-onset form of this disease is called Citrullinemia Type II and symptoms include abnormally high levels of ammonia in the blood with neuropsychiatric symptoms including delirium, aggression, irritability, hyperactivity, delusions, disorientation, restlessness, drowsiness, loss of memory, flapping tremor, convulsive seizures, and coma. In some cases, death can result from episodes of disease.

What is my risk of having an affected child?

Citrin 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?

Consistent with the course of most urea cycle disorders, the degree of intellectual impairment depends on how much ammonia is in the blood and how often these episodes of the disease occur. Symptoms are often provoked by alcohol and sugar intake, medication, and/or surgery. Appropriate lifestyle modifications may reduce the overall disease burden. The neonatal form of the disease is generally not severe as symptoms often resolve by one year of age with appropriate treatment, however, some infants require liver transplantation or die due to infection. With appropriate treatment, survival into adulthood is possible and has been documented.

What mutation was detected?

The detected heterozygous variant was NM_014251.3:c.1591+2T>C (p.?). This intronic variant alters the highly conserved consensus sequence for the canonical splice site and is predicted by multiple splice site prediction tools queried to abolish canonical splice activity. This variant is expected to result in altered function of the gene product as a result of aberrant splicing. This splicing variant has not, to our knowledge, been previously reported in the literature. There's sufficient evidence that loss of function in this gene is a known disease mechanism for citrin deficiency (PubMed: 31809266, 31450232, 27405544, 14680984, 10369257). The laboratory classifies this variant as likely pathogenic.

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CONGENITAL ADRENAL HYPERPLASIA DUE TO 3-BETA-HYDROXYSTEROID DEHYDROGENASE 2 DEFICIENCY

Patient	18197, Donor	Partner
Result	Carrier	N/A
Variant Details	***HSD3B2*** (NM_000198.4) c.29C>T (p.Ala10Val)	N/A

What is Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency?

Classic 3-beta-hydroxysteroid dehydrogenase deficiency (3Beta-HSD) is a disease characterized by a severe impairment of steroid biosynthesis in both the adrenals and the gonads, resulting in decreased secretion of vital hormones throughout the body. Affected newborns exhibit signs and symptoms of glucocorticoid and mineralocorticoid deficiencies, which may be fatal especially in the severe salt-wasting form. Children with this condition may also present with hermaphroditism.

What is my risk of having an affected child?

Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase 2 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?

People with the salt-wasting form of 3-beta–hydroxysteroid dehydrogenase (3BHSD) deficiency need the replacement of glucocorticoids, mineralocorticoids, and sex steroids. In people with late-onset (non-classic) 3BHSD deficiency, the need for replacement therapy varies depending on the severity of the condition.

What mutation was detected?

The detected heterozygous variant was NM_000198.4:c.29C>T (p.Ala10Val). This variant was reported in the homozygous state in an individual with 3-beta-hydroxysteroid dehydrogenase deficiency (PubMed: 10599696). Invitro functional studies showed that this variant affected enzyme activity (PubMed: 10599696, 11196452). Another variant at this position in the gene (p.Ala10Glu) has been associated with 3-beta-hydroxysteroid dehydrogenase deficiency, suggesting that a change at this position adversely affects protein structure and/or function and is potentially disease-causing (PubMed: 10843183). The laboratory classifies this variant as likely pathogenic.

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AUTOSOMAL RECESSIVE SPASTIC ATAXIA OF CHARLEVOIX-SAGUENAY

Patient	18197, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***SACS*** (NM_014363.6) c.6434T>A (p.Leu2145*)	N/A

What is Autosomal recessive spastic ataxia of Charlevoix-Saguenay?

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a progressive, neurodegenerative disorder that affects muscle movement. Onset usually begins between 12 to 18 months of age. ARSACS is characterized by muscle spasticity, ataxia, muscle wasting, involuntary eye movements, speech difficulties, deformities of the fingers and feet, reduced sensation and weakness of the arms and legs, and buildup of fatty tissue on the retina leading to vision problems.

What is my risk of having an affected child?

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay 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?

Signs and symptoms of disease worsen over time with most affected individuals requiring a wheelchair by their thirties or forties followed by death, typically in the fifties. Treatment includes supportive care and occupational therapy.

What mutation was detected?

The detected heterozygous variant was NM_014363.6:c.6434T>A (p.Leu2145*). 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 2434 (53%) amino acids of the original protein. The truncated or altered region is critical to protein function, as indicated by at least one pathogenic variant downstream of this position (PubMed: 29538656). There's sufficient evidence that loss of function in this gene is a known disease mechanism for spastic paraplegia or autosomal recessive spastic ataxia of Charlevoix-Saguenay or hereditary motor and sensory neuropathy (PubMed: 35008978, 32368540, 30460542, 26288984, 23250129, 15156359).This variant was reported in an individual with Spastic ataxia, Charlevoix-Saguenay type (PubMed: 31216405). The laboratory classifies this variant as likely 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, 99.56% and 99.51% 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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CLIA: 22D0957540

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 **9/3/2024**
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
18197, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Fasting: U Phone: 303.970.5897 Patient ID: 18197 Health ID: 8573035127737282	Specimen: DV191086N Requisition: 0000139 Collected: 08/13/2024 / 12:41 MDT Received: 08/13/2024 / 21:46 MDT Reported: 08/25/2024 / 18:13 MDT	Client #: 70413924 DN99999 DENVER SPERM BANK 1601 E 19TH AVE STE 4500 DENVER, CO 80218-1289

COMMENTS: FASTING:UNKNOWN

Cytogenetic Report

CHROMOSOME ANALYSIS, BLOOD - 14596 Lab:EZ

CHROMOSOME ANALYSIS, BLOOD

Order ID: 24-383566
Specimen Type: Blood
Clinical Indication: GAMETE DONOR, RULE OUT CHROMOSOME

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 SJC3.

Peter H. Bui, PhD, FACMG (800) NICHOLS-4307

Electronic Signature: 8/25/2024 7:28 PM

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