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CLIA: 22D0957540

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Cohen Dermatopathology
Therapath Partners

Patient Information:
13150, DONOR
DOB: [redacted]
Sex: M
MR#:
Patient#: FT-PT8735236

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: **Jun 01,2024**

Accession:
FT-7018628
Test#: FT-TS14841967
Specimen Type: Blood (EDTA)
Collected: May 15,2024

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	13150, DONOR	Partner
WNT10A-related ectodermal dysplasias *WNT10A*	AR	⊕ Carrier c.321C>A (p.Cys107*)	N/A
Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) *ARSB*	AR	⊕ Carrier c.629A>G (p.Tyr210Cys)	N/A

INTERPRETATION:

Notes and Recommendations:

- **PLEASE NOTE: Heterozygous carriers of a WNT10A variant may be at risk of autosomal dominant selective tooth agenesis-4 (STHAG4) (PubMed: 29772684; OMIM: 606268). Autosomal dominant phenotypes have also been described to include dry skin, abnormal sweating, nail abnormalities and sparse hair in some patients (OMIM: 150400). As such, correlation with clinical and family history is recommended. Consultation with a medical geneticist and/or other specialist is recommended.**
- Based on these results, this individual is positive for carrier mutations in 2 genes. Carrier screening for the reproductive partner is recommended to accurately assess the risk for any autosomal recessive conditions. A negative result reduces, but does not eliminate, the chance to be a carrier for any condition included in this screen. Please see the supplemental table for details.
- Testing for 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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WNT10A-RELATED ECTODERMAL DYSPLASIAS

Patient	13150, DONOR	Partner
Result	Carrier	N/A
Variant Details	***WNT10A*** (NM_025216.3) c.321C>A (p.Cys107*)	N/A

What is WNT10A-related ectodermal dysplasias?

The WNT10A gene produces proteins that aid in the formation of several types of tissues that arise from an embryonic cell layer called the ectoderm. There are several conditions associated with this gene including Schopf-Schulz-Passarge syndrome and Odonto-onycho-dermal dysplasia.

- Schopf-Schulz-Passarge syndrome (SSPS) and Odonto-onycho-dermal dysplasia (OODD) are rare ectodermal dysplasias characterized by hypodontia, keratoderma, nail dystrophy, and hair abnormalities. Individuals with SPSS also have multiple eyelid cysts, and hypotrichosis. Dry hair, smooth tongue with marked reduction of fungiform and filiform papillae, hyperhidrosis of palms and soles, and hyperkeratosis of the skin are additional features seen in individuals with OODD. For both conditions, some features may not be present until adulthood, causing diagnoses to be delayed in some cases.

What is my risk of having an affected child?

Schopf-Schulz-Passarge syndrome and Odontoonychodermal dysplasia are inherited in an autosomal recessive manner. If the patient and the partner are both carriers, the risk for an affected child is 1 in 4 (25%).

What kind of medical management is available?

Each condition is managed differently based on its symptoms. The treatment of SSPS and OODD is symptomatic. Standard dental care is indicated in most cases. Eyelid cysts seen in those with SSPS may be improved by electrocautery. If necessary, counseling and psychological support and dermatological examination to detect non-melanoma skin cancer should be offered.

What mutation was detected?

The detected heterozygous variant was NM_025216.3:c.321C>A (p.Cys107*). This nonsense 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 Odontoonychodermal dysplasia and Schopf-Schulz-Passarge syndrome (PubMed: 17847007, 20163410, 30974434, 30569517). This variant has been reported in either the homozygous or compound heterozygous state in several individuals with odontoonychodermal dysplasia (OODD), hypohidrotic ectodermal dysplasia (HED), and Schopf-Schulz-Passarge syndrome (PubMed: 19559398, 22581971, 26964878, 24702986, 24902757) and has been found to segregate with disease in one family (PubMed: 19559398).This variant has been identified by this laboratory in the compound heterozygous state in 1 individual with symptoms consistent with a WNT10A-related condition.This variant is classified as "Pathogenic" in ClinVar, with multiple submitters in agreement (ClinVar: 4461). The laboratory classifies this variant as pathogenic.

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MUCOPOLYSACCHARIDOSIS TYPE VI (MAROTEAUX-LAMY SYNDROME)

Patient	13150, DONOR	Partner
Result	Carrier	N/A
Variant Details	***ARSB*** (NM_000046.5) c.629A>G (p.Tyr210Cys)	N/A

What is Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)?

The symptoms and severity of Maroteaux-Lamy syndrome can vary dramatically from one person to another; some individuals only develop mild symptoms, while others develop severe, even life-threatening complications. Common symptoms can include coarse facial features, corneal clouding, joint abnormalities, various skeletal malformations, an abnormally enlarged liver and/or spleen (hepatosplenomegaly), and hearing loss. Cardiac disease and restrictive pulmonary disease can also occur. Intelligence is usually not affected.

What is my risk of having an affected child?

Maroteaux-Lamy syndrome is inherited in an autosomal recessive manner. If both parents are carriers of this condition, the risk for an affected child is 1 in 4.

What kind of medical management is available?

The symptoms, onset and rate of progression of Maroteaux-Lamy syndrome vary greatly from one person to another. The disorder can be thought of as a spectrum or continuum of disease. Some individuals may only have a few symptoms and others may have serious symptoms affecting several different organ systems simultaneously. Maroteaux-Lamy syndrome can potentially cause life-threatening complications. Some individuals will have severe symptoms during infancy, while others have slowly progressive symptoms that develop over the course of multiple decades. Enzyme replacement therapy is now available to help minimize symptoms.

What mutation was detected?

The detected heterozygous variant was NM_000046.5:c.629A>G (p.Tyr210Cys). This missense variant, p.Tyr210Cys, has been reported in trans or in the unknown phase with either a pathogenic or variant of unknown significance in multiple unrelated individuals affected with mucopolysaccharidosis type VI (MPS VI) (PubMed: 8651289, 23557332, 14974081, 24221504). In addition, this variant has been reported in the homozygous state in one individual and in the heterozygous state, without an identified second variant, in multiple individuals affected with MPS VI of their disease (PubMed: 8651289, 21514195, 24221504). Furthermore, this variant has been found to segregate with disease in two different families (PubMed: 8651289, 21791832). Functional analysis of this variant indicates that this change results in reduced enzyme activity in the protein 4S (PubMed: 8651289).This variant is classified as "Pathogenic" or "Likely Pathogenic" in ClinVar, with multiple submitters in agreement (ClinVar: 885). 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 99.4% 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, 99.52% and 99.45% 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:

Yan Meng, Ph.D., CGMB, FACMG on **6/1/2024**
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

INVITAE

INVITAE PROACTIVE TESTING RESULTS

Patient name:	Donor 13150	**Sample type:**	Saliva	**Report date:**	15-MAR-2024
DOB:	[redacted]	**Sample collection date:**	06-MAR-2024	**Invitae #:**	RQ6273586
Sex assigned at birth:	Male	**Sample accession date:**	09-MAR-2024	**Clinical team:**	Guadalupe Martinez Dr. James Kuan
Gender:					
Patient ID (MRN):					

Test performed

Sequence analysis and deletion/duplication testing of the 83 genes listed in the Genes Analyzed section.

- Invitae Cardio Screen

RESULT: NEGATIVE

This test did not identify any genetic variation that is currently recognized as clinically significant.

About this test

This test evaluates 83 genes for variants (genetic changes) that indicate a significantly increased risk of developing certain heart-related conditions. These are disorders for which effective medical interventions and preventive measures are known and available. Genetic changes of uncertain significance are not included in this report; however, if additional evidence becomes available to indicate that a previously uncertain genetic change is clinically significant, Invitae will update this report and provide notification.

Next steps

- You can request a referral for genetic counseling to further discuss this test result and to review your family health history. A complete family history may point to health risks not evaluated by this test. It is important to note that while this test has found no genetic risk factors for certain types of conditions, at least a baseline, population-level risk remains for developing these types of disorders and age-appropriate screenings are still recommended.

- Register your test at **www.invitae.com/patients** to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.

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Clinical summary

There were no known, clinically significant genetic changes identified that confer a genetic predisposition to, or carrier status for, certain heart-related conditions tested with this panel (see complete list of genes and conditions evaluated below). However, other types of risk based on factors including personal and family history, genetic causes not evaluated with this test, lifestyle, or other environmental influences may still be of clinical significance.

Genes analyzed

This table represents a complete list of genes analyzed for this individual. Genes listed in this table may also have additional reported clinical associations outside of the conditions listed. Additional information about gene-condition associations can be found at http://www.omim.org. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

Cardiovascular-related genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
ACTA2	NM_001613.2	Aortopathy
ACTC1*	NM_005159.4	Cardiomyopathy, Congenital Heart Disease
ACTN2*	NM_001103.3	Arrhythmia, Cardiomyopathy
ACVRL1	NM_000020.2	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
APOB	NM_000384.2	Familial Hypercholesterolemia, Familial Hypobetalipoproteinemia
BAG3	NM_004281.3	Cardiomyopathy, Neuromuscular Condition
BMPR2	NM_001204.6	Pulmonary Arterial Hypertension
CACNA1C*	NM_000719.6;NM_001129840.1	Arrhythmia, Cardiomyopathy, Congenital Heart Disease
CACNB2	NM_201590.2	Arrhythmia
CALM1	NM_006888.4	Arrhythmia
CALM2	NM_001743.4	Arrhythmia
CALM3	NM_005184.2	Arrhythmia
CASQ2	NM_001232.3	Arrhythmia
CAV1	NM_001753.4	Pulmonary Arterial Hypertension
CAV3	NM_033337.2	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
COL3A1*	NM_000090.3	Connective tissue disorder
COL5A1	NM_000093.4	Connective tissue disorder
COL5A2	NM_000393.3	Connective tissue disorder
CRYAB	NM_001885.2	Cardiomyopathy, Neuromuscular Condition
CSRP3	NM_003476.4	Cardiomyopathy
DES	NM_001927.3	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
DMD	NM_004006.2	Cardiomyopathy, Neuromuscular Condition
DSC2	NM_024422.4	Arrhythmia, Cardiomyopathy
DSG2	NM_001943.3	Arrhythmia, Cardiomyopathy
DSP	NM_004415.2	Arrhythmia, Cardiomyopathy
EMD	NM_000117.2	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
ENG*	NM_000118.3	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
F2	NM_000506.3	Hemophilia, Hereditary Thrombophilia
F5	NM_000130.4	Hemophilia, Hereditary Thrombophilia
F9	NM_000133.3	Hemophilia, Hereditary Thrombophilia
FBN1	NM_000138.4	Connective tissue disorder
FHL1	NM_001449.4	Cardiomyopathy, Neuromuscular Condition
FLNC*	NM_001458.4	Cardiomyopathy, Neuromuscular Condition
GDF2	NM_016204.2	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
GLA	NM_000169.2	Cardiomyopathy, Lysosomal Storage Disease
GPD1L	NM_015141.3	Arrhythmia
HCN4	NM_005477.2	Arrhythmia, Cardiomyopathy
JUP	NM_002230.2	Arrhythmia, Cardiomyopathy
KCNE1	NM_000219.5	Arrhythmia
KCNE2	NM_172201.1	Arrhythmia
KCNH2	NM_000238.3	Arrhythmia
KCNJ2	NM_000891.2	Arrhythmia
KCNQ1	NM_000218.2	Arrhythmia
LAMP2	NM_002294.2	Cardiomyopathy, Arrhythmia, Glycogen Storage Disease
LDLR	NM_000527.4	Familial Hypercholesterolemia
LDLRAP1	NM_015627.2	Familial Hypercholesterolemia
LMNA	NM_170707.3	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
MYBPC3	NM_000256.3	Cardiomyopathy
MYH11	NM_001040113.1	Aortopathy
MYH7	NM_000257.3	Cardiomyopathy, Neuromuscular Condition
MYL2	NM_000432.3	Cardiomyopathy
MYL3	NM_000258.2	Cardiomyopathy
MYLK	NM_053025.3	Aortopathy
NKX2-5	NM_004387.3	Arrhythmia, Congenital Heart Disease
PCSK9*	NM_174936.3	Familial Hypercholesterolemia
PKP2	NM_004572.3	Arrhythmia, Cardiomyopathy
PLN	NM_002667.3	Arrhythmia, Cardiomyopathy
PRKAG2	NM_016203.3	Arrhythmia, Cardiomyopathy
PRKG1	NM_006258.3	Aortopathy
PROC	NM_000312.3	Hereditary Thrombophilia
PROS1	NM_000313.3	Hereditary Thrombophilia

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
RBM20	NM_001134363.2	Arrhythmia, Cardiomyopathy
RYR2	NM_001035.2	Arrhythmia, Cardiomyopathy
SCN5A	NM_198056.2	Arrhythmia, Cardiomyopathy
SERPINC1	NM_000488.3	Hereditary Thrombophilia
SGCD	NM_000337.5	Cardiomyopathy, Neuromuscular Condition
SMAD3	NM_005902.3	Aortopathy
SMAD4	NM_005359.5	Hereditary Hemorrhagic Telangiectasia
SMAD9	NM_001127217.2	Pulmonary arterial hypertension (PAH)
TCAP	NM_003673.3	Cardiomyopathy, Neuromuscular Condition
TGFB2	NM_003238.3	Aortopathy
TGFB3	NM_003239.3	Aortopathy, Arrhythmia, Cardiomyopathy
TGFBR1	NM_004612.2	Aortopathy
TGFBR2	NM_003242.5	Aortopathy
TMEM43	NM_024334.2	Arrhythmia, Cardiomyopathy
TNNC1	NM_003280.2	Cardiomyopathy
TNNI3	NM_000363.4	Arrhythmia, Cardiomyopathy
TNNT2	NM_001001430.2	Arrhythmia, Cardiomyopathy
TPM1	NM_001018005.1	Cardiomyopathy
TRDN	NM_006073.3	Arrhythmia
TTN*	NM_001267550.2	Arrhythmia, Cardiomyopathy, Neuromuscular condition
TTR	NM_000371.3	Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)
VCL	NM_014000.2	Cardiomyopathy

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated in the Genes Analyzed table. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed. Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Confirmation of the presence and location of reportable variants is performed as needed based on stringent criteria using one of several validated orthogonal approaches (PubMed ID 30610921). Sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). Confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). RNA sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778).

  The following additional analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. For C9orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Interpretation Reference Ranges: Benign (Normal Range): <25 repeat units, Uncertain: 25-30 repeat units, Pathogenic (Full Mutation): >=31 repeat units (PMID: 21944779, 22406228, 23111906, 28689190, 31315673, 33168078, 33575483). A second round of RP-PCR utilizing a non-overlapping set of primers is used to confirm the initial call in the case of suspected allele sizes of 22 or more repeats. For RNA analysis of the genes indicated in the Genes Analyzed table, complementary DNA is synthesized by reverse transcription from RNA derived from a blood specimen and enriched for specific gene sequences using capture hybridization. After high-throughput sequencing using Illumina technology, the output reads are aligned to a reference sequence (genome build GRCh37; custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test specimen is assessed quantitatively and compared to the usage seen in control specimens. Abnormal exon junction usage is evaluated as evidence in the Sherloc variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above, the presence of the variant is confirmed by targeted DNA sequencing.

- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at **http://www.ncbi.nlm.nih.gov/pubmed**.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (**http://exac.broadinstitute.org**), gnomAD (**http://gnomad.broadinstitute.org**), and dbSNP (**http://ncbi.nlm.nih.gov/SNP**).
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at **http://www.ncbi.nlm.nih.gov/medgen**. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance in Man (OMIM). Search by OMIM number at **http://omim.org/**.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

Limitations

Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination. Interpretations are made on the assumption that any clinical information provided, including specimen identity, is accurate. Invitae's RNA analysis is not designed for use as a stand-alone diagnostic method and cannot determine absolute RNA levels. Results from the RNA analysis may not be informative for interpreting copy number events. Additionally, sensitivity to detect RNA splicing events may be reduced for variants in the first donor site of each gene.

ACTC1: Sequencing analysis for exons 6 includes only cds +/- 10 bp. ACTN2: Deletion/duplication analysis is not offered for exon 9. CACNA1C: Deletion/duplication and sequencing analysis is not offered for exons 44-45. COL3A1: Deletion/duplication analysis is not offered for exons 23-24. ENG: Sequencing analysis for exons 7 includes only cds +/- 10 bp. PCSK9: Sequencing analysis for exons 9 includes only cds +/- 10 bp. FLNC: Deletion/duplication analysis is not offered for exon 47. Sensitivity and specificity for single nucleotide variants, insertions and deletions in exons 47-48 may be reduced due to the presence of segmental duplications overlapping the region. TTN: Exons 45-46, 147, 149, 164, 172-201 (NM_001267550.2) are excluded from analysis. TTN variants are included in the primary report based on functional effect and/or location. A complete list of variants of uncertain significance, likely benign and benign variants in TTN is available upon request. Variants are named relative to the NM_001267550.2 (meta) transcript. Variants in the coding sequence and intronic boundaries of the clinically relevant NM_133378.4 (N2A) and fetal isoforms are reported (PMID: 25589632, 29598826, 29691892, 31660661), with the exception of the PEVK tandem repeat region (172-198) (PMID: 28040389).

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

This report has been released utilizing a validated procedure approved by:

Jeana DaRe

Jeana DaRe, Ph.D., FACMG
Laboratory Director

jd_0835_pr

INVITAE

NEGATIVE RESULTS GUIDE

What negative results mean for you

Your genetic test results were negative. This means that no significant genetic changes ("pathogenic variants" or "mutations") were found. Your risk for disease could still be influenced by a combination of unidentified genetic, personal, lifestyle and/or environmental risk factors.

Create a plan with your healthcare provider

Whether or not you develop a disease is not determined by your genetics alone. It is still important to share your genetic test results with your healthcare provider so they can help you make informed medical decisions.

What negative results mean for your family

Your genetic test was negative, however, your family members have their own unique genetic makeup. Genetic testing can help them understand their overall chance of developing a genetic disease.

We (and others) are here to help

Although your test didn't find any genetic changes, you may still have questions about your results or your personal or family medical history. A genetic counselor can help.

Log in to your patient portal (invitae.com) to view your results, search for a local or Invitae genetic counselor, or join Invitae's Patient Insight Network (PIN), a community where you can connect with other patients and share your experience.

This information in this results guide is meant to be used along with your genetic test results and other health information. It is not meant to replace a discussion with your healthcare provider and should not be considered or interpreted as medical advice.

1400 16th Street, San Francisco, CA 94103 • www.invitae.com • 800-436-3037 • 415-276-4164

Patient Information	Specimen Information	Client Information
13150, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Fasting: U Phone: 206.588.1484 Patient ID: 13150 Health ID: 8573034587318634	Specimen: OW372357A Requisition: 0000660 Collected: 05/15/2024 / 11:05 PDT Received: 05/16/2024 / 04:51 PDT Reported: 05/29/2024 / 18:11 PDT	Client #: 98105026 VNLZR00 KUAN, JAMES K SEATTLE SPERM BANK 4915 25TH AVE NE STE 204W SEATTLE, WA 98105-5668

COMMENTS: FASTING:UNKNOWN

Cytogenetic Report

CHROMOSOME ANALYSIS, BLOOD - 14596 Lab:EZ

CHROMOSOME ANALYSIS, BLOOD

Order ID: 24-232518
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:

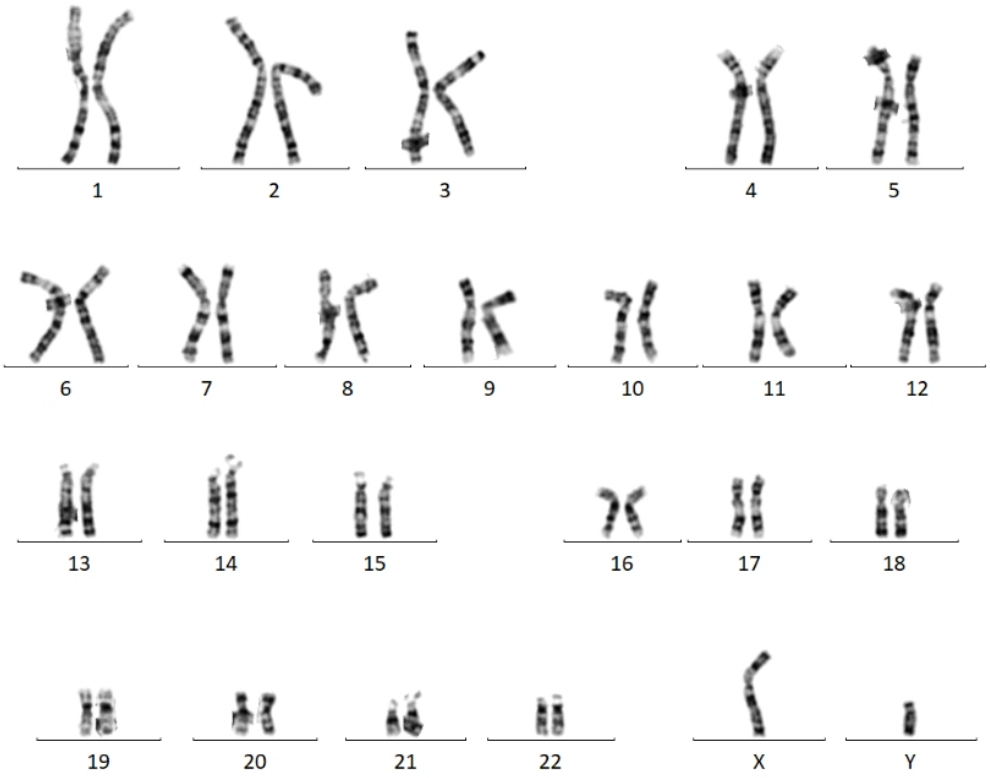
Method: G-Band (Digital Analysis: MetaSyst
Cells Counted: 20
Band Level: 450
Cells Analyzed: 5
Cells Karyotyped: 5

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.

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

Electronic Signature: 5/29/2024 8:29 PM

Patient Information	Specimen Information	Client Information
13150, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Fasting: U Patient ID: 13150 Health ID: 8573034587318634	Specimen: OW372357A Collected: 05/15/2024 / 11:05 PDT Received: 05/16/2024 / 04:51 PDT Reported: 05/29/2024 / 18:11 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