Genzeva
9430 Key West Ave, STE 130, Rockville, MD 20850
CLIA# 21D2119113

Test Performed: IMMUNODEFICIENCY

Report Date **Feb 6, 2023**
Status **FINAL**

Patient

Patient Name
Date of Birth Dec 29, 1946
Sex Female

Symptoms Not Applicable
Indication Hereditary Disorder

Client

Client Molecular Clinical Laboratory
Physician Pierce

Specimen

Accession ID 23-52
Specimen Saliva
Collection Dec 12, 2022
Accession Feb 4, 2023

Result: Positive

1
Pathogenic

Variant Summary

Gene / Variant	Genotype	Assessment	Mode of Inheritance	Phenotype
CCDC107 c.-432T>C g.35657948T>C	Heterozygous	Pathogenic	recessive	Cartilage-hair hypoplasia

Individual Variant Interpretations

Gene ***CCDC107***
Exon 0
Amino Acid
Nucleotide NM_174923.3:
g.35657948T>C
c.-432T>C
Assessment Pathogenic
Genotype Heterozygous

Interpretation

Cartilage-hair hypoplasia is a disorder of bone growth characterized by short stature (dwarfism) with other skeletal abnormalities; fine, sparse hair (hypotrichosis); and abnormal immune system function (immune deficiency) that can lead to recurrent infections.

People with cartilage-hair hypoplasia have unusually short limbs and short stature from birth. They typically have malformations in the cartilage near the ends of the long bones in the arms and legs (metaphyseal chondrodysplasia), which then affects development of the bone itself. Most people with cartilage-hair hypoplasia are unusually flexible in some joints, but they may have difficulty extending their elbows fully.

Affected individuals have hair that is lighter in color than that of other family members because the core of each hair, which contains some of the pigment that contributes the hair's color, is missing. The missing core also makes each strand of hair thinner, causing the hair to have a sparse appearance overall. Unusually light-colored skin (hypopigmentation), malformed nails, and dental abnormalities may also be seen in this disorder.

The extent of the immune deficiency in cartilage-hair hypoplasia varies from mild to severe. Affected individuals with the most severe immune problems are considered to have severe combined immunodeficiency (SCID). People with SCID lack virtually all immune protection from

bacteria, viruses, and fungi and are prone to repeated and persistent infections that can be very serious or life-threatening. These infections are often caused by "opportunistic" organisms that ordinarily do not cause illness in people with a normal immune system. Most people with cartilage-hair hypoplasia, even those who have milder immune deficiency, experience infections of the respiratory system, ears, and sinuses. In particular, the chicken pox virus (varicella) often causes dangerous infections in people with this disorder. Autoimmune disorders, which occur when the immune system malfunctions and attacks the body's tissues and organs, occur in some people with cartilage-hair hypoplasia. Affected individuals are also at an increased risk of developing cancer, particularly certain skin cancers (basal cell carcinomas), cancer of blood-forming cells (leukemia), and cancer of immune system cells (lymphoma).

Some people with cartilage-hair hypoplasia experience gastrointestinal problems. These problems may include an inability to properly absorb nutrients or intolerance of a protein called gluten found in wheat and other grains (celiac disease). Affected individuals may have Hirschsprung disease, an intestinal disorder that causes severe constipation, intestinal blockage, and enlargement of the colon. Narrowing of the anus (anal stenosis) or blockage of the esophagus (esophageal atresia) may also occur.

Genes Tested

ACD, ACP5, ACTA2, ACTB, ACTC1, ACVRL1, ADA, ADA2, ADAM17, ADAMTS13, ADAR, AICDA, AIRE, AK2, AP1S3, AP3B1, AP3D1, APC, APOB, APOL1, ARPC1B, ATM, ATP6AP1, ATP7B, B2M, BACH2, BCL10, BCL11B, BLM, BLNK, BLOC1S3, BLOC1S6, BMPR1A, BRCA1, BRCA2, BRIP1, BTD, BTK, C1QA, C1QB, C1QC, C1R, C1S, C2, C3, C4BPA, C5, C6, C7, C8A, C8B, C8G, C9, CACNA1S, CARD11, CARD14, CARD9, CARMIL2, CASP10, CASP8, CASQ2, CAVIN1, CCBE1, CCDC103, CCDC39, CCDC40, CCDC65, CCNO, CD19, CD247, CD27, CD3D, CD3E, CD3G, CD40, CD40LG, CD46, CD55, CD59, CD70, CD79A, CD79B, CD81, CD8A, CDCA7, CEBPE, CENPF, CFAP298, CFB, CFD, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, CFP, CFTR, CHD7, CIITA, CLCN7, CLEC7A, CLPB, COG6, COL3A1, COLEC11, COPA, CORO1A, CR2, CREBBP, CSF2RA, CSF2RB, CSF3R, CTC1, CTLA4, CTPS1, CTSC, CXCR4, CYBA, CYBB, DCLRE1B, DCLRE1C, DDX58, DGKE, DHFR, DKC1, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5, DNAH1, DNAH11, DNAH5, DNAI1, DNAI2, DNAJC21, DNAL1, DNASE1L3, DNASE2, DNMT3B, DOCK2, DOCK8, DRC1, DSC2, DSG2, DSP, DTNBP1, ELANE, ENG, EPG5, ERCC2, ERCC3, ERCC4, ERCC6L2, ETV6, EXTL3, F11, F13A1, F13B, F5, F7, F8, F9, FAAP24, FADD, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FASLG, FAT4, FBN1, FCGR3A, FCN3, FERMT3, FGA, FGB, FLNC, FOXN1, FOXP3, FPR1, G6PC3, G6PD, GAA, GAS8, GATA1, GATA2, GFI1, GINS1, GLA, GP1BA, GP1BB, GP9, GTF2H5, HAX1, HELLS, HFE, HNF1A, HPS1, HPS3, HPS4, HPS5, HPS6, HYDIN, HYOU1, ICOS, IFIH1, IFNAR2, IFNGR1, IFNGR2, IGLL1, IKBKB, IKZF1, IL10, IL10RA, IL10RB, IL12RB1, IL17F, IL17RA, IL17RC, IL1RN, IL2, IL21, IL21R, IL2RA, IL2RG, IL36RN, IL7R, INO80, INSR, INVS, IRAK1, IRAK4, IRF2BP2, IRF3, IRF7, IRF8, ISG15, ITCH, ITGAM, ITGB2, ITK, JAGN1, JAK1, JAK2, JAK3, KCNH2, KCNQ1, KDM6A, KMT2D, KRAS, LAMTOR2, LAT, LCK, LDLR, LIG1, LIG4, LMNA, LPIN2, LRBA, LRRC8A, LYST, MAGT1, MALT1, MAN2B1, MANBA, MAP3K14, MASP1, MASP2, MAX, MBL2, MC2R, MCM4, MEFV, MEN1, MLH1, MLPH, MOGS, MPL, MPO, MRE11, MS4A1, MSH2, MSH6, MSN, MTHFD1, MUTYH, MVK, MYBPC3, MYD88, MYH11, MYH7, MYH9, MYL2, MYL3, MYO5A, MYSM1, NBAS, NBN, NCF1, NCF2, NCF4, NCSTN, NF2, NFAT5, NFKB1, NFKB2, NFKBIA, NHEJ1, NHP2, NKX2-5, NLRC4, NLRP1, NLRP12, NLRP3, NME8, NOD2, NOP10, NRAS, NSMCE3, OFD1, ORAI1, OSTM1, OTC, OTULIN, PALB2, PARN, PCCA, PCCB, PCSK9, PEPD, PGM3, PI4KA, PIGA, PIK3CD, PIK3R1, PKP2, PLCG2, PLEKHM1, PLG, PMM2, PMS2, PNP, POLA1, POLE, POLE2, PRF1, PRKAG2, PRKCD, PRKDC, PROC, PROS1, PSENEN, PSMB8, PSTPIP1, PTEN, PTPRC, RAB27A, RAC2, RAD50, RAD51C, RAG1, RAG2, RANBP2, RASGRP1, RB1, RBCK1, RBM8A, RECQL4, RELB, RET, RFX5, RFXANK, RFXAP, RHOH, RMRP, RNASEH2A, RNASEH2B, RNASEH2C, RNF168, RNF31, RORC, RPE65, RPGR, RPL11, RPL15, RPL26, RPL35A, RPL36, RPL5, RPS10, RPS15, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27A, RPS28, RPS29, RPS7, RPSA, RSPH1, RSPH3, RSPH4A, RSPH9, RTEL1, RUNX1, RYR1, RYR2, SAMD9, SAMD9L, SAMHD1, SBDS, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SEMA3E,

SERPING1, SH2D1A, SH3BP2, SKIV2L, SLC29A3, SLC35A1, SLC35C1, SLC37A4, SLC39A4, SLC46A1, SLC7A7, SLX4, SMAD3, SMAD4, SMARCAL1, SMARCD2, SNX10, SP110, SPAG1, SPINK5, SRP54, SRP72, STAT1, STAT2, STAT3, STAT5B, STIM1, STK11, STK4, STN1, STX11, STXBP2, TAP1, TAP2, TAPBP, TBK1, TBX1, TCF3, TCIRG1, TCN2, TERC, TERT, TFRC, TGFBR1, TGFBR2, THBD, TICAM1, TINF2, TIRAP, TLR3, TMC6, TMC8, TMEM127, TMEM43, TNFAIP3, TNFRSF11A, TNFRSF13B, TNFRSF13C, TNFRSF1A, TNFRSF4, TNFSF11, TNFSF12, TNNI3, TNNT2, TP53, TPM1, TPP1, TPP2, TRADD, TRAF3, TRAF3IP2, TRDN, TREX1, TRNT1, TSC1, TSC2, TTC37, TTC7A, TTN, TYK2, UNC119, UNC13D, UNC93B1, UNG, USB1, USP18, VHL, VPS13B, VPS45, WAS, WDR1, WIPF1, WRAP53, WT1, XIAP, XK, ZAP70, ZBTB24, ZMYND10

Methods and Limitations

DNA is extracted from patient specimens using a solid-phase technology. Individual samples are barcoded and enriched for exonic or coding portions of the genome using the IDT x-Gen Exome Research Panel v2. Sequencing is performed using Illumina SBS technology on the NovaSeq 6000.

Sequencing data from the NovaSeq 6000 is uploaded to the BaseSpace cloud and demultiplexed using the FASTQ generation workflow and bcl2fastq2 software. The resulting FASTQ files are processed using the DRAGEN germline 3.6.3 app with predefined targets via two custom biosample workflows (Genzeva_Dragen_v0_1 and Genzeva_Dragen_v0_2).

Genzeva uses the following software packages and scripts to perform analysis:

Illumina Software Packages

DRAGEN germline v3.6.3
FASTQ generation v1.0.0
bcl2fastq2 v2.2

Genzeva Server Software

Python v3.6.9
bcftools v1.9
htslib v1.9
bedtools 2.25.0
tabix v1.9
bgzip v1.9
BaseSpace CLI v1.2.1
Ubuntu v18.04 LTS

Python packages

sample-sheet v0.12.0
certifi v2020.6.20
chardet v3.0.4
click v7.1.2
idna v2.10
requests 2.24.0
tabulate v0.8.7
terminaltables v3.1.0
urllib3 v1.25.11

Custom Scripts

parse.gvcf.sh
parse.gvcf.py

parse_split.gvcf.py
bssh_interface.sh
bssh_interface_wrapper.sh
parse_json.py

Automated passing of DRAGEN analysis output from BaseSpace to Genzeva Laboratory Information System utilizes BASH script bssh_interface.sh and underlying BaseSpace command line interface (CLI).

Specimens must pass the following QC criteria before variant interpretation and analysis.

Uniformity of coverage (Min) 97.015%
Covered Bases >20X (Min) 95.966%
Total Reads (Min) 49143135
Average Alignment (Min) 64.796%
Duplicate Reads (Max) 23.381%

Relevant panels for analysis are created virtually by analyzing the genes described above. Panel variant interpretation is performed to the ACMG Guidelines (PMID: 25741868), with relevant pathogenic and likely pathogenic variants published on the final patient report.

Performance metrics as determined by our validations are listed below:

Entire Exome Region
Accuracy- 99.999%
Sensitivity- 99.246%
Specificity- 100%
Positive Predictive Value- 99.927%
Negative Predictive Value- 99.999%

Limitations

This test aims to detect all clinically relevant variants within the coding regions of the genes listed using the methodology above. Pathogenic and Likely Pathogenic variants should be confirmed by orthogonal technology. Please contact client services for more information, or to order as a separate test. Intronic (within 20bp of coding region), homopolymer regions with single base repeats > 5bp, dinucleotide repeats > 10bp, and trinucleotide repeats > 15 bp and larger expansions cannot be captured by the standard NGS target enrichment protocols and/or sequenced accurately. At this time the assay does not detect large deletions or duplications. This test is not designed to detect complex gene rearrangements or genomic aneuploidy events. This analysis also cannot detect pathogenic variants within regions which were not analyzed (e.g. other genes not tested, introns, promoter and enhancer regions, long repeat regions, or mitochondrial sequences). This assay is not designed to detect mosaicism. Patients that are hemizygous for an allele are reported out as homozygous due to current pipeline constraints, this is most common on the X-chromosome for male patients.

Genzeva only interprets and reports findings within the genes that are included within the panel ordered. It is important to understand that there may be variants in these genes undetectable using current technology. Additionally, there may be genes associated with the patient's phenotype that are not part of the panel sequenced.

Regulatory Disclaimer

This test was developed and its performance characteristics determined Genzeva (CLIA# 21D2119113) It has not been cleared or approved by the US Food and Drug Administration. The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (9.0.0.20220826), Ingenuity Knowledge Base (H-release), CADD (v1.6), NCBI Gene (2022-02-22), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2022-02-22), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2022-11-12 13:22:36.407), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (H-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Jul 13 22:57), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 37), CentoMD (5.3), dbVar (2021_04), OMIM (April 13, 2022), gnomAD (GRCh37 (hg19) 2.1.1, GRCh38 (hg38) 3.1.2), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2022-04-14), DGV (2016-05-15), COSMIC (v95), HGMD (2022.3), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 154, GRCh38 154), SIFT4G (2016-02-23)

Reviewed and approved by:

Dr. William G Kearns

Approved on: Feb 6, 2023

Selected Citations

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