Blueprint Genetics

*Sample report as of June 14, 2022. Regional differences may apply. For complete and up-to-date test methodology description, please see your report in Nucleus online portal. Accreditation and certification information available at **blueprintgenetics.com/certifications***

Comprehensive Skeletal Dysplasias and Disorders Panel Plus

REFERRING HEALTHCARE PROFESSIONAL

NAME **HOSPITAL**

PATIENT

NAME	DOB	AGE	GENDER	ORDER ID
		6		

PRIMARY SAMPLE TYPE	SAMPLE COLLECTION DATE	CUSTOMER SAMPLE ID

SUMMARY OF RESULTS

PRIMARY FINDINGS

The patient is heterozygous for *TRPV4* c.2396C>T, p.(Pro799Leu), which is classified as pathogenic.

Del/Dup (CNV) analysis

Negative for explaining the patient's phenotype.

PRIMARY FINDINGS: SEQUENCE ALTERATIONS

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
TRPV4	NM_021625.4	c.2396C>T, p.(Pro799Leu)	HET	missense_variant	AD	**Pathogenic**
	ID	**ASSEMBLY**	**POS**	**REF/ALT**		
		GRCh37/hg19	12:110222183	G/A		
					PHENOTYPE	
	gnomAD AC/AN	**POLYPHEN**	**SIFT**	**MUTTASTER**	Brachyolmia (autosomal dominant type), Charcot-Marie-Tooth disease, Familial Digital arthropathy with brachydactyly, Hereditary motor and sensory neuropathy, Metatropic dysplasia, Parastremmatic dwarfism, Spinal muscular atrophy, Spondyloepiphyseal dysplasia Maroteaux type, Spondylometaphyseal dysplasia Kozlowski type	
	0/0	possibly damaging	deleterious	disease causing		

SEQUENCING PERFORMANCE METRICS

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Comprehensive Skeletal Dysplasias and Disorders Panel	411	6300	1268401	1266215	295	99.83

TARGET REGION AND GENE LIST

The Blueprint Genetics Comprehensive Skeletal Dysplasias and Disorders Panel Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: *ACAN#, ACP5, ACVR1, ADAMTS10, ADAMTS17, ADAMTSL2#*, AGA, AGPS, AIFM1, AKT1, ALPL, ALX1, ALX3, ALX4, AMER1, ANKH, ANKRD11*, ANO5, ANTXR2, ARCN1, ARHGAP31, ARID1B, ARSB, ARSE*, ATP6V0A2, ATR, B3GALT6#, B3GAT3#*, B4GALT7, BGN, BHLHA9, BMP1, BMP2, BMPER, BMPR1B, C21ORF2, C2CD3, CA2, CANT1, CASR, CC2D2A#, CDC45, CDC6, CDH3, CDKN1C, CDT1, CENPE, CEP120, CEP152, CEP290*, CHST14, CHST3, CHSY1, CKAP2L, CLCN5, CLCN7, COG1, COG4, COL10A1, COL11A1, COL11A2, COL1A1, COL1A2, COL27A1, COL2A1, COL9A1, COL9A2, COL9A3, COMP, CREB3L1, CREBBP, CRIPT, CRLF1, CRTAP, CSF1R, CSPP1, CTSA, CTSK, CUL7, CYP27B1, CYP2R1, DDR2, DDX58, DHCR24, DHODH, DLL3, DLL4, DLX3, DLX5, DMP1, DNAJC21, DNMT3A, DOCK6, DONSON, DSE*, DVL1, DVL3, DYM, DYNC2H1, DYNC2LI1, EBP, EDN1, EDNRA, EFL1*, EFNB1, EFTUD2, EIF2AK3, EIF4A3, ENAM, ENPP1, EOGT, EP300, ERF, ESCO2, EVC, EVC2, EXT1, EXT2, EXTL3, EZH2, FAM111A, FAM20A, FAM20C, FAM46A, FAM83H, FANCB, FANCC, FBN1, FBN2, FERMT3, FGF9, FGF10, FGF23, FGFR1, FGFR2, FGFR3, FIG4, FKBP10, FKBP14, FLNA, FLNB, FN1, FTO, FUCA1, FZD2, GALNS, GALNT3, GCM2, GDF3, GDF5, GDF6, GJA1*, GLB1, GLI3, GMNN, GNAI3, GNAS, GNPAT, GNPTAB, GNPTG, GNS, GORAB, GPC6, GSC, GUSB*, GZF1, HAAO, HDAC4, HDAC8, HES7, HOXA11, HOXA13#, HOXD13, HPGD, HRAS, HSPA9, HSPG2, IARS2, ICK, IDH2, IDS*, IDUA, IFIH1, IFITM5, IFT122*, IFT140, IFT172, IFT43, IFT52, IFT57, IFT80, IFT81#, IGF2, IHH, IL1RN, IMPAD1, INPPL1, INTU, KAT6B, KCNJ2, KIAA0586#, KIAA0753, KIF22, KIF7, KL, KMT2A, KYNU, LBR, LEMD3, LFNG#, LIFR, LMNA, LMX1B, LONP1, LPIN2, LRP4, LRP5*, LTBP2, LTBP3, MAFB, MAP2K1, MAP3K7, MATN3, MBTPS2, MECOM, MEGF8, MEOX1, MESP2, MET, MGP, MKS1, MMP13, MMP2, MMP9, MNX1#, MSX2*, MYCN, MYH3, MYO18B, NANS, NBAS, NEK1, NF1*, NFIX, NIPBL, NKX3-2, NOG, NOTCH1, NOTCH2*, NPR2, NSD1, NSDHL, OBSL1, OFD1, ORC1, ORC4, ORC6, OSTM1, P3H1, P4HB, PAM16, PAPSS2, PAX3, PCNT, PCYT1A, PDE3A, PDE4D, PEX5, PEX7, PGM3, PHEX, PIGV, PIK3CA*, PISD, PITX1, PLCB4, PLEKHM1*, PLOD1, PLOD2, PLS3, POC1A, POLR1A, POLR1C#, POLR1D, POLR3A, POLR3B, POP1, POR, PPIB, PRKAR1A, PTDSS1, PTH1R, PTHLH, PTPN11, PYCR1, RAB23, RAB33B, RAD21*, RBBP8, RBM8A*, RBPJ*, RECQL4, RIPPLY2, RMRP, RNU4ATAC, ROR2, RPGRIP1L#, RSPRY1, RUNX2, SALL1*, SALL4, SBDS*, SC5D, SEC24D, SERPINF1, SERPINH1, SETBP1, SETD2, SF3B4, SFRP4, SGMS2, SGSH, SH3BP2, SH3PXD2B, SHH, SHOX#*, SKI, SLC10A7, SLC17A5, SLC26A2, SLC29A3, SLC34A3, SLC35D1, SLC39A13, SLCO2A1, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCAL1, SMARCB1, SMARCE1, SMC1A, SMC3, SNRPB, SNX10, SOST, SOX9, SP7, SPARC, SQSTM1, SRP54, STAMBP, SUMF1, TAB2, TAPT1, TBCE, TBX15, TBX3, TBX4, TBX5, TBX6, TBXAS1, TCF12, TCIRG1, TCOF1, TCTEX1D2, TCTN3, TGDS, TGFB1, TGFB2, TGFB3, TGFBR1, TGFBR2, THPO, TMEM165, TMEM216, TMEM38B, TMEM67, TNFRSF11A, TNFRSF11B, TNFSF11, TONSL, TP63, TRAF3IP1, TRAPPC2*, TREM2, TRIP11*, TRPS1, TRPV4, TRPV6, TTC21B, TWIST1, TYROBP, UFSP2, VDR, VIPAS39, WDR19, WDR34, WDR35, WDR60, WISP3, WNT1, WNT10B, WNT5A, WNT7A, XRCC4, XYLT1, XYLT2, ZMPSTE24 and ZSWIM6.* The following exons are not included in the panel as they are not covered with sufficient high quality sequence reads: ADAMTSL2 (NM_014694:11-19), B3GAT3 (NM_001288722:5), POLR1C (NM_001318876:9) and SHOX (NM_006883:6). This panel targets protein coding exons, exon-intron boundaries (± 20 bps) and selected noncoding, deep intronic variants (listed in Appendix 5). This panel should be used to detect single nucleotide variants and small insertions and deletions (INDELs) and copy number variations defined as single exon or larger deletions and duplications. This panel should not be used for the detection of repeat expansion disorders or diseases caused by mitochondrial DNA (mtDNA) mutations. The test does not recognize balanced translocations or complex inversions, and it may not detect low-level mosaicism.

*Some, or all, of the gene is duplicated in the genome. Read more: https://blueprintgenetics.com/pseudogene/
#The gene has suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads.
The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#).

STATEMENT

CLINICAL HISTORY

Patient is a 6-year-old child with suspected spondyloepiphyseal chondrodysplasia or pseudoachondroplasia.

CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) Comprehensive Skeletal Dysplasias and Disorders Panel identified a heterozygous missense variant *TRPV4* c.2396C>T, p.(Pro799Leu).

TRPV4 c.2396C>T, p.(Pro799Leu)

This variant is absent in the Genome Aggregation Database control population cohorts (gnomAD, n>120,000 exomes and >15,000 genomes). The affected amino acid is highly conserved in mammals as well as in evolutionarily more distant species, which suggests that this position does not tolerate variation. All in silico tools utilized predict this variant to be damaging to protein structure and function. Pro799 is the most commonly mutated codon in *TRPV4*-related metatropic dysplasia (MD) with four different amino acid substitutions reported (PMID: 21658220, 20577006). The p.(Pro799Leu) variant has been reported in multiple patients with MD, including also patients with a de novo mutation (PMID: 19232556, 20425821, 20577006, 21658220, 31808622). The p.(Pro799Leu) variant has been also reported in patients with Spondylo-epiphyseal dysplasia (SED), Maroteaux type (PMID: 20503319). The variant has been detected by several other laboratories in the context of clinical testing and submitted to ClinVar (variation ID 4998). Experimental studies have demonstrated that the Pro799Leu change results in constitutive activation of the TRPV4 protein channel (PMID: 20425821, 21573172, 26170305).

TRPV4

The *TRPV4* (MIN *605427) gene encodes a member of the OSM9-like transient receptor potential channel (OTRPC) subfamily in the transient receptor potential (TRP) superfamily of ion channels. The encoded protein is a Ca2+-permeable, nonselective cation channel that is thought to be involved in the regulation of systemic osmotic pressure. Pathogenic variants in the *TRPV4* gene are the cause of autosomal dominant *TRPV4*-associated disorders (GeneReviews NBK201366) that are grouped into neuromuscular disorders and skeletal dysplasia. Neuromuscular disorders from mildest to most severe include: Charcot-Marie-Tooth disease type 2C (CMT2C, also known as Hereditary motor and sensory neuropathy, type IIc, MIM #606071), Scapuloperoneal spinal muscular atrophy (SPSMA, MIM #181405) and congenital distal spinal muscular atrophy (CDSMA, MIM #600175). The neuromuscular disorders are characterized by a progressive peripheral neuropathy with variable combinations of laryngeal dysfunction (i.e. vocal fold paresis), respiratory dysfunction, and joint contractures. The skeletal dysplasia associated with *TRPV4* include: Familial digital arthropathy-brachydactyly (mildest) (MIM #606835), Autosomal dominant brachyolmia (MIM #113500), SED, Maroteaux type (MIM #184095) Spondylometaphyseal dysplasia, Kozlowski type (intermediate) (SMDK, MIM #184252), Parastremmatic dysplasia (MIM #168400) and Metatropic dysplasia (most severe) (MIM #156530). The skeletal dysplasia are characterized by brachydactyly. Patients with intermediate and severe skeletal dysplasia have short stature that varies from mild to severe with progressive spinal deformity and involvement of the long bones and pelvis. In the mildest of the *TRPV4*-associated disorders life span is normal, while in the most severe it is shortened. In general, specific sets of *TRPV4* pathogenic variants have been associated with either neuromuscular disorders or skeletal dysplasia. However, making precise genotype-phenotype correlations is challenging due to considerable overlap between the phenotypes. In the surveillance of *TRPV4*-related bone dysplasias, it is important to obtain flexion/extension cervical spine films before school age or general anesthesia to determine if there is atlanto-axial instability secondary to odontoid hypoplasia. Scoliosis requires yearly evaluation.

More than 80 mutations have been reported in association with *TRPV4*-associated disorders, the vast majority being missense variants (90%) (HGMD Professional 2020.1). Two *TRPV4* variants causing a frameshift (1-bp deletion and insertion) have been reported in association with intellectual disability and autism spectrum disorder (PMID: 25473036, 25621899). ClinVar reports more than 50 pathogenic or likely pathogenic missense variants in *TRPV4* detected in clinical testing (May 2020). Pro799 and Arg594 are the most commonly mutated codons in the *TRPV4* skeletal dysplasias; Pro799 in exon 15 is a hot codon for metatropic dysplasia (MD) mutations with four different amino acid substitutions reported, while Arg594 in exon 11 is a hotspot for SMDK mutations (PMID: 21658220, 20577006).

Mutation nomenclature is based on GenBank accession NM_021625.4 (*TRPV4*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

TRPV4 c.2396C>T, p.(Pro799Leu) is classified as pathogenic, based on currently available evidence supporting its disease-causing role. Disease caused by *TRPV4* variants is inherited in an autosomal dominant manner. Any offspring of the patient are at 50% risk of inheriting the variant and of being affected. *TRPV4*-related disease may be caused by a de novo variant. Genetic counseling and family member testing are recommended.

STEP	DATE
Order date	
Sample received	
Sample in analysis	
Reported	

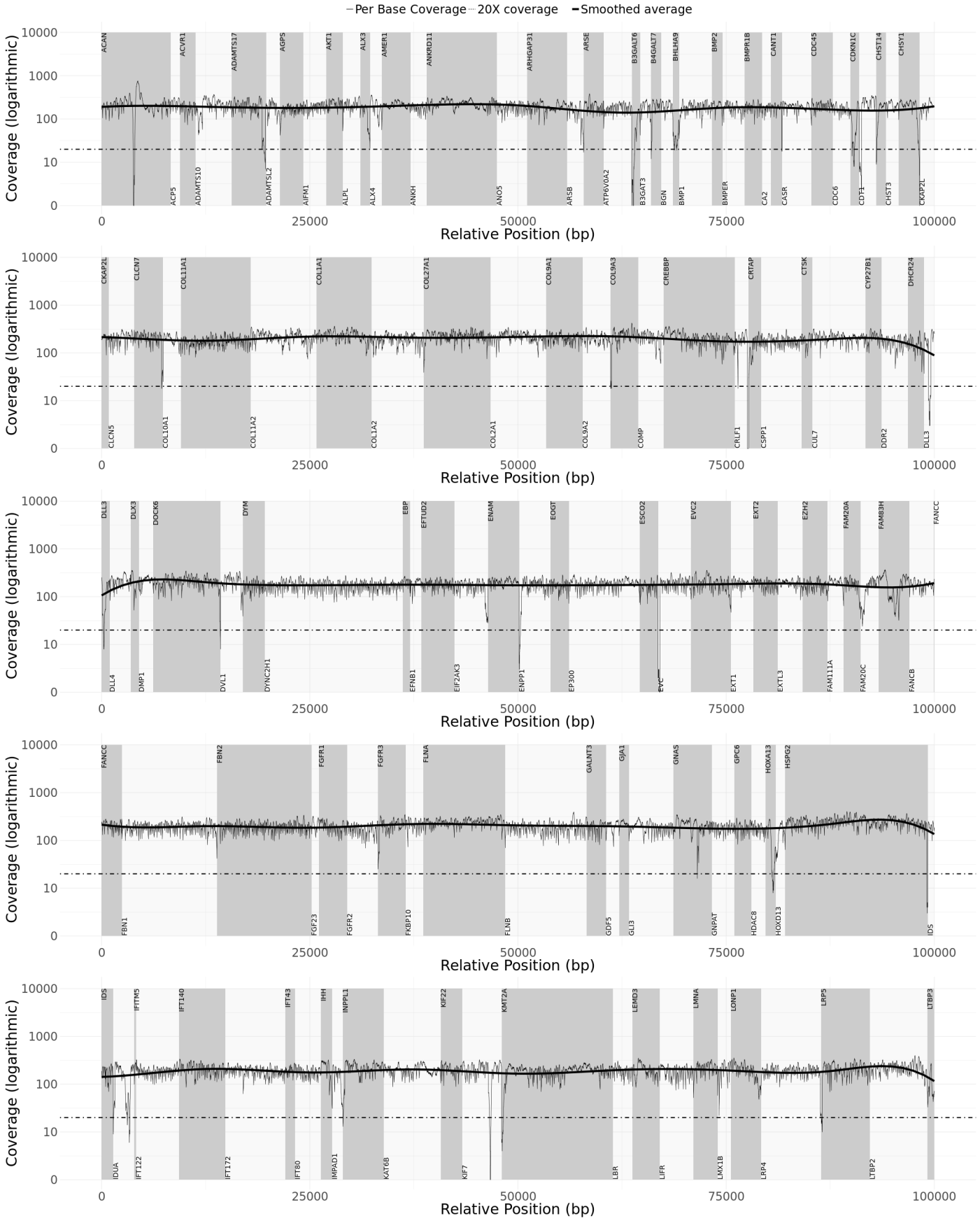
(This statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results.)

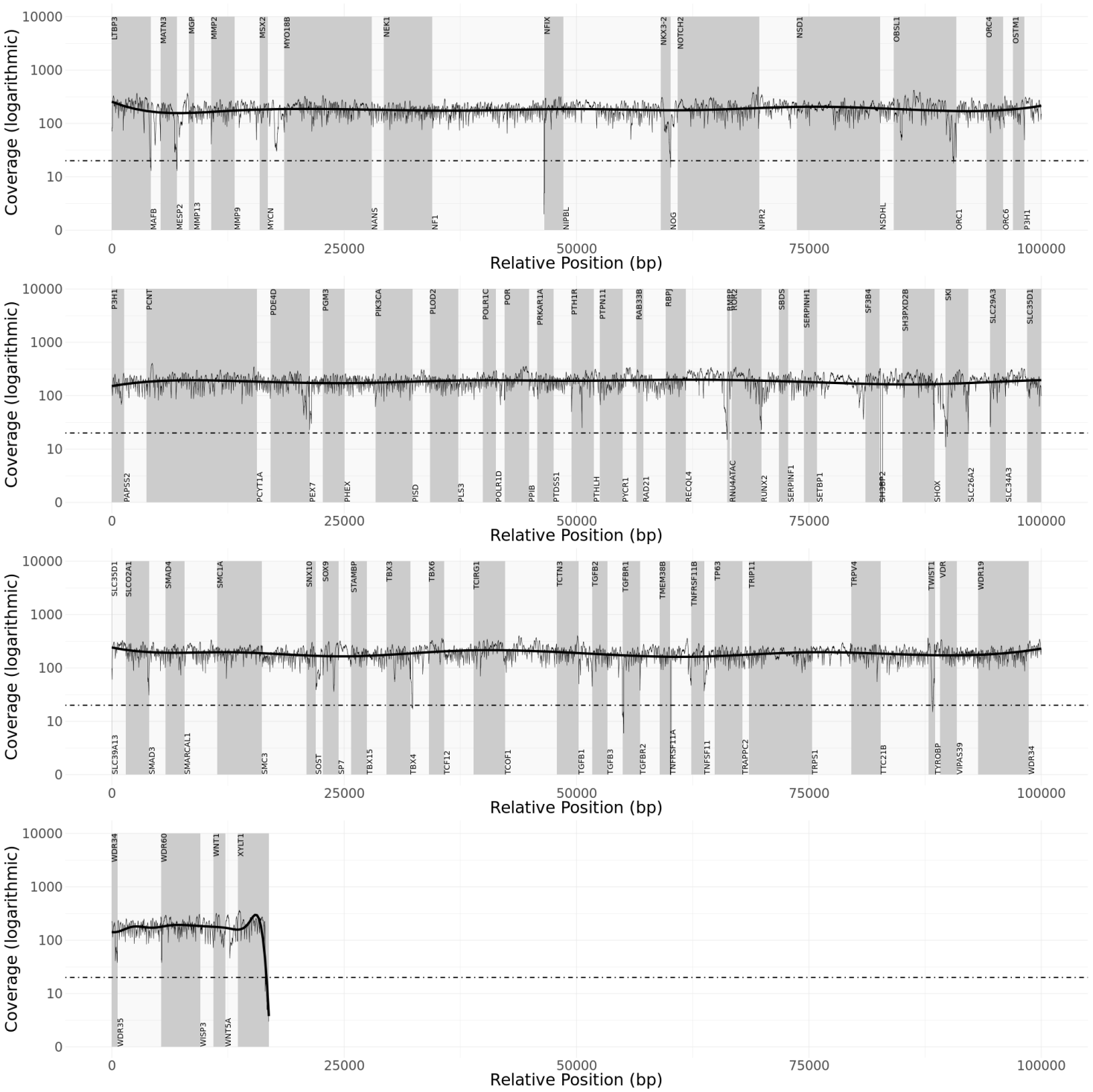
Signature

Name

Title

Readability of the coverage plot may be hindered by faxing. A high quality coverage plot can be found with the full report on nucleus.blueprintgenetics.com.

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MGP
MMP2
MSX2
MYO18B
NEK1
NFIX
NKX3-2
NOTCH2
NSD1
OBSL1
ORC4
OSTM1
MAFB
MESP2
MMP13
MMP9
MYCN
NANS
NF1
NIPBL
NOG
NPR2
NSDHL
ORC1
ORC6
P3H1
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50000
75000
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Relative Position (bp)
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PCNT
PDE4D
PGM3
PIK3CA
PLOD2
POLR1C
POR
PRKAR1A
PTH1R
PTPN11
RAB33B
RBPJ
SBDS
SERPINH1
SF3B4
SH3PXD2B
SKI
SLC29A3
SLC35D1
PAPSS2
PCYT1A
PEX7
PHEX
PISD
PLS3
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PPIB
PTDSS1
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SERPINF1
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SMX10
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TCIRG1
TCTN3
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TNFRSF11B
TP63
TRIP11
TRPV4
TWIST1
VDR
WDR19
SLC39A13
SMAD3
SMARCAL1
SMC3
SOST
SP7
TBX15
TBX4
TCF12
TCOF1
TGFB1
TGFB3
TGFBR2
TNFRSF11A
TNFSF11
TRAPPC2
TRPS1
TTC21B
TYRO8P
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50000
75000
100000
Relative Position (bp)
Coverage (logarithmic)
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1000
100
10
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WDR60
WNT1
XYLT1
WDR35
WISP3
WNT5A
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25000
50000
75000
100000
Relative Position (bp)

APPENDIX 5: SUMMARY OF THE TEST

PLUS ANALYSIS

Laboratory process: When required, the total genomic DNA was extracted from the biological sample using bead-based method. DNA quality and quantity were assessed using electrophoretic methods. After assessment of DNA quality, qualified genomic DNA sample was randomly fragmented using non-contact, isothermal sonochemistry processing. Sequencing library was prepared by ligating sequencing adapters to both ends of DNA fragments. Sequencing libraries were size-selected with bead-based method to ensure optimal template size and amplified by polymerase chain reaction (PCR). Regions of interest (exons and intronic targets) were targeted using hybridization-based target capture method. The quality of the completed sequencing library was controlled by ensuring the correct template size and quantity and to eliminate the presence of leftover primers and adapter-adapter dimers. Ready sequencing libraries that passed the quality control were sequenced using the Illumina's sequencing-by-synthesis method using paired-end sequencing (150 by 150 bases). Primary data analysis converting images into base calls and associated quality scores was carried out by the sequencing instrument using Illumina's proprietary software, generating CBCL files as the final output.
Bioinformatics and quality control: Base called raw sequencing data was transformed into FASTQ format using Illumina's software (bcl2fastq). Sequence reads of each sample were mapped to the human reference genome (GRCh37/hg19). Burrows-Wheeler Aligner (BWA-MEM) software was used for read alignment. Duplicate read marking, local realignment around indels, base quality score recalibration and variant calling were performed using GATK algorithms (Sentieon) for nDNA. Variant data for was annotated using a collection of tools (VcfAnno and VEP) with a variety of public variant databases including but not limited to gnomAD, ClinVar and HGMD. The median sequencing depth and coverage across the target regions for the tested sample were calculated based on MQ0 aligned reads. The sequencing run included in-process reference sample(s) for quality control, which passed our thresholds for sensitivity and specificity. The patient's sample was subjected to thorough quality control measures including assessments for contamination and sample mix-up. Copy number variations (CNVs), defined as single exon or larger deletions or duplications (Del/Dups), were detected from the sequence analysis data using a proprietary bioinformatics pipeline. The difference between observed and expected sequencing depth at the targeted genomic regions was calculated and regions were divided into segments with variable DNA copy number. The expected sequencing depth was obtained by using other samples processed in the same sequence analysis as a guiding reference. The sequence data was adjusted to account for the effects of varying guanine and cytosine content.
Interpretation: The clinical interpretation team assessed the pathogenicity of the identified variants by evaluating the information in the patient requisition, reviewing the relevant scientific literature and manually inspecting the sequencing data if needed. All available evidence of the identified variants was compared to classification criteria. Reporting was carried out using HGNC-approved gene nomenclature and mutation nomenclature following the HGVS guidelines. Likely benign and benign variants were not reported.
Variant classification: Our variant classification follows the Blueprint Genetics Blueprint Genetics Variant Classification Schemes modified from the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report.
Databases: The pathogenicity potential of the identified variants were assessed by considering the predicted consequence of the change, the degree of evolutionary conservation as well as the number of reference population databases and mutation databases such as, but not limited to, the gnomAD, ClinVar, HGMD Professional and Alamut Visual. In addition, the clinical relevance of any identified CNVs was evaluated by reviewing the relevant literature and databases such as Database of Genomic Variants and DECIPHER. For interpretation of mtDNA variants specific databases including e.g. Mitomap, HmtVar and 1000G were used.
Confirmation of sequence alterations: Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) were confirmed using bi-directional Sanger sequencing when they did not meet our stringent NGS quality metrics for a true positive call. In addition, prenatal case with diagnostic findings were confirmed.
Confirmation of copy number variants: CNVs (Deletions/Duplications) were confirmed using a digital PCR assay if they covered less than 10 exons (heterozygous), less than 3 exons (homo/hemizygous) or were not confirmed at least three times previously at our laboratory. Furthermore, CNVs of any size were not confirmed when the breakpoints of the call could be determined.
Analytic validation: The detection performance of this panel is expected to be in the same range as our high-quality, clinical grade NGS sequencing assay used to generate the panel data (nuclear DNA: sensitivity for SNVs 99.89%, indels 1-50 bps 99.2%, one-exon deletion 100% and five exons CNV 98.7%, and specificity >99.9% for most variant types). It does not

detect very low level mosaicism as a variant with minor allele fraction of 14.6% can be detected in 90% of the cases. Detection performance for mtDNA variants (analytic and clinical validation): sensitivity for SNVs and INDELs 100.0% (10-100% heteroplasmy level), 94.7% (5-10% heteroplasmy level), 87.3% (<5% heteroplasmy level) and for gross deletions 100.0%. Specificity is >99.9% for all.

Test restrictions: A normal result does not rule out the diagnosis of a genetic disorder since some DNA abnormalities may be undetectable by the applied technology. Test results should always be interpreted in the context of clinical findings, family history, and other relevant data. Inaccurate, or incomplete information may lead to misinterpretation of the results.

Technical limitations: This test does not detect the following: complex inversions, gene conversions, balanced translocations, repeat expansion disorders unless specifically mentioned, noncoding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see the list of noncoding variants covered by the test). Additionally, this test may not reliably detect the following: low level mosaicism, stretches of mononucleotide repeats, indels larger than 50bp, single exon deletions or duplications, and variants within pseudogene regions/duplicated segments. The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics. Laboratory error is also possible. Please see the Analytic validation above.

Regulation and accreditations: This test was developed and its performance characteristics determined by Blueprint Genetics (see Analytic validation). It has not been cleared or approved by the US Food and Drug Administration. This analysis has been performed in a CLIA-certified laboratory (#99D2092375), accredited by the College of American Pathologists (CAP #9257331) and by FINAS Finnish Accreditation Service, (laboratory no. T292), accreditation requirement SFS-EN ISO 15189:2013. All the tests are under the scope of the ISO 15189 accreditation (excluding mtDNA testing and digital PCR confirmation).

NONCODING VARIANTS COVERED BY THE PANEL:

NM_004208.3(AIFM1):c.697-44T>G
NM_004208.3(AIFM1):c.-123G>C
NM_000478.4(ALPL):c.-195C>T
NM_000478.4(ALPL):c.793-30_793-11delGGCATGTGCTGACACAGCCC
NM_054027.4(ANKH):c.-11C>T
NM_001199.3(BMP1):c.*241T>C
NM_001203.2(BMPR1B):c.-113+2T>G
NM_138793.3(CANT1):c.-342+1G>A
NM_001178065.1(CASR):c.1378-19A>C
NM_000076.2(CDKN1C):c.*5+20G>T
NM_001287.5(CLCN7):c.916+57A>T
NM_001287.5(CLCN7):c.739-18G>A
NM_080629.2(COL11A1):c.3744+437T>G
NM_080629.2(COL11A1):c.1027-24A>G
NM_080629.2(COL11A1):c.781-450T>G
NM_000088.3(COL1A1):c.2668-11T>G
NM_000088.3(COL1A1):c.2451+94G>T
NM_000088.3(COL1A1):c.2451+77C>T
NM_000088.3(COL1A1):c.2343+31T>A
NM_000088.3(COL1A1):c.1354-12G>A
NM_000088.3(COL1A1):c.1003-43_1003-32delTGCCATCTCTTC
NM_000088.3(COL1A1):c.958-18_958-15delTTCC
NM_000088.3(COL1A1):c.904-14G>A
NM_000088.3(COL1A1):c.904-15T>A
NM_000089.3(COL1A2):c.70+717A>G
NM_000089.3(COL1A2):c.226-22_226-11delTTTTTTTTTTTT
NM_001844.4(COL2A1):c.1527+135G>A
NM_004380.2(CREBBP):c.4281-11C>G
NM_006371.4(CRTAP):c.472-1021C>G
NM_000396.3(CTSK):c.244-29A>G
NM_001168370.1(CUL7):c.3897+29G>A

NM_001080463.1(DYNC2H1):c.2819-14A>G
NM_001080463.1(DYNC2H1):c.6478-16G>A
NM_004429.4(EFNB1):c.-411C>G
NM_004429.4(EFNB1):c.-95T>C/G
NM_004429.4(EFNB1):c.-95T>C
NM_004429.4(EFNB1):c.-95T>G
NM_001429.3(EP300):c.1879-12A>G
NM_001017420.2(ESCO2):c.1354-18G>A
NM_153717.2(EVC):c.940-150T>G
NM_000136.2(FANCC):c.-78-2A>G
NM_000136.2(FANCC):c.-79+1G>A
NM_000138.4(FBN1):c.8051+375G>T
NM_000138.4(FBN1):c.6872-14A>G
NM_000138.4(FBN1):c.6872-961A>G
NM_000138.4(FBN1):c.5672-87A>G
NM_000138.4(FBN1):c.5672-88A>G
NM_000138.4(FBN1):c.4211-32_4211-13delGAAGAGTAACGTGTGTTTCT
NM_000138.4(FBN1):c.2678-15C>A
NM_000138.4(FBN1):c.1589-14A>G
NM_000138.4(FBN1):c.863-26C>T
NM_001999.3(FBN2):c.3974-24A>C
NM_001999.3(FBN2):c.3974-26T>G
NM_001999.3(FBN2):c.3725-15A>G
chr10:g.123099960-123099960
NM_001110556.1(FLNA):c.6023-27_6023-16delTGACTGACAGCC
NM_080425.2(GNAS):c.2242-11A>G
NM_005529.5(HSPG2):c.1654+15G>A
NM_005529.5(HSPG2):c.574+481C>T
NM_000202.5(IDS):c.1181-15C>A
NM_006123.4(IDS):c.*57A>G
NM_000202.5(IDS):c.709-657G>A
NM_001025295.2(IFITM5):c.-14C>T
NM_052985.3(IFT122):c.2005-13T>A
NM_014714.3(IFT140):c.2577+25G>A
NM_170707.3(LMNA):c.513+45T>G
NM_170707.3(LMNA):c.937-11C>G
NM_170707.3(LMNA):c.1608+14G>A
NM_170707.3(LMNA):c.1609-12T>G
NM_001174146.1(LMX1B):c.140-37_140-21delGGCGCTGACGGCCGGGC
NM_001042492.2(NF1):c.-273A>C
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NM_001042492.2(NF1):c.889-12T>A
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NM_001042492.2(NF1):c.1392+754T>G
NM_001042492.2(NF1):c.1393-592A>G
NM_001042492.2(NF1):c.1527+1159C>T

NM_001042492.2(NF1):c.1642-449A>G
NM_001128147.2(NF1):c.*481A>G
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NM_001042492.2(NF1):c.2410-12T>G
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NM_001042492.2(NF1):c.4110+945A>G
NM_001042492.2(NF1):c.4173+278A>G
NM_001042492.2(NF1):c.4578-20_4578-18delAAG
NM_001042492.2(NF1):c.4578-14T>G
NM_001042492.2(NF1):c.5269-38A>G
NM_001042492.2(NF1):c.5610-456G>T
NM_001042492.2(NF1):c.5812+332A>G
NM_001042492.2(NF1):c.5813-279A>G
NM_001042492.2(NF1):c.6428-11T>G
NM_001042492.2(NF1):c.6642+18A>G
NM_001042492.2(NF1):c.7190-12T>A
NM_001042492.2(NF1):c.7190-11_7190-10insGTTT
NM_001042492.2(NF1):c.7971-321C>G
NM_001042492.2(NF1):c.7971-17C>G
NM_001042492.2(NF1):c.8113+25A>T
NM_133433.3(NIPBL):c.-321_-320delCCinsA
NM_133433.3(NIPBL):c.-94C>T
NM_133433.3(NIPBL):c.-79-2A>G
NM_133433.3(NIPBL):c.5329-15A>G
NM_133433.3(NIPBL):c.5710-13_5710-12delCTinsAA
NM_015922.2(NSDHL):c.*129C>T
NM_000288.3(PEX7):c.-45C>T
NM_000444.4(PHEX):c.349+11149A>T
NM_000444.4(PHEX):c.849+1268G>T
NM_000444.4(PHEX):c.1701-16T>A
NM_000444.4(PHEX):c.1768+177_1768+180dupGTAA
NM_000444.4(PHEX):c.*231A>G
NM_005032.5(PLS3):c.74-24T>A
NM_000941.2(POR):c.-5+4A>G
NM_002734.4(PRKAR1A):c.-97G>A
NM_002734.4(PRKAR1A):c.-7G>A
NM_002734.4(PRKAR1A):c.-7+1G>A
NM_002734.4(PRKAR1A):c.550-17T>A
NM_002734.4(PRKAR1A):c.709-7_709-2delTTTTTA
NM_000316.2(PTH1R):c.544-25_544-23delCTG
NM_000316.2(PTH1R):c.1049+29C>T
NM_002834.3(PTPN11):c.934-59T>A
chr9:g.35658026-35658026
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chr9:g.35658029-35658029
chr9:g.35658029-35658029
chr9:g.35658032-35658032
NM_002615.5(SERPINF1):c.-9+2dupT
NM_002615.5(SERPINF1):c.439+34C>T
NM_002615.5(SERPINF1):c.440-40_440-38delTCG
NM_002615.5(SERPINF1):c.787-617G>A
NM_000451.3(SHOX):c.-645_-644insGTT
NM_000451.3(SHOX):c.-645_-644insGTT
NM_000451.3(SHOX):c.-432-3C>A
NM_000451.3(SHOX):c.-65C>A
NM_000112.3(SLC26A2):c.-26+2T>C
NM_018344.5(SLC29A3):c.*413G>A
NM_000346.3(SOX9):c.-185G>A
NM_006463.4(STAMBP):c.1005+358A>G
chr12:g.115122148-115122148
NM_004608.3(TBX6):c.*21C>T
NM_207036.1(TCF12):c.1468-20T>A
NM_006019.3(TCIRG1):c.-5+1G>C/T
NM_006019.3(TCIRG1):c.-5+1G>C
NM_006019.3(TCIRG1):c.-5+1G>T
NM_006019.3(TCIRG1):c.1887+132T>C
NM_006019.3(TCIRG1):c.1887+142T>A
NM_006019.3(TCIRG1):c.1887+146G>A
NM_006019.3(TCIRG1):c.1887+149C>T
NM_003239.2(TGFB3):c.*495C>T
NM_003239.2(TGFB3):c.-30G>A
NM_001024847.2(TGFBR2):c.-59C>T
NM_014112.2(TRPS1):c.2824-23T>G
NM_000474.3(TWIST1):c.-255G>A
NM_000474.3(TWIST1):c.-263C>A
NM_001006657.1(WDR35):c.1434-684G>T
NM_001006657.1(WDR35):c.143-18T>A
NM_198239.1(WISP3):c.103-763G>T
NM_198239.1(WISP3):c.643+27C>G

GLOSSARY OF USED ABBREVIATIONS:

AD = autosomal dominant
AF = allele fraction (proportion of reads with mutated DNA / all reads)
AR = autosomal recessive
CNV = Copy Number Variation, eg, one exon or multiexon deletion or duplication
gnomAD = genome Aggregation Database (reference population database; >138,600 individuals)
gnomAD AC/AN = allele count/allele number in the genome Aggregation Database (gnomAD)
HEM = hemizygous
HET = heterozygous
HOM = homozygous
ID = rsID in dbSNP
MT = Mitochondria

MutationTaster = *in silico* prediction tools used to evaluate the significance of identified amino acid changes.
Nomenclature = HGVS nomenclature for a variant in the nucleotide and the predicted effect of a variant in the protein level
OMIM = Online Mendelian Inheritance in Man®
PolyPhen = *in silico* prediction tool used to evaluate the significance of amino acid changes.
POS = genomic position of the variant in the format of chromosome:position
SIFT = *in silico* prediction tool used to evaluate the significance of amino acid changes.