*Sample report as of July 7, 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***

Ataxia Panel Plus

REFERRING HEALTHCARE PROFESSIONAL

NAME	HOSPITAL

PATIENT

NAME	DOB	AGE	GENDER	ORDER ID
		56		

CUSTOMER SAMPLE ID

PRIMARY SAMPLE TYPE	SAMPLE COLLECTION DATE
DNA	

SUMMARY OF RESULTS

PRIMARY FINDINGS

The patient is heterozygous for *CACNA1A* c.3992+1G>A, which is pathogenic.

PRIMARY FINDINGS: SEQUENCE ALTERATIONS

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
CACNA1A	NM_001127221.1	c.3992+1G>A	HET	splice_donor_variant	AD	**Pathogenic**
	ID	**ASSEMBLY**	**POS**	**REF/ALT**		
		GRCh37/hg19	19:13386663	C/T		
	gnomAD AC/AN	**POLYPHEN**	**SIFT**	**MUTTASTER**	**PHENOTYPE**	
	0/0	N/A	N/A	disease causing	Epileptic encephalopathy, early infantile, 42, Episodic ataxia, Migraine, familial hemiplegic, Spinocerebellar ataxia 6	

SEQUENCING PERFORMANCE METRICS

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Ataxia Panel	220	3566	698528	697826	212	99.9

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 1000X	MEDIAN COVERAGE	PERCENT > 1000X
Mitochondrial genome	37	-	15358	15358	10970	100

TARGET REGION AND GENE LIST

The Blueprint Genetics Ataxia Panel Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: *AARS2*, *ABCA2*, *ABCB7*, *ABCD1**, *ABHD12*, *ACO2*, *ADCK3*, *ADPRHL2*, *AFG3L2**, *AGTPBP1*, *AHI1*, *ALDH5A1*, *ANO10*, *APTX*, *ARL13B*, *ARL6*, *ATCAY*, *ATM*, *ATP13A2*, *ATP1A3*, *ATP2B3*, *ATP7B*, *ATP8A2*, *AUH*, BBS1, BBS10,

BBS12, *BBS2*, *BBS4*, *BBS5*, *BBS7*, *BBS9*, *BEAN1#*, *C10ORF2*, *C12ORF4*, *C5ORF42*, *CA8*, *CACNA1A*, *CACNA1G*, *CACNA2D2*, *CACNB4*, *CAMTA1*, *CAPN1*, *CASK*, *CC2D2A#*, *CCDC88C*, *CEP290**, *CEP41*, *CHCHD10*, *CLCN2*, *CLN5*, *CLN6*, *CLN8*, *CLPB*, *CLPP*, *COA7*, *COASY*, *COQ2*, *COQ4*, *COX20*, *CP**, *CSTB*, *CTBP1*, *CTDP1*, *CTSA*, *CWF19L1*, *CYP27A1*, *CYP2U1*, *CYP7B1*, *DHPS#*, *DNAJC19*, *DNAJC5*, *DNMT1*, *DOCK3*, *EBF3*, *EEF2*, *ELOVL4*, *ELOVL5*, *FA2H*, *FBXL4*, *FDXR*, *FGF14*, *FLVCR1*, *FMR1*, *FXN**, *GBA2*, *GFAP*, *GOSR2**, *GRID2*, *GRM1*, *GSS*, *HARS2*, *HEXB*, *HIBCH*, *INPP5E*, *IRF2BPL*, *ITM2B*, *ITPR1*, *KCNA1*, *KCNC3*, *KCND3*, *KCNJ10*, *KIF1C**, *KIF5A*, *KIF7*, *LAMA1*, *LARS2*, *LMNB1*, *LRPPRC*, *LRSAM1*, *MARS2*, *MECR*, *MGME1*, *MKKS*, *MKS1*, *MME*, *MRE11A*, *MSTO1#**, *MT-ATP6*, *MT-ATP8*, *MT-CO1*, *MT-CO2*, *MT-CO3*, *MT-CYB*, *MT-ND1*, *MT-ND2*, *MT-ND3*, *MT-ND4*, *MT-ND4L*, *MT-ND5*, *MT-ND6*, *MT-RNR1*, *MT-RNR2*, *MT-TA*, *MT-TC*, *MT-TD*, *MT-TE*, *MT-TF*, *MT-TG*, *MT-TH*, *MT-TI*, *MT-TK*, *MT-TL1*, *MT-TL2*, *MT-TM*, *MT-TN*, *MT-TP*, *MT-TQ*, *MT-TR*, *MT-TS1*, *MT-TS2*, *MT-TT*, *MT-TV*, *MT´-TW*, *MT-TY*, *MTFMT*, *MTPAP*, *MTTP*, *NDUFAF6*, *NDUFS2*, *NDUFS4*, *NDUFS7*, *NDUFS8*, *NDUFV1*, *NKX2-1*, *NKX6-2*, *NOL3*, *NPC1*, *NPC2*, *NPHP1*, *NUBPL*, *OFD1*, *OPA1*, *OPHN1*, *PANK2*, *PAX6*, *PDYN*, *PEX10*, *PEX16*, *PEX2*, *PEX3*, *PEX6*, *PEX7*, *PHYH*, *PMM2*, *PNKD*, *PNKP*, *PNPLA6*, *POLG*, *PRKCG*, *PRRT2*, *PUM1*, *RNF216**, *RORA*, *RPGRIP1L#*, *RUBCN*, *SACS*, *SAMD9L*, *SCYL1*, *SERAC1*, *SETX*, *SH3TC2*, *SIL1*, *SLC17A5*, *SLC1A3*, *SLC20A2*, *SLC25A15**, *SLC25A46*, *SLC2A1*, *SLC52A2*, *SLC9A1*, *SLC9A6*, *SNX14*, *SPG11*, *SPG20*, *SPG7*, *SPTBN2*, *SQSTM1*, *STUB1*, *STXBP1*, *SUOX*, *SYNE1*, *SYT14#**, *TCTN1#*, *TCTN2*, *TCTN3*, *TDP1*, *TDP2*, *TGM6*, *TMEM138*, *TMEM216*, *TMEM231*, *TMEM237*, *TMEM240*, *TMEM67*, *TPP1*, *TRAPPC11*, *TRIM32*, *TTBK2*, *TTC19*, *TTC8*, *TTPA*, *TUBB4A**, *UBA5**, *UBTF*, *UCHL1*, *VAMP1*, *VLDLR*, *VPS13D*, *VWA3B*, *WDPCP*, *WDR81*, *WFS1*, *WWOX*, *XRCC1*, *ZFYVE26* and *ZNF423*. The following exons are not included in the panel as they are not covered with sufficient high quality sequence reads: BEAN1 (NM_001178020:5), CC2D2A (NM_020785:7), DHPS (NM_001206974:1), RPGRIP1L (NM_015272:23), SYT14 (NM_001146261:3) and TCTN1 (NM_001173976:2;NM_024549:6).

*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 a mapping quality score of 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 56-year-old individual with ataxia, dysarthria attacks since teenager. Dizzy spells. Intermittent, affects gait, dysarthria (slurred words), diplopia, to the extent that the patient can't stand. Before, this happened quite regular every 3-4 weeks/occasionally with headache. Episodes last 15-60 mins but the frequency decreased. The patient gets them at work usually first half hour, stress related. Episodes resolve CNS - slowed horizontal saccades with abnormal HIJ to the right (catch up saccades). Slight DDK, poor past point and clumsiness on left. Tone, reflex, power normal in upper limbs. Lower limbs gait and tandem walk ok. Family history: Mother (dizzy when stressed), son affected - (dizzy occasionally, especially when unwell), affected brother - diagnosed early adulthood (dizzy, no headaches), brother's daughter - affected (dizzy, no headaches), and affected sister - milder symptoms (dizzy, vomits, sleepy), and one asymptomatic sister.

CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) Ataxia Panel identified a heterozygous splice donor variant *CACNA1A* c.3992+1G>A.

CACNA1A c.3992+1G>A

This variant is absent in gnomAD, a large reference population database (n>120,000 exomes and >15,000 genomes) which aims to exclude individuals with severe pediatric disease. The variant substitutes a nucleotide within a canonical splice donor site and is therefore likely to lead to abnormal splicing. Loss of *CACNA1A* function is an established disease mechanism, and other truncating variants in the gene have been described in patients with phenotypes consistent with *CACNA1A*-related disease (HGMD). The variant has been seen in a heterozygous state in four family members with episodic ataxia (PMID: 8898206), as well as in a mother and her son, both with episodic ataxia (PMID: 22942164). The variant has been submitted to ClinVar (variation ID 8492).

CACNA1A

The *CACNA1A* gene encodes encodes the transmembrane pore-forming subunit of the P/Q-type or CaV2.1 voltage-gated calcium channel (VGCC) (PMID: 16595610). Voltage-dependent calcium channels mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, and gene expression. Calcium channels are multisubunit complexes composed of alpha-1, beta, alpha-2/delta, and gamma subunits. The channel activity is directed by the pore-forming alpha-1 subunit, whereas, the others act as auxiliary subunits regulating this activity. The distinctive properties of the calcium channel types are related primarily to the expression of a variety of alpha-1 isoforms, alpha-1A, B, C, D, E, and S. The *CACNA1A* (MIM **601011*) gene on chromosome 19p13.13 encodes the alpha-1A subunit, which is predominantly expressed in neuronal tissue.

Pathogenic variants in this gene are associated with autosomal dominant neurologic disorders. Familial hemiplegic migraine (FHM; MIM #*141500*) is a rare variety of migraine with aura characterized by the presence of a motor weakness during the aura (MIM #*157300*). Severe attacks may occur in FHM with prolonged hemiplegia, confusion, coma, fever and seizures. The clinical spectrum also includes permanent cerebellar signs (nystagmus, ataxia, dysarthria) and less frequently various types of seizures and intellectual deficit. The prevalence of FHM is 1/10,000 (*ORPHA569*). Episodic ataxia (EA) is a genetically heterogeneous neurologic condition characterized by spells of incoordination and imbalance, often associated with progressive ataxia. Episodic ataxia 2 (EA2; MIM #*108500*; GeneReviews *NBK1501*), caused by *CACNA1A* mutations is the most common form of EA. Its prevalence has been estimated at lower than 1/100,000. About 50% of individuals with EA2 have migraine headaches. Onset is typically in childhood or early adolescence (age range 2-32 years). Spinocerebellar ataxia 6 (SCA6; MIM #*183086*) is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. The most common mutation is an expanded CAG(n) repeat in exon 47 of the *CACNA1A* gene. Normal alleles contain 4 to 18 repeats, whereas pathogenic alleles contain 19 to 33 repeats.

Early infantile epileptic encephalopathy-42 (EIEE42; MIM #*617106*) is also caused by *CACNA1A* variants. Targeted sequencing in an unsolved cohort of individuals with a diverse range of epileptic encephalopathies revealed 4/531 patients with pathogenic missense variants in *CACNA1A* (PMID 27476654). All except one of them, including one patient from an earlier cohort, had onset of seizures during the first day of life, and subsequent seizures typically included focal, tonic and tonic-clonic seizures and occasional myoclonic seizures accompanied by moderate to severe intellectual disability. Missense variants were clustered in the transmembrane domains of the protein. Jiang et al (2019) also described four patients with severe developmental epileptic encephalopathies and *de novo* missense variants in *CACNA1A* (PMID: 31468518). The patients presented with mixed seizure disorders, global DD, moderate-severe ID, and signs of cerebellar dysfunction (ataxia, tremors). Three of the *CACNA1A* variants were localized on the cytoplasmic side of the S4-S6 segments of the channel's transmembrane domains, and one variant was positioned in the transmembrane S5 segment of Domain III, towards the extracellular milieu. Functional studies indicated loss and gain of function effects for these variants, respectively (PMID: 31468518). In children with *CACNA1A* mutations, eye movement disorder has been found to be a presenting feature in conjunction with developmental delay, cerebellar atrophy, FHM, ataxia and seizures (PMID: *26814174*); also hypertonia and contractures have been reported in association with EIEE42 (MIM #*617106*).

Loss-of-function *CACNA1A* variants classically present as episodic ataxia EA2 (PMID: 17575281), while gain-of-function variants have been associated with FHM1 (PMID: 8898206). However, phenotypic heterogeneity has been reported in association with loss-of-function variants including cognitive and epileptic manifestations caused by the loss of CaV2.1 channel function (PMID: 25735478). Damaj et al. (2015) reported loss-of-function variants in *CACNA1A* in 16 unrelated individuals presenting with a spectrum of cognitive impairment including intellectual deficiency, executive dysfunction, ADHD and/or autism, as well as childhood-onset epileptic encephalopathy with refractory absence epilepsy, febrile seizures, downbeat nystagmus and episodic ataxia (PMID: 25735478). Both gain and loss of function *de novo* missense variants have been reported in severe epileptic encephalopathies (PMID: 27476654, 31468518).

Currently, >260 disease-causing variants in *CACNA1A* are reported in the Human Gene Mutation Database (HGMD Professional 2021.4). This includes missense variants (49%), nonsense variants (13%), splice variants (6%), small deletions (13%), small insertions (6%), gross deletions (11%), complex rearrangements (0.5%) and repeat variations (2.5%). These variants are mainly implicated in ataxia phenotypes, and most of these in episodic ataxia (136 disease-causing variants reported in HGMD).

Mutation nomenclature is based on GenBank accession NM_001127221.1 (*CACNA1A*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

CACNA1A c.3992+1G>A, is classified as pathogenic, based on the established association between the gene and the

patient’s phenotype, the variant's rarity in control populations, identification of the variant in 7 individuals with the same phenotype, moderate proof of segregation, and variant type (consensus splice site). Disease caused by *CACNA1A* 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. *CACNA1A*-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	

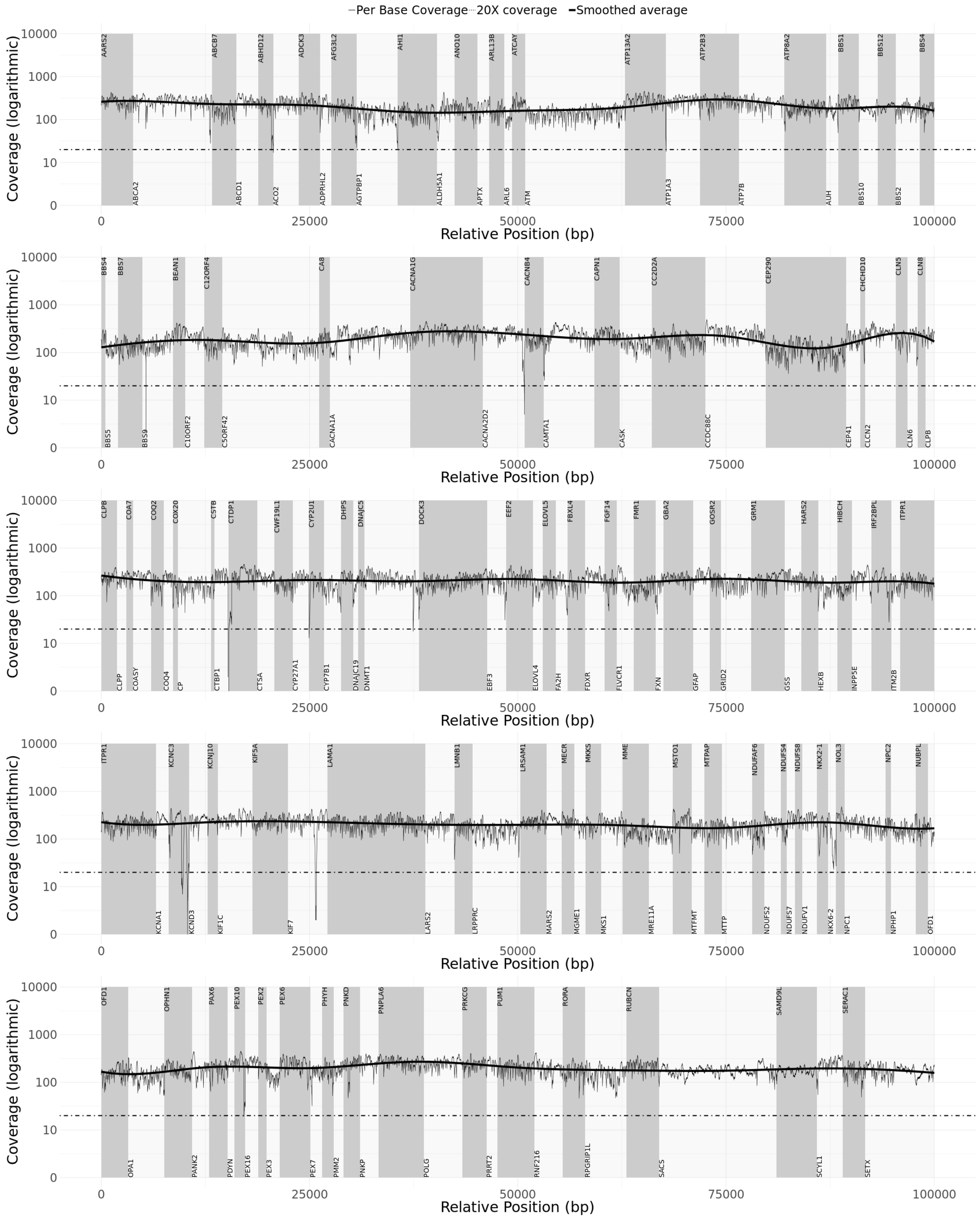
This statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results:

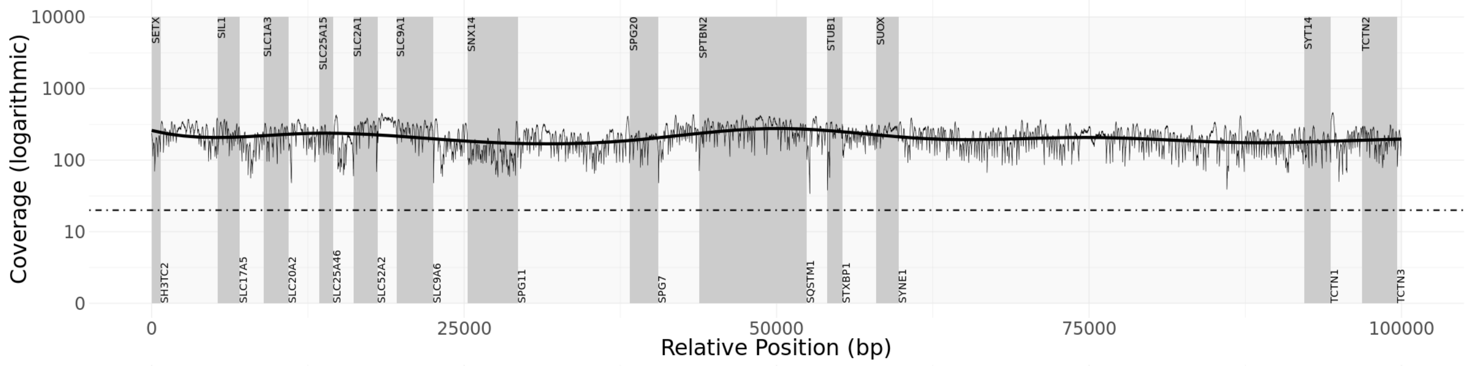
Signature

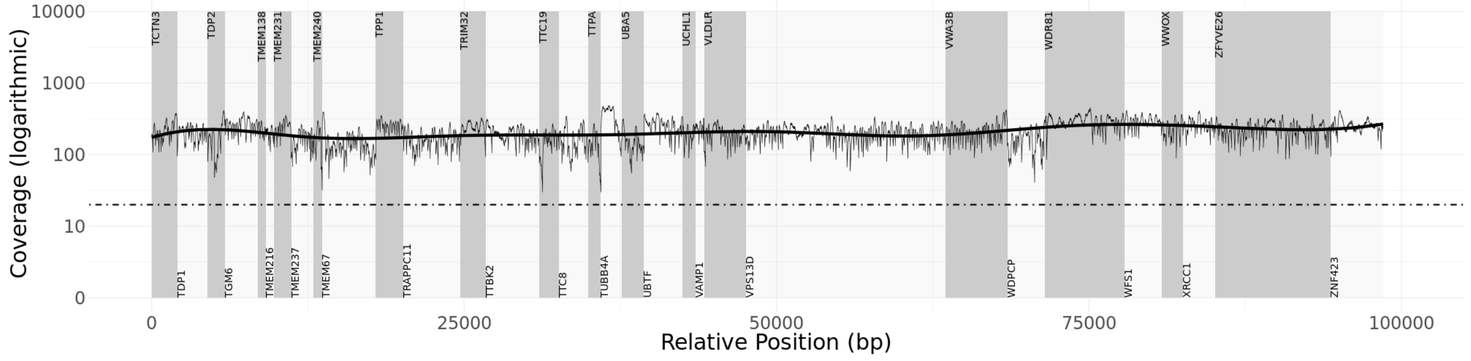
Name

Title

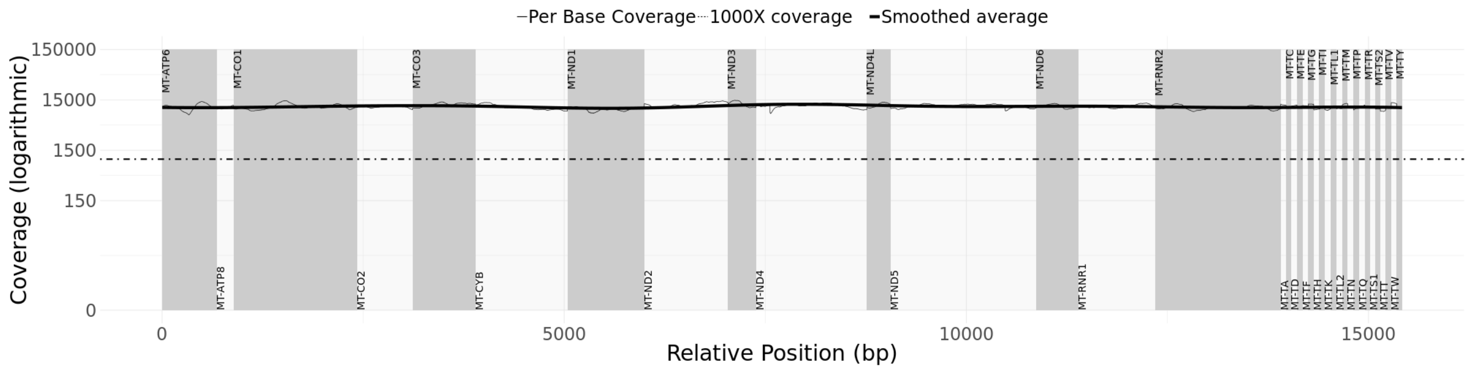
Readability of the coverage plot may be hindered by faxing. A high quality coverage plot can be found with the full report on nucleus.blueprintgenetics.com.







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.



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 at Blueprint Genetics. 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.These steps were performed at Blueprint Genetics.
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. Bioinformatics and quality control processes were performed by Blueprint Genetics.
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. The interpretation was performed at Blueprint Genetics.
Variant classification: Our variant classification follows the 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. The classification and interpretation of the variant(s) identified reflect the current state of Blueprint Genetics’ understanding at the time of this report. Variant classification and interpretation are subject to professional judgment, and may change for a variety of reasons, including but not limited to, updates in classification guidelines and availability of additional scientific and clinical information. This test result should be used in conjunction with the health care provider's clinical evaluation. Inquiry regarding potential changes to the classification of the variant is strongly recommended prior to making any future clinical decision. For questions regarding variant classification updates, please contact us at support@blueprintgenetics.com
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.The confirmation of sequence alterations was performed at Blueprint Genetics.
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.The confirmation of copy number variants was performed at Blueprint Genetics.
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, non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see the list of non-coding 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).

PERFORMING SITE:

BLUEPRINT GENETICS OY, KEILARANTA 16 A-B, 02150 ESPOO, FINLAND Laboratory Director: MD, PhD, CLIA: 99D2092375

NON-CODING VARIANTS COVERED BY THE PANEL:

NM_006516.2(*SLC2A1*):c.680-11G>A, NM_006516.2(*SLC2A1*):c.-107G>A, NM_002241.4(*KCNJ10*):c.-1+1G>T, NM_020247.4(*ADCK3*):c.*72dupG, NM_000391.3(*TPP1*):c.887-18A>G, NM_000280.4(*PAX6*):c.*125537G>T, NM_000280.4(*PAX6*):c.1033-42_1033-26delATGTGTTCCTCAGTAACinsG, NM_000280.4(*PAX6*):c.524-41T>G, NM_000280.4(*PAX6*):c.142-14C>G, NM_000280.4(*PAX6*):c.-52+5delG, NM_000280.4(*PAX6*):c.-52+3_-52+6delAAGTinsTG, NM_000280.4(*PAX6*):c.-52+3_-52+4delAA, NM_000280.4(*PAX6*):c.-52+1delG, NM_000280.4(*PAX6*):c.-52+1G>A, NM_000280.4(*PAX6*):c.-115_-112delACTA, NM_000280.4(*PAX6*):c.-118_-117delTT, NM_000280.4(*PAX6*):c.-125dupG, NM_000280.4(*PAX6*):c.-128-1G>T, NM_000280.4(*PAX6*):c.-128-2delA, NM_000280.4(*PAX6*):c.-138_-129+3delCCTCATAAAGGTG, NM_000280.4(*PAX6*):c.-129+2T>A, NM_000280.4(*PAX6*):c.-129+1G>A, NM_024649.4(*BBS1*):c.951+58C>T, NM_000051.3(*ATM*):c.-174A>G, NM_000051.3(*ATM*):c.-31+595G>A, NM_000051.3(*ATM*):c.-30-1G>T, NM_000051.3(*ATM*):c.2639-384A>G, NM_000051.3(*ATM*):c.2839-579_2839-576delAAGT, NM_000051.3(*ATM*):c.3403-12T>A, NM_000051.3(*ATM*):c.3994-159A>G, NM_000051.3(*ATM*):c.4612-12A>G, NM_000051.3(*ATM*):c.5763-1050A>G, NM_000051.3(*ATM*):c.8418+681A>G, NM_025114.3(*CEP290*):c.6012-12T>A, NM_025114.3(*CEP290*):c.2991+1655A>G, NM_025114.3(*CEP290*):c.1910-11T>G, NM_025114.3(*CEP290*):c.103-18_103-13delGCTTTT, NM_000053.3(*ATP7B*):c.3061-12T>A, NM_000053.3(*ATP7B*):c.-78A>C, NM_000053.3(*ATP7B*):c.-123C>A, NM_000053.3(*ATP7B*):c.-128_-124delAGCCG, NM_000053.3(*ATP7B*):c.-133A>C, NM_000053.3(*ATP7B*):c.-210A>T, chr13:g.52585894-52585894, chr13:g.52585897-52585897, NM_000053.3(*ATP7B*):c.-442G>A, NM_017882.2(*CLN6*):c.297+113G>C, NM_033028.4(*BBS4*):c.77-216delA, NM_005861.2(*STUB1*):c.*240T>C, chr16:g.8891573-8891573, NM_000303.2(*PMM2*):c.179-25A>G,

NM_000303.2(*PMM2*):c.640-15479C>T, NM_000303.2(*PMM2*):c.640-23A>G, NM_001256443.1(*PRRT2*):c.*345G>A, NM_001077416.2(*TMEM231*):c.824-11T>C, NM_017775.3(*TTC19*):c.-42G>T, NM_000271.4(*NPC1*):c.1554-1009G>A, NM_000271.4(*NPC1*):c.882-28A>G/T, NM_000271.4(*NPC1*):c.882-28A>G, NM_000271.4(*NPC1*):c.882-28A>T, NM_001127221.1(*CACNA1A*):c.*1500_*1504dupCTTTT, NM_001127221.1(*CACNA1A*):c.5404-13G>A, chr19:g.13617793-13617793, NM_007254.3(*PNKP*):c.1387-33_1386+49delCCTCCTCCCCTGACCCC, NM_152384.2(*BBS5*):c.619-27T>G, NM_153638.2(*PANK2*):c.*40G>C, NM_000178.2(*GSS*):c.129+1663A>G, NM_000178.2(*GSS*):c.-9+5G>A, NM_130837.2(*OPA1*):c.449-34dupA, NM_130837.2(*OPA1*):c.2179-40G>C, NM_006005.3(*WFS1*):c.-43G>T, NM_000253.2(*MTTP*):c.619-5_619-2delTTTA, NM_000253.2(*MTTP*):c.1237-28A>G, NM_000521.3(*HEXB*):c.1243-17A>G, NM_000521.3(*HEXB*):c.1509-26G>A, NM_000521.3(*HEXB*):c.1613+15_1613+18dupAAGT, NM_000521.3(*HEXB*):c.1614-16_1615dupTTCATGTTATCTACAGAC, NM_000521.3(*HEXB*):c.1614-14C>A, NM_022464.4(*SIL1*):c.1030-18G>A, NM_024577.3(*SH3TC2*):c.2873-14T>A, NM_024577.3(*SH3TC2*):c.386-15G>A, NM_000287.3(*PEX6*):c.2301-15C>G, NM_000287.3(*PEX6*):c.2300+28G>A, NM_000288.3(*PEX7*):c.-45C>T, NM_182961.3(*SYNE1*):c.16237-13C>G, NM_182961.3(*SYNE1*):c.15918-12A>G, NM_032861.3(*SERAC1*):c.92-165C>T, NM_032861.3(*SERAC1*):c.92-239G>C, NM_006749.4(*SLC20A2*):c.289+937G>A, NM_152416.3(*NDUFAF6*):c.298-768T>C, NM_152416.3(*NDUFAF6*):c.420+784C>T, NM_024531.4(*SLC52A2*):c.-110-1G>A, NM_003611.2(*OFD1*):c.935+706A>G, NM_003611.2(*OFD1*):c.1130-22_1130-19delAATT, NM_003611.2(*OFD1*):c.1130-20_1130-16delTTGGT, NM_002024.5(*FMR1*):c.*746T>C

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 e.g. 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.