Blueprint Genetics

*Sample report as of June 14th, 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 Epilepsy Panel Plus

REFERRING HEALTHCARE PROFESSIONAL

NAME	HOSPITAL

PATIENT

NAME	DOB	AGE	GENDER	ORDER ID
		0	Female	

PRIMARY SAMPLE TYPE	SAMPLE COLLECTION DATE	CUSTOMER SAMPLE ID
DNA		

SUMMARY OF RESULTS

TEST RESULTS

The patient is heterozygous for *DDC* c.476C>T, p.(Ala159Val), which is likely pathogenic.
The patient is heterozygous for *DDC* c.1337T>C, p.(Leu446Pro), which is a variant of uncertain significance (VUS).

Del/Dup (CNV) analysis did not detect any known disease-causing or rare copy number variants which could explain the patient’s reported phenotype.

PRIMARY VARIANT TABLE: SEQUENCE ALTERATIONS

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
DDC	NM_000790.3	c.476C>T, p.(Ala159Val)	HET	missense_variant	AR	**Likely pathogenic**
	ID	**ASSEMBLY**	**POS**	**REF/ALT**		
		GRCh37/hg19	7:50597000	G/A		
	gnomAD AC/AN	**POLYPHEN**	**SIFT**	**MUTTASTER**	**PHENOTYPE**	
	3/277124	probably damaging	deleterious	disease causing	Aromatic l-amino acid decarboxylase deficiency	
GENE	**TRANSCRIPT**	**NOMENCLATURE**	**GENOTYPE**	**CONSEQUENCE**	**INHERITANCE**	**CLASSIFICATION**
DDC	NM_000790.3	c.1337T>C, p.(Leu446Pro)	HET	missense_variant	AR	**Variant of uncertain significance**
	ID	**ASSEMBLY**	**POS**	**REF/ALT**		
		GRCh37/hg19	7:50531035	A/G		
	gnomAD AC/AN	**POLYPHEN**	**SIFT**	**MUTTASTER**	**PHENOTYPE**	
	1/246242	probably damaging	deleterious	disease causing	Aromatic l-amino acid decarboxylase deficiency	

SEQUENCING PERFORMANCE METRICS

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Comprehensive Epilepsy Panel	474	7147	1398564	1391317	181	99.48

TARGET REGION AND GENE LIST

The Blueprint Genetics Comprehensive Epilepsy Flex Panel Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: *AARS, ABAT, ABCA2, ABCD1**, *ACTL6B, ACY1, ADAM22, ADAR, ADNP, ADPRHL2, ADSL, AFG3L2**, *AGA, AIFM1, AIMP1, ALDH3A2, ALDH5A1, ALDH7A1, ALG13, ALG6, ALKBH8, AMACR, AMT, ANKRD11**, *AP2M1, AP3B2, AP4B1, AP4E1, AP4M1, AP4S1#**, *APOPT1, ARG1, ARHGEF9, ARID1B, ARSA, ARV1#, ARX#, ASAH1, ASNS**, *ASPA, ASXL3, ATAD1**, *ATP13A2, ATP1A1, ATP1A2, ATP1A3, ATP6V1A, ATRX, BCKDK, BRAT1, BTD, C12ORF57, CACNA1A, CACNA1B, CACNA1D, CACNA1E, CACNA1G, CACNA1H, CACNA2D2, CACNB4, CAD, CAMK2B, CARS2, CASK, CASR, CC2D1A, CDK9, CDKL5, CERS1#, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN2, CLCN4, CLN3, CLN5, CLN6, CLN8, CLTC, CNKSR2, CNPY3, CNTNAP2, COA7, COL4A1, COL4A2, COL4A3BP, COQ2, COQ4, COX15, COX6B1, CPLX1, CPT2, CSF1R, CSNK2B, CSTB, CTC1, CTSD, CTSF, CUL4B, CUX2, CYFIP2, CYP27A1, D2HGDH, DARS, DARS2, DCX, DDC, DDX3X, DEAF1, DEGS1#, DENND5A, DEPDC5, DHDDS, DHFR**, *DHPS#, DIAPH1, DMXL2, DNAJC5, DNM1**, *DNM1L, DOCK7, DOLK, DPAGT1, DPM1, DPM2, DPYD, DPYS, DYNC1H1, DYRK1A, EARS2, ECHS1, ECM1, EEF1A2, EFHC1, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EIF3F, EML1, EPM2A, EPRS, ETFA, ETFB, ETFDH, ETHE1, FA2H, FAM126A, FAR1**, *FARS2, FDFT1, FDX1L, FGF12, FH, FKTN, FLNA, FOLR1, FOXG1, FOXRED1, FRRS1L, FUT8, GABBR2, GABRA1, GABRB1, GABRB2, GABRB3, GABRG2#, GALC, GAMT, GCDH, GCH1, GCSH, GFAP, GFM1, GFM2, GJC2, GLB1, GLDC, GLRB, GLS, GLUD1**, *GNAO1, GNB1, GNE, GOLGA2, GOSR2**, *GPAA1, GPHN, GRIA3, GRIA4, GRIK2, GRIN1, GRIN2A, GRIN2B, GRIN2D, GRN, GTPBP3, GUF1, HACE1, HCN1, HCN2#**, *HECW2, HEPACAM, HIBCH, HNRNPU, HSD17B10, HSPD1**, *HTRA1, HTT, IBA57, ICK, IER3IP1, IFIH1, IQSEC2, IRF2BPL, ITPA, KCNA1, KCNA2, KCNB1, KCNC1, KCNH1, KCNJ10, KCNMA1, KCNQ2, KCNQ3, KCNQ5, KCNT1, KCNT2, KCTD3, KCTD7, KDM5C, KIAA1715, KIAA2022, KIF1A, KIF5A, KIF5C, KMT2E, L2HGDH, LGI1, LIAS, LMNB1, LMNB2, LRPPRC, LYRM7, MACF1, MAGI2, MARS2, MBD5, MBOAT7, MDH2, MECP2, MED12, MED17, MEF2C, MFSD8, MIPEP**, *MLC1, MOCS1**, *MOCS2, MRPL44, 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, MTHFR, MTOR, NACC1, NBEA**, *NDST1, NDUFAF3, NDUFAF5, NDUFAF6, NDUFS2, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NECAP1**, *NEU1, NEUROD2, NFU1, NHLRC1, NKX6-2, NOTCH3, NPRL2, NPRL3, NR2F1, NRXN1, NSDHL, NT5C2, NTRK2, NUBPL, NUS1**, *OCLN#**, *OFD1, OPHN1, P4HTM, PACS1, PACS2, PAFAH1B1, PARS2, PCDH19, PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26, PGK1, PHACTR1, PHF6, PIGA**, *PIGB, PIGC**, *PIGG, PIGN**, *PIGO, PIGP, PIGQ, PIGS, PIGT, PIGV, PIGW, PITRM1, PLAA, PLCB1, PLP1, PNKP, PNPO, POLG, POLR3A, POLR3B, PPP2CA, PPP3CA, PPT1, PRICKLE1, PRICKLE2, PRIMA1, PRODH**, *PROSC, PRRT2, PRUNE, PSAP, PSAT1**, *PTPN23, PTS, PUM1, PURA, PYCR2, QARS, QDPR, RAB11A, RAB11B, RAB39B, RALA**, *RARS, RELN, RHOBTB2, RMND1**, *RNASEH2A, RNASEH2B, RNASEH2C, RNASET2, RNF13**, *RNF216**, *ROGDI, RORA, RORB, RUSC2, SAMHD1, SCARB2, SCN1A, SCN1B, SCN2A, SCN3A, SCN8A, SCN9A, SCO1, SDHAF1, SERAC1, SERPINI1, SETBP1, SETD1B, SGSH, SIK1, SLC12A5, SLC13A5, SLC19A3, SLC1A2, SLC1A4, SLC25A1, SLC25A15**, *SLC25A22, SLC25A42, SLC2A1, SLC35A1, SLC35A2, SLC39A8#, SLC46A1, SLC6A1, SLC6A5, SLC6A8**, *SLC9A6, SMARCA2, SMC1A, SMS, SNAP25, SNORD118, SOX10, SPATA5, SPTAN1, SPTBN4, SSR4, ST3GAL3, ST3GAL5, STRADA, STX1B, STXBP1, SUMF1, SUOX, SYN1, SYNGAP1, SYNJ1, SZT2, TAF1, TANGO2, TBC1D20, TBC1D24, TBCD, TBCE, TBCK, TBL1XR1**, *TCF4, TK2#, TPK1, TPP1, TRAK1, TREX1, TRIM8, TRIT1, TSC1, TSC2, TSFM#, TTC19, TUBA1A**, *TUBB2A#**, *TUBB2B#**, *TUBB4A**, *UBA5**, *UBE2A, UBE3A**, *UBTF, UNC80, VAMP2, VARS, VPS13A, WARS2, WASF1, WDR26, WDR45, WWOX, YWHAG, YY1, ZDHHC9, ZEB2**, *ZFYVE26, ZNHIT3# and ZSWIM6*. The following exons are not included in the panel as they are not covered with sufficient high quality sequence reads: AP4S1 (NM_001254727:6), DEGS1 (NM_001321541:3), DHPS (NM_001206974:1), GABRG2 (NM_198903:6) and SLC39A8 (NM_001135148:1). This panel targets protein coding exons, exon-intron boundaries (± 20 bps) and selected non-coding, 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.

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*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 9-month-old girl with clinical symptoms suggestive of Aromatic L-amino acid decarboxylase deficiency. Suspicion for neurotransmitter disorder. There is no family history of the disease.

CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) FLEX Comprehensive Epilepsy Panel Plus identified two heterozygous missense variants in *DDC:* c.476C>T, p.(Ala159Val) and c.1337T>C, p.(Leu446Pro). Due to the large genomic distance between these variants, NGS-based methods cannot determine whether they occur on the same (in *cis*) or different (in *trans*) parental alleles.

DDC c.476C>T, p.(Ala159Val)

There are 3 individuals heterozygous for this variant in the Genome Aggregation Database (gnomAD, n>120,000 exomes and >15,000 genomes). No homozygotes were observed in the dataset. Database curators have made every effort to exclude individuals with severe pediatric diseases from these cohorts. Alanine is a highly conserved amino acid and there is a small physicochemical difference between alanine and valine. All *in silico* tools utilized predict this variant to be damaging to protein structure and function. The variant has been identified in homozygous state in a patient with aromatic L-Amino acid decarboxylase deficiency (ClinVar ID: 800536). In addition, next to this variant locates *DDC* c.478C>T, p.(Arg160Trp) variant that has been identified in compound heterozygous state with *DDC* c.1040G>A, p.(Arg347Gln) variant in a patient with aromatic L-amino acid decarboxylase deficiency (PMID: 23430870), and in clinical testing (ClinVar ID: 360437).

DDC c.1337T>C, p.(Leu446Pro)

There is 1 individual heterozygous for this variant in the Genome Aggregation Database (gnomAD, n>120,000 exomes and >15,000 genomes). Database curators have made every effort to exclude individuals with severe pediatric diseases from these cohorts. Leucine is a highly conserved amino acid and there is a moderate physicochemical difference between leucine and proline. All *in silico* tools utilized predict this variant to be damaging to protein structure and function. To the best of our knowledge, this variant has not been described in the medical literature or reported in disease-related variation databases such as ClinVar or HGMD. Next to this variant locates *DDC* c.1340G>A, p.(Arg447His) variant that has been identified in homozygous state in a patient with aromatic L-amino acid decarboxylase deficiency (PMID: 17240182).

DDC

The *DDC* gene (MIM *107930) on chromosome 7p12 encodes DOPA decarboxylase, which is also known as aromatic L-amino acid decarboxylase, AADC. This enzyme is implicated in metabolic pathways of important neurotransmitters. It is involved in the catalysis of decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) to dopamine, L-5-hydroxytryptophan to serotonin and L-tryptophan to tryptamine. Defects in the *DDC* gene cause autosomal recessive aromatic L-amino-acid decarboxylase deficiency (AADCD, MIM #608643). AADCD deficiency is a rare inborn error in neurotransmitter metabolism that leads to combined serotonin and catecholamine deficiency. In a review of 78 patients with AADCD, Brun et al (2010) reported that 96% of the patients had symptoms that were evident in infancy or childhood (PMID: 20505134). The most typical symptoms were hypotonia (95%), oculogyric crises (an acute dystonic reaction of the ocular muscles characterized by bilateral dystonic elevation of visual gaze, 86%), and developmental retardation (63%). Variable features included autonomic symptoms, such as excessive sweating or temperature instability, feeding or speech difficulty, and movement disorders, including hypokinesia, dystonia, athetosis, and chorea. Many patients had insomnia and irritability, and 63% had motor or mental retardation. Laboratory analyses showed low CSF levels of homovanillic acid, 5-hydroxyindoleacidic acid, and 3-methoxy-4-hydroxyphenolglycole, with increased 3-O-methyl-L-DOPA, L-DOPA, and 5-hydroxytryptophan. Plasma AADC activity was low or absent in the patients from whom it was measured. More than 20% of patients had an abnormal brain MRI, showing cerebral atrophy, degenerative changes of the white matter, thinning of the corpus callosum, or a leukodystrophy-like pattern (PMID: 20505134). Also hyperreflexia has been reported. Over 40 *DDC* variants are reported as disease-causing in HGMD (2019.4), most of them are missense variants but splicing, frameshift and gross deletion variants have also been reported in

association with AADCD.

Mutation nomenclature is based on GenBank accession NM_000790.3 (*DDC*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

DDC c.476C>T, p.(Ala159Val) is classified as likely pathogenic, based on the established association between the gene and the patient’s phenotype, the variant's rarity in control populations, *in silico* predicted pathogenicity, and identification of the variant in one individual with the same phenotype. *DDC* c.1337T>C, p.(Leu446Pro) is classified as a variant of uncertain significance (VUS), as there is currently insufficient evidence to support its role in disease. However, these *DDC* variants are consistent with the patient’s phenotype, and *DDC* c.1337T>C, p.(Leu446Pro) is rare in control populations and predicted to be deleterious by *in silico* tools. Disease caused by *DDC* variants is inherited in an autosomal recessive manner. Testing of parental samples is needed to determine whether the variants occur in *cis* (on the same allele) or in *trans* (on different alleles). Compound heterozygosity of the variants (in *trans*) would likely explain the patient’s clinical presentation. Genetic counselling and family member testing are recommended.

STEP	DATE
Order date	
Sample received	
Sample in analysis	
Reported	

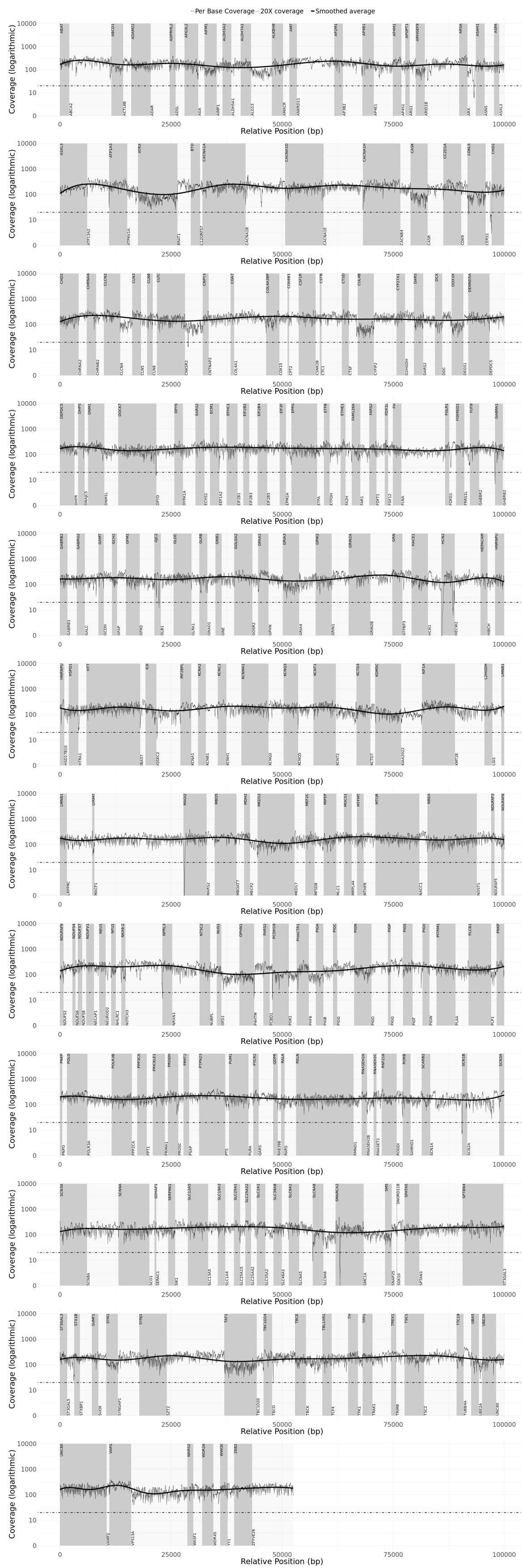
(This statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results.)

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.



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***

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 quantitative-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, 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 and digital PCR confirmation).

NON-CODING VARIANTS COVERED BY THE PANEL:

NM_000026.2(ADSL):c.-49T>C
NM_004208.3(AIFM1):c.697-44T>G
NM_004208.3(AIFM1):c.-123G>C
NM_001031806.1(ALDH3A2):c.681-14T>A/G
NM_001031806.1(ALDH3A2):c.681-14T>A
NM_001031806.1(ALDH3A2):c.681-14T>G
NM_000481.3(AMT):c.550-11T>C
NM_000487.5(ARSA):c.1108-12C>G
NM_000487.5(ARSA):c.1108-20A>G
NM_000060.2(BTD):c.310-15delT
NM_000060.2(BTD):c.*159G>A
NM_001127221.1(CACNA1A):c.*1500_*1504dupCTTTT
NM_001127221.1(CACNA1A):c.5404-13G>A
chr19:g.13617793-13617793
NM_001178065.1(CASR):c.1378-19A>C
NM_003159.2(CDKL5):c.-162-2A>G
NM_000086.2(CLN3):c.1056+34C>A
NM_000086.2(CLN3):c.461-13G>C
NM_017882.2(CLN6):c.297+113G>C
NM_001845.4(COL4A1):c.*35C>A
NM_001845.4(COL4A1):c.*32G>A/T
NM_001845.4(COL4A1):c.*31G>T
NM_005211.3(CSF1R):c.1859-119G>A
NM_152783.3(D2HGDH):c.293-23A>G
NM_018122.4(DARS2):c.228-22T>C
NM_018122.4(DARS2):c.228-22T>A
NM_018122.4(DARS2):c.228-21_228-20delTTinsC
NM_018122.4(DARS2):c.228-21_228-20delTTinsCC
NM_018122.4(DARS2):c.228-16C>A
NM_018122.4(DARS2):c.228-16C>G
NM_018122.4(DARS2):c.228-15C>G

NM_018122.4(DARS2):c.228-15C>A
NM_018122.4(DARS2):c.228-12C>A
NM_018122.4(DARS2):c.228-11C>G
NM_001242896.1(DEPDC5):c.-57G>C
chr6:g.52284844-52284844
NM_003907.2(EIF2B5):c.685-13C>G
NM_004453.2(ETFDH):c.-75A>G
NM_004453.2(ETFDH):c.176-636C>G
chr19:g.44031407-44031407
chr8:g.11660094-11660094
NM_004462.3(FDFT1):c.880-24_880-23delTCinsAG
NM_021032.4(FGF12):c.*4722T>C
NM_001110556.1(FLNA):c.6023-27_6023-16delTGACTGACAGCC
NM_000806.5(GABRA1):c.-248+1G>T
NM_000814.5(GABRB3):c.-53G>T
NM_000814.5(GABRB3):c.-902A>T
NM_000814.5(GABRB3):c.-2204G>A
NM_000814.5(GABRB3):c.-2290T>C
NM_000153.3(GALC):c.*12G>A
NM_000153.3(GALC):c.-66G>C
NM_000153.3(GALC):c.-67T>G
NM_001201402.1(GALC):c.-74T>A
NM_001201402.1(GALC):c.-128C>T
NM_138924.2(GAMT):c.391+15G>T
NM_000159.3(GCDH):c.1244-11A>G
NM_000161.2(GCH1):c.-22C>T
NM_020435.3(GJC2):c.-170A>G
NM_020435.3(GJC2):c.-167A>G
NM_020435.3(GJC2):c.-20+1G>C
NM_002087.2(GRN):c.-9A>G
NM_002087.2(GRN):c.-8+3A>T
NM_002087.2(GRN):c.-8+3A>G
NM_002087.2(GRN):c.-8+5G>C
NM_024884.2(L2HGDH):c.906+354G>A
NM_002397.4(MEF2C):c.-510_-497delTCTTCCTCCTCCTC
NM_015166.3(MLC1):c.895-226T>G
NM_015166.3(MLC1):c.-42C>T
NM_005943.5(MOCS1):c.*365_*366delAG
NM_005943.5(MOCS1):c.*7+6T>C
NM_005943.5(MOCS1):c.251-418delT
NM_005957.4(MTHFR):c.1753-18G>A
NM_005957.4(MTHFR):c.-13-28_-13-27delCT
NM_024120.4(NDUFAF5):c.223-907A>C
NM_152416.3(NDUFAF6):c.298-768T>C
NM_152416.3(NDUFAF6):c.420+784C>T
NM_000435.2(NOTCH3):c.341-26_341-24delAAC
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_000291.3(PGK1):c.1214-25T>G
NM_000533.3(PLP1):c.4+78_4+85delGGGGGTTC
NM_000533.3(PLP1):c.453+28_453+46delTAACAAGGGGTGGGGGAAA
NM_000533.3(PLP1):c.454-322G>A
NM_000533.3(PLP1):c.454-314T>A/G
NM_000533.3(PLP1):c.454-314T>A

NM_000533.3(PLP1):c.454-314T>G
NM_007254.3(PNKP):c.1387-33_1386+49delCCTCCTCCCCTGACCCC
NM_007055.3(POLR3A):c.*18C>T
NM_007055.3(POLR3A):c.3337-11T>C
NM_007055.3(POLR3A):c.1909+22G>A
NM_007055.3(POLR3A):c.1909+18G>A
NM_018082.5(POLR3B):c.967-15A>G
NM_018082.5(POLR3B):c.1857-12A>G
NM_000310.3(PPT1):c.*526_*529delATCA
NM_000310.3(PPT1):c.125-15T>G
NM_001256443.1(PRRT2):c.*345G>A
NM_001042465.1(PSAP):c.778-26C>A
NM_000317.2(PTS):c.84-323A>T
NM_000317.2(PTS):c.84-291A>G
NM_000317.2(PTS):c.164-716A>T
NM_000317.2(PTS):c.187-38dupG
NM_000320.2(QDPR):c.436+2552A>G
NM_024570.3(RNASEH2B):c.65-13G>A
NM_024570.3(RNASEH2B):c.511-13G>A
NM_024589.2(ROGDI):c.46-30_45+37delGGCGGGGC
NM_006920.4(SCN1A):c.4820-14T>G
NM_006920.4(SCN1A):c.4306-14T>G
NM_006920.4(SCN1A):c.964+14T>G
NM_006920.4(SCN1A):c.474-13T>A
NM_032861.3(SERAC1):c.92-165C>T
NM_032861.3(SERAC1):c.92-239G>C
NM_025243.3(SLC19A3):c.980-14A>G
NM_006516.2(SLC2A1):c.680-11G>A
NM_006516.2(SLC2A1):c.-107G>A
chr17:g.8076761-8076761
chr17:g.8076761-8076761
chr17:g.8076762-8076762
NM_006941.3(SOX10):c.-84-2A>T
NM_006941.3(SOX10):c.-31954C>T
NM_006941.3(SOX10):c.-32520C>G
NM_001130438.2(SPTAN1):c.6690-17G>A
chrX:g.70749635-70749635
NM_005993.4(TBCD):c.1564-12C>G
NM_199292.2(TH):c.1198-24T>A
NM_199292.2(TH):c.738-34G>C
NM_199292.2(TH):c.-69T>A
NM_199292.2(TH):c.-70G>A
NM_199292.2(TH):c.-71C>T
NM_000391.3(TPP1):c.887-18A>G
NM_000368.4(TSC1):c.363+668G>A
NM_000548.3(TSC2):c.-30+1G>C
NM_000548.3(TSC2):c.600-145C>T
NM_000548.3(TSC2):c.848+281C>T
NM_000548.3(TSC2):c.976-15G>A
NM_000548.3(TSC2):c.2838-122G>A
NM_000548.3(TSC2):c.5069-18A>G
NM_017775.3(TTC19):c.-42G>T
NM_007075.3(WDR45):c.236-18A>G
NM_014795.3(ZEB2):c.-69-1G>A
NM_014795.3(ZEB2):c.-69-2A>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.