Dante Labs Inc
325 5th Ave, Suite 38A
New York City , United States
10016
WGS

dante labs

Provider Information
Institution
Dante Labs Inc
Patient Id
Case Id

Sample Information

Sample Type
Human DNA - germline
Collection Method
DNA Genotek - DNA saliva collection kit Oragene OGD-500
Panel Coverage
WGS: Full DNA(introns and exons)
Avg. Read Depth
WGS 30X
Report Date

Results

Dante Labs ranks the variants according to the ClinVar database.
ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence.
(https://www.ncbi.nlm.nih.gov/clinvar/intro/)

For a representation of clinical significance in ClinVar:
https://www.ncbi.nlm.nih.gov/clinvar/docs/clinsig/#conflicts

Positive: Variants with established pathogenicity detected in genes surveyed.

Affected Genes

ABAT (0)	*ABCC8* (0)	*ABCD1* (0)	*ACY1* (0)	***ADAR*** **(1)**	*ADGRG1* (0)	*ADGRV1* (0)	*ADRA2B* (0)	*ADSL* (0)	*AFG3L2* (0)	*AGA* (0)
AHI1 (0)	*AIFM1* (0)	*AIMP1* (0)	*AKT3* (0)	*ALDH3A2* (0)	*ALDH4A1* (0)	*ALDH5A1* (0)	***ALDH7A1*** **(1)**	*ALG1* (0)	*ALG12* (0)	*ALG13* (0)
ALG2 (0)	*ALG3* (0)	*ALG6* (0)	*ALG8* (0)	***ALG9*** **(1)**	*AMACR* (0)	*AMT* (0)	*ANK3* (0)	*AP4B1* (0)	*AP4E1* (0)	*AP4M1* (0)
AP4S1 (0)	*APOPT1* (0)	***ARFGEF2*** **(1)**	*ARG1* (0)	*ARHGEF15* (0)	*ARHGEF9* (0)	*ARL13B* (0)	***ARSA*** **(1)**	*ARSB* (0)	*ARX* (0)	*ASAH1* (0)
ASNS (0)	*ASPA* (0)	*ASPM* (0)	*ATIC* (0)	*ATP13A2* (0)	*ATP1A2* (0)	*ATP1A3* (0)	*ATP1A3ATRX* (0)	*ATP2A2* (0)	*ATP6AP2* (0)	*ATP6V0A2* (0)
ATPAF2	*ATRX*	*AUH*	*B4GALT1*	*BCKDK*	*BCS1L*	*BOLA3*	***BRAF***	*BRAT1*	*BRD2*	*BTD*

(0)	(0)	(0)	(0)	(0)	(0)	(0)	**(1)**	(0)	(0)	(0)
BUB1B (0)	*C12ORF57* (0)	***CACNA1A*** **(1)**	*CACNA1H* (0)	*CACNA2D2* (0)	*CACNB4* (0)	*CARS2* (0)	*CASK* (0)	*CASR* (0)	*CBL* (0)	*CC2D1A* (0)
CC2D2A **(1)**	*CCDC88C* (0)	*CCL2* (0)	*CDKL5* (0)	*CDKL5CHD2* (0)	*CENPJ* (0)	*CEP290* (0)	*CERS1* (0)	*CHD2* (0)	*CHRNA2* (0)	*CHRNA4* (0)
CHRNB2 **(1)**	***CLCN2*** **(1)**	*CLCN4* (0)	*CLN2* (0)	*CLN3* (0)	*CLN5* (0)	*CLN5CLN6* (0)	***CLN6*** **(3)**	*CLN8* (0)	*CNTN2* (0)	*CNTN2CPA6* (0)
CNTNAP2 **(1)**	*COG7* (0)	*COG8* (0)	*COL18A1* (0)	*COL4A1* (0)	***COQ2*** **(1)**	*COQ8A* (0)	*COQ9* (0)	*COX10* (0)	*COX15* (0)	*COX6B1* (0)
CPA6 (0)	*CPT2* (0)	*CRH* (0)	*CSF1R* (0)	*CSTB* (0)	*CTC1* (0)	*CTSA* (0)	*CTSD* (0)	*CTSF* (0)	*CUL4B* (0)	*CYP27A1* (0)
D2HGDH (0)	*DARS* (0)	*DARS2* (0)	*DCX* (0)	*DDC* (0)	*DEPDC5* (0)	*DHCR7* (0)	***DHFR*** **(1)**	*DIAPH1* (0)	*DLD* (0)	*DNAJC5* (0)
DNM1 (0)	*DNM1DOCK7* (0)	*DNM1L* (0)	*DOCK7* (0)	*DOLK* (0)	*DPAGT1* (0)	*DPM1* (0)	*DPM2* (0)	*DPYD* (0)	*DPYS* (0)	*DYNC1H1* (0)
DYRK1A (0)	*EARS2* (0)	*ECHS1* (0)	*ECM1* (0)	*EEF1A2* (0)	*EFHC1* (0)	*EHMT1* (0)	*EIF2B1* (0)	*EIF2B2* (0)	*EIF2B3* (0)	*EIF2B4* (0)
EIF2B5 (0)	*EMX2* (0)	*EPM2A* (0)	*ETFA* (0)	*ETFB* (0)	*ETFDH* (0)	*ETHE1* (0)	*FA2H* (0)	*FAM126A* (0)	*FAR1* (0)	*FARS2* (0)
FASN (0)	*FGD1* (0)	*FGF12* (0)	*FGFR3* (0)	*FH* (0)	*FKRP* (0)	***FKTN*** **(2)**	*FLNA* (0)	***FOLR1*** **(1)**	*FOLR1FOXG1* (0)	*FOXG1* (0)
FOXRED1 (0)	*FRRS1L* (0)	*FUCA1* (0)	*GABBR2* (0)	*GABRA1* (0)	*GABRB2* (0)	*GABRB3* (0)	*GABRD* (0)	*GABRG2* (0)	*GAL* (0)	***GALC*** **(1)**
GAMT (0)	*GAMTGATM* (0)	***GATM*** **(1)**	***GCDH*** **(3)**	*GCH1* (0)	*GCSH* (0)	*GFAP* (0)	*GFM1* (0)	*GJC2* (0)	*GLB1* (0)	***GLDC*** **(1)**
GLI2 **(1)**	*GLI3* (0)	*GLRA1* (0)	*GLRB* (0)	*GLUD1* (0)	*GNAO1* (0)	*GNB1* (0)	*GNE* (0)	*GNS* (0)	*GOSR2* (0)	*GPC3* (0)
GPHN (0)	*GRIA3* (0)	*GRIK2* (0)	*GRIN1* (0)	*GRIN2A* (0)	*GRIN2B* (0)	*GRN* (0)	*GTPBP3* (0)	*HACE1* (0)	*HCN1* (0)	*HCN1HNRNPU* (0)
HCN4 (0)	*HDAC4* (0)	*HECW2* (0)	***HEPACAM*** **(1)**	*HEXA* (0)	*HEXB* (0)	*HGSNAT* (0)	*HIBCH* (0)	*HNRNPU* (0)	*HPD* (0)	*HRAS* (0)

HSD17B10 (0)	*HSPD1* (0)	*HTRA1* (0)	*HTT* (0)	*IBA57* (0)	*IDS* (0)	*IER3IP1* (0)	*IQSEC2* (0)	*ITPA* (0)	***JMJD1C*** **(1)**	*KANSL1* (0)
KCNA1 (0)	*KCNA2* (0)	*KCNAB2* (0)	*KCNB1* (0)	*KCNB1KCNC1* (0)	*KCNC1* (0)	*KCND2KCNH5* (0)	*KCNH1* (0)	*KCNH2* (0)	***KCNJ10*** **(2)**	*KCNJ11* (0)
KCNMA1 (0)	*KCNQ2* (0)	*KCNQ3* (0)	*KCNT1* (0)	*KCNV2* (0)	*KCTD7* (0)	*KCTD7LGI1* (0)	*KDM5C* (0)	*KDM6A* (0)	*KIF1A* (0)	*KIF1BP* (0)
KMT2D (0)	*KPNA7* (0)	*KRAS* (0)	*L2HGDH* (0)	***LAMA2*** **(1)**	*LARGE1* (0)	*LBR* (0)	*LGI1* (0)	*LIAS* (0)	*LMNB1* (0)	*LMNB2* (0)
LRPPRC **(1)**	*LYRM7#* (0)	*MAGI2* (0)	*MAP2K1* (0)	*MAP2K2* (0)	*MAPK10* (0)	*MARS2* (0)	*MBD5* (0)	*MCOLN1* (0)	*MCPH1* (0)	*MDH2* (0)
ME2 (0)	*MECP2* (0)	*MED12* (0)	*MED17* (0)	*MEF2C* (0)	*MFSD8* (0)	*MGAT2* (0)	*MLC1* (0)	*MOCS1* (0)	*MOCS2* (0)	*MOGS* (0)
MPDU1 (0)	*MRPL44* (0)	*MTFMT* (0)	***MTHFR*** **(2)**	*MTOR* (0)	*NACC1* (0)	*NAGLU* (0)	*NDE1* (0)	*NDUFA1* (0)	*NDUFA2* (0)	*NDUFAF5* (0)
NDUFAF6 (0)	***NDUFS1*** **(1)**	*NDUFS2* (0)	*NDUFS3* (0)	*NDUFS4* (0)	*NDUFS7* (0)	*NDUFS8* (0)	*NDUFV1* (0)	*NECAP1* (0)	*NEDD4L* (0)	*NEDD4LNEXMIF* (0)
NEU1 (0)	*NEXMIF* (0)	*NF1* (0)	*NFU1* (0)	*NGLY1* (0)	*NHLRC1* (0)	*NIPBL* (0)	*NOTCH3* (0)	*NPC1* (0)	*NPC2* (0)	*NPHP1* (0)
NPRL3 (0)	*NR2F1* (0)	***NRXN1*** **(4)**	*NSD1* (0)	*NTNG1* (0)	*NUBPL* (0)	*OFD1* (0)	*OPHN1* (0)	*PACS1* (0)	***PAFAH1B1*** **(1)**	*PAK3* (0)
PANK2 (0)	*PC* (0)	***PCDH19*** **(1)**	***PCNT*** **(1)**	*PDHA1* (0)	*PDSS2* (0)	***PEX1*** **(2)**	*PEX12* (0)	*PEX14* (0)	*PEX2* (0)	*PEX26* (0)
PEX3 (0)	*PEX5* (0)	*PEX6* (0)	*PEX7* (0)	*PGK1* (0)	*PHF6* (0)	*PIGA* (0)	*PIGAPIGN* (0)	*PIGG* (0)	*PIGN* (0)	*PIGO* (0)
PIGQ (0)	*PIGT* (0)	*PIGV* (0)	*PIK3AP1* (0)	*PLA2G6* (0)	***PLCB1*** **(1)**	*PLP1* (0)	*PMM2* (0)	*PNKD* (0)	*PNKP* (0)	*PNPO* (0)
POLG **(1)**	*POLR3A* (0)	***POLR3B*** **(1)**	*POMGNT1* (0)	*POMT1* (0)	*POMT2* (0)	*PPP3CA* (0)	*PPT1* (0)	*PPT1PRICKLE1* (0)	*PQBP1* (0)	*PRDM8PRICKLE* (0)
PRICKLE1 **(1)**	*PRICKLE2* (0)	*PRIMA1* (0)	***PRODH*** **(1)**	*PRRT2* (0)	*PSAP* (0)	*PTCH1* (0)	***PTPN11*** **(1)**	*PTS* (0)	*PURA* (0)	*PYCR2#* (0)

QARS (0)	*QDPR* (0)	*RAB39B* (0)	*RAB3GAP1* (0)	*RAI1* (0)	*RARS* (0)	*RARS2* (0)	*RBFOX1* (0)	*RBFOX3* (0)	***RELN*** **(3)**	*RFT1* (0)
RMND1 (0)	*RNASEH2A* (0)	*RNASEH2B* (0)	*RNASEH2C* (0)	*RNASET2* (0)	*RNF216* (0)	*ROGDI* (0)	*RPGRIP1L* (0)	*RYR3* (0)	*SAMHD1* (0)	*SATB2SCARB2* (0)
SCARB2 (0)	*SCN10A* (0)	***SCN1A*** **(1)**	*SCN1B* (0)	***SCN2A*** **(1)**	*SCN3A* (0)	*SCN4A* (0)	*SCN5A* (0)	*SCN8A* (0)	*SCN9A* (0)	*SCO1* (0)
SCO2 (0)	*SDHA* (0)	*SDHAF1* (0)	*SERAC1* (0)	*SERPINI1* (0)	*SERPINI1SGSH* (0)	*SETBP1* (0)	*SETD2* (0)	*SGSH* (0)	*SHH* (0)	*SHOC2* (0)
SIK1 (0)	***SIX3*** **(1)**	*SLC12A5* (0)	*SLC13A5* (0)	*SLC17A5* (0)	*SLC19A3* (0)	*SLC1A3* (0)	*SLC25A1* (0)	*SLC25A12* (0)	***SLC25A15*** **(1)**	*SLC25A19* (0)
SLC25A22 (0)	*SLC2A1* (0)	*SLC2A1SLC35A2* (0)	*SLC35A1* (0)	*SLC35A2* (0)	*SLC35A3* (0)	*SLC35C1* (0)	*SLC39A8* (0)	*SLC46A1* (0)	*SLC4A10* (0)	*SLC6A1* (0)
SLC6A8 (0)	*SLC9A6* (0)	*SMARCA2* (0)	*SMC1A* (0)	*SMC3* (0)	*SMS* (0)	*SNAP25* (0)	*SNAP25SRPX2* (0)	*SNORD118* (0)	*SNX27* (0)	*SOX10* (0)
SPATA5 (0)	*SPRED1* (0)	*SPTAN1* (0)	*SPTAN1ST3GAL5* (0)	*SRCAP* (0)	*ST3GAL3* (0)	*ST3GAL5* (0)	*STIL* (0)	*STRADA* (0)	*STX1B* (0)	*STXBP1* (0)
SUMF1 (0)	*SUOX* (0)	*SURF1* (0)	*SYN1* (0)	*SYNGAP1* (0)	*SYNJ1* (0)	*SYP* (0)	*SZT2* (0)	*SZT2TBC1D24* (0)	*TACO1* (0)	*TAF1* (0)
TBC1D24 (0)	*TBCD* (0)	***TBCE*** **(1)**	*TBCK* (0)	*TBL1XR1* (0)	*TBX1* (0)	***TCF4*** **(1)**	*TMEM67* (0)	*TMEM70* (0)	*TNK2* (0)	*TPK1* (0)
TPP1 **(1)**	*TREX1* (0)	*TSC1* (0)	*TSC2* (0)	*TSEN2* (0)	*TSEN34* (0)	***TSEN54*** **(1)**	***TTC19*** **(1)**	*TUBA1A* (0)	*TUBA8* (0)	*TUBB2A* (0)
TUBB2B (0)	*TUBB4A* (0)	*TWNK* (0)	*UBA5* (0)	*UBE2A* (0)	*UBE3A* (0)	*UNC80* (0)	*VPS13A* (0)	***VPS13B*** **(2)**	*WDR26* (0)	*WDR45* (0)
WWOX (0)	*WWOXZDHHC9* (0)	*YY1* (0)	***ZEB2*** **(2)**	*ZFYVE26* (0)	*ZIC2* (0)					

Primary Findings

Gene	Zygosity	Variant	Exon	Pathogenicity
CC2D2A	Heterozygous	NM_001080522.2:c.685_687delGAA(NP_001073991.2:p.Glu229del)	9	Conflicting
PEX1	Heterozygous	NM_000466.2:c.2584-10delT(?)	16	Conflicting
PEX1	Heterozygous	NM_000466.2:c.2584-10delT(?)	16	Conflicting
RELN	Heterozygous	NM_005045.3:c.5284G>A(NP_005036.2:p.Val1762Ile)	35	Conflicting
RELN	Heterozygous	NM_005045.3:c.3477C>A(NP_005036.2:p.Asn1159Lys)	25	Conflicting
RELN	Heterozygous	NM_005045.3:c.-6_-1dupGGCGGC(?)	1	Conflicting
VPS13B	Heterozygous	NM_017890.4:c.5681C>T(NP_060360.3:p.Thr1894Met)	34	Conflicting
GALC	Homozygous Variant	NM_000153.3:c.1162-4delT(?)	11	Conflicting
CLN6	Heterozygous	NM_017882.2:c.*159_*160dupGT(?)	7	Conflicting
TSEN54	Heterozygous	NM_207346.2:c.624-9G>A(?)	8	Conflicting
GCDH, SYCE2	Heterozygous	NM_000159.3:c.*165A>G(?)	12,5	Conflicting
GCDH, SYCE2	Heterozygous	NM_000159.3:c.*288G>T(?)	12,5	Conflicting
ARSA	Heterozygous	NM_000487.5:c.*96A>G(?)	8	Conflicting
PCDH19	Heterozygous	NM_001184880.1:c.3319C>G(NP_001171809.1:p.Arg1107Gly)	6	Conflicting
MTHFR	Heterozygous	NM_005957.4:c.1286A>C(NP_005948.3:p.Glu429Ala)	8	Drug Response
MTHFR	Heterozygous	NM_005957.4:c.665C>T(NP_005948.3:p.Ala222Val)	5	Drug Response
CHRNB2	Homozygous Variant	NM_000748.2:c.*472G>A(?)	6	Drug Response
SCN1A	Homozygous Variant	NM_001165963.1:c.603-91G>A(?)	5	Drug Response
COQ2	Homozygous Variant	NM_015697.7:c.779-1022C>G(?)	5	Drug Response
GATM	Heterozygous	NM_001321015.1:c.-394-272A>G(?)	4	Drug Response
TPP1	Heterozygous	NM_000391.3:c.509-1G>C(?)	6	Pathogenic
POLG	Heterozygous	NM_002693.2:c.2542G>A(NP_002684.1:p.Gly848Ser)	16	Pathogenic
CACNA1A	Heterozygous	NM_001127221.1:c.*185_*187delCAG(?)	47	Pathogenic
CNTNAP2	Heterozygous	NM_014141.5:c.2099-26267A>G(?)	14	Risk Factor
ADAR	Homozygous Variant	NM_001111.4:c.*2323_*2330dupCATGCCCC(?)	15	Uncertain Significance
KCNJ10	Heterozygous	NM_002241.4:c.*2012_*2019delGTGTGTGT(?)	2	Uncertain Significance
KCNJ10	Heterozygous	NM_002241.4:c.*2012_*2019delGTGTGTGT(?)	2	Uncertain Significance
TBCE	Heterozygous	NM_003193.4:c.100+64_100+65delGT(?)	2	Uncertain Significance
LRPPRC	Homozygous Variant	NM_133259.3:c.*1449_*1456dupTTTTTTTT(?)	38	Uncertain Significance
SIX3	Heterozygous	NM_005413.3:c.369G>A(NP_005404.1:p.Glu123=)	1	Uncertain Significance
NRXN1	Heterozygous	NM_001135659.2:c.*1235_*1246delACACACACACAC(?)	24	Uncertain Significance
NRXN1	Heterozygous	NM_001135659.2:c.-1453_-1452dupCT(?)	1	Uncertain Significance
NRXN1	Heterozygous	NM_001135659.2:c.-1463_-1452delCTCTCTCTCTCT(?)	1	Uncertain Significance
NRXN1	Heterozygous	NM_001135659.2:c.-1463_-1452delCTCTCTCTCTCT(?)	1	Uncertain Significance
GLI2	Homozygous Variant	NM_005270.4:c.*1373_*1376dupACAC(?)	13	Uncertain Significance
ZEB2	Heterozygous	NM_014795.3:c.*4845dupA(?)	10	Uncertain Significance
ZEB2	Heterozygous	NM_014795.3:c.*2404_*2405dupTA(?)	10	Uncertain Significance
SCN2A	Homozygous Variant	NM_021007.2:c.-150_-149delAA(?)	1	Uncertain Significance
NDUFS1	Homozygous Variant	NM_005006.6:c.154-10_154-9delTT(?)	4	Uncertain Significance
CLCN2	Heterozygous	NM_004366.5:c.2003C>G(NP_004357.3:p.Thr668Ser)	17	Uncertain Significance

Gene	Zygosity	Variant	Exon	Pathogenicity
DHFR	Heterozygous	NM_000791.3:c.86+59_86+60ins(19)(?)	1	Uncertain Significance
ALDH7A1	Heterozygous	NM_001182.4:c.*999_*1000dupAA(?)	18	Uncertain Significance
LAMA2	Heterozygous	NM_000426.3:c.-99A>G(?)	1	Uncertain Significance
BRAF	Homozygous Variant	NM_004333.4:c.2128-28dupT(?)	18	Uncertain Significance
VPS13B	Heterozygous	NM_017890.4:c.6491A>G(NP_060360.3:p.Asn2164Ser)	36	Uncertain Significance
GLDC	Heterozygous	NM_000170.2:c.*505_*506delTT(?)	25	Uncertain Significance
FKTN	Heterozygous	NM_001079802.1:c.*5041G>A(?)	11	Uncertain Significance
FKTN	Heterozygous	NM_001079802.1:c.*5062G>A(?)	11	Uncertain Significance
JMJD1C	Heterozygous	NM_032776.2:c.4286C>T(NP_116165.1:p.Ser1429Leu)	10	Uncertain Significance
FOLR1	Heterozygous	NM_016725.2:c.-9+161G>A(?)	1	Uncertain Significance
ALG9	Heterozygous	NM_024740.2:c.*2473A>T(?)	16	Uncertain Significance
HEPACAM	Heterozygous	NM_152722.4:c.*456_*460delTTTTG(?)	7	Uncertain Significance
PRICKLE1	Homozygous Variant	NM_153026.2:c.*552delA(?)	8	Uncertain Significance
POLR3B	Heterozygous	NM_018082.5:c.-1C>T(?)	1	Uncertain Significance
PTPN11	Heterozygous	NM_002834.4:c.*1199_*1201dupATG(?)	16	Uncertain Significance
SLC25A15	Heterozygous	NM_014252.3:c.-273C>G(?)	1	Uncertain Significance
CLN6	Heterozygous	NM_017882.2:c.*157_*160delGTGT(?)	7	Uncertain Significance
CLN6	Heterozygous	NM_017882.2:c.*157_*160delGTGT(?)	7	Uncertain Significance
PAFAH1B1	Heterozygous	NM_000430.3:c.*1042_*1043delAG(?)	11	Uncertain Significance
TTC19	Heterozygous	NM_017775.3:c.*1886T>C(?)	10	Uncertain Significance
TCF4	Homozygous Variant	NM_001083962.1:c.*3870delA(?)	20	Uncertain Significance
PLCB1	Heterozygous	NM_015192.3:c.2309-15A>C(?)	22	Uncertain Significance
ARFGEF2	Heterozygous	NM_006420.2:c.*1969G>A(?)	39	Uncertain Significance
PCNT	Heterozygous	NM_006031.5:c.9707G>A(NP_006022.3:p.Arg3236Gln)	45	Uncertain Significance
PRODH	Homozygous Variant	NM_016335.4:c.1741C>T(NP_057419.4:p.Leu581=)	15	Uncertain Significance

Recommendations

Dante Labs suggests you to discuss your results with a doctor/geneticist or Genetic Counselor in order to correctly interpret the relevance of the variants. As Science progresses, variants may be subject to score changes or reclassification. Dante Labs decided to provide customers with unbiased information about variants by reporting findings as they have been originally reported in ClinVar.

Individual Variant Interpretations

NP_001073991.2:p.Glu229del in Exon 9 of *CC2D2A* (NM_001080522.2:c.685_687delGAA) Conflicting

This is a Inframe Deletion located in the CC2D2A gene.

CC2D2A is a component of a protein complex in the basal body, a ring-like structure that functions in the transition zone at the base of cilia. This complex acts as a barrier to restrict protein diffusion between plasma and ciliary membranes (Chih et al., 2012).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with COACH syndrome, Joubert syndrome 9, and Meckel syndrome 6.

ClinVar Assessment from GeneDx

Classified as Benign on 2018-03-07 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

Intron Variant in *PEX1* (NM_000466.2:c.2584-10delT) Conflicting

This is a Intron Variant located in the PEX1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Heimler syndrome 1, Peroxisome biogenesis disorder 1A (Zellweger), and Peroxisome biogenesis disorder 1B (NALD/IRD).

ClinVar Assessment from Laboratory for Molecular Medicine,Partners HealthCare Personalized Medicine

Classified as Likely Benign on 2016-03-28 for Not Specified

Variant identified in a genome or exome case(s) and assessed due to predicted null impact of the variant or pathogenic assertions in the literature or databases. Disclaimer: This variant has not undergone full assessment. The following are preliminary notes: ExAC: 34.4% (31/90) South Asian chromosomes

Intron Variant in *PEX1* (NM_000466.2:c.2584-10delT) Conflicting

This is a Intron Variant located in the PEX1 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Heimler syndrome 1, Peroxisome biogenesis disorder 1A (Zellweger), and Peroxisome biogenesis disorder 1B (NALD/IRD).

ClinVar Assessment from Laboratory for Molecular Medicine,Partners HealthCare Personalized Medicine

Classified as Likely Benign on 2016-03-28 for Not Specified

Variant identified in a genome or exome case(s) and assessed due to predicted null impact of the variant or pathogenic assertions in the literature or databases. Disclaimer: This variant has not undergone full assessment. The following are preliminary notes: ExAC: 34.4% (31/90) South Asian chromosomes

NP_005036.2:p.Val1762Ile in Exon 35 of *RELN* (NM_005045.3:c.5284G>A) Conflicting

This is a Missense Variant located in the RELN gene.

The RELN gene encodes reelin, a large secreted glycoprotein that is produced by specific cell types within the developing brain and activates a signaling pathway in postmitotic migrating neurons required for proper positioning of neurons within laminated nervous system parenchyma (summary by Zaki et al., 2007).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Lissencephaly 2 (Norman-Roberts type) and Epilepsy familial temporal lobe 7.

ClinVar Assessment from GeneDx

Classified as Benign on 2015-11-19 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

ClinVar Assessment from Bioinformatics Core,Luxembourg Center for Systems Biomedicine

Classified as Pathogenic on 2017-01-01 for Not Provided

CAADphred>15

NP_005036.2:p.Asn1159Lys in Exon 25 of *RELN* (NM_005045.3:c.3477C>A) Conflicting

This is a Missense Variant located in the RELN gene.

The RELN gene encodes reelin, a large secreted glycoprotein that is produced by specific cell types within the developing brain and activates a signaling pathway in postmitotic migrating neurons required for proper positioning of neurons within laminated nervous system parenchyma (summary by Zaki et al., 2007).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Lissencephaly 2 (Norman-Roberts type) and Epilepsy familial temporal lobe 7.

ClinVar Assessment from Bioinformatics Core,Luxembourg Center for Systems Biomedicine

Classified as Pathogenic on 2017-01-01 for Not Provided

CAADphred>15

ClinVar Assessment from GeneDx

Classified as Likely Benign on 2017-11-08 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

5 Prime UTR Variant in *RELN* (NM_005045.3:c.-6_-1dupGGCGGC) Conflicting

This is a 5 Prime UTR Variant located in the RELN gene.

The RELN gene encodes reelin, a large secreted glycoprotein that is produced by specific cell types within the developing brain and activates a signaling pathway in postmitotic migrating neurons required for proper positioning of neurons within laminated nervous system parenchyma (summary by Zaki et al., 2007).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Lissencephaly 2 (Norman-Roberts type) and Epilepsy familial temporal lobe 7.

NP_060360.3:p.Thr1894Met in Exon 34 of *VPS13B* (NM_017890.4:c.5681C>T) Conflicting

This is a Missense Variant located in the VPS13B gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cohen syndrome.

ClinVar Assessment from Invitae

Classified as Uncertain Significance on 2017-10-23 for Not Provided

This sequence change replaces threonine with methionine at codon 1894 of the VPS13B protein (p.Thr1894Met). The threonine residue is weakly conserved and there is a moderate physicochemical difference between threonine and methionine. This variant is present in population databases (rs117148013, ExAC 0.1%). This variant has not been reported in the literature in individuals with VPS13B-related disease. ClinVar contains an entry for this variant (Variation ID: 196918). Algorithms developed to predict the effect of missense changes on protein structure and function output the following: SIFT: "Tolerated"; PolyPhen-2: "Benign"; Align-GVGD: "Class C0". The methionine amino acid residue is found in multiple mammalian species, suggesting that this missense change does not adversely affect protein function. These predictions have not been confirmed by published functional studies and their clinical significance is uncertain. In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Splice Region Variant in *GALC* (NM_000153.3:c.1162-4delT) Conflicting

This is a Splice Region Variant located in the GALC gene.

Galactosylceramidase ({EC 3.2.1.46}) is a lysosomal enzyme involved in the catabolism of galactosylceramide, a major lipid in myelin, kidney, and epithelial cells of the small intestine and colon (Chen et al., 1993).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Krabbe disease.

ClinVar Assessment from Integrated Genetics/Laboratory Corporation of America

Classified as Benign on 2016-05-16 for Not Provided

Variant summary: The GALC c.1162-4delT variant involves the alteration of a non-conserved intronic nucleotide. One in silico tool predicts a polymorphism outcome for this variant. This variant was found in 104106/106498 control chromosomes (50900 homozygotes) at a frequency of 0.9775395, which is approximately 437 times the estimated maximal expected allele frequency of a pathogenic GALC variant (0.0022361), suggesting this variant is likely a benign polymorphism and the major allele in general population. In addition, one clinical diagnostic laboratory classified this variant as benign. Taken together, this variant is classified as benign.

ClinVar Assessment from GeneDx

Classified as Benign on 2018-01-31 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

3 Prime UTR Variant in *CLN6* (NM_017882.2:c.*159_*160dupGT) Conflicting

This is a 3 Prime UTR Variant located in the CLN6 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ceroid lipofuscinosis neuronal 6 and Ceroid lipofuscinosis neuronal Kufs type adult onset.

Intron Variant in *TSEN54* (NM_207346.2:c.624-9G>A) Conflicting

This is a Intron Variant located in the TSEN54 gene.

tRNA splicing is a fundamental process required for cell growth and division. SEN54 is a subunit of the tRNA splicing endonuclease, which catalyzes the removal of introns, the first step in tRNA splicing (Paushkin et al., 2004).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Pontocerebellar hypoplasia type 5, Pontocerebellar hypoplasia type 2A, and Pontocerebellar hypoplasia type 4.

3 Prime UTR Variant in *GCDH* (NM_000159.3:c.*165A>G) Conflicting
Intron Variant in *SYCE2* (NM_001105578.1:c.612+298T>C) Conflicting

This is a 3 Prime UTR Variant (NM_000159.3) and Intron Variant (NM_001105578.1). It is located in the *GCDH and SYCE2* genes.

Glutaryl-CoA dehydrogenase (GCDH) ({EC 1.3.99.7}) is an acyl dehydrogenase involved in the metabolism of lysine, hydroxylysine, and tryptophan. Specifically, it is responsible for the dehydrogenation and decarboxylation of glutaryl-CoA to crotonyl-CoA in the degradative pathway of L-lysine, L-hydroxylysine, and L-tryptophan metabolism. The active enzyme exists as a homotetramer in the mitochondrial matrix.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Glutaricaciduria type I.

3 Prime UTR Variant in *GCDH* (NM_000159.3:c.*288G>T) Conflicting
Intron Variant in *SYCE2* (NM_001105578.1:c.612+175C>A) Conflicting

This is a 3 Prime UTR Variant (NM_000159.3) and Intron Variant (NM_001105578.1). It is located in the *GCDH and SYCE2* genes.

Glutaryl-CoA dehydrogenase (GCDH) ({EC 1.3.99.7}) is an acyl dehydrogenase involved in the metabolism of lysine, hydroxylysine, and tryptophan. Specifically, it is responsible for the dehydrogenation and decarboxylation of glutaryl-CoA to crotonyl-CoA in the degradative pathway of L-lysine, L-hydroxylysine, and L-tryptophan metabolism. The active enzyme exists as a homotetramer in the mitochondrial matrix.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Glutaricaciduria type I.

3 Prime UTR Variant in *ARSA* (NM_000487.5:c.*96A>G) Conflicting

This is a 3 Prime UTR Variant located in the ARSA gene.

In an individual homozygous for the ARSA pseudodeficiency (250100) allele, Gieselmann et al. (1989) found 2 A-to-G transitions: one changed asn350 to serine, leading to loss of an N-glycosylation site ({607574.0002}). This loss explained the smaller size of ARSA in ARSA pseudodeficient fibroblasts. Introduction of ser350 into normal ARSA cDNA did not affect the rate of synthesis, stability, or catalytic properties of ARSA in stably transfected baby hamster kidney cells, however. The other A-to-G transition changed the first polyadenylation signal downstream of the stop codon from AATAAC to AGTAAC. The latter change caused a severe deficiency of a 2.1-kb RNA species. The deficiency of the 2.1-kb RNA species explained the diminished synthesis of ARSA in pseudodeficiency fibroblasts. The same change was found in 4 unrelated individuals with pseudodeficiency. In those who are homozygous for the pseudodeficiency allele or carry it in heterozygous state with a normal allele, enough arylsulfatase A is synthesized to prevent clinically apparent disease. In combination with other mutant alleles, it may cause metachromatic leukodystrophy. Nelson et al. (1991) likewise found the A-to-G change at nucleotide 1620 in the first polyadenylation signal of the ARSA gene resulting in loss of its major mRNA species and a greatly reduced level of enzyme activity. This change was found to be closely linked to another A-to-G transition at nucleotide 1049 which changed asparagine-350 to serine but did not affect ARSA activity. The findings of Nelson et al. (1991) supported the conclusion of Gieselmann et al. (1989) that the change in nucleotide 1620 is always associated with that at nucleotide 1049. Barth et al. (1994) stated that the 2 mutations do not always occur together and that at least the N350S mutation may be found alone. The carrier frequency of the ARSA pseudodeficiency mutation in Australia was estimated to be about 20%. Li et al. (1992) described a polymerase chain reaction (PCR)-based method for genotypically identifying pseudodeficiency.

Barth et al. (1994) used PCR and restriction endonuclease digestion to determine the frequency of A-to-G transitions at bases 1049 (N350S) and 1620 in healthy persons from England. Mutations were found in 24 of 77 screened persons. Two were homozygous for both mutations, 16 were heterozygous for both, 5 were heterozygous for the N350S mutation alone, and 1 was homozygous for the N350S mutation. Study of the 16 persons heterozygous for both mutations showed that in 15 persons both mutations were located on the same chromosome, and in 1 person the mutations were located on different chromosomes. Persons homozygous for both mutations had the lowest activities of ARSA.

Harvey et al. (1998) presented evidence that the combined effect of reduction in ARSA mRNA due to the polyadenylation defect and the lowering of ARSA activity and aberrant targeting of the expressed N350S ARSA protein ({607574.0002}) to the lysosome was estimated to reduce ARSA activity in pseudodeficiency homozygotes to approximately 8% of normal.

The ARSA gene encodes the lysosomal enzyme arylsulfatase A ({EC 3.1.6.8}).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Metachromatic leukodystrophy.

NP_001171809.1:p.Arg1107Gly in Exon 6 of *PCDH19* (NM_001184880.1:c.3319C>G) Conflicting

This is a Missense Variant located in the PCDH19 gene.

Protocadherins form a subfamily of calcium-dependent cell-cell adhesion molecules in the cadherin superfamily. Protocadherin-19 belongs to a subclass of protocadherins that share a highly conserved 17-amino acid cytoplasmic motif (Wolverton and Lalande, 2001). PCDH19 belongs to the delta-2 protocadherin subclass of the cadherin superfamily (Dibbens et al., 2008).

This gene has been observed to exhibit X-linked inheritance pattern.

It has been associated with Epileptic encephalopathy early infantile 9.

ClinVar Assessment from Bioinformatics Core,Luxembourg Center for Systems Biomedicine

Classified as Pathogenic on 2017-01-01 for Not Provided

CAADphred>15

ClinVar Assessment from GeneDx

Classified as Likely Benign on 2018-02-01 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

NP_005948.3:p.Glu429Ala in Exon 8 of *MTHFR* (NM_005957.4:c.1286A>C) Drug Response

This is a Missense Variant located in the MTHFR gene.

Van der Put et al. (1998) identified another polymorphism of the MTHFR gene: a 1298A-C mutation resulting in a glu429-to-ala (E429A) substitution. The mutation destroyed an MboII recognition site and had an allele frequency of 0.33. Whereas the 677C-T transition ({607093.0003}) occurs within the predicted catalytic domain of the MTHFR enzyme, the 1298A-C transversion is located in the presumed regulatory domain. The 1298A-C mutation resulted in decreased MTHFR activity, which was more pronounced in the homozygous than heterozygous state. Neither the homozygous nor the heterozygous state was associated with higher plasma homocysteine (Hcy) nor a lower plasma folate concentration--phenomena that are evident with homozygosity for the 677C-T mutation. However, van der Put et al. (1998) found that combined heterozygosity at the 2 polymorphic sites was associated with reduced MTHFR-specific activity, higher Hcy, and decreased plasma folate levels. Thus, combined heterozygosity for both MTHFR mutations resulted in features similar to those observed in homozygotes for the 677C-T mutation. This combined heterozygosity was observed in 28% of the neural tube defect (NTD) patients compared with 20% among controls, resulting in an odds ratio of 2.04. The data suggested that combined heterozygosity for the 2 common mutations accounts for a proportion of folate-related NTDs, which is not explained by homozygosity for the 677C-T mutation.

Yamada et al. (2001) studied the biochemical characteristics of the products of both the 677C-T and the 1298A-C polymorphisms by overexpressing the genes and purifying the protein to homogeneity in quantities suitable for the characterization. The E429A protein had biochemical properties indistinguishable from the wildtype enzyme. The A222V MTHFR, however, had an enhanced propensity to dissociate into monomers and to lose its FAD cofactor on dilution. Protein that had both changes revealed no additive effect in these biochemical studies. This prompted Scott (2001) to suggest that the claim of van der Put et al. (1998) that the double variant increases risk needed to be reevaluated.

Donnelly (2000) argued that the change described by van der Put et al. (1998) as 1298A-C is in fact 1289A-C. The mutation was expected to change the codon from GAA (glu) to GCA (ala). In a reply to Donnelly (2000), van der Put and Blom (2000) stated that the second SNP was designated 1298A-C for consistency with the first SNP, 677C-T. Although the first SNP was said to occur at nucleotide 677, the actual location may be nucleotide 665 of the coding region.

Isotalo et al. (2000) analyzed 119 neonatal cord blood samples and 161 fetal tissue samples for MTHFR 677C-T and 1298A-C mutations to determine whether certain MTHFR genotype combinations were associated with decreased in utero viability. Mutation analysis demonstrated that all possible MTHFR genotype combinations were represented in the fetal group; 677T and 1298C alleles could occur in either cis or trans configurations. Combined 677CT/1298CC and 677TT/1298CC genotypes, which contained 3 and 4 mutant alleles, respectively, were not observed in the neonatal group ($p = 0.0402$). This suggested decreased viability among fetuses carrying these

mutations and a possible selection disadvantage among fetuses with increased numbers of mutant MTHFR alleles. This was the first report to describe the existence of human MTHFR 677CT/1298CC and 677TT/1298CC genotypes and demonstrated their potential role in compromised fetal viability.

Volcik et al. (2001) presented data supporting the conclusion of Isotalo et al. (2000) concerning decreased viability among fetuses with the 677TT/1298CC genotype, which they did not observe in the United States and Canadian populations studied. Because they observed, in 3 different populations, the 677CT/1298CC genotype in frequencies nearing those expected, Volcik et al. (2001) concluded that this genotype does not result in a significant selective disadvantage.

Zetterberg et al. (2002) examined the distribution of the 677C-T and 1298A-C polymorphisms in 80 fetal tissue samples from spontaneous abortions occurring between the sixth and twentieth week of pregnancy, compared to 125 healthy blood donors (both cases and controls were from Crete, Greece). Only 1 of the 80 spontaneously aborted embryos had the wildtype combined genotype 677CC/1298AA as compared to 19 of 125 controls (p = 0.001). Combined genotypes which contain 3 or 4 mutant alleles were not detected in any of the groups, suggesting complete linkage disequilibrium between the 2 polymorphisms. A significant odds ratio of 14.2 (95% CI, 1.78-113) for spontaneous abortion was obtained when comparing the prevalence of at least 1 MTHFR mutation in abortions and controls (p = 0.001). Zetterberg et al. (2002) concluded from the data that the effect of 1 or more MTHFR mutated alleles may be detrimental during embryogenesis when the folate requirement is high.

Both the 677C-T and 1298A-C SNPs in the MTHFR gene decrease the activity of the enzyme, leading to hyperhomocysteinemia (603174), particularly in folate-deficient states. Ogino and Wilson (2003) calculated the haplotype frequencies of the polymorphisms at nucleotides 677 and 1298 in pooled general populations derived from data published in 16 articles. They found that most 677T and 1298C alleles were associated with 1298A and 677C alleles, respectively. There may be an increased frequency of the very rare cis 677T/1298C haplotype in some parts of the United Kingdom and Canada, possibly due to a founder effect.

Among Turkish women, Boduroglu et al. (2004) could find no support for a relationship between the 677C-T and 1298A-C SNPs in the MTHFR gene and risk of having a child with Down syndrome (190685).

Among 200 Indian individuals, Kumar et al. (2005) found that plasma homocysteine levels were significantly increased in those adhering to a vegetarian diet and in those with a 1298C allele. However, the increase in homocysteine levels in vegetarians was irrespective of MTHFR genotype. Among a larger group of over 400 Indian individuals, Kumar et al. (2005) found that the frequency of the 1298CC genotype was 19.46%, which was much higher than that reported for Caucasian (9.4%), Chinese (3.3%), or Japanese (1.6%) populations. The authors concluded that the 1298A-C polymorphism is relevant for increased plasma homocysteine levels in the Indian population.

Hobbs et al. (2006) observed an apparent protective effect of the MTHFR 1298C allele against congenital heart defect.

Allen et al. (2008) performed a metaanalysis comparing 1,211 cases of schizophrenia with 1,729 controls and found that the MTHFR 1298C allele ({dbSNP 1801133}) was associated with susceptibility to schizophrenia (odds ratio, 1.19; 95% CI, 1.07- 1.34; p = 0.002). According to the Venice guidelines for the assessment of cumulative evidence in genetic association studies (Ioannidis et al., 2008), the MTHFR association showed a 'strong' degree of epidemiologic credibility.

Methylenetetrahydrofolate reductase ({EC 1.5.1.20}) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubstrate for homocysteine remethylation to methionine.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Homocystinuria due to MTHFR deficiency, Neural tube defects susceptibility to, Schizophrenia susceptibility to, and Thromboembolism susceptibility to.

ClinVar Assessment from PharmGKB

Classified as Drug Response on 2016-05-18 for Fluorouracil, Leucovorin, And Oxaliplatin Response - Efficacy

PharmGKB Level of Evidence 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

ClinVar Assessment from GeneDx

Classified as Benign on 2016-04-25 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

NP_005948.3:p.Ala222Val in Exon 5 of *MTHFR* (NM_005957.4:c.665C>T) Drug Response

This is a Missense Variant located in the MTHFR gene.

Frosst et al. (1995) identified a 677C-T mutation in the MTHFR gene, resulting in an ala222-to-val (A222V) substitution. The alteration created a HinfI site that was used to screen 114 unselected French Canadian chromosomes; the allele frequency of the substitution was 0.38. The mutation in the heterozygous or homozygous state correlated with reduced enzyme activity and increased thermolability in

lymphocyte extracts; in vitro expression of the mutagenized cDNA containing the mutation confirmed its effect on thermolability of MTHFR. Individuals homozygous for the mutation had significantly elevated plasma homocysteine levels. Thus, the 677C-T mutation may represent an important genetic risk factor in vascular disease.

In a study of 101 Caucasians and 102 African Americans, McAndrew et al. (1996) found that the allele frequency for the thermolabile form, 677T, was 0.30 in Caucasians and 0.10 in African Americans. No val/val homozygotes were found among the African Americans and 9 were found among the Caucasians.

Mogk et al. (2000) used DNA from Guthrie blood spots to determine the frequency of various MTHFR genotypes in Manitoba. Of 977 newborns, 7% were homozygous T/T. The frequency of the T allele was calculated as 0.2497.

Schneider et al. (1998) found the 677C-T polymorphism in every population tested. Unlike other mutations, such as factor V Leiden ({612309.0001}), the CCR5 deletion ({601273.0001}), and the HFE cys282-to-tyr ({235200.0001}) and his63-to-asp ({235200.0002}) hemochromatosis mutations, which are common only in Europe, the 677C-T mutation was found to have a relatively high frequency throughout the world. Schneider et al. (1998) pointed out that the frequency of 677C-T was lowest in Africa (6.6%) compared with Europe and Asia.

Rosenberg et al. (2002) analyzed the question of whether the MTHFR 677T alteration has an ancestral origin or has occurred repeatedly. They analyzed the frequency distribution of the previously described polymorphism 1298A/C ({607093.0004}) in exon 7 and of 3 intronic dimorphisms, in white Israelis (Jews and Arabs), Japanese, and Ghanaian Africans. Remarkably, the 677T allele was associated with 1 haplotype in white and Japanese homozygotes. Among the Africans, analysis of maximum likelihood also disclosed an association with the same haplotype, although none of the 174 subjects examined was homozygous for MTHFR 677T. These result suggested that the MTHFR 677T alteration occurred on a founder haplotype that may have had a selective advantage.

Both the 677C-T and 1298A-C SNPs in the MTHFR gene decrease the activity of the enzyme, leading to hyperhomocysteinemia (603174), particularly in folate-deficient states. Ogino and Wilson (2003) calculated the haplotype frequencies of the polymorphisms at nucleotides 677 and 1298 in pooled general populations derived from data published in 16 articles. They found that most 677T and 1298C alleles were associated with 1298A and 677C alleles, respectively. There may be an increased frequency of the very rare cis 677T/1298C haplotype in some parts of the United Kingdom and Canada, possibly due to a founder effect.

Stevenson et al. (1997) provided data on the frequency of the 677C-T polymorphism of MTHFR. Among 151 consecutively born white infants in South Carolina, 20 were homozygous and 65 were heterozygous for T; among consecutive black newborns, none of 146 were homozygous, and 31 were heterozygous. The estimated allele frequency of the mutation was 0.35 among white newborns and 0.11 among black newborns.

In 1992 and 1993, Guttormsen et al. (1996) screened 18,043 subjects, aged 40 to 67, and found 67 cases (0.4%) with total plasma homocysteine equal to or greater than 40 micromol/l. Compared to 329 controls, the cases had lower plasma folate and cobalamin levels, lower intake of vitamin supplements, consumed more coffee, and were more frequently smokers. Homozygosity for the 677C-T mutation in the methylenetetrahydrofolate reductase gene was observed in 73.1% of the cases and 10.2% of controls. Two years after screening, 58 subjects were reinvestigated; 41 still had homocysteine levels greater than 20 mmol/l, and in 37 of these, intervention with low dose folic acid (0.2 mg/d) was started. Notably, 34 of 37 (92%) had homozygosity for the 677C-T mutation. Plasma homocysteine was reduced in all but 2 after 7 weeks and became normal within 7 months in 21 of 37 subjects. Most of their remaining subjects obtained a normal homocysteine level with 5 mg/d of folic acid. Guttormsen et al. (1996) concluded that most subjects with hyperhomocysteinemia greater than 40 micromol/l in the general population have the 677C-T mutation combined with low folate status. They concluded that daily supplement of low-dose folic acid will reduce and often normalize their homocysteine levels.

Folate acts to stabilize the thermolabile enzyme with the 677C-T mutation (Frosst et al., 1995). Serum folate levels greater than 15.4 nM appeared to neutralize the effects of 677C-T mutations (Jacques et al., 1996).

Bagley and Selhub (1998) used a chromatographic method for folate analysis to test the hypothesis that the 677C-T mutation is associated with altered distribution of red blood cell (RBC) folates. An alteration was found as manifested by the presence of formylated tetrahydrofolate polyglutamates in addition to methylated derivatives in the RBCs from homozygous mutant individuals. 5-Methylenetetrahydrofolate polyglutamates were the only folate form found in RBCs from individuals with the wildtype genotype. Existence of formulated folates in RBCs only from individuals with the thermolabile MTHFR is consistent with the hypothesis that there is in vivo impairment in the activity of the thermolabile variant of MTHFR and that this impairment results in an altered distribution of RBC folates.

Friso et al. (2002) sought to determine the effect of folate status on genomic DNA methylation with an emphasis on interaction with the common 677C-T mutation in the MTHFR gene. They used the liquid chromatography/mass spectrometry method for the analysis of nucleotide bases to assess genomic DNA methylation in peripheral blood mononuclear cell DNA from 105 subjects homozygous for the TT genotype and 187 homozygous for the wildtype (CC) MTHFR genotype. The results showed the genomic DNA methylation directly correlates with folate status and inversely with plasma homocysteine levels (P less than 0.01). TT genotypes had a diminished level of DNA methylation compared with those with the CC wildtype. When analyzed according to folate status, however, only the TT subjects with low levels of folate accounted for the diminished DNA methylation. Moreover, in TT subjects DNA methylation status correlated with the methylated proportion of red blood cell folate and was inversely related to the formylated proportion of red blood cell folates that is known to be solely represented in those individuals. These results indicated that the MTHFR 677C-T polymorphism influences DNA methylation status through interaction with folate status.

Kvittingen et al. (1997) observed a child with typical features of methionine synthase deficiency (see 156570) but no hemolytic anemia, which is usually a feature of that disorder. They found that the child was also homozygous for the 677C-T mutation and suggested that this polymorphism protected the patient against anemia. Furthermore, they speculated that it may account for the dissociation between the hematologic and neurologic disease seen in some patients with vitamin B12 deficiency.

Fletcher and Kessling (1998) performed a metaanalysis of 19 case-control studies seeking an association between thermolabile MTHFR, raised plasma homocysteine, and/or arteriosclerotic disease. They also tabulated homozygote percentage and allele frequency of the thermolabile variant in different healthy populations. A review of the data from individual case-control studies neither confirmed nor dismissed an association between thermolabile MTHFR, raised homocysteine levels, and/or vascular disease. They pointed out the overwhelming predominance of investigations conducted in white Caucasian populations and the paucity of detail given about the population of origin. Population specificity of allelic association is well established and has been the cause of several errors of inference in association studies.

Among control individuals from 2 groups, Rozen et al. (1999) found that the percentage of females with the homozygous 677C-T mutation was decreased from the expected 50%. The combined percentage of females from both control groups was 33% (p less than 0.01). The authors suggested that decreased viability in utero for 677C-T homozygotes, particularly females, requires further consideration and study. Anderson et al. (2005) also reported a decreased number of female 677TT homozygotes compared to males in a study of 559 Caucasian individuals: 13.9% of males were TT homozygotes compared to 7.8% of females. However, a metaanalysis performed using a literature search of 20 previous reports showed no consistent gender difference in homozygosity for the 677C-T polymorphism. Anderson et al. (2005) concluded that there is no prenatal selection against female 677TT homozygotes and that the results obtained by their own study and that of Rozen et al. (1999) must have reflected sampling error.

In Leiden, Holland, Heijmans et al. (1999) studied the effect of the val/val genotype on mortality by comparing its frequency in 365 subjects, aged 85 years or over, and 250 blood donors, aged 18 to 40 years. The val/val genotype was underrepresented in the elderly as compared to the younger subjects (frequency of 0.3 and 0.36, respectively; p = 0.03); the association was only present in men.

Bagley and Selhub (1998) discussed the inconsistent findings of the thermolabile MTHFR variant as a risk factor for coronary artery disease or neural tube defects. They suggested that some of the inconsistency may be attributable to improper selection of control populations but that some may also be caused by factors that affect the activity of the thermolabile enzyme in its natural milieu. In their study, wide differences were found in the proportion of formylated folate between individuals in the homozygous T/T group, suggesting that other factors affect the synthesis of 5-methyltetrahydrofolate by the thermolabile MTHFR.

The 677C-T polymorphism of MTHFR was investigated in the analysis of Ioannidis et al. (2004), which undertook to study the genetic effects of 43 validated gene-disease associations across populations of various descents. They found that the frequencies of the genetic marker of interest in control populations often (58%) showed large heterogeneity (i.e., statistical variability) between 'races.' Conversely, they saw large heterogeneity in the genetic effects (odds ratios) between 'races' in only 14% of cases. Thus, genetic markers for gene-associations varied in frequency across populations, but their biologic impact on the risk for common diseases may usually be consistent across traditional 'racial' boundaries.

Goldstein and Hirschhorn (2004) reported allele frequency differences between African Americans and European Americans for pharmacogenetic polymorphisms, i.e., variants reported to influence drug response. The difference in allele frequencies for MTHFR was more than 35%. The biologic impact in the 2 ethnic groups was consistent.

In a study of 10,601 adults from the Norwegian Colorectal Cancer Prevention Cohort, Hustad et al. (2007) found that the mean concentrations of total plasma homocysteine were 10.4 micromol/liter, 10.9 micromol/liter, and 13.3 micromol/liter in subjects with the CC (51%), CT (41%), and TT (8%) genotypes, respectively. The authors concluded that individuals with the TT genotype were particularly sensitive to the status of several B vitamins and suggested that they might be considered candidates for individualized nutritional recommendations.

In a population-based study with a cross-sectional design that included 10,601 healthy men and women aged 50 to 64 years, Holm et al. (2007) studied the effect of betaine total homocysteine (tHcy) concentration within the frame of variable B-vitamin status and according to the MTHFR 677C-T genotype. Betaine was a strong determinant of plasma tHcy in subjects with low serum folate and the MTHFR TT genotype. The association was further strengthened at low levels in the circulation of the other B vitamins (B2, B6, and B12). Thus, in subjects with the combination of serum folate in the lowest quartile, low vitamin B2, B6, and B12 status, and the MTHFR TT genotype, the difference in tHcy (mean, 95% confidence interval) across extreme plasma betaine quartiles was 8.8 (1.3-16.2) mol/liter.

Lange et al. (2010) performed a genomewide association study for plasma homocysteine (Hcy) in 1,786 unrelated Filipino women from the Cebu Longitudinal Health and Nutrition Survey (CLHNS). The most strongly associated single-nucleotide polymorphism (SNP), {dbSNP rs7422339} (p = 4.7 x 10(-13)), encodes thr1405 to asn in CPS1 ({608307.0006}) and explained 3.0% of variation in the Hcy level. The widely studied MTHFR C677T SNP ({dbSNP rs1801133}) was also highly significant (p = 8.7 x 10(-10)) and explained 1.6% of the trait variation. In a follow-up genotyping of these 2 SNPs in 1,679 CLHNS gender-combined young adult offspring, the MTHFR C677T SNP was strongly associated (p = 1.9 x 10(-26)) with Hcy and explained 5.1% of the variation. In contrast, the CPS1 variant was significant only in females. Combined analysis of all samples confirmed that the MTHFR variant was more strongly associated with Hcy in the offspring. Although there was evidence for a positive synergistic effect between the CPS1 and MTHFR SNPs in the offspring, there was no significant evidence for an interaction in the mothers. The authors suggested that genetic effects on Hcy may differ across developmental stages.

VASCULAR DISEASE

From studies of the 677C-T mutation in cardiovascular patients and controls, Kluijtmans et al. (1996) concluded that homozygosity for this frequent mutation in the MTHFR gene is associated with a 3-fold increase in risk for premature cardiovascular disease.

Morita et al. (1997) studied 362 Japanese male patients with angiographically confirmed coronary artery disease and 778 controls. They reported a significantly higher frequency of the rarer 677C-T allele, corresponding to a valine substitution, in the disease group. The association was stronger in homozygotes than in heterozygotes, which, Morita et al. (1997) concluded, suggests that the 677C-T polymorphism may be a risk factor for coronary artery disease. van Bockxmeer et al. (1997) did not, however, find such a relationship in their study of 555 white Western Australians with angiographically documented coronary artery disease and 143 unrelated controls. Schwartz et al. (1997) studied allele frequencies of the MTHFR 677C-T polymorphism in 69 non-Hispanic white female survivors of myocardial infarction and 338 controls. They found a similar distribution of alleles in both groups. Schwartz et al. (1997) concluded that this polymorphism was not a risk factor for myocardial infarction in their population.

Kelly et al. (2002) performed a metaanalysis to determine the risk for ischemic stroke (601367) associated with hyperhomocyst(e)inemia and the 677C-T polymorphism of MTHFR. They concluded that the data support an association between mild to moderate hyperhomocyst(e)inemia and ischemic stroke. The MTHFR TT genotype may have a small influence in determining the susceptibility to ischemic stroke.

Klerk et al. (2002) performed a metaanalysis of the risk of coronary heart disease related to the 677C-T polymorphism. They concluded that individuals with the 677TT genotype have a significantly higher risk of coronary heart disease, particularly in the setting of low folate status. These results supported the hypothesis that impaired folate metabolism, resulting in high homocysteine levels, is causally related to increased risk of coronary heart disease.

NEURAL TUBE DEFECTS

Motulsky (1996) reviewed the possible role of homocysteine elevations in general and the MTHFR polymorphism specifically in vascular disease and neural tube defects (NTD; 601634). He cited evidence from the Centers for Disease Control (Anonymous, 1992) that folic acid given before and during the first 4 weeks of pregnancy can prevent 50% or more of neural tube defects. Mills et al. (1995) showed that mothers of infants with neural tube defects have increased homocysteine levels. Furthermore, van der Put et al. (1995) found that the frequency of the homozygous MTHFR polymorphism was 2 to 3 times increased among Dutch mothers, fathers, and patients with neural tube defect. The lower frequency (approximately 1% homozygotes) of the MTHFR polymorphism among the African American population is of some interest, in view of the lower incidence of neural tube defects among blacks.

Stevenson et al. (1997) cited unpublished observations indicating that the prevalence of neural tube defects in South Carolina is 16 in 10,000 pregnancies in whites and 10 in 10,000 pregnancies in blacks.

Ou et al. (1996) studied fibroblast cultures from 41 NTD-affected fetuses and compared their genotypes with 109 blood specimens from the general population. They demonstrated that 677C-T homozygosity was associated with a 7.2-fold increased risk for NTD ($p = 0.001$). Ou et al. (1996) concluded that the 677C-T polymorphism of MTHFR may provide a partial biologic explanation for the prevention of neural tube defects by folic acid.

In a study of French patients with neural tube defects prenatally diagnosed, Mornet et al. (1997) could find no higher frequency of the 677C-T mutation than in controls. Likewise, Speer et al. (1997) investigated the MTHFR thermolabile variant in 65 sporadic American Caucasian patients with lumbosacral NTD and their unaffected parents, using both case-control design and assessment of linkage disequilibrium. They found no evidence to support variation in MTHFR as a significant risk factor for NTD in this population. De Franchis et al. (1998) studied 203 living individuals with spina bifida and 583 controls in Italy. They found an odds ratio for spina bifida associated with individuals homozygous for the 677C-T mutation of 1.73 and no increased risk for patients heterozygous for this mutation.

Christensen et al. (1999) stated that the 677C-T polymorphism of the MTHFR gene was the first genetic risk factor for neural tube defects identified at the molecular level. Homozygosity for the 677C-T allele has been shown to be more prevalent in individuals with NTD and in their parents, as compared to controls ({103,101:van der Put et al., 1995, 1997}; Whitehead et al., 1995; Ou et al., 1996). Christensen et al. (1999) assessed genotypes and folate status in 56 patients with spina bifida, 62 mothers of patients, 97 children without NTDs (controls), and 90 mothers of controls to determine the impact of these factors on NTD risk. In 20% of cases and 18% of case mothers, they found homozygosity for the MTHFR polymorphism, compared to 11% of controls and 11% of control mothers, indicating that the mutant genotype conferred an increased risk for NTDs. The risk was further increased if both mother and child had this genotype. RBC folate was lower in cases and in case mothers, compared to their respective controls. The combination of homozygous mutant MTHFR genotype and RBC folate in the lowest quartile conferred an odds ratio for being an NTD case of 13.43 and an odds ratio for having a child with NTD of 3.28. Christensen et al. (1999) proposed that the genetic-nutrient interaction, i.e., MTHFR polymorphism and low folate status, is associated with a greater risk for NTDs than either variable alone.

{63:Munoz-Moran et al. (1998)} studied the evolution with age of the allele and genotype frequencies of the A222V mutation, which they called A225V, in a healthy population of 695 individuals in southern Spain. They excluded persons older than 40 years to prevent changes in frequency due to the possible implication of this gene in different pathologies and to nutritional habits. All the individuals were genotyped for the insertion/deletion polymorphism of the ACE gene ({106180.0001}) to assess the genetic homogeneity of the adult and young populations. The allele and genotype frequencies of the ACE polymorphism did not differ significantly between the 2 populations. Unexpectedly, {63:Munoz-Moran et al. (1998)} found a substantial increase in frequency of the VV homozygous genotype in individuals younger than 20 years. They found a shift in the VV genotype frequency, from 13% to 26%, that started in people born between 1977 and 1982 and that remained at this high proportion. They also found that the population from which these individuals were derived was in

Hardy-Weinberg equilibrium. In 1982, early folate treatment for all pregnant women was recommended by the Spanish national health service to prevent neural tube defects. {63:Munoz-Moran et al. (1998)} hypothesized an association between early folate supplementation during pregnancy and an increased number of babies born with the VV genotype, especially in VV mothers.

{75:Reyes-Engel et al. (2002)} assessed the effect of the 677C-T and 1298A-C ({607093.0004}) polymorphisms of the MTHFR gene in relation to possible selection for these polymorphisms. Based on random pairs and linkage disequilibrium of the 2 polymorphisms, they estimated the rate of fetal nonviability according to the combinations of these 2 polymorphisms to be 4.63% for the group more than 24 years of age and 6.31% for the group less than 24 years of age. They detected an increased frequency of mutant alleles in the youngest age group, coincident with a generally increased folate intake by pregnant women in Spain. The genetic selection detected would lead to an increase in mutated individuals, the number of whom the authors predicted could increase 4-fold within 75 years. Although generally reduced in the younger age groups, the homocysteine plasma levels were shown to increase in individuals according to the number of mutations, especially those of the 677T allele.

CLEFT LIP/PALATE

Shaw et al. (1998) hypothesized that infants homozygous for the 677C-T genotype would be at increased risk for cleft lip with or without cleft palate (CL/P; see 119530) because of lower MTHFR enzymatic activity. In their study of 310 infants with isolated CL/P and 383 control infants without a congenital anomaly, analysis of DNA (which was available from newborn screening blood specimens) did not indicate an increased risk for CL/P among 677C-T homozygotes, nor did the results indicate an interaction between infant 677C-T genotype and maternal multivitamin use on the occurrence of CL/P.

Mills et al. (1999) examined the prevalence of the 677C-T mutation in subjects with oral cleft from a national Irish support group and an anonymous control group randomly selected from a neonatal screening program covering all births in Ireland. Among 848 control subjects, 83 (9.8%) were homozygous (TT) thermolabile MTHFR. This genotype was almost 3 times as common in the 27 subjects (25.9%) with isolated cleft palate and somewhat more common in the 66 subjects with cleft lip with or without cleft palate. When the 2 groups with different etiologies were combined, the overall odds ratio was 2.06. Thus, in the Irish population, homozygosity for the common folate-related polymorphism associated with thermolabile MTHFR is significantly more frequent in those with isolated cleft palate, and could be etiologically important.

Zhu et al. (2006) studied the thermolabile 677C-T polymorphism in 170 Chinese case-parent trios and observed a moderate association between the polymorphism and nonsyndromic cleft lip/palate in families from northern China but not in those from southern China. Heterozygous parents in the north were about twice as likely to transmit the high-risk T allele to affected cases as parents in the south (OR = 2.24). Zhu et al. (2006) suggested that there may be genetic heterogeneity in the development of nonsyndromic cleft lip/palate among northern and southern populations in China.

Mostowska et al. (2006) did not find a significant association between the 677C-T polymorphism and cleft lip/palate among 122 Polish women with affected children.

In a case-control study of Brazilian families with CL/P, Gaspar et al. (2004) observed that with the presence of a maternal MTHFR 677T allele there was an increased likelihood of offspring having the less common non-135-bp BCL3 (109560) allele (OR, 2.3, 95% CI, 1.1-4.8, p = 0.03). Gaspar et al. (2004) suggested that maternal MTHFR genotype plays a significant role in susceptibility to CL/P, but its teratogenic effect depends on the genotype of the offspring.

HYPERTENSION

Nishio et al. (1996) provided information on the frequency of the MTHFR 677C-T polymorphism in the Japanese population. They could find no significant relationship between the polymorphism and hypertension.

Qian et al. (2007) performed a metaanalysis of 25 published studies involving the C677T MTHFR polymorphism and more than 2,800 hypertensive individuals from Caucasian and Asian populations and found evidence for a significant association in both populations. The authors suggested that C677T is an independent risk factor for hypertension.

PREECLAMPSIA SUSCEPTIBILITY

Sohda et al. (1997) found that the 677T allele and homozygosity for the 677T allele was significantly increased in a group of patients with preeclampsia (189800). They concluded that the 677T variant of the MTHFR gene is one of the genetic risk factors for preeclampsia.

In a study of 101 Japanese women with hypertension in pregnancy, including 73 cases of preeclampsia, and 215 normal pregnancy controls, Kobashi et al. (2000) found no association between the 677T MTHFR variant and preeclampsia. The authors hypothesized that the lack of association in their population may be secondary to differences in dietary folate intake and suggested that dietary factors and/or folate levels be analyzed in future studies of MTHFR and preeclampsia.

THROMBOSIS

Tonetti et al. (2002) described 2 sisters who were homozygous for the 677C-T mutation and heterozygous for 3 other mutations: 2 missense mutations inherited from the father and a donor splice site mutation causing skipping of exon 6 inherited from the mother. The abnormalities of the MTHFR gene became evident when 1 of the sisters, an obese 27-year-old woman, developed pulmonary embolism due to venous thrombosis (see 188050) 8 months after taking oral contraceptives. She had walking problems since childhood and had encountered difficulties at school. Neurologic examination revealed bilateral Babinski signs. Computerized tomography studies revealed bilateral pulmonary embolism and duplex ultrasonography revealed left iliac vein thrombosis. Fibrinolysis treatment restored cardiopulmonary capacity. However, massive hyperhomocysteinemia and homocystinuria associated with hypomethioninemia were found.

She became progressively confused and disoriented with walking difficulties. Severe MTHFR deficiency was diagnosed and she was treated with folic acid, hydroxocobalamin, betaine, and fluindione. Her clinical status improved gradually and she recovered superior intellectual functions. Her sister, aged 26 years, had intellectual retardation and a slow gait. At the age of 5 years, she developed seizures, walking difficulties, and mental retardation, and showed bilateral pyramidal syndrome of the lower limbs. Hyperhomocysteinemia was treated as in her sister, but her symptoms did not respond to folic acid treatment. The parents, both 54 years of age, were in professional occupations. Neurologic assessment was normal in both. The father had developed myocardial infarction at the age of 48 years. He had been treated with folic acid because of moderate hyperhomocysteinemia. The mother had never experienced venous or arterial thrombosis but had been treated with folic acid because of mild hyperhomocysteinemia.

Queffeulou et al. (2002) reported a case of renal artery thrombosis in a 42-year-old man who was homozygous for the 677C-T mutation and had a low folate level. They suggested that smoking contributed to the pathogenesis of renal arterial thrombosis.

In a study in Greece of venous thromboembolism, Zalavras et al. (2002) found that homozygosity for the 677T allele of the MTHFR gene was slightly more prevalent in patients compared to controls; however, they could not establish an association with venous thromboembolism.

Quere et al. (2002) found a strong concentration-dependent association between concentrations of methylfolate in RBCs and risk of venous thromboembolism that varied according to 677C-T genotype. Their method for measurement of RBC methylfolate was criticized by Lucock and Yates (2002).

Lu et al. (2002) could find no evidence that the 677C-T mutation was a risk factor for pulmonary thromboembolism in a Chinese population.

Keijzer et al. (2002) concluded that both hyperhomocysteinemia due to the 677C-T mutation and factor V Leiden are risk factors for recurrent venous thrombosis. They found that the risk of thrombosis appeared higher for individuals who had both risk factors.

In a study in China, Li et al. (2002) investigated the role of hyperhomocysteinemia and the 677C-T mutation in patients with Budd-Chiari syndrome (600880). They compared 41 affected patients with 80 sex- and age-matched healthy controls. The mean plasma homocysteine level was significantly higher in affected patients compared with normal controls. The frequency of 677TT homozygotes was significantly increased, and the frequency of 677C-T heterozygotes was not increased, compared with controls.

In a comprehensive metaanalysis of 22 case-control studies including 3,387 white adult patients, Casas et al. (2004) found a statistically significant association between ischemic stroke (601367) and the 677C-T substitution (odds ratio of 1.24).

RETINAL ARTERY OCCLUSION

Talmon et al. (1997) described retinal arterial occlusion in a child heterozygous for the factor V R506Q mutation ({612309.0001}) and homozygous for thermolabile methylene tetrahydrofolate reductase. Thus the coexistence of 2 mild hereditary thrombophilic states can result in severe thrombotic manifestations in young people. Although factor V Leiden had been associated clearly with venous thrombosis, most studies had failed to demonstrate an association between isolated factor V Leiden and arterial thrombosis.

Weger et al. (2002) investigated whether hyperhomocysteinemia and/or homozygosity for the C677T mutation in the MTHFR gene were associated with an increased risk for retinal artery occlusion. They found that mean plasma homocysteine levels were significantly higher in patients with retinal artery occlusion compared with normal controls. However, the prevalence of the homozygous genotype of the C677T mutation did not differ significantly between patients and controls.

DOWN SYNDROME

Hobbs et al. (2000) found that the MTHFR 677C-T polymorphism is more prevalent among mothers of children with Down syndrome (190685) than among control mothers, with an odds ratio of 1.91. In addition, the homozygous MTRR 66A-G polymorphism ({602568.0003}) was independently associated with a 2.57-fold increase in estimated risk. The combined presence of both polymorphisms was associated with a greater risk of Down syndrome than was the presence of either alone. The 2 polymorphisms appeared to act without a multiplicative interaction. O'Leary et al. (2002) examined the prevalence of the MTHFR 677C-T variant among 48 mothers who had given birth to a child with Down syndrome and 192 control mothers. The frequency of the MTHFR 677C-T genotype was not significantly higher in mothers of children with Down syndrome ($p = 0.74$). However, mothers who were heterozygous or homozygous for the MTHFR variant and homozygous for the 66A-G variant in MTRR ({602568.0003}) had a 2.98-fold risk of having a child with Down syndrome ($p = 0.02$).

Stuppia et al. (2002) studied the presence of the MTHFR 677C-T polymorphism in 64 mothers of children with trisomy 21 and 112 control mothers from central Italy. The frequency of the T allele was higher in control mothers (48%) than in trisomy 21 mothers (44%). The results did not support the presence of an increased risk of Down syndrome among carriers of the T allele in the Italian population.

Hobbs et al. (2002) examined the transmission frequencies of the MTHFR 677T and 677C alleles from heterozygous parents to children with Down syndrome in 202 Caucasian families. The results indicated that the 677T allele was transmitted to children with Down syndrome at a significantly higher rate than would be expected based on mendelian inheritance patterns, and the C allele was transmitted at a significantly lower rate (P less than 0.009). The authors also examined transmission frequencies independently for maternally and paternally transmitted alleles to assess potential parent-of-origin effects. Because the vast majority of conceptions with trisomy 21 end in pregnancy loss, Hobbs et al. (2002) questioned whether the observed preferential transmission of the T allele for this population of liveborn infants with Down syndrome could reflect a survival advantage. They presented a plausible biochemical interpretation of these results based on a maternal-fetal MTHFR 677T allele interaction in the context of the constitutive overexpression of 3 copies of the cystathionine beta-synthase gene (CBS; 236200) in the trisomy 21 fetus.

Yanamandra et al. (2003) analyzed 22 pregnant Caucasian patients with fetal karyotype of trisomy 21 and 375 control Caucasian infants for the MTHFR 677C-T polymorphism. Homozygosity for the 677T allele in the Down syndrome pregnancies was 13.6% as compared to 13.3% in the control infants, and the frequency of the mutant 677T allele was 0.364 in the Down syndrome pregnancies versus 0.356 in the controls (odds ratio of 1 for both). Yanamandra et al. (2003) found no correlation of MTHFR mutant 677TT homozygosity or mutant 677T allele frequency with prenatal Down syndrome cases.

Among Turkish women, Boduroglu et al. (2004) could find no support for a relationship between the 677C-T and 1298A-C SNPs in the MTHFR gene and risk of having a child with Down syndrome.

CANCER

Aberrant DNA methylation is a common feature of human neoplasia. Paz et al. (2002) studied interindividual inherited susceptibility to the epigenetic processes of CpG island hypermethylation and global genomic hypomethylation, which are observed simultaneously in cancer cells. They genotyped 233 patients with colorectal, breast, or lung tumors for 4 germline variants in 3 key genes involved in the metabolism of the methyl group. A positive association was found between aberrant methylation and the 677T allele. A second association of aberrant methylation was with homozygosity for the 2756G allele of methionine synthase ({156570.0008}).

Castro et al. (2004) investigated the effect of the 677C-T and 1298A-C MTHFR polymorphisms on leukocyte genomic DNA methylation status in 96 healthy unrelated white Portuguese subjects. The authors found that both mutations when homozygous were associated with decreased DNA methylation status, although the effect was slightly less pronounced for the 1298A-C transversion. Regression analyses corroborated the concept that mutant 677C-T MTHFR activity is mediated by folate availability. Castro et al. (2004) suggested that the 1298CC MTHFR genotype, independently of folate availability, and the 677TT MTHFR genotype with concomitant low folate levels, might be potential risk factors for disease states associated with DNA hypomethylation status.

Hubner et al. (2007) analyzed the microsatellite instability (MSI) phenotype in 1,685 colorectal cancer (CRC) specimens and MTHFR 677C-T genotype in germline DNA for all cases and 2,692 cancer-free controls. Compared to homozygous wildtype individuals, those with the 677TT genotype were more likely to have MSI than microsatellite stable (MSS) CRC (odds ratio (OR), 1.90). When MTHFR 677C-T genotype frequencies in MSS CRC cases were compared to controls, individuals with a 677TT genotype were at 19% reduced risk of cancer compared to wildtype (OR, 0.81). Conversely, when MSI CRC cases were compared to controls, individuals with 1 or 2 677T alleles were at 42% increased cancer risk (OR, 1.42). Hubner et al. (2007) concluded that MTHFR 677TT homozygous individuals are more likely to develop MSI CRC than those with wildtype genotype, and that this common polymorphism has differential influences on MSI and MSS CRC risk.

DEPRESSION

Bjelland et al. (2003) examined the association between folate, total homocysteine, vitamin B12, and the MTHFR 677C/T polymorphism and anxiety and depression (see 608516) in a large population-based study. Using the Hospital Anxiety and Depression Scale, Bjelland et al. (2003) measured anxiety and depression in 5,948 subjects, aged 46 to 49 years and 70 to 74 years, from the Hordaland Homocysteine Study cohort. Hyperhomocysteinemia (plasma total homocysteine level greater than or equal to 15.0 micromol/L) and the T/T genotype, but not low plasma folate or B12 levels, were significantly related to depression without comorbid anxiety disorder. Bjelland et al. (2003) concluded that the results provided evidence for impaired 1-carbon metabolism in depression.

Lewis et al. (2006) genotyped the 677C/T polymorphism in 3,478 women in the British Women's Heart and Health Study to look for an association between genotype and 3 indicators of depression: ever diagnosed as depressed, currently taking antidepressants, and the EuroQol mood question. Subsequently, they performed a systematic review and metaanalysis of all published studies associated with this polymorphism. In the British Women's Heart and Health Study, they found an increased risk of having been diagnosed as depressed in TT compared to CC individuals (OR, 1.35; 95% CI, 1.01, 1.80). A metaanalysis of the other studies combined with this study yielded an OR of 1.36 (95% CI, 1.11, 1.67, p = 0.003), suggesting that folate or its derivatives may be causally related to risk of depression.

SCHIZOPHRENIA

Lewis et al. (2005) conducted a metaanalysis of 6 studies (1,119 cases, 1,308 controls) involving the MTHFR 677CT polymorphism and schizophrenia (181500) risk. They found that TT homozygotes had a significantly increased risk (odds ratio, 1.48; 95% CI, 1.18-1.86), supporting the role of this gene and folate metabolism as schizophrenia risk factors.

Muntjewerff et al. (2005) conducted a case-control study to quantify the risk of schizophrenia in the presence of elevated homocysteine concentrations and the 677TT MTHFR haplotype in 254 patients with schizophrenia and 414 healthy controls of Dutch ancestry. Homocysteine concentrations were stratified into quartiles, revealing that the risk of schizophrenia increased in the fourth and third quartile versus the lowest quartile (OR, 3.3, 95% CI, 1.2-9.2 and OR, 3.1, 95% CI, 1.2-8.0, respectively). A significant dose-response relationship of increasing homocysteine levels and increasing risk of schizophrenia was observed (p = 0.036). The 677TT genotype was associated with an odds ratio of 1.6 (95% CI, 0.96-2.8) of having schizophrenia. Heterozygosity for the T allele compared to homozygosity for the C allele accounted for an odds ratio of 1.3 (95% CI, 0.91-1.8). Elevated homocysteine levels and the TT genotype were associated with increased risk of schizophrenia.

Muntjewerff et al. (2006) conducted a metaanalysis of retrospective studies of homocysteine concentrations (812 cases and 2,113 controls) to examine the association between homocysteine in schizophrenia. In addition, a metaanalysis of 10 studies (2,265 cases and 2,721 controls) on the MTHFR 677C/T polymorphism was carried out to assess if this association was causal. A 5 micromol/l higher homocysteine level was associated with a 70% (95% CI, 27-129) higher risk of schizophrenia. The TT genotype was associated with a

36% (95% CI, 7-72) higher risk of schizophrenia compared to the CC genotype. Evidence for the association of homocysteine with schizophrenia and the association of schizophrenia with the homozygous 677TT genotype of the MTHFR gene provides support for causality between disturbed homocysteine metabolism and the risk of schizophrenia.

In an SzGene metaanalysis (1,211 patients, 1,729 controls), Allen et al. (2008) found an association between susceptibility to schizophrenia and 2 MTHFR variants, 677C-T ({dbSNP 1801133}) and 2298C-T ({607093.0004}). The authors noted that both substitutions had been found to reduce MTHFR enzyme activity.

In a study of 200 outpatients with schizophrenia who were evaluated with the Positive and Negative Syndrome Scale (PANSS), Roffman et al. (2008) found that negative symptom scores were significantly related with the 677T allele dose, with T/T subjects exhibiting the most pronounced symptoms (likelihood ratio test (LRT) = 4.18, p = 0.041); protection against positive symptoms was related to a higher 677T allele load (LRT = 5.07, p = 0.024). The effect of the 677T allele on negative symptom severity correlated with serum folate levels.

MIGRAINE WITH AURA

Among Japanese patients with migraine, 22 with aura (MA) and 52 without aura (MO) (see 157300), Kowa et al. (2000) found an association between the 677TT genotype and MA (odds ratio of 6.5).

In Spanish patients with migraine (78 MA and 152 MO), Oterino et al. (2004) found that the 677TT genotype was more common in those with MA aura compared to MO (odds ratio of 2.34). However, there was no association between migraine and the 677CT polymorphism overall when compared to 204 controls.

Among 187 Dutch MA patients, 226 MO patients and 1,212 controls, Scher et al. (2006) found that the TT genotype was associated with increased risk for MA (odds ratio of 2.05). There was a significant trend for the number of T alleles and MA, but not MO. The association was not mediated by cardiovascular risk factors or by plasma levels of folate or vitamin B12, which are involved in homocysteine metabolism, although the odds ratio was decreased slightly after adjustment for total homocysteine levels. In contrast, Todt et al. (2006) found no association between the T allele and migraine with aura among 656 German patients with MA and 625 controls. There was also no association in an independent family-based study of 155 German MA trios.

GLAUCOMA

Junemann et al. (2005) estimated the prevalence of the C677T single-nucleotide polymorphism in the MTHFR gene in primary open-angle glaucoma (POAG; 137760) and pseudoexfoliation open-angle glaucoma (PEXG; see 177650). The authors found significant evidence of a higher prevalence of C677T in POAG (9% homozygotes, 49% heterozygote, 42% wildtype, p = 0.01, OR = 2.38) than in PEXG (9% homozygotes, 41% heterozygote, 50% wildtype, p = 0.09, OR 1.78) compared with controls (3% homozygotes, 34% heterozygote, 63% wildtype). Thus, Junemann et al. (2005) concluded that the MTHFR C677T variant leading to moderate hyperhomocysteinemia might play a role as a genetic risk factor in the pathogenesis of POAG.

Methylenetetrahydrofolate reductase ({EC 1.5.1.20}) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubstrate for homocysteine remethylation to methionine.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Homocystinuria due to MTHFR deficiency, Neural tube defects susceptibility to, Schizophrenia susceptibility to, and Thromboembolism susceptibility to.

ClinVar Assessment from PharmGKB

Classified as Drug Response on 2017-02-17 for Methotrexate Response - Dosage, Efficacy, Toxicity/Adr

PharmGKB Level of Evidence 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

ClinVar Assessment from GeneDx

Classified as Benign on 2016-04-25 for Not Specified

This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease.

3 Prime UTR Variant in *CHRNB2* (NM_000748.2:c.*472G>A) Drug Response

This is a 3 Prime UTR Variant located in the CHRNB2 gene.

The nicotinic acetylcholine receptors (nAChRs) are members of a superfamily of ligand-gated ion channels that mediate fast signal transmission at synapses. The nAChRs are thought to be heteropentamers composed of homologous subunits. See 118508 for additional background information on nAChRs.

It has been associated with Epilepsy nocturnal frontal lobe 3.

ClinVar Assessment from PharmGKB

Classified as Drug Response on 2017-02-17 for Nicotine Response - Efficacy, Toxicity/Adr

PharmGKB Level of Evidence 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Intron Variant in *SCN1A* (NM_001165963.1:c.603-91G>A) Drug Response

This is a Intron Variant located in the SCN1A gene.

In a 2-stage case-control study including a total of 234 patients with febrile seizures (FEB3A; see 604403), Schlachter et al. (2009) found a significant association between the major A allele of {dbSNP rs3812718} and febrile seizures (first stage p value of 0.000017; replication p value of 0.00069). The data suggested that homozygosity for the A allele confers a 3-fold increased relative risk of febrile seizures and may account for a population attributable risk factor of up to 50%. The data were consistent with the hypothesis that low-risk variants with a high population frequency contribute to the risk of common and genetically complex diseases such as epilepsy.

The SCN1A IVS5N+5G-A polymorphism, formerly SCN1A IVS5-91G-A ({dbSNP rs3812718}), was shown by Tate et al. (2005) to affect the alternative splicing of exon 5. The major allele, A, disrupts the consensus sequence of fetal exon 5N, resulting in decreased expression of the fetal SCN1A isoform compared to the adult isoform. Among a total of 706 patients with epilepsy, Tate et al. (2005) found maximum required antiepileptic drug dose to be lowest in patients with a GG genotype, intermediate in those with the GA genotype, and highest in those with the AA genotype. Tate et al. (2005) emphasized that their findings required replication. In a separate study by Tate et al. (2006) that involved patients of Chinese ancestry, an association was found between SCN1A IVS5N+5G-A and phenytoin serum concentrations at maintenance dose; presence of the A allele was associated with higher doses.

Heinzen et al. (2007) found that in human brain tissue, the SCN1A IVS5N+5G-A polymorphism has a substantial effect on the percentage of transcripts containing exon 5N (neonatal form) of SCN1A. Individuals with the AA genotype had a mean of 0.7% of SCN1A transcripts in the neonatal form, whereas subjects with the GG genotype had 41% of transcripts containing exon 5N. The G allele elicited a dominant effect, with those with the AG genotype having 28% of transcripts in the neonatal form. Heinzen et al. (2007) noted that individuals with the AA genotype require increased doses of antiepileptic drugs compared to those with the GG genotype, suggesting that patients with the AA genotype have a more severe form of epilepsy. Alternatively, the different splice forms may cause alterations in pharmacology, since the drugs act on the SCN1A gene. The authors noted that future work was required to elucidate the functional differences between the transcripts containing exons 5A and 5N. The findings emphasized an emerging role of genetic polymorphisms in modulation of drug effect, and illustrated the importance of considering the activity of compounds at alternative splice forms of drug targets.

Petrovski et al. (2009) was unable to replicate the association between {dbSNP rs3812718} and febrile seizures in a study of 558 Australian patients with seizures, including 76 (14%) with febrile seizures and 482 (86%) without febrile seizures. Only 10 (2%) had isolated febrile seizures. The association was also not replicated in a second cohort of 1,589 European patients with focal epilepsy, consisting of 232 with febrile seizures and 1,357 without febrile seizures.

The vertebrate sodium channel is a voltage-gated ion channel essential for the generation and propagation of action potentials, chiefly in nerve and muscle. Voltage-sensitive sodium channels are heteromeric complexes consisting of a large central pore-forming glycosylated alpha subunit and 2 smaller auxiliary beta subunits. Functional studies have indicated that the transmembrane alpha subunit of the brain sodium channels is sufficient for expression of functional sodium channels (Goldin et al., 1986; Isom, 2002).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Epilepsy generalized with febrile seizures plus type 2, Epileptic encephalopathy early infantile 6 (Dravet syndrome), Febrile seizures familial 3A, and Migraine familial hemiplegic 3.

ClinVar Assessment from PharmGKB

Classified as Drug Response on 2016-05-18 for Carbamazepine Response - Dosage

PharmGKB Level of Evidence 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Intron Variant in *COQ2* (NM_015697.7:c.779-1022C>G) Drug Response

This is a Intron Variant located in the COQ2 gene.

CoQ (ubiquinone) serves as a redox carrier in the mitochondrial respiratory chain and is a lipid-soluble antioxidant. COQ2, or parahydroxybenzoate-polyprenyltransferase ({EC 2.5.1.39}), catalyzes one of the final reactions in the biosynthesis of CoQ, the prenylation of parahydroxybenzoate with an all-trans polyprenyl group (Forsgren et al., 2004).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Coenzyme Q10 deficiency primary 1 and Multiple system atrophy susceptibility to.

ClinVar Assessment from PharmGKB

Classified as Drug Response on 2016-05-18 for Hmg Coa Reductase Inhibitors Response - Toxicity/Adr

PharmGKB Level of Evidence 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Intron Variant in *GATM* (NM_001321015.1:c.-394-272A>G) Drug Response

This is a Intron Variant located in the GATM gene.

Creatine and phosphocreatine play important roles in the energy metabolism of muscle and nerve tissues. The enzyme L-arginine:glycine amidinotransferase (GATM; {EC 2.1.4.1}) catalyzes the transfer of a guanido group from arginine to glycine, forming guanidinoacetic acid, the immediate precursor of creatine. The major sites of creatine biosynthesis are pancreas, kidney, and liver, where GATM appears to be located in mitochondria of cells (summary by Humm et al., 1994).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cerebral creatine deficiency syndrome 3.

ClinVar Assessment from PharmGKB

Classified as Drug Response on 2016-05-18 for Hmg Coa Reductase Inhibitors Response - Toxicity/Adr

PharmGKB Level of Evidence 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Splice Acceptor Variant in *TPP1* (NM_000391.3:c.509-1G>C) Pathogenic

This is a Splice Acceptor Variant located in the TPP1 gene.

Sleat et al. (1997) described compound heterozygosity in 2 sibs with late-infantile onset of neuronal ceroid lipofuscinosis-2 (CLN2; 204500). One allele of the CLN2 gene carried the R208X nonsense mutation ({607998.0003}); the other allele showed a splice site mutation, a G-to-C transversion of the consensus AG 3-prime splice acceptor site immediately preceding 523T of the cDNA sequence.

In affected members of a Dutch family with autosomal recessive spinocerebellar ataxia-7 (SCAR7; 609270), originally reported by Breedveld et al. (2004), Sun et al. (2013) identified compound heterozygous mutations in the TPP1 gene: a G-to-C transversion in intron 5 (c.509-1G-C) resulting in a frameshift and premature termination (Val170GlyfsTer29), and V466G ({607998.0010}). The mutations, which were found by whole-exome sequencing and confirmed by Sanger sequencing, segregated with the disorder in the family. An unrelated Dutch woman with the disorder was also found to be compound heterozygous for these 2 mutations, although a founder effect could not be confirmed. Residual TPP1 activity in patient lymphocytes was 10 to 15% that of controls, with 5% activity in patient fibroblasts.

In an 11-year-old girl with SCAR7, Dy et al. (2015) identified compound heterozygous mutations in the TPP1 gene: c.509-1G-C, and a missense mutation (E343D; {607998.0011}).

TPP1 ({EC 3.4.14.9}) is a lysosomal exopeptidase that sequentially removes tripeptides from the N termini of proteins. It also has a minor endoprotease activity (Golabek et al., 2005).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ceroid lipofuscinosis neuronal 2 and Spinocerebellar ataxia autosomal recessive 7.

ClinVar Assessment from GenomeConnect, ClinGen

Classified as Not Provided on 2017-10-13 for Not Provided

GenomeConnect assertions are reported exactly as they appear on the patient-provided report from the testing laboratory. GenomeConnect staff make no attempt to reinterpret the clinical significance of the variant.

ClinVar Assessment from Knight Diagnostic Laboratories,Oregon Health and Sciences University

Classified as Pathogenic on 2015-10-23 for Not Provided

he c.509-1G>C variant is one of the most common pathogenic variants associated with LINCL and is found in both the homozygous or compound heterozygous state (Sleat DE et al., 1999; Zhong N et al., 1998; Kousi M et al., 2011). This variant was shown to segregate with disease in a non-consanguineous sib ship and in affected individuals who harbor this variant; enzyme activity in the leukocytes and fibroblasts was very low to almost absent respectively (Sun Y et al., 2013). Furthermore, the frequency of this variant is very low in the population database (1000 Genome, Exome Sequencing Project and ExAC). This locus is conserved across species and several computational algorithms predict the loss of splice-acceptor site in intron 5. Finally, several reputable clinical sources have classified this variant as pathogenic. In summary, the evidence meets our laboratoryâ€™s criteria for a Pathogenic classification

ClinVar Assessment from GeneDx

Classified as Pathogenic on 2017-08-07 for Not Provided

The c.509-1 G>C variant in the TPP1 gene is a common pathogenic variant, sometimes reported using alternate nomenclature of T523-1 G>C or c.3556 G>C, that has been reported previously in both the homozygous and compound heterozygous state in association with infantile, late-infantile, and juvenile neuronal ceroid lipofuscinosis (Zhong et al., 1998; Sleat et al., 1999; Kousi et al., 2012). This pathogenic

variant destroys the canonical splice acceptor site in intron 5, and is expected to cause abnormal gene splicing. The c.509-1 G>C variant, in trans with a pathogenic nonsense variant, resulted in a significant decrease in TPP1 enzyme activity in patient-derived lymphoblast cell lines (Miller et al., 2013). Therefore, the c.509-1 G>C variant is considered to be a pathogenic variant.

ClinVar Assessment from Ambry Genetics

Classified as Pathogenic on 2017-09-06 for Inborn Genetic Diseases

Lines of evidence used in support of classification: Functionally-validated splicing mutation ,Detected in individual(s) satisfying established diagnostic criteria for classic disease in trans with a mutation or mutation is homozygous,Rare (0.1%) in general population databases (dbsnp, esp, 1000 genomes) ,In silico models in agreement (deleterious) and/or completely conserved position in appropriate species,Alterations at the canonical donor/acceptor sites (+/- 1, 2) without splicing assay data in support of pathogenicity

ClinVar Assessment from Integrated Genetics/Laboratory Corporation of America

Classified as Pathogenic on 2017-07-10 for Not Provided

Variant summary: The TPP1 c.509-1G>C variant (also known as G3556C) involves the alteration of a highly conserved nucleotide at canonical splice acceptor site in intron 5. 5/5 splice prediction tools predict abrogation of the splice-site. This variant was found in 43/121262 control chromosomes from ExAC at a frequency of 0.0003546, which does not exceed the estimated maximal expected allele frequency of a pathogenic TPP1 variant (0.002958). This variant is one of the most common pathogenic variants associated with LINCL and is found in both the homozygous and compound heterozygous state, including evidence of cosegregation with disease (Sleat_ 1999; Ju_2002; Worgall_2007). Enzyme activity in the in patients carrying this variant was very low to absent, suggesting it leads to loss of protein function (Sleat_1999). In addition, several clinical diagnostic laboratories/reputable databases have classified this variant as pathogenic. Taken together, this variant is classified as pathogenic.

ClinVar Assessment from Invitae

Classified as Pathogenic on 2018-01-02 for Not Provided

This sequence change affects an acceptor splice site in intron 5 of the TPP1 gene. It is expected to disrupt RNA splicing and likely results in an absent or disrupted protein product. This variant is present in population databases (rs56144125, ExAC 0.06%). This variant has been reported in the homozygous or compound heterozygous state in individuals with late-infantile neuronal ceroid lipofuscinosis (PMID: 9295267, 9788728, 10330339, 12376936). This variant is also known as c.523-1G>C, c.3556G>C, and IVS5-1G>C in the literature. ClinVar contains an entry for this variant (Variation ID: 2644). Donor and acceptor splice site variants typically lead to a loss of protein function (PMID: 16199547), and loss-of-function variants in TPP1 are known to be pathogenic (PMID: 10330339). For these reasons, this variant has been classified as Pathogenic.

NP_002684.1:p.Gly848Ser in Exon 16 of *POLG* (NM_002693.2:c.2542G>A) Pathogenic

This is a Missense Variant located in the POLG gene.

In a patient with autosomal recessive PEO (PEOB1; 258450), Lamantea et al. (2002) identified compound heterozygosity for 2 mutations in the POLG gene: gly848-to-ser (G848S) and thr251-to-ile (T251I; {174763.0007}).

In a patient with PEO, Van Goethem et al. (2003) identified a heterozygous G848S mutation in the POLG gene and a heterozygous arg334-to-gln mutation in the C10ORF2 gene (R334Q; {606075.0008}), indicating a digenic mode of inheritance.

In 4 children with mitochondrial DNA depletion syndrome-4A (MTDPS4A; 203700), manifest as Alpers syndrome, Davidzon et al. (2005) identified compound heterozygosity for 2 mutations in the POLG gene: G848S and W748S ({174763.0013}). All patients died in childhood. Davidzon et al. (2005) noted that the G848S mutation occurs within the polymerase motif C of the enzyme.

Nguyen et al. (2005) reported 2 unrelated patients with mtDNA depletion syndrome-4A, manifest as Alpers syndrome. One was compound heterozygous for G848S and A467T ({174763.0002}), and the other was compound heterozygous for G848S and W748S.

Hakonen et al. (2007) presented evidence that the G848S disease chromosome originated from a common founder, possibly of European origin.

In an infant with mtDNA depletion syndrome-4B (MTDPS4B; 613662), manifest as severe hypotonia and gastrointestinal dysmotility (MNGIE), Giordano et al. (2009) identified compound heterozygosity for 2 mutations in the POLG gene: G848S and a 697C-T transition, resulting in an arg227-to-trp (R227W; {174763.0021}) substitution. Other features included hearing loss and clubfoot. Brain MRI showed enlarged ventricles, but leukoencephalopathy was not noted. There was no liver damage aside from that resulting from parenteral nutrition. Analysis of the bowel showed that mtDNA depletion was mainly confined to the external layer of the muscularis propria.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Mitochondrial DNA depletion syndrome 4A (Alpers type), Mitochondrial DNA depletion syndrome 4B (MNGIE type), Mitochondrial recessive ataxia syndrome (includes SANDO and SCAE), Progressive external ophthalmoplegia autosomal dominant 1, and Progressive external ophthalmoplegia autosomal recessive 1.

ClinVar Assessment from GenomeConnect, ClinGen

Classified as Not Provided on 2017-10-13 for Polg-Related Disorders

GenomeConnect assertions are reported exactly as they appear on the patient-provided report from the testing laboratory. GenomeConnect staff make no attempt to reinterpret the clinical significance of the variant.

ClinVar Assessment from GeneDx

Classified as Pathogenic on 2017-10-26 for Not Provided

The G848S variant is a commonly reported pathogenic variant in the POLG gene, representing approximately 10% of disease-causing variants in this gene (Tang et al., 2011). G848S was initially identified in a patient with autosomal recessive progressive external ophthalmoplegia (arPEO) and has subsequently been identified in individuals with Alpers syndrome, Leigh syndrome, SANDO, and other POLG-related disorders causing epilepsy, ataxia, neuropathy, hepatopathy, and/or myopathy (Lamantea et al., 2002). G848S alters a highly conserved position in the polymerase domain of POLG, and functional studies indicate that it significantly impairs the enzyme's polymerase activity and DNA binding ability (Kasiviswanathan et al., 2009). The G848S variant was not observed with any significant frequency in approximately 6,500 individuals of European and African American ancestry in the NHLBI Exome Sequencing Project and was not observed in the homozygous state in any individual within these populations. We interpret G848S as a pathogenic variant.

ClinVar Assessment from Invitae

Classified as Pathogenic on 2017-09-12 for Not Provided

This sequence change replaces glycine with serine at codon 848 of the POLG protein (p.Gly848Ser). The glycine residue is highly conserved and there is a small physicochemical difference between glycine and serine. This variant is present in population databases (rs113994098, ExAC 0.03%). This variant has been reported in several individuals affected with autosomal recessive progressive external ophthalmoplegia, Alpers syndrome, sensory ataxic neuropathy, dysarthria/ dysphagia and external ophthalmoplegia, Leigh syndrome, and other POLG-related disorders causing epilepsy, sensory neuronopathy, and optic atrophy (PMID: 18500570, 12872260, 22616202, 22006280, 22342071, 21670405, 22189570). This variant is considered a common cause of POLG-related disorders accounting for 10% of the mutations (PMID: 21880868, 17426723). ClinVar contains an entry for this variant (Variation ID: 13502). Experimental studies have shown that this missense change severely impairs the binding and enzyme activity of the POLG protein (PMID: 19478085, 17980715). For these reasons, this variant has been classified as Pathogenic.

ClinVar Assessment from Illumina Clinical Services Laboratory,Illumina

Classified as Pathogenic on 2016-06-14 for Polg-Related Spectrum Disorders

The c.2542G>A (p.Gly848Ser) variant is well-documented as one of the three most common disease-causing variants in the POLG gene (Cohen et al. 2014). Haplotype analysis suggests it is most likely derived from a single ancient ancestor of European origin (Hakonen et al. 2007). Across a selection of the available literature, the p.Gly848Ser variant is reported in a compound heterozygous state in ten patients with POLG-related spectrum disorders (Lamantea et al. 2002; Weiss et al. 2009; Milone et al. 2011; GÃ¡ti et al. 2011; Lax et al. 2012; Scalais et al. 2012; Uusimaa et al. 2013; Simon et al. 2013). The variant is absent from 100 control individuals and 180 control chromosomes, but is reported at a frequency of 0.00031 in the total population of the Exome Sequencing Project. Lamantea et al. (2002) note that the Gly848 residue is highly conserved. Functional studies by Kasiviswanathan et al. (2009) indicate that the p.Gly848Ser variant significantly impairs POLG activity and DNA binding affinity. Based on the collective evidence, the p.Gly848Ser variant is classified as pathogenic for POLG-related spectrum disorders.

3 Prime UTR Variant in *CACNA1A* (NM_001127221.1:c.*185_*187delCAG) Pathogenic

This is a 3 Prime UTR Variant located in the CACNA1A gene.

The CACNA1A gene encodes the transmembrane pore-forming subunit of the P/Q-type or CaV2.1 voltage-gated calcium channel (VGCC) (Kordasiewicz et al., 2006). Voltage-dependent Ca(2+) channels not only mediate the entry of Ca(2+) ions into excitable cells but are also involved in a variety of Ca(2+)-dependent processes, including muscle contraction, hormone or neurotransmitter release, and gene expression. Diriong et al. (1995) noted that calcium channels are multisubunit complexes and that the channel activity is directed by a pore-forming alpha-1 subunit, which is often sufficient to generate voltage-sensitive Ca(2+) channel activity. There are at least 6 classes of alpha-1 subunits: alpha-1A, B, C, D, E, and S, which are derived from 6 genes representing members of a gene family. The auxiliary subunits beta (e.g., 114207), alpha-2/delta, and gamma (e.g., 114209) regulate channel activity.

In addition to full-length CACNA1A, use of an internal ribosomal entry site in the CACNA1A transcript generates the CACNA1A C-terminal polypeptide, or alpha-1ACT, which functions as a transcription factor that mediates cerebellar development (Du et al., 2013).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Epileptic encephalopathy early infantile 42, Episodic ataxia type 2, Migraine familial hemiplegic 1, Migraine familial hemiplegic 1 with progressive cerebellar ataxia, and Spinocerebellar ataxia 6.

Intron Variant in *CNTNAP2* (NM_014141.5:c.2099-26267A>G) Risk Factor

This is a Intron Variant located in the CNTNAP2 gene.

In a 2-stage analysis of a 10-Mb quantitative trait locus for autism-related traits on 7q35-q36 (AUTS15; 612100) using parent-child trios, Alarcon et al. (2008) identified an association between variation at {dbSNP rs2710102} in the CNTNAP2 gene and age at first word in autism spectrum disorder samples from male-only families (p = 0.005). The authors noted that the SNP association results did not imply

that variation at {dbSNP rs2710102} is causally related to autism spectrum disorder, but rather that variation here is likely to be in linkage disequilibrium with an untested functional variant.

A genomewide association study by Ma et al. (2009) of 438 Caucasian families with 1,390 individuals with autism and validation in an additional cohort of 2,390 samples from 457 families did not show a significant association between autism and {dbSNP rs2710102}, which was the tagging SNP in the study of Alarcon et al. (2008). No tested markers linking to the CNTNAP2 gene were significant after correction.

The CNTNAP2 gene encodes a neuronal transmembrane protein member of the neurexin superfamily involved in neural-glia interactions and clustering of potassium channels in myelinated axons. Rapid conduction in myelinated axons depends on the generation of specialized subcellular domains to which different sets of ion channels are localized. Contactin-associated protein (CNTNAP1; 602346) is another member of the neurexin superfamily (summary by Poliak et al., 1999).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cortical dysplasia-focal epilepsy syndrome, Pitt-Hopkins like syndrome 1, and Autism susceptibility 15.

3 Prime UTR Variant in *ADAR* (NM_001111.4:c.*2323_*2330dupCATGCCCC) Uncertain Significance

This is a 3 Prime UTR Variant located in the ADAR gene.

Double-stranded RNA-specific adenosine deaminase (DSRAD), or RNA-specific adenosine deaminase (ADAR), was identified as a developmentally regulated dsRNA unwinding activity in early antisense experiments with Xenopus oocytes (Bass and Weintraub, 1988). The enzyme converts adenosine to inosine in dsRNA, which destabilizes the dsRNA helix. The RNA modifying activity of DSRAD is important for various functions. Among these are site-specific RNA editing of transcripts of the glutamate receptors (see 138248), which are channels for the neurotransmitter L-glutamate in the brain. DSRAD also functions to modify viral RNA genomes and may be responsible for hypermutation of certain negative-stranded viruses, such as measles, which may result in lethal measles inclusion body encephalitis (Weier et al., 1995).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Aicardi-Goutieres syndrome 6 and Dyschromatosis symmetrica hereditaria.

3 Prime UTR Variant in *KCNJ10* (NM_002241.4:c.*2012_*2019delGTGTGTGT) Uncertain Significance

This is a 3 Prime UTR Variant located in the KCNJ10 gene.

The KCNJ10 gene encodes an inwardly rectifying potassium channel that is expressed in renal epithelial cells, inner ear cells, and glial cells in the central nervous system (Scholl et al., 2009) Potassium channels are generally classified into voltage-dependent (Kv) type (e.g., 176258 and 176264) and inwardly rectifying (Kir) type (e.g., 602106 and 600937). The former possesses 6 putative transmembrane regions, while the latter has 2 putative transmembrane regions. Doupnik et al. (1995) reported that Kir channels exhibit various physiologic functions, such as the maintenance of the resting membrane potential, the generation of prolonged action potentials, the modulation of cell excitability, and the transport of potassium ions.

Kir4.1 subunits form homotetrameric channels or coassemble with Kir5.1 (KCNJ16; 605722) in heterotetramers with distinct physiologic properties (summary by {12:Sala-Rabanal et al., 2010}).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Enlarged vestibular aqueduct digenic and SESAME syndrome.

3 Prime UTR Variant in *KCNJ10* (NM_002241.4:c.*2012_*2019delGTGTGTGT) Uncertain Significance

This is a 3 Prime UTR Variant located in the KCNJ10 gene.

The KCNJ10 gene encodes an inwardly rectifying potassium channel that is expressed in renal epithelial cells, inner ear cells, and glial cells in the central nervous system (Scholl et al., 2009) Potassium channels are generally classified into voltage-dependent (Kv) type (e.g., 176258 and 176264) and inwardly rectifying (Kir) type (e.g., 602106 and 600937). The former possesses 6 putative transmembrane regions, while the latter has 2 putative transmembrane regions. Doupnik et al. (1995) reported that Kir channels exhibit various physiologic functions, such as the maintenance of the resting membrane potential, the generation of prolonged action potentials, the modulation of cell excitability, and the transport of potassium ions.

Kir4.1 subunits form homotetrameric channels or coassemble with Kir5.1 (KCNJ16; 605722) in heterotetramers with distinct physiologic properties (summary by {12:Sala-Rabanal et al., 2010}).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Enlarged vestibular aqueduct digenic and SESAME syndrome.

Intron Variant in *TBCE* (NM_003193.4:c.100+64_100+65delGT) Uncertain Significance

This is a Intron Variant located in the TBCE gene.

The TBCE gene encodes one of several chaperone proteins required for the proper folding of alpha-tubulin subunits and the formation of alpha-beta-tubulin heterodimers (Parvari et al., 2002). See 602971 for further information.

Proteins contain within their primary amino acid sequence information sufficient to dictate 3-dimensional structure. Proper folding of many proteins requires facilitation via interaction with a class of multisubunit toroidal complexes called chaperonins (Lewis et al., 1996).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Encephalopathy progressive with amyotrophy and optic atrophy, Hypoparathyroidism-retardation-dysmorphism syndrome, and Kenny-Caffey syndrome type 1.

3 Prime UTR Variant in *LRPPRC* (NM_133259.3:c.*1449_*1456dupTTTTTTTT) Uncertain Significance

This is a 3 Prime UTR Variant located in the LRPPRC gene.

LRPPRC is part of a large protein complex that regulates posttranscriptional gene expression in mitochondria (Sasarman et al., 2010).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Leigh syndrome French-Canadian type.

NP_005404.1:p.Glu123= in Exon 1 of *SIX3* (NM_005413.3:c.369G>A) Uncertain Significance

This is a Synonymous Variant located in the SIX3 gene.

The vertebrate SIX genes are homologs of the Drosophila 'sine oculis' (so) gene, which is expressed primarily in the developing visual system of the fly. Members of the SIX gene family encode proteins that are characterized by a divergent DNA-binding homeodomain and an upstream SIX domain, which may be involved both in determining DNA-binding specificity and in mediating protein-protein interactions. Genes in the SIX family have been shown to play roles in vertebrate and insect development or have been implicated in maintenance of the differentiated state of tissues (summary by Boucher et al., 2000).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Holoprosencephaly 2 and Schizencephaly.

3 Prime UTR Variant in *NRXN1* (NM_001135659.2:c.*1235_*1246delACACACACACAC) Uncertain Significance

This is a 3 Prime UTR Variant located in the NRXN1 gene.

Neurexins, including NRXN1, are cell-surface receptors that bind neuroligins (see NLGN1; 600568) to form a Ca(2+)-dependent neurexin/neuroligin complex at synapses in the central nervous system. This transsynaptic complex is required for efficient neurotransmission and is involved in the formation of synaptic contacts (Reissner et al., 2008).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Pitt-Hopkins-like syndrome 2 and Schizophrenia susceptibility to 17.

5 Prime UTR Variant in *NRXN1* (NM_001135659.2:c.-1453_-1452dupCT) Uncertain Significance

This is a 5 Prime UTR Variant located in the NRXN1 gene.

Neurexins, including NRXN1, are cell-surface receptors that bind neuroligins (see NLGN1; 600568) to form a Ca(2+)-dependent neurexin/neuroligin complex at synapses in the central nervous system. This transsynaptic complex is required for efficient neurotransmission and is involved in the formation of synaptic contacts (Reissner et al., 2008).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Pitt-Hopkins-like syndrome 2 and Schizophrenia susceptibility to 17.

5 Prime UTR Variant in *NRXN1* (NM_001135659.2:c.-1463_-1452delCTCTCTCTCTCT) Uncertain Significance

This is a 5 Prime UTR Variant located in the NRXN1 gene.

Neurexins, including NRXN1, are cell-surface receptors that bind neuroligins (see NLGN1; 600568) to form a Ca(2+)-dependent neurexin/neuroligin complex at synapses in the central nervous system. This transsynaptic complex is required for efficient neurotransmission and is involved in the formation of synaptic contacts (Reissner et al., 2008).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Pitt-Hopkins-like syndrome 2 and Schizophrenia susceptibility to 17.

5 Prime UTR Variant in *NRXN1* (NM_001135659.2:c.-1463_-1452delCTCTCTCTCTCT) Uncertain Significance

This is a 5 Prime UTR Variant located in the NRXN1 gene.

Neurexins, including NRXN1, are cell-surface receptors that bind neuroligins (see NLGN1; 600568) to form a Ca(2+)-dependent neurexin/neuroligin complex at synapses in the central nervous system. This transsynaptic complex is required for efficient neurotransmission and is involved in the formation of synaptic contacts (Reissner et al., 2008).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Pitt-Hopkins-like syndrome 2 and Schizophrenia susceptibility to 17.

3 Prime UTR Variant in *GLI2* (NM_005270.4:c.*1373_*1376dupACAC) Uncertain Significance

This is a 3 Prime UTR Variant located in the GLI2 gene.

The GLI2 gene encodes a vertebral transcription factor involved in SHH (600275) signal transduction (Roessler et al., 2003).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Culler-Jones syndrome and Holoprosencephaly 9.

3 Prime UTR Variant in *ZEB2* (NM_014795.3:c.*4845dupA) Uncertain Significance

This is a 3 Prime UTR Variant located in the ZEB2 gene.

The ZEB2 gene is a member of the ZEB1 (189909)/Drosophila Zfh1 family of 2-handed zinc finger/homeodomain proteins and functions as a DNA-binding transcriptional repressor that interacts with activated SMADs (see 601595), the transducers of TGF-beta (190180) signaling, and interacts with the nucleosome remodeling and histone deacetylation (NURD) complex (Verstappen et al., 2008).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Mowat-Wilson syndrome.

3 Prime UTR Variant in *ZEB2* (NM_014795.3:c.*2404_*2405dupTA) Uncertain Significance

This is a 3 Prime UTR Variant located in the ZEB2 gene.

The ZEB2 gene is a member of the ZEB1 (189909)/Drosophila Zfh1 family of 2-handed zinc finger/homeodomain proteins and functions as a DNA-binding transcriptional repressor that interacts with activated SMADs (see 601595), the transducers of TGF-beta (190180) signaling, and interacts with the nucleosome remodeling and histone deacetylation (NURD) complex (Verstappen et al., 2008).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Mowat-Wilson syndrome.

5 Prime UTR Variant in *SCN2A* (NM_021007.2:c.-150_-149delAA) Uncertain Significance

This is a 5 Prime UTR Variant located in the SCN2A gene.

In many cell types the sodium channel is responsible for generation and propagation of action potentials, chiefly in nerve and muscle. Voltage-sensitive sodium channels are heteromeric complexes consisting of a large glycosylated alpha subunit (approximately 260 kD) and 2 smaller beta subunits (33-39 kD). See SCN1A (182389).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Epileptic encephalopathy early infantile 11 and Seizures benign familial infantile 3.

Intron Variant in *NDUFS1* (NM_005006.6:c.154-10_154-9delTT) Uncertain Significance

This is a Intron Variant located in the NDUFS1 gene.

The multisubunit NADH:ubiquinone oxidoreductase (complex I; {EC 1.6.5.3}) is the first enzyme complex in the electron transport chain of mitochondria. By use of chaotropic agents, complex I can be fragmented into 3 different fractions: a flavoprotein fraction, an iron-sulfur protein (IP) fraction, and a hydrophobic protein (HP) fraction. The IP fraction contains NDUFS1, NDUFS2 (602985), NDUFS3 (603846), NDUFS4 (602694), NDUFS5 (603847), NDUFS6 (603848), and NDUFA5 (601677) (Loeffen et al., 1998). The 75-kD Fe-S protein of the mitochondrial NADH-CoQ reductase is an integral part of the respiratory chain and is one of several Fe-S proteins operating within complex I of the mitochondrial respiratory chain assembly (Ragan, 1987). Functionally, this enzyme is thought to be the first of the Fe-S proteins to accept electrons from an NADH-flavoprotein reductase within the complex.

This gene has been observed to exhibit X-linked dominant, Autosomal recessive, and Mitochondrial inheritance pattern.

It has been associated with Mitochondrial complex I deficiency.

NP_004357.3:p.Thr668Ser in Exon 17 of *CLCN2* (NM_004366.5:c.2003C>G) Uncertain Significance

This is a Missense Variant located in the CLCN2 gene.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Leukoencephalopathy with ataxia, Epilepsy idiopathic generalized susceptibility to 11, Epilepsy juvenile absence susceptibility to 2, and Epilepsy juvenile myoclonic susceptibility to 8.

Intron Variant in *DHFR* (NM_000791.3:c.86+59_86+60ins(19)) Uncertain Significance

This is a Intron Variant located in the DHFR gene.

Dihydrofolate reductase ({EC 1.5.1.3}) converts dihydrofolate into tetrahydrofolate, a methyl group shuttle required for the de novo synthesis of purines, thymidylic acid, and certain amino acids. DHFR is inhibited by methotrexate (MTX), a folate analog used as an antineoplastic and immunosuppressive agent. In addition to the functional DHFR gene, there are at least 4 intronless genes that are probably pseudogenes. Each of the 5 is on a separate chromosome. The pseudogenes do not undergo amplification when such occurs at the functional locus (Anagnou et al., 1984).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Megaloblastic anemia due to dihydrofolate reductase deficiency.

3 Prime UTR Variant in *ALDH7A1* (NM_001182.4:c.*999_*1000dupAA) Uncertain Significance

This is a 3 Prime UTR Variant located in the ALDH7A1 gene.

The ALDH7A1 gene encodes an aldehyde dehydrogenase. Mills et al. (2006) determined that the protein is an alpha-aminoadipic semialdehyde dehydrogenase in the pipecolic acid pathway of lysine catabolism.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Epilepsy pyridoxine-dependent.

5 Prime UTR Variant in *LAMA2* (NM_000426.3:c.-99A>G) Uncertain Significance

This is a 5 Prime UTR Variant located in the LAMA2 gene.

Laminin is a heterotrimeric extracellular matrix protein consisting of 3 chains: alpha-1 (LAMA1; 150320), beta-1 (LAMB1; 150240), and gamma-1, formerly called beta-2 (LAMC1; 150290). Several isoforms of each chain have been identified. Laminin-2 (merosin) is a heterotrimer composed of laminin subunits alpha-2, beta-1, and gamma-1. It is the main laminin found in muscle fibers. The LAMA2 gene encodes the alpha-2 chain of laminin-2.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Muscular dystrophy congenital merosin-deficient and Muscular dystrophy congenital due to partial LAMA2 deficiency.

Intron Variant in *BRAF* (NM_004333.4:c.2128-28dupT) Uncertain Significance

This is a Intron Variant located in the BRAF gene.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Adenocarcinoma of lung somatic, Cardiofaciocutaneous syndrome, LEOPARD syndrome 3, and Noonan syndrome 7.

NP_060360.3:p.Asn2164Ser in Exon 36 of *VPS13B* (NM_017890.4:c.6491A>G) Uncertain Significance

This is a Missense Variant located in the VPS13B gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cohen syndrome.

ClinVar Assessment from Invitae

Classified as Uncertain Significance on 2017-10-23 for Not Provided

This sequence change replaces asparagine with serine at codon 2164 of the VPS13B protein (p.Asn2164Ser). The asparagine residue is weakly conserved and there is a small physicochemical difference between asparagine and serine. This variant is present in population databases (rs142248228, ExAC 0.1%). This variant has not been reported in the literature in individuals with VPS13B-related disease. ClinVar contains an entry for this variant (Variation ID: 196985). Algorithms developed to predict the effect of missense changes on protein structure and function output the following: SIFT: "Tolerated"; PolyPhen-2: "Benign"; Align-GVGD: "Class C0". The serine amino acid residue is found in multiple mammalian species, suggesting that this missense change does not adversely affect protein function. These predictions have not been confirmed by published functional studies and their clinical significance is uncertain. Algorithms developed to

predict the effect of sequence changes on RNA splicing suggest that this variant may create or strengthen a splice site, but this prediction has not been confirmed by published transcriptional studies. In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

3 Prime UTR Variant in *GLDC* (NM_000170.2:c.*505_*506delTT) Uncertain Significance

This is a 3 Prime UTR Variant located in the GLDC gene.

The enzyme system for cleavage of glycine (glycine cleavage system; GCS; {EC 2.1.2.10}), which is confined to the mitochondria, is composed of 4 protein components: P protein (a pyridoxal phosphate-dependent glycine decarboxylase), H protein (a lipoic acid-containing protein, 238330), T protein (a tetrahydrofolate-requiring enzyme, 238310), and L protein (a lipoamide dehydrogenase, 238331).

Mutations in the P, T, and H proteins have been found to cause glycine encephalopathy (GCE; 605899).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Glycine encephalopathy.

3 Prime UTR Variant in *FKTN* (NM_001079802.1:c.*5041G>A) Uncertain Significance

This is a 3 Prime UTR Variant located in the FKTN gene.

The FKTN gene encodes a type II transmembrane protein that is targeted to the Golgi apparatus through an N-terminal signal anchor (Esapa et al., 2002).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cardiomyopathy dilated 1X, Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) type A 4, Muscular dystrophy-dystroglycanopathy (congenital without mental retardation) type B 4, and Muscular dystrophy-dystroglycanopathy (limb-girdle) type C 4.

3 Prime UTR Variant in *FKTN* (NM_001079802.1:c.*5062G>A) Uncertain Significance

This is a 3 Prime UTR Variant located in the FKTN gene.

The FKTN gene encodes a type II transmembrane protein that is targeted to the Golgi apparatus through an N-terminal signal anchor (Esapa et al., 2002).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Cardiomyopathy dilated 1X, Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) type A 4, Muscular dystrophy-dystroglycanopathy (congenital without mental retardation) type B 4, and Muscular dystrophy-dystroglycanopathy (limb-girdle) type C 4.

NP_116165.1:p.Ser1429Leu in Exon 10 of *JMJD1C* (NM_032776.2:c.4286C>T) Uncertain Significance

This is a Missense Variant located in the JMJD1C gene.

The JMJD1C gene encodes a putative histone demethylase and is involved in the epigenetic control of gene transcription (summary by Saez et al., 2016).

ClinVar Assessment from Invitae

Classified as Uncertain Significance on 2017-07-28 for Not Provided

This sequence change replaces serine with leucine at codon 1429 of the JMJD1C protein (p.Ser1429Leu). The serine residue is weakly conserved and there is a large physicochemical difference between serine and leucine. This variant is present in population databases (rs201627592, ExAC 0.07%). This variant has not been reported in the literature in individuals with JMJD1C-related disease. Algorithms developed to predict the effect of missense changes on protein structure and function (SIFT, PolyPhen-2, Align-GVGD) all suggest that this variant is likely to be tolerated, but these predictions have not been confirmed by published functional studies and their clinical significance is uncertain. In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Intron Variant in *FOLR1* (NM_016725.2:c.-9+161G>A) Uncertain Significance

This is a Intron Variant located in the FOLR1 gene.

The FOLR1 gene encodes the adult folate receptor, or folate-binding protein (FBP), which has a high affinity for folic acid and for several reduced folic acid derivatives, and mediates delivery of 5-methyltetrahydrofolate to the interior of cells. Membrane-bound and soluble forms of a high-affinity folate binding protein have been found in kidney, placenta, serum, milk, and in several cell lines. The 2 forms have similar binding characteristics for folates, are immunologically cross-reactive, and, based upon limited amino acid sequence data, are

nearly identical. There may be a precursor-product relationship between the membrane and soluble forms, the membrane form having additional amino acid residues and greater molecular weight. The membrane form has been shown to mediate the transport of folate in cells grown in physiologic concentrations of folate (Lacey et al., 1989). There is also a distinct fetal folate receptor (FOLR2; 136425).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Neurodegeneration due to cerebral folate transport deficiency.

3 Prime UTR Variant in *ALG9* (NM_024740.2:c.*2473A>T) Uncertain Significance

This is a 3 Prime UTR Variant located in the ALG9 gene.

The ALG9 gene encodes an alpha-1,2-mannosyltransferase that catalyzes 2 steps in the lipid-linked precursor oligosaccharide (LLO) in the N-linked pathway of glycosylation (summary by Tham et al., 2016).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Congenital disorder of glycosylation type II and Gillessen-Kaesbach-Nishimura syndrome.

3 Prime UTR Variant in *HEPACAM* (NM_152722.4:c.*456_*460delTTTTG) Uncertain Significance

This is a 3 Prime UTR Variant located in the HEPACAM gene.

HEPACAM is a cell adhesion molecule of the immunoglobulin (Ig) family (Sirisi et al., 2014).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Megalencephalic leukoencephalopathy with subcortical cysts 2A and Megalencephalic leukoencephalopathy with subcortical cysts 2B remitting with or without mental retardation.

3 Prime UTR Variant in *PRICKLE1* (NM_153026.2:c.*552delA) Uncertain Significance

This is a 3 Prime UTR Variant located in the PRICKLE1 gene.

PRICKLE proteins, such as PRICKLE1, are core constituents of the planar cell polarity signaling pathway that establishes cell polarity during embryonic development (Liu et al., 2013).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Epilepsy progressive myoclonic 1B.

5 Prime UTR Variant in *POLR3B* (NM_018082.5:c.-1C>T) Uncertain Significance

This is a 5 Prime UTR Variant located in the POLR3B gene.

The POLR3B gene encodes the second largest subunit of RNA polymerase (pol) III. RNA polymerase III consists of 17 subunits and is involved in the transcription of small noncoding RNAs, such as 5S ribosomal RNA (180420), U6 small nuclear RNA (see 180692), and short interspersed nuclear elements (SINEs), as well as all transfer RNAs (summary by Saitsu et al., 2011).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Leukodystrophy hypomyelinating 8 with or without oligodontia and/or hypogonadotropic hypogonadism.

3 Prime UTR Variant in *PTPN11* (NM_002834.4:c.*1199_*1201dupATG) Uncertain Significance

This is a 3 Prime UTR Variant located in the PTPN11 gene.

The protein-tyrosine phosphatases are a highly pleomorphic set of molecules that have a role in regulating the responses of eukaryotic cells to extracellular signals (Dechert et al., 1995). They achieve this by regulating the phosphotyrosine content of specific intracellular proteins. The PTPases have been grouped by virtue of the characteristic catalytic domain sequence similarities that define this family. Dechert et al. (1995) noted that the noncatalytic domain shows a striking degree of sequence heterogeneity. In general, however, mammalian PTPases can be subdivided into 1 of 2 broad categories: (1) transmembrane receptor PTPases that contain linked cytoplasmic catalytic domains, and (2) intracellular PTPases. Included within the latter category are 2 closely related mammalian intracellular PTPases whose sequences encode 2 tandem SRC homology 2 (SH2) domains that are located at the amino-terminal side of a single PTPase catalytic domain. SH2 domains enable the binding of these SH2 domain-containing PTPases to specific phosphotyrosine residues within protein sequences. The first mammalian SH2 domain-containing PTPase identified was PTP1C (PTPN6; 176883). The second mammalian SH2 domain-containing PTPase identified is encoded by the PTPN11 gene.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with LEOPARD syndrome 1, Leukemia juvenile myelomonocytic somatic, Metachondromatosis, and Noonan syndrome 1.

5 Prime UTR Variant in *SLC25A15* (NM_014252.3:c.-273C>G) Uncertain Significance

This is a 5 Prime UTR Variant located in the SLC25A15 gene.

The SLC25A15 gene encodes the mitochondrial ornithine transporter, which transports ornithine across the inner mitochondrial membrane from the cytosol to the mitochondrial matrix. This is a vital step in the urea cycle, which serves to eliminate toxic ammonium ions from the breakdown of nitrogen (summary by Camacho et al., 1999).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome.

3 Prime UTR Variant in *CLN6* (NM_017882.2:c.*157_*160delGTGT) Uncertain Significance

This is a 3 Prime UTR Variant located in the CLN6 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ceroid lipofuscinosis neuronal 6 and Ceroid lipofuscinosis neuronal Kufs type adult onset.

3 Prime UTR Variant in *CLN6* (NM_017882.2:c.*157_*160delGTGT) Uncertain Significance

This is a 3 Prime UTR Variant located in the CLN6 gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Ceroid lipofuscinosis neuronal 6 and Ceroid lipofuscinosis neuronal Kufs type adult onset.

3 Prime UTR Variant in *PAFAH1B1* (NM_000430.3:c.*1042_*1043delAG) Uncertain Significance

This is a 3 Prime UTR Variant located in the PAFAH1B1 gene.

Platelet-activating factor acetylhydrolase (PAFAH) catalyzes the removal of the acetyl group at the sn-2 position of the glycerol backbone of platelet-activating factor (PAF), producing biologically inactive lyso-PAF. Isoform 1B of PAFAH consists of 3 subunits: alpha (PAFAH1B1), beta (PAFAH1B2; 602508), and gamma (PAFAH1B3; 603074). The catalytic activity of the enzyme resides in the beta and gamma subunits, whereas the alpha subunit has regulatory activity (summary by Adachi et al., 1995).

This gene has been observed to exhibit Isolated cases inheritance pattern.

It has been associated with Lissencephaly 1 and Subcortical laminar heterotopia.

3 Prime UTR Variant in *TTC19* (NM_017775.3:c.*1886T>C) Uncertain Significance

This is a 3 Prime UTR Variant located in the TTC19 gene.

TTC19 is a subunit of mitochondrial respiratory chain complex III ({EC 1.10.2.2}), which transfers electrons from coenzyme Q to cytochrome c (CYCS; 123970). This electron transfer powers the extrusion of protons across the inner mitochondrial membrane and thereby contributes to the mitochondrial electrochemical potential (summary by Ghezzi et al., 2011).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Mitochondrial complex III deficiency nuclear type 2.

3 Prime UTR Variant in *TCF4* (NM_001083962.1:c.*3870delA) Uncertain Significance

This is a 3 Prime UTR Variant located in the TCF4 gene.

TCF4 is a broadly expressed basic helix-loop-helix (bHLH) protein that functions as a homodimer or as a heterodimer with other bHLH proteins. These dimers bind DNA at Ephrussi (E) box sequences. Alternative splicing produces numerous N-terminally distinct TCF4 isoforms that differ in their subcellular localization and transactivational capacity (summary by Sepp et al., 2012).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Corneal dystrophy Fuchs endothelial 3 and Pitt-Hopkins syndrome.

Intron Variant in *PLCB1* (NM_015192.3:c.2309-15A>C) Uncertain Significance

This is a Intron Variant located in the PLCB1 gene.

Phospholipase C-beta (PLCB) catalyzes the generation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate (IP2), a key step in the intracellular transduction of many extracellular signals. The PLCB1 gene encodes a mammalian PLCB isoform that is expressed in select areas of the brain, including cerebral cortex, hippocampus, amygdala, lateral septum, and olfactory bulb (summary by Koh et al., 2008).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Epileptic encephalopathy early infantile 12.

3 Prime UTR Variant in *ARFGEF2* (NM_006420.2:c.*1969G>A) Uncertain Significance

This is a 3 Prime UTR Variant located in the ARFGEF2 gene.

For general information about brefeldin A (BFA)-inhibited guanine nucleotide exchange proteins, see BIG1 (604141).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Periventricular heterotopia with microcephaly.

NP_006022.3:p.Arg3236Gln in Exon 45 of *PCNT* (NM_006031.5:c.9707G>A) Uncertain Significance

This is a Missense Variant located in the PCNT gene.

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Microcephalic osteodysplastic primordial dwarfism type II.

NP_057419.4:p.Leu581= in Exon 15 of *PRODH* (NM_016335.4:c.1741C>T) Uncertain Significance

This is a Synonymous Variant located in the PRODH gene.

Proline dehydrogenase ({EC 1.5.5.2}) is involved in the degradation of the amino acid proline. It catalyzes the conversion of proline to pyrroline-5-carboxylate, or P5C.

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Hyperprolinemia type I and Schizophrenia susceptibility to 4.

References

Additional Information

Test

Comprehensive Epilepsy Panel

Indication

Data produced by tertiary bioinformatic analysis on WGS 30X

Background

WGS was performed using Next-Generation-Sequencing Technology.Variants are reported according to the HGVS nomenclature (www.hgvs.org/mutnomen) and ACMG Guidelines (https://www.acmg.net/)

Method

Whole genome sequencing

The qualified genomic DNA sample was randomly fragmented by Covaris technology and the fragment of 350bp was obtained after fragment selection. The end repair of DNA fragments was performed and an "A" base was added at the 3'-end of each strand. Adapters were then ligated to both ends of the end repaired/dA tailed DNA fragments, then amplification by ligation-mediated PCR (LM-PCR), then single strand separation and cyclization. The rolling circle amplification (RCA) was performed to produce DNA Nanoballs (DNBs). The qualified DNBs were loaded into the patterned nanoarrays and pair-end read were read through on the BGISEQ-500 platform and high-throughput sequencing are performed for each library to ensure that each sample meet the average sequencing coverage requirement. Sequencing-derived raw image files were processed by BGISEQ-500 basecalling Software for base-calling with default parameters and the sequence data of each individual is generated as paired-end reads, which is defined as "raw data" and stored in FASTQ format.

Sequencing of this individual's genome was performed and covered an average of 30X. 99.66% on average of the whole genome excluding gap regions were covered by at least 1X coverage, 99.27% had at least 4X coverage and 98.28% had at least 10X coverage.

Bioinformatic analysis

Reads were aligned to the human reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). The GATK Variant Quality Score Recalibration (VQSR) that uses machine learning algorithm was used to filter the raw variant callset. The SNPs and InDels marked PASS in the output VCF file were high-confident variation set. All the variants with pathogenic or unknown significance for causing or contributing to diseases are reported.

Data Quality Control

The strict data quality control (QC) was performed in the whole analysis pipeline for the clean data , the mapping data, the variant calling, etc. Several quality control items for each sample were checked.

Variant classification

The classification of variants is largely based on the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., Genet. Med., 2015, http://www.ncbi.nlm.nih.gov/pubmed/25741868, and Richards et al.,Genet. Med., 2008, http://www.ncbi.nlm.nih.gov/pubmed/18414213). Based on the evidence available, a given variant will be classified according to the weighted classification system as set out by the ACMG (for more information about the specific criteria, see also tables 3 and 4 in http://www.ncbi.nlm.nih.gov/pubmed/25741868).

In general, variant evidence can comprise previous reports and functional data about that specific variant if available (e.g. described as pathogenic, reports about the effect of that specific variant on protein expression and function, as verified in functional in vitro or in vivo experiments), reports and functional data about other similar variants within the same gene (e.g. information about the type of known pathogenic and benign variants within a specific gene, known mutational hot spots or certain protein domains, are also taken into account when classifying a variant within the same gene), phenotype data (e.g. the clinical phenotype of the patient is taken into account when classifying a variant, the match between the phenotype in the patient and the gene's disease association is of relevance), population data (e.g. variant and disease population frequencies), segregation data (e.g. whether the variant co-segregates with the disease in a family), and computational data (e.g. in silico predictive algorithms).

Limitations

CNVs are not included into the report.

Disclaimer

The genetic analysis and reporting conducted by the Dante Labs are based on information from one or more published third- party scientific and medical studies. We do not independently judge the validity or accuracy of such published scientific information. Because scientific and medical information changes over time, your risk assessment for one or more of the conditions contained within this report may also change over time. For example, opinions differ on the importance and relative weights given to genetic factors. Also, epidemiologic data aren't available for some conditions, and this Report may not be able to provide definitive information about the severity of a particular condition. We recommend to ask help to your healthcare provider to correctly interpret them. Therefore, this report may not be 100% accurate (e.g., new research could mean different results) and may not predict actual results or outcomes.

This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.