iGenome

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Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name :	-	**Date Received :**	-
Medical ID :	-	**Date of Report :**	-
Date of Birth :	-	**Req. Physician :**	-
Location :	-	**Barcode :**	-
Material :	WHOLE PERIPHERAL BLOOD	**Reason of referal:**	e.g seizures, cognitive decline, cerebellar atrophy

Whole Genome analysis (WGS) by Next Generation Sequencing

Results associated with the reason of referral

NEGATIVE

NO PATHOGENIC VARIANT IDENTIFIED

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Results from the analysis of genes associated with neurological disorders due to nucleotide repeat expansions

Disorders caused by nucleotide repeat expansions	Gene	Nucleotide repeats	Number of repeat expansions per allele	cutoff pathogenic repeats	Mode of inheritance
Amyotrophic lateral sclerosis (ALS)	NIPA1	GCG	n/n	≥11	AD
Amyotrophic lateral sclerosis and/or familial frontotemporal dementia (ALS)	C9orf72	GGGGCC	n/n	>30	AD
Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS)	RFC1	AAGGG / ACAGG	n/n	≥400	AR
Congenital central hypoventilation syndrome (CCHS)	PHOX2B	GCN	n/n	≥25	AD
Dentatorubro-pallidoluysian atrophy (DRPLA)	ATN1	CAG	n/n	≥49	AD
Epilepsy, progressive myoclonic 1A (Unverricht and Lundborg)	CSTB	CCCCGCCCCGCG	n/n	≥60	AR
Fragile X syndrome (FXS)	FMR1	CGG	n/n	≥201	XLD
Fragile X-associated tremor/ataxia syndrome (FXTAS)	FMR1	CGG	n/n	55-200	XLD
Friedreich ataxia (FRDA)	FXN	GAA	n/n	≥70	AR
Global developmental delay, progressive ataxia, and elevated glutamine (GDPAG)	GLS	GCA	n/n	>680	AR
Huntington disease-like 2 (HDL2)	JPH3	CTG	n/n	≥41	AD
Huntington's disease (HD)	HTT	CAG	n/n	≥40 Full penetrance	AD
Intellectual developmental disorder, FRA12A type (MRFRA12A)	DIP2B	CGG	n/n	≥273	AD
Intellectual developmental disorder, FRAXE type (FRAXE)	AFF2	CCG	n/n	≥200	XLR
Jacobsen syndrome (JBS)	CBL	CCG	n/n	≥100	AD
Muscle-type NIID or Oculopharyngeal muscular dystrophy (OPDM)	NOTCH2NL	GGC	n/n	>200	AD
Myotonic dystrophy type 1 (DM1)	DMPK	CTG	n/n	≥50	AD
Myotonic dystrophy type 2 (DM2)	CNBP	CCTG	n/n	≥55	AD
Neuronal intranuclear inclusion disease (NIID)	NOTCH2NL	GGC	n/n	≥90	AD
Oculopharyngeal muscular dystrophy (OPMD)	PABPN1	GCN	n/n	>8	AD
Oculopharyngodistal myopathy 2 (OPDM2)	GIPC1	GGC	n/n	≥73	AD
Spinal and bulbar muscular atrophy of Kennedy (SBMA)	AR	CAG	n/n	>38	XLR
Spinocerebellar ataxia 1 (SCA1)	ATXN1	CAG	n/n	≥39	AD
Spinocerebellar ataxia 10 (SCA10)	ATXN10	ATTCT	n/n	≥800	AD
Spinocerebellar ataxia 12 (SCA12)	PPP2R2B	GCT	n/n	≥51	AD
Spinocerebellar ataxia 17 (SCA17)	TBP	CAG	n/n	≥43	AD
Spinocerebellar ataxia 2 (SCA2)	ATXN2	CAG	n/n	≥35	AD
Spinocerebellar ataxia 27B (SCA27B)	FGF14	GAA	n/n	≥300 Full penetrance	AD
Spinocerebellar ataxia 3 (SCA3)	ATXN3	CAG	n/n	≥61	AD
Spinocerebellar ataxia 36 (SCA36)	NOP56	GGCCTG	n/n	≥30	AD
Spinocerebellar ataxia 6 (SCA6)	CACNA1A	CAG	n/n	>20	AD
Spinocerebellar ataxia 7 (SCA7)	ATXN7	CAG	n/n	>36	AD
Spinocerebellar ataxia 8 (SCA8)	ATXN8OS	CTG	n/n	≥74	AD
Tremor, hereditary essential, 6 (ETM6) /Oculopharyngodistal myopathy 3	NOTCH2NL	GGC	n/n	≥60	AD

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Notes:

- In cases where a pathological nucleotide expansion is detected, confirmation with an alternative method is recommended.
- Whole genome sequencing shows 97.3% sensitivity (95% CI 94.2–99.0) and 99.6% specificity (99.1–99.9) for detecting repeat expansions (PMID: 35182509) using ExpansionHunter Denovo (PMID: 32345345).
- AD: autosomal dominant, AR: autosomal recessive, XLD: X-linked dominant, XLR: X-linked recessive.

Methodology

Genomic DNA was extracted and a library was prepared from the sample under examination. The Nextera DNA Flex (Illumina) was used for library preparation. Sequencing was performed using the NGS NovaSeq 6000 platform (Illumina). Bioinformatics analysis of the obtained DNA sequence was conducted and compared with a reference sequence (GRCh37). The impact of missense mutations on the protein's structure and function was assessed using the MetaSVM consensus prediction algorithm (PMID: 25552646), which combines predictions from 10 different algorithms: SIFT, PolyPhen-2 HDIV, PolyPhen-2 HVAR, GERP++, MutationTaster, Mutation Assessor, FATHMM, LRT, SiPhy, and PhyloP, providing a score ranging from -2 to 3. The average coverage depth was >30X.

According to the available information about the patient, the following diagnostic algorithm was followed:

- Selection of genes described in the OMIM and HPO databases as related to the patient's phenotype.
- Categorization of findings was based on ACMG and AMP criteria (PMID: 25741868).
- Analysis of variants with potentially deleterious effects (e.g., frame shifts, creation of stop codons, missense mutations, splicing changes) as well as de novo variants.
- Analysis of nucleotide repeat expansions was performed using ExpansionHunter Denovo (PMID: 32345345).
- All clinically significant findings were confirmed by Sanger sequencing.

*Note: Each molecular analysis carries an inherent error probability of 0.5-1%. This is due to rare molecular events and factors involved in sample preparation and analysis.

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Details about non-pathogenic variants

All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of the disease. Genetic variants that are considered benign or likely benign according to bioinformatics analysis and ACMG and AMP criteria are not reported, as they are documented to likely do not cause increased risk for the disease. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings. Additionally, point mutations and CNVs that are not related to the reason for referral are not reported.

Variants of Uncertain Significance (VUS) are provided for genes potentially associated with the phenotype that might affect the functional of the protein (damaging), as indicated by the majority of computational algorithms (REVEL and MetaLR). VUS findings in autosomal recessive diseases are not reported unless they are found in conjunction with another finding (pathogenic, likely pathogenic, or VUS in the same gene).

Genes Analyzed (e.g Table 1 based on patient's phenotype)

AARS1	*AARS2*	*ABAT*	*ABCA1*	*ABCC9*	*ABCD1*	*ABCD4*	*ABHD5*	*ACADS*
ACBD5	*ACER3*	*ACO2*	*ACOX1*	*ACP5*	*ACSF3*	*ACTA2*	*ACTB*	*ACTL6B*
ACY1	*ADAR*	*ADGRG1*	*ADK*	*ADNP*	*ADSL*	*AGA*	*AHDC1*	*AHI1*
AIFM1	*AIMP1*	*AIMP2*	*ALDH18A1*	*ALDH3A2*	*ALDH5A1*	*ALDH6A1*	*ALDH7A1*	*ALG12*
ALG13	*ALG2*	*ALG6*	*ALG8*	*ALG9*	*AMACR*	*AMPD2*	*AMT*	*ANK3*
AP1S2	*AP3B2*	*AP4B1*	*AP4E1*	*AP4M1*	*AP4S1*	*AP5Z1*	*APC2*	*APP*
ARCN1	*ARFGEF2*	*ARHGAP31*	*ARHGEF9*	*ARID2*	*ARNT2*	*ARSA*	*ARX*	*ASH1L*
ASL	*ASNS*	*ASPA*	*ASS1*	*ASXL1*	*ASXL2*	*ATP13A2*	*ATP5F1A*	*ATP6AP2*
ATP6V1A	*ATP7A*	*ATP7B*	*ATP8A2*	*ATPAF2*	*ATRX*	*AUH*	*B3GALNT2*	*B4GALNT1*
BCAP31	*BCAT2*	*BCKDHA*	*BCKDHB*	*BCL11B*	*BCS1L*	*BICD2*	*BMP4*	*BOLA3*
BPTF	*BRAT1*	*BRF1*	*BTD*	*C12orf57*	*C19orf12*	*C2CD3*	*CA2*	*CACNA1A*
CACNA1E	*CACNG2*	*CAMK2A*	*CAMK2B*	*CARS2*	*CBS*	*CC2D2A*	*CCDC88A*	*CDC42*
CDH15	*CDKL5*	*CEP290*	*CHAMP1*	*CHMP1A*	*CHMP2B*	*CIC*	*CLCN2*	*CLCN4*
CLCN7	*CLN3*	*CLN5*	*CLN6*	*CLN8*	*CLP1*	*CLPP*	*CLTC*	*CNKSR2*
CNNM2	*CNOT1*	*CNP*	*CNTNAP1*	*CNTNAP2*	*COA7*	*COA8*	*COASY*	*COG7*
COL18A1	*COL3A1*	*COL4A1*	*COL4A2*	*COLGALT1*	*COQ2*	*COQ6*	*COQ7*	*COQ8A*

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COQ9	*COX10*	*COX14*	*COX15*	*COX20*	*COX6B1*	*COX7B*	*COX8A*	*CP*
CPLANE1	*CPLX1*	*CPS1*	*CRAT*	*CREBBP*	*CRIPT*	*CRLF1*	*CSF1R*	*CSNK2B*
CSPP1	*CTBP1*	*CTC1*	*CTDP1*	*CTNS*	*CTSA*	*CTSD*	*CTSF*	*CUL4B*
CUX1	*CYB5R3*	*CYFIP2*	*CYP27A1*	*CYP2U1*	*CYP7B1*	*D2HGDH*	*DAG1*	*DARS1*
DARS2	*DBT*	*DCAF17*	*DCX*	*DDC*	*DDHD1*	*DDHD2*	*DDOST*	*DDX3X*
DEAF1	*DEGS1*	*DGUOK*	*DHCR24*	*DHFR*	*DHX37*	*DLD*	*DLL1*	*DLL4*
DMXL2	*DNAJC5*	*DNM1L*	*DNM2*	*DNMT1*	*DOCK6*	*DOCK7*	*DOCK8*	*DOLK*
DONSON	*DPAGT1*	*DPM1*	*DPM2*	*DPM3*	*DPYS*	*DYNC1H1*	*DYRK1A*	*EARS2*
ECHS1	*EDNRB*	*EEF1A2*	*EHMT1*	*EIF2AK2*	*EIF2B1*	*EIF2B2*	*EIF2B3*	*EIF2B4*
EIF2B5	*ELOVL1*	*ELOVL4*	*ENTPD1*	*EOGT*	*EPB41L1*	*EPG5*	*EPRS1*	*ERBB4*
ERCC1	*ERCC2*	*ERCC3*	*ERCC6*	*ERCC8*	*ETFA*	*ETFB*	*ETFDH*	*ETHE1*
EXOSC2	*EXOSC3*	*EXOSC5*	*EXOSC8*	*EXOSC9*	*FA2H*	*FAR1*	*FARS2*	*FARSA*
FARSB	*FASTKD2*	*FBXL4*	*FCSK*	*FDX2*	*FH*	*FIG4*	*FKRP*	*FKTN*
FLVCR2	*FOLR1*	*FOXC1*	*FOXG1*	*FOXRED1*	*FTL*	*FUCA1*	*GAA*	*GABBR2*
GABRA1	*GABRB1*	*GABRB2*	*GABRB3*	*GALC*	*GALT*	*GAN*	*GATAD2B*	*GBE1*
GCDH	*GDAP1*	*GFAP*	*GFM1*	*GFM2*	*GJA1*	*GJB1*	*GJC2*	*GLA*
GLB1	*GLDC*	*GLRX5*	*GLUL*	*GLYCTK*	*GM2A*	*GMNN*	*GMPPB*	*GNAO1*
GNB2	*GNS*	*GOT2*	*GPHN*	*GRIN1*	*GRIN2B*	*GRM7*	*GRN*	*GTF2E2*
GTF2H5	*GTPBP2*	*GTPBP3*	*HACE1*	*HCN1*	*HEPACAM*	*HERC1*	*HEXA*	*HEXB*
HIBCH	*HIKESHI*	*HIVEP2*	*HK1*	*HLCS*	*HMGCL*	*HNRNPU*	*HSD17B10*	*HSD17B4*
HSPD1	*HTRA1*	*HYCC1*	*IARS1*	*IARS2*	*IBA57*	*IDH2*	*IDS*	*IDUA*
IER3IP1	*IFIH1*	*INPP5E*	*ISCA1*	*ISCA2*	*ITPA*	*ITPR1*	*IVD*	*JAM3*
KARS1	*KAT6B*	*KATNB1*	*KATNIP*	*KCNJ10*	*KCNJ2*	*KCNMA1*	*KCNN2*	*KCNQ2*
KCNQ5	*KCNT1*	*KCTD7*	*KDM1A*	*KDM5B*	*KIAA0586*	*KIAA0753*	*KIDINS220*	*KIF1A*
KIF1C	*KIF5A*	*KLHL7*	*KMT2E*	*L2HGDH*	*LAGE3*	*LAMA1*	*LAMA2*	*LAMB1*
LARS2	*LETM1*	*LIAS*	*LIG3*	*LIPT1*	*LIPT2*	*LMNB1*	*LMX1B*	*LONP1*
LRPPRC	*LYRM7*	*MAG*	*MAGEL2*	*MAN2B1*	*MANBA*	*MAPT*	*MARS2*	*MAST1*
MAT1A	*MBD5*	*MCCC1*	*MCCC2*	*MCOLN1*	*MDH2*	*MECP2*	*MED12L*	*MED17*
MED25	*MEF2C*	*MFSD2A*	*MFSD8*	*MGP*	*MICU1*	*MKS1*	*MLC1*	*MLYCD*
MMACHC	*MMADHC*	*MMUT*	*MOCS1*	*MOCS2*	*MOGS*	*MORC2*	*MPLKIP*	*MPV17*
MPZ	*MRPL12*	*MRPL44*	*MRPS16*	*MRPS22*	*MRPS34*	*MSTO1*	*MTFMT*	*MTHFR*
MTHFS	*MTO1*	*MTOR*	*MTR*	*MTRFR*	*MTRR*	*MYORG*	*MYT1L*	*NACC1*
NADK2	*NAGA*	*NAGLU*	*NAGS*	*NANS*	*NARS2*	*NAXD*	*NAXE*	*NBEA*
NDRG1	*NDUFA1*	*NDUFA10*	*NDUFA11*	*NDUFA12*	*NDUFA13*	*NDUFA2*	*NDUFA4*	*NDUFA6*
NDUFA9	*NDUFAF1*	*NDUFAF2*	*NDUFAF3*	*NDUFAF4*	*NDUFAF5*	*NDUFAF6*	*NDUFAF8*	*NDUFB10*

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NDUFB11	*NDUFB3*	*NDUFB8*	*NDUFB9*	*NDUFC2*	*NDUFS1*	*NDUFS2*	*NDUFS3*	*NDUFS4*
NDUFS6	*NDUFS7*	*NDUFS8*	*NDUFV1*	*NDUFV2*	*NEK1*	*NFE2L2*	*NFU1*	*NGLY1*
NKX6-2	*NMNAT1*	*NOTCH1*	*NOTCH3*	*NPC1*	*NPC2*	*NPHP1*	*NRROS*	*NRXN1*
NSD2	*NSUN3*	*NT5C2*	*NTRK2*	*NUBPL*	*NUP62*	*OAT*	*OCRL*	*ODC1*
OPA1	*OPA3*	*OSGEP*	*OTC*	*PACS1*	*PAFAH1B1*	*PAH*	*PAK1*	*PANK2*
PARS2	*PAX1*	*PC*	*PCCA*	*PCCB*	*PCDH12*	*PCGF2*	*PDGFB*	*PDGFRB*
PDHA1	*PDHB*	*PDHX*	*PDP1*	*PDYN*	*PET100*	*PEX1*	*PEX10*	*PEX11B*
PEX12	*PEX13*	*PEX14*	*PEX16*	*PEX19*	*PEX2*	*PEX26*	*PEX3*	*PEX5*
PEX6	*PEX7*	*PGAP1*	*PGK1*	*PHGDH*	*PHYH*	*PI4KA*	*PIGA*	*PIGB*
PIGG	*PIGL*	*PIGM*	*PIGN*	*PIGP*	*PIGQ*	*PIGT*	*PIGU*	*PIGV*
PIK3C2A	*PIK3R2*	*PINK1*	*PLA2G6*	*PLAA*	*PLEKHG2*	*PLP1*	*PLPBP*	*PMM2*
PMP22	*PMPCB*	*PNKP*	*PNPT1*	*POLG*	*POLG2*	*POLR1A*	*POLR1C*	*POLR3A*
POLR3B	*POMGNT1*	*POMT1*	*POMT2*	*PPP1R15B*	*PPP2R1A*	*PPP3CA*	*PPT1*	*PRF1*
PRKDC	*PRNP*	*PRODH*	*PRPS1*	*PRR12*	*PRUNE1*	*PSAP*	*PSAT1*	*PSEN1*
PSPH	*PTEN*	*PTPN23*	*PUF60*	*PURA*	*PUS3*	*PYCR2*	*QARS1*	*QRSL1*
RAB11B	*RAB3GAP1*	*RAB3GAP2*	*RAC1*	*RARS1*	*RARS2*	*RBPJ*	*REPS1*	*RERE*
RHOBTB2	*RIN2*	*RMND1*	*RNASEH2A*	*RNASEH2B*	*RNASEH2C*	*RNASET2*	*RNF113A*	*RNF216*
RPGRIP1L	*RPIA*	*RPL10*	*RRM2B*	*RTTN*	*RXYLT1*	*SAMD9L*	*SAMHD1*	*SCN3A*
SCO1	*SCO2*	*SCP2*	*SDHA*	*SDHAF1*	*SDHB*	*SDHD*	*SEPSECS*	*SERAC1*
SET	*SETBP1*	*SETD1B*	*SGSH*	*SH3TC2*	*SHANK3*	*SHOC2*	*SHPK*	*SLC12A2*
SLC12A5	*SLC12A6*	*SLC13A5*	*SLC16A2*	*SLC17A5*	*SLC19A3*	*SLC1A2*	*SLC1A3*	*SLC1A4*
SLC20A2	*SLC25A1*	*SLC25A12*	*SLC25A15*	*SLC25A19*	*SLC25A22*	*SLC25A4*	*SLC25A42*	*SLC25A46*
SLC2A1	*SLC30A10*	*SLC33A1*	*SLC35A2*	*SLC39A14*	*SLC39A8*	*SLC46A1*	*SLC6A19*	*SLC6A8*
SLC6A9	*SLC9A1*	*SLC9A6*	*SMC1A*	*SNAP29*	*SNIP1*	*SNRPB*	*SNX14*	*SOD1*
SNORD118	*SON*	*SOX10*	*SOX2*	*SP110*	*SPART*	*SPAST*	*SPATA5*	*SPATA5L1*
SPG11	*SPG7*	*SPTAN1*	*SPTBN1*	*SQSTM1*	*SRD5A3*	*SSR4*	*ST3GAL5*	*STAG2*
STAMBP	*STAT1*	*STAT2*	*STN1*	*STRADA*	*STX11*	*STXBP1*	*STXBP2*	*SUCLA2*
SUCLG1	*SUGCT*	*SUMF1*	*SUOX*	*SURF1*	*SYNE1*	*SYNGAP1*	*SYNJ1*	*TACO1*
TAF2	*TANGO2*	*TAOK1*	*TARS1*	*TARS2*	*TBC1D24*	*TBCD*	*TBCE*	*TBCK*
TBX1	*TCF4*	*TCTN2*	*TET3*	*TIMM50*	*TIMMDC1*	*TM4SF20*	*TMEM106B*	*TMEM126B*
TMEM165	*TMEM216*	*TMEM222*	*TMEM63A*	*TMEM67*	*TMEM70*	*TMTC3*	*TOE1*	*TP53RK*
TPI1	*TPK1*	*TPP1*	*TRAPPC11*	*TRAPPC9*	*TREM2*	*TREX1*	*TRMT1*	*TRMT10A*
TRMT5	*TSC1*	*TSC2*	*TSEN54*	*TTC19*	*TTC5*	*TUBA1A*	*TUBA8*	*TUBB2A*
TUBB2B	*TUBB3*	*TUBB4A*	*TUBG1*	*TUFM*	*TWNK*	*TXN2*	*TYMP*	*TYROBP*
UBA1	*UBA5*	*UBE2A*	*UBE3A*	*UFM1*	*UNC13D*	*UPB1*	*USP7*	*VARS2*

Electronically Signed by **- Georgia Pepe, MSc Molecular Biologist, AMKA:09038403029**
- George Nasioulas, PhD Molecular Biologist, Scientific Director, AMKA:26025301255

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VCP	*VPS11*	*VPS13A*	*VPS13D*	*VPS33A*	*WARS2*	*WDR45*	*WDR73*	*WWOX*
XK	*XPR1*	*YARS1*	*YME1L1*	*ZEB2*	*ZFYVE26*	*ZIC1*	*ZMYND11*	*ZNF335*

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Family tree

Note: **The information shown on the family tree has been provided by the patient and not by medical records.**

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Literature

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