MyWES

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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:**	Referral for hypotonia, long bone fractures

Whole Exome analysis (WES) by Next Generation Sequencing

Results associated with the reason of referral

PATHOGENIC VARIANT IDENTIFIED

Gene	Variant	Clinical Significance	Zygosity
TRIP4	NM_016213.5:c.832C>T, p.(Arg278*)	Pathogenic variant	Homozygous

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Variants Details

***TRIP4*, Exon 7, NM_016213.5:c.832C>T, p.(Arg278*)** ClinGen HPO ClinVar

This is a single base substitution, replacing Arginine with a Termination codon in the TRIP4 gene (p.Arg278*). This results in the production of a truncated, non-functional protein. This variant has been described in international bibliography in homozygosity or compound heterozygosity in 2 families with affected individuals presented with prenatal-onset spinal muscular atrophy (SMA), multiple congenital contractures (arthrogryposis multiplex congenita), respiratory distress, and congenital bone fractures. (PMID: 26924529). This particular variant has been described mutation database ClinVar (Variation ID: 224632).. For these reasons this variant has been classified as pathogenic. According to international guidelines it is recommended that relatives of the patient are tested for the above mutation.

The *TRIP4* gene encodes a subunit of the tetrameric ASC-1 transcriptional cointegrator complex. The other subunits include ASCC1 (614215), ASCC2 (614216), and ASCC3 (614217). The complex associates with transcription factors or with nuclear receptors and can bidirectionally affect the link between receptor and transcription machinery, either as corepressor or coactivator. This complex also likely participates in pre-mRNA processing and regulation of splicing. Pathogenic/likely pathogenic variants are cause spinal muscular atrophy with congenital bone fractures 1 and are inherited in the recessive manner.

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Methodology

Genomic DNA was extracted from the sample under investigation and was analysed by a solution based capture approach using the target enrichment panel KAPA HyperExome Probes, 43Mb, Roche. Sequencing was carried out using MGI technology. Reads were aligned to the reference sequence (GRCh37), and sequence changes were identified and interpreted in the context of a single clinically relevant transcript. Unless otherwise stated, this assay targets all coding regions of the indicated transcripts and 10 base pairs of flanking intronic sequences. All targeted regions were sequenced with >=10x depth.

Based on the available patient information, the following diagnostic algorithm was used.

- The genes described in the OMIM and HPO databases were selected as genes associated with the patient phenotype.
- Variant classification was performed according to the ACMG AND AMP guidelines (PMID: 25741868)
- Analysis of the mutations described in the HGMD, the mutations with damaging effect (frameshift, nonsense, missense, splicing mutations etc.) as well as de novo mutations was obtained.
- All clinically significant observations were confirmed by Sanger Sequencing.

*Note:

Every molecular test has an internal 0,5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples. Unless otherwise stated, this assay targets all coding regions of the indicated transcripts and 10 base pairs of flanking intronic sequences. Therefore, this method cannot detect variants in deep intronic or enhancer/promoter regions.

The method used achieves 99% sensitivity and specificity for single nucleotide variants and insertions and deletions.

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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. When identified, variants of uncertain significance (VUS) are reported. Findings of variants of uncertain significance (VUS) in autosomal recessive diseases are not reported unless they co-exist with another finding (pathogenic, likely pathogenic or VUS in the same gene). Benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased risk of 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.

Genes Analyzed (Table 1)

ACAN	*ACP5*	*ACTB*	*ACTG1*	*ACVR1*	*ADAMTS10*	*ADAMTS17*	*ADAMTS2*	*ADAMTSL2*
AFF4	*AGA*	*AGPS*	*AIFM1*	*AKT1*	*ALPL*	*ALX1*	*ALX3*	*ALX4*
AMER1	*AMMECR1*	*ANKH*	*ANKRD11*	*ANO5*	*ANTXR2*	*ARCN1*	*ARHGAP31*	*ARID1A*
ARID1B	*ARSB*	*ASAH1*	*ASCC1*	*ASXL1*	*ATP6V0A2*	*ATP7A*	*ATR*	*B3GALT6*
B3GAT3	*B4GALT7*	*BCOR*	*BCS1L*	*BGN*	*BHLHA9*	*BICD2*	*BLM*	*BMP1*
BMP2	*BMPER*	*BMPR1B*	*BRAF*	*BRCA2*	*BRIP1*	*BSCL2*	*C2CD3*	*CA2*
CANT1	*CASR*	*CBL*	*CC2D2A*	*CCDC47*	*CCDC8*	*CDC42*	*CDC45*	*CDC6*
CDH11	*CDH3*	*CDKN1C*	*CDT1*	*CENPE*	*CENPJ*	*CEP120*	*CEP152*	*CEP290*
CEP63	*CHCHD10*	*CHST14*	*CHST3*	*CHSY1*	*CKAP2L*	*CLCN5*	*CLCN7*	*COG4*
COL10A1	*COL11A1*	*COL11A2*	*COL1A1*	*COL1A2*	*COL27A1*	*COL2A1*	*COL3A1*	*COL5A1*
COL5A2	*COL9A1*	*COL9A2*	*COL9A3*	*COMP*	*CREB3L1*	*CREBBP*	*CRIPT*	*CRLF1*
CRTAP	*CSF1R*	*CSPP1*	*CTSK*	*CUL7*	*CWC27*	*CYP27B1*	*CYP2R1*	*DCTN1*
DDR2	*DDRGK1*	*DHCR24*	*DHCR7*	*DHODH*	*DLL3*	*DLL4*	*DLX3*	*DLX5*
DMP1	*DNAJB2*	*DNAJC21*	*DNMT3A*	*DOCK6*	*DSE*	*DVL1*	*DVL3*	*DYM*
DYNC1H1	*DYNC2H1*	*DYNC2LI1*	*EBP*	*EDN1*	*EDNRA*	*EFL1*	*EFNB1*	*EFTUD2*
EIF2AK3	*EIF4A3*	*ENAM*	*ENPP1*	*EOGT*	*EP300*	*ERCC4*	*ERF*	*ESCO2*
EVC	*EVC2*	*EXOSC2*	*EXOSC3*	*EXOSC8*	*EXT1*	*EXT2*	*EXTL3*	*EZH2*
FAM111A	*FAM20A*	*FAM20C*	*FAM83H*	*FANCA*	*FANCB*	*FANCC*	*FANCD2*	*FANCE*
FANCF	*FANCG*	*FANCI*	*FANCL*	*FANCM*	*FBN1*	*FBN2*	*FBXO38*	*FERMT3*
FGD1	*FGF10*	*FGF23*	*FGF9*	*FGFR1*	*FGFR2*	*FGFR3*	*FIG4*	*FKBP10*
FKBP14	*FLNA*	*FLNB*	*FN1*	*FTO*	*FUCA1*	*FZD2*	*GALNS*	*GALNT3*
GCM2	*GDF3*	*GDF5*	*GDF6*	*GH1*	*GHR*	*GHRHR*	*GHSR*	*GJA1*

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GLB1	*GLI1*	*GLI2*	*GLI3*	*GMNN*	*GNAI3*	*GNAS*	*GNPAT*	*GNPTAB*
GNPTG	*GNS*	*GORAB*	*GPC6*	*GSC*	*GUSB*	*GZF1*	*HAAO*	*HDAC4*
HDAC8	*HES7*	*HESX1*	*HEXA*	*HOXA11*	*HOXA13*	*HOXD13*	*HPGD*	*HRAS*
HSPA9	*HSPB1*	*HSPB3*	*HSPB8*	*HSPG2*	*IARS2*	*IDH2*	*IDS*	*IDUA*
IFIH1	*IFITM5*	*IFT122*	*IFT140*	*IFT172*	*IFT43*	*IFT52*	*IFT80*	*IFT81*
IGF1	*IGF2*	*IGFALS*	*IGHMBP2*	*IHH*	*IL1RN*	*INPPL1*	*INSR*	*INTU*
IRS1	*KAT6B*	*KCNJ2*	*KIAA0586*	*KIAA0753*	*KIF22*	*KIF7*	*KL*	*KMT2A*
KRAS	*KYNU*	*LARP7*	*LAS1L*	*LBR*	*LEMD3*	*LFNG*	*LHX3*	*LHX4*
LIFR	*LMNA*	*LMX1B*	*LONP1*	*LPIN2*	*LRP4*	*LRP5*	*LTBP2*	*LTBP3*
LZTR1	*MAFB*	*MAN2B1*	*MANBA*	*MAP2K1*	*MAP2K2*	*MAP3K7*	*MATN3*	*MBTPS2*
MECOM	*MEGF8*	*MEOX1*	*MESP2*	*MET*	*MGP*	*MKS1*	*MMP13*	*MMP2*
MMP9	*MNX1*	*MSX2*	*MYCN*	*MYH3*	*MYO18B*	*NAGLU*	*NANS*	*NBAS*
NEK1	*NEU1*	*NF1*	*NFIX*	*NIPBL*	*NKX3-2*	*NOG*	*NOTCH1*	*NOTCH2*
NPR2	*NRAS*	*NSD1*	*NSDHL*	*OBSL1*	*OCRL*	*OFD1*	*ORC1*	*ORC4*
ORC6	*OSGEP*	*OSTM1*	*OTX2*	*P3H1*	*P4HB*	*PALB2*	*PAM16*	*PAPSS2*
PAX3	*PCGF2*	*PCNT*	*PCYT1A*	*PDE3A*	*PDE4D*	*PEX14*	*PEX19*	*PEX5*
PEX7	*PGM3*	*PHEX*	*PIGV*	*PIK3CA*	*PISD*	*PITX1*	*PITX2*	*PLCB4*
PLEKHG5	*PLEKHM1*	*PLK4*	*PLOD1*	*PLOD2*	*PLS3*	*POC1A*	*POLA1*	*POLR1A*
POLR1C	*POLR1D*	*POLR3A*	*POLR3B*	*POP1*	*POR*	*POU1F1*	*PPIB*	*PPP3CA*
PRKAR1A	*PRMT7*	*PROP1*	*PTDSS1*	*PTH1R*	*PTHLH*	*PTPN11*	*PUF60*	*PYCR1*
RAB23	*RAB33B*	*RAD21*	*RAD51C*	*RAF1*	*RALA*	*RASA2*	*RBBP8*	*RBM8A*
RBPJ	*RECQL4*	*REEP1*	*RIPPLY2*	*RIT1*	*RMRP*	*RNU4ATAC*	*ROR2*	*RPGRIP1L*
RRAS	*RSPRY1*	*RTTN*	*RUNX2*	*SALL1*	*SALL4*	*SBDS*	*SC5D*	*SCO2*
SEC24D	*SERPINF1*	*SERPINH1*	*SETBP1*	*SETD2*	*SF3B4*	*SFRP4*	*SGMS2*	*SGSH*
SH3BP2	*SH3PXD2B*	*SHH*	*SHOC2*	*SHOX*	*SKI*	*SLC10A7*	*SLC17A5*	*SLC26A2*
SLC29A3	*SLC34A3*	*SLC35D1*	*SLC39A13*	*SLC5A7*	*SLCO2A1*	*SLX4*	*SMAD2*	*SMAD3*
SMAD4	*SMARCA2*	*SMARCA4*	*SMARCAL1*	*SMARCB1*	*SMARCE1*	*SMC1A*	*SMC3*	*SMN1*
SMN2	*SNRPB*	*SNX10*	*SOS1*	*SOST*	*SOX11*	*SOX2*	*SOX3*	*SOX9*
SP7	*SPARC*	*SRCAP*	*SRP54*	*STAG2*	*STAMBP*	*STAT5B*	*SUMF1*	*TAB2*
TALDO1	*TAPT1*	*TBCE*	*TBX15*	*TBX19*	*TBX2*	*TBX3*	*TBX4*	*TBX5*
TBX6	*TBXAS1*	*TCF12*	*TCIRG1*	*TCOF1*	*TCTN3*	*TGDS*	*TGFB1*	*TGFB3*
TGFBR1	*TGFBR2*	*THPO*	*TMEM165*	*TMEM216*	*TMEM38B*	*TMEM67*	*TNFRSF11A*	*TNFRSF11B*
TNFSF11	*TONSL*	*TOP3A*	*TP63*	*TRAF3IP1*	*TRAPPC2*	*TREM2*	*TRIM37*	*TRIP11*
TRIP4	*TRMT10A*	*TRPS1*	*TRPV4*	*TRPV6*	*TTC21B*	*TUBGCP6*	*TWIST1*	*TYROBP*
UBA1	*UFSP2*	*VAPB*	*VDR*	*VIPAS39*	*VRK1*	*WDR19*	*WDR35*	*WNT1*

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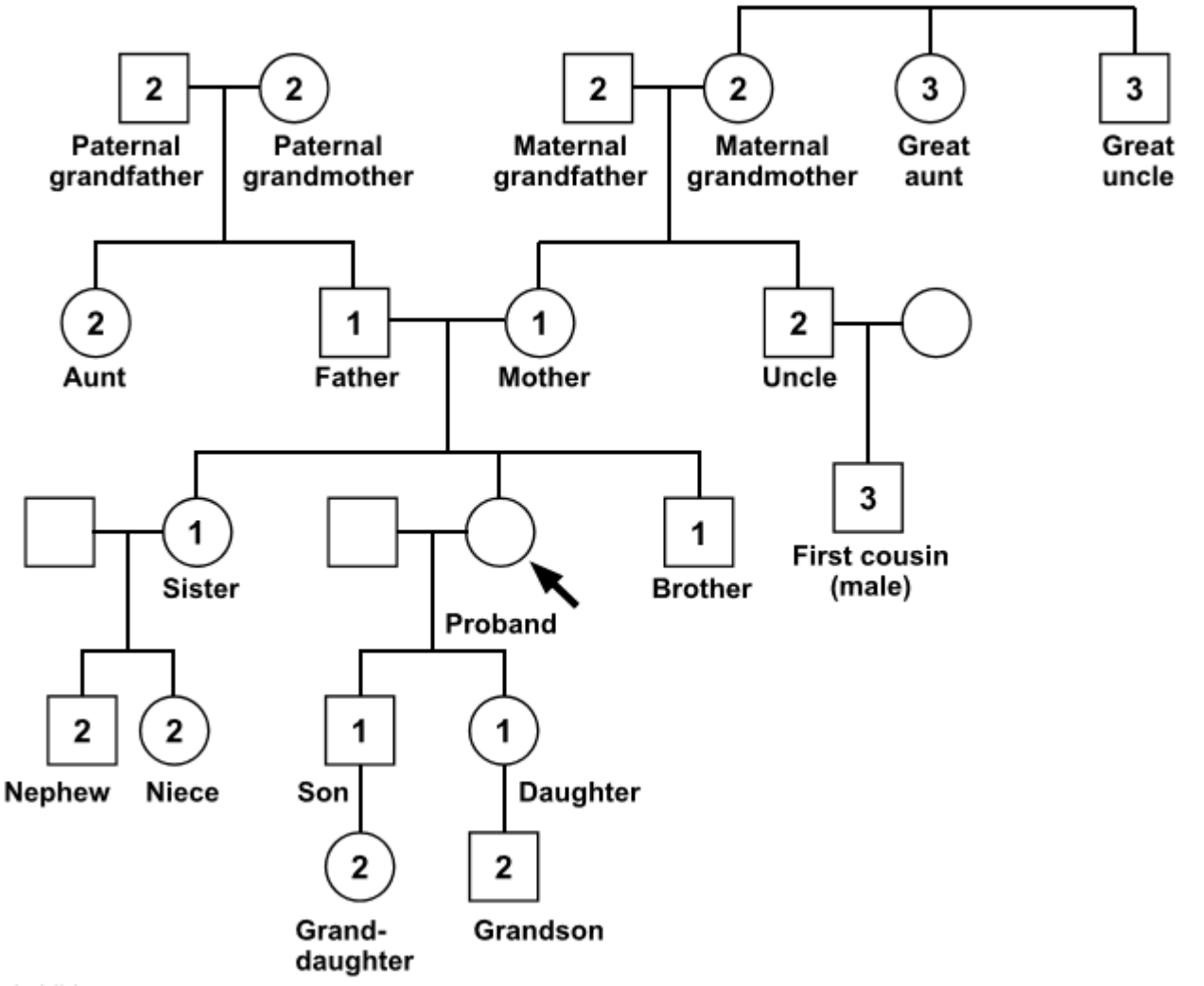
WNT10B	*WNT5A*	*WNT7A*	*XRCC2*	*XRCC4*	*XYLT1*	*XYLT2*	*ZMPSTE24*	*ZSWIM6*

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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Group. **ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG).** Genet Med. 2021 May 20. doi: 10.1038/s41436-021-01172-3. Epub ahead of print. (PMID: 34012068)

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