REFERENCE LABORATORY GENETICS

ENAC ISO15189 Nº 1065/LE2112

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# GENETIC STUDY OF NEUROLOGICAL DISORDERS (NeuroRef Global®) BY MASSIVE SEQUENCING (NGS)

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|---|---|---|---|
| **Request No.:** | 000 | | |
| **Client:** | - | | |
| **Analysis code:** | 55620 | | |
| **Patient Name:** | xxx | | |
| **Date of Birth:** | N/A | **Patient Ref.:** | xxx |
| **Gender:** | Male | **Sample Type:** | Blood EDTA |
| **Sample Arrival Date:** | DD/MM/AAAA | **Date of Result:** | DD/MM/AAAA |

**Clínical information:** 22-year-old patient with suspected metabolic myopathy with hyperCKemia, myalgias and fatigue.

## RESULT AND INTERPRETATION

**No pathogenic or likely pathogenic variants have been identified in the sequence of the analysed genes.**

The presence of a heterozygous variant of uncertain clinical significance (VUS) has been identified. (See Recommendations)

The complete list of studied genes is available in Annex 1. (Methodology)

The list of reported genes and coverage details is available in Table 1. (Methodology)

| Gene | Variant* | Zygosity | Inheritance pattern | Classification^ |
|---|---|---|---|---|
| *SYT2* | NM_177402.4: **c.576G>C p.(Glu192Asp)** | Heterozygosis | Autosomal Dominant | **VUS** |

* Nomenclature according to HGVS v15.11
^ Based on the recommendations of the *American College of Medical Genetics and Genomics (ACMG)*

The *SYT2* variant **c.576G>C p.(Glu192Asp)** *is a missense* that predicts an amino acid change from Glutamic acid to Aspartic acid at position 192 of the protein, affecting several functional domains. It is not described in the bibliography or in the clinical databases consulted. The variant appears in the dbSNP database (rs201523966) and in the gnomAD population frequency database (0,0016%). The bioinformatic predictors SIFT and Polyphen-2 estimate that the change has a tolerated effect, while the MutationTaster predictor estimates that the change has a pathogenic effect.

Based on these data, the variant is classified as a **Variant of Uncertain Clinical Significance.**

Pathogenic variants in the *SYT2* gene (OMIM: 600104) are associated with presynaptic congenital myasthenic syndrome 7 (OMIM: 616040) with an autosomal dominant inheritance pattern.

## RECOMMENDATIONS

In order to establish co-segregation with the disease and thus the possible pathogenicity of a variant of uncertain clinical significance, it is necessary to extend the study to the parents and/or affected and unaffected relatives.

If the segregation study does not allow to determine the pathogenicity of the identified variant, and considering an accurate clinical diagnosis, it is possible to complete the study with the identification of large deletions/duplications (Copy Number Variant; CNV) (code 25232) of the studied genes.

Genetic counselling should be offered to the patient by the prescriber physician. If additional information regarding the results or genetic counselling is required, the physician can contact our team at genetics@referencelaboratory.es.

## METHODOLOGY

DNA extraction and quantitative and qualitative evaluation of the DNA obtained.

Capture and enrichment of exonic regions and flanking intronic areas of genes contained in the REFLAB MedExome (Roche) sequencing panel with the Roche NimbleGen SeqCap EZ HyperCap Library™ technology.

Massive sequencing with the NextSeq™(Illumina) sequencer.

Identification of the variants of interest in regard to the reference genome (hg19) after filtering, according to specific quality criteria. Annotation of the obtained variants with a specific bioinformatic software: Alamut Visual™ (Interactive Biosoftware), Ingenuity Variant Analysis™ (QIAGEN), Variant interpreter™ (Illumina) and VarAFT™. The used reference databases have been the population databases dbSNP, 1000genomes, EXAC and gnomAD; the clinical databases Human Gene Mutation Database (HGMD version 2019.3), ClinVar and LOVD; the disease specific databases, if applicable, and Reference Laboratory Genetics´own databases. The bioinformatic analysis to evaluate the possible impact of the variants of interest on the structure and functionality of the protein has been carried out with the bioinformatic programs Mutation Taster, SIFT and PolyPhen-2. These analyses are only a predictive tool; they were not experimentally proven.

The nomenclature used to define the variants follows the criteria of the *Human Genome Variation Society (HGVS)* (http://www.HGVS.org/varnomen).

Classification of variants based on the recommendations of the *American College of Medical Genetics and Genomics (ACMG)* (Richards S. *et al*., 2015). Only those variants that, based on current information, are considered pathogenic, likely pathogenic or of uncertain clinical significance, are reported. (The complete list of identified variants is available upon request).

The obtained average reading depth was 133,9x being > 20x in 98,6% of the regions analysed.

LIMITATIONS: The results obtained do not exclude variants outside the analysed regions of the genome or genetic anomalies not detectable by massive sequencing such as large rearrangements, large deletions/duplications (Copy Number Variant; CNV), insertions / deletions of> = 10 nucleotides, variants in repetitive regions or with a high percentage of GC, and variants in genes with pseudogenes with highly homologous sequences.
*It is not possible to rule out the presence of variants in other unanalysed genes.*

## Annex 1. List of studied genes

*A2M, AAAS, AANAT, AARS, AARS2, AASS, ABAT, ABCA1, ABCB7, ABCC6, ABCC8, ABCD1, ABCD4, ABHD12, ABHD5, ACACA, ACAD9, ACADL, ACADM, ACADS, ACADSB, ACADVL, ACAT1, ACE, ACKR1, ACO2, ACOX1, ACSF3, ACSL4, ACTA1, ACTA2, ACTB, ACTG1, ACVRL1, ACY1, ADAM10, ADAR, ADCY5, ADGRG1, ADGRV1, ADK, ADNP, ADSL, AFF2, AFG3L2, AGA, AGK, AGL, AGRN, AGXT, AHCY, AHI1, AIFM1, AIMP1, AKT1, AKT3, ALAD, ALDH18A1, ALDH3A2, ALDH4A1, ALDH5A1, ALDH7A1, ALDOA, ALDOB, ALG1, ALG11, ALG12, ALG13, ALG2, ALG3, ALG6, ALG8, ALG9, ALMS1, ALOX5AP, ALS2, ALX1, ALX3, ALX4, AMACR, AMN, AMPD1, AMPD2, AMT, ANG, ANK3, ANKRD11, ANO10, ANO3, ANO5, AP1S1, AP1S2, AP3B1, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, APOA1, APOE, APP, APTX, AR, ARFGEF2, ARG1, ARHGAP31, ARHGEF10, ARHGEF6, ARHGEF9, ARID1A, ARID1B, ARL13B, ARL6, ARSA, ARSB, ARSE, ARSI, ARX, ASAH1, ASCL1, ASL, ASNS, ASPA, ASPM, ASS1, ASXL1, ASXL3, ATCAY, ATIC, ATL1, ATM, ATP13A2, ATP1A2, ATP1A3, ATP2A1, ATP2A2, ATP2B3, ATP2B4, ATP5E, ATP6AP2, ATP6V0A2, ATP7A, ATP7B, ATP8A2, ATPAF2, ATR, ATRX, ATXN3, B3GLCT, B4GALNT1, B4GALT1, B9D1, B9D2, BAG3, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BCAP31, BCKDHA, BCKDHB, BCKDK, BCOR, BCS1L, BDNF, BEST1, BICD2, BIN1, BLOC1S3, BLOC1S6, BOLA3, BRAF, BRAT1, BRWD3, BSCL2, BSND, C12orf57, c12orf65, C19orf12, C5orf42, C9orf72, CA8, CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1H, CACNA1S, CACNB4, CACNG2, CAMTA1, CAPN3, CASC5, CASK, CASR, CAV3, CBL, CC2D1A, CC2D2A, CCDC28B, CCDC78, CCDC88C, CCM2, CCT5, CD207, CD320, CD36, CD59, CD96, CDH15, CDK5RAP2, CDKL5, CDON, CENPJ, CEP135, CEP152, CEP290, CEP41, CEP63, CERS1, CFL2, CHAT, CHCHD10, CHD2, CHD7, CHD8, CHMP1A, CHMP2B, CHRM3, CHRNA1, CHRNA2, CHRNA4, CHRNB1, CHRNB2, CHRND, CHRNE, CHRNG, CHSY1, CISD2, CISH, CIZ1, CLCN1, CLCN2, CLCNKA, CLCNKB, CLIC2, CLN3, CLN5, CLN6, CLN8, CNBP, CNTN1, COA5, COASY, COG1, COG4, COG5, COG6, COG7, COG8, COL12A1, COL18A1, COL4A1, COL4A2, COL6A1, COL6A2, COL6A3, COL7A1, COLQ, COQ2, COQ8A, COQ9, COX10, COX15, COX6A1, COX6B1, CP, CPA6, CPT2, CR1, CRADD, CRBN, CREBBP, CRYAB, CSF1R, CSF2RB, CSPP1, CST3, CSTB, CTC1, CTDP1, CTNNB1, CTSD, CUL4B, CWF19L1, CYP11B2, CYP27A1, CYP2U1, CYP7B1, DAG1, DARS2, DBT, DCAF17, DCTN1, DCX, DDHD1, DDHD2, DDOST, DEPDC5, DES, DGUOK, DHCR7, DHH, DHTKD1, DIAPH3, DKC1, DLD, DLG3, DMD, DNAH9, DNAJB2, DNAJB6, DNAJC19, DNAJC5, DNAJC6, DNM1L, DNM2, DNMT1, DOCK8, DOK7, DOLK, DPAGT1, DPM1, DPM3, DRD3, DSC3, DST, DTNBP1, DYNC1H1, DYNC2H1, DYRK1A, DYSF, EARS2, EBP, EDN3, EDNRB, EEF2, EFHC1, EFTUD2, EGR2, EHMT1, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EIF4E, EIF4G1, ELK1, ELOVL4, ELOVL5, EMD, EMX2, ENO3, ENTPD1, EOMES, EP300, EPB41L1, EPM2A, ERBB4, ERCC1, ERCC2, ERCC5, ERCC6, ERLIN1, ERLIN2, ESCO2, ETFA, ETFB, ETFDH, ETHE1, EXOSC3, EXOSC8, F2, F5, FA2H, FADD, FAM126A, FAM134B, FANCB, FASTKD2, FBLN5, FBXO38, FBXO7, FCGR2B, FGA, FGD1, FGD4, FGF10, FGF14, FGFR1, FGFR2, FGFR3, FH, FHL1, FIG4, FKRP, FKTN, FLNA, FLNC, FLRT1, FLVCR1, FLVCR2, FMR1, FOLR1, FOXG1, FOXP1, FOXP2, FOXP3, FOXRED1, FREM1, FRG1, FRMD7, FTL, FTO, FTSJ1, FUS, FXN, FZD9, GAA, GABRA1, GABRB3, GABRD, GABRG2, GAD1, GALC, GALNS, GAMT, GAN, GARS, GATM, GBA, GBA2, GBE1, GCDH, GCH1, GCSH, GDAP1, GDI1, GDNF, GFAP, GFER, GFM1, GFPT1, GIGYF2, GJB1, GJB3, GJC2, GK, GLB1, GLDC, GLI2, GLI3, GLRA1, GLRB, GM2A, GMPPB, GNAL, GNB4, GNE, GNPAT, GNS, GOSR2, GP1BA, GPC3, GPR143, GRIA3, GRID2, GRIK2, GRIN1, GRIN2A, GRIN2B, GRIP1, GRM1, GRN, GSN, GUSB, GYG1, GYS1, HADHA, HADHB, HCCS, HDAC4, HDAC8, HEPACAM, HERC2, HESX1, HEXA, HEXB, HFE, HGSNAT, HINT1, HK1, HMGCS2, HNRNPDL, HOXA1, HOXD10, HPCA, HPD, HPRT1, HPS1, HPS3, HPS4, HPS5, HPS6, HPSE2, HRAS, HSD17B10, HSD17B4, HSPB1, HSPB3, HSPB8, HSPD1, HTRA1, HTRA2, HTT, HUWE1, HYAL1, ICAM1, ICK, IDS, IDUA, IER3IP1, IFRD1, IFT140, IFT27, IGBP1, IGF1, IGHMBP2, IKBKAP, IKBKG, IL11RA, IL1RAPL1, IL1RN, INF2, INPP5E, INS, IQSEC2, IRX5, ISPD, ITM2B, ITPR1, JRK, KANK1, KARS, KAT6B, KBTBD13, KCNA1, KCNC3, KCND3, KCNE5, KCNJ1, KCNJ10, KCNJ11, KCNK18, KCNK9, KCNMA1, KCNQ2, KCNQ3, KCNT1, KCTD7, KDM5C, KDM6A, KIAA2022, KIF11, KIF1A, KIF1B, KIF1C, KIF21A, KIF5A, KIF7, KIRREL3, KLF8, KMT2A, KMT2D, KRAS, KRIT1, KRT5, L1CAM, LAMA2, LAMB1, LAMB2, LAMC3, LAMP2, LARGE, LBR, LDB3, LDHA, LGI1, LHX4, LIMS2, LINS, LITAF, LMBRD1, LMNA, LMNB1, LPIN1, LPIN2, LRP2, LRPPRC, LRRK2, LRSAM1, LYZ, LZTFL1, MAG, MAGEL2, MAGI2, MAGT1, MAMLD1, MAN1B1, MAOA, MAPK10, MAPT, MARS, MARS2, MASP1, MATR3, MBD5, MBTPS2, MCEE, MCPH1, MECP2, MED12, MED17, MED23, MED25, MEF2C, MET, MFN2, MFSD8, MGAT2, MID1, MKKS, MKS1, MLC1, MMAA, MMAB, MMACHC, MMADHC, MOGS, MPDU1, MPDZ, MPI, MPV17, MPZ, MRE11A, MSX1, MSX2, MTFMT, MTHFR, MTM1, MTMR14, MTMR2, MTO1, MTOR, MTPAP, MTR, MTRR, MUSK, MUT, MVK, MYCN, MYF6, MYH14, MYH7, MYH9, MYO5A, MYOT, NAA10, NAGA, NAGLU, NAT8L, NBN, NDE1, NDP, NDRG1, NDST1, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFB3, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NEB, NEDD4L, NEFH, NEFL, NEU1, NF1, NFIX, NFU1, NGF, NHEJ1, NHLRC1, NHS, NIPA1, NIPBL, NKX2-1, NLGN3, NLGN4X, NLRP12, NLRP3, NOD2, NOG, NOL3, NOP56, NOS2, NOS3, NOTCH2, NOTCH3, NPC1, NPC2, NPHP1, NPHP3, NRAS, NRG1, NRXN1, NSD1, NSDHL, NSUN2, NT5C2, NTRK1, NTRK2, NUBPL, NXF5, OCLN, OCRL, OFD1, OPA1, OPA3, OPHN1, OPTN, ORC1, OTC, PAFAH1B1, PAH, PAK3, PANK2, PARK2, PARK7, PAX6, PC, PCBD1, PCDH19, PCK2, PCNT, PDCD10, PDE6D, PDE8B, PDHA1, PDK3, PDSS1, PDSS2, PDYN, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PFKM, PFN1, PGAM2, PGAP1, PGK1, PGM1, PHF6, PHF8, PHKA1, PHOX2B, PHYH, PIEZO2, PIGA, PIGL, PIGN, PIGO, PIGV, PIK3CA, PIK3R2, PIK3R5, PINK1, PLA2G6, PLCB1, PLEC, PLEKHG4, PLEKHG5, PLP1, PMM2, PMP22, PNKD, PNKP, PNPLA2, PNPLA6, PNPO, POGZ, POLG, POLG2, POLR3A, POLR3B, POMGNT1, POMGNT2, POMK, POMT1, POMT2, PORCN, PPT1, PQBP1, PREPL, PRICKLE1, PRICKLE2, PRKAG2, PRKCG, PRKCH, PRKRA, PRNP, PROP1, PRPH2, PRPS1, PRRT2, PRRX1, PRSS12, PRX, PSAP, PSEN1, PSEN2, PTCH1, PTEN, PTF1A, PTPN11, PTS, PUS1, PVRL1, PYGM, QARS, QDPR, RAB18, RAB39B, RAB3GAP1,*

*RAB3GAP2, RAB40AL, RAB7A, RABGGTA, RAD21, RAD50, RAF1, RAI1, RANBP2, RAPSN, RARS2, RBBP8, RBFOX1, RBFOX3, RBM10, RBM8A, REEP1, REEP2, RELN, RET, RFT1, RIN2, RNASEH2A, RNASEH2B, RNASEH2C, RNASET2, RNF135, RNF170, RNU4ATAC, ROGDI, ROR2, RPGRIP1L, RPL10, RPS6KA3, RRM2B, RTN2, RUBCN, RYR1, SACS, SAMHD1, SBF1, SBF2, SCARB2, SCN10A, SCN1A, SCN1B, SCN2A, SCN3A, SCN4A, SCN5A, SCN8A, SCN9A, SCO1, SCO2, SCP2, SDCCAG8, SDHA, SDHAF1, SELENON, SEPSECS, SERPINI1, SETBP1, SETD2, SETX, SGCA, SGCB, SGCD, SGCE, SGCG, SGSH, SH3TC2, SHANK2, SHANK3, SHH, SHOC2, SHROOM4, SIGMAR1, SIL1, SIX3, SIX6, SKI, SLC12A6, SLC13A5, SLC16A2, SLC17A5, SLC19A3, SLC1A3, SLC20A2, SLC22A5, SLC25A12, SLC25A19, SLC25A20, SLC25A22, SLC25A3, SLC25A4, SLC2A1, SLC30A10, SLC33A1, SLC35A1, SLC35A2, SLC35C1, SLC3A1, SLC4A1, SLC4A4, SLC5A7, SLC6A1, SLC6A3, SLC6A5, SLC6A8, SLC9A6, SLC9A9, SMARCA2, SMARCA4, SMARCB1, SMC1A, SMC3, SMCHD1, SMN1, SMN2, SMPD1, SMS, SNAP29, SNCA, SNCAIP, SNCB, SNIP1, SNX3, SOBP, SOD1, SORL1, SOS1, SOX10, SOX3, SPAST, SPG11, SPG20, SPG21, SPG7, SPR, SPTAN1, SPTBN2, SPTLC1, SPTLC2, SRD5A3, SRPX2, ST3GAL3, ST3GAL5, STIL, STRADA, STUB1, STXBP1, SUCLA2, SUCLG1, SUMF1, SURF1, SYN1, SYNE1, SYNE2, SYNGAP1, SYNJ1, SYP, SYT14, SZT2, TACO1, TAF1, TAF2, TARDBP, TAS2R38, TAZ, TBC1D24, TBCE, TBL1XR1, TBX1, TCAP, TCF4, TCTN1, TCTN2, TCTN3, TDP1, TECPR2, TECR, TFAP2A, TFAP2B, TFG, TG, TGFB1, TGFB2, TGFBR1, TGFBR2, TGIF1, TGM6, TH, THAP1, TICAM1, TIMM8A, TIRAP, TK2, TLR3, TLR5, TMCO1, TMEM126A, TMEM138, TMEM165, TMEM216, TMEM231, TMEM237, TMEM67, TMEM70, TMLHE, TNF, TNFSF4, TNNT1, TNPO3, TOR1A, TP63, TPK1, TPM2, TPM3, TPP1, TRAF3, TRAPPC11, TRAPPC9, TREM2, TREX1, TRIM2, TRIM32, TRPM6, TRPM7, TRPS1, TRPV4, TSC1, TSC2, TSEN2, TSEN34, TSEN54, TSFM, TSHB, TSHR, TSPAN7, TTBK2, TTC19, TTC21B, TTC8, TTI2, TTN, TTPA, TTR, TUBA1A, TUBA4A, TUBA8, TUBB2B, TUBB3, TUBB4A, TUBGCP6, TUSC3, TWIST1, TWNK, TYMP, TYROBP, UBA1, UBE2A, UBE3A, UBQLN2, UCHL1, UMPS, UNC93B1, UPB1, UPF3B, UQCRB, UQCRQ, USP8, USP9X, VAMP1, VANGL1, VAPB, VAX1, VCP, VDAC1, VEGFA, VHL, VIPAS39, VLDLR, VPS13A, VPS13B, VPS35, VPS37A, VRK1, WAC, WASHC5, WDPCP, WDR45, WDR48, WDR62, WDR81, WFS1, WNK1, WNT10A, WNT3, WNT5A, WNT7A, WWOX, XBP1, XK, YAP1, YARS, YWHAE, ZBTB16, ZBTB18, ZCCHC12, ZDHHC15, ZDHHC9, ZEB2, ZFR, ZFYVE26, ZFYVE27, ZIC2, ZIC3, ZNF335, ZNF423, ZNF592, ZNF711, ZNF81,*

Table 1. List of reported genes and coverage details

| Gene | NM | 10x % | Exons with coverage < 100%* |
|---|---|---|---|
| *SYT2* | NM_177402 | 100,00 | - |

*Due to the current intrinsic limitations associated with massive sequencing technology, some gene exons analysed may be insufficiently covered. If it is considered appropriated by a medical specialist, it would be possible to sequence exons with coverage below 100% using the Sanger method or other alternative molecular technique.

## IMPORTANT NOTE

The information contained in this report is based on current scientific knowledge and the results obtained from the application of the technology in this report, are detailed. Due to continuous advances, the documented information may be modified in the future as a result of the emergence of new scientific evidence.
The genetic/genomic studies carried out by Reference Laboratory S.A. are exclusively intended for qualified health professionals for their interpretation. The results obtained are not, per se, a medical consultation, diagnosis or treatment, nor should they be interpreted as such. Only a specialized professional can correctly interpret the results and offer a diagnosis or prescribe a treatment to a patient based on these. Consequently, no information obtained from our studies can be used to replace the advice and diagnosis of a specialized professional.

**Signed: Cristina Camprubí, PhD**

**Head of Diagnosis and Genetic Counseling**

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College of Biologists of Catalonia

Accredited by AEGH

**Signed: Irina Royo, MSc**

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