Spastic paraplegia type 78 associated to *ATP13A2* gene variants in compound heterozygosity

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Supporting information

Whole-exome sequencing and variant selection

A whole-exome analysis was performed from an EDTA-blood sample from the proband. Whole-exome sequencing was carried out using a SureSelect V6-Post (Agilent, USA) capture kit and HiSeq 4000 platform (Illumina, USA). A total of 51,651,565 reads were obtained with a mean depth of 51,7X. Table S1 summarizes the variants detected in the proband's sample.

Table S1. Variants detected in a hereditary spastic paraplegia proband by whole-exome sequencing

Variant type	Detected number
Single nucleotide polymorphisms	91,389
Synonymous variants	11,780
Missense variants	11,209
Stop gained	102
Stop lost	38
Insertions/deletions	9,885
Frameshift variants	99
In-frame insertions	153
In-frame deletions	152

The BioVisor NGS software (Progenie Molecular, Spain) was employed to analyse the identified variants, by performing a filtering process based on 5,863 variants located in 901 genes related to neuromuscular diseases (Table S2). The software excluded benign variants by the following criteria: frequency ≥ 0.01; classified as benign in the ClinVar database; intronic variants, deletions, insertions and duplications at ± 2 nt; 5' UTR and 3' UTR variants at ± 2 nt; variants in non-coding exons and synonymous variants. 19 potentially pathogenic variants within 18 genes, all found in heterozygosity, were selected for individual analysis according to clinical features and pathogenic potential (Table S3).

Table S2. Genes included in the panel for neuromuscular diseases

A2M	*ATP2B3*	*COL6A2*	*EIF2B5*	*GJB3*	*KCNJ18*	*MTFMT*	*PEX11B*	*PRX*	*SLC19A3*	*TDP2*	*WASHC5*
AAAS	*ATP2B4*	*COL6A3*	*EIF4G1*	*GLA*	*KCNJ2*	*MTM1*	*PEX12*	*PSAP*	*SLC1A3*	*TECPR2*	*WDR45*
AARS	*ATP7A*	*COLQ*	*ELOVL4*	*GLB1*	*KCNJ5*	*MTMR14*	*PEX13*	*PSEN1*	*SLC1A4*	*TENM4*	*WDR48*
AARS2	*ATP7B*	*COQ2*	*ELOVL5*	*GLDN*	*KCNMA1*	*MTMR2*	*PEX14*	*PSEN2*	*SLC20A2*	*TFG*	*WDR73*
ABCA1	*ATP8A2*	*COQ8A*	*ELP1*	*GLE1*	*KCNQ2*	*MTPAP*	*PEX16*	*PTRH2*	*SLC22A5*	*TGFB3*	*WDR81*
ABCA7	*ATXN1*	*COQ9*	*EMD*	*GLRA1*	*KCNQ3*	*MTTP*	*PEX19*	*PTS*	*SLC25A1*	*TGM6*	*WFS1*
ABCB7	*ATXN10*	*COX10*	*ENO3*	*GLRB*	*KCNT1*	*MUSK*	*PEX2*	*PUS1*	*SLC25A12*	*TH*	*WNK1*
ABHD12	*ATXN3*	*COX15*	*ENTPD1*	*GLUD2*	*KCTD17*	*MYBPC1*	*PEX26*	*PYCR2*	*SLC25A15*	*THAP1*	*WWOX*
ABHD5	*ATXN7*	*COX6A1*	*EPHA4*	*GM2A*	*KCTD7*	*MYF6*	*PEX3*	*PYGM*	*SLC25A19*	*TIA1*	*XK*
ACAD9	*AUH*	*CP*	*EPM2A*	*GMPPB*	*KDM5C*	*MYH14*	*PEX5*	*PYROXD1*	*SLC25A20*	*TK2*	*XPA*
ACADL	*B3GALNT2*	*CPLX1*	*EPRS*	*GNAL*	*KIAA0556*	*MYH2*	*PEX7*	*QDPR*	*SLC25A3*	*TMEM106B*	*XPC*
ACADM	*B4GALNT1*	*CPOX*	*ERBB3*	*GNAO1*	*KIAA0586*	*MYH3*	*PFKM*	*RAB39B*	*SLC25A4*	*TMEM126B*	*XPR1*
ACADS	*B4GALT1*	*CPT1C*	*ERBB4*	*GNB4*	*KIAA0753*	*MYH7*	*PFN1*	*RAB3GAP2*	*SLC25A46*	*TMEM138*	*YARS*
ACADVL	*B4GAT1*	*CPT2*	*ERCC2*	*GNE*	*KIDINS220*	*MYH8*	*PGAM2*	*RAB7A*	*SLC2A1*	*TMEM216*	*YARS2*
ACER3	*B9D1*	*CRAT*	*ERCC3*	*GOLGA2*	*KIF14*	*MYO18B*	*PGAP1*	*RAI1*	*SLC30A10*	*TMEM231*	*ZBTB42*
ACOX1	*BAG3*	*CRYAB*	*ERCC4*	*GOSR2*	*KIF1A*	*MYO9A*	*PGK1*	*RAPSN*	*SLC33A1*	*TMEM237*	*ZC4H2*
ACTA1	*BCAP31*	*CSF1R*	*ERCC5*	*GRID2*	*KIF1B*	*MYOD1*	*PGM1*	*RARS*	*SLC35A3*	*TMEM240*	*ZFR*
ACVR1	*BCS1L*	*CSPP1*	*ERCC6*	*GRM1*	*KIF1C*	*MYOT*	*PHGDH*	*RARS2*	*SLC39A14*	*TMEM43*	*ZFYVE26*
ADAM10	*BEAN1*	*CSTB*	*ERCC8*	*GRN*	*KIF21A*	*MYPN*	*PHKA1*	*RBCK1*	*SLC52A2*	*TMEM5*	*ZFYVE27*
ADAR	*BICD2*	*CTC1*	*ERGIC1*	*GSN*	*KIF5A*	*NAGLU*	*PHKA2*	*RBM7*	*SLC52A3*	*TMEM67*	*ZNF423*
ADCY5	*BIN1*	*CTDP1*	*ERLIN1*	*GYG1*	*KIF7*	*NAIP*	*PHKB*	*REEP1*	*SLC5A7*	*TNNI2*	*ZNF592*
ADCY6	*BSCL2*	*CTNND2*	*ERLIN2*	*GYS1*	*KLC2*	*NALCN*	*PHKG2*	*REEP2*	*SLC6A3*	*TNNT1*	
ADGRG6	*BVES*	*CTSA*	*ETFA*	*HACD1*	*KLHL24*	*NDRG1*	*PHYH*	*REPS1*	*SLC6A5*	*TNNT3*	
ADH1C	*C19orf12*	*CTSD*	*ETFB*	*HACE1*	*KLHL40*	*NDUFA1*	*PIBF1*	*RETREG1*	*SLC7A2*	*TNPO3*	
ADRA2B	*C21orf2*	*CWF19L1*	*ETFDH*	*HADH*	*KLHL41*	*NDUFA10*	*PIEZO2*	*RIPK4*	*SLC9A6*	*TOR1A*	
ADSSL1	*C5orf42*	*CYP27A1*	*ETHE1*	*HADHA*	*KLHL7*	*NDUFA12*	*PIGA*	*RNASEH2A*	*SLURP1*	*TOR1AIP1*	
AFG3L2	*C9orf72*	*CYP2U1*	*EXOSC3*	*HADHB*	*KLHL9*	*NDUFA2*	*PIGN*	*RNASEH2B*	*SMAD3*	*TPK1*	
AGK	*CA2*	*CYP7B1*	*EXOSC8*	*HARS*	*KMT2B*	*NDUFA4*	*PIGT*	*RNASEH2C*	*SMCHD1*	*TPM2*	
AGL	*CA8*	*DAG1*	*FA2H*	*HEXA*	*KY*	*NDUFA9*	*PIK3R5*	*RNASET2*	*SMN1*	*TPM3*	
AGRN	*CACNA1A*	*DAO*	*FAM126A*	*HEXB*	*L1CAM*	*NDUFAF5*	*PINK1*	*RNF168*	*SMPD1*	*TPP1*	
AHI1	*CACNA1B*	*DARS*	*FARS2*	*HIBCH*	*L2HGDH*	*NDUFAF6*	*PIP5K1C*	*RNF170*	*SNAP25*	*TRAPPC11*	
AIFM1	*CACNA1G*	*DARS2*	*FBLN5*	*HIKESHI*	*LAMA1*	*NDUFS1*	*PLA2G6*	*RNF216*	*SNCA*	*TREM2*	
AIMP1	*CACNA1S*	*DCAF17*	*FBN1*	*HINT1*	*LAMA2*	*NDUFS2*	*PLAA*	*RPGRIP1L*	*SNCB*	*TREX1*	
AIMP2	*CACNB4*	*DCAF8*	*FBN2*	*HK1*	*LAMB2*	*NDUFS3*	*PLAU*	*RPIA*	*SNTB1*	*TRIM2*	
ALAD	*CAMTA1*	*DCTN1*	*FBN3*	*HMBS*	*LAMP2*	*NDUFS4*	*PLEC*	*RRM2B*	*SNX14*	*TRIM32*	
ALDH18A1	*CAPN1*	*DCTN2*	*FBXL4*	*HNRNPA1*	*LARGE1*	*NDUFS7*	*PLEKHG2*	*RTN2*	*SOD1*	*TRIM54*	
ALDH3A2	*CAPN3*	*DDB2*	*FBXO38*	*HNRNPA2B1*	*LAS1L*	*NDUFS8*	*PLEKHG4*	*RUBCN*	*SORL1*	*TRIM63*	
ALDOA	*CASK*	*DDC*	*FBXO7*	*HOXD10*	*LDB3*	*NDUFV1*	*PLEKHG5*	*RXYLT1*	*SOX10*	*TRIP4*	
ALG14	*CASQ1*	*DDHD1*	*FDX1L*	*HPCA*	*LGI4*	*NEB*	*PLOD2*	*RYR1*	*SPART*	*TRMU*	
ALG2	*CAV3*	*DDHD2*	*FECH*	*HPRT1*	*LIMS2*	*NEFL*	*PLP1*	*SACS*	*SPAST*	*TRPA1*	
ALG3	*CAVIN1*	*DES*	*FGD4*	*HRAS*	*LIPT1*	*NEK1*	*PMM2*	*SAMD9L*	*SPEG*	*TRPC3*	
ALS2	*CC2D2A*	*DGAT2*	*FGF14*	*HSD17B4*	*LITAF*	*NEK9*	*PMP2*	*SAMHD1*	*SPG11*	*TRPV4*	
AMACR	*CCDC78*	*DHCR24*	*FHL2*	*HSPB1*	*LMNA*	*NFU1*	*PMP22*	*SBF1*	*SPG20*	*TSEN15*	
AMPD1	*CCDC88C*	*DHTKD1*	*FIG4*	*HSPB3*	*LMNB1*	*NGF*	*PMPCA*	*SBF2*	*SPG21*	*TSEN2*	
AMPD2	*CCNF*	*DLAT*	*FKBP10*	*HSPB8*	*LMNB2*	*NHLRC1*	*PNKD*	*SCARB2*	*SPG7*	*TSEN54*	
ANG	*CCT5*	*DMD*	*FKBP14*	*HSPG2*	*LMOD3*	*NIPA1*	*PNKP*	*SCN10A*	*SPR*	*TSFM*	
ANO10	*CEP104*	*DMPK*	*FKRP*	*HTRA2*	*LPIN1*	*NKX2-1*	*PNPLA2*	*SCN11A*	*SPTAN1*	*TTBK2*	
ANO3	*CEP120*	*DMXL2*	*FKTN*	*HTT*	*LRP4*	*NOP56*	*PNPLA6*	*SCN1A*	*SPTBN2*	*TTN*	
ANO5	*CEP290*	*DNA2*	*FLAD1*	*HYLS1*	*LRPPRC*	*NOS3*	*PNPLA8*	*SCN1B*	*SPTLC1*	*TTR*	
ANXA11	*CEP41*	*DNAJB2*	*FLNC*	*IARS2*	*LRRK2*	*NOTCH3*	*PNPT1*	*SCN2A*	*SPTLC2*	*TUBA4A*	
AP4B1	*CFL2*	*DNAJB5*	*FLRT1*	*IBA57*	*LRSAM1*	*NPC1*	*POGLUT1*	*SCN4A*	*SQSTM1*	*TUBB2B*	
AP4E1	*CHAT*	*DNAJC12*	*FLVCR1*	*ICK*	*LTBP4*	*NPC2*	*POLG*	*SCN8A*	*STAC3*	*TUBB3*	
AP4M1	*CHKB*	*DNAJC13*	*FLVCR2*	*IDS*	*LYRM7*	*NPHP1*	*POLG2*	*SCN9A*	*STIM1*	*TUBB4A*	
AP4S1	*CHMP2B*	*DNAJC5*	*FOLR1*	*IFIH1*	*LYST*	*NT5C2*	*POLR1C*	*SCO1*	*STN1*	*TUFM*	
AP5Z1	*CHRNA1*	*DNAJC6*	*FOXRED1*	*IFRD1*	*MAG*	*NTRK1*	*POLR3A*	*SCO2*	*STUB1*	*TWNK*	
APOA1	*CHRNB1*	*DNM2*	*FRG1*	*IFT140*	*MAMLD1*	*NUP62*	*POLR3B*	*SCP2*	*STXBP1*	*TYMP*	
APOE	*CHRND*	*DNMT1*	*FTL*	*IFT172*	*MAP3K20*	*OCLN*	*POMGNT1*	*SCYL1*	*SUCLA2*	*TYROBP*	
APOPT1	*CHRNE*	*DOK7*	*FUCA1*	*IGHMBP2*	*MAPT*	*OPA1*	*POMGNT2*	*SDHA*	*SUCLG1*	*UBA1*	
APP	*CHRNG*	*DOLK*	*FUS*	*INF2*	*MARS*	*OPA3*	*POMK*	*SDHAF1*	*SUMF1*	*UBE3A*	
APTX	*CHST14*	*DPAGT1*	*G6PC*	*INPP5E*	*MARS2*	*OPTN*	*POMT1*	*SELENON*	*SURF1*	*UBQLN2*	
AR	*CHUK*	*DPM1*	*GAA*	*INPP5K*	*MATR3*	*ORAI1*	*POMT2*	*SEMA3A*	*SYNE1*	*UCHL1*	
ARHGEF10	*CIZ1*	*DPM2*	*GABRA1*	*IRF6*	*MCM3AP*	*P4HA1*	*PON2*	*SEPSECS*	*SYNE2*	*UNC13A*	
ARL13B	*CLCF1*	*DPM3*	*GABRD*	*ISCA2*	*MCOLN1*	*PANK2*	*PON3*	*SEPT9*	*SYNJ1*	*UQCRQ*	
ARMC9	*CLCN1*	*DRD2*	*GABRG2*	*ISCU*	*MECP2*	*PARK7*	*PPARGC1A*	*SERAC1*	*SYT14*	*UROD*	
ARSA	*CLCN2*	*DRP2*	*GAD1*	*ISPD*	*MECR*	*PAX6*	*PPOX*	*SERPINI1*	*SYT2*	*UROS*	
ARSI	*CLN3*	*DSE*	*GALC*	*ITGA7*	*MED25*	*PC*	*PPP2R2B*	*SETX*	*TACO1*	*USP8*	
ASAH1	*CLN5*	*DST*	*GAN*	*ITM2B*	*MEGF10*	*PCDH19*	*PPT1*	*SGCA*	*TAF1*	*VAC14*	
ASCC1	*CLN6*	*DSTYK*	*GARS*	*ITPR1*	*MFN2*	*PDE10A*	*PRDM12*	*SGCB*	*TAF15*	*VAMP1*	
ASPA	*CLN8*	*DUX4*	*GBA*	*JPH1*	*MFSD8*	*PDE6D*	*PRDM8*	*SGCD*	*TANGO2*	*VAPB*	
ATAD3A	*CLTCL1*	*DYNC1H1*	*GBA2*	*JPH3*	*MICU1*	*PDE8B*	*PREPL*	*SGCE*	*TARDBP*	*VCP*	
ATCAY	*CNBP*	*DYSF*	*GBE1*	*JRK*	*MKS1*	*PDGFB*	*PRICKLE1*	*SGCG*	*TAZ*	*VIPAS39*	
ATL1	*CNTN1*	*EARS2*	*GCDH*	*KARS*	*MLC1*	*PDGFRB*	*PRICKLE2*	*SGPL1*	*TBC1D24*	*VLDLR*	
ATL3	*CNTN2*	*ECHS1*	*GCH1*	*KAT6B*	*MME*	*PDHA1*	*PRKAG2*	*SH3TC2*	*TBCE*	*VMA21*	
ATM	*CNTNAP1*	*EEF2*	*GDAP1*	*KBTBD13*	*MORC2*	*PDHB*	*PRKCG*	*SIGMAR1*	*TBK1*	*VPS11*	
ATN1	*COASY*	*EFHC1*	*GFAP*	*KCNA1*	*MPO*	*PDHX*	*PRKN*	*SIL1*	*TBP*	*VPS13A*	
ATP13A2	*COL12A1*	*EGR2*	*GFER*	*KCNA2*	*MPV17*	*PDK3*	*PRKRA*	*SLC12A6*	*TCAP*	*VPS13C*	
ATP1A1	*COL13A1*	*EIF2B1*	*GFM1*	*KCNC1*	*MPZ*	*PDSS2*	*PRNP*	*SLC16A1*	*TCTN1*	*VPS33B*	
ATP1A2	*COL4A1*	*EIF2B2*	*GFPT1*	*KCND3*	*MR1*	*PDYN*	*PRPH*	*SLC17A5*	*TCTN2*	*VPS35*	
ATP1A3	*COL4A2*	*EIF2B3*	*GIGYF2*	*KCNE3*	*MRE11*	*PEX1*	*PRPS1*	*SLC18A2*	*TCTN3*	*VPS37A*	
ATP2A1	*COL6A1*	*EIF2B4*	*GJB1*	*KCNJ10*	*MSTN*	*PEX10*	*PRRT2*	*SLC18A3*	*TDP1*	*VRK1*	

Table S3. Neuromuscular-related variants selected after whole-exome sequencing and software filtering

Chromosome	Position	Gene	Reference sequence	HGVSc	HGVSp	Exon	Depth (X)	dbSNP	1000Gp3_AF	SIFT	Polyphen2
19	1,043,794	*ABCA7*	NM_019112.3	c.1001G>A	p.Arg334Gln	10/47	51	rs147846250	0,000599042	T;T	B;B
4	107,253,029	*AIMP1*	NM_001142416.1	c.664C>T	p.Pro222Ser	5/7	60	rs138106524	0,000399361	D;D;D;D	B;B
1	17,318,532	*ATP13A2*	NM_022089.3	c.2097delC	p.Pro699fs	19/29	34	-	-	-	-
1	17,328,585	*ATP13A2*	NM_022089.3	c.649G>A	p.Gly217Ser	8/29	74	rs199961048	-	D;D;D;D	D;P;D
19	30,193,654	*C19orf12*	NM_001031726.3	c.424A>G	p.Lys142Glu	3/3	39	rs146170087	0,00219649	D;D;D;T	B;B
7	143,049,017	*CLCN1*	NM_000083.2	c.2926C>T	p.Arg976*	23/23	28	rs142539932	0,000599042	-	-
1	205,039,031	*CNTN2*	NM_005076.3	c.2273_2274delGGinsAT	p.Trp758Tyr	18/23	106	rs1064796187	-	-	-
13	37,581,148	*EXOSC8*	NM_181503.2	c.427G>A	p.Asp143Asn	8/11	64	rs542265577	0,000199681	T;T;T	B;B
8	75,274,121	*GDAP1*	NM_018972.2	c.487C>T	p.Gln163*	4/6	42	rs104894077	0,000199681	.;.	-
1	22,149,826	*HSPG2*	NM_001291860.1	c.13162C>T	p.Arg4388Cys	97/97	32	-	-	D	D;P
4	3,180,083	*HTT*	NM_002111.7	c.4522C>T	p.Arg1508Cys	35/67	75	rs572039089	0,000199681	T	D
9	111,693,276	*IKBKAP*	NM_003640.3	c.150+1G>A	-	2/36	35	-	-	-	-
2	8,870,884	*KIDINS220*	NM_020738.2	c.5282C>T	p.Thr1761Ile	30/30	29	-	-	D;D;D;D	B;B;B
18	6,975,995	*LAMA1*	NM_005559.3	c.6430C>G	p.Leu2144Val	45/63	30	rs117225191	0,0071885	T	D
2	11,943,118	*LPIN1*	NM_001261428.1	c.2119G>A	p.Val707Ile	16/22	12	rs146048019	-	T;T;T;T;T;T;T	B
21	47,703,705	*MCM3AP*	NM_003906.4	c.1267A>G	p.Thr423Ala	2/28	36	rs144151494	0,000798722	T;T	B
1	29,527,028	*MECR*	NM_016011.3	c.830C>T	p.Ala277Val	7/10	71	rs148978800	0,00179712	T;T	B
1	46,661,543	*POMGNT1*	NM_001243766.1	c.474G>C	p.Glu158Asp	6/23	39	-	-	T;T;T;T;T	B;B;B;B
2	179,613,347	*TTN*	NM_133379.4	c.13780G>C	p.Asp4594His	46/46	45	-	-	D	B

B: benign; T: tolerated; P: possibly damaging; D: deleterious or damaging