**Supplementary Data**

**Table e-1:** *NR4A2* mutations

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Nucleotide Change | Amino Acid Change | Type of mutation | Clinical picture | References |
| c.-469delG | - | Small deletion | Schizophrenia | (1) |
| c.-309C>T | - | Regulatory | Parkinson disease | (2) |
| c.-291delT | - | Small deletion | Parkinson disease | (3) |
| c.289A>G | p.M97V | Missense | Schizophrenia | (4) |
| c.308A>G | p.H103R | Missense | Bipolar disorder | (4) |
| c.326dupA | p.S110Vfs\*2 | Small insertion | a Epilepsy, language impairment & intellectual deficiency  b Mild intellectual disability & dystonia-parkinsonism | a (5)  b (6) |
| c.364\_366delTAC | p.Y122del | Small deletion | Schizophrenia | (4) |
| c.374C>G | p.S125C | Missense | Parkinson disease | (7) |
| c.881dupA | p.N294Kfs\*10 | Small insertion | Mild intellectual disability & dystonia-parkinsonism | (6) |
| c.920T>G | p.V307G | Missense | Pediatric, psychomotor retardation | (8) |
| c.956G>A | p.R319Q | Missense | Mild intellectual disability, dystonia-parkinsonism & motor tics | Present paper |
| Nucleotide Alteration | Deletion size | Type of mutation | Clinical picture | References |
| - | ~89 kb | Gross deletion | Neurodevelopmental disorder with language impairment | (9) |
| c.-27827\_\*87408del121845 | 122 kb | Gross deletion | Neurodevelopmental disorder including language impairment, developmental delay, intellectual disability and/or autism spectrum disorder | (10) |
| c.-126883\_\*40976del174469 | 174 kb including exon 1 of *GPD2* | Gross deletion | Neurodevelopmental disorder including language impairment, developmental delay, intellectual disability and/or autism spectrum disorder | (10) |
| c.-27827\_\*40976del75413 | 75 kb | Gross deletion | Neurodevelopmental disorder including language impairment, developmental delay, intellectual disability and/or autism spectrum disorder | (10) |

**Table e-2:** Ancillary tests developed during the diagnosis work-out.

|  |  |
| --- | --- |
| Laboratory test | Result |
| Plasma copper and ceruloplasmin  24 hours urine copper  Urine organic acids  Hemogram  Tiroid profile  Lipids a  Proteinogram  B12 and D vitamins a  Folic acid a  Iron profile  Blood smear  NH4  Chitotriosidasi enzime activity a | Normal  Normal  Normal  Normal  Normal  Triglycerides 240 mg/dl (0-170)  Normal  265 pg/ml (211-946), 66.5 nmol/l (50-250)  6.5 ng/ml (2.9-16.9)  Normal  Normal, no acantocytos  Normal  40.8 mmol/ml/h (4-76) |

a The normal ranges according to the local laboratory are listed in parentheses.

**Table e-3:** Novel candidate causative genes detected in heterozygosis in the proband by whole exome sequencing

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene | \*MIM | Position | Nucleotide  Change | Amino Acid  Change | Type of  Mutation | Clinical Picture [Reference or MIM#] |
| *NR4A2* | 601828 | 2:157184954 | c.956G>A | p.R319Q | missense | Schizophrenia, bipolar disorder (1, 4)  Parkinson Disease (2, 3, 7)  Epilepsy, language impairment and intellectual deficiency (5)  Mild intellectual disability & dystonia-parkinsonism (6)  Neurodevelopmental disorder with language impairment (9)  Autism spectrum disorder & intellectual disability (10)  Pediatric, psychomotor retardation (8) |
| *CEP170* | 613023 | 1:243328887 | c.2375C>A | p.S792\* | stop gained | Schizophrenia (11)  Chiari malformation (12)  Intellectual disability, gross motor delay, seizures, scoliosis, hearing & sight issues (13) |
| *KCNQ2* | 602235 | 20:62044939 | c.1807-5A>T | --- | splicing variant | Epileptic encephalopathy [MIM# 613720]  Myokimia, seizures [MIM# 121200] |

**Table e-4:** Twenty rare variants detected in the proband and inherited in an autosomal dominant fashion from the patient’s father or mother (shaded files).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Genotype | | | Chr:position | Nucleotide  Change | Amino Acid  Protein | Gene | dbSNP | Allele Count/ Allele Number  (gnomAD)a |
| Proband  NBIA-277 | Father  NBIA-387 | Mother  NBIA-388 |
| 0/1 | 0/1 | 0/0 | 8:39646218 | c.612A>C | p.K204N | *ADAM2* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 13:39266417 | c.4936A>T | p.I1646F | *FREM2* | rs765560306 | 1/251068 |
| 0/1 | 0/1 | 0/0 | 17:66890387 | c.2843T>C | p.I948T | *ABCA8* | rs201434277 | 3/250908 |
| 0/1 | 0/1 | 0/0 | 18:8783996 | c.886G>A | p.E296K | *SOGA2* | rs1193304665 | 2/250386 |
| 0/1 | 0/1 | 0/0 | 7:25218815 | c.113G>A | p.R38H | *C7orf31* | rs531648664 | 8/279760 |
| 0/1 | 0/1 | 0/0 | 12:53170945 | c.131G>A | p.C44Y | *KRT76* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 19:41762491 | c.2171G>A | p.R724H | *AXL* | rs1441087022 | 1/251468 |
| 0/1 | 0/1 | 0/0 | 14:57938225 | c.739C>T | p.L247F | *C14orf105* | rs1374191015 | 1/251250 |
| 0/1 | 0/1 | 0/0 | 1:227333410 | c.923C>T | p.T308I | *CDC42BPA* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 15:40259830 | c.1303G>A | p.A435T | *EIF2AK4* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 4:100349278 | c.373C>A | p.R125S | *ADH7* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 2:74044007 | c.2657C>T | p.A886V | *C2orf78* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 7:105658301 | c.1436G>T | p.R479L | *CDHR3* | rs1302095045 | 3/228838 |
| 0/1 | 0/1 | 0/0 | 17:9497556 | c.454C>T | p.P152S | *WDR16* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 8:105360764 | c.-12-5T>C | NA | *DCSTAMP* | [rs1228062399](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=rs1228062399" \t "_blank) | 2/232824 |
| 0/1 | 0/1 | 0/0 | 22:20709738 | c.1470C>A | p.V490V | *FAM230A* | [rs1394317999](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=rs1394317999" \t "_blank) | 1/29046 |
| 0/1 | 0/1 | 0/0 | 19:35608266 | c.57G>A | p.L19L | *FXYD3* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 4:106156084 | C.985T>C | p.F329L | *TET2* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 11:4936814 | c.80G>C | p.R27P | *OR51G2* | NA | Novel |
| 0/1 | 0/1 | 0/0 | 20:1471949 | c.57G>C | p.L19L | *SIRPB2* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 2:242573083 | c.489C>T | p.S163S | *THAP4* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 19:1054061 | c.3529C>G | p.R1177G | *ABCA7* | rs141885771 | 1/250896 |
| 0/1 | 0/0 | 0/1 | 15:83499561 | c.1852G>A | p.V618I | *WHAMM* | rs1460546047 | 1/242040 |
| 0/1 | 0/0 | 0/1 | 20:60884471 | c.11009T>C | p.V3670A | *LAMA5* | rs368953531 | 2/202630 |
| 0/1 | 0/0 | 0/1 | 19:14262418 | c.3692T>C | p.L1231S | *LPHN1* | rs1296491013 | 1/231548 |
| 0/1 | 0/0 | 0/1 | 9:116279851 | c.1705C>T | p.L569F | *RGS3* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 19:9072490 | c.14956C>A | p.Q4986K | *MUC16* | rs1377856289 | 3/248620 |
| 0/1 | 0/0 | 0/1 | 11:47354779 | c.3296G>A | p.G1099E | *MYBPC3* | rs1168771733 | 1/214272 |
| 0/1 | 0/0 | 0/1 | 7:144094488 | c.1921C>G | p.P641A | *NOBOX* | rs1458557917 | 2/172252 |
| 0/1 | 0/0 | 0/1 | 1:110019519 | c.376T>A | p.F126I | *SYPL2* | rs1359589422 | 1/249588 |
| 0/1 | 0/0 | 0/1 | 11:61727479 | c.884G>C | p.R295P | *BEST1* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 3:58849553 | c.949C>A | p.L317I | *C3orf67* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 13:111286942 | c.546G>A | p.A182A | *CARKD* | rs768098549 | 2/282826 |
| 0/1 | 0/0 | 0/1 | 14:105349779 | c.985G>A | p.V329I | *CEP170B* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 11:105795230 | c.1582A>C | p.K528Q | *GRIA4* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 10:20534350 | c.1389G>T | p.L463L | *PLXDC2* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 8:125499130 | c.1240T>C | p.Y414H | *RNF139* | [rs1443907767](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=rs1443907767" \t "_blank) | 3/251342 |
| 0/1 | 0/0 | 0/1 | 2:55071240 | c.904G>T | p.D302Y | *EML6* | [rs1456438351](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=rs1456438351" \t "_blank) | 1/156552 |
| 0/1 | 0/0 | 0/1 | 1:6639323 | c.2205T>C | p.N735N | *TAS1R1* | NA | Novel |
| 0/1 | 0/0 | 0/1 | 22:42418293 | c.447C>T | p.F149F | *WBP2NL* | NA | Novel |

adbSNP and gnomAD: last accessed March 3, 2020.

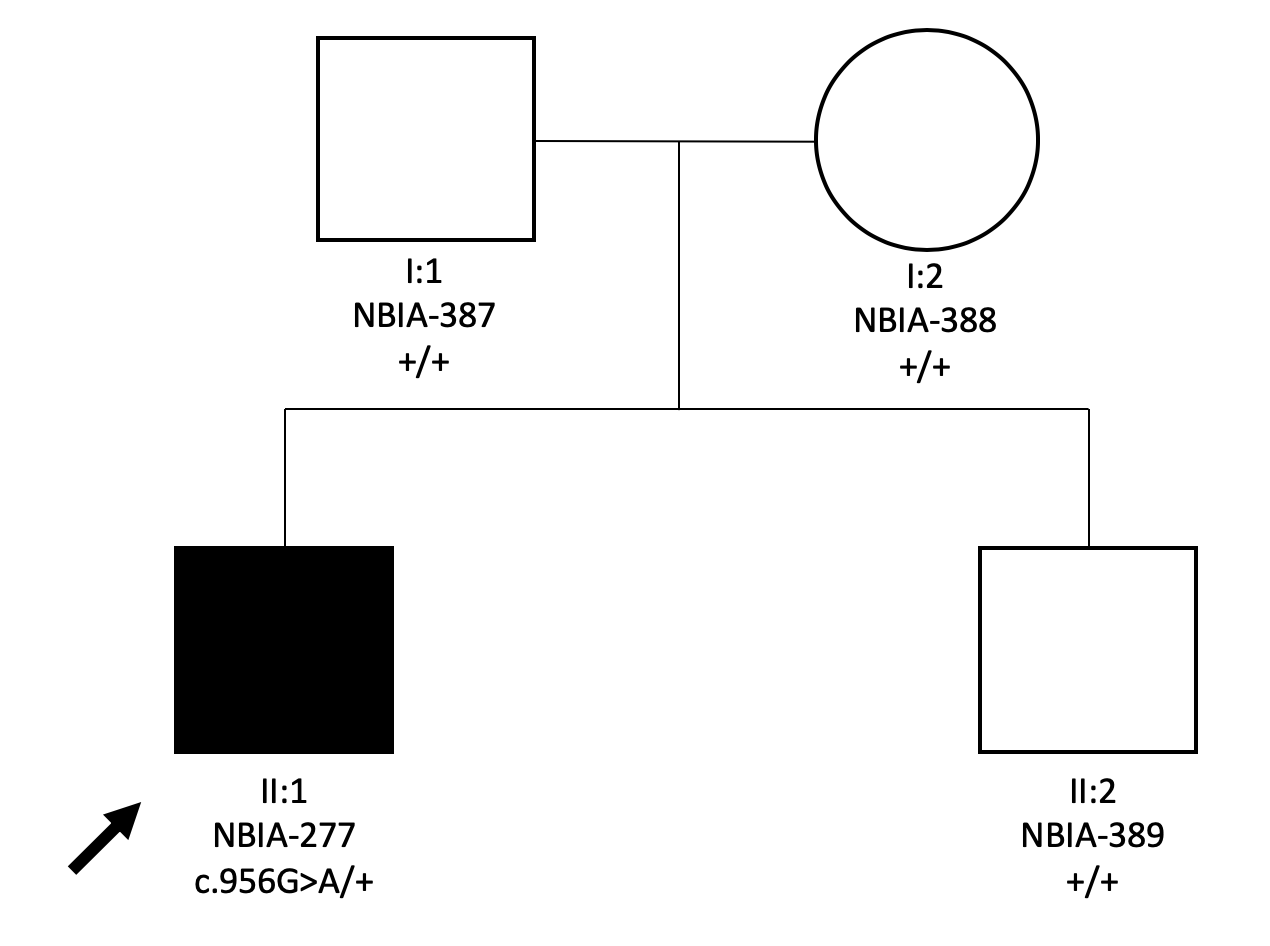
**Figure e-1.** Non-Motor Symptoms Scale for Parkinson’s Disease,

Non-Motor Symptoms Scale for Parkinson’s Disease, with a major affectation on gastro-intestinal (13/36) and sleep/fatigue (12/48) domains.

**Figure e-2**. The 39-item Parkinson's Disease Questionnaire (PDQ-39).

The score was 87/156 with maximum score for mobility (40/40) and communication (12/12) domains. Abbreviation: ADL: activities of daily living.

**Figure e-3:** Family’s pedigree.



The proband (marked with an arrow) is the only carrier of the novel *NR4A2* c.956G>A (p.R319Q) mutation in heterozygosis.

**Figure e-4:** Distribution of reported disease-causing mutations in *NR4A2*.

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The p.R319Q mutation (in red) detected in the proband is located in the Zf-C4/DBD (DNA binding domain). Changes in bold are associated with the dystonia-parkinsonism phenotype. Missense variants are marked with a green circle; stop mutations are marked with a black circle; and deletions are marked with a brown circle.

**Supplementary material:**

**Genetic analysis**

The proband was analyzed using a custom gene panel MovDisord-498 and finally, whole exome sequencing (WES) of the proband and healthy parents (trio). Filtering data from the gene panel MovDisord-498, previously reported (14, correa Vela) and from WES, as well as the analysis of the novelty of the candidate variants was carried out as previously reported (14). 15 Conservation of the residues was investigated using Clustal Omega tool. Sanger sequencing on an ABI Prism 3130XL analyzer (Applied Biosystems, Foster City, CA, USA) was performed for validation and segregation analysis.

Additionally, we confirmed maternity and paternity by the segregation analysis of 40 selected rare variants distributed throughout the genome from WES data (Supplementary Table 4).

**List of genes included in the gene panel MovDisord-498.**

*AARS2,ABCB7,ABCD1,ABHD12,ACAT1,ACO2,ACTB,ADAR,ADCK3,ADCY5,AFG3L2,AHI1,AIFM1,AIMP1,ALDH18A1,ALDH3A2,ALG6,ALS2,AMACR,AMPD2,AMT,ANO10,ANO3,AP4B1,AP4E1,AP4M1,AP4S1,AP5Z1,APTX,ARG1,ARL13B,ARL6IP1,ARSA,ARSI,ARX,ASPA,ASS1,ATCAY,ATL1,ATM,ATN1,ATP13A2,ATP1A2,ATP1A3,ATP2B3,ATP6AP2,ATP7A,ATP7B,ATP8A2,ATR,ATXN1,ATXN10,ATXN2,ATXN3,ATXN7,B4GALNT1,BCAP31,BCKDHA,BCKDHB,BCS1L,BEAN1,BICD2,BSCL2,BTD,C10ORF2,C12ORF65,C19ORF12,C5ORF42,C9ORF72,CA8,CACNA1A,CACNA1B,CACNA1G,CACNB4,CAMTA1,CASK,CC2D2A,CCDC88C,CCT5,CEP290,CEP41,CHCHD2,CHMP1A,CIZ1,CLCN2,CLN5,CLN6,CLP1,COASY,COL18A1,COL6A3,COQ2,COQ4,COQ7,COQ9,COX10,COX15,COX20,COX8A,CP,CPT1C,CSTB,CTDP1,CTSD,CUL4B,CWF19L1,CYP27A1,CYP2U1,CYP7B1,DARS2,DBT,DCAF17,DCLRE1B,DCTN1,DDB2,DDC,DDHD1,DDHD2,DKC1,DLAT,DLD,DNAJC13,DNAJC19,DNAJC6,DNMT1,DYRK1A,EARS2,ECHS1,EEF2,EIF2B1,EIF2B2,EIF2B3,EIF2B4,EIF2B5,EIF4G1,ELOVL4,ELOVL5,EMC1,ENTPD1,EPM2A,ERCC2,ERCC3,ERCC5,ERCC6,ERCC8,ERLIN1,ERLIN2,ETFA,ETFB,ETFDH,ETHE1,EXOSC3,EXOSC8,FA2H,FAAH2,FAM126A,FAM134B,FARS2,FBXL4,FBXO7,FGF14,FLRT1,FLVCR1,FMR1,FOLR1,FOXC1,FOXG1,FOXRED1,FTH1,FTL,FUCA1,FUS,FXN,GAD1,GALC,GAMT,GAN,GATM,GBA,GBA2,GCDH,GCH1,GFAP,GFM1,GFM2,GJB1,GJC2,GLB1,GLDC,GLRX5,GNAL,GNAO1,GOSR2,GPR56,GRID2,GRM1,GTPBP2,GTPBP3,HACE1,HEXA,HEXB,HIBCH,HPCA,HPRT1,HSD17B4,HSPD1,HTRA1,HTRA2,HTT,IARS2,IBA57,IFIH1,IFRD1,INPP5E,ISG15,ITM2B,ITPR1,JPH3,KCNA1,KCNA2,KCNC3,KCND3,KCNJ10,KCTD17,KCTD7,KDM6A,KIAA0196,KIAA0226,KIF1A,KIF1C,KIF5A,KIF7,KLC2,KMT2B,KMT2D,L1CAM,L2HGDH,LAMA1,LIAS,LIPT1,LMNB1,LMNB2,LRPPRC,LRRK2,LYST,MAG,MAN2B1,MARS,MARS2,MCEE,MECP2,MECR,MICU1,MLC1,MMACHC,MMADHC,MME,MPZ,MRE11A,MRPL10,MTFMT,MTHFR,MTPAP,MTTP,MUT,NALCN,NARS2,NDUFA1,NDUFA10,NDUFA11,NDUFA12,NDUFA2,NDUFA4,NDUFA9,NDUFAF2,NDUFAF5,NDUFAF6,NDUFS1,NDUFS2,NDUFS3,NDUFS4,NDUFS7,NDUFS8,NDUFV1,NDUFV2,NHLRC1,NIPA1,NKX21,NOL3,NOP56,NPC1,NPC2,NPHP1,NT5C2,NUP62,OFD1,OPA1,OPA3,OPHN1,PANK2,PARK2,PARK7,PARN,PAX6,PC,PCBD1,PCCA,PCCB,PCNA,PDE10A,PDE8B,PDGFB,PDGFRB,PDHA1,PDHB,PDHX,PDSS1,PDSS2,PDYN,PET100,PEX10,PEX7,PGAP1,PHYH,PIK3R5,PINK1,PITX2,PLA2G6,PLEKHG4,PLP1,PMM2,PMPCA,PNKD,PNKP,PNPLA6,PNPT1,POLG,POLR3A,POLR3B,PPCDC,PPCS,PPP2R2B,PRICKLE1,PRKCG,PRKRA,PRNP,PRPS1,PRRT2,PSEN1,PTEN,PTS,QDPR,RAB39B,RAB3GAP2,RAD1,RARS,RARS2,REEP1,REEP2,RELN,RIPPLY1,RNASEH2A,RNASEH2B,RNASEH2C,RNF170,RNF216,RPGRIP1L,RPIA,RTEL1,RTN2,SACS,SAMD9L,SAMHD1,SCARB2,SCN1A,SCN4A,SCO2,SCP2,SCYL1,SDHA,SDHAF1,SEPSECS,SERAC1,SETX,SGCE,SIL1,SLC16A2,SLC17A5,SLC19A3,SLC1A3,SLC20A2,SLC25A15,SLC25A19,SLC25A42,SLC2A1,SLC30A10,SLC33A1,SLC39A14,SLC46A1,SLC52A2,SLC52A3,SLC6A19,SLC6A3,SLC6A8,SLC9A1,SLC9A6,SMPD1,SNAP25,SNCA,SNX14,SPAST,SPG11,SPG20,SPG21,SPG7,SPR,SPTAN1,SPTBN2,SQSTM1,STUB1,SUCLA2,SUCLG1,SUOX,SURF1,SYNE1,SYNJ1,SYT14,TACO1,TAF1,TARDBP,TBCE,TBP,TCTN1,TCTN2,TCTN3,TDP1,TDP2,TECPR2,TENM4,TERT,TFG,TGFB1,TGM6,TH,THAP1,TIMM8A,TINF2,TK1,TMEM138,TMEM216,TMEM231,TMEM237,TMEM240,TMEM67,TOR1A,TPK1,TPP1,TRAPPC11,TREX1,TRMU,TRPC3,TSEN2,TSEN54,TSFM,TTBK2,TTC19,TTPA,TTR,TUBB4A,TXN2,UBA5,UCHL1,UQCRQ,USP8,VAMP1,VCP,VHL,VLDLR,VPS13A,VPS35,VPS37A,VPS53,VRK1,VWA3B,WDR45,WDR48,WDR73,WDR81,WFS1,WWOX,XK,XPA,XPC,XPR1,ZFR,ZFYVE26,ZFYVE27,ZNF592*

**Video legend**

At examination a marked craniocervical dystonia is shown. There is a severe retrocollis with right laterocollis and jaw opening dystonia that improved with a postural trick by touching the face. In the pull test there is not clear instability. No cerebellar signs were present. The sagittal view demonstrated an important axial involvement with a forward posture. At walking, the patient showed dragging steps, being mainly affected the left side of the body.

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