The genetic and phenotypic spectra of adult genetic leukoencephalopathies in a cohort of 309 patients

SUPPLEMENTARY MATERIALS

Supplementary Table 1: List of genes reported to be associated with genetic leukoencephalopathies

Gene	Disorder name	MIM#	Inheritance pattern
GJA1	Oculodentodigital dysplasia	164200	AD, AR
PLP1	Pelizaeus-Merzbacher disease	312080	XLR
GJC2	Leukodystrophy, hypomyelinating, 2	608804	AR
MT-ATP6	Mitochondrial complex deficiencies due to mitochondrial DNA variants	-	MIT
MT-ND3		-	MIT
MT-ND5		-	MIT
MT-ND6		-	MIT
MT-CO3		-	MIT
MT-ND1		-	MIT
MT-ND2		-	MIT
MT-ND4		-	MIT
MT-TI	Leigh syndrome due to mitochondrial DNA variants	-	MIT
MT-TK		-	MIT
MT-TL1		-	MIT
MT-TL2		-	MIT
MT-TV		-	MIT
MT-TW		-	MIT
MT-TL1	MELAS	-	MIT
MT-ND5		-	MIT
MT-TC		-	MIT
MT-TF		-	MIT
MT-TH		-	MIT
MT-TK		-	MIT
MT-TL2		-	MIT
MT-TQ		-	MIT
MT-TV		-	MIT
MT-TW		-	MIT
MT-TS1		-	MIT
MT-ND1		-	MIT
MT-TS2		-	MIT
MT-ND6		-	MIT
MT-CO2		-	MIT
MT-CO3		-	MIT
MT-CYB		-	MIT
Mitochondrial DNA deletion	Kearns Sayre syndrome	530000	MIT
CPS1	Carbamoylphosphate synthetase I deficiency	237300	AR
OTC	Ornithine transcarbamylase deficiency	311250	XLR
NAGS	N-acetylglutamate synthase deficiency	237310	AR
SLC25A15	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome	238970	AR
PDHA1	Pyruvate Dehydrogenase deficiency	312170	XLD
MPV17	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)	256810	AR
LRPPRC	Leigh syndrome, French-Canadian type	220111	AR
BOLA3	Multiple mitochondrial dysfunctions syndrome 2 with hyperglycinemia	614299	AR
NFU1	Multiple mitochondrial dysfunctions syndrome 1	605711	AR
IBA57	Multiple mitochondrial dysfunctions syndrome 3	615330	AR
ISCA1	Multiple mitochondrial dysfunctions syndrome 5	617613	AR
PMPCB	Multiple mitochondrial dysfunctions syndrome 6	617954	AR
ISCA2	Multiple mitochondrial dysfunctions syndrome 4	616370	AR
FDX2	Mitochondrial myopathy, episodic, with optic atrophy and reversible leukoencephalopathy	251900	AR
PC	Pyruvate carboxylase deficiency	266150	AR

CLPP	Perrault syndrome 3	614129	AR
MMADHC	Methylmalonic aciduria and homocystinuria	277410	AR
HSPD1	Leukodystrophy, hypomyelinating, 4	612233	AR
NDUFA10	Mitochondrial complex I deficiency, nuclear type 22	618243	AR
NDUFAF3	Mitochondrial complex I deficiency, nuclear type 18	618240	AR
TIMMDC1	Mitochondrial complex I deficiency, nuclear type 31	618251	AR
NDUFAF2	Mitochondrial complex I deficiency, nuclear type 10	618233	AR
NDUFAF4	Mitochondrial complex I deficiency, nuclear type 15	618237	AR
NDUFS1	Mitochondrial complex I deficiency, nuclear type 5	618226	AR
NDUFS4	Mitochondrial complex I deficiency, nuclear type 1	252010	AR
NDUFA2	?Mitochondrial complex I deficiency, nuclear type 13	618235	AR
NDUFV1	Mitochondrial complex I deficiency, nuclear type 4	618225	AR
NDUFS8	Mitochondrial complex I deficiency, nuclear type 2	618222	AR
NUBPL	Mitochondrial complex I deficiency, nuclear type 21	618242	AR
NDUFAF6	Mitochondrial complex I deficiency, nuclear type 17	618239	AR
NDUFB8	Mitochondrial complex I deficiency, nuclear type 32	618252	AR
NDUFS3	Mitochondrial complex I deficiency, nuclear type 8	618230	AR
FOXRED1	Mitochondrial complex I deficiency, nuclear type 19	618241	AR
NDUFA9	Mitochondrial complex I deficiency, nuclear type 26	618247	AR
NDUFA12	?Mitochondrial complex I deficiency, nuclear type 23	618244	AR
MTFMT	Mitochondrial complex I deficiency, nuclear type 27	618248	AR
NDUFV2	Mitochondrial complex I deficiency, nuclear type 7	618229	AR
NDUFS7	Mitochondrial complex I deficiency, nuclear type 3	618224	AR
NDUFAF5	Mitochondrial complex I deficiency, nuclear type 16	618238	AR
NDUFA6	Mitochondrial complex I deficiency, nuclear type 33	618253	AR
NDUFA1	Mitochondrial complex I deficiency, nuclear type 12	301020	XLR
SDHA	Mitochondrial complex II deficiency	252011	AR
SDHB		-	AR
SDHAF1		252011	AR
SDHD		252011	AR
BCS1L	Mitochondrial complex III deficiency, nuclear type 1	124000	AR
TTC19	Mitochondrial complex III deficiency, nuclear type 2	615157	AR
LYRM7	Mitochondrial complex III deficiency, nuclear type 8	615838	AR
COX20	Mitochondrial complex IV deficiency	220110	AR
COX8A		220110	AR
COX14		220110	AR
SCO1		220110	AR
COX10		220110	AR
TACO1		220110	AR
PET100		220110	AR
APOPT1		220110	AR
COX6B1		220110	AR
TMEM70	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2	614052	AR
ATPAF2	?Mitochondrial complex V (ATP synthase) deficiency, nuclear type 1	604273	AR
ATP5A1	?Mitochondrial complex V (ATP synthase) deficiency, nuclear type 4	615228	AR
ATP5E	?Mitochondrial complex V (ATP synthase) deficiency, nuclear type 3	614053	AR
SURF1	Leigh syndrome, due to COX IV deficiency	256000	AR, Mi
COX15	Leigh syndrome due to cytochrome c oxidase deficiency	256000	AR, Mi
PNPT1	Combined oxidative phosphorylation deficiency 13	614932	AR
GFM1	Combined oxidative phosphorylation deficiency 1	609060	AR
MTO1	Combined oxidative phosphorylation deficiency 10	614702	AR
MRPS2	Combined oxidative phosphorylation deficiency 36	617950	AR
MRPS22	Combined oxidative phosphorylation deficiency 5	611719	AR

RMND1	Combined oxidative phosphorylation deficiency 11	614922	AR
MTFMT	Combined oxidative phosphorylation deficiency 15	614947	AR
TSFM	Combined oxidative phosphorylation deficiency 3	610505	AR
FASTKD2	Combined oxidative phosphorylation deficiency 44	618855	AR
C12orf65	Combined oxidative phosphorylation deficiency 7	613559	AR
TRMT5	Combined oxidative phosphorylation deficiency 26	616539	AR
MRPS34	Combined oxidative phosphorylation deficiency 32	617664	AR
TUFM	Combined oxidative phosphorylation deficiency 4	610678	AR
ELAC2	Combined oxidative phosphorylation deficiency 17	615440	AR
GTPBP3	Combined oxidative phosphorylation deficiency 23	616198	AR
TXN2	?Combined oxidative phosphorylation deficiency 29	616811	AR
GFM2	Combined oxidative phosphorylation deficiency 39	618397	AR
SUCLG1	Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)	245400	AR
RRM2B	Mitochondrial DNA depletion syndrome 8A and 8B	612075	AR
SUCLA2	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)	612073	AR
POLG	Mitochondrial DNA depletion syndrome 4B (MNGIE type)	613662	AR
POLG	Mitochondrial DNA depletion syndrome 4A (Alpers type)	203700	AR
TK2	Mitochondrial DNA depletion syndrome 2 (myopathic type)	609560	AR
DGUOK	Mitochondrial DNA depletion syndrome 3 (hepatocerebral type)	251880	AR
TYMP	Mitochondrial DNA depletion syndrome 1 (MNGIE type)	603041	AR
FBXL4	Mitochondrial DNA depletion syndrome 13 (encephalomyopathic type)	615471	AR
SPG7	Spastic paraplegia 7 (SPG7)	607259	AD, AR
COA7	Spinocerebellar ataxia, autosomal recessive, with axonal neuropathy 3	618387	AR
DEGS1	Leukodystrophy, hypomyelinating, 18	618404	AR
GLRX5	Spasticity, childhood-onset, with hyperglycinemia	616859	AR
SCO2	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 1	604377	AR
NADK2	?2,4-dienoyl-CoA reductase deficiency	616034	AR
NAXE	Encephalopathy, progressive, early-onset, with brain edema and/or leukoencephalopathy	617186	AR
NAXD	Encephalopathy, progressive, early-onset, with brain edema and/or leukoencephalopathy, 2	618321	AR
TIMM50	3-methylglutaconic aciduria, type IX	617698	AR
SLC25A46	Neuropathy, hereditary motor and sensory, type VIB	616505	AR
ETFDH	Glutaric acidemia IIC	231680	AR
ETFA		231680	AR
ETFB		231680	AR
MSTO1	Myopathy, mitochondrial, and ataxia	617675	AD, AR
MDH2	Epileptic encephalopathy, early infantile, 51	617339	AR
SLC17A5	Free salic acid storage disorders	269920	AR
FUCA1	Fucosidosis	230000	AR
GALC	Krabbe disease	245200	AR
ARSA	Metachromatic leukodystrophy	250100	AR
SUMF1	Multiple sulfatase deficiency	272200	AR
AGA	Aspartylglucosaminuria	208400	AR
PPT1	Ceroid lipofuscinosis, neuronal, 1	256730	AR
MFSD8	Ceroid lipofuscinosis, neuronal, 7	610951	AR
CLN8	Ceroid lipofuscinosis, neuronal, 8	600143	AR
CLN8	Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant	610003	AR
CTSD	Ceroid lipofuscinosis, neuronal, 10	610127	AR
TPP1	Ceroid lipofuscinosis, neuronal, 2	204500	AR
CTSF	Ceroid lipofuscinosis, neuronal, 13, Kufs type	615362	AR
CLN5	Ceroid lipofuscinosis, neuronal, 5	256731	AR
CLN6	Ceroid lipofuscinosis, neuronal, Kufs type, adult onset	204300	AR
CLN6	Ceroid lipofuscinosis, neuronal, 6	601780	AR
CLN3	Ceroid lipofuscinosis, neuronal, 3	204200	AR

GRN	Ceroid lipofuscinosis, neuronal, 11	614706	AR
DNAJC5	Ceroid lipofuscinosis, neuronal, 4, Parry type	162350	AD
CLN9	Ceroid lipofuscinosis, neuronal, 9	609055	AR
VPS11	VPS11- related hypomyelination	616683	AR
PSAP	Metachromatic leukodystrophy	249900	AR
GLB1	GM1-gangliosidosis, type III	230650	AR
HEXA	Tay-Sachs disease	272800	AR
NPC2	Niemann-Pick type C2	607625	AR
NPC1	Niemann-Pick type C1	257220	AR
MAN2B1	Mannosidosis, alpha-, types I and II	248500	AR
GM2A	GM2-gangliosidosis, AB variant	272750	AR
IDS	Mucopolysaccharidosis II	309900	XLR
IDUA	Mucopolysaccharidosis Ih	607014	AR
CTSA	Galactosialidosis	256540	AR
PEX1	Peroxisome biogenesis disorder 1A (Zellweger)	214100	AR
PEX1	Peroxisome biogenesis disorder 1B	601539	AR
PEX2	Peroxisome biogenesis disorder 5A	614866	AR
PEX2	Peroxisome biogenesis disorder 5B	614867	AR
PEX3	Peroxisome biogenesis disorder 10A	614882	AR
PEX6	Peroxisome biogenesis disorder 4A and	614862	AR
PEX6	Peroxisome biogenesis disorder 4B	614863	AR
PEX10	Peroxisome biogenesis disorder 6A (Zellweger)	614870	AR
PEX10	Peroxisome biogenesis disorder 6B	614871	AR
PEX12	Peroxisome biogenesis disorder 3A	614859	AR
PEX12	Peroxisome biogenesis disorder 3B	266510	AR
PEX11B	?Peroxisome biogenesis disorder 14B	614920	AR
PEX16	Peroxisome biogenesis disorder 8A (Zellweger)	614876	AR
PEX14	Peroxisome biogenesis disorder 13A (Zellweger)	614887	AR
PEX19	Peroxisome biogenesis disorder 12A (Zellweger)	614886	AR
PEX26	Peroxisome biogenesis disorder 7A (Zellweger)	614872	AR
PEX5	Peroxisome biogenesis disorder 2A (Zellweger)	214110	AR
HSD17B4	D-bifunctional protein deficiency	261515	AR
ACOX1	Peroxisomal acyl-CoA oxidase deficiency	264470	AR
SCP2	?Leukoencephalopathy with dystonia and motor neuropathy	613724	AR
ABCD1	X-linked adrenoleukodystrophy	300100	XLR
AMACR	α-Methylacyl-CoA racemase deficiency	614307	AR
HSD17B4	Perrault syndrome 1	233400	AR
ASPA	Canavan disease	271900	AR
L2HGDH	L-2-hydroxyglutaric aciduria	236792	AR
D2HGDH	D-2-hydroxyglutaric aciduria	600721	AR
SLC25A1	Combined D-2- and L-2-hydroxyglutaric aciduria	615182	AR
PAH	Phenylketonuria	261600	AR
QDPR	Hyperphenylalaninemia, BH4-deficient, C	261630	AR
DNAJC12	Hyperphenylalaninemia, mild, non-BH4-deficient	617384	AR
HMGCL	HMG-CoA lyase deficiency	246450	AR
MTHFR	Homocystinuria	236250	AR
MMACHC	Methylmalonic aciduria and homocystinuria, cblC type	277400	AR
PRDX1		277400	AR
LMBRD1	Methylmalonic aciduria and homocystinuria, cblF type	277380	AR
ABCD4	Methylmalonic aciduria and homocystinuria, cblJ type	614857	AR
FOLR1	Neurodegeneration due to cerebral folate transport deficiency	613068	AR
ABAT	GABA-transaminase deficiency	613163	AR
BCKDHA	Maple syrup urine disease	248600	AR

BCKDHB		248600	AR
DBT		248600	AR
PHGDH	Phosphoglycerate dehydrogenase deficiency	601815	AR
PSAT1	Phosphoserine aminotransferase deficiency	610992	AR
GCDH	Glutaricaciduria, type I	231670	AR
PYCR2	Leukodystrophy, hypomyelinating, 10	616420	AR
AUH	3-methylglutaconic aciduria, type I	250950	AR
DPYD	Dihydropyrimidine dehydrogenase deficiency	274270	AR
TPK1	Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type)	614458	AR
ALDH5A1	Succinic semialdehyde dehydrogenase deficiency	271980	AR
AHCY	Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase	613752	AR
ASNS	Asparagine synthetase deficiency	615574	AR
MTR	Homocystinuria-megaloblastic anemia, cblG complementation type	250940	AR
GLS	Epileptic encephalopathy, early infantile, 71	618328	AR
GCSH	Glycine encephalopathy	605899	AR
PRMT7	Short stature, brachydactyly, intellectual developmental disability, and seizures	617157	AR
ELOVL1	Ichthyosis, acanthosis nigricans, hypomyelination, spastic paraplegia, high frequency deafness and optic atrophy	618527	AD
PLA2G6	Infantile neuroaxonal dystrophy 1	256600	AR
FAR1	Peroxisomal fatty acyl-CoA reductase 1 disorder	616154	AR
ACER3	?Leukodystrophy, progressive, early childhood-onset	617762	AR
PIGA	Multiple congenital anomalies-hypotonia-seizures syndrome 2	300868	XLR
PIGN	Multiple congenital anomalies-hypotonia-seizures syndrome 1	614080	AR
PIGQ	Epileptic encephalopathy, early infantile, 77	618548	AR
PIGB	Epileptic encephalopathy, early infantile, 80	618580	AR
RPIA	Ribose 5 phosphate isomerase deficiency	608611	AR
GLYCTK	D-glyceric aciduria	220120	AR
GFPT1	Myasthenia, congenital, 12, with tubular aggregates	610542	AR
GALT	Galactosemia	230400	AR
VAC14	Striatonigral degeneration	617054	AR
PLAA	Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain anomalies	617527	AR
KIF5A	Myoclonus, intractable, neonatal	617235	AD
RAB11B	Neurodevelopmental disorder with ataxic gait, absent speech, and decreased cortical white matter	617807	AD
TRAPPC9	Mental retardation, autosomal recessive 13	613192	AR
AP4M1	Spastic paraplegia 50, autosomal recessive	612936	AR
ACP33	Spastic paraplegia 21 (SPG21)	248900	AR
RAB27A	Griscelli syndrome, type 2	607624	AR
AP5Z1	Spastic paraplegia 48, autosomal recessive	613647	AR
BCAP31	Deafness, dystonia, and cerebral hypomyelination	300475	XLR
STXBP2	Familial hemophagocytic lymphohistiocytosis 5	613101	AR
UNC13D	Familial hemophagocytic lymphohistiocytosis 3	608898	AR
STX11	Familial hemophagocytic lymphohistiocytosis 4	603552	AR
SPG11	Spastic paraplegia 11	604360	AR
DDHD2	Spastic paraplegia 54, autosomal recessive	615033	AR
TRAK1	Epileptic encephalopathy, early infantile, 68	618201	AR
STXBP1	Epileptic encephalopathy, early infantile, 4	612164	AD
VAC14	Yunis-Varon Syndrome	-	AR
TBC1D24	Epileptic encephalopathy, early infantile, 16	615338	AR
AP4B1	Spastic paraplegia, 47	614066	AR
RAB18	Warburg micro syndrome 3	618222	AR
MLC1	Megalencephalic leukoencephalopathy with subcorticle cysts	604004	AR
LAMA2	Merosin deficient congenital muscular dystrophy	607855	AR
POMT1	Muscular dystrophy-dystroglycanopathy type A, 1	236670	AR
POMGNT1	Muscular dystrophy-dystroglycanopathy type A, 3	253280	AR

FKTN	Muscular dystrophy-dystroglycanopathy type A, 4	253800	AR
FKRP	Muscular dystrophy-dystroglycanopathy type A, 5	613153	AR
ISPD	Muscular dystrophy-dystroglycanopathy type A, 7	614643	AR
LARGE1	Muscular dystrophy-dystroglycanopathy type A, 7	613154	AR
GPR56	Polymicrogyria, bilateral frontoparietal	615752	AR
MYRF	Encephalitis/encephalopathy, mild, with reversible myelin vacuolization	618113	AD
MCOLN1	Mucolipidosis IV	252650	AR
ATP7B	Wilson disease	277900	AR
ATP7A	Menkes disease	309400	XLR
CLCN2	Leukoencephalopathy with ataxia	615651	AR
SLC13A5	Epileptic encephalopathy, early infantile, 25	615905	AR
DMPK	Myotonic dystrophy 1	160900	AD
SPTAN1	Epileptic encephalopathy, early infantile, 5	613477	AD
CLCN4	Raynaud-Claes syndrome	300114	XLD
SLC9A6	Mental retardation, X-linked syndromic, Christianson type	300243	XLD
KCNJ2	Andersen syndrome	170390	AD
SLC39A14	Hypermanganesemia with dystonia 2	617013	AR
TBCD	Encephalopathy, progressive, early-onset, with brain atrophy and thin corpus callosum	617193	AR
ATP6V1A	Cutis laxa, autosomal recessive, type IID	617403	AR
SLC12A5	Epileptic encephalopathy, early infantile, 34	616645	AR
KCNT1	Epileptic encephalopathy, early infantile, 14	614959	AD
HCN1	Epileptic encephalopathy, early infantile, 24	615871	AD
KCNQ2	Epileptic encephalopathy, early infantile, 7	613720	AD
SLC12A6	Agenesis of the corpus callosum with peripheral neuropathy	218000	AR
SLC6A19	Hartnup disorder	234500	AR
SLC25A22	Epileptic encephalopathy, early infantile, 3	609304	AR
GABRA2	Epileptic encephalopathy, early infantile, 78	618557	AD
GABRG2	Epileptic encephalopathy, early infantile, 74	618396	AD
SLC1A2	Epileptic encephalopathy, early infantile, 41	617105	AD
GABRB3	Epileptic encephalopathy, early infantile, 43	617113	AD
GABRA5	Epileptic encephalopathy, early infantile, 79	618559	AD
SLC16A2	Allan-Herndon-Dudley syndrome	300523	XL
OCLN	Band-like intracranial calcification with simplified gyration and polymicrogyria	251290	AR
SLC25A12	Epileptic encephalopathy, early infantile, 39	612949	AR
TMEM63A	Leukodystrophy, hypomyelinating, 19, transient infantile	618688	AD
SOX2	Optic nerve hypoplasia and abnormalities of the central nervous system	206900	AD
ACTB	Baraitser-Winter syndrome 1	243310	AD
PURA	Mental retardation, autosomal dominant 31	616158	AD
PCGF2	Turnpenny-Fry syndrome	618371	AD
ZNHIT3	PEHO syndrome	260565	AR
ASXL1	Bohring-Opitz syndrome	605039	AD
SATB2	Glass syndrome	612313	AD
NACC1	Neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination	617393	AD
NEUROD2	Epileptic encephalopathy, early infantile, 72	618374	AD
SIN3A	Witteveen-Kolk syndrome	613406	AD
HNRNPU	Epileptic encephalopathy, early infantile, 51	617391	AD
RNASEH2B	Aicardi-Goutières syndrome type 2	610181	AR
RNASEH2C	Aicardi-Goutières syndrome type 3	610329	AR
RNASEH2A	Aicardi-Goutières syndrome type 4	610333	AR
SAMHD1	Aicardi-Goutières syndrome type 5	612952	AR
CTC1	Cerebroretinal microangiopathy with calcifications and cysts	612199	AR
STN1	Cerebroretinal microangiopathy with calcifications and cysts 2	617341	AR
ERCC8	Cockayne syndrome, type A	216400	AR

ERCC2	Xeroderma pigmentosum -Cockayne syndrome complex	278730	AR
ERCC3	Trichothiodystrophy 2, photosensitive	616390	AR
GTF2H5	Trichothiodystrophy 3, photosensitive	616395	AR
ERCC6	Cockayne syndrome type B	133540	AR
ERCC2	Trichothiodystrophy 1, photosensitive	601675	AR
SPG20	Spastic paraplegia 20 (SPG20)	275900	AR
ADPRHL2	Neurodegeneration, childhood-onset, stress-induced, with variable ataxia and seizures	618170	AR
PRKDC	Immunodeficiency 26, with or without neurologic abnormalities	615966	AR
TREX1	Aicardi-Goutières syndrome type 1	225750	AD, AR
POLR3A	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism	607694	AR
POLR3B	Pol III related leukodystrophiesLeukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism	614381	AR
EIF2B1	Childhood ataxia with CNS hypomyelination/vanishing white matter disorder	603896	AR
EIF2B2		603896	AR
EIF2B3		603896	AR
EIF2B4		603896	AR
EIF2B5		603896	AR
DARS2	Leukoencephalopathy with brainstem and spinal cord involvement	611105	AR
EPRS	Leukodystrophy, hypomyelinating, 15	617951	AR
POLR1C	Leukodystrophy, hypomyelinating, 11	616494	AR
POLR3K	Hypomyelinating leukodystrophy	-	AR
LARS2	Perrault syndrome 4	615300	AR
KARS1	KARS-related leukodystrophy	-	AR
AARS1	Epileptic encephalopathy, early infantile, 29	616339	AR
AIMP1	Hypomyelinating leukodystrophy 3	260600	AR
EARS2	Combined oxidative phosphorylation deficiency 12	614924	AR
DARS1	Hypomyelination wit Brainstem and Spinal Cord Involvement and Leg Spasticity (HBSL)	615281	AR
AARS2	Progressive leukoencephalopathy with ovarian failure	615889	AR
WARS2	Neurodevelopmental disorder, mitochondrial, with abnormal movements and lactic acidosis, with or without seizures	617710	AR
PARS2	Epileptic encephalopathy, early infantile, 75	618437	AR
AIMP2	Leukodystrophy, hypomyelinating, 17	618006	AR
ZEB2	Mowat-Wilson syndrome	235730	AD
FARS2	Combined oxidative phosphorylation deficiency 14	614946	AR
VARS2	Combined oxidative phosphorylation deficiency 20	615917	AR
NARS2	Combined oxidative phosphorylation deficiency 24	616239	AR
MARS2	?Combined oxidative phosphorylation deficiency 25	616430	AR
CARS2	Combined oxidative phosphorylation deficiency 27	616672	AR
TARS2	?Combined oxidative phosphorylation deficiency 21	615918	AR
EXOSC8	Pontocerebellar hypoplasia, type 1C	616081	AR
GEMIN4	Neurodevelopmental disorder with microcephaly, cataracts, and renal abnormalities	617913	AR
IARS	Growth retardation, impaired intellectual development, hypotonia, and hepatopathy	617093	AR
SEPSECS	Pontocerebellar hypoplasia type 2D	613811	AR
RARS1	Leukodystrophy, hypomyelinating 9	616140	AR
DCAF17	Woodhouse-Sakati syndrome	241080	AR
RXYLT1	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 10	615041	AR
LIPT2	Encephalopathy, neonatal severe, with lactic acidosis and brain abnormalities	617668	AR
SIAT9	Salt and pepper developmental regression syndrome	609056	AR
B3GALNT2	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies, type A, 11	615181	AR
LIPT1	Lipoyltransferase 1 deficiency	616299	AR
GJB1	Charcot-Marie-Tooth neuropathy, X-linked dominant, 1	302800	XLD
ADAR	Aicardi-Goutières syndrome type 6	615010	AR
ADGRG1	Polymicrogyria, bilateral frontoparietal	606854	AR
CNTNAP1	Hypomyelinating neuropathy, congenital, 3	618186	AR
MAG	Spastic paraplegia 75, autosomal recessive	616680	AR

LAMA1	Poretti-Boltshauser syndrome	615960	AR
PDP1	Pyruvate dehydrogenase phosphatase deficiency	608782	AR
TBCK	Hypotonia, infantile, with psychomotor retardation and characteristic facies 3	616900	AR
PRUNE1	Neurodevelopmental disorder with microcephaly, hypotonia, and variable brain anomalies	617481	AR
HEPACAM	Megalencephalic leukoencephalopathy with subcorticle cysts type 2A	613925	AR
HEPACAM	Megalencephalic leukoencephalopathy with subcorticle cysts type 2B	613926	AD
MPLKIP	Trichothiodystrophy, nonphotosensitive	234050	AR
SPAST	Spastic paraplegia 4 (SPG4)	182601	AD
ZFYVE26	Spastic paraplegia 15 (SPG15)	270700	AR
APP	Cerebral amyloid angiopathy, Dutch, Italian, Iowa, Flemish, Arctic variants	605714	AD
ITM2B	Dementia, familial British	176500	AD
NOTCH3	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	125310	AD
HTRA1	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)	616779	AD
HTRA1	CARASIl syndrome	600142	AR
PRF1	Familial hemophagocytic lymphohistiocytosis 2	603553	AR
RNF216	Cerebellar ataxia and hypogonadotropic hypogonadism	212840	AR
RNF13	Epileptic encephalopathy, early infantile, 73	618379	AD
CST3	Cerebral amyloid angiopathy	105150	AD
GBE1	Adult polyglucosan body disease (APBD)	263570	AR
LMNB1	Adult onset leukodystophy (ADLD)	169500	AD
CSF1R	Hereditary diffuse leukoencephalopathy with spheroids	221820	AD
NOTCH2NLC	Neuronal intranuclear inclusion disease	603472	AD
ALDH3A2	Sjögren-Larsson syndrome	270200	AR
SOX10	PCWH syndrome	609136	AD
SOX10	Waardenburg syndrome, type 2E, with or without neurologic involvement	611584	AD
ADSL	Adenylosuccinate lyase deficiency	103050	AR
MOCS1	Molybdenum cofactor deficiency A	252150	AR
ASS1	Citrullinemia type I	215700	AR
ASL	Argininosuccinic aciduria	207900	AR
ARG1	Argininemia	207800	AR
AIFM1	Combined oxidative phosphorylation deficiency 6	300816	XLR
SLC13A3	Leukoencephalopathy, acute reversible, with increased urinary alpha-ketoglutarate	618384	AR
GAN	Giant axonal neuropathy	256850	AR
CYP27A1	Cerebrotendinous xanthomatosis	213700	AR
FMR1	Fragile X tremor/ataxia syndrome	300623	XLD
TREM2	Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy 2	618193	AD
ATN1	Dentatorubropallidoluysian atrophy	125370	AD
UFM1	Leukodystrophy, hypomyelinating, 14	617899	AR
TMEM106B	Leukodystrophy, hypomyelinating, 16	617964	AD
NKX6-2	Spastic ataxia 8, autosomal recessive, with hypomyelinating leukodystrophy	617560	AR
HIKESHI	Leukodystrophy, hypomyelinating, 13	616881	AR
NFE2L2	Immunodeficiency, developmental delay, and hypohomocysteinemia	617744	AD
FIG4	Yunis-Varon syndrome	216340	AR
PUS3	Mental retardation, autosomal recessive 55	617051	AR
TUBB4A	Hypomyelinating leukodystrophy 6	612438	AD
TUBB4A	Dystonia, type4	128101	AD
CYP7B1	Spastic paraplegia 5A	270800	AR
FA2H	Spastic paraplegia 35	612319	AR
CYP2U1	Spastic paraplegia 56	CYP2U1	AR
TYROBP	Nasu-Hakola disease	221770	AR
OCRL	Lowe syndrome	309000	XLR
COL3A1	Polymicrogyria with or without vascular-type EDS	618343	AR
ITPA	Epileptic encephalopathy, early infantile, 35	616647	AR

COLGALT1	Brain small vessel disease 3	618360	AR
SLC19A3	Thiamine metabolism dysfunction syndrome 2 (biotin- or thiamine-responsive encephalopathy type 2)	607483	AR
PDGFRB	Kosaki overgrowth syndrome	616592	AD
PLEKHG2	Leukodystrophy and acquired microcephaly with or without dystonia	616763	AR
MGP	Keutel syndrome	245150	AR
NOTCH1	Adams-Oliver syndrome 5	616028	AD
CRLF1	Cold-induced sweating syndrome 1	272430	AR
DDC	Aromatic L-amino acid decarboxylase deficiency	608643	AR
ACTA2	Multisystemic smooth muscle dysfunction syndrome	613834	AD
SLC1A4	Spastic tetraplegia, thin corpus callosum, and progressive microcephaly	616657	AR
KIDINS220	Spastic paraplegia, intellectual disability, nystagmus, and obesity	617296	AD
DCC	Gaze palsy, familial horizontal, with progressive scoliosis, 2	617542	AR
UFC1	Neurodevelopmental disorder with spasticity and poor growth	618076	AR
EHMT1	Kleefstra syndrome 1	610253	AD
UBA5	Epileptic encephalopathy, early infantile, 44	617132	AR
OTUD6B	Intellectual developmental disorder with dysmorphic facies, seizures, and distal limb anomalies	617452	AR
PHACTR1	Epileptic encephalopathy, early infantile, 70	618298	AD
MAPK8IP3	Neurodevelopmental disorder with or without variable brain abnormalities	618443	AD
NGLY1	Congenital disorder of deglycosylation	615273	AR
NHLRC2	FINCA syndrome	618278	AR
PPP3CA	Epileptic encephalopathy, infantile or early childhood, 1	617711	AD
ALG13	Epileptic encephalopathy, early infantile, 36	300884	XLD
GNAO1	Epileptic encephalopathy, early infantile, 17	615473	AD
WWOX	Epileptic encephalopathy, early infantile, 28	616211	AR
NTRK2	Epileptic encephalopathy, early infantile, 3	617830	AD
RHOBTB2	Epileptic encephalopathy, early infantile, 64	618004	AD
COL4A2	Brain small vessel disease 2	614483	AD
SNORD118	Leukodystrophy with calcifications and cysyts	614561	AR
COL4A1	Microangiopathy and leukoencephalopathy, pontine	618564	AD
GLA	Fabry disease	301500	XL
IFIH1	Aicardi-Goutières syndrome type 7	615846	AD
RNASET2	RNAse T2-deficient leukoencephalopathy	612951	AR
C1R	Periodontal Ehlers Danlos syndrome	130080	AD
GFAP	Alexander disease	203450	AD
FAM126A	Hypomyelination with congenital cataract	610532	AR
BTD	Biotinidase deficiency	253260	AR
KLHL7	PERCHING syndrome	617055	AR
SPATA5	Epilepsy, hearing loss, and mental retardation syndrome	616577	AR
MMAB	Methylmalonic aciduria, vitamin B12-responsive, due to defect in synthesis of adenosylcobalamin, cblB complementation type	607568	AR
GRIN2B	Epileptic encephalopathy, early infantile, 27	616139	AD
HEXB	Sandhoff disease	268800	AR

AD = autosomal dominant inheritance, AR = autosomal recessive inheritance, XL = X linked, XLD = X linked dominant inheritance, XLR = X linked recessive inheritance

Supplementary Table 2: Clinical and imaging features of hereditary nonvascular leukoencephalopathy in our cohort

Clinical characteristics of hereditary nonvascular leukoencephalopathy	
Psychiatric symptoms	ALD, CblC disease, NIID, AARS2-L, ALSP, VWMD
Cognitive impairment	ALD, CblC disease, NIID, AARS2-L, ALSP, VWMD
Mental retardation	PKU, CTX, Pol-III-related disorders, PMLD, VWMD
Severe headache	NIID, Glutaricaciduria, LKPAT
Early prominent ataxia	CTX, Alexander's disease, Pol-III-related disorders, GHS, ALD, LBSL, ALSP, VWMD
Parkinsonism	NIID, ALSP
Spastic paraplegia	HSP, ALD, Krabbe disease, CblC disease, MTHFR deficiency, ADLD
Palatal myoclonus	Alexander's disease
Epilepsy	LGMDR23, ALD, CblC disease, NIID, mitochondrial disease, VWMD
Peripheral neuropathy	ALD, Krabbe disease, CTX, CMT-X, CblC disease, MTHFR deficiency, NIID, LBSL, Mitochondrial disease, HSP
Lower motor neuron syndrome	Sandhoff disease, Krabbe disease,
Autonomic symptoms	ADLD, NIID
Myopathy	DM1, LGMDR23, Mitochondrial disease, AARS2-L, NIID
Episodic neurological events	NIID
Rapid deterioration following head trauma	ALD, VWMD
Optic nerve atrophy	ALD, LBSL, AARS2-L, mitochondrial disease, VWMD, DM1
Cataract	CTX, DM1
Oligodontia	Pol-III-related disorders
Adrenocortical insufficiency	ALD
Premature ovarian failure	VWMD, AARS2-L
Hypogonadotrophic hypogonadism	GHS, Pol-III-related disorders
Tendon Xanthoma	CTX
Abnormal skin colour	ALD, PKU
Imaging characteristics of hereditary nonvascular leukoencephalopathy	
Anterior temporal lobe involvement	DM, LGMDR23
Corpus callosum involvement	ALSP, VWMD, AARS2-L, HSP (SPG11, SPG15, SPG7), ADLD, NIID
Abnormal signal along pyramidal tract	Krabbe disease, Pol-III-related disorders
Spinal cord and brainstem involvement	Alexander's disease, LBSL
Cerebellar dentate nucleus	CTX, ALD
Cerebellar vermis	NIID
Middle cerebellar peduncles	NIID, LKPAT, ALD, LBSL, VWMD
Cystic degeneration	VWMD
Punctate calcification	ALSP, ALD
Contrast enhancement	ALD
Deep white matter diffusion dots	ALSP, AARS2-L, LBSL
High signals along the corticomedullary junction on DWI	NIID
Transient and reversible white matter lesions	CMT-X

AARS2-L = AARS2-related leukodystrophy; ADLD = adult-onset autosomal dominant leukodystrophy; ALD = adrenoleukodystrophy; ALSP = adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; CblC = methylmalonic aciduria and homocystinuria cblC type; CMT-X = X-linked Charcot-Marie-Tooth; CTX = cerebrotendinous xanthomatosis; DM1 = myotonic dystrophy type1; GHS = Gordon Holmes syndrome; HSP = hereditary spastic paraplegia; LBSL = leukoencephalopathy with brainstem and spinal cord involvement with elevated lactate; LGMDR23 = autosomal recessive limb-girdle muscular dystrophy-23; LKPAT = leukoencephalopathy with ataxia; MTHFR deficiency = methylenetetrahydrofolate reductase deficiency; NIID = neuronal intranuclear inclusion disease; PKU = phenylketonuria; PMLD = Pelizaeus–Merzbacher-like disease; SPG = spastic paraplegia; VWMD = vanishing white matter disease.

Supplementary Table 3: Novel pathogenic or likely pathogenic variants of *NOTCH3* gene identified in our cohort

Clinical features				*NOTCH3* mutations		Location		Population frequency			Bioinformatics Prediction			Skin biopsy [a]	Pathogenicity
Patients	Gender	AAO	Neurological manifestations	Nucleotide change	Amino acid change	Exon	EGF repeat	1000G	ExAc	gnomAD	SIFT	Polyphen-2	Mutation Taster		
1	M	46	Ischemic stroke, cognitive impairment	c.202_203insACC	p. P68delinsHP	3	1	0	0	0	-	-	Polymorphism	GOM (+)	P
2	F	67	Cognitive impairment	c.202_203insACC	p. P68delinsHP	3	1	0	0	0	-	-	Polymorphism	NA	P
3	F	49	Ischemic stroke, cognitive impairment	c.239A>T	p. D80V	3	2	0	0	0	D	B	D	NA	LP
4	F	34	Ischemic stroke, haemorrhagic stroke, cognitive impairment, psychiatric symptoms, gait disturbance	c.242C>A	p. P81H	3	2	0	0	0	D	Pro_D	D	NA	LP
5	M	32	Ischemic stroke	c.454G>T	p. G152C	4	3	0	0	0	D	Pro_D	D	GOM (+)	P
6	M	32	Ischemic stroke, cognitive impairment, psychiatric symptoms	c.535G>T	p. G179C	4	4	0	0	0	D	Pro_D	D	GOM (+)	P
7	M	35	Transient numbness of limbs	c.1369T>C	p. C457R	8	11	0	0	0	D	Pro_D	D	NA	LP
8	F	43	Hemianesthesia	c.1597T>G	p. C533G	10	13	0	0	0	D	Pro_D	D	NA	LP
9	M	28	Migraine, TIA	c.1969G>T	p. E657*	13	17	0	0	0	-	-	D	NA	LP
10	M	43	haemorrhagic stroke, cognitive impairment, psychiatric symptoms	c.2041_2042insCGCT	p. C681Sfs*23	13	17	0	0	0	-	-	D	GOM (+)	P

AAO = age at onset; F = female; M = male; TIA = transient ischemic attacks; EGF = epidermal growth factor; 1000G = 1000 Genomes Project database; ExAC = Exome Aggregation Consortium database; gnomAD = the Genome Aggregation Database; SIFT = Sorting Tolerant From Intolerant; Polyphen-2 = Polymorphism Phenotyping v2; B = benign; D = damaging, deleterious, or disease-causing; Pro_D = probably damaging; P = pathogenic; LP = likely pathogenic; NA = not available.

[a] GOM (+): positive GOM (granular osmiophilic material) deposit in skin biopsies

Supplementary Table 4: Mutations identified in CADASIL patients in our cohort

Exon	Nucleotide change	Amino acid change	EGF repeat domain	Number of pedigrees
Exon 2	c.160C>T	p. R54C	1	1
Exon 3	c.202_203insACC	p. P68delinsHP	1	2
	c.224G>A	p. R75Q	1	1
	c.239A>T	p. D80V	2	1
	c.242C>A	p. P81H	2	1
	c.268C>T	p. R90C	2	1
	c.328C>T	p. R110C	2	2
Exon 4	c.391G>T	p. G131C	3	1
	c.397C>T	p. R133C	3	1
	c.421C>T	p. R141C	3	2
	c.437G>A	p. C146Y	3	1
	c.454G>T	p. G152C	3	1
	c.457C>T	p. R153C	3	3
	c.505C>T	p. R169C	4	4
	c.535G>T	p. G179C	4	1
	c.544C>T	p. R182C	4	1
	c.566A>G	p. Y189C	4	1
	c.602G>A	p. C201Y	5	1
	c.636C>G	p. C212W	5	1
	c.665G>A	p. C222Y	5	1
Exon 5	c.719G>C	p. C240S	6	3
	c.752G>A	p. C251Y	6	1
Exon 6	c.994C>T	p. R332C	8	1
Exon 8	c.1258G>T	p. G420C	10	1
	c.1279C>T	p. R427C	10	2
	c.1369T>C	p. C457R	11	1
Exon 10	c.1597T>G	p. C533G	13	1
Exon 11	c.1630C>T	p. R544C	13-14	4
	c.1672C>T	p. R558C	14	2
	c.1759C>T	p. R587C	15	1
	c.1819C>T	p. R607C	15	2
Exon 13	c.1969G>T	p. E657*	17	1
	c.2041_2042insCGCT	p. C681Sfs*23	17	1
Exon 19	c.3091C>T	p. R1031C	26	1

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; EGF: epidermal growth factor

Supplementary Table 5: Heterozygous *HTRA1* mutations identified in our cohort

Clinical features						*HTRA1* mutations		Location		Population frequency			Bioinformatics Prediction			HGMD	Pathogenicity
Family	Gender	AAO	Neurological manifestations	Spondylosis deformans	Alopecia	Nucleotide	Amino acid	Exon	Domain	1000G	ExAc	gnomAD	SIFT	Polyphen-2	Mutation Taster		
1	M	42	Ischemic stroke, cognitive impairment, psychiatric symptoms, gait disturbance	NA	-	c.523G>A	p. V175M	2	...	0	0.000008	0.000004	D	Pro_D	D	Known	P
2	M	42	Ischemic stroke, cognitive impairment, psychiatric symptoms	NA	-	c.832T>C	p. F278L	4	Serine protease	0	0.000008	0.000004	D	Pro_D	D	Novel	LP
3	F	44	Ischemic stroke, cognitive impairment, psychiatric symptoms, gait disturbance	NA	-	c.834C>G	p. F278L	4	Serine protease	0	0	0	D	Pro_D	D	Novel	LP
4	F	40	Ischemic stroke, cognitive impairment, psychiatric symptoms, gait disturbance	NA	-	c.854C>T	p. P285L	4	Serine protease	0	0	0.000004	D	Pro_D	D	Known	P
5	F	44	Cognitive impairment, psychiatric symptoms, gait disturbance	NA	-	c.905G>A	p. R302Q	4	Serine protease	0	0	0	D	Pro_D	D	Known	P
6	M	38	Ischemic stroke, cognitive impairment	+	-	c.954G>C	p. Q318H	4	Serine protease	0	0	0.000004	D	Pro_D	D	Novel	LP
6	M	41	Ischemic stroke, cognitive impairment, psychiatric symptoms	+	-	c.954G>C	p. Q318H	4	Serine protease	0	0	0.000004	D	Pro_D	D	Novel	LP
6	M	38	Cognitive impairment, gait disturbance	NA	-	c.954G>C	p. Q318H	4	Serine protease	0	0	0.000004	D	Pro_D	D	Novel	LP
7	M	45	Ischemic stroke, cognitive impairment, psychiatric symptoms, gait disturbance	NA	-	c.983C>T	p. S328L	5	Serine protease	0	0	0	D	Pro_D	D	Novel	LP
8	F	42	Cognitive impairment, psychiatric symptoms, gait disturbance	NA	-	c.1015G>A	p. V339M	6	Serine protease	0	0	0	D	Pro_D	D	Novel	LP
9	M	37	Cognitive impairment, psychiatric symptoms, gait disturbance	+	+	c.1049G>A	p. G350E	6	Serine protease	0	0	0	D	Pro_D	D	Novel	LP

AAO = age at onset; F = female; M = male; 1000G = 1000 Genomes Project database; ExAC = Exome Aggregation Consortium database; gnomAD = the Genome Aggregation Database; SIFT = Sorting Tolerant From Intolerant; Polyphen-2 = Polymorphism Phenotyping v2; HGMD = Human Gene Mutation Database; D = damaging, deleterious, or disease-causing; Pro_D = probably damaging; P = pathogenic; LP = likely pathogenic; + = present; - = absent; NA = not available.

Supplementary Table 6: Heterozygous *COL4A1/2* mutations identified in our cohort

Clinical features					*COL4A1/2* mutations			Location	Population frequency			Bioinformatics Prediction			Biopsy [a]	Phenotype	HGMD	Pathogenicity
Patients	Gender	AAO	Neurological manifestations	Systematic symptoms	Gene	Nucleotide	Amino acid	Exon	1000G	ExAc	gnomAD	SIFT	Polyphen-2	Mutation Taster				
1	F	39	Recurrent brainstem infarction	Patent foramen ovale, paroxysmal atrial tachycardia	*COL4A1*	c.*34G>T	-	3`UTR	0	0	0	-	-	-	+	PADMAL	Novel	LP
2	F	48	Muscle cramps, psychiatric disorder	Chronic glomerulonephritis, renal cyst, coronary heart disease	*COL4A1*	c.1A>G	p.M1?	1	0	0	0	-	-	-	+	HANAC	Novel	P
3	F	38	Intracranial haemorrhage, cognitive impairment, psychiatric disorder, muscle cramps	Cataract, intracranial aneurysm	*COL4A1*	c.1961C>A	p. P654Q	27	0	0.0000174	0.00001314	T	B	D	+	HANAC	Novel	LP
4	F	36	Cognitive impairment	Cataract	*COL4A1*	c.2008G>A	p. G670R	28	0	0	0	D	Pro_D	D	NA	BSVD1	Known	P
5	M	48	Cognitive impairment, gait disturbance	Retinal arteriolar tortuosity, proteinuria	*COL4A2*	c.1735C>T	p. R579C	24	0	0.0001673	0.00000813	D	Pos_ D	polymorphism	+	BSVD2	Novel	LP
6	F	66	Intracranial haemorrhage	Retinal arteriolar tortuosity, retinal detachment	*COL4A2*	c.4514C>T	p. P1505L	46	0	0.0003623	0.000452	D	Pro_D	D	+	BSVD2	Novel	LP

AAO = age at onset; F = female; M = male; 1000G = 1000 Genomes Project database; ExAC = Exome Aggregation Consortium database; gnomAD = the Genome Aggregation Database; SIFT = Sorting Tolerant From Intolerant; Polyphen-2 = Polymorphism Phenotyping v2; HGMD = Human Gene Mutation Database; B = benign; D = damaging, deleterious, or disease-causing; Pro_D = probably damaging; Pos_ D = possibly damaging; T = tolerated; P = pathogenic; LP = likely pathogenic; NA = not available; PADMAL = pontine autosomal dominant microangiopathy and leukoencephalopathy; HANAC = hereditary angiopathy with nephropathy, aneurysm, and muscle cramps; BSVD1 = brain small vessel disease 1 with or without ocular anomalies; BSVD2 = brain small vessel disease 2.

[a] Biopsy: + means that skin biopsy revealed thickening of vascular basement membrane in the dermal layer of the skin, proliferation of vascular endothelial cells, and stenosis of vascular lumen.

Supplementary Table 7: Clinical and genetic features of patients of myelin disorders identified in our cohort

Patients	Gene	Nucleotide changes	AA changes	Geno type	Gender	AAO	Initial symptoms	Other neurological symptoms	Extraneurological symptoms	Biochemical results	HGMD	Pathogenicity
1	*GJC2*	c.167G>C	p.C56S	Het	F	Infancy	Psychomotor retardation	Nystagmus, spasticity, ataxia, dysarthria	No	-	Novel	LP
		c.704A>G	p.Y235C	Het							Novel	LP
2	*GALC*	c.1901T>C	p.L634S	Het	M	30	Spastic paraplegia	Sphincter dysfunction	No	GALC enzyme activity of leukocytes: 1.0nmol/17h/mgpr (normal range 19-68.2nmol/17h/mgpr)	Known	P
		c.658C>T	p.R220*	Het							Known	P
3	*GALC*	c.655delC	p.Q219Sfs*3	Het	F	16	Spastic paraplegia	No	No	NA	Novel	P
		c.1901T>C	p.L634S	Het							Known	P
4	*GALC*	c.1861C>T	p.R621C	Het	M	45	Spastic hemiplegia	Hemiparesthesia, ataxia	No	GALC enzyme activity of leukocytes: 2.6nmol/17h/mgpr (normal range 19-68.2nmol/17h/mgpr)	Novel	LP
		c.175G>A	p.G59S	Het							Novel	P
5	*GALC*	c.136G>T	p.D46Y	Hom	F	38	Left upper limb wasting and weakness	Pyramidal signs	No	NA	Known	P
6	*CYP27A1*	c.379C>T	p.R127W	Het	M	Infancy	Ataxia	Mental retardation, dysarthria, spastic paraplegia, peripheral neuropathy, sensorineural deafness	Cataract, arrhythmia, chronic diarrhoea	NA	Known	P
		c.380G>A	p.R127Q	Het							Known	P
7	*CYP27A1*	c.369_375delGTACCCA	p.P125Gfs*16	Het	F	7	Ataxia	Mental retardation, dysarthria, nystagmus, spastic paraplegia, peripheral neuropathy	Cataract, arrhythmia, tendon xanthomata	Biopsy of tendon xanthomata revealed rod-shaped cholesterol crystals	Novel	P
		c.73delG	p.A25Pfs*33	Het							Novel	P
8	*GJB1*	c.103G>A	p.V35M	Hem	M	11	Peripheral neuropathy	Dysarthria	No	-	Known	P
9	*GJB1*	c.423delC	p.R142Gfs*54	Hem	M	15	Peripheral neuropathy	Pes cavus	Sensorineural hearing loss	-	Novel	P
10	*GJB1*	c.547C>T	p.R183C	Hem	M	44	Peripheral neuropathy	Pes cavus, pyramidal signs	No	-	Known	P
11	*PAH*	c.1316-2A>C	-	Het	M	Infancy	Mental retardation	Psychiatric symptoms, febrile convulsion, pyramidal signs	Musty odor, light pigmentation of skin	Serum phenylalanine level: 1025.29umol/L(20-120)	Known	P
		c.1208C>A	p.A403D	Het							Novel	P
12	*PAH*	c.278A>T	p.N93I	Het	M	Infancy	Mental retardation	Pyramidal sign	Musty odor, light pigmentation of skin	Serum phenylalanine level: 955.21umol/L (20-120)	Novel	P
		c.422-1G>A	-	Het							Known	P
13	*PAH*	c.442-1G>A	-	Hom	M	Infancy	Mental retardation	Febrile convulsion, spastic hemiplegia	Musty odor, light pigmentation of skin	Serum phenylalanine level: 1152.54umol/L (20-120)	Known	P
14	*PAH*	c.728G>A	p.R243Q	Hom	M	Infancy	Mental retardation	No	Musty odor, light pigmentation of skin	Serum phenylalanine level: 463.98umol/L (20-120)	Known	P
15	*MMACHC*	c.482G>A	p.R161Q	Het	M	13	Epilepsy	Cognitive impairment, psychiatric symptoms, spastic paraplegia, peripheral neuropathy	No	Urinary methylmalonic acid level: 309.69μmol/L (0.2-3.6); Serum homocysteine level: 164.7umol/L (5-15)	Known	P
		c.609G>A	p.W203*	Het							Known	P
16	*MMACHC*	c.566G>A	p.R189H	Het	F	18	Cognitive impairment	Spastic paraplegia, ataxia, peripheral neuropathy	Anaemia	Urinary methylmalonic acid level: 34.2μmol/L (0.2-3.6); Serum homocysteine level: 210.69umol/L (5-15)	Known	P
		c.609G>A	p.W203*	Het							Known	P

17	*MMACHC*	c.609G>A	p.W203*	Het	M	25	Cognitive impairment	psychological disorders, peripheral neuropathy	No	Serum homocysteine level: 76.6umol/L (5-15)	Known	P
		c.239A>G	p.D80G	Het							Novel	LP
18	*MMACHC*	c.445_446insA	p.C149*	Het	M	35	Peripheral neuropathy	Spastic paraplegia	No	Urinary methylmalonic acid level: 271.65μmol/L(0.2-3.6); Serum homocysteine level: 144.87umol/L (5-15)	Known	P
		c.482G>A	p.R161Q	Het							Known	P
19	*MTHFR*	c.994G>T	p.V332L	Het	M	12	Spastic paraplegia	Peripheral neuropathy	No	Serum homocysteine level: 101.0umol/L (5-15)	Novel	LP
		c.389G>A	p.C130Y	Het							Novel	LP
20	*MTHFR*	c.1916C>T	p.T639I	Het	M	18	Spastic paraplegia	Cognitive impairment	No	Serum homocysteine level: 200.9umol/L (5-15)	Novel	LP
		c.584C>T	p.A195V	Het							Known	P
21	*GCDH*	c.383G>A	p.R128Q	Hom	M	21	Severe headache	Cognitive impairment	No	NA	Known	P
22	*LMNB1*	*LMNB1* duplication	-	Het	M	59	Spastic paraparesis	Parkinsonism, dysarthria, chronic constipation, insomnia	No	-		

AA changes = amino acid changes; AAO = age of onset; F = female; M = male; HGMD = Human Gene Mutation Database; LP = likely pathogenic; P = pathogenic; NA = not available.

Supplementary Table 8: Clinical and genetic features of ALD patients identified in our cohort

Patients	Nucleotide changes	AA changes	Gender	AAO	Initial symptoms	Other neurological symptoms	Adrenocortical insufficiency	Increased VLCFA in plasma	Phenotype	HGMD	Pathogenicity
1	c.24delG	p.W10Gfs*6	M	15	Cognitive impairment	Epilepsy, psychiatric symptoms, ataxia	+	NA	AdolCALD	Novel	P
2	c.290_299delACTCGGCCGC	p.H97Pfs*3	M	40	Cognitive impairment	Psychiatric symptoms, pyramidal signs, sphincter dysfunction	+	+	ACALD	Novel	P
3	c.422C>T	p.A141V	M	43	Psychiatric symptoms	Cognitive impairment, ataxia, pyramidal signs, sphincter dysfunction	-	+	ACALD	Known	P
4	c.423_431dupCCTCCCTGC	p.A144_T145insLPA	M	34	Psychiatric symptoms	Cognitive impairment, epilepsy, ataxia, pyramidal signs, sphincter dysfunction, deterioration after head trauma	-	+	ACALD	Novel	P
5	c.848A>G	p.H283R	M	30	Cognitive impairment	Ataxia, pyramidal signs, peripheral neuropathy	+	NA	ACALD	Known	P
6	c.1209_1214delGTCGTC	p.403_405del	M	12	Epilepsy	Cognitive impairment, psychiatric symptoms, pyramidal signs, peripheral neuropathy, deterioration after head trauma	-	NA	AdolCALD	Novel	P
7	c.1488+1G>A	-	M	38	Spastic paraplegia	Cognitive impairment, psychiatric symptoms, peripheral neuropathy, sphincter dysfunction	+	+	ACALD	Known	P
8	c.1804A>T	p.K602*	M	42	Psychiatric symptoms	Cognitive impairment, deterioration after brain biopsy	-	NA	ACALD	Known	P
9	c.1876G>A	p.A626T	M	9	Epilepsy	Cognitive impairment, psychiatric symptoms, pyramidal signs, ataxia	-	NA	CCALD	Known	P
10	c.253dupC	p.R85Pfs*110	M	28	Spastic paraplegia	-	-	NA	AMN	Known	P
11	c.346G>C	p.G116R	M	27	Spastic paraplegia	Peripheral neuropathy, deep sensory disturbance, sphincter dysfunction	-	NA	AMN	Known	P
12	c.371G>C	p.R124P	M	51	Spastic paraplegia	Peripheral neuropathy, sphincter dysfunction	+	+	AMN	Novel	LP
13	c.1028G>A	p.G343D	M	25	Spastic paraplegia	Sphincter dysfunction, impotence	+	NA	AMN	Known	P
14	c.1202G>A	p.R401Q	M	25	Spastic paraplegia	Memory decline, peripheral neuropathy, sphincter dysfunction	-	NA	AMN	Known	P
15	c.1214_1216delCGT	p.S405del	M	23	Ataxia	Spastic paraplegia, memory decline, sphincter dysfunction	-	NA	AMN	Novel	P
16	c.1552C>T	p.R518W	M	25	Ataxia	Spastic paraplegia, sphincter dysfunction	-	NA	AMN	Known	P
17	c.1978C>T	p.R660W	M	25	Spastic paraplegia	Deep sensory disturbance,	+	+	AMN	Known	P
18	c.1252C>T	p.R418W	M	30	Dysarthria	Dysphagia, ataxia, pyramidal signs	-	NA	Spinocerebellar variant	Known	P
19	c.1390C>T	p.R464*	M	22	Ataxia	Dysarthria, pyramidal signs, peripheral neuropathy	-	+	Spinocerebellar variant	Known	P

AA changes = amino acid changes; AAO = age of onset; M = male; HGMD = Human Gene Mutation Database; VLCFA = very long-chain fatty acids; ALD = adrenoleukodystrophy; AdolALD = adolescent cerebral ALD; ACALD = adult cerebral ALD; CCALD = childhood cerebral ALD; AMN = adrenomyeloneuropathy; P = pathogenic; LP = likely pathogenic; - = absent; + = present; NA = not available.

Supplementary Table 9: Clinical and genetic features of NIID patients identified in our cohort

Patients	Numbers of GGC Repeat	Gender	AAO	Initial symptoms	Episodic neurogenic events	Cognitive impairment	Autonomic dysfunction	Unconsciousness	Encephalitic episode	Stoke-like episode	Parkinsonism	Tremor	Ataxia	Headache	Seizure	Muscle weakness	Sensory disturbance	Visual loss	Psychiatric disorder
1	113	F	50	Autonomic dysfunction	+	+	+	-	-	-	-	+	+	-	-	-	-	-	-
2	104	F	42	Headache	+	+	-	-	-	-	-	+	-	+	-	-	-	-	-
3	88	M	47	Autonomic dysfunction	+	+	+	-	+	-	-	-	+	+	-	-	-	-	+
4	131	F	62	Tremor	+	+	-	-	-	+	-	+	-	-	-	-	-	-	-
5	159	F	53	Cognitive impairment	-	+	-	-	-	+	-	-	-	-	-	-	+	-	+
6	127	M	50	Unconsciousness	+	+	+	+	+	-	-	-	-	-	+	+	-	-	+
7	107	F	62	Encephalitic episode	+	-	+	-	+	-	-	-	-	+	-	-	-	+	-
8	138	F	58	Headache	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-
9	109	F	49	Seizure	+	+	+	+	-	-	-	-	-	-	+	-	-	-	+
10	125	F	59	Tremor	+	-	+	-	-	-	-	+	-	+	-	-	-	+	-
11	104	F	66	Cognitive impairment	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-
12	120	M	58	Autonomic dysfunction	-	+	+	-	-	-	-	-	-	-	-	-	-	-	+
13	123	F	54	Tremor	+	+	+	-	-	+	-	+	-	+	-	-	+	+	-
14	94	M	69	Unconsciousness	+	+	-	+	-	-	-	-	-	-	-	-	-	-	+
15	139	M	65	Parkinsonism	-	+	+	-	-	-	+	-	-	-	-	-	-	-	-
16	87	M	64	Cognitive impairment	+	+	+	-	-	-	-	+	-	+	-	-	-	-	-
17	122	F	54	Cognitive impairment	+	+	+	-	-	-	+	+	-	-	-	-	-	+	-
18	109	F	62	Involuntary movement	-	+	+	-	-	-	-	-	-	-	-	-	-	-	+
19	121	F	55	Autonomic dysfunction	+	+	+	-	-	-	-	+	-	-	-	-	-	-	+
20	141	F	57	Cognitive impairment	-	+	-	-	-	-	-	-	-	+	-	-	-	+	-
21	120	F	59	Cognitive impairment	-	+	+	-	-	-	-	+	+	+	-	-	-	-	+
22	139	M	51	Visual loss	+	+	+	-	-	-	-	-	+	-	+	-	-	+	+
23	128	F	18	Headache	+	+	-	-	-	-	-	+	+	+	-	-	-	-	+
24	93	F	48	Autonomic dysfunction	+	+	+	+	-	-	-	-	+	-	-	+	-	-	+
25	150	F	35	Tremor	-	+	+	-	-	-	+	+	+	-	-	-	-	-	+
26	89	F	54	Headache	+	+	+	+	-	-	-	+	+	+	-	-	-	+	-
27	153	M	61	Dizziness	+	+	+	-	-	-	+	+	-	-	-	+	+	-	+
28	111	M	60	Psychiatric	+	+	+	-	-	-	-	+	-	+	-	-	-	+	+

				symptoms														
29	115	M	56	Cognitive impairment	-	+	+	-	-	-	-	-	+	-	-	-	-	+
30	101	F	62	Cognitive impairment	+	+	+	+	-	-	-	-	+	+	-	-	+	-	-
31	105	F	58	Autonomic dysfunction	-	+	+	-	-	-	-	+	+	-	-	-	-	-	-
32	123	F	59	Cognitive impairment	+	+	+	-	-	-	-	-	-	+	-	-	-	-	+
33	107	M	61	Cognitive impairment	+	+	+	+	-	-	+	-	-	+	-	-	-	+	+
34	105	M	67	Cognitive impairment	-	+	+	-	-	-	-	+	-	+	-	+	+	-	-
35	114	F	48	Dizziness	+	+	+	-	-	-	-	+	-	-	-	+	+	-	+
36	135	F	50	Tremor	-	+	+	-	-	-	-	+	-	+	-	-	+	+	-
37	93	M	51	Tremor	+	+	+	-	-	+	-	+	+	-	-	-	-	-	-
38	128	M	48	Tremor	-	+	+	-	-	-	-	+	-	-	-	-	-	+	-
39	134	F	59	Sensory disturbance	-	-	+	-	-	-	-	+	-	+	-	-	+	-	-

NIID = neuronal intranuclear inclusion disease; AAO = age of onset; F = female; M = male; - = absent; + = present.

Supplementary Table 10: Clinical and genetic features of patients of other leuko-axonopathies identified in our cohort

Patients	Gene	Nucleotide changes	AA changes	Genotype	Gender	AAO	Initial symptoms	Other neurological symptoms	Extraneurological symptoms	HGMD	Pathogenicity
1	*AARS2*	c.452T>C	p.M151T	Hom	M	37	Cognitive impairment	Fatigability	No	Known	P
2	*AARS2*	c.452T>C	p.M151T	Het	M	28	Spastic hemiplegia	Cognitive impairment, psychiatric symptoms, nystagmus, dysarthria, tremor	Arrhythmia	Known	P
		c.1871G>A	p.W624*	Het						Known	P
3	*AARS2*	c.637G>C	p.G213R	Het	F	40	Cognitive impairment	Psychiatric changes, involuntary movement	premature ovarian failure	Novel	LP
		c.965G>A	p.R322H	Het						Known	P
4	*AARS2*	c.802A>G	p.M268V	Het	M	3m	Delayed motor development	cognitive impairment, psychiatric symptoms, ataxia, pyramidal signs, tremor, nystagmus, dysarthria	No	Known	P
		c.1871G>A	p.W624*	Het						Known	P
5	*DARS2*	c.213G>T	p.W71C	Het	F	infancy	Delayed motor development	Ataxia, dysarthria, cognitive decline, pyramidal signs, deep sensory disturbance, peripheral neuropathy	Visual impairment	Novel	LP
		c.228-16C>A	-	Het						Known	P
6	*Mt-DNA*	Mt-DNA: ND2 deletion	-	-	M	15	Cognitive impairment	Fatigability	No	Known	P
7	*Mt-DNA*	Mt DNA: 8284_14751del	-	-	M	8	Sensorineural deafness	Cognitive impairment, psychiatric changes, epilepsy, dysarthria, ataxia, fatigability, tremor, peripheral neuropathy	Arrhythmia (left bundle branch block)	Known	P
8	*Mt-DNA*	Mt-ND3: 10197G>A	-	-	M	15	Diplopia	Dystonia, rigidity, dysarthria, ataxia, fatigability, cognitive impairment, myopathy	No	Known	P
9	*POLR3A*	c.2564G>A	p.R855Q	Het	F	Infancy	Progressive ataxia	Spastic paraplegia, dysarthria	Poor pubertal development	Novel	LP
		c.1771-6C>G	-	Het						Known	P
10	*POLR3A*	c.3407G>A	p.R1136Q	Het	M	Infancy	Progressive ataxia	Mental retardation, pyramidal signs, dysarthria	Oligodontia, short stature, poor pubertal development	Known	P
		c.1771-7C>G	-	Het						Known	P
11	*SPG11*	c.2531_2534delAACA	p.K844Rfs*7	Het	M	15	Spastic paraplegia	dysarthria	No	Novel	P
		c.7151+4_7151+7delAGTA	-	Het						Novel	LP
12	*SPG11*	c.4307_4308delAA	p.Q1436Rfs*7	Hom	M	16	Spastic paraplegia	No	No	Known	P
13	*SPG11*	c.2480_2481insT	p.K827Nfs*11	Het	F	12	Spastic paraplegia	dysarthria	No	Novel	P
		c.2757delT	p.L920*	Het						Novel	P
14	*SPG11*	c.6739_6742delGAGT	p.E2247Lfs*14	Hom	M	12	Spastic quadriplegia	Cognitive impairment, dysarthria, extrapyramidal signs, bladder dysfunction	Strabismus	Known	P
15	*SPG11*	c.2123dupT	p.R709Qfs*3	Het	M	15	Spastic paraplegia	Dysarthria	No	Novel	P
		c.4636-2A>G	-	Het						Novel	P
16	*ZFYVE26*	c.4278G>A	p.W1426*	Het	M	14	Spastic paraplegia	Cognitive impairment, psychiatric symptoms, bladder dysfunction, peripheral neuropathy	No	Novel	P
		c.4804C>T	p.R1602*	Het						Known	P
17	*ZFYVE26*	c.6498C>A	p.Y2166*	Het	M	14	Spastic paraplegia	Peripheral neuropathy	No	Novel	P
		c.6588+1G>A	-	Het						Novel	P
18	*SPG7*	E1-E3 deletion	-	Hom	F	56	Spastic paraplegia	Psychiatric symptoms	No	Novel	P
19	*RNF216*	c.1549C>T	p.R517*	Hom	M	26	Ataxia	Dysarthria, cognitive impairment	Hypogonadotropic hypogonadism	Novel	P
20	*HEXB*	c.1514G>A	p.R505Q	Het	F	23	Weakness of limbs	No	No	Known	P
		c.1614-9_1619TATCTACAGACGTG	-	Het						Novel	P

		G									
21	*IDS*	c.265G>C	p.V89L	Hem	M	8	Recurrent upper respiratory tract infections	No	Abdominal protuberance, macrocephaly, skeletal deformities, amblyopia	Novel	LP
22	*DMPK*	Numbers of CTG Repeat: >100	-	het	M	27	Myotonic myopathy	Cognitive impairment, dysarthria, Sensorineural deafness	Strabismus, alopecia		
23	*DMPK*	Numbers of CTG Repeat: >100	-	het	M	15	Myotonic myopathy	Cognitive impairment, sensorineural deafness	Cataract, alopecia		
24	*DMPK*	Numbers of CTG Repeat: >100	-	het	M	20	Myotonic myopathy	Cognitive impairment, dysarthria	Alopecia		

AA changes = amino acid changes; AAO = age of onset; F = female; M = male; HGMD = Human Gene Mutation Database; LP = likely pathogenic; P = pathogenic.

Supplementary Table 11: Clinical and genetic features of patients with heterozygous mutations in *CSF1R* gene identified in our cohort

Patients	Nucleotide changes	AA changes	Genotype	Exon	Gender	AAO	Initial symptoms	Cognitive impairment	Psychiatric symptoms	Ataxia	Parkinsonism	Pyramidal sign	Other symptoms	HGMD	Pathogenicity
1	c.2294G>A	p.G765D	Het	17	F	53	Cognitive impairment	+	+	+	-	+	Bladder dysfunction	Known	LP
2	c.2308G>A	p.A770T	Het	17	M	24	Spastic paraplegia	-	-	-	-	+	Dysarthria, incontinence	Novel	LP
3	c.2330G>A	p.R777Q	Het	17	M	30	Hemianesthesia	-	-	-	-	+	Dysarthria, dysphagia, hemiplegia	Known	LP
4	c.2344C>T	p.R782C	Het	18	F	43	Cognitive impairment	+	-	+	+	-	No	Known	LP
5	c.2381T>C	p.I794T	Het	18	M	27	Spastic hemiplegia	-	-	-	-	+	Dysarthria, Bladder dysfunction	Known	P
6	c.2381T>C	p.I794T	Het	18	M	35	Cognitive impairment	+	-	-	-	+	Dysarthria	Known	P
7	c.2381T>C	p.I794T	Het	18	M	39	Psychiatric changes	+	+	-	-	+	Dysphagia	Known	LP
8	c.2466G>A	p.M822I	Het	19	F	30	Ataxia	+	+	+	-	+	No	Known	P
9	c.2468C>A	p.A823D	Het	19	M	44	Ataxia	-	+	+	+	+	Dysarthria, dysphagia	Known	LP
10	c.2468C>T	p.A823V	Het	19	M	38	Cognitive impairment	+	-	-	-	+	No	Known	P
11	c.2528T>C	p.I843T	Het	19	F	43	Ataxia	+	+	+	-	+	Bladder dysfunction	Novel	LP
12	c.2552T>C	p, L851P	Het	19	F	24	Ataxia	+	+	+	-	+	Dysarthria	Known	P
13	c.2695_2696insC	p.H899Pfs*43	Het	21	M	49	Cognitive impairment	+	-	+	-	-	Bladder dysfunction	Novel	LP
14	c.2701C>T	p.P901S	Het	21	F	37	Ataxia	+	-	+	-	+	No	Known	LP

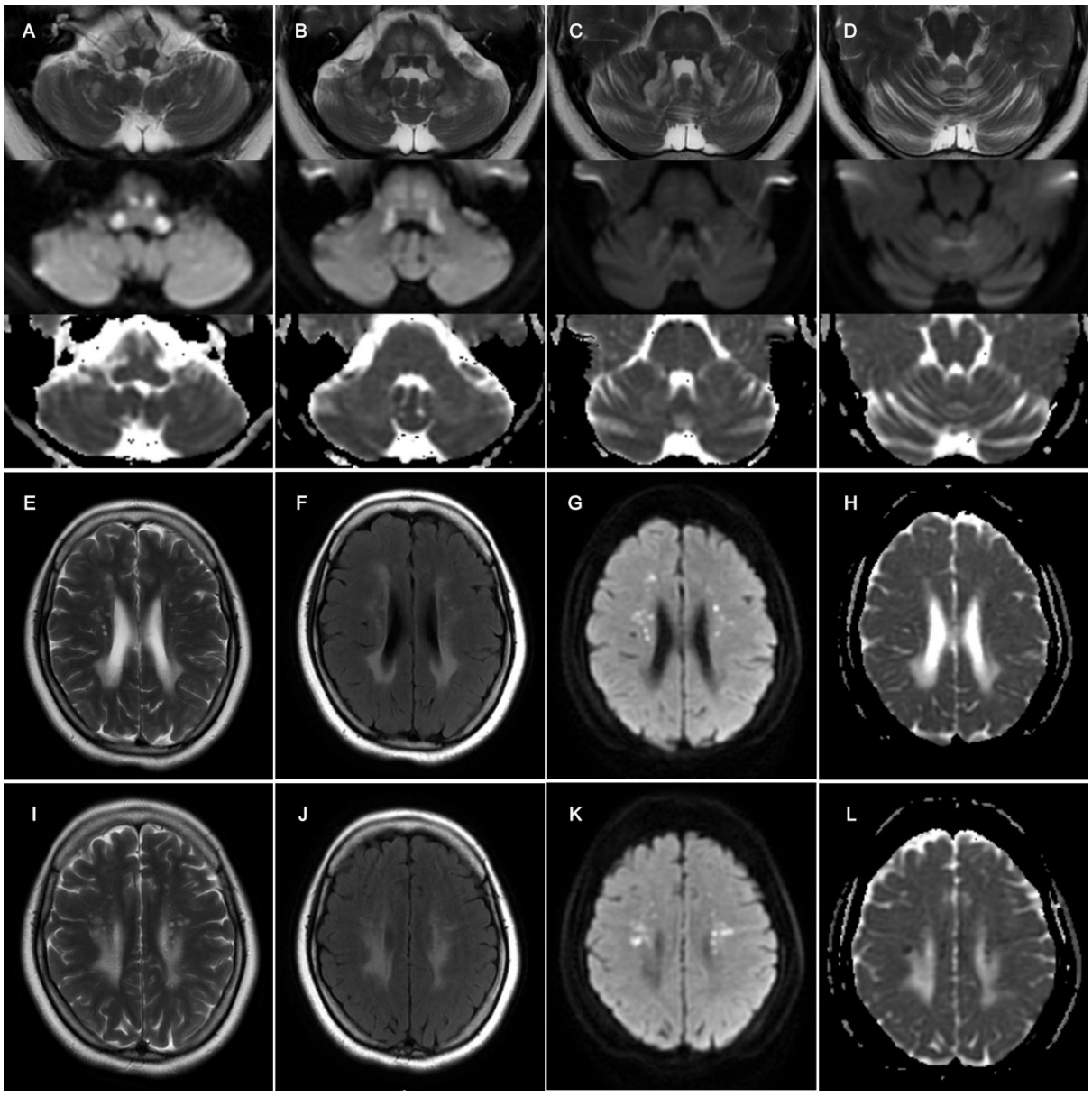
AA changes = amino acid changes; AAO = age of onset; F = female; M = male; HGMD = Human Gene Mutation Database; LP = likely pathogenic; P = pathogenic; - = absent; + = present.

Supplementary Table 12: Clinical and genetic features of astrocytopathies patients identified in our cohort

Patients	Gene	Nucleotide changes	AA changes	Genotype	Gender	AAO	Initial symptoms	Other neurological symptoms	Extraneurological symptoms	HGMD	Pathogenicity
1	*EIF2B2*	c.3G>T	p.M1?	Hom	M	infancy	Mental retardation	Epilepsy, dysarthria, ataxia, headache	No	Novel	P
2	*EIF2B3*	c.1261A>T	p.I421F	Het	F	31	Ataxia	Cognitive impairment, psychiatric symptoms, spastic paraplegia, tremor	Optic atrophy, premature ovarian failure	Novel	US
		c.686T>G	p.I229S	Het						Novel	LP
3	*EIF2B3*	c.130G>A	p.E44K	Het	F	41	Psychiatric symptoms	Cognitive impairment, spastic paraplegia, ataxia, deterioration following head trauma	Optic atrophy, somnolence, premature ovarian failure	Known	LP
		c.965C>G	p.A322G	Het						Known	LP
4	*EIF2B4*	c.882+2T>G	-	Het	M	7	Ataxia	Spastic quadriplegia, cognitive impairment, nystagmus, bladder dysfunction, rapid deterioration following head trauma	No	Novel	P
		c.1334G>A	p.R445H	Het						Known	P
5	*EIF2B5*	c.1025T>C	p.I342T	Het	F	infancy	Mental retardation	Spastic quadriplegia, ataxia, dysarthria, hemianesthesia, incontinence	Optic atrophy	Novel	LP
		c.1054C>T	p.H352Y	Het						Novel	LP
6	*EIF2B5*	c.1087G>A	p.G363S	Het	F	41	Headache	Cognitive impairment, psychiatric symptoms, tremor, incontinence	Sleep disturbance, premature ovarian failure	Novel	LP
		c.806G>A	p.R269Q	Het						Known	P
7	*GFAP*	c.262C>T	p.R88C	Het	F	infancy	Delayed motor development	Dysarthria, ataxia, pyramidal signs	Sleep disturbance	Known	P
8	*GFAP*	c.1246C>T	p.R416W	Het	M	8	Ataxia	Pyramidal signs, palatal myoclonus, bladder dysfunction	Scoliosis	Known	P
9	*GFAP*	c.1246C>T	p.R416W	Het	F	19	Ataxia	Dysarthria, nystagmus, pyramidal signs, cognitive impairment, bladder dysfunction	No	Known	P
10	*LAMA2*	c.439C>T	p.P147S	Hom	M	30	Epilepsy	No	No	Novel	LP
11	*LAMA2*	c.437C>A	p.S146Y	Het	M	13	Progressive weakness of distal lower extremities	Epilepsy	No	Known	P
		c.7186delG	p.H2397Tfs*2	Het						Novel	P
12	*CLCN2*	c.2507G>C	p.R836P	Hom	M	41	Severe headache	No	No	Novel	LP

AA changes = amino acid changes; AAO = age of onset; F = female; M = male; HGMD = Human Gene Mutation Database; LP = likely pathogenic; P = pathogenic; US = uncertain significance.

Supplementary Figure 1 The imaging appearance of the patient with LBSL. (A-D) Axial T2-weighted MRI images showed hyperintensity in the medullary pyramids (A), middle cerebellar peduncles (B), cerebellar dentate nucleus (C), and cerebellar vermis (D), which was hyperintense on diffusion weighted imaging and isointense or hypointense on apparent diffusion coefficient. (E-F, I-J) T2-weighted and FLAIR imaging showed symmetric hyperintensities in periventricular white matter. Multiple punctate hyperintensities on DWI were distributed in periventricular white matter (G, K), which were hypointense on ADC (H, L). ADC: apparent diffusion coefficient; DWI: diffusion weighted imaging; FLAIR: fluid-attenuated inversion recovery images; LBSL: leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation.



Supplementary Figure 2 Punctate diffusion restriction in patients with LBSL, ALSP, and AARS2-related leukodystrophy. (A-D) Imaging appearance of LBSL. (E-H) Imaging appearance of ALSP. (I-L) Imaging appearance of AARS2-related leukodystrophy. The punctate diffusion restriction changes in the periventricular white matter appear similar among LBSL, ALSP, and AARS2-related leukodystrophy. ALSP: adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; LBSL: leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation.