Supplemental Methods

Exome sequencing and variant calling and variant classification For WES analysis, capture was performed using the SeqCap EZ Human Exome Kit v3.0 (Roche Nimblegen, USA) with 100-bp paired-end read sequences, and for WGS, a PCR-free library with 150-bp paired-end read sequences was generated on a HiSeq 2000-4000 platform (Illumina, Inc. USA) at Centre Nacional d'Anàlisi Genòmica (CNAG Barcelona, Spain). Sequences were aligned to hg19 by Burrows-Wheeler Aligner (BWA mem), and single nucleotide variants and small insertions/deletions (indels) were identified using GATK, applying GATK's best practices for germline SNP & indel discovery in WES and annotated[1] by ANNOVAR software[2]. Copy number variants (CNVs) were analyzed by the R package ExomeDepth[3] that uses read-depth data from targeted sequencing experiments and filtered with the Database of Genomic Variants that provides a comprehensive summary of structural variation in the human genome.

Variant filtering and classification

Variants were filtered for each sequenced individual using the following criteria: i) hypothesized mode of transmission coherent with family pedigree, ii) allele frequency lower than 1% in each of the following databases: 1000 Genomes Project, NHLBI GO Exome Sequencing Project (ESP), ExAC, and gnomAD; Dopazo DB, or specific ethnicity DB (Iraniome), iii) predicted deleterious effect on protein function: frameshift insertions/deletions, nonsense and conserved nonsynonymous amino acid substitution variants with prediction of deleterious damage, iv) canonical variants putatively altering splice sites. Noncanonical effects of variants on splicing were analyzed by BDGP and FSPLICE in SoftBerry and NetGene2. The candidate variants were strictly classified following the Standards and guidelines for the interpretation of sequence variants of the

American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP)[4,5].

Predicted deleterious effect was carried out by using 3 meta-predictors, namely, PredictSNP2, MetaLR and MetaSVM. PredictSNP2 (https://loschmidt.chemi.muni.cz/predictsnp2/), generates a consensus score from prediction of five tools- CADD, DANN, FATHMM, FunSeq2, and GWAVA. It can predict for nucleotide variants located in both coding and non-coding regions[6]. MetaSVM and MetaLR, developed by the dbNSFP project (https://sites.google.com/site/jpopgen/dbNSFP) utilizes the predictors SIFT, PolyPhen-2 HDIV, PolyPhen-2 HVAR, GERP++, MutationTaster, Mutation Assessor, FATHMM, LRT, SiPhy & PhyloP to score variants, together with the maximum frequency observed in the 1000 genomes project populations[7].

Single variants and insertions/deletions (indels) were filtered (e.g., zygosity, allele frequency in control populations) and ranked according to the hypothesized mode of inheritance based on family history, *in silico* pathogenicity scores and gene constraint scores (pLI, pRec, missense Z-score). Sanger sequencing was used in all cases to confirm the findings and for family segregation. Especially for novel variants, downstream targeted inheritance testing by was critical to the variant classification.

The variants were categorized according to ACMG/AMP criteria for pathogenicity[4,5,8]. A case was considered solved if variants were classified as pathogenic or likely pathogenic. Cases with a variant of unknown significance (VUS) but compatible segregation studies and specific clinical and MRI findings highly suggestive for a given disease, were also considered solved. Incidental findings were reviewed in all the patients according to published guidelines[9].

Functional validation

Several VUS variants were functionally tested by different methods, including lipidomics (Pant *et al.*[10] and Vélez-Santamaria *et al.*[11])) cDNA sequencing or minigene splicing assays (Rodríguez-Palmero *et al.*[12]).

Interactome-driven prioritization method

We used a network-based approach, as previously applied in Novarino *et al.*[13], in two main steps: (1) calculation of a phenotypic metric by phenotype comparisons between the patient and existing human disease databases (prior knowledge) and (2) iterative propagation of this phenotypic score within a protein-protein network. For the first step, we extracted more than 300000 HPO-gene associations from the OMIM and HPO databases. We used the same PRINCE logistic function to transform the final phenotypic metric into a value [0,1]; see details in Vanunu *et al.*[13,14]. The phenotypic metric propagates to adjacent proteins within the global human network built with physical and functional protein-protein interactions (PPIs). For a physical interactome, we integrated PPIs from five large-scale databases: the BioPlex 2.0 Network[15], the Lit-BM-13 dataset[16], the HI Yeast-Two-Hybrid datasets HI-I-05 and HI-II-14[16,17] and the recently published Human Reference Interactome (HuRI), downloaded from http://www.interactome-atlas.org[18]. For a functional interactome, we integrated HumanNet-CF v.2 interactions[19], metabolome substrate-product connections from KEGG[20] and RECON[21], and signaling connections from the Signor 2.0 database[22]. Merging of the physical and functional databases yielded a global human interactome with 20146 proteins and 696301 connections. For clarity, the way our algorithm reaches

to the candidate genes not formerly linked to disease, is through their neighborhood connections with known disease genes that do match with the HPO terms of the particular case under study. A paradigmatic example is the novel candidate DEGS1 gene, which we identified and functionally validated in 2019[10], which was prioritized because it interacts functionally in a network with other sphingolipid enzymes causative of diseases with similar HPO terms, such as ARSA, GALC, FA2H or ACER3 (Figure 4B). The same occurs with PI4KA (Verdura et al., Brain *in press*); this gene ranked first as it is an interactor of genes causing white matter disorders such as FAM126A, PIK3CA, PIK3C2A or OCRL (Figure 4C).

In addition, we integrated in the prioritization tool a deleteriousness metric that predicts the impact of the variant, scoring as "high" for loss-of-function and canonical splicing variants, "moderate" for missense variants, and "low" for synonymous variants.

Enrichment analysis

To evaluate which pathways or functional categories were enriched in the GWMD network, we followed a similar strategy as described elsewhere[23]. Briefly, we used hypergeometric-based tests from the GOstats package[24]. We used $p < 0.001$ as the cutoff point for GO terms with fewer than 1000 protein members to determine which GO terms were significantly enriched.

Supplemental Results

Illustrative Clinical Cases

MRI images are displayed in Figure 2 in the main text.

a) Novel phenotypes

LNF-48: a 13-year-old male patient and his 9-year-old sister, born from nonconsanguineous parents after uneventful pregnancies and deliveries. Both presented global developmental delay with hypotonia evolving to spastic paraparesis with ataxia and were able to walk with assistance at the last examination. They also had erratic ocular movements and bimanual stereotypies, but none of them had seizures. MRI showed periatrial T2 WM hyperintensity with frontoparietal atrophy and a thin corpus callosum. Metabolic studies were normal. Both patients were compound heterozygous for missense variants in *PARS2* (p.Arg186Gly) and (p.Lys187Arg), classified as likely pathogenic according to the ACMG criteria[1,2], and segregation studies were consistent with an autosomal recessive mode of inheritance. Although developmental delay, spasticity, predominantly anterior cortico-subcortical atrophy and a thin corpus callosum had been reported in association with *PARS2*, the few cases reported to date had presented a severe seizure disorder, most of them with hyperlactatemia and MRI findings of basal ganglia abnormalities or hypomyelination[3]. Therefore, this family expands the clinical phenotype associated with *PARS2*.

LNF-105: a 11-year-old male harbouring a duplication encompassing both the *HNRNPH1* and *RUFY1* genes (5q53.3(178950829-179067861)x3). The phenotype was reported in a previous publication[4].

b) Atypical phenotypes

LNF-29: two brothers aged 14 and 7 years, born from nonconsanguineous parents after an uneventful pregnancy and delivery. Both had shown severe global developmental delay with hypotonia since the first months of life, which had evolved to spastic-dystonic tetraparesis. They also had microcephaly, nystagmus and erratic ocular movements, and the older brother also presented generalized and myoclonic seizures between 3 months and 3 years of age. MRI showed bilateral periatrial and temporal anterior subcortical T2 WM hyperintensities, WM volume loss, a thin corpus callosum and cysts in the anterior temporal regions. They harbor one variant in homozygosis in the *PNPT1* gene (p.Ala507Ser), classified as pathogenic. The MRI pattern in these two brothers, resembling RNASET2, Aicardi-Goutières syndrome or a congenital CMV infection, has been reported recently to be associated with mutations in *PNPT1*[5].

LNF-47: a 4-year-old male compound heterozygous variants in *POLR3A* (p.Leu1129= and c.1771-7C>G) clinical and radiological phenotype reported in a previous publication[6].

LNF-77: biallelic heterozygous variants *in trans* were found in *POLR1C*, a gene associated with POLR3-related leukodystrophy and Treacher Collins syndrome.

Although it has been suggested that mutations in these two diseases act via different mechanisms (impairment of the assembly and nuclear import of POLR3 in leukodystrophy cases), one of the variants present in this patient (p.Arg279Gln) had previously been described exclusively in Treacher Collins syndrome cases to date and had been shown to impair nucleolar targeting[7]. Given that our patient did not show any features of Treacher Collins syndrome, we propose that pathogenic variants already described in Treacher Collins syndrome cases may also cause leukodystrophy, at least when found in compound heterozygosis with another causative mutations.

LNF-85: a 64-year-old woman presented cognitive decline and pyramidal signs starting at 48 years of age. She had no previous remarkable family or personal history. MRI showed diffuse T2 WM hyperintensities with cortical and cerebellar atrophy. We identified the variant (p.Thr350Ile) in heterozygosis in *PSEN1*, a gene that has been associated with Alzheimer disease but also with spastic paraparesis[8]. Although white matter hyperintensities have been identified as a core feature in autosomal dominant forms of Alzheimer's disease[9], the pattern in this case resembled leukodystrophy.

LNF-88: two sisters, aged 15 and 16 years, who were born from consanguineous parents and presented a clinical picture with predominant progressive spastic paraparesis since the first year of life with proximal weakness, dysarthria and cognitive deficits. MRI of both sisters performed at 2 and 12 years old in one and at 3 and 15 years old in the other, showed nonprogressive T2 WM hyperintensities in predominantly deep cerebral WM, the inner layer of the corpus callosum and the middle cerebellar peduncles, sparing the periventricular and subcortical cerebral WM and the outer layers of the corpus callosum.

EMG revealed a myopathic pattern. We identified a missense variant in *GFPT1* (p.Asp296Val) in homozygosis, a gene that is mainly associated with myasthenic syndromes but has also been reported very recently to cause a leukoencephalopathy[10] that shows an MRI pattern overlapping with our two cases **(Figure 2, F)**.

LNF-114: a male patient, currently 3 years old, with no remarkable family or perinatal history, who presented neonatal seizures since the first minutes of life and hyperekplexia-like episodes in response to sounds. He also had global developmental delay; global hypotonia; and phenotypic abnormalities consisting of a long face, prominent forehead, low hairline, low-set and dysplastic ears, bilateral inguinal and abdominal hernias, arthrogryposis, and bone dysplasia with bilateral hip luxation. MRI performed at 5 months showed an important myelination delay, thin corpus callosum and signs of cerebral and cerebellar atrophy. WES revealed a *de novo* heterozygous missense variant in *SCN8A* (p.Val409Met). Previously reported manifestations associated with *SCN8A* did not include bone dysplasia, dysmorphic traits or giant hernias. Severe myelination delay is not a frequent feature, although it has been reported in two patients previously[11]. Similarly, hyperekplexia-like episodes have been described in a single patient[12].

SPG-2: a 76-year-old male patient with spastic paraparesis and upper limb hyperreflexia and dysarthria with onset at 40 years of age. He was born at full term to nonconsanguineous parents after an unremarkable pregnancy and delivery. His development was considered normal during childhood. He had two older healthy siblings. MRI performed at clinical onset showed bands of periventricular WM hyperintensities on T2 and FLAIR sequences. He was homozygous for a pathogenic variant (c.1605+5G>A)

in *CAPN1* that had been previously described to result in exon skipping, generating a frameshifted transcript[13]. The presence of white matter abnormalities had been reported previously in only one case of spastic paraplegia 76 (OMIM # 616907)[14]

SPG-25: a family with 4 affected generations (the index case (male) and his mother, grandmother, sister and nephew) with predominant ataxia beginning in youth, slow saccades, nystagmus, cephalic tremor, dysarthria, dysphagia, and demyelinating neuropathy with motor, sensitive and autonomic involvement. Brain MRI showed diffuse WM signal abnormalities compatible with hypomyelination without cerebellar atrophy. WES revealed a heterozygous missense novel variant (p.Tyr83Asp) in *SOX10* that was firstly classified as a VUS according to ACMG criteria, but cosegregation studies in this family including three affected members were consistent. *SOX10* mutations are known to cause Waardenburg syndrome with Hirschsprung disease (OMIM # 613266) and a more severe phenotype, including peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease (PCWH) (OMIM # 609136)[15]. In this family, there are predominant neurological manifestations but are not associated with Hirschsprung or Waardenburg syndrome, thus expanding the clinical spectrum associated with *SOX10* variants.

c) **Cases with dual diagnoses**

LNF40: a family with 3 affected siblings (13, 21 and 20 years old) who were born from consanguineous parents of Palestinian origin and presented global developmental delay and spasticity starting in the first two years of life. A metabolic neonatal screening study was not performed in the country of origin. MRI showed confluent symmetric

periventricular T2 hyperintensities in LNF40.0 and LNF40.3 and delayed myelination in LNF40.4. We identified a previously unreported, homozygous VUS variant (p. Arg178Thr) in *CYP2U1* in the first two siblings (SPG56, OMIM: 615030), while LNF40.4 harbored a homozygous pathogenic variant in *PAH* (p.Thr380Met), already described as causing phenylketonuria, which was biochemically confirmed after the molecular report was handed. Segregation analysis was compatible in this family.

LNF-56: a 15-year-old female patient who presented moderate intellectual disability, ADHD, behavioral abnormalities (obsessions, mood disorder, emotional lability, visual hallucinations), absence and myoclonic seizures beginning at thirteen years old. She also showed nystagmus, strabismus and instability starting in the first years of life. MRI showed periventricular heterogeneous T2 WM hyperintensities and hypointensity in the globus pallidus, thalamic anterolateral nuclei, dentate nuclei, optic radiations and pyramidal tracts, with mild atrophy of the cerebellar superior vermis. WES analysis identified two variants in *POLR3A* in compound heterozygosis, classified as pathogenic (p.Cys724Tyr) and likely pathogenic (p.Pro705Ala), as well as a heterozygous loss-of-function variant in *CACNA1A* (p.Tyr546Ter) that was revealed to be *de novo* after the segregation study. The patient's clinical picture could be more related to the variant in *CACNA1A*, but the radiological pattern was more consistent with *POLR3A.*

LNF-89: two siblings, 21 and 18 years old, who presented with microcytic and hypochromic anemia with low plasma and urinary copper, low ceruloplasmin and high plasmatic ferritin. Hepatic MRI showed iron overload, which, together with the biochemical abnormalities found, was fully compatible with aceruloplasminemia. Cranial MRI showed accumulation of paramagnetic material in the *substantia nigra* and red nuclei on SWI in both, but also periventricular symmetric T2 hyperintensity with necrosis and cystic degeneration and pyramidal tract involvement and corpus callosum atrophy in

LNF89.3, who also manifested a global developmental delay since the first months of life with spastic paraparesis and dysarthria. Taking into account that neurological manifestations in aceruloplasminemia usually appear during adulthood and consist of chorea, dystonia, tremors or ataxia related to iron accumulation in the basal ganglia, thalamus and dentate nucleus, a WES study was performed and allowed identification of a homozygous variant (p.Gly868GlufsTer26) in the *CP* gene in both brothers, confirming aceruloplasminemia, but also a *NDUFS1* missense homozygous VUS variant in LNF89.3 (p.Ser701Asn), probably accounting for the neurological manifestations in this patient.

SPG-62: a 7-year-old patient with global developmental delay that progressed to mild cognitive impairment and autism spectrum disorder. At 2 ½ years, he presented a convulsive status epilepticus with respiratory depression and Todd's paralysis of the right side of the body and later seizures in the context of fever, for which he was treated with valproic acid. Beginning at 3.5 years of age, he developed progressive spastic paraparesis. He also had dysarthria and strabismus. His older brother had a delayed language acquisition. MRI showed a mild myelination delay. WES revealed a pathogenic variant in *ATP1A3* (p.Pro775Leu) in heterozygosis, which has been reported in ClinVar in several patients with neurodevelopmental disorders, as well as a hemizygous variant in *NEXMIF* (p.Pro789Leu). The clinical phenotype of the patient was compatible with these two genes[16,17].

GWMD expanded network validation

To assess whether there was greater connectivity in the GWMD expanded network than in the global network, we calculated i) the number of edges between protein pairs and ii) the average path length in the GWMD network by calculating the shortest paths between

all protein pairs. We then compared these statistics for 1000 permutations of a randomly selected set of 1530 proteins derived from the global network. Next, we calculated the Z scores to describe how far the measures of the GWMD expanded network deviate from the expected mean (μ) to finally obtain that the GWMD expanded network is significantly much more cohesive than expected by chance (P<1E-25).

Among the 1530 proteins conforming to the expanded GWMD network, there were 100 candidates that were not previously associated with diseases, providing reasonable functional candidates for further research (eTable 6). To evaluate the possible disease association of the new gene candidates, we analyzed their gene constraints, including loss-of-function intolerance (pLI) or missense variation intolerance (missense Z-score). Among the 100 new candidates, we found 26 proteins extremely loss-of-function intolerant with a pLI ≥ 0.9 (the closer pLI is to one, the more LoF-intolerant the gene appears to be. pLI ≥ 0.9 was considered extremely LoF intolerant, such as nuclear receptor binding SET domain protein 2 (*NSD2*), and 8 missense variation intolerant proteins with a Z-score ≥ 3.08 (i.e. with probability P< 0.001), such as GA binding protein transcription factor subunit alpha (*GABPA*).

eFigure Legends

eFigure 1. Inheritance pattern of the diagnosed cases and distribution of variant classification.

eFigure 2. 1p36 deletion array-CGH. Detail of the molecular karyotype showing the terminal 7.6 Mb deletion identified in the short arm of chromosome 1 in case LNF-45. arr[GRCh37] 1p36.33p36.23(757093_7686264)x1.

eTable legends

eTable 1. Clinical table. Clinical manifestations, main complementary exams and genes identified in diagnosed cases. Specific therapeutic options.

eTable 2. ACMG criteria for the classification of identified variants

eTable 3. List of identified genes, OMIM nomenclature and numbers of cases identified in our cohort.

eTable 4. Atypical cases. Patients with new phenotypes, atypical forms of presentation and blended phenotypes in families with more than one gene associated with the phenotype.

eTable 5. Cases with functionally validated variants.

eTable 6. Cases with experimentally validated CNV variants.

eTable 7. New variants. Table with the 73 novel variants indentified in our cohort.

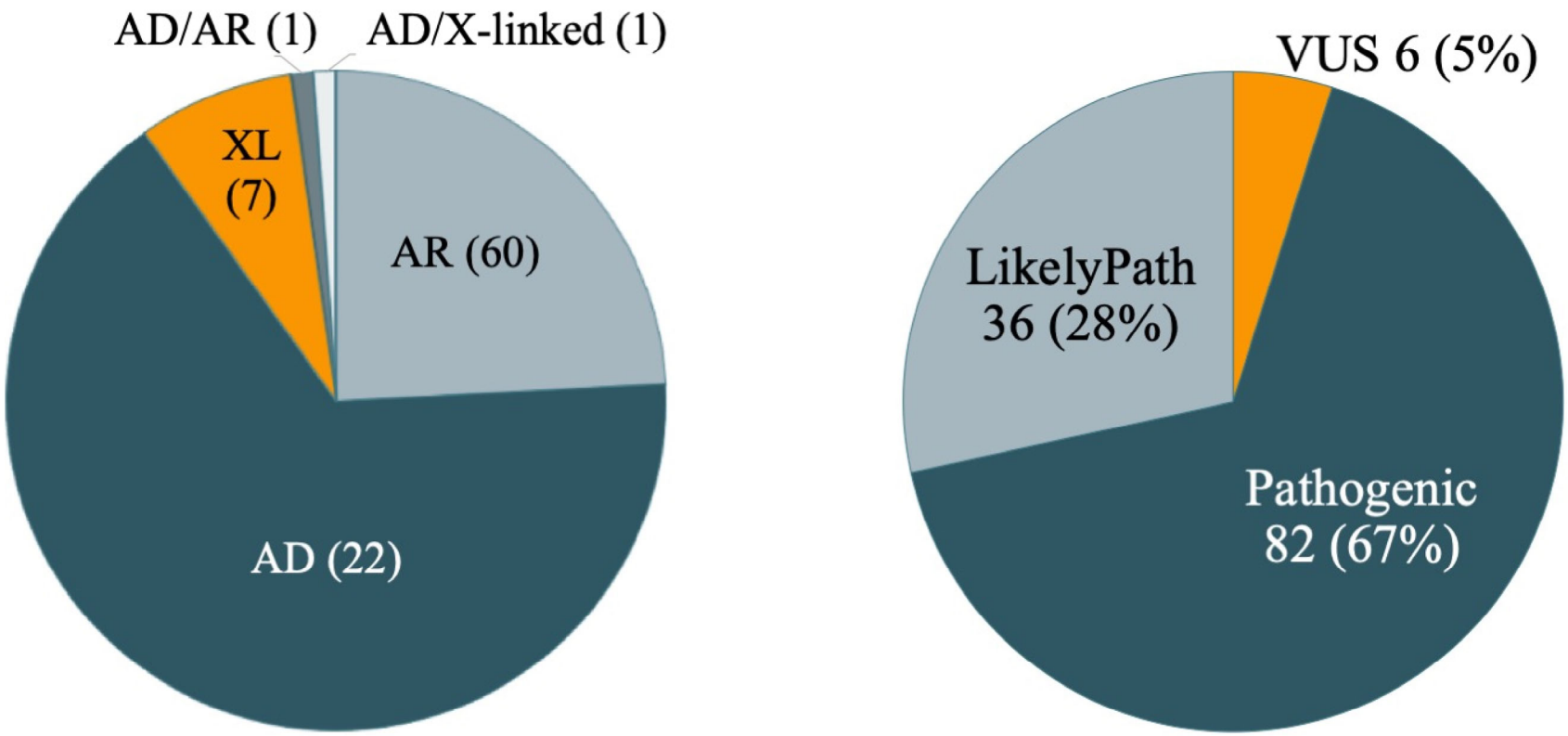
eTable 8. Enrichment of GO terms of molecular function in the GWMD network. Top 50 molecular function (MF) GO terms enriched in the GWMD network integrating proteins by using hypergeometric distribution function statistical analysis.

eTable 9. Enrichment of GO terms of biological process in the GWMD network. Top 50 biological process (BP) GO terms enriched in the GWMD network integrating proteins by using a hypergeometric distribution function statistical analysis.

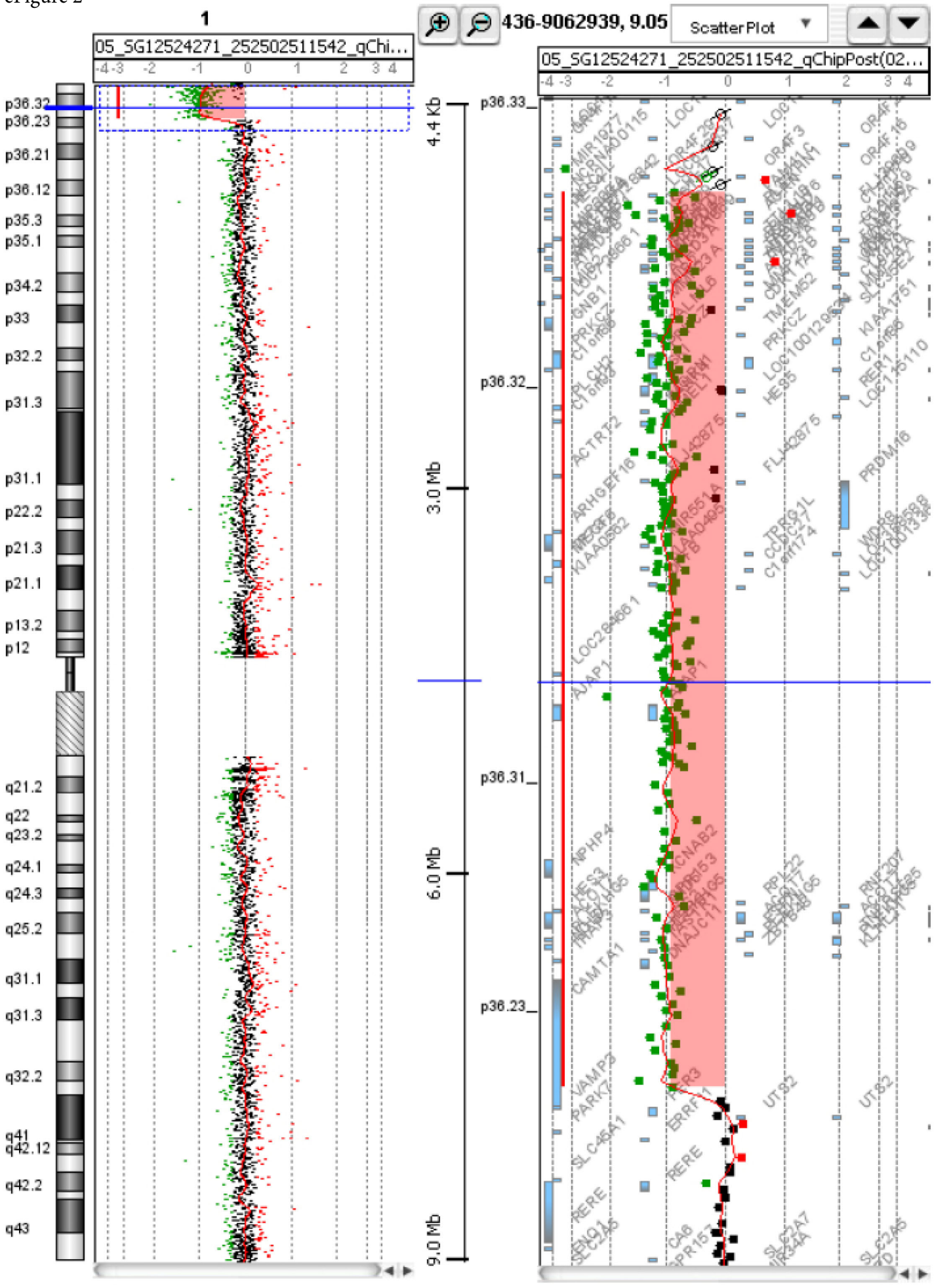
eTable 10. Enrichment of GO terms of cellular compartment in the GWMD network. Top 50 cellular compartment (CC) GO terms enriched in the GWMD network integrating proteins by using a hypergeometric distribution function statistical analysis.

eTable 11. Candidate genes in the GWMD network. One hundred candidate genes predicted by the prioritization tool to be associated with GWMD.

eFigure 1


AD/AR (1)
AD/X-linked (1)
XL
(7)
AR (60)
AD (22)
VUS 6 (5%)
LikelyPath
36 (28%)
Pathogenic
82 (67%)

eFigure 2


1
05_SG12524271_252502511542_qChi...
436-9062939, 9.05
Scatter Plot
05_SG12524271_252502511542_qChipPost(02...
p36.32
p36.23
p36.21
p36.12
p35.3
p35.1
p34.2
p33
p32.2
p31.3
p31.1
p22.2
p21.3
p21.1
p13.2
p12
q21.2
q22
q23.2
q24.1
q24.3
q25.2
q31.1
q31.3
q32.2
q41
q42.12
q42.2
q43
4.4 Kb
3.0 Mb
6.0 Mb
9.0 Mb
p36.33
p36.32
p36.31
p36.23

eTable 1

Patient ID	Sex, current age	Age at onset	Family history	Motor symptoms	Cognitive-Behavior	Ataxia	Epilepsy	Head Growth	Ophthalmologic	MRI involvement	Others / Investigation findings	Gene	Diagnostic technique	Specific therapeutic / management options
LNF-1	F, 33 y	4 y	YES (sister)	Pyramidal signs Wheelchair (19 y)	GDD / ID	YES	YES	N	Myopia magna	Hypomyelination	Dysarthria, dysmetria Hypogonadotrophic hypogonadism Dysphagia Unilateral hip dislocation, scoliosis	*POLR3A*	WES	Hypogonadism management
LNF-6	F, 40 y	27 y	YES (mother and sister)	Pyramidal and Extrapyramidal signs, weakness	N	NO	NO	Macrocephaly	N	Frontal T2 WM HI	Hypopalestesia Suprarenal insufficiency Episodic dystonic movements	*CSF1R*	WES	HSCT
LNF-15	M, 7 y	3 m	NO	Hypotonia	GDD-ID	Instability	YES, neonatal focal seizures	Macrocephaly	Nystagmus	Hypomyelination, Subarachnoid space enlargement in FT areas Thin CC	(3m) Irritability, opisthotonus Lumbosacral hemivertebrae, kyphosis, sparse hair, absent osteo-tendinous reflexes Abnormal VEPs, BAEPs	*TMEM63A*	WES (Re-analysis)	NO
LNF-16	M, 45 y	28 y	NO	Pyramidal signs	Manic depressive	NO	NO	N	Optic neuritis	Frontal T2 WM HI	Motor apraxia Language disorder	*CSF1R*	WES	HSCT
LNF-18	F, 19 y	18 m	Consanguinity	Pyramidal signs Lower limb weakness Wheelchair (3 y)	GDD-ID	NO	YES, clonic seizures	N	Nystagmus, optic nerve atrophy	Parieto-occipital, posterior arm of internal capsule, brainstem and cerebellar peduncles T2 WM HI	Irritability Demyelinating PNP Low GALC activity GALC gene sequencing: no variants identif.	*GALC*	WES	HSCT
LNF-19	F, 18 y	3 y	NO	Pyramidal signs Lower limb weakness Wheelchair (10 y)	Learning disability	YES	YES, generalized myoclonic	N	N	Diffuse T2 WM HI Cystic lesions	Tremor, dysmetria Relapses: lethargic, dizziness, headache, weakness (fever)	*EIF2B5*	WES	Avoidance of head trauma
LNF-20	F, 26 y	4 y	NO	Athetosis	GDD / ID	YES	NO	Normal	N	Hypomyelination Thin CC Cerebellar atrophy	Dysmetria, scanning speech	*POLR3B*	WES	NO
LNF-23	F, 25 y	2 y	NO	NO	GDD-ID Manic depressive psychosis	YES	NO	N	N	Hypomyelination Thalamus T2 hypointensity Enlarged ventricles CC and brainstem atrophy Thickening of the cranial diploe	Severe dysphagia Hereditary multiple exostosis Urinary incontinence	*POLR3A*	WES	NO
LNF-28	M, 23 y	<6 m	Consanguinity	Rigid-akinetic syndrome	GDD-ID	Instability	YES, epileptic encephalopathy	N	Nystagmus Strabismus Microphthalmia Congenital bilateral cataract Upgaze limitation	Hypomyelination Mild brain atrophy Thin CC	Dysmorphic traits Abn. VLCFA Abn. ERG, VEPs, BAEPs	*PEX11b*	WES	NO

LNF-29	M, 4 y	<6 m	YES (brother)	Spastic-dystonic tetraparesis	GDD LDD	NO	NO	Microcephaly	Erratic movements Nystagmus	Periventricular and subcortical temporal anterior T2 WM HI Temporal cystic lesions WM and CC atrophy MRS periventricular decrease NAA	Areflexia	*PNPT1*	WES (Re-analysis)	NO
LNF-30	F, 21 y	4 y	NO	Spastic-dystonic tetraparesis	Normal	NO	NO	N	N	Posterior T2 WM HI		*TUBB4A*	WES	NO
LNF-31	F, 27 y	17 y	NO	Spastic tetraparesis	Behavioral disorder Dysthymia	NO	YES, generalized	N	N	Periventricular, inferior colliculi, dentate nuclei and cerebellar hemispheres T2 WM HI (progressive) Cystic lesions Cervical medullar atrophy	Episode: headache, weakness in the right limbs and urinary incontinence	*EIF2B5*	WES	Avoidance of head trauma
LNF-32	F, 3 y	10 m	NO	Spastic-dystonic tetraparesis	GDD-ID	NO	NO	N	N	Hypomyelination White matter atrophy. Colpocephaly	Startle response. Irritability Dysarthria CSF neopterin increase Abn. SSEP, VEPs	*RNASEH2B*	WES	JAK1 and JAK2 inhibitors Monitoring of immuno-mediated manifestations
LNF-33	M, 14 y	2 y	Consanguinity	Spastic-dystonic tetraparesis Orofacial and arms dystonia	Language regression	YES	NO	N	N	Periventricular T2 WM HI, with cerebellar, CC and posterior medullar involvement		*DARS2*	WES (Re-analysis)	NO
LNF-34	M, 50 y	30 y	NO	Spastic paraparesis	N	YES	NO	N	N	Diffuse T2 WM HI Cerebellar and medulla atrophy	Urinary incontinence	*LMNB1*	WES	NO
LNF-36	M, 5 y	< 12 m	NO	Hypotonia	GDD-ID	YES	NO	N	N	Hypomyelination T2 HI pyramid bulbs Cortico-subcortical atrophy. Thin CC	Dysmorphic traits Adrenal insufficiency Hepatomegaly Abn. VLCFA Demyelinating PNP Abn. BAEPs	*PEX6*	WES	NO
LNF-37	F, 32 y	26 y	NO	Pyramidal signs Dystonia Lower limb paresthesia	N	Instability	NO	N	N	Periventricular, cerebellar peduncles and protuberance T2 WM HI Cerebral and medullar atrophy Thin CC	Precocious menopause Abn. SSEP, VEPs	*EIF2B5*	WES	POF treatment Avoidance of head trauma
LNF-40.0 and 40.3	M, 10 y	10 m	Consanguinity YES (affected sister and brother)	Spastic-dystonic tetraparesis	GDD-ID	NO	YES	N	Nystagmus	Periventricular WM HI WM, CC and BS atrophy	Dysphagia, Dysarthria	*CYP2U1*	WES	NO

LNF-40.4 (brother)	M, 16 y	< 1 m	Consanguinity YES (affected sister and brother)	Spasticity	GDD-ID	YES	NO	N	N	Hypomyelination Short CC	Increased pl Phe	*PAH*	WES	Dietary treatment
LNF-41	F, 1.5 y (exitus)	NN	Consanguinity	Spastic tetraparesis	GDD	NO	NO	IHG	Nystagmus	Hypomyelination Mild ventriculomegaly	Pondo-statural delay Sucking-swallowing difficulties NN myoclonus Demyelinating PNP Abn. SSEP; VEPs, BAEPs	*DEGS1*	WES	Fingolimod (under investigation)
LNF-42	F, 5 y	NN	NO	Spastic tetraparesis	GDD / ID	NO	YES	Microcephaly / IHG	Congenital nystagmus Oculogyric crisis	Hypomyelination CC, BG and cerebellar atrophy Lactate peak (MRS)	Hypodontia Articular contractures Cachexia	*DEGS1*	WES	Fingolimod (under investigation)
LNF-43	M, 12 y	6 y	NO	Spastic paraparesis	N	NO	NO	Normal	Normal	Diffuse T2 WM HI		*EIF2B5*	WES	Avoidance of head trauma
LNF-45	F, 5 y	<1 m	NO	Pyramidal signs	GDD	NO	YES NN clonic and myoclonic Pharmacoresistant epilepsy	N	Nystagmus	Periventricular WM HI Supratentorial cerebral atrophy. Thin CC Persistent *cavum septum interpositum* and *cavum vergae* MRS mild increase NAA, Cho	Dysmorphic traits Dehydration episodes Anemia, thrombocytopenia Abn. BAEPs	1p36 del	WES	NO
LNF-47	M, 4 y	6 m	NO	Pyramidal and Extrapyramidal	GDD / ID	YES	NO	Normal	Normal	Subcortical T2 WM HI as well as in centrum semiovale, corona radiata, optic radiation and also in dentate nuclei and superior and inferior cerebellar peduncles Striatal necrosis	Increased motochondria in muscle biopsy Decreased activity of complex I, II, III	*POLR3A*	WES (Re-analysis)	NO
LNF-48.0	M, 9 y	6 m	YES (brother affected)	Pyramidal signs	GDD	YES	NO	N	Erratic movements	Periventricular, dentate nuclei WM HI Cortico-subcortical atrophy with anterior predominance Thin CC	Stereotypies Abnormal SSEP Abnormal VEPs	*PARS2*	WES	NO
LNF-51	M, 3 y	6 m	NO	Spastic paraparesis	GDD Irritability	NO	NO	N	N	Multifocal, parietal T2 WM HI Cystic lesions Restricted diffusion T-O	Hyperlactatemia	*NDUFS1*	WES	NO
LNF-56	F, 16 y	11 m	NO	NO	GDD Behaviour disorder	YES	YES	N	Nystagmus Strabismus	Periventricular T2 WM HI	Hepatic steatosis Obesity Amenorrhea Hypertrichosis	*POLR3A* *CACNA1A*	WES	Hypogonadism management Acetazolamide (CACNA1A)

LNF-57	M, 7 y	5 y	NO	NO	N	NO	YES Generalized	N	N	Periventricular WM HI, anterior predominance		*GFAP*	WES	NO
LNF-66	F, 1 y	5 m	NO	Hypotonia Dyskinetic movements	GDD	NO	YES	Microcephaly	No visual tracking	Bilateral capsule-thalamic focal T2 HI Delayed myelination Mild CC atrophy (5m) Restricted diffusion posterior limb of IC and optic radiations (7m)	Plagiocephaly Low pl uric acid and homocysteine Abn. VEPs Normal cardiologic study	*ITPA*	WES	NO
LNF-69	M, 3 y	4 m	Consanguinity	Spastic tetraparesis	GDD	NO	NO	N	Nystagmus	Hypomyelination Bilateral hippocampus atrophy	Opisthotonus Pondo-statural delay Gastroesophageal reflux Demyelinating PNP	RNASEH2B	WES	JAK1 and JAK2 inhibitors Monitoring of immuno-mediated manifestations
LNF-70	F, 41 y	38 y	NO	Pyramidal signs	Cognitive decline Behaviour disorder	NO	NO	N	N	Frontal T2 WM HI		CSF1R	WES	HSCT
LNF-71	M, 6 y	1 y	Consanguinity NO	Motor clumsiness	ID	YES	NO	N		Periventricular T2 WM HI. Involvement of U fibers in frontal areas Mega cisterna magna	Tremor Normal metabolic study (plasma, urine, CSF) OXPHOS (ms) normal	*EIF2B5* *GFM1*	WES (Re-analysis)	Avoidance of head trauma
LNF-72	F, 3 y	4 m	NO	Pyramidal and Extrapyramidal	GDD	NO	NO	Microcephaly	Hypermetropia, strabismus	Periventricular T2 WM HI	Hip dysplasia CSF increased lactate OXPHOS N (muscle)	*MSTO1*	WES (Re-analysis)	NO
LNF-76	F, 3 y	4 m	Consanguinity YES (sister)	Pyramidal and Extrapyramidal	GDD / ID	NO	YES	Microcephaly / Insufficient head growth	Erratic movements	Diffuse T2 WM HI Thin CC	Startle response Irritability Pondo-statural delay	*TREX1*	WES (Re-analysis)	JAK1 and JAK2 inhibitors Monitoring of immuno-mediated manifestations
LNF-77	M, 21 y	3 y	NO	Spastic-dystonic tetraparesis Motor apraxia	ID	YES	NO	N	Upgaze limitation Slow saccades Hypermetropia	Hypomyelination	Dysmetria, tremor Abn. BAEPs, VEPs Ms biopsy: subsarcolemmal normal mitochondria	*POLR1C*	WES	NO
LNF-80	F, 5 y	4 m	NO	Spastic tetraparesis	GDD, ID	NO	NO	Microcephaly	N	Diffuse T2 WM HI, anterior predominance White matter atrophy Thin CC	Pondo-statural delay 25 leucocytes in CSF (MN predominance)	*RNASEH2B*	WES	JAK1 and JAK2 inhibitors Monitoring of immuno-mediated manifestations

LNF-81	M, 5 y	<6 m	NO	Hypotonia Choreoathetosis. Dystonia	GDD LDD	YES	YES Refractory epilepsy (3y). Reflex palpebral myoclonus	Microcephaly	Nystagmus	Hypomyelination Anterior cortical atrophy CC atrophy	Pondo-statural delay Feeding difficulties GI dysmotility OXPHOS (ms): complex II deficiency	*PYCR2*	WES	NO
LNF-83	M, 1.6 y	4 m	NO	Spastic-dystonic tetraparesis	GDD	NO	NO	IHG	Strabismus	Hypomyelination Thin CC		*SLC16A2*	WES	NO
LNF-84	M, 74 y	72 y	Consanguinity	Pyramidal signs	Cognitive decline	NO	NO	N	Bilateral lens subluxation (73 y)	Periventricular T2 WM HI	Increased urine methylmalonic acid Dysphagia Osteopenia	*MMUT* *DSTYK*	WES	Dietary treatment
LNF-85	F, 61 y	48 y	NO	Pyramidal signs	Cognitive decline	Instability	NO	N	N	Periventricular T2 WM HI Cerebral and cerebellar atrophy	Neurogenic bladder Normal CSF Aβ42, T-tau, and P-tau	*PSEN1*	WES	NO
LNF-86	F, 30 y	2 y	NO	Pyramidal and Extrapyramidal	N	YES	NO	Normal	Normal	Periventricular Cerebellar WM involvement Brainstem involvement	Dysarthria, tremor	*DARS2*	WGS	NO
LNF-87	M, 7 y	3 m	NO	Spasticity	ID	NO	YES	Macrocephaly	Nystagmus ON atrophy	Hypomyelination Diffuse cerebral atrophy	Dysplastic toenails Delayed dentition. Drooling Abn. BAEPs, VEPs Elevated urine glutamine	*TMEM63A*	WES (Re-analysis)	NO
LNF-88	F, 12 y	6 m	Consanguinity YES (sister)	Pyramidal Proximal weakness	GDD / ID	NO	NO	Normal	Normal	Periventricular T2 WM HI	EMG myopathic Abnormal SSEP Abnormal BAEPs Ms biopsy: multilamellar bodies	*GFPT1*	WES	Pyridostigmine
LNF-89.3	M, 16 y	<1 m	Consanguinity YES (brother)	Spastic paraparesis	GDD-ID LDD Memory problems	YES	NO	Microcephaly	N	Periventricular T2 WM HI SWI: pallidal and dentate nuclei hypointensity CC atrophy	Microcytic and hypochromic anemia. Low Cu pl, low Cu u, low ceruloplasmin. Low IST and High ferritin. Hepatic MRI: iron overload. Normal echocardiogram	*CP* *NDUFS1*	WES	Iron chelating treatment
LNF-90	M, 10 m	6 m	Consanguinity	Spastic-dystonic tetraparesis Hypokinesia	GDD	NO	NO	IHG	Poor eye contact Upgaze episodes	Hypomyelination Thin CC	Hypomimia 10m: somnolence episode with fever Frequent febrile episodes	*RNASEH2B*	WES	JAK1 and JAK2 inhibitors Monitoring of immuno-mediated manifestations
LNF-91	M, 4 y	1 y	NO	Hypotonia	N	YES	NO	Normal	Normal	Hypomyelination	Dysmetria Delayed dentition	*POLR3B*	WGS	NO
LNF-92	F, 9 y	1 y	NO	Hypotonia Motor clumsiness	LDD	NO	NO	N	Limited extraocular movements	Subcortical bifrontal and periatrial WM lesions Superior vermis atrophy	Dysmorphic traits	*USP7*	WES (Re-analysis)	NO
LNF-93	M, 2 y	<6 m	NO	N	N	NO	NO	Progressive macrocephaly	N	Diffuse T2 WM HI. Temporal cysts		*MLC1*	WGS	NO
LNF-94	M, 4 y	3 m	NO	Spastic-dystonic tetraparesis	GDD	NO	NO	N	N	Hypomyelination MRS: diminished NAA. Mild increase choline	Drooling Dysarthria	*PLP1*	WES	NO

LNF-95	M, 9 y	11 m	NO	Spastic-dystonic tetraparesis	GDD-ID LDD	NO	YES Absences, clonic	N	N	(11m) Fronto-temporal T2 WM HI, anterior predominance (6y) Improvement	OXPHOS (ms): complex II and III deficiency	*RNASEH2B*	WES	JAK1 and JAK2 inhibitors Monitoring of immuno-mediated manifestations
LNF-96	M, 12 y	6 m	NO	Hypotonia	GDD / ID Behavior (ASD)	NO	YES	Normal	Normal	Periventricular T2 WM HI	Prematurity (34w). IUGR (birthweight 1350g), Thrombopenia. Dysmorphic traits: prominent ears Inguinal and umbilical hernias Acute encephalopathy with hemiparesis, VI and VII nerve paresis (7yo)	*SON*	WES (Re-analysis)	NO
LNF-97	F, 4 y	6 m	NO	Pyramidal and Extrapyramidal	GDD / ID	NO	NO	Normal	Strabismus	Periventricular T2 WM HI	Hypothyroidism Episodic hypotonia, hemiparesis and drooling. Dystonic postures Upper limb myoclonus Absences	*TANGO2*	WES	NO
LNF-104	F, 46 y	22 y	NO	Pyramidal signs	Cognitive decline	NO	YES	Normal	Normal	Periventricular T2 WM HI	Urinary incontinence Relapses	*EIF2B5*	WES	Avoidance of head trauma
LNF-105	M, 11 y	6 m	NO	Spastic tetraparesis	GDD-ID	YES	YES Focal seizures (4y)	Microcephaly	Nystagmus Strabismus	Periventricular T2 WM HI Cystic lesions Cerebellar atrophy	Dysmetria, intentional tremor Hypogonadism. Micropenis Overweight Cryptorchidism. Posterior uretral valves Increased lactate	*HNRNPH1*	WES	NO
LNF-106	M, 7 y	1 y	YES (brother)	Pyramidal	GDD / ID	NO	NO	Normal	Normal	Hypomyelination	Peripheral neuropathy	*PLP1*	WES	NO
LNF-107	F, 3 y	NN	NO	Pyramidal and Extrapyramidal	GDD	NO	YES	Normal	Normal	Hypomyelination CC hypoplasia Pontocerebellar hypoplasia		*PI4KA*	WES	NO
LNF-109	F, 5 y	1 y	NO	NO	Psychiatric / ASD	NO	NO	Macrocephaly	Normal	Periventricular T2 WM HI		*PTEN*	WES	NO
LNF-110	M, 9 y	6 m	NO	Pyramidal signs	GDD / ID	YES	YES	Normal	Strabismus	Hypomyelination	Scanning speech Dysphagia Drooling	*PLP1*	WES	NO
LNF-112	F, 13 y	4 m	NO	Pyramidal signs	GDD / ID	NO	NO	Normal	Congenital nystagmus Strabismus	Hypomyelination	Bilateral hip subluxation Scoliosis Abnormal SSEP Abnormal BAEPs	*GJC2*	WES	NO
LNF-114	M, 1.3 y	< 1 m	NO	Hypotonia	GDD / ID	NO	YES	Normal	NN abnormal ocular movements	Hypomyelination Thin CC	Dysmorphic traits: long face, prominent forehead, low-set and dysmorphic ears Inguinal and umbilical hernias Bone dysplasia, arthrogryposis Adducted thumbs Hyperekplexia-like episodes OXPHOS (fibroblasts): hyperactivity in all complexes and citrate synthase, indicating mitochondrial proliferation. Referred to citrate synthase, it suggests mild complex II deficiency.	*SCN8A*	WES	NO

LNF-115	F, 10 y	4 m	Consanguinity	Pyramidal signs	GDD / ID Behavior	NO	YES	Microcephaly	Normal	Hypomyelination Thin CC	Dysmorphic traits: epicanthus, upturned nose, thin upper lip, low-set ears. SNHL. Axonal polyneuropathy.	*SPATA5*	WES	NO
LNF-116	M, 4 y	<6 m	YES (uncle)	Spastic tetraparesis	GDD	NO	NO	N	Nystagmus	Hypomyelination	Dysarthria Abnormal VEPs	*PLP1*	WES	NO
LNF-118	M, 35 y	12 m	NO	Pyramidal and Extrapyramidal	GDD / ID	YES	NO	Normal	Ophtalmoparesis Slow saccades Vertical gaze difficulties	Hypomyelination BG hypointensity	Scanned speech, dysdiadochokinesia Hypogonadism. Obesity	*POLR3A*	WES	Hypogonadism management
LNF-120	F, 12 y	12 m	NO	Pyramidal	Normal	NO	NO	Normal	Normal	Periventricular T2 WM HI	Abnormal SSEP	*RNASEH2B*	WES	JAK1 and JAK2 inhibitors Monitoring of immuno-mediated manifestations
LNF-121	M, 5 y	4 m	NO	Pyramidal and Extrapyramidal	GDD / ID	NO	NO	Normal	Nystagmus	Periventricular T2 WM HI Cerebellar atrophy	Contractures	*SEPSECS*	WES	NO
LNF-126	M, 3 y	NN	NO	Pyramidal and Extrapyramidal	GDD / ID	NO	YES	Microcephaly	N	Periventricular T2 WM HI Thin CC Cervical spinal cord T2 HI	EEG: multifocal paroxysmal activity	*HECW2*	WGS	NO
LNF-128	M, 10 m	4 m	NO	NO	GDD	NO	YES	N	N	Periventricular T2 WM HI, frontal predominance Cystic lesions Putaminal and caudate involvement		*GFAP*	WES	NO
LNF-130	M, 2 y	2 y	NO	Spastic-dystonic tetraparesis	GDD	NO	NO	N	Nystagmus	Diffuse T2 WM HI Thin CC		*PLP1*	WES	NO
VH-1	M, 8 y	10 m	YES (mother, grandfather)	Pyramidal signs	GDD-ID	NO	YES Focal seizures	Macrocephaly	Nystagmus	T2 WM HI, frontal subcortical predominance Cystic lesions Anterior CC involvement 8yo: brainstem and cerebellar involvement	Neuroblastoma Def alpha1 AT	*GFAP*	WES	NO
VH-2	M, 5 y	4 m	NO	Pyramidal signs	N	YES	NO	N	Nystagmus	Hypomyelination Mild cerebellar atrophy	Dysarthria, dysmetria IUGR Abn. BAEPs, VEPs	*GJC2*	WES	NO
VH-3	M, 14 m	NN	NO	Hypotonia	GDD	NO	YES	Microcephaly / Insufficient head growth	Nystagmus	Hypomyelination Thin CC	Axonal sensory neuropathy, startle, low weight, recurrent infections, AA neutropenia, NN anemia, cryptorchidism	*PI4KA*	WES	NO
SPG-2	M, 71 y	40 y	YES (brother)	Spastic paraparesis	N	NO	NO	N	N	Periventricular T2 WM HI Cerebral atrophy	Dysarthria	*CAPN1*	WES	NO

SPG-14	M, 45 y	15 y	YES (sister)	Pyramidal	Normal	YES	NO	Normal	Normal	Periventricular T2 WM HI		*POLR3A*	WES (Re-analysis)	NO
SPG-20	F, 36 y	28 y	NO	Spastic paraparesis	N	NO	NO	N	N	Periventricular T2 WM HI	Congenital hip luxation Psoriasis	*SPG11*	WES	NO
SPG-21	M, 51 y	39 y	NO	Pyramidal	GDD / ID	YES	NO	Normal	Abnormal extraocular mov. Ptosis	Frontal T2 WM HI	Dysarthria	*SPG7*	WGS	NO
SPG-24	M, 18 y	18 y	NO	Spastic paraparesis	ID	NO	NO	N	N	Periventricular T2 WM HI	ADHD	*SPG11*	WES	NO
SPG-25	M, 42 y	18 y	YES (mother, grandmother)	N	N	YES	NO	N	Nystagmus	Diffuse T2 WM HI	Demyelinating polyneuropathy Pes cavus	*SOX10*	WES	NO
SPG-40	F, 25 y	15 y	NO	Spastic paraparesis Distal weakness	N	NO	NO	N	N	Periventricular T2 WM HI	Peripheral neuropathy	*SPG11*	WES	NO
SPG-48	M, 21 y	2 y	NO	Spasticity	GDD Attention disorder	NO	NO	N	N	Periatrial T2 WM HI Mild atrophy Thin CC	Abn. VEPs	*SPG11*	WES	NO
SPG-61	F, 6 y	2 y	Consanguinity	Spastic tetraparesis	GDD-ID	NO	NO	Microcephaly	Strabismus Disc pallor	Periventricular T2 WM hyperintensities Thin CC	Scoliosis Enuresis	*DDHD2*	WES	NO
SPG-62	M, 4 y	1 y	NO	Spastic paraparesis	ID ASD	NO	YES Focal status (2.5 y)	N	N	Periventricular T2 WM HI	ASD. Short attention span Dysarthria	*ATP1A3* *NEXMIF*	WES	NO
SPG-69	F, 13 y	1 y	Consanguinity	Spastic paraparesis	N	NO	NO	N	N	Periventricular T2 WM HI, posterior		*ACER3*	WES (Re-analysis)	NO
SPG-72	F, 21 y	18 y	YES (brother)	Spastic paraparesis	N	YES	NO	N	N	Periventricular T2 WM HI, posterior predominance	Dysmetria, dysdiadochokinesia Sensory-motor polyneuropathy	*GALC*	WES	HSCT
SPG-73	M, 18 y	2 y	NO	Pyramidal	Language disorder	NO	NO	Normal	Congenital nystagmus	Periventricular T2 WM HI		*SPAST*	WES	NO
SPG-106	M, 3 y	4 m	NO	Spastic-dystonic tetraparesis	GDD	NO	NO	Microcephaly	N	Hypomyelination Thin CC Cerebral atrophy	IUGR (3rd trimester) Swallowing difficulties. Chocking Pondostatural delay Increased T3	*SLC16A2*	WES	NO
CPR	F, 4 y	12 m	NO	Pyramidal and Extrapyramidal	GDD / ID	YES	NO	Normal	Normal	Hypomyelination		*TUBB4A*	WES	NO
GLA	M, 2m	NN	NO	Hypotonia	GDD	NO	YES			Hypomyelination Abnormal gyration pattern Colpocephaly	Abnormal wide anterior fontanel Glomerulocystic kidney disease, bilateral pelvic ectasia Liver insufficiency, cholestasis Perimembranous VSD Hypertransaminasemia, hyperammonemia, hyperbilirubinemia Abnormal VLCFA, diminished plasmalogens	*PEX2*	WES	NO
LMSR	F, 24 y	23 y	YES (father)	Pyramidal	Cognitive decline	NO	NO	Normal	Normal	Frontal		*CSF1R*	WES	HSCT

Abn- abnormal; ASD-autism spectrum disorder; BAEPs-brainstem auditory evoked potentials; CC-corpus callosum; CSF-cerebrospinal fluid; F-female; FS-febrile seizures; GDD-global developmental delay; HI-hyperintensity; ID-intellectual disability; IHG-insufficient head growth; IS-infantile spasms; LDD-language developmental delay; M-male; N-normal; NN-neonatal; ON-optic nerve; OXPHOS-oxidative phosphorylation; SSEP-somatosensory evoked potentials; VEPs-visual evoked potentials; VSD-ventricular septal defect; WM-white matter

cR_`jc 0

ID	Gene	Inheritance	Chr	Start base (VCF)	Ref	Alt	Type	Nomenclature	PVS1	PS2	PS3	PM1	PM2	PM3	PM4	PM5	PM6	PP1	PP2	PP3	PP4	PP5	CLASSIF.
LNF-1	*POLR3A*	Compound Heterozygous	10	79760778	C	T	nonsynonymous SNV	POLR3A:NM_007055.3:c.2434G>A:NP_008986.2:p.(Gly812Ser)	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	VUS
LNF-1	*POLR3A*	Compound Heterozygous	10	79767546	A	G	nonsynonymous SNV	POLR3A:NM_007055.3:c.1988T>C:NP_008986.2:p.(Ile663Thr)	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	VUS
LNF-6	*CSF1R*	Heterozygous	5	149441340	T	C	nonsynonymous SNV	CSF1R:NM_001288705.2:c.1699A>G:NP_001275634.1:p.(Thr567Ala)	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-15	*TMEM63A*	Heterozygous	1	226041470	C	T	nonsynonymous SNV	TMEM63A:NM_014698.2:c.1657G>A:NP_055513.2:p.(Gly553Ser)	NO	YES	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-16	*CSF1R*	Heterozygous	5	149441339	G	A	nonsynonymous SNV	CSF1R:NM_001288705.2:c.1700C>T:NP_001275634.1:p.(Thr567Met)	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-18	*GALC*	Homozygous	14	88450739	C	G	nonsynonymous SNV	GALC:NM_000153.3:c.581G>C:NP_000144.2:p.(Gly194Ala)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-19	*EIF2B5*	Compound Heterozygous	3	183854522	A	T	nonsynonymous SNV	EIF2B5:NM_003907.2:c.318A>T:NP_003898.2:p.(Leu106Phe)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-19	*EIF2B5*	Compound Heterozygous	3	183855425	G	A	nonsynonymous SNV	EIF2B5:NM_003907.2:c.338G>A:NP_003898.2:p.(Arg113His)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	YES	PATHOGENIC
LNF-20	*POLR3B*	Homozygous	12	106895121	T	C	nonsynonymous SNV	POLR3B:NM_018082.5:c.3005T>C:NP_060552.4:p.(Ile1002Thr)	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES	NO	Likely Pathogenic
LNF-23	*POLR3A*	Compound Heterozygous	10	79741983	C	T	nonsynonymous SNV	POLR3A:NM_007055.3:c.3688G>A:NP_008986.2:p.(Asp1230Asn)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	Likely Pathogenic
LNF-23	*POLR3A*	Compound Heterozygous	10	79778956	G	A	nonsynonymous SNV	POLR3A:NM_007055.3:c.1253C>T:NP_008986.2:p.(Ala418Val)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-28	*PEX11B*	Homozygous	1	145518171	CA	C	frameshift deletion	PEX11B:NM_001184795.1:c.233del:NP_001171724.1:p.(Asn78IlefsTer42)	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	PATHOGENIC
LNF-29	*PNPT1*	Homozygous	2	55874565	C	A	nonsynonymous SNV	PNPT1:NM_033109.3:c.1519G>T:NP_149100.2:p.(Ala507Ser)	NO	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-30	*TUBB4A*	Heterozygous	19	6495765	C	T	nonsynonymous SNV	TUBB4A:NM_006087.2:c.745G>A:NP_006078.2:p.(Asp249Asn)	NO	NO	YES	YES	YES	NO	NO	NO	YES	NO	YES	YES	YES	YES	PATHOGENIC
LNF-31	*EIF2B5*	Compound Heterozygous	3	183858258	G	A	nonsynonymous SNV	EIF2B5:NM_003907.2:c.896G>A:NP_003898.2:p.(Arg299His)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-31	*EIF2B5*	Compound Heterozygous	3	183855425	G	A	nonsynonymous SNV	EIF2B5:NM_003907.2:c.338G>A:NP_003898.2:p.(Arg113His)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	YES	PATHOGENIC
LNF-32	*RNASEH2B*	Compound Heterozygous	13	51519581	G	A	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.529G>A:NP_001135751.1:p.(Ala177Thr)	NO	NO	YES	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-32	*RNASEH2B*	Compound Heterozygous	13	51517465	G	T	stopgain	RNASEH2B:NM_001142279.2:c.445G>T:NP_001135751.1:p.(Glu149Ter)	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-33	*DARS2*	Homozygous	1	173797454	C	G	splicing	DARS2:NM_018122.5:c.228-17C>G	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	Likely Pathogenic
LNF-34	*LMNB1*	Heterozygous	5	126112000			duplication	5q23.2(126112000-126172800)x3	NO	NO	NO	NO	YES	NO	NO	NO	YES	NO	NO	NO	YES	YES	PATHOGENIC
LNF-36	*PEX6*	Compound Heterozygous in ci	6	42931627	GTTTA	G	3'UTR	PEX6:NM_000287.3:c.*442_*445del	NO	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	PATHOGENIC
LNF-36	*PEX6*	Compound Heterozygous in ci	6	42933000	G	A	nonsynonymous SNV	PEX6:NM_000287.3:c.2578C>T:NP_000278.3:p.(Arg860Trp)	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-37	*EIF2B5*	Compound Heterozygous	3	183855994	A	G	nonsynonymous SNV	EIF2B5:NM_003907.2:c.725A>G:NP_003898.2:p.(Tyr242Cys)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-37	*EIF2B5*	Compound Heterozygous	3	183858531	G	A	splicing	EIF2B5:NM_003907.2:c.1156+13G>A	YES	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-40.0 & LNF-40.3	*CYP2U1*	Homozygous	4	108866168	G	C	nonsynonymous SNV	CYP2U1:NM_183075.2:c.533G>C:NP_898898.1:p.(Arg178Thr)	NO	NO	NO	NO	YES	NO	NO	NO	NO	YES	YES	YES	YES	NO	Likely Pathogenic
LNF-40.4	*PAH*	Homozygous	12	103237484	G	A	nonsynonymous SNV	PAH:NM_000277.2:c.1139C>T:NP_000268.1:p.(Thr380Met)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-41	*DEGS1*	Homozygous	1	224377798	AT	A	frameshift deletion	DEGS1:NM_003676.3:c.604del:NP_003667.1:p.(Tyr202ThrfsTer8)	YES	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	PATHOGENIC
LNF-42	*DEGS1*	Compound Heterozygous	1	224377714	G	C	nonsynonymous SNV	DEGS1:NM_003676.3:c.518G>C:NP_003667.1:p.(Arg173Pro)	NO	NO	YES	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-42	*DEGS1*	Compound Heterozygous	1	224377794	A	AT	frameshift insertion	DEGS1:NM_003676.3:c.601dup:NP_003667.1:p.(Tyr201LeufsTer7)	YES	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	PATHOGENIC
LNF-43	*EIF2B5*	Compound Heterozygous	3	183854522	A	T	nonsynonymous SNV	EIF2B5:NM_003907.2:c.318A>T:NP_003898.2:p.(Leu106Phe)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-43	*EIF2B5*	Compound Heterozygous	3	183855425	G	A	nonsynonymous SNV	EIF2B5:NM_003907.2:c.338G>A:NP_003898.2:p.(Arg113His)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-45	1p36	Heterozygous	1	757093			deletion	1p36.33p36.23(757093_7686264)x1	YES	NO	NO	NO	YES	NO	NO	NO	YES	NO	NO	NO	YES	YES	PATHOGENIC
LNF-47	*POLR3A*	Compound Heterozygous	10	79769440	G	C	splicing	POLR3A:NM_007055.3:c.1771-7C>G	NO	NO	YES	NO	YES	NO	YES	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-47	*POLR3A*	Compound Heterozygous	10	79743720	G	T	Exonic Splicing	POLR3A:NM_007055.3:c.3387C>A:NP_008986.2:p.(Leu1129=)	NO	NO	YES	YES	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-48	*PARS2*	Compound Heterozygous	1	55224279	T	C	nonsynonymous SNV	PARS2:NM_152268.3:c.556A>G:NP_689481.2:p.(Arg186Gly)	NO	NO	NO	YES	YES	NO	NO	NO	NO	YES	YES	YES	NO	NO	Likely Pathogenic
LNF-48	*PARS2*	Compound Heterozygous	1	55224275	T	C	nonsynonymous SNV	PARS2:NM_152268.3:c.560A>G:NP_689481.2:p.(Lys187Arg)	NO	NO	NO	YES	YES	NO	NO	NO	NO	YES	YES	YES	NO	NO	Likely Pathogenic
LNF-51	*NDUFS1*	Homozygous	2	207009733	T	C	nonsynonymous SNV	NDUFS1:NM_005006.6:c.755A>G:NP_004997.4:p.(Asp252Gly)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-56	*POLR3A*	Compound Heterozygous	10	79764550	C	T	nonsynonymous SNV	POLR3A:NM_007055.3:c.2171G>A:NP_008986.2:p.(Cys724Tyr)	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-56	*POLR3A*	Compound Heterozygous	10	79764608	G	C	nonsynonymous SNV	POLR3A:NM_007055.3:c.2113C>G:NP_008986.2:p.(Pro705Ala)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-56	*CACNA1A*	Heterozygous	19	13423516	G	GT	stopgain	CACNA1A:NM_001127221.1:c.1637dup:NP_001120693.1:p.(Tyr546Ter)	YES	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	PATHOGENIC
LNF-57	*GFAP*	Heterozygous	17	42992614	C	T	nonsynonymous SNV	GFAP:NM_002055.4:c.241G>A:NP_002046.1:p.(Ala81Thr)	NO	YES	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-66	*ITPA*	Compound Heterozygous	20	3199198	T	TCAGC	frameshift insertion	ITPA:NM_033453.3:c.333_336dup:NP_258412.1:p.(Tyr113SerfsTer47)	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	PATHOGENIC
LNF-66	*ITPA*	Compound Heterozygous	20	3199224	A	ACTCAGCA	frameshift insertion	ITPA:NM_033453.3:c.359_366dup:NP_258412.1:p.(Gly123SerfsTer104)	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	YES	PATHOGENIC
LNF-69	*RNASEH2B*	Compound Heterozygous	13	51517505	A	C	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.485A>C:NP_001135751.1:p.(Lys162Thr)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-69	*RNASEH2B*	Compound Heterozygous	13	51519581	G	A	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.529G>A:NP_001135751.1:p.(Ala177Thr)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-70	*CSF1R*	Heterozygous	5	149435607	A	G	nonsynonymous SNV	CSF1R:NM_001288705.2:c.2536T>C:NP_001275634.1:p.(Trp846Arg)	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-71	*EIF2B5*	Homozygous	3	183855425	G	A	nonsynonymous SNV	EIF2B5:NM_003907.2:c.338G>A:NP_003898.2:p.(Arg113His)	NO	NO	YES	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	PATHOGENIC
LNF-71	*GFM1*	Homozygous	3	158408053	C	T	nonsynonymous SNV	GFM1:NM_024996.5:c.2011C>T:NP_079272.4:p.(Arg671Cys)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	YES	PATHOGENIC
LNF-72	*MSTO1*	Compound Heterozygous	1	155583446	A	G	splicing	MSTO1:NM_001256532.1:c.1389-2A>G	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-72	*MSTO1*	Compound Heterozygous	1	155581130	G	A	splicing	MSTO1:NM_001256532.1:c.366+48G>A	NO	NO	YES	NO	YES	YES	YES	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-76	*TREX1*	Homozygous	3	48508912	GCTGCTGGCC CCACTGGGT	G	nonframeshift deletion	TREX1:NM_016381.5:c.1033_1050del:NP_057465.1:p.(Pro345_Ala350del)	NO	NO	NO	YES	YES	NO	YES	NO	NO	YES	NO	NO	YES	YES	PATHOGENIC
LNF-77	*POLR1C*	Compound Heterozygous	6	43487122	A	G	nonsynonymous SNV	POLR1C:NM_203290.3:c.193A>G:NP_976035.1:p.(Met65Val)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-77	*POLR1C*	Compound Heterozygous	6	43488700	G	A	nonsynonymous SNV	POLR1C:NM_203290.3:c.836G>A:NP_976035.1:p.(Arg279Gln)	NO	NO	YES	NO	YES	NO	NO	YES	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-80	*RNASEH2B*	Compound Heterozygous	13	51517496	G	T	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.476G>T:NP_001135751.1:p.(Ser159Ile)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-80	*RNASEH2B*	Compound Heterozygous	13	51519581	G	A	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.529G>A:NP_001135751.1:p.(Ala177Thr)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-81	*PYCR2*	Compound Heterozygous	1	226109290	G	A	nonsynonymous SNV	PYCR2:NM_001271681.1:c.373C>T:NP_001258610.1:p.(Arg125Trp)	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	PATHOGENIC
LNF-81	*PYCR2*	Compound Heterozygous	1	226110025	A	C	nonsynonymous SNV	PYCR2:NM_001271681.1:c.197T>G:NP_001258610.1:p.(Leu66Arg)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-83	*SLC16A2*	Hemizygous	X	73641674	G	T	stopgain	SLC16A2:NM_006517.4:c.202G>T:NP_006508.2:p.(Glu68Ter)	YES	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	PATHOGENIC
LNF-84	*MMUT*	Homozygous	6	49425727	G	A	nonsynonymous SNV	MMUT:NM_000255.3:c.430C>T:NP_000246.2:p.(Arg144Cys)	NO	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-84	*DSTYK*	Homozygous	1	205156545	C	T	splicing	DSTYK:NM_015375.2:c.654+1G>A	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	YES	PATHOGENIC
LNF-85	*PSEN1*	Heterozygous	14	73678582	C	T	nonsynonymous SNV	PSEN1:NM_007318.2:c.1049C>T:NP_015557.2:p.(Thr350Ile)	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	VUS
LNF-86	*DARS2*	Heterozygous	1	173797450	T	C	splicing	DARS2:NM_018122.5:c.228-21T>C	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-86	*DARS2*	Heterozygous	1	173822598	C	T	nonsynonymous SNV	DARS2:NM_018122.5:c.1456C>T:NP_060592.2:p.(Leu486Phe)	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	YES	NO	Likely Pathogenic
LNF-87	*TMEM63A*	Heterozygous	1	226041427	C	A	nonsynonymous SNV	TMEM63A:NM_014698.2:c.1700G>T:NP_055513.2:p.(Gly567Val)	NO	YES	NO	YES	YES	NO	NO	YES	NO	NO	NO	YES	YES	NO	PATHOGENIC
LNF-88	*GFPT1*	Homozygous	2	69575425	T	A	nonsynonymous SNV	GFPT1:NM_001244710.1:c.887A>T:NP_001231639.1:p.(Asp296Val)	NO	NO	NO	NO	YES	NO	NO	NO	NO	YES	YES	YES	YES	NO	Likely Pathogenic
LNF-89	*CP*	Homozygous	3	148897400	TC	T	frameshift deletion	CP:NM_000096.3:c.2603del:NP_000087.1:p.(Gly868GlufsTer26)	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	YES	PATHOGENIC
LNF-89	*NDUFS1*	Homozygous	2	206988991	C	T	nonsynonymous SNV	NDUFS1:NM_005006.6:c.2102G>A:NP_004997.4:p.(Ser701Asn)	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	VUS

LNF-90	***RNASEH2B***	**Homozygous**	13	51519581	G	A	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.529G>A:NP_001135751.1:p.(Ala177Thr)	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	**PATHOGENIC**
LNF-91	***POLR3B***	**Compound Heterozygous**	12	106807883	C	A	splicing	POLR3B:NM_018082.5:c.1101+3145C>A	NO	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	**YES**	NO	**YES**	NO	**Likely Pathogenic**
LNF-91	***POLR3B***	**Compound Heterozygous**	12	106826199	T	A	nonsynonymous SNV	POLR3B:NM_018082.5:c.1568T>A:NP_060552.4:p.(Val523Glu)	NO	NO	NO	NO	**YES**	NO	NO	NO	NO	**YES**	**YES**	**YES**	**YES**	**YES**	**PATHOGENIC**
LNF-92	***USP7***	**Heterozygous**	16	9002201	T	C	nonsynonymous SNV	USP7:NM_003470.2:c.1268A>G:NP_003461.2:p.(Asp423Gly)	NO	**YES**	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
LNF-93	***MLC1***	**Compound Heterozygous**	22	50515233	G	C	splicing	MLC1:NM_015166.3:c.597+37C>G	**YES**	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	NO	**PATHOGENIC**
LNF-93	***MLC1***	**Compound Heterozygous**	22	50523919	A	G	5'UTR	MLC1:NM_015166.3:c.-195T>C	NO	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
LNF-94	***PLP1***	**Hemizygous**	X	103040672	C	T	stopgain	PLP1:NM_000533.3:c.166C>T:NP_000524.3:p.(Gln56Ter)	**YES**	**YES**	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	NO	**PATHOGENIC**
LNF-95	***RNASEH2B***	**Homozygous**	13	51519581	G	A	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.529G>A:NP_001135751.1:p.(Ala177Thr)	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	**PATHOGENIC**
LNF-96	***SON***	**Heterozygous**	21	34927287	CAGTT	C	frameshift deletion	SON:NM_138927.2:c.5753_5756del:NP_620305.2:p.(Val1918GlufsTer87)	**YES**	**YES**	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**PATHOGENIC**
LNF-97	***TANGO2***	**Homozygous**	22	20030879			deletion	22q11.21(20030879-20052185)x0	**YES**	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**PATHOGENIC**
LNF-104	***EIF2B5***	**Homozygous**	3	183855425	G	A	nonsynonymous SNV	EIF2B5:NM_003907.2:c.338G>A:NP_003898.2:p.(Arg113His)	NO	NO	**YES**	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	**PATHOGENIC**
LNF-105	***HNRNPH1***	**Heterozygous**	5	*178950829*			duplication	5q53.3(178950829-179067861)x3	NO	**YES**	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
LNF-106	***PLP1***	**Hemizygous**	X	103041532	C	T	Exonic Splicing	PLP1:NM_000533.3:c.330C>T:NP_000524.3:p.(Gly110=)	NO	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**VUS**
LNF-107	***PI4KA***	**Compound Heterozygous**	22	21098918	C	T	nonsynonymous SNV	PI4KA:NM_058004.3:c.3454G>A:NP_477352.3:p.(Glu1152Lys)	NO	NO	**YES**	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
LNF-107	***PI4KA***	**Compound Heterozygous**	22	21119188	A	AG	frameshift insertion	PI4KA:NM_058004.3:c.2624dup:NP_477352.3:p.(Pro876SerfsTer36)	**YES**	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
LNF-109	***PTEN***	**Heterozygous**	10	89717611	TC	T	frameshift deletion	PTEN:NM_000314.4:c.638del:NP_000305.3:p.(Pro213LeufsTer8)	**YES**	NO	NO	NO	**YES**	NO	NO	NO	**YES**	NO	NO	NO	**YES**	NO	**PATHOGENIC**
LNF-110	***PLP1***	**Hemizygous**	X	103031928	G	A	splicing	PLP1:NM_000533.3:c.4+1G>A	**YES**	**YES**	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
LNF-112	***GJC2***	**Homozygous**	1	228345542	T	TCA	frameshift insertion	GJC2:NM_020435.3:c.85_86dup:NP_065168.2:p.(Val30ArgfsTer10)	**YES**	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**PATHOGENIC**
LNF-114	***SCN8A***	**Heterozygous**	12	52099291	G	A	nonsynonymous SNV	SCN8A:NM_014191.3:c.1225G>A:NP_055006.1:p.(Val409Met)	NO	**YES**	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	NO	**PATHOGENIC**
LNF-115	***SPATA5***	**Homozygous**	4	123949435	G	A	nonsynonymous SNV	SPATA5:NM_145207.2:c.1964G>A:NP_660208.2:p.(Arg655Gln)	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	NO	**Likely Pathogenic**
LNF-116	***PLP1***	**Hemizigous**	X	103043441	T	C	splicing	PLP1:NM_000533.3:c.696+2T>C	NO	NO	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	**YES**	**YES**	**YES**	NO	**Likely Pathogenic**
LNF-118	***POLR3A***	**Homozygous**	10	79767519	C	T	nonsynonymous SNV	POLR3A:NM_007055.3:c.2015G>A:NP_008986.2:p.(Gly672Glu)	NO	NO	NO	NO	**YES**	NO	NO	NO	NO	**YES**	NO	**YES**	**YES**	**YES**	**PATHOGENIC**
LNF-120	***RNASEH2B***	**Compound Heterozygous**	13	51519581	G	A	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.529G>A:NP_001135751.1:p.(Ala177Thr)	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	**YES**	**PATHOGENIC**
LNF-120	***RNASEH2B***	**Compound Heterozygous**	13	51522161	T	C	nonsynonymous SNV	RNASEH2B:NM_001142279.2:c.655T>C:NP_001135751.1:p.(Tyr219His)	NO	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	**YES**	**YES**	**YES**	**YES**	**PATHOGENIC**
LNF-121	***SEPSECS***	**Homozygous**	4	25161875	T	C	splicing	SEPSECS:NM_016955.3:c.114+3A>G	**YES**	NO	**YES**	NO	**YES**	NO	NO	NO	NO	**YES**	NO	**YES**	**YES**	NO	**PATHOGENIC**
LNF-126	***HECW2***	**Homozygous**	2	197065797	C	T	3'UTR	HECW2:NM_020760.3:c.*204G>A	NO	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**VUS**
LNF-128	***GFAP***	**Heterozygous**	17	42988611	C	T	nonsynonymous SNV	GFAP:NM_002055.4:c.1120G>A:NP_002046.1:p.(Glu374Lys)	NO	**YES**	NO	**YES**	**YES**	NO	**YES**	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
LNF-130	***PLP1***	**Hemizygous**	X	103044333	T	G	splicing	PLP1:NM_000533.3:c.762+6T>G	NO	NO	**YES**	NO	**YES**	NO	**YES**	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
VH-1	***GFAP***	**Heterozygous**	17	42988640	G	A	nonsynonymous SNV	GFAP:NM_002055.4:c.1091C>T:NP_002046.1:p.(Ala364Val)	NO	NO	NO	NO	**YES**	NO	NO	**YES**	NO	NO	NO	**YES**	**YES**	**YES**	**PATHOGENIC**
VH-2	***GJC2***	**Compound Heterozygous**	1	228345727	C	T	nonsynonymous SNV	GJC2:NM_020435.3:c.268C>T:NP_065168.2:p.(Pro90Ser)	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	**YES**	**PATHOGENIC**
VH-2	***GJC2***	**Compound Heterozygous**	1	228345743	T	G	nonsynonymous SNV	GJC2:NM_020435.3:c.284T>G:NP_065168.2:p.(Leu95Arg)	NO	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	NO	**Likely Pathogenic**
VH-3	***PI4KA***	**Homozygous**	22	21066803	C	G	nonsynonymous SNV	PI4KA:NM_058004.3:c.5773G>C:NP_477352.3:p.(Gly1925Arg)	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
SPG-2	***CAPN1***	**Homozygous**	11	64974295	G	A	splicing	CAPN1:NM_001198868.1:c.1605+5G>A	**YES**	NO	**YES**	NO	**YES**	NO	NO	NO	NO	**YES**	NO	**YES**	NO	**YES**	**PATHOGENIC**
SPG-14	***POLR3A***	**Compound Heterozygous**	10	79769273	C	T	splicing	POLR3A:NM_007055.3:c.1909+22G>A	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	**YES**	NO	NO	**YES**	**YES**	**PATHOGENIC**
SPG-14	***POLR3A***	**Compound Heterozygous**	10	79785447	C	T	nonsynonymous SNV	POLR3A:NM_007055.3:c.251G>A:NP_008986.2:p.(Gly84Glu)	NO	NO	NO	NO	**YES**	**YES**	NO	NO	NO	**YES**	**YES**	**YES**	**YES**	NO	**Likely Pathogenic**
SPG-20	***SPG11***	**Compound Heterozygous**	15	44856746	T	A	stopgain	SPG11:NM_001160227.1:c.6811A>T:NP_001153699.1:p.(Lys2271Ter)	NO	NO	NO	NO	**YES**	**YES**	**YES**	NO	NO	NO	NO	NO	**YES**	NO	**Likely Pathogenic**
SPG-20	***SPG11***	**Compound Heterozygous**	15	44862719	T	C	splicing	SPG11:NM_001160227.1:c.6138+4A>G	**YES**	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	**PATHOGENIC**
SPG-21	***SPG7***	**Compound Heterozygous**	16	89623308	T	C	nonsynonymous SNV	SPG7:NM_003119.3:c.2195T>C:NP_003110.1:p.(Leu732Pro)	NO	NO	**YES**	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
SPG-21	***SPG7***	**Compound Heterozygous**	16	89577853	A	G	splicing	SPG7:NM_003119.3:c.286+853A>G	**YES**	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**PATHOGENIC**
SPG-24	***SPG11***	**Compound Heterozygous**	15	44876685	C	T	stopgain	SPG11:NM_001160227.1:c.5193G>A:NP_001153699.1:p.(Trp1731Ter)	**YES**	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	NO	**YES**	NO	**PATHOGENIC**
SPG-24	***SPG11***	**Compound Heterozygous**	15	44949427	CAT	C	frameshift deletion	SPG11:NM_001160227.1:c.733_734del:NP_001153699.1:p.(Met245ValfsTer2)	**YES**	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**PATHOGENIC**
SPG-25	***SOX10***	**Heterozygous**	22	38379545	A	C	nonsynonymous SNV	SOX10:NM_006941.3:c.247T>G:NP_008872.1:p.(Tyr83Asp)	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	NO	**Likely Pathogenic**
SPG-40	***SPG11***	**Compound Heterozygous**	15	44859637	C	CA	frameshift insertion	SPG11:NM_001160227.1:c.6399dup:NP_001153699.1:p.(Glu2134Ter)	**YES**	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	NO	**YES**	NO	**PATHOGENIC**
SPG-40	***SPG11***	**Compound Heterozygous**	15	44912518	C	A	stopgain	SPG11:NM_001160227.1:c.2704G>T:NP_001153699.1:p.(Glu902Ter)	**YES**	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	NO	NO	**YES**	NO	**PATHOGENIC**
SPG-48	***SPG11***	**Homozygous**	15	44949427	CAT	C	frameshift deletion	SPG11:NM_001160227.1:c.733_734del:NP_001153699.1:p.(Met245ValfsTer2)	**YES**	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**PATHOGENIC**
SPG-61	***DDHD2***	**Homozygous**	8	38103267	C	T	stopgain	DDHD2:NM_001164232.1:c.856C>T:NP_001157704.1:p.(Gln286Ter)	**YES**	NO	NO	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	NO	**YES**	NO	**PATHOGENIC**
SPG-62	***ATP1A3***	**Heterozygous**	19	42474634	G	A	nonsynonymous SNV	ATP1A3:NM_152296.4:c.2324C>T:NP_689509.1:p.(Pro775Leu)	NO	**YES**	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	**PATHOGENIC**
SPG-62	***NEXMIF***	**Hemizygous**	X	73962026	G	A	nonsynonymous SNV	NEXMIF:NM_001008537.2:c.2366C>T:NP_001008537.1:p.(Pro789Leu)	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
SPG-69	***ACER3***	**Homozygous**	11	76727750	G	T	nonsynonymous SNV	ACER3:NM_018367.5:c.631G>T:NP_060837.3:p.(Gly211Cys)	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
SPG-72	***GALC***	**Compound Heterozygous**	14	88450776	C	G	nonsynonymous SNV	GALC:NM_000153.3:c.544G>C:NP_000144.2:p.(Ala182Pro)	NO	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
SPG-72	***GALC***	**Compound Heterozygous**	14	88454813	C	G	nonsynonymous SNV	GALC:NM_000153.3:c.250G>C:NP_000144.2:p.(Asp84His)	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
SPG-73	***SPAST***	**Heterozygous**	2	32361662	C	G	nonsynonymous SNV	SPAST:NM_014946.1:c.1276C>G:NP_055761.2:p.(Leu426Val)	NO	NO	**YES**	**YES**	**YES**	NO	NO	**YES**	NO	NO	NO	**YES**	**YES**	**YES**	**PATHOGENIC**
SPG-106	***SLC16A2***	**Hemizygous**	X	73744432	GTTC	G	nonframeshift deletion	SLC16A2:NM_006517.4:c.817_819del:NP_006508.2:p.(Leu273del)	NO	**YES**	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	**YES**	NO	**Likely Pathogenic**
CPR	***TUBB4A***	**Heterozygous**	19	6495282	C	T	nonsynonymous SNV	TUBB4A:NM_006087.3:c.1228G>A:NP_006078.2:p.(Glu410Lys)	NO	**YES**	NO	NO	**YES**	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	**YES**	**PATHOGENIC**
GLA	***PEX2***	**Homozygous**	8	77895633	T	C	nonsynonymous SNV	PEX2:NM_001172087.1:c.782A>G:NP_001165558.1:p.(His261Arg)	NO	NO	**YES**	NO	**YES**	NO	NO	NO	NO	NO	NO	**YES**	**YES**	NO	**Likely Pathogenic**
LMSR	***CSF1R***	**Heterozygous**	5	149434890	G	A	nonsynonymous SNV	CSF1R:NM_001288705.2:c.2564C>T:NP_001275634.1:p.(Pro855Leu)	NO	NO	NO	**YES**	**YES**	NO	NO	NO	NO	NO	**YES**	**YES**	**YES**	NO	**Likely Pathogenic**

Gene	Associated condition in OMIM	Inheritance	Nº of families
EIF2B5	Leukoencephalopathy with vanishing white matter (CACH)	AR	6
POLR3A	Leukodystrophy, hypomyelinating, with or without oligodontia and/or hypogonadotropic hypogonadism 4H syndrome	AR	6
RNASEH2B	Aicardi-Goutières syndrome	AR	6
PLP1	Pelizaeus-Merzbacher disease	X-linked	5
CSF1R	Leukoencephalopathy, diffuse hereditary, with spheroids	AD	4
SPG11	Spastic paraplegia 11	AR	4
GFAP	Alexander disease	AD	3
DARS2	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation	AR	2
DEGS1	Leukodystrophy, hypomyelinating, 18	AR	2
GALC	Krabbe disease	AR	2
GJC2	Leukodystrophy, hypomyelinating, 2	AR	2
NDUFS1	Mitochondrial complex I deficiency	AR	2
PI4KA		AR	2
POLR3B	Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism	AR	2
SLC16A2	Allan-Herndon-Dudley syndrome	AR	2
TMEM63A	Leukodystrophy, hypomyelinating, 19, transient infantile	AD	2
TUBB4A	Leukodystrophy, hypomyelinating, 6	AR	2
1p36 deletion	Chromosome 1p36 deletion syndrome	AD	1
ACER3	Leukodystrophy, progressive, early childhood-onset	AR	1
ATP1A3	Alternating hemiplegia of childhood 2/ / CAPOS syndrome	AD	1
CACNA1A	Episodic ataxia, type 2/ / Epileptic encephalopathy, early infantile, 42	AD	1
CAPN1	Spastic paraplegia 76, autosomal recessive	AR	1
CP	Aceruloplasminemia	AR	1
CYP2U1	Spastic paraplegia 56	AR	1
DDHD2	Spastic paraplegia 54	AR	1
DSTYK	Spastic paraplegia 23	AR	1
GFM1	Combined oxidative phosphorylation deficiency 1	AR	1
GFPT1	Myasthenia, congenital, 12, with tubular aggregates	AR	1
HECW2	Neurodevelopmental disorder with hypotonia, seizures, and absent language	AD	1
HNRNPH1		AD	1
ITPA	Epileptic encephalopathy, early infantile, 35	AR	1
LMNB1	Leukodystrophy, adult-onset, autosomal dominant	AD	1
MLC1	Megalencephalic leukoencephalopathy with subcortical cysts	AR	1
MMUT	Methylmalonic aciduria, mut(0) type	AR	1
MSTO1	Myopathy, mitochondrial, and ataxia	AD/AR	1
NEXMIF	Mental retardation, X-linked 98	X-linked	1
PAH	Phenylketonuria	AR	1
PARS2	Epileptic encephalopathy, early infantile, 75	AR	1
PEX2	Peroxisome biogenesis disorder 5A (Zellweger)	AR	1
PEX6	Peroxisome biogenesis disorder 4A (Zellweger)	AR	1
PEX11B	Peroxisome biogenesis disorder 14B	AR	1
PNPT1	Combined oxidative phosphorylation deficiency 13	AR	1
POLR1C	Leukodystrophy, hypomyelinating, with or without oligodontia and/or hypogonadotropic hypogonadism 4H syndrome	AR	1
PSEN1	Alzheimer disease, type 3	AD	1
PTEN	Macrocephaly/autism syndrome	AD	1
PYCR2	Leukodystrophy, hypomyelinating, 10	AR	1
SCN8A	Epileptic encephalopathy, early infantile, 13	AD	1
SEPSECS	Pontocerebellar hypoplasia type 2D	AR	1
SLC16A2	Allan-Herndon-Dudley syndrome	X-linked	1
SON	ZTTK syndrome	AD	1
SOX10	PCWH syndrome	AD	1
SPAST	Spastic paraplegia 4, autosomal dominant	AD	1
SPATA5	Epilepsy, hearing loss, and mental retardation syndrome	AR	1
SPG7	Spastic paraplegia 7, autosomal recessive	AR	1
TANGO2	Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration	AR	1
TREX1	Aicardi-Goutières Goutieres syndrome	AR	1
USP7	Hao-Fountain syndrome	AD	1

eTable 4

NEW PHENOTYPES

Patient	Sex, current age (y)	Age at Onset	Family history	Main Clinical Features	MRI	Relevant Investigation findings	Gene	Inheritance	ACMG classif.	Comments
LNF-48.0	M, 13	6mo	YES (affected sister)	PS, GDD/ID, ataxia, erratic ocular movements, stereotypies	Periventricular Thin CC	Abnormal SSEP Abnormal VEPs	***PARS2***	AR	LP / LP	All the previously reported patients had seizures, most of them with high plasma lactate levels[25]. The two brothers here reported had no seizures and normal plasma lactate and spectroscopy study. Compatible family segregation study.
LNF-105	M, 15	5mo	NO	PS, GDD/ID, ataxia, epilepsy, microcephaly Strabismus, optic disc pallor, nystagmus	Periventricular Cysts Cerebellar atrophy	Hyperlactacidemia	***HNRNPH1***	AD	P	Pyramidal signs with T2 WM HI with cystic lesions, not reported in other *HNRNPH1* patients[26].

ATYPICAL PHENOTYPES

LNF-29.0	M, 9	4mo	YES (affected brother)	PS-EPS, GDD/ID, microcephaly, nystagmus, erratic ocular mov	Periventricular Cystic lesions	CSF NT:3-ortometildopa and neopterin elevation	***PNPT1***	AR (XL)	P	Evident temporal cystic lesions reported previously in only two cases in association with *PNPT1*[27].
LNF-47	M, 8	6mo	NO	PS-EPS, GDD/ID, ataxia	Striatal necrosis Mild subcortical T2 hyperintensity as well as in centrum semiovale, corona radiata, optic radiation and also in dentate nuclei and superior and inferior cerebellar peduncles	Increased motochondria in muscle biopsy Decreased activity of complex I, II, III	***POLR3A***	AR	P / P	Prominent extrapyramidal involvement and basal ganglia necrosis on neuroimaging, distinct from 4H leukodystrophy[28].
LNF-85	F, 64	48y	NO	PS, CD, ataxia, neurogenic bladder	Periventricular		***PSEN1***	AD	VUS	Exceptionally, white matter lesions resembling leukodystrophy have been reported in association with *PSEN1* variants[30].
LNF-88.0	M, 16	6mo	YES (affected sister) Consanguinity	PS, GDD/ID	Periventricular	EMG myopathic Abnormal SSEP Abnormal BAEPs Ms biopsy: multilamelar bodies	***GFPT1***	AR	LP	Gene associated with congenital myasthenia, recently associated also with leukoencephalopathy[32]. Paraparesis predominance in this case, whereas others are predominantly hypotonic.
LNF-114	M, 3	NN	NO	Hypotonia, GDD/ID, epilepsy NN abnormal ocular movements Hyperekplexia-like episodes Abnormal phenotype, inguinal hernias, arthrogryposis, bone dysplasia, bilateral hip luxation	Delayed myelination Thin CC	OXPHOS (fibroblasts): hyperactivity in all complexes but citrate syntase too, which indicates mitochondrial proliferation. Referred to citrate syntase, it suggests mild complex II defficiency.	***SCN8A***	AD	P	Severe myelination delay, osteal dysplasia and hyperekplexia-like episodes are unusual in these patients[33,34]. Atypicial dysmorphic traits in this case, with giant inguinal and umbilical hernias not previously reported.
SPG-2	M, 76	40y	YES (affected brother)	PS, Dysarthria	Periventricular		***CAPN1***	AR	P	White matter involvement not described in other reported patients[35,36].
SPG-25	M, 46	18y	YES (three generations)	Ataxia, nystagmus Pes cavus, hypopalestesia, hyporeflexia (ankle)	Diffuse	NO	***SOX10***	AD	LP	Neurological disorder in the absence of associated Waardemburg syndrome or Hirschprung disease[37].

BLENDED PHENOTYPES

LNF-40.0	M, 15	10mo	YES (two brothers and sister affected) Consanguinity	PS-EPS, GDD/ID, epilepsy, nystagmus, dysphagia, dysarthria	Periventricular Delayed myelination		***PAH*** ***CYP2U1***	AR	P LP	Similar phenotype but different disease causing genes between brothers.
LNF-56	F, 20	11mo	NO	GDD/ID, behaviour disorder, ataxia, epilepsy, nystagmus, strabismus Obesity, amenorrea, hypertrichosis	Periventricular	Mildly increased CSF lactate	***POLR3A*** ***CACNA1A***	AR	LP / P P	Possible complex phenotype, in which *CACNA1A* may play a role in ataxic symptoms and cerebellar atrophy.
LNF-71	M, 6	1y	NO	GDD/ID, ataxia	Periventricular Mega cisterna magna	Normal metabolic study (plasma, urine, CSF) OXPHOS (ms) normal	***EIF2B5*** ***GFM1***	AR	P / P	Both genes can contribute to the patient's phenotype
LNF-84	M, 74	72y	NO	PS, cognitive decline, instability Bilateral lens subluxation	Periventricular	Increased urine methylmalonic acid Dysphagia Osteopenia	***MMUT*** ***DSTYK***	AR	P / P	An atypical presentation of these two genes can contribute to the patient's phenotype
LNF-89.3	M, 20	NN	YES (two brothers) Consanguinity	PS, GDD/ID, ataxia, microcephaly	Periventricular	Mycrocytic and hypocromic anemia. Low plCu, uCu and ceruloplasmin. Low IST and High ferritin. Hepatic MRI: iron overload. Normal echocardiogram	***CP*** ***NDUFS1***	AR	P VUS	One brother with progressive spastic paraparesis with white matter involvement, probably related to *NDUFS1* variant.
SPG-62	M, 8	12mo	NO	PS, GDD/ID, ASD, epilepsy, dysarthria, short attention span	Periventricular	Focal EEG abnormalities	***ATP1A3*** ***NEXMIF***	XL AD	P LP	Atypical presentation associated with *ATP1A3*[38], although some features mey be associated with *NEXMIF*[39].

CD, cognitive decline; CSF, cerebro-spinal fluid; EPS, extrapyramidal signs; F, female; GDD, global developmental delay; ID, intellectual disability; LP, likely-pathogenic; M, male; mo, months; P, Pathogenic; PS, pyramidal signs; SNHL, sensoryneural hearing lossVUS, variant of unknown significance; XL, X-linked; Y, years

eTable 5

ID	Genes	Inheritance	Chromosom	start base	Ref	Alt	type	Nomenclature	Functional testing performed	Description
LNF-37	*EIF2B5*	ound Heteroz	3	183858531	G	A	splicing	EIF2B5:NM_003907.2:c.1156+13G>A	cDNA and minigene analysis	Minigene splicing assay, as well as Sanger sequencing of PBMC cDNA, revealed that the variant c.1156+13G>A resulted into the inclusion of 10 bp from EIF2B5's intron 7, creating an out-of-frame truncated transcript targeted by NMD [12].
LNF-41	*DEGS1*	Homozygous	1	224377798	AT	A	meshift delet	DEGS1:NM_003676.3:c.604del:NP_003667.1:p.(Tyr202ThrfsTer8)	targeted lipidomics	Targeted lipidomics analysis towards sphingolipids detecting dihydroceramide and ceramide demonstrated increased reaction substrate and decreased product [10].
LNF-42	*DEGS1*	ound Heteroz	1	224377714	G	C	ssynonymous	DEGS1:NM_003676.3:c.518G>C:NP_003667.1:p.(Arg173Pro)	targeted lipidomics	Targeted lipidomics analysis towards sphingolipids detecting dihydroceramide and ceramide demonstrated increased reaction substrate and decreased product 10.
LNF-42	*DEGS1*	ound Heteroz	1	224377794	A	AT	meshift insert	DEGS1:NM_003676.3:c.601dup:NP_003667.1:p.(Tyr201LeufsTer7)	targeted lipidomics	Targeted lipidomics analysis towards sphingolipids detecting dihydroceramide and ceramide demonstrated increased reaction substrate and decreased product 10.
LNF-47	*POLR3A*	ound Heteroz	10	79743720	G	T	Exonic Splicing	POLR3A:NM_007055.3:c.3387C>A:NP_008986.2:p.(Leu1129=)	cDNA analysis	Sanger sequencing of PBMC cDNA revealed that p.Leu1129Leu synonymous variant resulted into skipping of POLR3A's exon 26 (93 pb, in-frame), which corresponds to a functional domain of POLR3A.
LNF-72	*MSTO1*	ound Heteroz	1	155581130	G	A	splicing	MSTO1:NM_001256532.1:c.366+48G>A	cDNA analysis	Sanger sequencing of PBMC cDNA revealed that c.366+48G>A variant resulted into skipping of MSTO1 exon 4 (69 pb, in-frame), which corresponds to a functional domain of MSTO1.
LNF-93	*MLC1*	ound Heteroz	22	50515233	G	C	splicing	MLC1:NM_015166.3:c.597+37C>G	minigene analysis	Minigene splicing assay revealed that c.597+37C>G results into the creation of 2 novel mRNA isoforms which include 159 and 168 bp of MLC1's intron 7 (in-frame insertions), containing 2 stop codons resulting into transcripts targeted by NMD.
LNF-107	*PI4KA*	ound Heteroz	22	21098918	C	T	ssynonymous	PI4KA:NM_058004.3:c.3454G>A:NP_477352.3:p.(Glu1152Lys)	targeted lipidomics	A targeted lipidomics analysis detecting phosphatidylinositol (PI) and its phosphorylated forms (PIP and PIP2) was performed. All of the patients showed a significantly decreased PIP/PI ratio compared to age-matched controls, indicating decreased PI4KA activity in these patients.Moreover, Western Blot with an antibody anti-PI4KA (12411-1-AP Proteintech) corroborated lower protein levels. Finally, immunofluorescence detecting decreased reaction product with an antibody anti-PI(4)P (Z-P004, Echelon Biosciences Inc.) was performed as described in Verdura et al, Brain in press.
LNF-107	*PI4KA*	ound Heteroz	22	21119188	A	AG	meshift insert	PI4KA:NM_058004.3:c.2624dup:NP_477352.3:p.(Pro876SerfsTer36)	targeted lipidomics	A targeted lipidomics analysis detecting phosphatidylinositol (PI) and its phosphorylated forms (PIP and PIP2) was performed. All of the patients showed a significantly decreased PIP/PI ratio compared to age-matched controls, indicating decreased PI4KA activity in these patients.Moreover, Western Blot with an antibody anti-PI4KA (12411-1-AP Proteintech) corroborated lower protein levels. Finally, immunofluorescence detecting decreased reaction product with an antibody anti-PI(4)P (Z-P004, Echelon Biosciences Inc.) was performed as described in Verdura et al, Brain in press.
LNF-110	*PLP1*	Hemizygous	X	103031928	G	A	splicing	PLP1:NM_000533.3:c.4+1G>A	qRT-PCR	qRT-PCR using PBMC cDNA from this patient revealed a strongly reduced quantity of PLP1 mRNA compared to controls, confirming a loss of function effect from variant c.4+1G>A
LNF-121	*SEPSECS*	Homozygous	4	25161875	T	C	splicing	SEPSECS:NM_016955.3:c.114+3A>G	cDNA and minigene analysis	Minigene splicing assay revealed that variant c.32+3A>G results into skipping of SEPSECS's exon 1, which contains the ATG start codon, and thus results into a loss of function. This skipping was also confirmed in PBMC's cDNA from a patient carrying the same variant in homozygosis.
LNF-130	*PLP1*	Hemizygous	X	103044333	T	G	splicing	PLP1:NM_000533.3:c.762+6T>G	cDNA analysis	Sanger sequencing of cDNA analysis from fibroblasts revealed that c.762+6T>G results into skipping of PLP1's exon 7 (63 pb, in-frame), deleting 21 amino acids located in a strongly conserved region of PLP1.
VH-3	*PI4KA*	Homozygous	22	21066803	C	G	ssynonymous	PI4KA:NM_058004.3:c.5773G>C:NP_477352.3:p.(Gly1925Arg)	targeted lipidomics	A targeted lipidomics analysis detecting phosphatidylinositol (PI) and its phosphorylated forms (PIP and PIP2) was performed. All of the patients showed a significantly decreased PIP/PI ratio compared to age-matched controls, indicating decreased PI4KA activity in these patients.Moreover, Western Blot with an antibody anti-PI4KA (12411-1-AP Proteintech) corroborated lower protein levels. Finally, immunofluorescence detecting decreased reaction product with an antibody anti-PI(4)P (Z-P004, Echelon Biosciences Inc.) was performed as described in Verdura et al, Brain in press.
SPG-20	*SPG11*	ound Heteroz	15	44862719	T	C	splicing	SPG11:NM_001160227.1:c.6138+4A>G	cDNA analysis	Sanger sequencing of PBMC cDNA revealed that variant c.6138+4A>G results into skipping of SPG11's exon 34 (134 pb), resulting into an out-of-frame transcript targeted by NMD.
SPG-21	*SPG7*	ound Heteroz	16	89577853	A	G	splicing	SPG7:NM_003119.3:c.286+853A>G	cDNA analysis	Sanger sequencing of fibroblast cDNA revealed that c.286+853A>G results into creation of a transcript which includes a 75 bp pseudoexon located in SPG7's intron 2. This in-frame pseudoexon includes at least two codon stops. Western Blot showed reduced levels of SPG7, confirming a loss of function effect [40].
SPG-69	*ACER3*	Homozygous	11	76727750	G	T	ssynonymous	ACER3:NM_018367.5:c.631G>T:NP_060837.3:p.(Gly211Cys)	targeted lipidomics	A targeted lipidomics analysis on sphingolipids demostrated a similar lipid profile as published, Edvardson et al. [41]. Moreover, q-PCR analysis of the ACER3 gene showed reduced expression compared to 4 controls.

eTable 6

ID	Genes	Inheritance	Chr	Start base	End base	Type	Nomenclatu	CNV validation
LNF-34	*LMNB1*	Heterozygou	5	126112000	126172800	duplication	5q23.2(1261	Q-PCR was carried out to measure the relative copy number of the human LMNB1 gene (exon 1 - exon 1, exon 4 - exon 4, and exon 7 - exon 7) compared to the human FGF1 (exon 4- exon 4) or ELOVL7 (exon 4- exon 4) gene. LNF34.0 exhibits 1.5-fold increase copy number of the LMNB1 gene compared to the parents and 7 healthy individuals.
LNF-45	*1p36*	Heterozygou	1	757093	7686264	deletion	1p36.33p36.	The deletion in 1p36 has been validated by array-CGH with the qChip Post microarray performed in Qgenomics (http://www.qgenomics.com/es), which revealed a deletion of approximately 7.6 Mb long in heterozygous (eFigure2).
LNF-97	*TANGO2*	Homozygous	22	20030879	20052185	deletion	22q11.21(20	Q-PCR was carried out to measure the relative copy number of the human TANGO2 gene (exon 1, exon 5, and exon 9) relative to the human ARVCF or ZDHHC8 genes. LNF-97.0 exhibited 2.0-fold decreased levels of TANGO2 gene compared to 11 healthy individuals, parents showed 1.5-fold decrease levels of this gene.
LNF-105	*HNRNPH1*	Heterozygou	5	178950829	179067861	duplication	5q53.3(1789	Q-PCR was carried out to measure the relative copy number of the human HNRNPH1 gene (intron 5 - exon 6 and exon 9 - intron 9) relative to the human C5ORF60 gene. LNF-105.0 exhibited 1.5-fold increased levels of HNRNPH1 gene compared to parents and 10 healthy individuals, demonstrating that it was a de novo CNV [26].

eTable 7

Case	Inheritance	Gene	Chromosome	Start base	Ref.	Alt.	Nomenclature
LNF-1	compound heteozygous	*POLR3A*	10	79760778	C	T	POLR3A:NM_007055.3:c.2434G>A:NP_008986.2:p.(Gly812Ser)
LNF-1	compound heteozygous	*POLR3A*	10	79767546	A	G	POLR3A:NM_007055.3:c.1988T>C:NP_008986.2:p.(Ile663Thr)
LNF-6	heteozygous	*CSF1R*	5	149441340	T	C	CSF1R:NM_001288705.2:c.1699A>G:NP_001275634.1:p.(Thr567Ala)
LNF-15	heteozygous	*TMEM63A*	1	226041470	C	T	TMEM63A:NM_014698.2:c.1657G>A:NP_055513.2:p.(Gly553Ser)
LNF-16	heteozygous	*CSF1R*	5	149441339	G	A	CSF1R:NM_001288705.2:c.1700C>T:NP_001275634.1:p.(Thr567Met)
LNF-18	homozygous	*GALC*	14	88450739	C	G	GALC:NM_000153.3:c.581G>C:NP_000144.2:p.(Gly194Ala)
LNF-20	homozygous	*POLR3B*	12	106895121	T	C	POLR3B:NM_018082.5:c.3005T>C:NP_060552.4:p.(Ile1002Thr)
LNF-23	compound heteozygous	*POLR3A*	10	79778956	G	A	POLR3A:NM_007055.3:c.1253C>T:NP_008986.2:p.(Ala418Val)
LNF-28	homozygous	*PEX11B*	1	145518171	CA	C	PEX11B:NM_001184795.1:c.233del:NP_001171724.1:p.(Asn78IlefsTer42)
LNF-32	compound heteozygous	*RNASEH2B*	13	51517465	G	T	RNASEH2B:NM_001142279.2:c.445G>T:NP_001135751.1:p.(Glu149Ter)
LNF-37	compound heteozygous	*EIF2B5*	3	183855994	A	G	EIF2B5:NM_003907.2:c.725A>G:NP_003898.2:p.(Tyr242Cys)
LNF-37	compound heteozygous	*EIF2B5*	3	183858531	G	A	EIF2B5:NM_003907.2:c.1156+13G>A
F-40.0 & LNF-4	homozygous	*CYP2U1*	4	108866168	G	C	CYP2U1:NM_183075.2:c.533G>C:NP_898898.1:p.(Arg178Thr)
LNF-41	homozygous	*DEGS1*	1	224377798	AT	A	DEGS1:NM_003676.3:c.604del:NP_003667.1:p.(Tyr202ThrfsTer8)
LNF-42	compound heteozygous	*DEGS1*	1	224377714	G	C	DEGS1:NM_003676.3:c.518G>C:NP_003667.1:p.(Arg173Pro)
LNF-42	compound heteozygous	*DEGS1*	1	224377794	A	AT	DEGS1:NM_003676.3:c.601dup:NP_003667.1:p.(Tyr201LeufsTer7)
LNF-47	compound heteozygous	*POLR3A*	10	79743720	G	T	POLR3A:NM_007055.3:c.3387C>A:NP_008986.2:p.(Leu1129=)
LNF-48	compound heteozygous	*PARS2*	1	55224279	T	C	PARS2:NM_152268.3:c.556A>G:NP_689481.2:p.(Arg186Gly)
LNF-48	compound heteozygous	*PARS2*	1	55224275	T	C	PARS2:NM_152268.3:c.560A>G:NP_689481.2:p.(Lys187Arg)
LNF-56	compound heteozygous	*POLR3A*	10	79764608	G	C	POLR3A:NM_007055.3:c.2113C>G:NP_008986.2:p.(Pro705Ala)
LNF-56	heteozygous	*CACNA1A*	19	13423516	G	GT	CACNA1A:NM_001127221.1:c.1637dup:NP_001120693.1:p.(Tyr546Ter)
LNF-57	heteozygous	*GFAP*	17	42992614	C	T	GFAP:NM_002055.4:c.241G>A:NP_002046.1:p.(Ala81Thr)
LNF-66	compound heteozygous	*ITPA*	20	3199198	T	TCAGC	ITPA:NM_033453.3:c.333_336dup:NP_258412.1:p.(Tyr113SerfsTer47)
LNF-69	compound heteozygous	*RNASEH2B*	13	51517505	A	C	RNASEH2B:NM_001142279.2:c.485A>C:NP_001135751.1:p.(Lys162Thr)
LNF-70	heteozygous	*CSF1R*	5	149435607	A	G	CSF1R:NM_001288705.2:c.2536T>C:NP_001275634.1:p.(Trp846Arg)
LNF-72	compound heteozygous	*MSTO1*	1	155583446	A	G	MSTO1:NM_001256532.1:c.1389-2A>G
LNF-72	compound heteozygous	*MSTO1*	1	155581130	G	A	MSTO1:NM_001256532.1:c.366+48G>A
LNF-80	compound heteozygous	*RNASEH2B*	13	51517496	G	T	RNASEH2B:NM_001142279.2:c.476G>T:NP_001135751.1:p.(Ser159Ile)
LNF-81	compound heteozygous	*PYCR2*	1	226110025	A	C	PYCR2:NM_001271681.1:c.197T>G:NP_001258610.1:p.(Leu66Arg)
LNF-83	hemizygous	*SLC16A2*	X	73641674	G	T	SLC16A2:NM_006517.4:c.202G>T:NP_006508.2:p.(Glu68Ter)
LNF-84	homozygous	*MMUT*	14	73678582	C	T	PSEN1:NM_007318.2:c.1049C>T:NP_015557.2:p.(Thr350Ile)
LNF-85	heteozygous	*PSEN1*	6	49425727	G	A	MMUT:NM_000255.3:c.430C>T:NP_000246.2:p.(Arg144Cys)
LNF-86	compound heteozygous	*DARS2*	1	173797450	T	C	DARS2:NM_018122.5:c.228-21T>C
LNF-86	compound heteozygous	*DARS2*	1	173822598	C	T	DARS2:NM_018122.5:c.1456C>T:NP_060592.2:p.(Leu486Phe)
LNF-87	heteozygous	*TMEM63A*	1	226041427	C	A	TMEM63A:NM_014698.2:c.1700G>T:NP_055513.2:p.(Gly567Val)
LNF-88	homozygous	*GFPT1*	2	69575425	T	A	GFPT1:NM_001244710.1:c.887A>T:NP_001231639.1:p.(Asp296Val)
LNF-89	homozygous	*NDUFS1*	2	206988991	C	T	NDUFS1:NM_005006.6:c.2102G>A:NP_004997.4:p.(Ser701Asn)
LNF-91	compound heteozygous	*POLR3B*	12	106807883	C	A	POLR3B:NM_018082.5:c.1101+3145C>A
LNF-92	heteozygous	*USP7*	16	9002201	T	C	USP7:NM_003470.2:c.1268A>G:NP_003461.2:p.(Asp423Gly)
LNF-93	compound heteozygous	*MLC1*	22	50515233	G	C	MLC1:NM_015166.3:c.597+37C>G
LNF-93	compound heteozygous	*MLC1*	22	50523919	A	G	MLC1:NM_015166.3:c.-195T>C
LNF-94	hemizygous	*PLP1*	X	103040672	C	T	PLP1:NM_000533.3:c.166C>T:NP_000524.3:p.(Gln56Ter)
LNF-105	heteozygous	*HNRNPH1*	5	*178950829*			5q53.3(178950829-179067861)x3
LNF-106	hemizygous	*PLP1*	X	103041532	C	T	PLP1:NM_000533.3:c.330C>T:NP_000524.3:p.(Gly110=)
LNF-107	compound heteozygous	*PI4KA*	22	21098918	C	T	PI4KA:NM_058004.3:c.3454G>A:NP_477352.3:p.(Glu1152Lys)
LNF-107	compound heteozygous	*PI4KA*	22	21119188	A	AG	PI4KA:NM_058004.3:c.2624dup:NP_477352.3:p.(Pro876SerfsTer36)
LNF-109	heteozygous	*PTEN*	10	89717611	TC	T	PTEN:NM_000314.4:c.638del:NP_000305.3:p.(Pro213LeufsTer8)
LNF-110	hemizygous	*PLP1*	X	103031928	G	A	PLP1:NM_000533.3:c.4+1G>A
LNF-114	heteozygous	*SCN8A*	12	52099291	G	A	SCN8A:NM_014191.3:c.1225G>A:NP_055006.1:p.(Val409Met)
LNF-115	homozygous	*SPATA5*	4	123949435	G	A	SPATA5:NM_145207.2:c.1964G>A:NP_660208.2:p.(Arg655Gln)
LNF-116	hemizygous	*PLP1*	X	103043441	T	C	PLP1:NM_000533.3:c.696+2T>C
LNF-121	homozygous	*SEPSECS*	4	25161875	T	C	SEPSECS:NM_016955.3:c.114+3A>G
LNF-126	homozygous	*HECW2*	2	197065797	C	T	HECW2:NM_020760.3:c.*204G>A
LNF-128	heteozygous	*GFAP*	17	42988611	C	T	GFAP:NM_002055.4:c.1120G>A:NP_002046.1:p.(Glu374Lys)
LNF-130	hemizygous	*PLP1*	X	103044333	T	G	PLP1:NM_000533.3:c.762+6T>G
VH-2	compound heteozygous	*GJC2*	1	228345743	T	G	GJC2:NM_020435.3:c.284T>G:NP_065168.2:p.(Leu95Arg)
VH-3	homozygous	*PI4KA*	22	21066803	C	G	PI4KA:NM_058004.3:c.5773G>C:NP_477352.3:p.(Gly1925Arg)
SPG-14	compound heteozygous	*POLR3A*	10	79785447	C	T	POLR3A:NM_007055.3:c.251G>A:NP_008986.2:p.(Gly84Glu)
SPG-20	compound heteozygous	*SPG11*	15	44856746	T	A	SPG11:NM_001160227.1:c.6811A>T:NP_001153699.1:p.(Lys2271Ter)
SPG-21	compound heteozygous	*SPG7*	16	89623308	T	C	SPG7:NM_003119.3:c.2195T>C:NP_003110.1:p.(Leu732Pro)
SPG-21	compound heteozygous	*SPG7*	16	89577853	A	G	SPG7:NM_003119.3:c.286+853A>G
SPG-24	compound heteozygous	*SPG11*	15	44876685	C	T	SPG11:NM_001160227.1:c.5193G>A:NP_001153699.1:p.(Trp1731Ter)
SPG-25	heteozygous	*SOX10*	22	38379545	A	C	SOX10:NM_006941.3:c.247T>G:NP_008872.1:p.(Tyr83Asp)
SPG-40	compound heteozygous	*SPG11*	15	44859637	C	CA	SPG11:NM_001160227.1:c.6399dup:NP_001153699.1:p.(Glu2134Ter)
SPG-40	compound heteozygous	*SPG11*	15	44912518	C	A	SPG11:NM_001160227.1:c.2704G>T:NP_001153699.1:p.(Glu902Ter)
SPG-61	homozygous	*DDHD2*	8	38103267	C	T	DDHD2:NM_001164232.1:c.856C>T:NP_001157704.1:p.(Gln286Ter)
SPG-62	hemizygous	*NEXMIF*	X	73962026	G	A	NEXMIF:NM_001008537.2:c.2366C>T:NP_001008537.1:p.(Pro789Leu)
SPG-69	homozygous	*ACER3*	11	76727750	G	T	ACER3:NM_018367.5:c.631G>T:NP_060837.3:p.(Gly211Cys)
SPG-72	compound heteozygous	*GALC*	14	88450776	C	G	GALC:NM_000153.3:c.544G>C:NP_000144.2:p.(Ala182Pro)
SPG-72	compound heteozygous	*GALC*	14	88454813	C	G	GALC:NM_000153.3:c.250G>C:NP_000144.2:p.(Asp84His)
SPG-106	hemizygous	*SLC16A2*	X	73744432	GTTC	G	SLC16A2:NM_006517.4:c.817_819del:NP_006508.2:p.(Leu273del)
GLA	homozygous	*PEX2*	8	77895633	T	C	PEX2:NM_001172087.1:c.782A>G:NP_001165558.1:p.(His261Arg)
LMSR	heteozygous	*CSF1R*	5	149434890	G	A	CSF1R:NM_001288705.2:c.2564C>T:NP_001275634.1:p.(Pro855Leu)

eTable 8

GOMFID	Pvalue	OddsRatio	ExpCount	Count	Size	Term
GO:0016491	6.08E-15	2.63	53.50	111	430	oxidoreductase activity
GO:0016651	3.51E-10	6.23	6.97	26	56	oxidoreductase activity, acting on NAD(P)H
GO:0031406	1.64E-09	3.36	17.29	44	139	carboxylic acid binding
GO:0043177	2.17E-09	3.27	18.04	45	145	organic acid binding
GO:0016597	2.38E-09	6.86	5.60	22	45	amino acid binding
GO:0046983	3.20E-09	1.91	79.00	129	635	protein dimerization activity
GO:0002020	4.66E-09	3.77	13.06	36	105	protease binding
GO:0042803	6.48E-09	2.10	53.50	95	430	protein homodimerization activity
GO:0008134	2.16E-08	2.03	55.49	96	446	transcription factor binding
GO:0047485	4.96E-08	4.01	10.08	29	81	protein N-terminus binding
GO:0019904	5.24E-08	1.94	61.08	102	491	protein domain specific binding
GO:0003954	5.38E-08	11.10	2.86	14	23	NADH dehydrogenase activity
GO:0008137	5.38E-08	11.10	2.86	14	23	NADH dehydrogenase (ubiquinone) activity
GO:0050136	5.38E-08	11.10	2.86	14	23	NADH dehydrogenase (quinone) activity
GO:0051087	1.72E-07	3.96	9.45	27	76	chaperone binding
GO:0000049	1.85E-07	8.23	3.48	15	28	tRNA binding
GO:0044877	2.73E-07	1.64	111.59	161	897	protein-containing complex binding
GO:0051536	3.39E-07	5.84	4.98	18	40	iron-sulfur cluster binding
GO:0051540	3.39E-07	5.84	4.98	18	40	metal cluster binding
GO:0015631	7.42E-07	2.36	26.37	52	212	tubulin binding
GO:0008022	8.69E-07	2.70	18.29	40	147	protein C-terminus binding
GO:0016655	1.03E-06	6.68	3.86	15	31	oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor
GO:0004812	1.29E-06	9.48	2.61	12	21	aminoacyl-tRNA ligase activity
GO:0016875	1.29E-06	9.48	2.61	12	21	ligase activity, forming carbon-oxygen bonds
GO:0051539	1.44E-06	7.12	3.48	14	28	4 iron, 4 sulfur cluster binding
GO:0009055	1.58E-06	3.52	9.83	26	79	electron transfer activity
GO:0019842	4.49E-06	3.27	10.33	26	83	vitamin binding
GO:0140297	4.56E-06	2.13	30.11	55	242	DNA-binding transcription factor binding
GO:0016874	5.83E-06	3.12	11.07	27	89	ligase activity
GO:0050660	6.22E-06	3.97	6.97	20	56	flavin adenine dinucleotide binding
GO:0030170	6.63E-06	5.86	3.86	14	31	pyridoxal phosphate binding
GO:0070279	6.63E-06	5.86	3.86	14	31	vitamin B6 binding
GO:0030554	1.01E-05	1.51	120.80	164	971	adenyl nucleotide binding
GO:0022890	1.36E-05	1.90	39.56	66	318	inorganic cation transmembrane transporter activity
GO:0032559	1.46E-05	1.50	119.80	162	963	adenyl ribonucleotide binding
GO:0016810	2.46E-05	3.66	6.97	19	56	hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds
GO:0008324	2.66E-05	1.83	41.93	68	337	cation transmembrane transporter activity
GO:0061629	3.76E-05	2.13	24.01	44	193	RNA polymerase II-specific DNA-binding transcription factor binding
GO:0015075	3.76E-05	1.69	56.85	86	457	ion transmembrane transporter activity
GO:0046873	4.35E-05	2.00	28.61	50	230	metal ion transmembrane transporter activity
GO:0001223	5.58E-05	6.01	2.99	11	24	transcription coactivator binding
GO:0005244	6.70E-05	2.57	13.19	28	106	voltage-gated ion channel activity
GO:0022832	6.70E-05	2.57	13.19	28	106	voltage-gated channel activity
GO:0005524	6.88E-05	1.46	115.20	153	926	ATP binding
GO:0044389	7.04E-05	1.97	28.36	49	228	ubiquitin-like protein ligase binding
GO:0019900	7.57E-05	1.60	67.93	98	546	kinase binding
GO:0070491	7.59E-05	3.80	5.72	16	46	repressing transcription factor binding
GO:0015318	7.86E-05	1.67	53.87	81	433	inorganic molecular entity transmembrane transporter activity
GO:0016653	8.19E-05	21.20	1.00	6	8	oxidoreductase activity, acting on NAD(P)H, heme protein as acceptor
GO:0022857	9.09E-05	1.59	66.56	96	535	transmembrane transporter activity

GOMFID, Gene Ontology term identification number; Pvalue, probability value for each GO term tested; OddsRatio, strength of association; ExpCount, expected number of selected genes annotated at the GO term; Count, number of genes present in the HSP network that are annotated at the GO term, Size, number of total proteins that are annotated at the GO term; Term, the GO term name.

GOBPID	Pvalue	OddsRatio	ExpCount	Count	Size	Term
GO:0007417	6.61E-32	3.16	87.91	198	700	central nervous system development
GO:0019752	1.66E-29	3.07	85.77	190	683	carboxylic acid metabolic process
GO:0060322	1.05E-26	3.19	68.19	158	543	head development
GO:0043436	1.51E-26	2.83	92.18	193	734	oxoacid metabolic process
GO:0006082	1.75E-26	2.81	93.68	195	746	organic acid metabolic process
GO:0007420	4.58E-25	3.16	64.42	149	513	brain development
GO:0007610	5.40E-25	3.47	52.37	130	417	behavior
GO:0042552	3.01E-24	8.02	13.94	58	111	myelination
GO:0007272	5.51E-24	7.87	14.06	58	112	ensheathment of neurons
GO:0008366	5.51E-24	7.87	14.06	58	112	axon ensheathment
GO:0070997	1.11E-23	4.18	34.03	97	271	neuron death
GO:1901214	1.62E-23	4.45	30.26	90	241	regulation of neuron death
GO:0045333	2.35E-22	7.19	14.44	57	115	cellular respiration
GO:0009628	2.81E-22	2.46	108.88	206	867	response to abiotic stimulus
GO:0055114	8.08E-21	2.72	74.59	155	594	oxidation-reduction process
GO:0010035	1.15E-20	3.08	53.87	124	429	response to inorganic substance
GO:0006520	5.18E-20	4.11	28.88	82	230	cellular amino acid metabolic process
GO:0060284	1.50E-19	2.55	82.38	163	656	regulation of cell development
GO:0030182	1.60E-19	2.28	116.66	209	929	neuron differentiation
GO:1901698	2.05E-19	2.37	101.72	189	810	response to nitrogen compound
GO:0042063	2.50E-19	4.05	28.38	80	226	gliogenesis
GO:0015980	2.54E-19	4.60	22.86	70	182	energy derivation by oxidation of organic compounds
GO:0006811	2.67E-19	2.24	123.32	217	982	ion transport
GO:1901215	1.43E-18	4.98	19.21	62	153	negative regulation of neuron death
GO:0051402	1.47E-18	4.40	23.48	70	187	neuron apoptotic process
GO:0060548	1.61E-18	2.44	87.15	167	694	negative regulation of cell death
GO:0099537	1.75E-18	2.71	64.42	135	513	trans-synaptic signaling
GO:0043523	2.69E-18	4.73	20.47	64	163	regulation of neuron apoptotic process
GO:0030900	2.85E-18	3.58	33.53	87	267	forebrain development
GO:1901566	3.28E-18	2.20	120.31	210	958	organonitrogen compound biosynthetic process
GO:0050767	3.50E-18	2.59	71.20	144	567	regulation of neurogenesis
GO:0051960	3.79E-18	2.50	79.12	155	630	regulation of nervous system development
GO:0099536	4.26E-18	2.65	66.43	137	529	synaptic signaling
GO:0007268	4.35E-18	2.70	63.67	133	507	chemical synaptic transmission
GO:0098916	4.35E-18	2.70	63.67	133	507	anterograde trans-synaptic signaling
GO:0022904	1.28E-17	9.12	8.54	38	68	respiratory electron transport chain
GO:0010243	1.45E-17	2.32	94.94	175	756	response to organonitrogen compound
GO:0048666	1.46E-17	2.29	98.71	180	786	neuron development
GO:0006979	1.59E-17	3.20	40.56	97	323	response to oxidative stress
GO:0051130	4.22E-17	2.24	103.48	185	824	positive regulation of cellular component organization
GO:0007005	6.64E-17	3.25	37.55	91	299	mitochondrion organization
GO:0010001	8.26E-17	4.44	20.60	62	164	glial cell differentiation
GO:1901605	1.46E-16	4.94	17.08	55	136	alpha-amino acid metabolic process
GO:0007568	2.08E-16	3.55	30.14	78	240	aging
GO:0006812	2.27E-16	2.32	86.90	161	692	cation transport
GO:0050877	2.46E-16	2.35	83.26	156	663	nervous system process
GO:0006629	4.42E-16	2.17	105.74	185	842	lipid metabolic process
GO:0031175	6.12E-16	2.28	87.78	161	699	neuron projection development
GO:0021537	6.23E-16	4.19	21.35	62	170	telencephalon development
GO:0044282	8.51E-16	3.10	38.30	90	305	small molecule catabolic process

GOBPID, Gene Ontology term identification number; Pvalue, probability value for each GO term tested; OddsRatio, strength of association; ExpCount, expected number of selected genes annotated at the GO term; Count, number of genes present in the HSP network that are annotated at the GO term, Size, number of total proteins that are annotated at the GO term; Term, the GO term name.

Ŝ¢I·ōfŜ мл

GOCCID	Pvalue	OddsRatio	ExpCount	Count	Size	Term
GO:0005739	8.61E-35	3.11	102.90	226	831	mitochondrion
GO:0005759	1.40E-22	4.39	29.35	87	237	mitochondrial matrix
GO:0030424	9.05E-22	3.12	55.60	129	449	axon
GO:0043005	3.98E-17	2.18	112.56	197	909	neuron projection
GO:0045202	2.84E-15	2.07	116.15	196	938	synapse
GO:0098803	1.00E-13	11.08	5.32	26	43	respiratory chain complex
GO:0005740	9.24E-13	2.59	45.32	94	366	mitochondrial envelope
GO:0031966	1.92E-12	2.61	43.09	90	348	mitochondrial membrane
GO:0070469	2.78E-12	8.15	6.32	27	51	respirasome
GO:0036477	8.17E-12	2.12	74.79	132	604	somatodendritic compartment
GO:0005746	1.58E-11	8.22	5.82	25	47	mitochondrial respirasome
GO:0031967	1.98E-11	2.07	78.75	136	636	organelle envelope
GO:0031975	1.98E-11	2.07	78.75	136	636	envelope
GO:0019866	2.11E-11	2.89	29.97	68	242	organelle inner membrane
GO:0005743	5.41E-11	3.05	25.38	60	205	mitochondrial inner membrane
GO:1990204	1.00E-10	5.84	8.05	29	65	oxidoreductase complex
GO:0098589	2.52E-10	2.62	33.56	71	271	membrane region
GO:0044297	8.38E-10	2.18	53.74	98	434	cell body
GO:0045121	1.13E-09	2.57	32.57	68	263	membrane raft
GO:0098857	1.13E-09	2.57	32.57	68	263	membrane microdomain
GO:0098796	1.26E-09	1.88	89.78	144	725	membrane protein complex
GO:0005777	2.37E-09	4.49	10.03	31	81	peroxisome
GO:0042579	2.37E-09	4.49	10.03	31	81	microbody
GO:0099503	2.47E-09	1.88	85.81	138	693	secretory vesicle
GO:0120111	3.14E-09	5.37	7.55	26	61	neuron projection cytoplasm
GO:0005778	5.35E-09	8.04	4.46	19	36	peroxisomal membrane
GO:0031903	5.35E-09	8.04	4.46	19	36	microbody membrane
GO:1904115	9.72E-09	7.59	4.58	19	37	axon cytoplasm
GO:0005747	9.88E-09	11.95	2.97	15	24	mitochondrial respiratory chain complex I
GO:0030964	9.88E-09	11.95	2.97	15	24	NADH dehydrogenase complex
GO:0045271	9.88E-09	11.95	2.97	15	24	respiratory chain complex I
GO:0005773	1.45E-08	1.99	61.17	104	494	vacuole
GO:0098794	1.87E-08	2.02	56.84	98	459	postsynapse
GO:0030141	1.97E-08	1.88	74.05	120	598	secretory granule
GO:0098800	4.75E-08	4.47	8.42	26	68	inner mitochondrial membrane protein complex
GO:0043025	5.95E-08	2.08	47.43	84	383	neuronal cell body
GO:0000323	7.18E-08	1.98	55.23	94	446	lytic vacuole
GO:0005764	7.18E-08	1.98	55.23	94	446	lysosome
GO:0098798	2.58E-07	3.13	14.36	35	116	mitochondrial protein complex
GO:0030425	2.76E-07	1.94	52.87	89	427	dendrite
GO:0048471	3.28E-07	1.88	59.31	97	479	perinuclear region of cytoplasm
GO:0097447	3.44E-07	1.93	53.12	89	429	dendritic tree
GO:0098793	3.71E-07	2.00	47.05	81	380	presynapse
GO:0043209	6.80E-07	6.37	4.21	16	34	myelin sheath
GO:0034774	7.17E-07	2.22	31.33	59	253	secretory granule lumen
GO:0032838	1.04E-06	3.15	12.63	31	102	plasma membrane bounded cell projection cytoplasm
GO:0060205	1.09E-06	2.19	31.70	59	256	cytoplasmic vesicle lumen
GO:0031983	1.43E-06	2.16	31.95	59	258	vesicle lumen
GO:0150034	1.48E-06	2.25	28.36	54	229	distal axon
GO:0005794	2.57E-06	1.57	111.20	156	898	Golgi apparatus

GOCCID, Gene Ontology term identification number; Pvalue, probability value for each GO term tested; OddsRatio, strength of association; ExpCount, expected number of selected genes annotated at the GO term; Count, number of genes present in the HSP network that are annotated at the GO term, Size, number of total proteins that are annotated at the GO term; Term, the GO term name.

eTable 11

Symbol	Full name	geneID	Classificatior	lof_z	mis_z	pLI	pRec	pNull
ACHE	acetylcholinesterase (Cartwright blood group)	43	candidate	4.25	2.75	0.998	0.00173	7.25E-09
ADRB2	adrenoceptor beta 2	154	candidate	2.46	1.35	0.525	0.471	0.00315
AGER	advanced glycosylation end-product specific receptor	177	candidate	0.198	0.0883	6.35E-16	0.0148	0.985
AHSA1	activator of HSP90 ATPase activity 1	10598	candidate	4.14	1.69	0.999	0.00104	1.03E-08
ALDH2	aldehyde dehydrogenase 2 family member	217	candidate	1.2	1.32	3.40E-10	0.515	0.485
BDNF	brain derived neurotrophic factor	627	candidate	2.69	1.94	0.656	0.343	0.00105
BECN1	beclin 1	8678	candidate	4.04	1.88	0.937	0.0628	4.15E-07
BMI1	BMI1 proto-oncogene, polycomb ring finger	648	candidate	3.48	2.43	0.943	0.0571	7.97E-06
CCN2	cellular communication network factor 2	1490	candidate	1.42	0.521	0.000502	0.89	0.109
CDKN2B	cyclin dependent kinase inhibitor 2B	1030	candidate	0.109	-0.695	0.00734	0.555	0.438
CLIP2	CAP-Gly domain containing linker protein 2	7461	candidate	5.79	2.36	1	3.40E-05	4.16E-15
CNR1	cannabinoid receptor 1	1268	candidate	2.42	2.62	0.507	0.49	0.00365
COMT	catechol-O-methyltransferase	1312	candidate	-0.043	0.429	1.14E-06	0.206	0.794
CRH	corticotropin releasing hormone	1392	candidate	1.89	1.1	0.716	0.271	0.0128
CRHR1	corticotropin releasing hormone receptor 1	1394	candidate	2.71	1.73	3.79E-05	0.998	0.002
CRK	CRK proto-oncogene, adaptor protein	1398	candidate	3.27	2.37	0.959	0.0406	1.67E-05
CYP2B6	cytochrome P450 family 2 subfamily B member 6	1555	candidate	0.737	-0.976	1.93E-10	0.232	0.768
DECR1	2,4-dienoyl-CoA reductase 1	1666	candidate	-0.582	0.0316	4.47E-14	0.00688	0.993
DEGS1	delta 4-desaturase, sphingolipid 1	8560	candidate	2.04	0.805	0.139	0.843	0.0178
DKK1	dickkopf WNT signaling pathway inhibitor 1	22943	candidate	2.17	0.176	0.174	0.814	0.0118
ENO2	enolase 2	2026	candidate	3.4	1.81	0.384	0.616	7.86E-05
FLII	FLII actin remodeling protein	2314	candidate	4.23	0.507	5.53E-12	1	8.57E-07
FOSB	FosB proto-oncogene, AP-1 transcription factor subunit	2354	candidate	3.45	1.55	0.976	0.0245	4.75E-06
GABPA	GA binding protein transcription factor subunit alpha	2551	candidate	4.47	3.12	0.998	0.00188	1.81E-09
GPT	glutamic--pyruvic transaminase	2875	candidate	-0.757	-1	3.59E-19	0.000676	0.999
GRAP2	GRB2 related adaptor protein 2	9402	candidate	2.39	1.12	0.000153	0.993	0.00652
GSK3B	glycogen synthase kinase 3 beta	2932	candidate	4.14	2.8	0.956	0.0443	1.72E-07
GSTK1	glutathione S-transferase kappa 1	373156	candidate	0.663	0.635	1.94E-06	0.463	0.537
GTF2H1	general transcription factor IIH subunit 1	2965	candidate	4.53	1.8	0.99	0.0102	4.56E-09
GTF2I	general transcription factor Iii	2969	candidate	4.76	3.08	0.996	0.00408	4.87E-10
GTF2IRD1	GTF2I repeat domain containing 1	9569	candidate	5.36	2.66	0.9	0.0996	9.27E-11
HDAC3	histone deacetylase 3	8841	candidate	3.93	3.72	0.567	0.433	3.84E-06
HMGB1	high mobility group box 1	3146	candidate	2.64	2.69	0.82	0.179	0.000776
HSPA1B	heat shock protein family A (Hsp70) member 1B	3304	candidate	0.774	1.11	0.00535	0.726	0.268
HSPA4	heat shock protein family A (Hsp70) member 4	3308	candidate	5.66	2.06	1	0.000463	9.89E-14
HSPA5	heat shock protein family A (Hsp70) member 5	3309	candidate	3.61	4.03	0.773	0.227	1.24E-05
HSPB2	heat shock protein family B (small) member 2	3316	candidate	0.626	0.517	0.00033	0.609	0.391
ICAM1	intercellular adhesion molecule 1	3383	candidate	2.79	0.019	0.0353	0.963	0.00146
IFNA13	interferon alpha 1	3447	candidate	.	-1.17	.	.	.
IFNA2	interferon alpha 2	3440	candidate	.	-0.995	.	.	.
IGFBP3	insulin like growth factor binding protein 3	3486	candidate	2.58	0.787	0.91	0.0891	0.000605
IL12A	interleukin 12A	3592	candidate	2	0.832	0.0475	0.931	0.0214
IL18	interleukin 18	3606	candidate	1.13	1.52	0.0307	0.823	0.146
IL6R	interleukin 6 receptor	3570	candidate	2.23	0.689	3.17E-05	0.988	0.0124
IRF5	interferon regulatory factor 5	3663	candidate	3.06	1.92	0.00904	0.991	0.000451
ISYNA1	inositol-3-phosphate synthase 1	51477	candidate	2.14	1.27	2.49E-05	0.983	0.0173
ITGAM	integrin subunit alpha M	3684	candidate	3.87	1.42	3.31E-11	1	7.91E-06
KCNA3	potassium voltage-gated channel subfamily A member 3	3738	candidate	3.25	3.02	0.894	0.106	3.88E-05
KCNAB2	potassium voltage-gated channel subfamily A regulatory beta subunit 2	8514	candidate	3.96	2.6	0.8	0.2	1.77E-06
KHDRBS1	KH RNA binding domain containing, signal transduction associated 1	10657	candidate	3.91	2.42	0.994	0.00577	1.37E-07
KLRC4	killer cell lectin like receptor C4	8302	candidate	0.81	0.508	0.00568	0.738	0.256
KLRK1	killer cell lectin like receptor K1	22914	candidate	-0.911	0.631	6.98E-14	0.00465	0.995
LETM1	leucine zipper and EF-hand containing transmembrane protein 1	3954	candidate	2.7	1.58	1.21E-06	0.998	0.00231
LIMK1	LIM domain kinase 1	3984	candidate	4.97	2.63	0.999	0.000629	2.52E-11
LY6E	lymphocyte antigen 6 family member E	4061	candidate	1.45	0.574	0.321	0.618	0.0611
MAPK14	mitogen-activated protein kinase 14	1432	candidate	3.39	3.31	0.375	0.625	8.44E-05
MAPK3	mitogen-activated protein kinase 3	5595	candidate	2.8	1.74	0.0369	0.962	0.00136
MIF	macrophage migration inhibitory factor	4282	candidate	2.14	0.358	0.000249	0.984	0.0156
MIR146A	microRNA 146a	406938	candidate	.	.		.	.
MOK	MOK protein kinase	5891	candidate	-1.05	0.333	8.84E-22	0.00014	1
MTG1	mitochondrial ribosome associated GTPase 1	92170	candidate	2.4	-0.524	0.0133	0.981	0.00617
NES	nestin	10763	candidate	4.3	0.438	1.62E-06	1	5.19E-07
NME1	NME/NM23 nucleoside diphosphate kinase 1	4830	candidate	1.16	0.537	0.00318	0.835	0.161
NOS1	nitric oxide synthase 1	4842	candidate	7.23	3.68	1	4.25E-07	1.62E-22
NPY	neuropeptide Y	4852	candidate	1.47	0.643	0.143	0.786	0.071
NQO1	NAD(P)H quinone dehydrogenase 1	1728	candidate	0.113	1.28	1.19E-09	0.101	0.899
NRG1	neuregulin 1	3084	candidate	4.57	0.637	0.997	0.00335	1.49E-09
NSD2	nuclear receptor binding SET domain protein 2	7468	candidate	7.14	3.9	1	6.25E-09	1.64E-23
NTF3	neurotrophin 3	4908	candidate	3.08	1.74	0.932	0.0679	6.11E-05
NTS	neurotensin	4922	candidate	0.239	-0.234	3.85E-05	0.396	0.604
OPRM1	opioid receptor mu 1	4988	candidate	0.526	-0.619	7.89E-11	0.143	0.857
PARP1	poly(ADP-ribose) polymerase 1	142	candidate	4.52	0.818	0.000334	1	1.48E-07
PDC	PNKD metallo-beta-lactamase domain containing	5132	candidate	0.676	0.603	0.000101	0.594	0.406
PI4KA	phosphatidylinositol 4-kinase alpha	5297	candidate	6.53	3.53	3.12E-12	1	9.17E-15
POLDIP2	DNA polymerase delta interacting protein 2	26073	candidate	3.44	1.94	0.414	0.586	6.24E-05
PON1	paraoxonase 1	5444	candidate	0.578	0.725	9.81E-11	0.161	0.839
PTBP1	polypyrimidine tract binding protein 1	5725	candidate	4.63	1.65	1	0.000393	1.96E-10
PTK2B	protein tyrosine kinase 2 beta	2185	candidate	6.05	1.5	0.935	0.0646	2.54E-13
PTPA	protein phosphatase 2 phosphatase activator	5524	candidate	3.76	1.69	0.991	0.00943	4.56E-07
RNF19A	ring finger protein 19A, RBR E3 ubiquitin protein ligase	25897	candidate	4	2.38	0.0253	0.975	4.05E-06
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase	6098	candidate	0.455	-0.501	1.62E-72	1.47E-10	1
RREB1	ras responsive element binding protein 1	6239	candidate	6.13	-0.427	1	2.19E-06	2.59E-17
S100B	S100 calcium binding protein B	6285	candidate	0.55	0.4	0.0439	0.682	0.274
SEMA6A	semaphorin 6A	57556	candidate	5.39	0.747	1	0.000244	5.07E-13
SIRT3	sirtuin 3	23410	candidate	1.45	0.0262	0.000163	0.889	0.111
SLC2A3	solute carrier family 2 member 3	6515	candidate	2.72	1.03	0.0103	0.988	0.00183
SOD2	superoxide dismutase 2	6648	candidate	2.11	0.887	0.155	0.83	0.0146
STAT4	signal transducer and activator of transcription 4	6775	candidate	5.15	2.74	0.766	0.234	9.34E-10
TGM2	transglutaminase 2	7052	candidate	0.703	0.536	6.81E-18	0.0271	0.973
TICAM2	toll like receptor adaptor molecule 2	353376	candidate	2.17	0.831	0.00259	0.984	0.0132
TLR4	toll like receptor 4	7099	candidate	1.59	0.647	4.61E-09	0.823	0.177
TMED7	transmembrane p24 trafficking protein 7	51014	candidate	2.37	1.5	0.48	0.516	0.00448
TMEM189	plasmanylethanolamine desaturase 1	387521	candidate	2.65	2.43	0.00839	0.989	0.00247
TNFSF12	TNF superfamily member 12	8742	candidate	3.6	0.983	0.77	0.23	1.30E-05
TNFSF13	TNF superfamily member 13	8741	candidate	3.02	0.526	0.817	0.183	0.000166
TXN	thioredoxin	7295	candidate	1.71	1.14	0.201	0.759	0.0399
TXNRD1	thioredoxin reductase 1	7296	candidate	2.79	1.32	1.61E-06	0.998	0.00155
UBE2V1	ubiquitin conjugating enzyme E2 V1	7335	candidate	0.769	1.55	0.000124	0.639	0.361
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon	7531	candidate	3.3	2.83	0.985	0.0152	7.27E-06
ZNF592	zinc finger protein 592	9640	candidate	5.37	0.804	1	1.55E-05	7.47E-14

Gene constraints: lof_z, the z-score value of being loss-of-function intolerant; mis_z, the z-score value of being intolerant to missense variation; pLI, the probability of being loss-of-function intolerant; pRec, the probability of being intolerant to homozygous variation.

1. Van der Auwera GA, Carneiro MO, Hartl C, et al. From FastQ data to high confidence variant calls: the Genome Analysis Toolkit best practices pipeline. *Curr Protoc Bioinforma*. 2013;43:11 10 1-33.

2. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res*. 2010;38(16):e164.

3. Plagnol V, Curtis J, Epstein M, et al. A robust model for read count data in exome sequencing experiments and implications for copy number variant calling. *Bioinformatics*. 2012;28(21):2747-2754.

4. Amendola LM, Jarvik GP, Leo MC, et al. Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. *Am J Hum Genet*. 2016;98(6):1067-1076.

5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424.

6. Bendl J, Musil M, Štourač J, Zendulka J, Damborský J, Brezovský J. PredictSNP2: A Unified Platform for Accurately Evaluating SNP Effects by Exploiting the Different Characteristics of Variants in Distinct Genomic Regions. *PLoS Comput Biol*. 2016;12(5):1-18.

7. Dong C, Wei P, Jian X, et al. Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. *Hum Mol Genet*. 2015;24(8):2125-2137.

8. Brandt T, Sack LM, Arjona D, et al. Adapting ACMG/AMP sequence variant classification guidelines for single-gene copy number variants. *Genet Med*. 2020;22(2):336-344.

9. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): A policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017;19(2):249-255.

10. Pant DC, Boespflug-tanguy O, Pujol A. Loss of the sphingolipid desaturase DEGS1 causes hypomyelinating leukodystrophy Graphical abstract Find the latest version : *J Clin Invest*. 2019;129(3):1240-1256.

11. Vélez-Santamaría V, Verdura E, Macmurdo C, et al. Expanding the clinical and genetic spectrum of PCYT2-related disorders. *Brain*. 2020;143(9):1-5.

12. Rodríguez-Palmero A, Schlüter A, Verdura E, et al. A novel hypomorphic splice variant in EIF2B5 gene is associated with mild ovarioleukodystrophy. *Ann Clin Transl Neurol*. 2020;7(9):1574-1579.

13. Novarino G, Fenstermaker AG, Zaki MS, et al. Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. *Science (80-)*. 2014;343(6170):506-511.

14. Vanunu O, Magger O, Ruppin E, Shlomi T, Sharan R. Associating genes and protein complexes with disease via network propagation. *PLoS Comput Biol*. 2010;6(1):e1000641.

15. Huttlin EL, Bruckner RJ, Paulo JA, et al. Architecture of the human interactome defines protein communities and disease networks. *Nature*. 2017;545(7655):505-509.

16. Rolland T, Tasan M, Charloteaux B, et al. A proteome-scale map of the human interactome network. *Cell*. 2014;159(5):1212-1226.

17. Rual JF, Venkatesan K, Hao T, et al. Towards a proteome-scale map of the human protein-protein

interaction network. *Nature*. 2005;437(7062):1173-1178.

18. Luck K, Kim DK, Lambourne L, et al. A reference map of the human binary protein interactome. *Nature*. 2020;580(7803):402-408.

19. Hwang S, Kim CY, Yang S, et al. HumanNet v2: Human gene networks for disease research. *Nucleic Acids Res*. 2019;47(D1):D573-D580.

20. Kanehisa M, Goto S, Sato Y, Kawashima M, Furumichi M, Tanabe M. Data, information, knowledge and principle: Back to metabolism in KEGG. *Nucleic Acids Res*. 2014;42:D199-205.

21. Brunk E, Sahoo S, Zielinski DC, et al. Recon3D enables a three-dimensional view of gene variation in human metabolism. *Nat Biotechnol*. 2018;36(3):272-281.

22. Licata L, Lo Surdo P, Iannuccelli M, et al. SIGNOR 2.0, the SIGnaling Network Open Resource 2.0: 2019 update. *Nucleic Acids Res*. 2020;48(D1):D504-D510.

23. Schluter A, Espinosa L, Fourcade S, et al. Functional genomic analysis unravels a metabolic-inflammatory interplay in adrenoleukodystrophy. *Hum Mol Genet*. 2012;21(5):1062-1077.

24. Falcon S, Gentleman R. Using GOstats to test gene lists for GO term association. *Bioinformatics*. 2007;23(2):257-258.

25. Almuqbil MA, Vernon HJ, Ferguson M, Kline AD. PARS2 -associated mitochondrial disease : A case report of a patient with prolonged survival and literature review. *Mol Genet Metab Reports*. 2020;24(March):100613.

26. Reichert SC, Li R, Turner S, et al. HNRNPH1 - related syndromic intellectual disability: Seven additional cases suggestive of a distinct syndromic neurodevelopmental syndrome. *Clin Genet*. 2020;98(1):91-98.

27. Pennisi A, Rötig A, Roux CJ, et al. Heterogeneity of PNPT1 neuroimaging: Mitochondriopathy, interferonopathy or both? *J Med Genet*. 2020.

28. Harting I, Al-Saady M, Krägeloh-Mann I, et al. POLR3A variants with striatal involvement and extrapyramidal movement disorder. *Neurogenetics*. 2020;21(2):121-133.

29. Thiffault I, Wolf NI, Forget D, et al. Recessive mutations in POLR1C cause a leukodystrophy by impairing biogenesis of RNA polymerase III. *Nat Commun*. 2015;6:7623.

30. Soosman SK, Joseph-Mathurin N, Braskie MN, et al. Widespread white matter and conduction defects in PSEN1-related spastic paraparesis. *Neurobiol Aging*. 2016;47:201-209.

31. Lee S, Viqar F, Zimmerman ME, et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. *Ann Neurol*. 2016;79(6):929-939.

32. Helman G, Sharma S, Crawford J, et al. Leukoencephalopathy due to variants in GFPT1-associated congenital myasthenic syndrome. *Neurology*. 2019;92(6):e587-e593.

33. Gardella E, Marini C, Trivisano M, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. *Neurology*. 2018;91(12):e1112-e1124.

34. Pons L, Lesca G, Sanlaville D, et al. Neonatal tremor episodes and hyperekplexia-like presentation at onset in a child with SCN8A developmental and epileptic encephalopathy. *Epileptic Disord*. 2018;20(4):289-294.

35. Gan-Or Z, Bouslam N, Birouk N, et al. Mutations in CAPN1 Cause Autosomal-Recessive

Hereditary Spastic Paraplegia. *Am J Hum Genet*. 2016;98(5):1038-1046.

36. Wang Y, Hersheson J, Lopez D, et al. Defects in the CAPN1 Gene Result in Alterations in Cerebellar Development and Cerebellar Ataxia in Mice and Humans. *Cell Rep*. 2016;16(1):79-91.

37. Bondurand N, Dastot-Le Moal F, Stanchina L, et al. Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. *Am J Hum Genet*. 2007;81(6):1169-1185.

38. Prange L, Pratt M, Herman K, et al. D-DEMØ, a distinct phenotype caused by ATP1A3 mutations. *Neurol Genet*. 2020;6(5):1-10.

39. Stamberger H, Hammer TB, Gardella E, et al. NEXMIF encephalopathy: an X-linked disorder with male and female phenotypic patterns. *Genet Med*. 2021;23(2):363-373.

40. Verdura E, Schlüter A, Fernández-Eulate G, et al. A deep intronic splice variant advises reexamination of presumably dominant SPG7 Cases. *Ann Clin Transl Neurol*. 2020;7(1):105-111.

41. Edvardson S, Yi JK, Jalas C, et al. Deficiency of the alkaline ceramidase ACER3 manifests in early childhood by progressive leukodystrophy. *J Med Genet*. 2016;53(6):389-396.