Whole exome sequencing in patients with white matter abnormalities

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Supplemental Note: Case Reports

The following section contains a summary of each case including a description of the radiologic findings of affected individuals, the phenotypic presentation of affected individuals and their families and the details of each candidate pathogenic variant identified.

The following abbreviations are used:

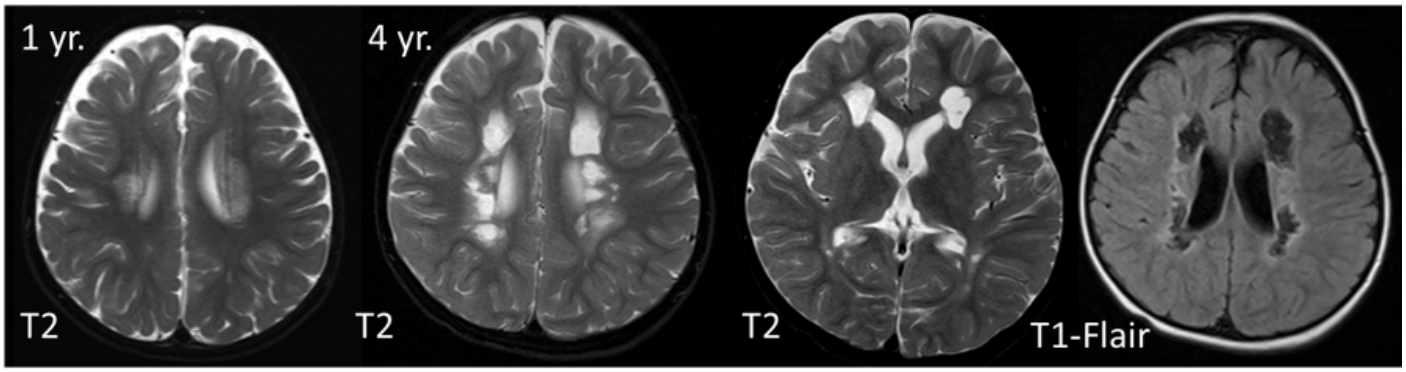
- **ADC** Apparent Diffusion Coefficient
- **AGS** Aicardi-Goutieres syndrome
- **CGH** Comparative genomic hybridization
- **CSF** Cerebrospinal Fluid
- **CT** Computed Tomography
- **FLAIR** Fluid Attenuated Inversion Recovery Imaging
- **GERD** Gastroesophageal Reflux Disease
- **MR** Magnetic Resonance
- **MRI** Magnetic Resonance Imaging
- **SIADH** Syndrome of inappropriate diuretic hormone secretion
- **T2-PD** T2 Proton Density
- **GAD** T1 with Gadolinium
- **XR** X-Ray

Each variant is scored according to the ACMG guidelines for the interpretation of sequence variants[1]. As detailed in the guidelines, the following criteria are used:

- **PVS1** Null variant (nonsense, frameshift, canonical ± 1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease.
- **PS1** Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.
- **PS2** De novo (both maternity and paternity confirmed) in a patient with the disease and no family history.
- **PS3** Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.
- **PS4** The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls.
- **PM1** Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation.
- **PM2** Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.
- **PM3** For recessive disorders, detected in trans with a pathogenic variant.
- **PM4** Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants.
- **PM5** Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.
- **PM6** Assumed de novo, but without confirmation of paternity and maternity.
- **PP1** Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease.
- **PP2** Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease.
- **PP3** Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.).
- **PP4** Patient's phenotype or family history is highly specific for a disease with a single genetic etiology.
- **PP5** Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.

LD_0025 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0025.0A.

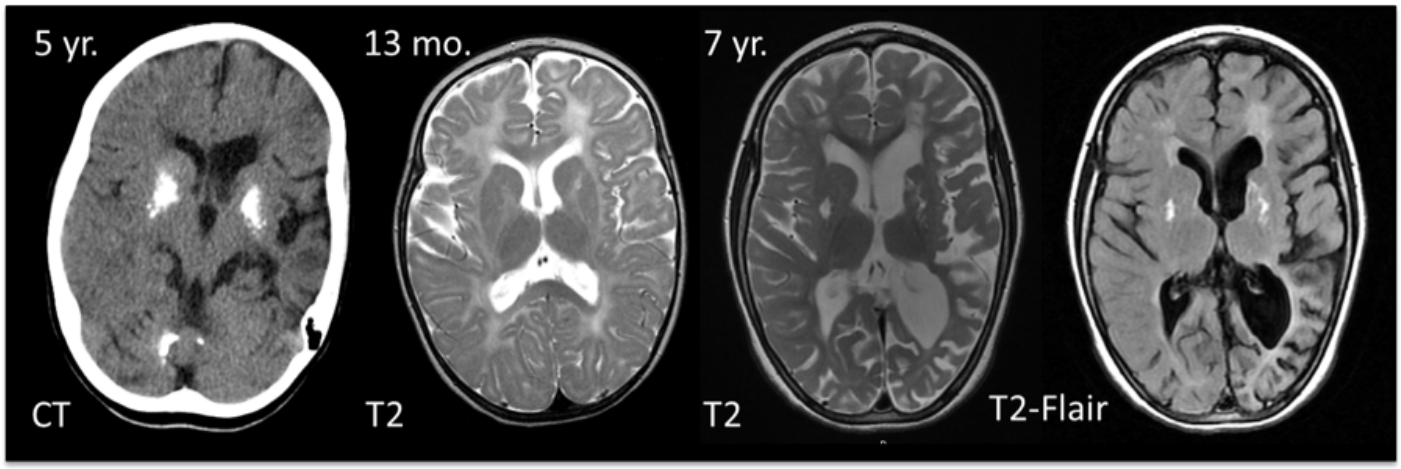
LD_0025.0A is a nine year old male from Pakistan with a history of of a chronic encephalopathy and seizures with exacerbation in the context of febrile events. During these events, hypertonia and extensor posturing were noted. The first MRI at 11 months showed periventricular white matter changes that evolved in confluence and developed cystic rarefaction (4 years of age). The brainstem and basal ganglia were relatively preserved. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0101 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0101.0A.

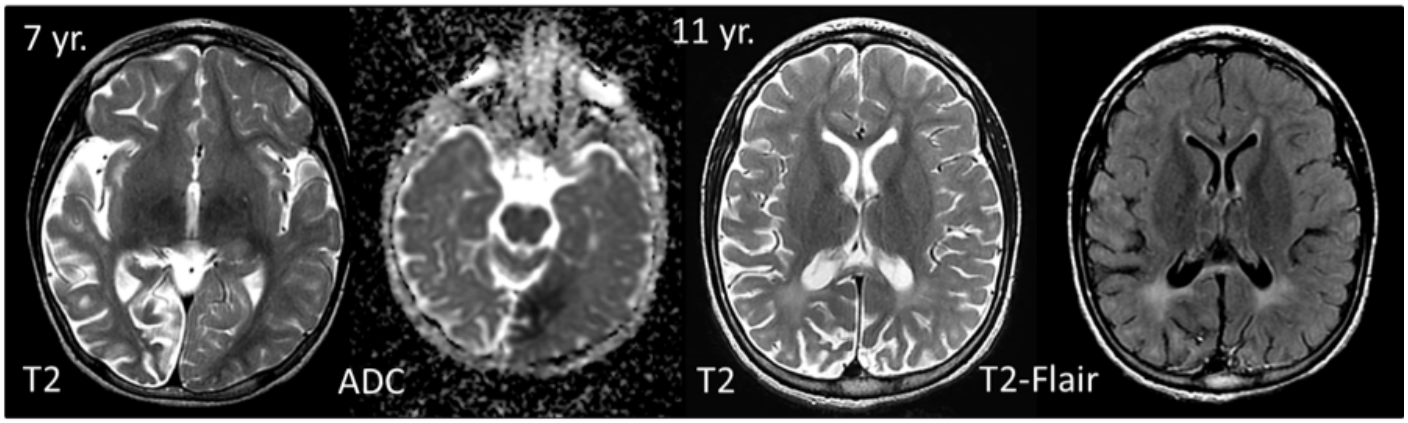
LD_0101.0A is a 10 year old female of Romanian descent with a clinical diagnosis of Aicardi-Goutières syndrome based on CSF leukocytosis, increased alpha-interferon and neopterin abnormalities with a history of delayed motor development and myoclonic seizures. AGS related gene screening was negative. An MRI at 13 months demonstrates abnormal signal intensity in the cerebral white matter. CT scan at 5 years of age demonstrates dense basal ganglia calcifications as well as calcifications in the cerebellar white matter. MRI at 7 years of age shows intracranial calcifications, periventricular white matter changes and progressive cerebral atrophy. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0106 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0106.0A.

LD_0106.0A is a 16 year old female from Gabon with a history of profound developmental delay, and refractory epilepsy. At seven years, symptoms worsened with administration of depakote, with stroke like episodes and subsequent cortical blindness. MRI studies at 11 years of age showed some left-sided parietal and occipital cortical atrophy with underlying white matter changes. There was no relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*GRIN1*	Het, *de novo*	chr9:140058297C>T	ENST00000371546	c.2593C>T	p.Arg865Cys

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

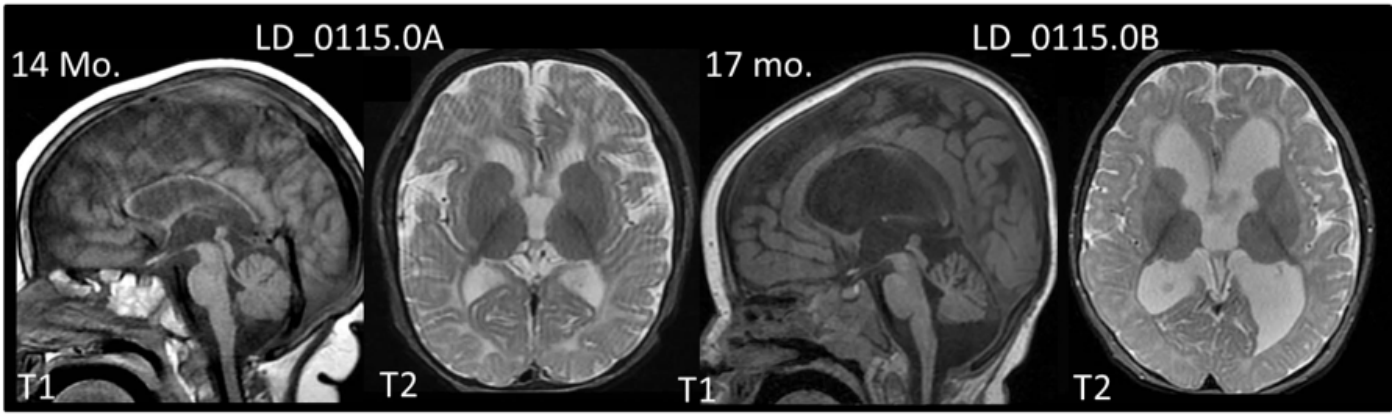
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PS2, PM2, PP2, PP3,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: GRIN1 related epileptic encephalopathy.

LD_0115 Case Summary

MR imaging and clinical summary



MR imaging of individuals LD_0115.0A and LD_0115.0B.

LD_0115.0A and LD_0115.0B are sisters of mixed European descent. LD_0115.0A is a seven year old female with a history of epileptic encephalopathy, microcephaly, dystonia, global developmental delay, congenital vertical tali, severe GERD, esoptropia, blepharospam, failure to thrive and short stature. MRI at fourteen months of age shows delayed myelination and white matter volume loss.

LD_0115.0B is a three year old female, with a similar yet less severe clinical phenotype including epileptic encephalopathy, microcephaly, dystonia, global developmental delay, congenital vertical tali, blepharospasm, failure-to-thrive and short stature. MRI at age 17 months showed severe delayed myelination and mild cerebellar atrophy as well as enlarged ventricles.

There was no other relevant family history.

LD_0115.0A and LD_0115.0B were previously reported in[2].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*AARS*	Het	chr16:70310960T>G	ENST00000261772	c.242A>C	p.Lys81Thr
#2	*AARS*	Het	chr16:70289666T>C	ENST00000261772	c.2251A>G	p.Arg751Gly

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Damaging	Damaging	DC
#2	rs143370729	0.000050	0.000116	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

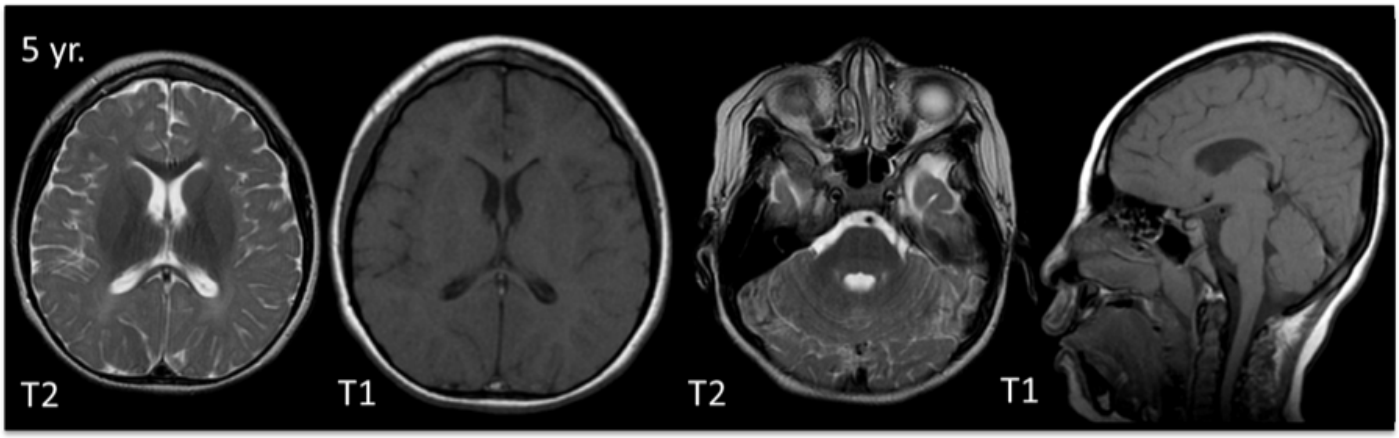
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS3, PM1, PM2, PM3, PP1, PP2, PP3, PP4,
#2	Pathogenic	PS3, PM1, PM2, PM3, PP1, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Epileptic encephalopathy, early infantile, 29 (MIM:616339).

LD_0119 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0119.0A.

LD_0119.0A is an 11 year old boy of Korean descent with microcephaly, mental retardation and refractory seizures. He has medically refractory choreathetosis and unexplained increased urine and CSF sialic acid. MRI at five years of age shows persistent hypomyelination, with relative preservation of the brainstem and cerebellum. There was no relevant family history.

LD_0119.0A was previously reported in[3].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*KCNT1*	Het, *de novo*	chr9:138671269T>A	ENST00000298480	c.2794T>A	p.Phe932Ile

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

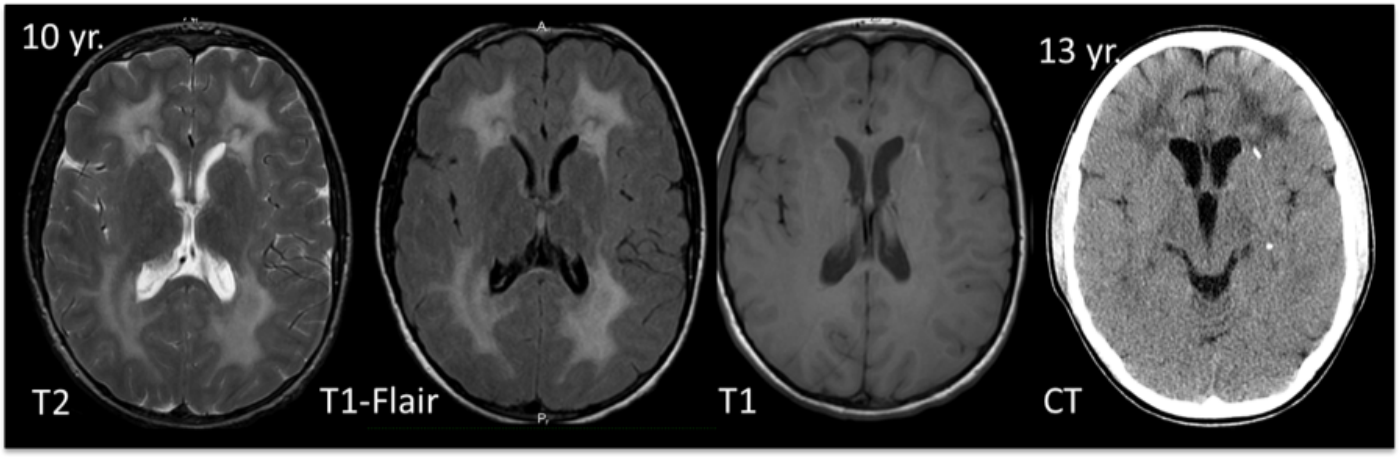
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS2, PM1, PM2, PP2, PP3,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Epileptic encephalopathy, early infantile, 14 (MIM:614959).

LD_0125 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0125.0A.

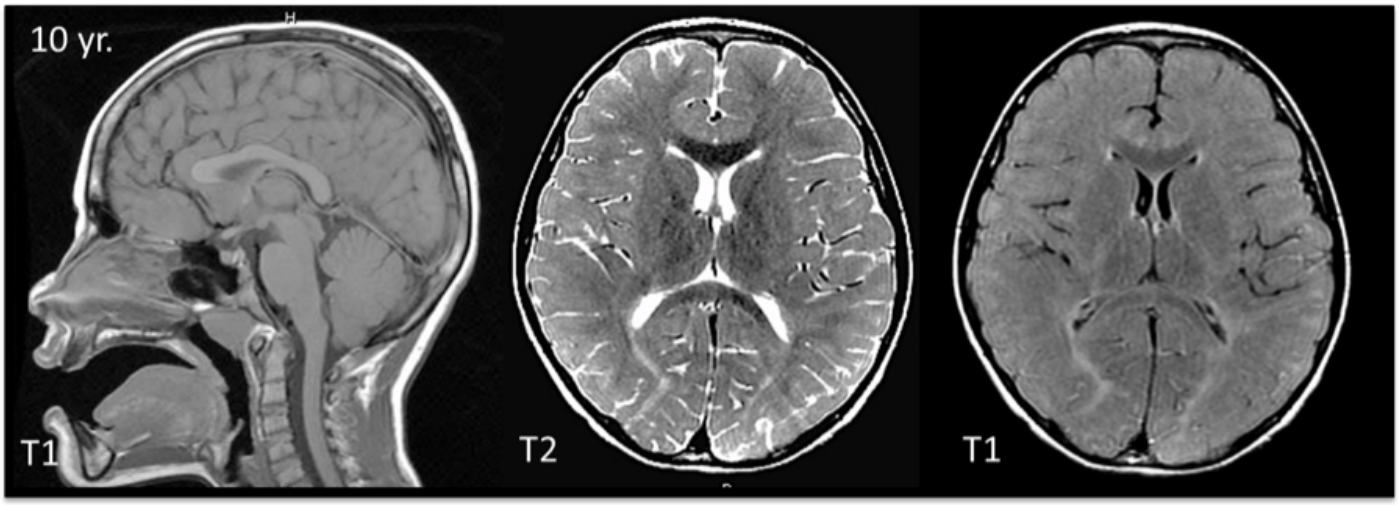
LD_0125.0A is a 16 year old male of mixed European descent with a history of macrocephaly, staring spells at with onset at 18 months, and developmental delay. Over time, he lost previously acquired motor skills. He presented with rigidity, hypomimia, gait ataxia, hyperreflexia, and parkinsonism with bradykinesia. MRI (ten years) and CT (13 years) showed calcifications of the basal ganglia and T2 signal hyperintensity of the supratentorial white matter bilaterally with sparing of the U-fibers. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0139 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0139.0A.

LD_0139.0A is a 14 year old boy of African American descent with a history of developmental delay, dysarthria, and appendicular weakness. Throughout childhood he has had progressive motor delays and increased tone in the upper extremities, in addition to autonomic dysregulation. Exam at 13 years revealed mild spastic diplegia with increased deep tendon reflexes and tone and choreiform movements of the upper extremities. MRI at age ten years showed mild hypomyelination and preserved putamen. There was no relevant family history.

LD_0139.0A was previously reported in[4].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*TUBB4A*	Het, *de novo*	chr19:6495338C>T	ENST00000264071	c.1172G>A	p.Arg391His

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

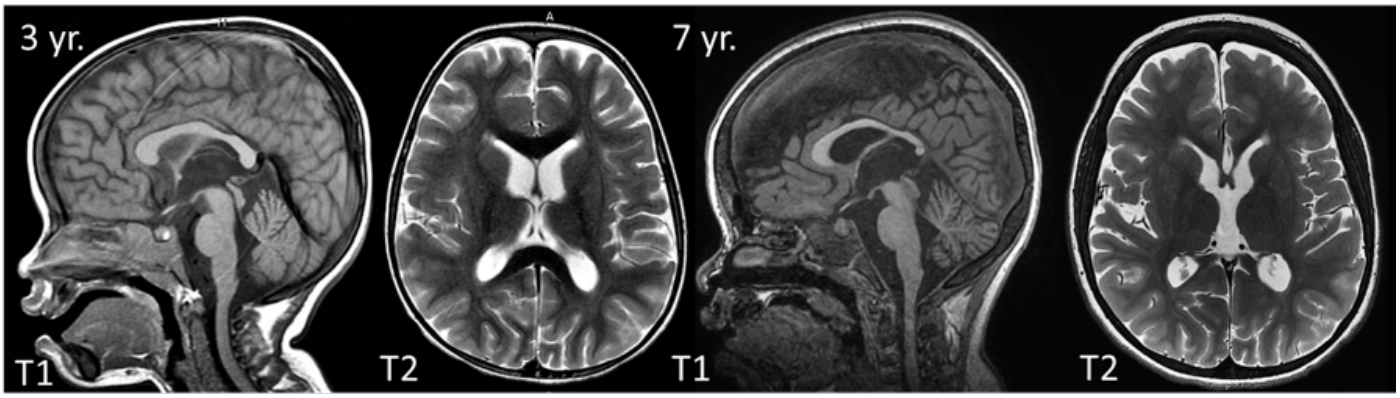
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PS2, PM2, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Leukodystrophy, hypomyelinating, 6 (MIM:612438).

LD_0157 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0157.0A.

LD_0157.0A is a seven year old girl of El Salvadorian descent with refractory epileptic encephalopathy and a history of developmental delay, macrocephaly, failure to thrive and hypotonia. She also has chronic lung disease, chronic pancreatitis, and syndrome of inappropriate diuretic hormone secretion (SIADH). MRI studies at three years and seven years of age showed persistent but improving deficits in myelination, mild cerebellar atrophy, and volume loss of the corpus callosum and frontal lobe. There was no relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*SZT2*	Het	chr1:43898722GC>G	ENST00000562955	c.5499del	p.Phe1834fs
#2	*SZT2*	Het	chr1:43905596G>A	ENST00000562955	c.6916G>A	p.Gly2306Arg

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	-	-	-
#2	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

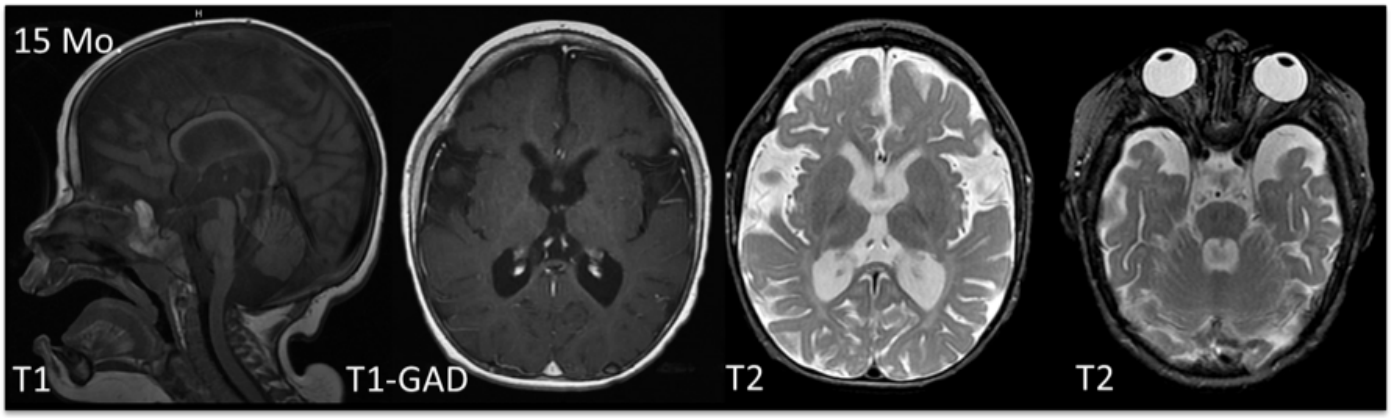
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PVS1, PS2, PM2, PM3, PP2,
#2	Likely pathogenic	PM2, PM3, PP2, PP3,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Epileptic encephalopathy, early infantile, 18 (MIM:615476).

LD_0158 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0158.0A.

LD_0158.0A is a six year old boy of Guatemalan descent with neonatal onset of respiratory failure requiring tracheostomy, bilateral hearing loss with submucosal left cleft palate and seizures which have been well controlled. He had an older brother who died in the neonatal period of respiratory failure. Physical examination identified a peripheral neuropathy which was confirmed by nerve biopsy which demonstrated a hypomyelinating neuropathy. He has been clinically stable though ventilator dependent. MRI at 15 months of age showed persistently delayed myelination including the brainstem and cerebral atrophy. There was no relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*CNTNAP1*	Hom	chr17:40839856G>C	ENST00000264638	c.1163G>C	p.Arg388Pro

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs779027563	0.000008	0.000061	Damaging	Benign	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

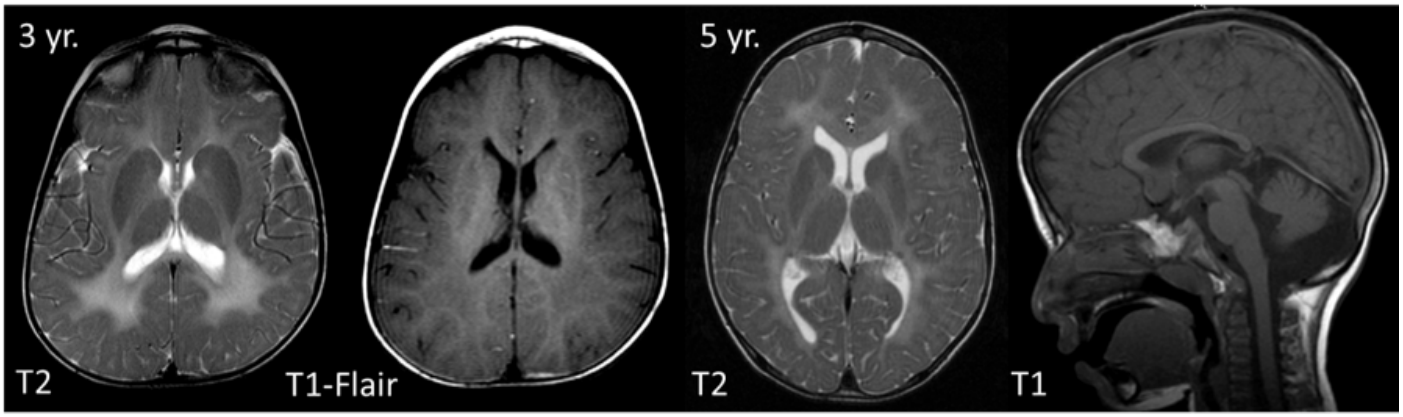
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PM2, PM3, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Lethal congenital contracture syndrome 7 (MIM:616286). Nonsyndromic arthrogryposis multiplex congenita (MIM:616286).

LD_0162 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0162.0A.

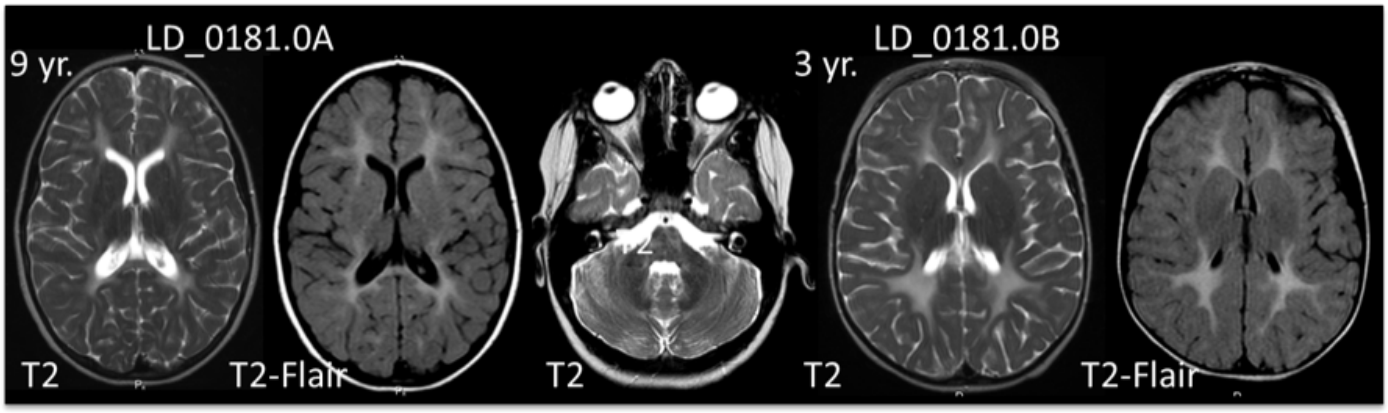
LD_0162.0A and LD_0162.0B are twin brothers of Ashkenazi Jewish heritage. LD_0162.0A died at 12 years of age. LD_0162.0A had a history of nystagmus, progressive spasticity, stunted growth, dystonia and developmental delay. LD_0162.0B died at five years of age due to GI illness. He also had progressive spasticity, dystonia, and developmental regression although had much more impairment in the lower extremities than the upper and cognition had been relatively spared. In LD_0162.0A MRI at three years of age showed diffuse hypomyelination, mild asymmetric thinning of the posterior corpus callosum, and normal cerebellum. On T1 imaging however, there were some periatrial regions showing mild hyperintensity, suggesting that it was not simple hypomyelination. Follow-up at five years of age was unchanged. LD_0162.0B had a very similar MRI pattern. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0181 Case Summary

MR imaging and clinical summary



MR imaging of individuals LD_0181.0A and LD_0181.0B.

LD_0181.0A and LD_0181.0B are sisters of mixed European descent. LD_0181.0A is a 12 year female with a history of GERD, lower extremity greater than upper extremity spasticity and neurologic decline after an upper respiratory infection. Subsequent episodes of regression occurred after vaccinations and urinary tract infection. MRI at nine years of age showed bilateral and symmetric white matter abnormalities extending to the subcortical U fibers. Brainstem tract involvement was present and includes the intra-parenchymal trajectory of the trigeminal nerve.

LD_0181.0B was well until 12-14 months when declines in motor function were noted. She also has a history of GERD, lower extremity greater than upper extremity spasticity, and bilateral equinovarus. MRI at three and a half years was significant for bilateral and symmetric white matter abnormalities, with similar tract involvement in the brainstem as her sister and extensive cord involvement. There was no FLAIR rarefaction in either patient. There was no additional relevant family history.

LD_0181.0A and LD_0181.0B were previously reported in[5].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*DARS*	Het	chr2:136668744C>T	ENST00000264161	c.1379G>A	p.Arg460His
#2	*DARS*	Het	chr2:136664912G>C	ENST00000264161	c.1480C>G	p.Arg494Gly

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs587776985	0.000042	0.000061	Damaging	Damaging	DC
#2	rs147077598	0.000058	0.000116	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

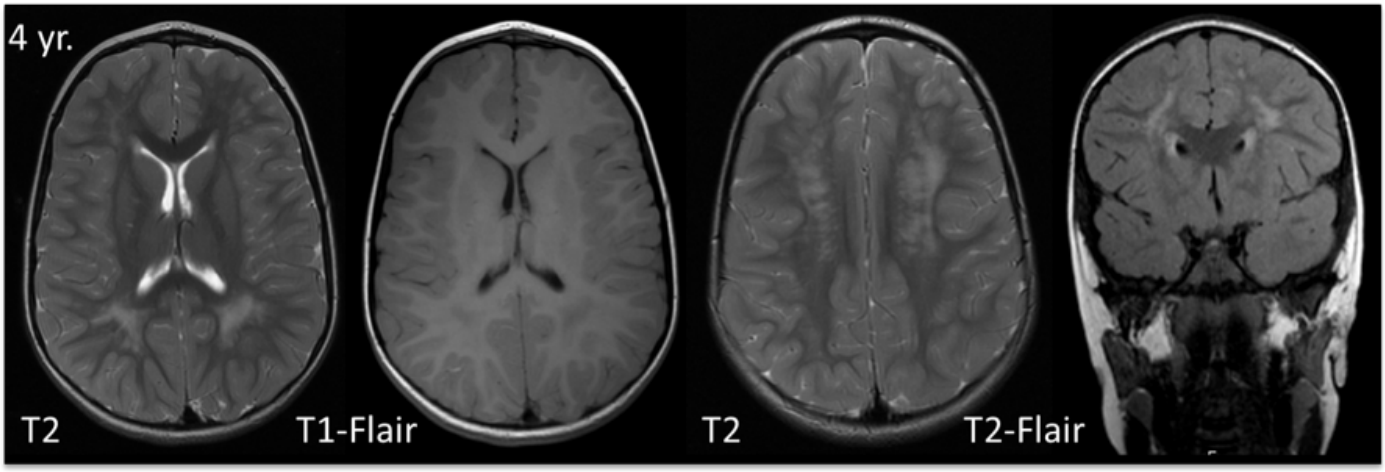
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PM2, PP1, PP2, PP3, PP4,
#2	Likely pathogenic	PM2, PM5, PP1, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Hypomyelination with brainstem and spinal cord involvement and leg spasticity (MIM:615281).

LD_0185 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0185.0A.

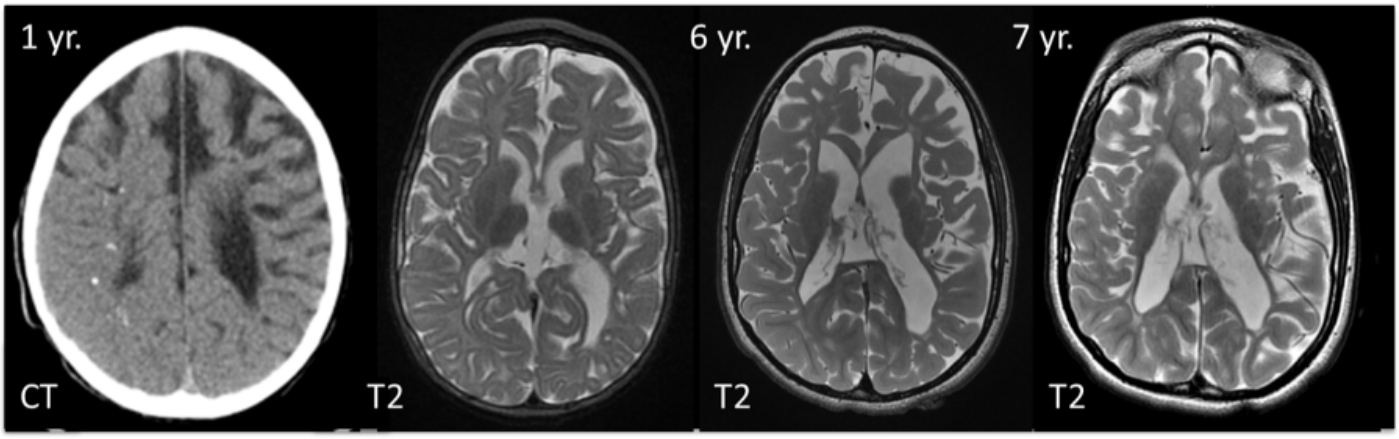
LD_0185.0A is a seven year old male of Northern European descent with a history of type I diabetes mellitus, seizures, and developmental regression. These episodes were initially attributed to hypoglycemia however subsequent episodes and developmental regression lead to diagnostic workup for an underlying cause. MRI at three and half years of age showed signal abnormality of the central WM involving all lobes with multifocal changes in a radiating pattern. There was no FLAIR rarefaction. Follow-up MRI at four years of age was stable. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0224 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0224.0A.

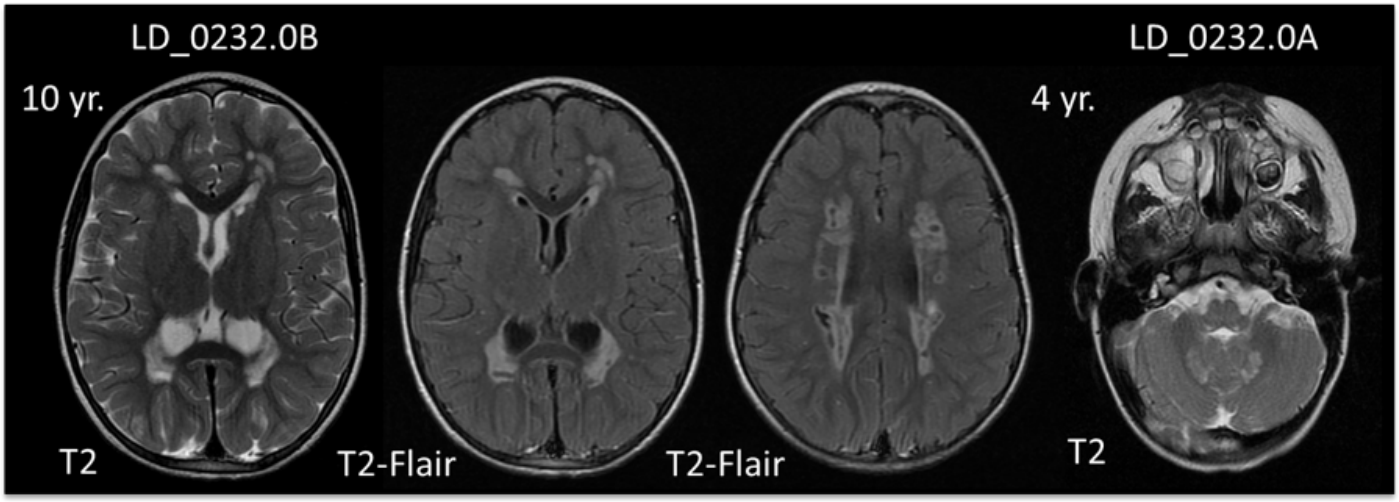
LD_0224.0A is a nine year old girl of African American descent. She has a history of hypoxic ischemic encephalopathy at birth with subsequent progressive encephalopathy, spastic quadriparesis, and seizure disorder. Neuroimaging was significant for progressive cerebral white matter atrophy over the first seven years of life, delayed myelination, enlarged ventricles, and bilateral periventricular calcifications (CT scan at one year, MRI at one year, six years and seven years). There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0232 Case Summary

MR imaging and clinical summary



MR imaging of individuals LD_0232.0A and LD_0232.0B.

LD_0232.0A and LD_0232.0B are siblings of Tunisian descent. LD_0232.0A is a 15 year old male and LD_0232.0B is a 17 year old female similarly affected with unsolved WM abnormalities of the brain and spine, short stature, recurrent lactic acidosis, failure to thrive, cardiac conduction defects and optic atrophy. MRI for LD_0232.0A at four years demonstrated multifocal T2 hyperintense changes in the periventricular white matter, centrum semiovale and bilateral cerebellar white matter with cystic rarefaction.

MRI for LD_0232.0B at ten years demonstrated multifocal T2 hyperintense changes in the periventricular white matter, centrum semiovale and bilateral cerebellar white matter with cystic rarefaction. There was no additional relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*MRPS22*	Het	chr3:139069088G>A	ENST00000310776	c.572G>A	p.Arg191Gln
#2	*MRPS22*	Het	chr3:139071496A>AC	ENST00000310776	c.741dup	p.Lys248fs

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs768880732	0.000041	0.000096	Damaging	Damaging	DC
#2	-	-	-	-	-	-

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

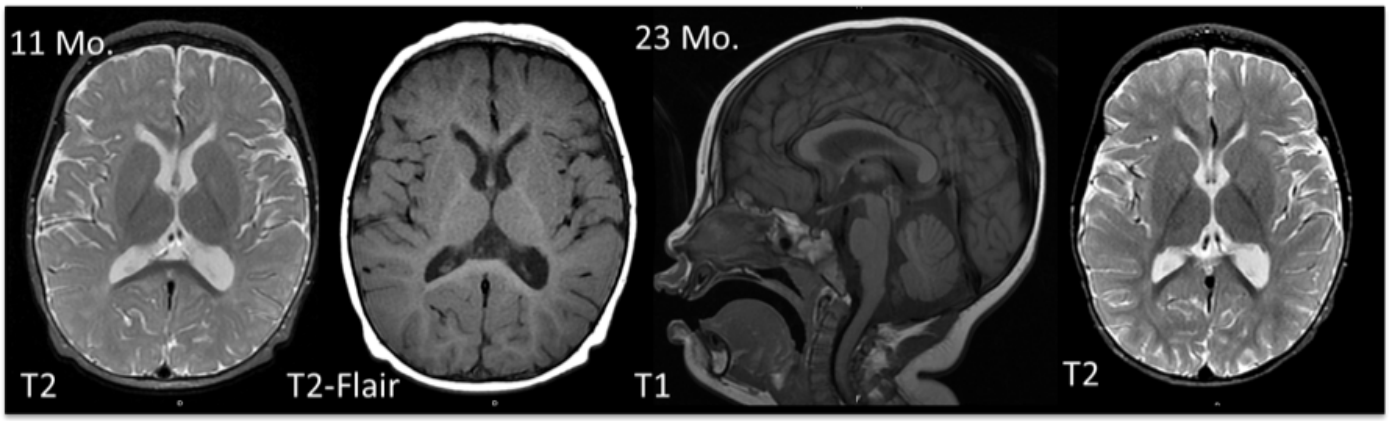
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PM2, PM3, PP1, PP2, PP3, PP4,
#2	Pathogenic	PVS1, PM2, PM3, PP1, PP2, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Combined oxidative phosphorylation deficiency 5 (MIM:611779).

LD_0246 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0246.0A.

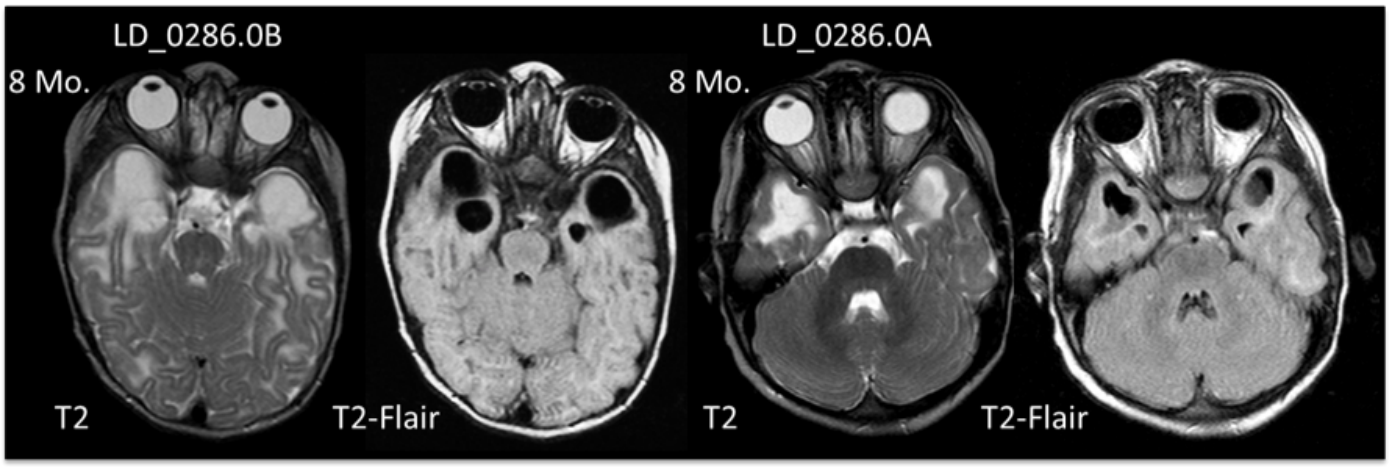
LD_0246 is a six year old male of Korean descent. He has a history of hypotonia, epilepsy and developmental delay. MRI at 11 months and two years of age were significant for delayed but progressing myelination and mild cerebral volume loss. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0286 Case Summary

MR imaging and clinical summary



MR imaging of individuals LD_0286.0A and LD_0286.0B.

LD_0286.0A A and LD_0286.0B are male siblings of mixed-European descent. LD_0286.0B is a six year old male with unsolved leukoencephalopathy coming to medical attention within the first months of life due to concerns of irritability, hypotonia, sensorineural hearing loss, febrile seizures and developmental delay. MRI at 24 months of age was significant for bilateral temporal lobe cysts, patchy scattered white matter abnormalities in the periventricular and subcortical white matter.

LD_0286.0B is a five year old male that is similarly affected. He came to attention during the first three months of life with irritability and failure to thrive. He has sensorineural hearing loss, developmental delay and febrile seizures. MRI at eight months of age was significant for bilateral temporal lobe cysts, small corpus callosum, and periatrial white matter abnormalities. There was no additional relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*RMND1*	Hom	chr6:151751289T>C	ENST00000367303	c.713A>G	p.Asn238Ser

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs144972972	0.000174	0.000466	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

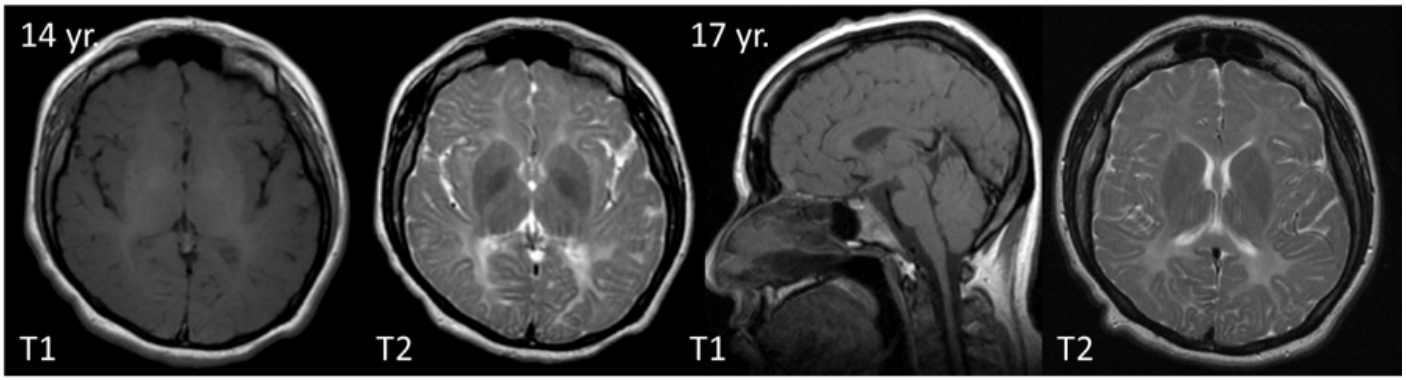
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PM2, PM3, PP1, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Combined oxidative phosphorylation deficiency 11 (MIM:614922).

LD_0306 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0306.0A.

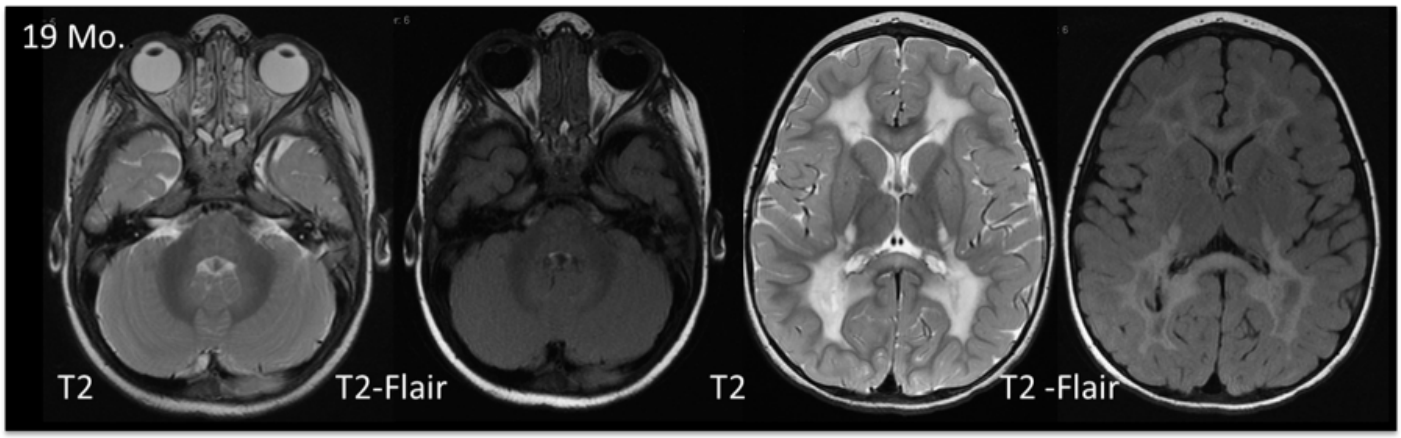
LD_0306.0A is a 26 year old female of mixed European descent who has had a progressive decline in physical abilities since three years of age including gait disturbance and speech issues. She has a history of progressive optic atrophy, dementia, ataxia, spasticity and sensorimotor peripheral neuropathy. MRI at 14 years of age was significant for diffuse hypomyelinating leukodystrophy with involvement of the corpus callosum and internal capsule and T1 signal abnormality in the putamen. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0315 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0315.0A.

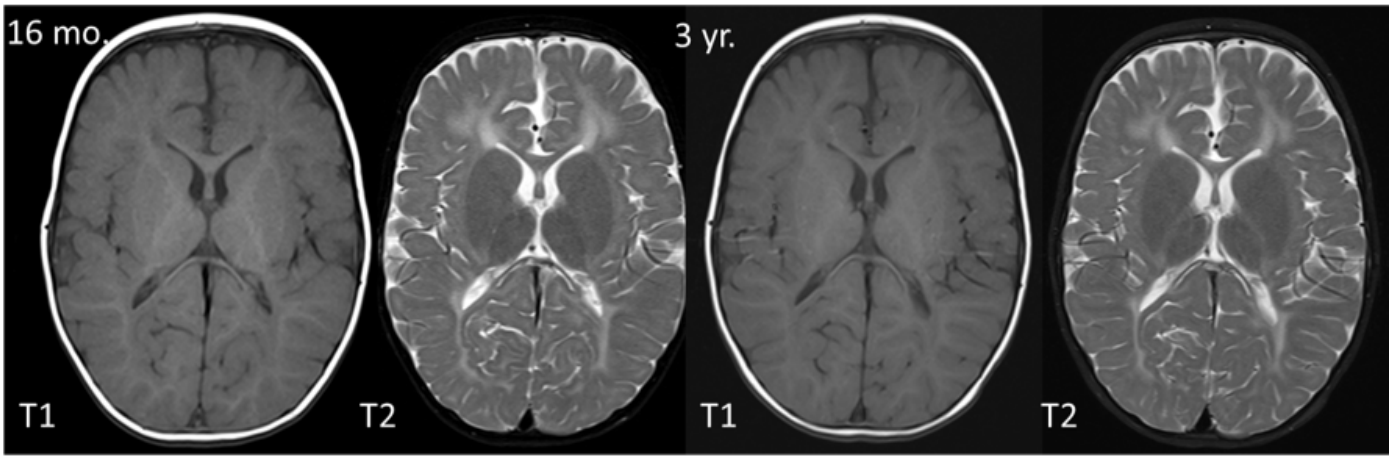
LD_0315.0A is a five year old African-American male with a history of right sided weakness, gait dysfunction, and poor fine motor control. He has been clinically stable since infancy. MRI at 19 months of age shows diffuse demyelination with basal ganglia and corpus callosum involvement, as well as cystic lesions. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0327 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0327.0A.

LD_0327.0A is a six year old female of mixed European descent. She has a history of developmental delay, hypotonia, poor cortical vision with no ocular abnormalities, and failure to thrive, along with episodes of focal motor seizures in the context of fever. MRI at 16 months is significant for hypomyelination in the periventricular, frontoparietal, and temporal regions. There is no brainstem or cerebellar involvement or other structural abnormalities. Myelination had not progressed on follow up images at age three. There was no relevant family history.

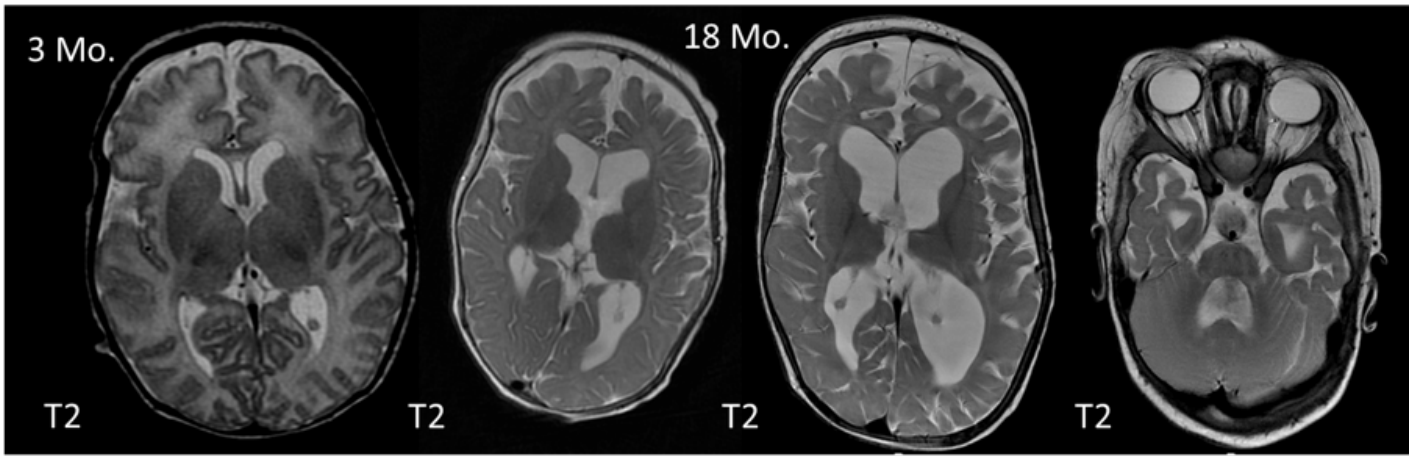
No candidate variants were identified in this case.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0333 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0333.0A.

LD_0333.0A is a six year old female of mixed-European descent. She came to attention at birth due to hypotonia and feeding issues. She has a history of developmental arrest, opisthotonic posturing, bilateral hydronephrosis, bilateral hearing loss, and GERD. EMG was significant for a demyelinating polyneuropathy and MRI at birth showed abnormal T2 signal and follow up at six months and 18 months showed diffuse progressive white matter volume loss and persistent hypomyelination involving the cerebrum and deep brain structures and brainstem,. She had a sister who died in the context of respiratory complications with a similar phenotype. There was no additional relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*CNTNAP1*	Het	chr17:40836203C>T	ENST00000264638	c.319C>T	p.Arg107*
#2	*CNTNAP1*	Het	chr17:40838987T>C	ENST00000264638	c.967T>C	p.Cys323Arg

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	-	-	DA
#2	rs768554986	0.000017	0.000030	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

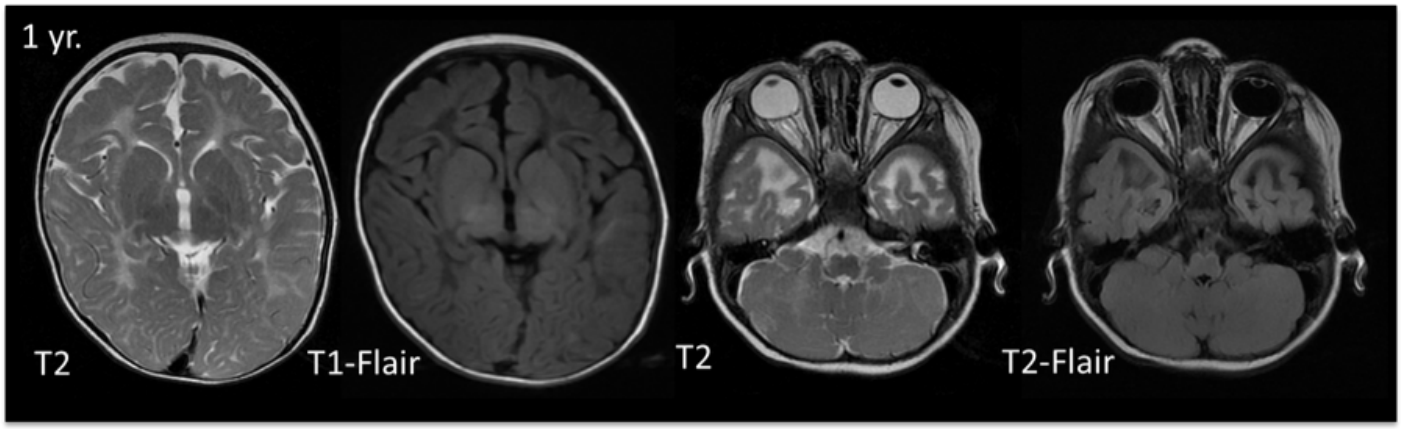
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PVS1, PM2, PP2, PP3, PP4,
#2	Likely pathogenic	PM2, PM3, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Lethal congenital contracture syndrome 7 (MIM:616286). Nonsyndromic arthrogryposis multiplex congenita (MIM:616286).

LD_0336 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0336.0A.

LD_0336 presented at two months of age with nystagmus stiffening episodes, marked hypotonia, developmental delay, and seizure disorder. Patient death at 15 months was due to G-tube complications and uncontrollable seizures. MRI of the brain at three and eight months of age showed persistent lack of myelination with white matter rarefaction in the temporal tips bilaterally. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0346 Case Summary

MR imaging and clinical summary

No MR imaging is avalible for this case.

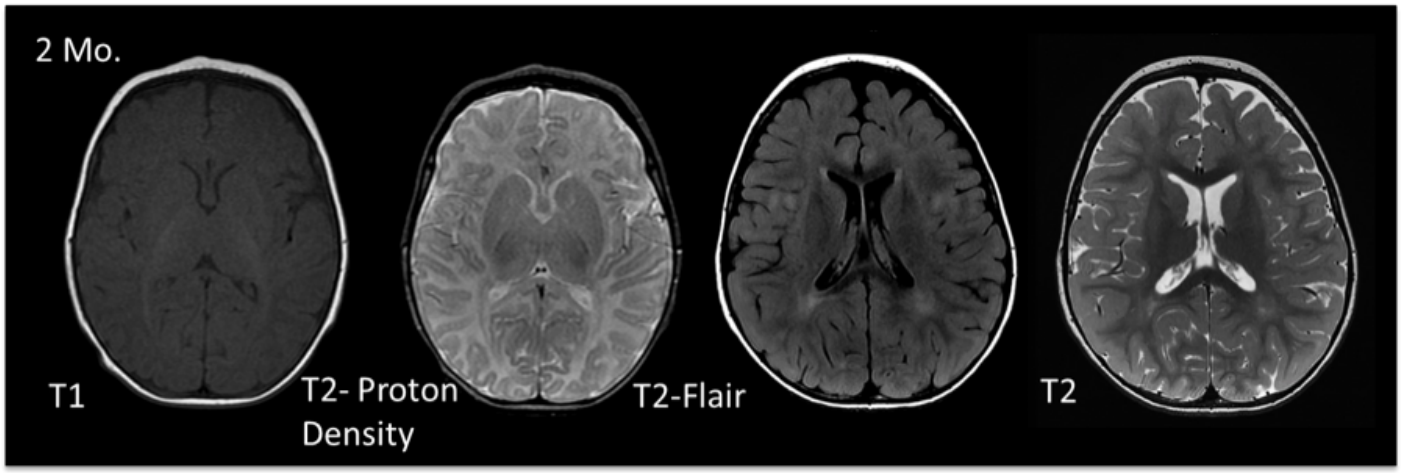
LD_0346.0A is a 16 year old male from Australia who came to medical attention at five years of age due to poor coordination, left-sided weakness, and fine motor skill issues. MRI was significant for prominent involvement of the cerebellar and middle cerebellar peduncles and brainstem. There was no relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0358 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0358.0A.

LD_0358.0A is a five year old female of mixed European descent who came to medical attention on day two of life due to seizures. She has motor and developmental delay, nystagmus, and medically refractory seizures. MRI at two months of age demonstrated delayed myelination and follow up at three years of age was notable for T2 hyperintensity in the bilateral periatrial white matter. There was no relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*STXBP1*	Het, *de novo*	chr9:130435529C>T	ENST00000373302	c.1099C>T	p.Arg367*

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	-	-	DA

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

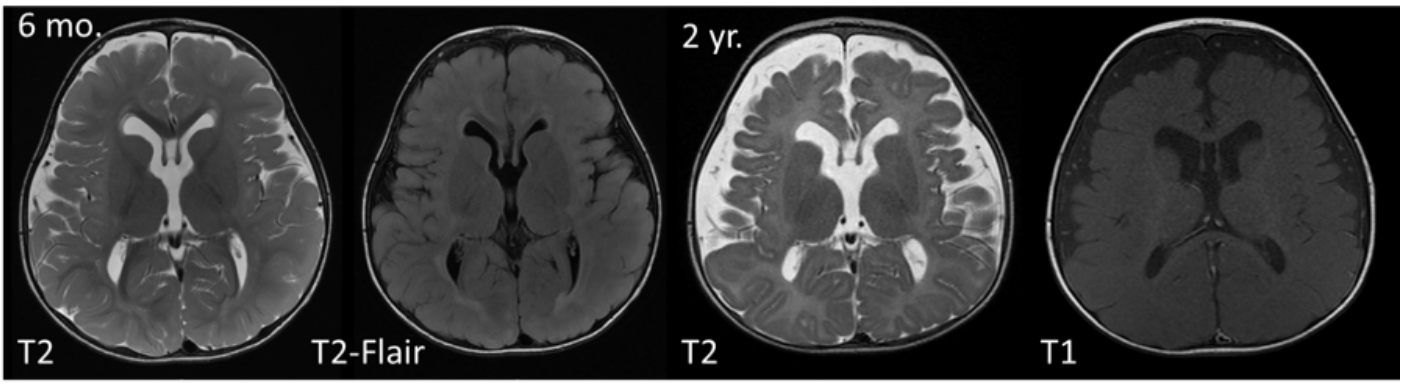
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PVS1, PS2, PM2, PP3,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Epileptic encephalopathy, early infantile, 4 (MIM:612164).

LD_0366 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0366.0A.

LD_0366.0A is a three year old male of mixed European descent. Patient came to medical attention at one week due to poor feeding. Over time he developed global developmental delay and dysmorphic features including macrocephaly, synophrys, bifid uvula, tapered fingers, and hypospadias. Initial MRI at six months of age showed a delayed pattern of myelination with probable cerebral volume loss and enlargement of the extra-axial CSF spaces. Subsequent MRI studies revealed prominent third and lateral ventricles and extra-axial spaces as well as delayed myelination. MRI at two years of age and showed interval progression of myelin a mild decrease in the prominence of the subarachnoid spaces and ventricular system. There was no relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*GATAD2B*	Het, *de novo*	chr1:153789928G>A	ENST00000368655	c.820C>T	p.Gln274*

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	-	-	DA

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

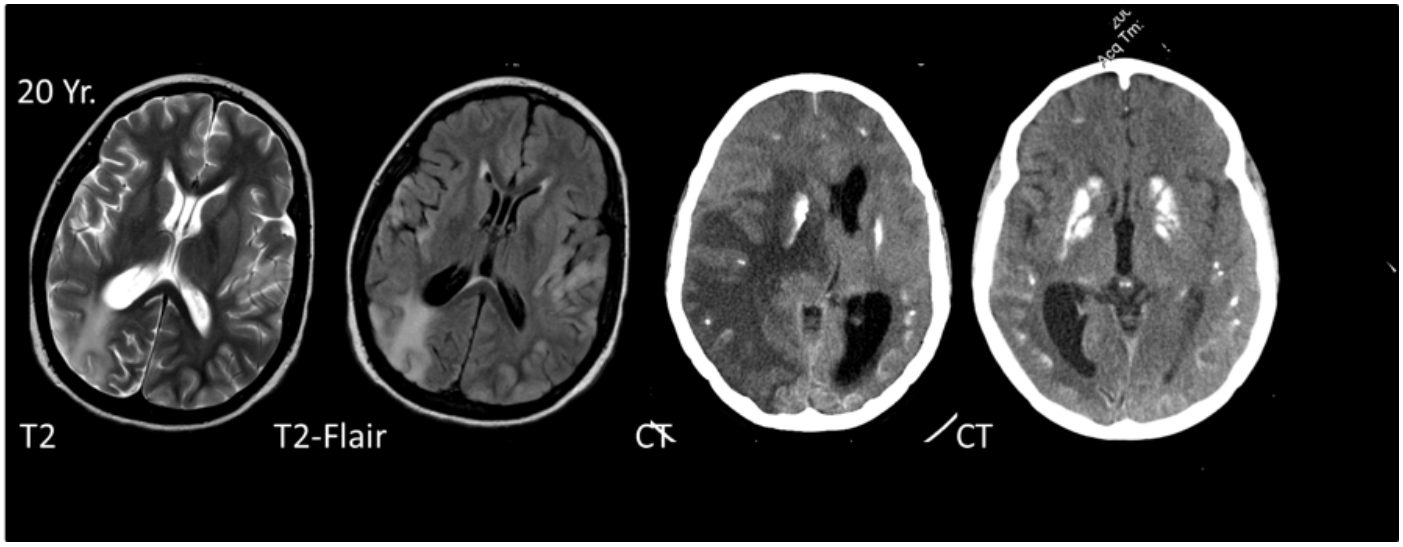
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PVS1, PS2, PM2, PP2, PP3,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Mental retardation, autosomal dominant 18 (MIM:615074).

LD_0373 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0373.0B.

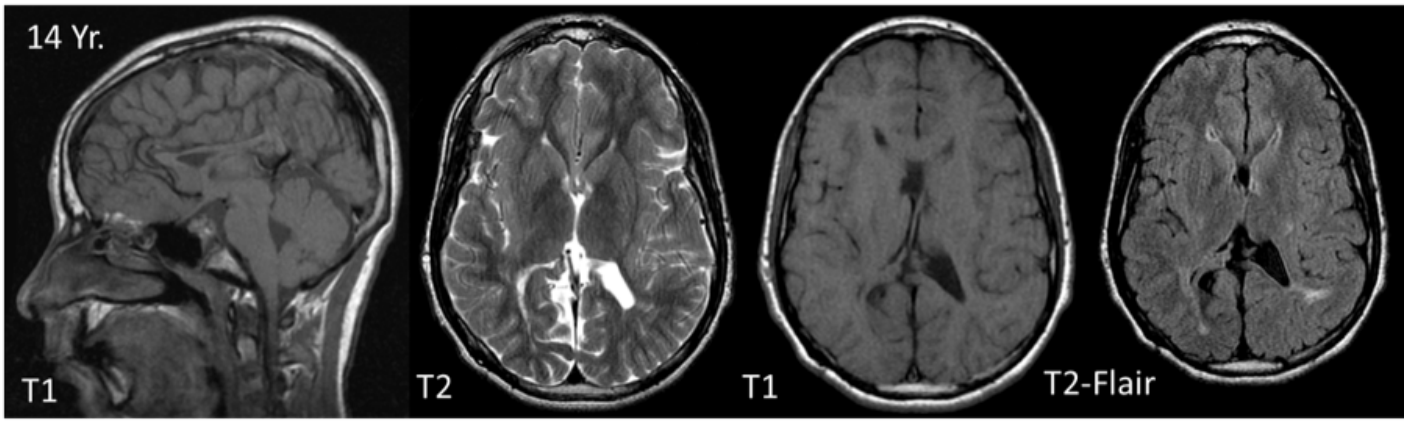
LD_0373.0A and LD_0373.0B are male siblings of mixed European descent. LD_0373.0A presented with neurologic symptoms at 19 years of age due to balance issues, visual loss, and seizures and had a history of Von Willebrand's disease and seronegative juvenile rheumatoid arthritis. CT scan was significant for symmetric basal ganglia calcifications, and further neuroimaging confirmed this on MRI with additional abnormal FLAIR signal in the right temporal hippocampal, bioccipital, and left temporal regions. LD_0373.0B is a 27 year old male who had sudden onset of seizures at 14 years of age and was also followed by endocrinology for short stature. Head CT performed at the time was significant for basal ganglia calcifications. Both young men died in the context of stroke like events with no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0393 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0393.0E.

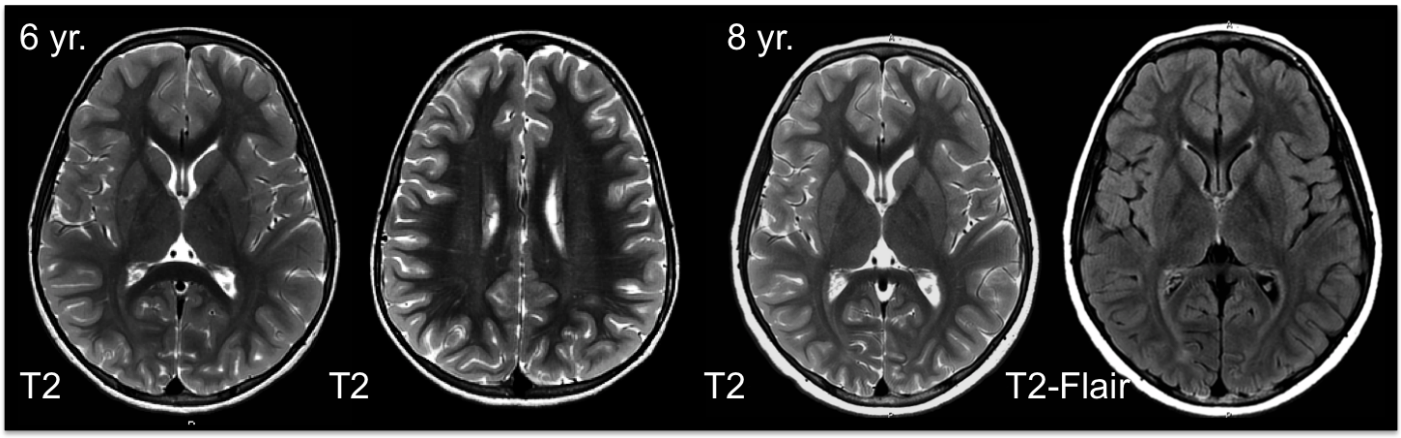
LD_0393.0A, LD_0393.0B, are siblings who are cousins to LD_0393.0C, LD_0393.0D, and LD_0393.0E, all of Middle-Eastern descent. LD_0393.0A is deceased. LD_0393.0C. LD_0393.0D had a clinical course marked by a neonatal hydrocephalus with cerebral calcifications. LD_0393.0A, LD_0393.0B had a normal neonatal period. All the affected children have a severe, subacute degeneration with pseudobulbar affect, dysarthria, dysphagia, and spastic quadriplegia, progressing over 2-3 years, with significant bony abnormalities. MRI Brain in all patients demonstrates mild atrophy with periventricular increased T2 and FLAIR signal. Basal ganglia demonstrate calcifications (image not shown). There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0461 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0461.0A.

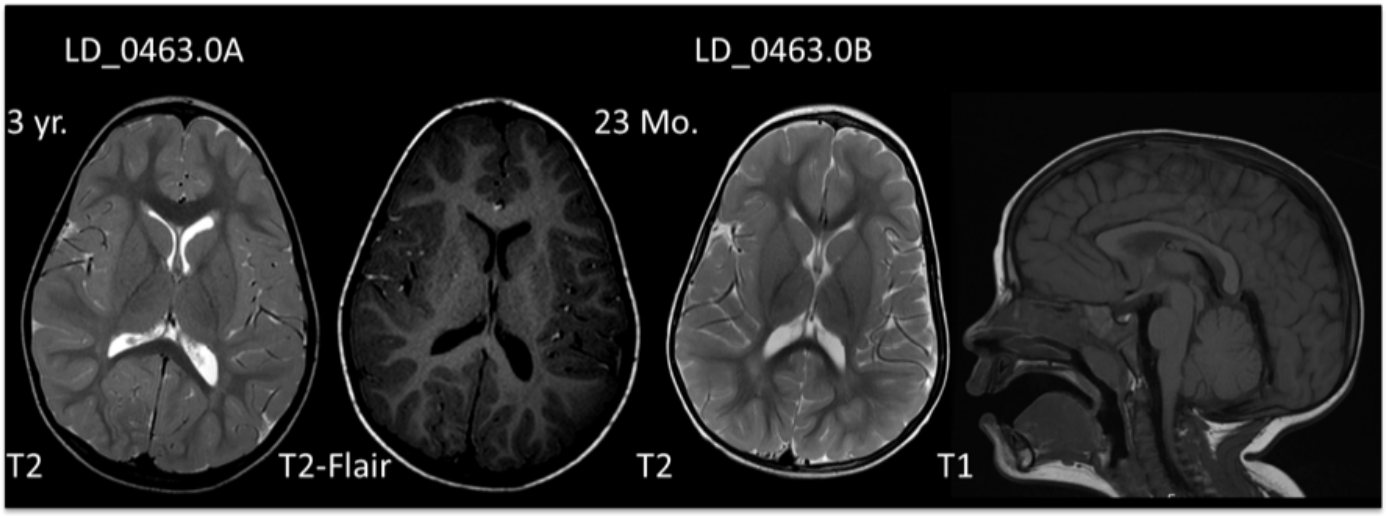
LD_0461.0A is a nine year old male from Puerto Rico seen in the context of autism spectrum disorder, elevated serum lactate levels, and paternally inherited copy number variant identified by oligonucleotide array (A 500-kb duplication of a region within cytogenetic band 1p31.3). He never developed speech but otherwise has no physical limitations. Initial MRI at six years of age was concerning for posterior fossa changes, resolved on follow-up two years subsequent to the initial MRI. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0463 Case Summary

MR imaging and clinical summary



MR imaging of individuals LD_0463.0A and LD_0463.0B.

LD_0463.0A and LD_0463.0B are a sibling pair with progressive spastic paraplegia and macrocpehaly and delays in both speech and language. LD_0463.0A (six year old male), the younger brother of LD_0463.0B (seven year old female) is more mildly affected with slightly later onset (18 months versus 15 months respectively). MRI at 23 months for LD_0463.0A was significant for abnormal signal in the periatrial white matter. MRI at two years of age for LD_0463.0B was significant for abnormal signal in the periatrial white matter. Follow-up scan at four years of age was stable. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*ALS2*	Het	chr2:202589115G>A	ENST00000264276	c.3415C>T	p.Arg1139*
#2	*ALS2*	Het	chr2:202591207C>T	ENST00000264276	c.3248G>A	p.Gly1083Glu

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs767350733	0.000017	0.000030	-	-	DA
#2	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

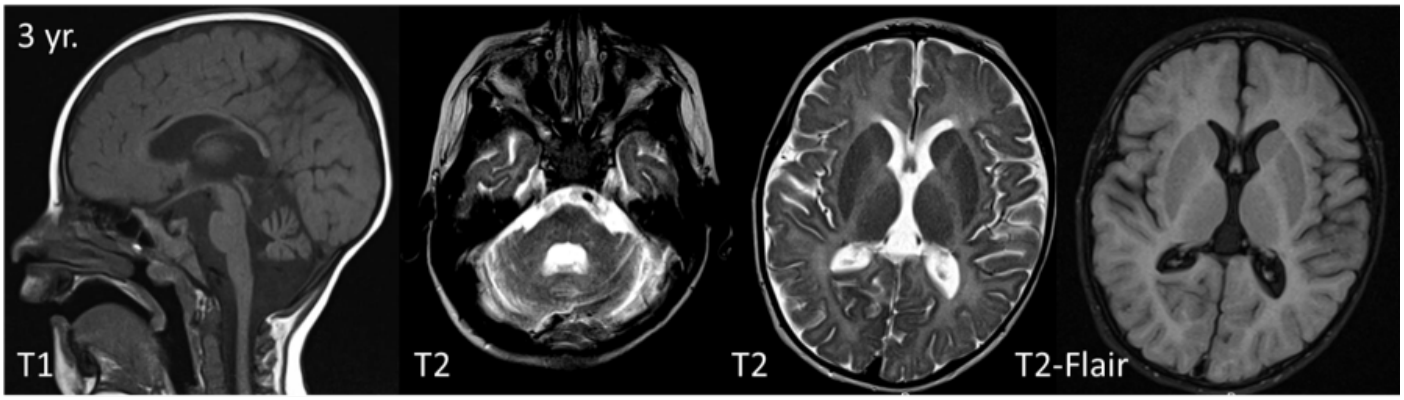
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PVS1, PM2, PM3, PP1, PP2,
#2	Pathogenic	PVS1, PM2, PM3, PP1, PP2, PP3,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Amyotrophic lateral sclerosis 2, juvenile (MIM:205100).

LD_0493 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0493.0A.

LD_0493.0A is a six year old male of mixed European descent with a history of congenital microcephaly, developmental arrest, hypotonia, epilepsy, dysmorphism and failure to thrive. He came to attention at birth with decreased prenatal movements, respiratory distress at birth, and developmental arrest. Epileptic encephalopathy was diagnosed at 14 months of age, significant for myoclonic jerks, upper extremity stiffening, and gelastic events. MRI at three years of age was significant for hypomyelination and supratentorial volume loss, as well as cerebellar atrophy or agenesis. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*FLNA*	Het, *de novo*	chrX:153580347A>C	ENST00000369850	c.6812T>G	p.Leu2271Arg

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

Variant	Classification	ACMG Criteria[a]
#1	VUS	PM2, PP2, PP3,

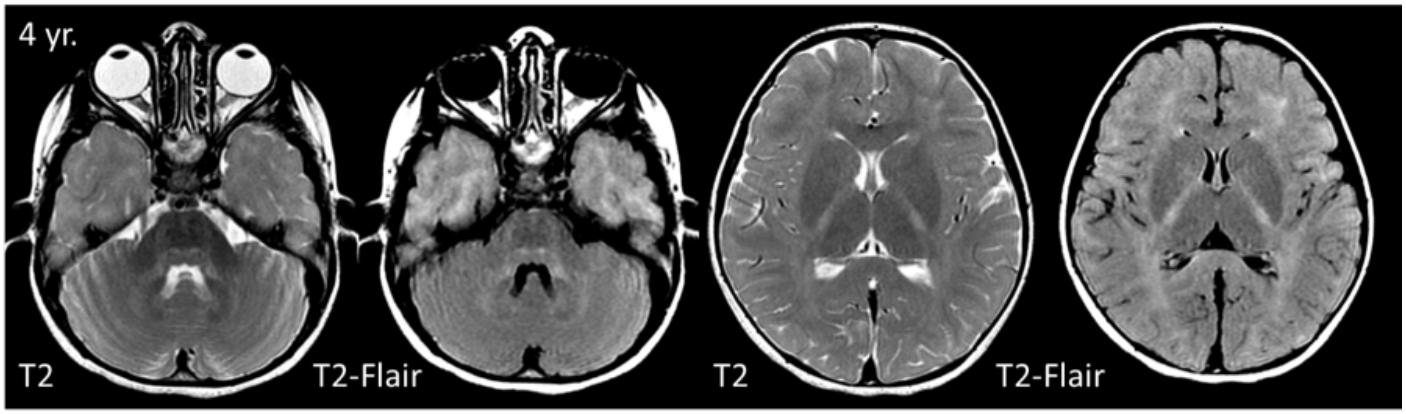
[a] ACMG criteria upon which classification is based[1].

Clinical Interpretation
Although the variant was classified as a VUS, this variant segregated within the family and given the phenotypic spectrum of FLNA related mutations, we felt this was consistent with this child's phenotype.

Final Diagnosis
Clinically Resolved: Heterotopia, periventricular (MIM:300049).

LD_0498 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0498.0A.

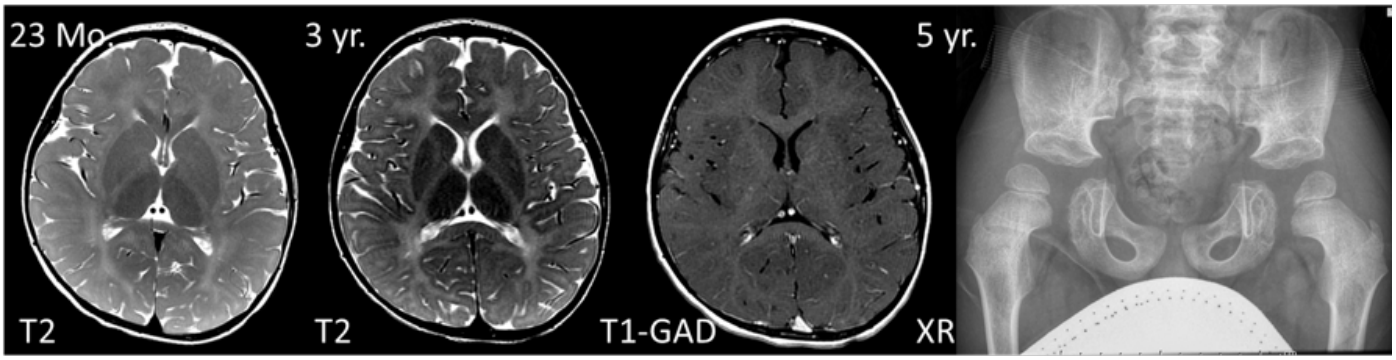
LD_0498.0A is a seven year old female from the United Arab Emirates with an undiagnosed leukodystrophy. She has a history of ataxia, erratic eye movements, retinal rod/cone dystrophy, developmental delay, and cleft palate. MRI at four years of age revealed increased T2 signal with sparing of the subcortical U-fibers. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0500 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0500.0A.

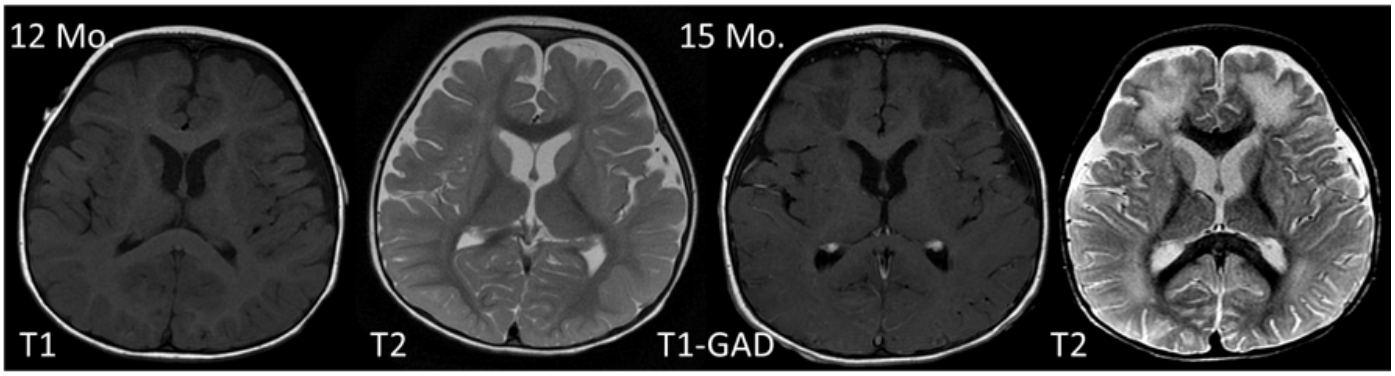
LD_0500.0A is a four year old male of Indian descent. He has a history of gross motor delay, gait disturbance, and hypotonia. He has since had progressive declines in vision and gait. MRI at two years of age showed hypomyelination that was persistent on follow up imaging at three years. Spondylometaphyseal dysplasia was also present on XR imaging of the hips. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0503 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0503.0A.

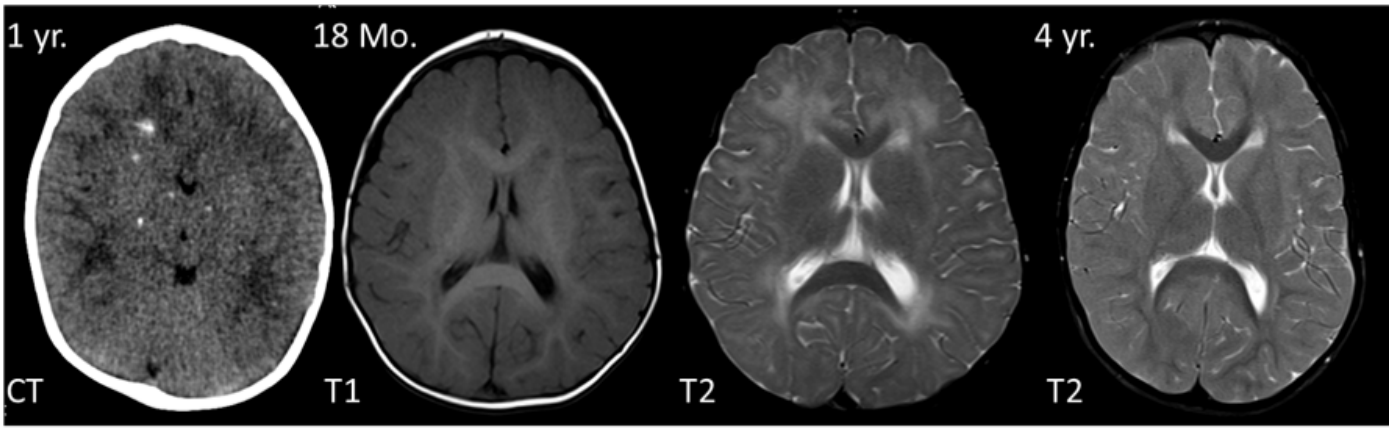
LD_0503.0A is a two year old male from Guatemala with congenital hearing loss and hypotonia. Family history is significant for a sibling with hearing loss that passed away due to pneumonia. He has had a history of febrile events and feeding difficulties. MRI at nine months was questionably for delayed myelination. Follow-up at 15 months after further clinical deterioration confirmed a demyelinating leukoencephalopathy. He died shortly thereafter of multisystem organ failure. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0513 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0513.0A.

LD_0513.0A is a six year old male of mixed European descent. He is seen in the context of unexplained microcephaly, craniosynostosis with multiple craniectomies for cranial vault expansion in constellation with increased intracranial pressures and developmental delay. Birth history is significant for IUGR and oligohydramnios. Initial MRI was performed at three months of age with signal abnormality noted in the internal capsule and cerebral white matter. Follow-up imaging was performed routinely at ages of 17 months and four years of age. This was significant for parenchymal and basal ganglia calcifications on CT and increased T2 signal findings in the supratentorial white matter in the periventricular regions with delayed but improving myelination. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0527 Case Summary

MR imaging and clinical summary

No MR imaging is avalible for this case.

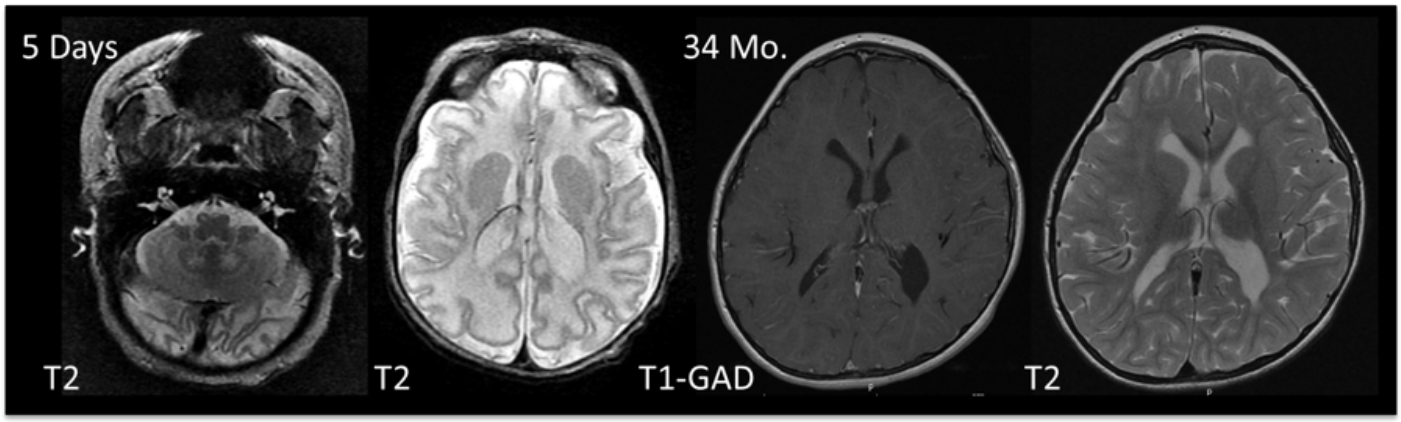
LD_0527.0A is a six year old male of European descent. He came to medical attention at one month of age with nystagmus and subsequent workup was significant for developmental delay, spasticity, and limited voluntary movement. MRI is not available but reportedly showed hypomyelination. Clinical testing excluded standard etiologies in the differential diagnosis of hypomyelination including PLP1 deletion/duplication and sequencing. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0536 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0536.0A.

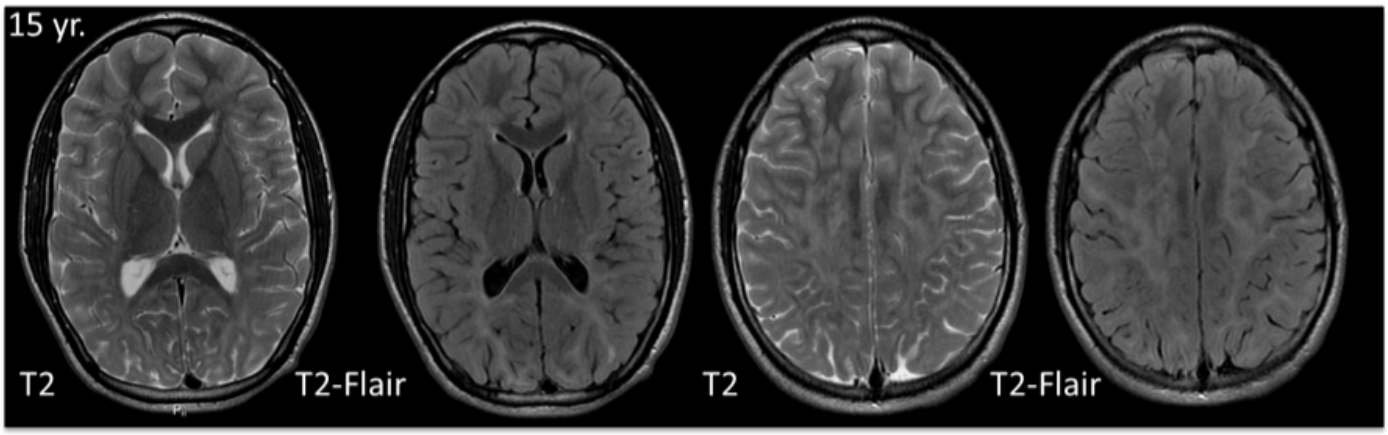
LD_0536.0A is a three year old female of mixed European descent who came to medical attention at birth with WM signal abnormalities on full term newborn imaging, irritability, and tremulousness. She also has a history of microcephaly, developmental delay and infantile spasms followed by myoclonic seizures. Perinatal imaging demonstrated overall increased white matter signal with multifocal subcortical hyper intensities. Gyration was immature for age though improved at one year of age but by 34 months there was persistently abnormal myelin, with loss of white matter volume in the deep white matter. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0542 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0542.0A.

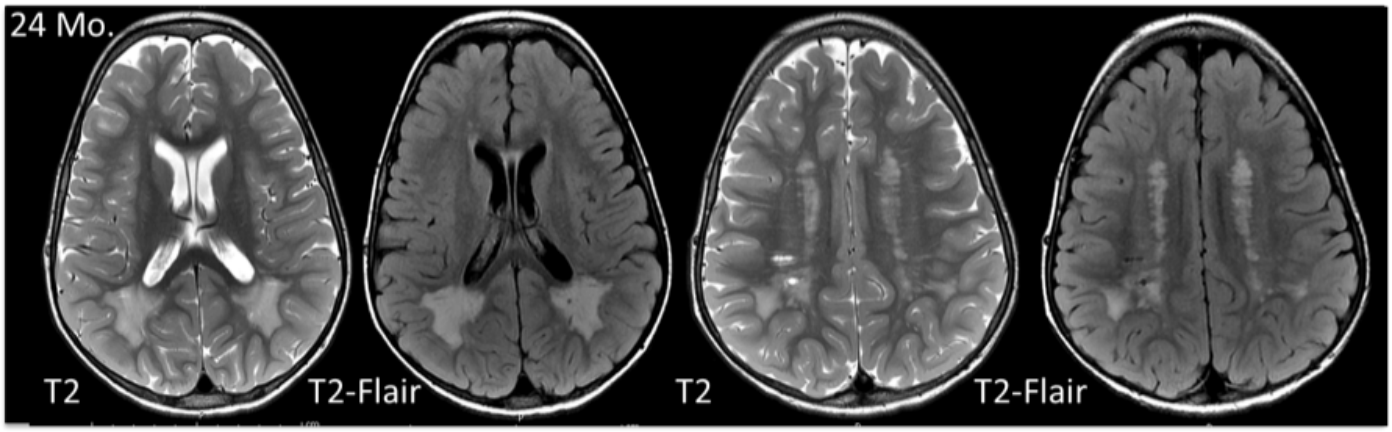
LD_0542.0A is an 18 year old male of mixed European descent seen in the context of abnormal MR imaging and a progressive spastic paraplegia. Gait abnormalities continued to worsen with reduced endurance. Elevations in CSF pterins were noted. MRI at 15 years demonstrated multifocal white matter abnormalities. Spinal cord abnormalities were not detected. MRIs have been stable over a period of four years. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0573 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0573.0A.

LD_0573.0A is a four year old male of African descent who presented at three months of age in the context of a respiratory infection and macrocephaly. He has a history of failure to thrive and congestive heart failure requiring surgery since which he has made rapid gains in development. CT scan at 18 months of age was performed due to macrocephaly and revealed low attenuation in the posterior cerebral white matter. Follow-up MRIs at 18 months and two years of age demonstrated symmetric bilateral paraventricular white matter T2 signal change with enlargement of the perivascular spaces. There was no other relevant family history.

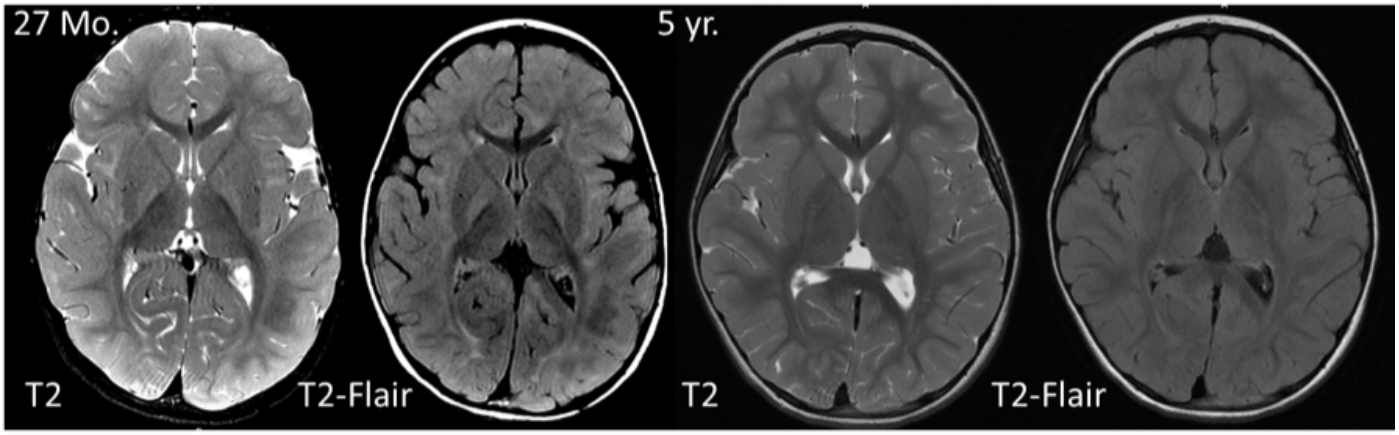
No candidate variants were identified in this patient.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0578 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0578.0B.

LD_0578.0A and LD_0578.0B are siblings of Puerto Rican descent. LD_0578.0B is an 8 year old female with behaviors consistent with autism spectrum disorder, speech delay, and hyperactivity. MRI at 6 years of age was significant for chiari one malformation and enlarged perivascular spaces but otherwise the exam was unremarkable.

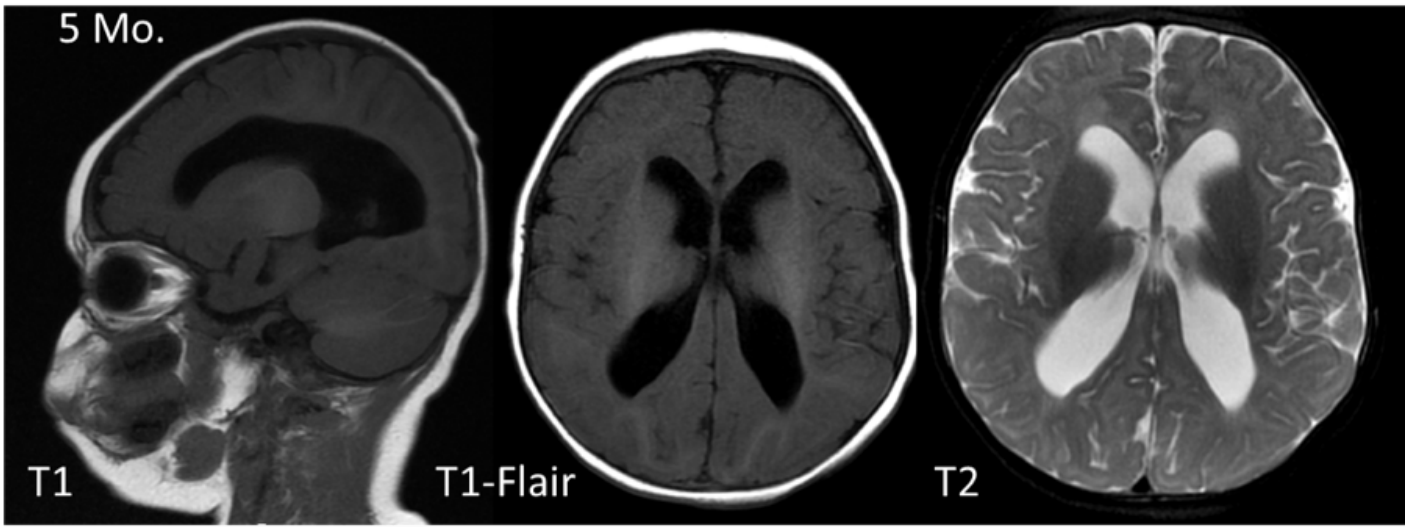
LD_0578.0A is seen in the context of sensorineuronal hearing loss and global developmental delay, and mild delayed visual maturation. MRI at two years showed abnormal signal in the globus pallidus, with enlarged perivascular spaces, more prominent than her sister. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0579 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0579.0A.

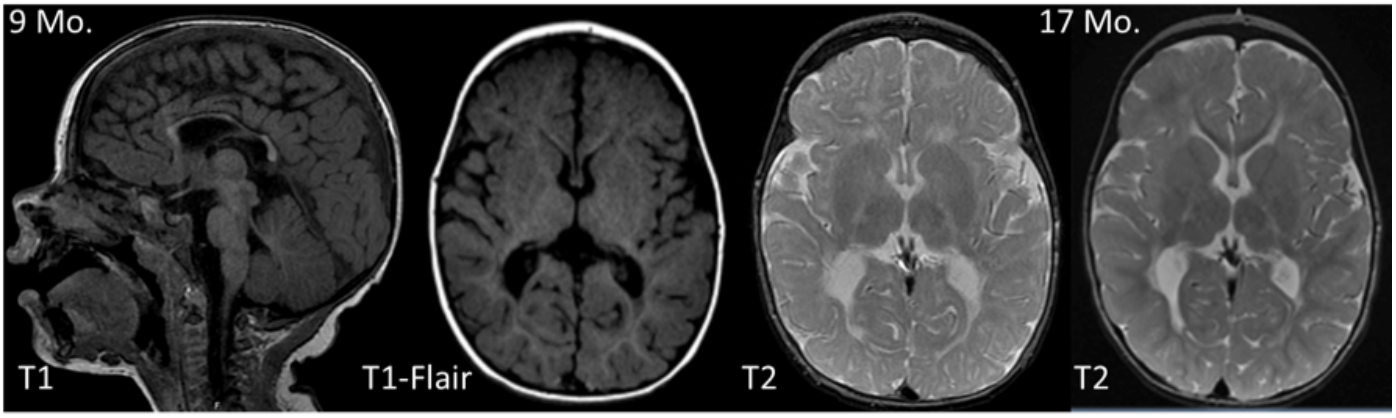
LD_0579.0A is a three year old male of Hispanic descent with epileptic encephalopathy characterized by infantile spasms and developmental delay. He was noted to have microcephaly, hydronephresis, and ventriculomegaly prenatally. At age five months parents noted exaggerated startle concerning for seizure as well as slowing of his development. An MRI demonstrated decreased white matter volume, delayed myelination, and generalized thinning of the corpus callosum. The patient was lost to follow up and no further imaging was obtained. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0583 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0583.0A.

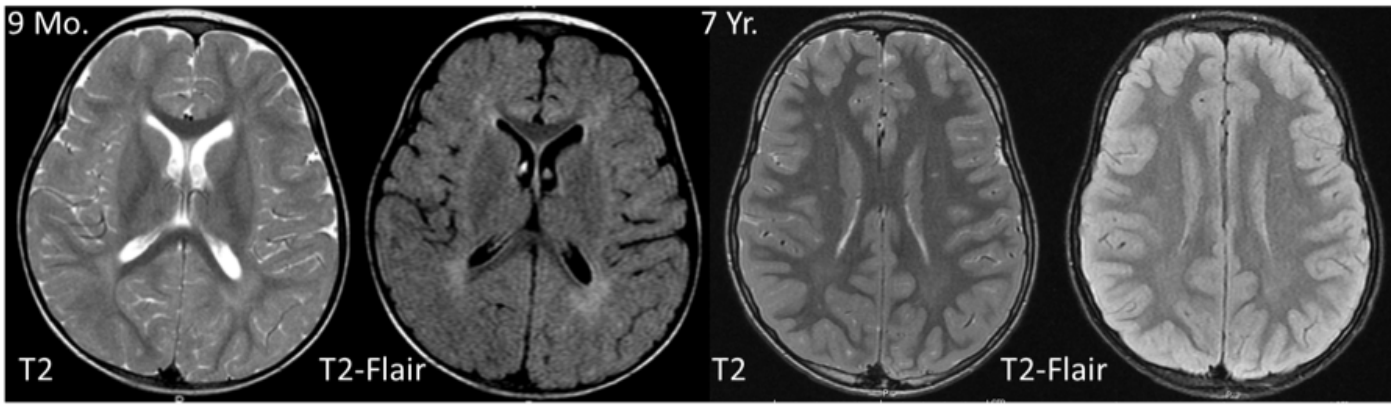
LD_0583.0A is a three year old male of mixed Northern European and Hispanic descent. He first came to medical attention at ten months of age due to inability to sit unsupported. He is seen in the context of bilateral esotropia, increased quadreparetic tone with spasticity and dystonia. MRI at nine months was significant for periventricular white matter volume loss and signal abnormality in the bilateral globus pallidi. Follow-up imaging showed improved myelination. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0587 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0587.0A.

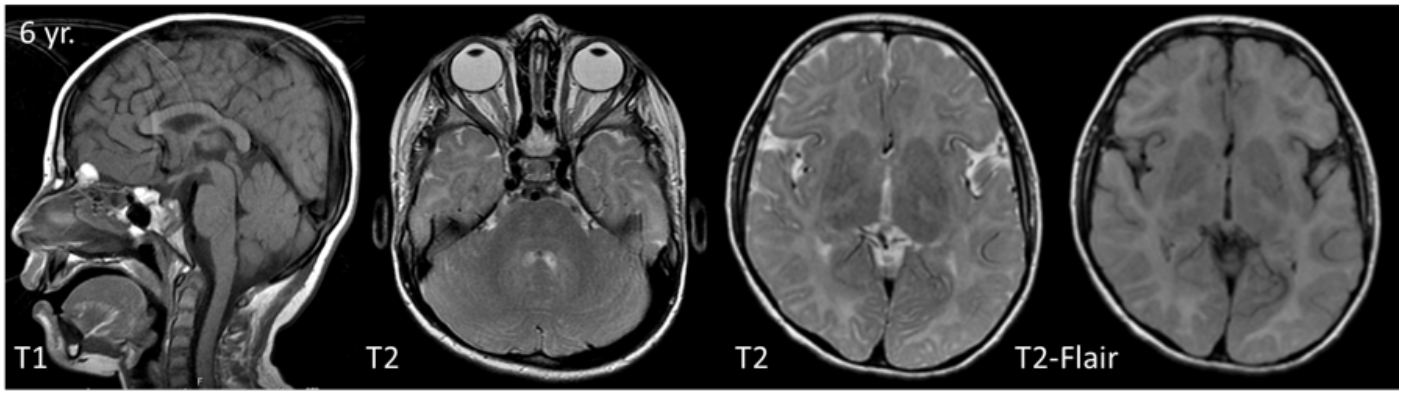
LD_0587.0A is a seven year old Caucasian male with global developmental delays noted before one year of age. Oligonucleotide microarray shows a maternally inherited deletion in chromosome 13q31 (Deletion of a 269-kilobyte band within cytogenetic region of 13q31.3). MRI at 16 months of age revealed multifocal, bilateral cerebral white matter abnormalities with hypoplastic posterior corpus callosum and brainstem. Follow-up imaging at seven years of age demonstrated progressive improvement in myelination with scattered T2 hyperintensities. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0594 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0594.0A.

LD_0594.0A is a nine year old male of mixed European descent with demyelinating peripheral polyneuropathy, global developmental delay, bilateral sensorineural hearing loss (diagnosed by newborn screening), early failure to thrive, and neuromuscular scoliosis. MRI at two months of age and follow-up at six years was significant for diffuse hypomyelination. Mother had sensorineural hearing loss without the other neurologic features seen in this child.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0600 Case Summary

MR imaging and clinical summary

No MR imaging is avalible for this case.

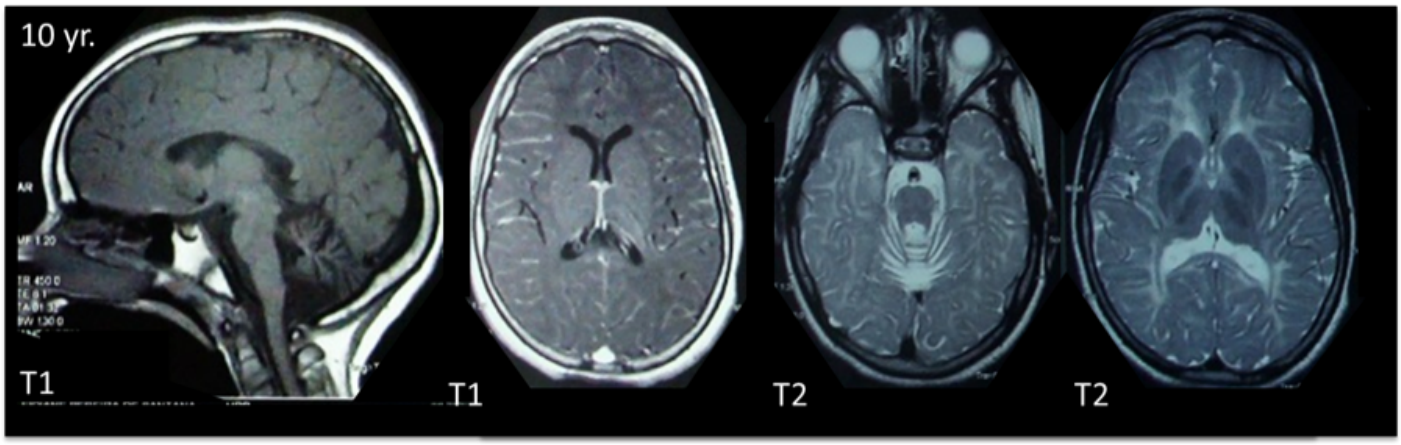
LD_0600.0A is a four year old African American male who came to medical attention at 17 months after normal development and growth. At 17 months he presented with three weeks of altered mental status in the context of low grade temperature, progressing to unsteadiness, difficulty swallowing, and loss of speech, followed by complete loss of developed skills and decreased responsiveness. MRI at 18 months of age showed diffuse white matter abnormality in the centrum semiovale and corona radiata involving in the parietal and temporal lobes. Follow up imaging at two years of age showed increased confluency of signal abnormalities with decreased swollen appearance. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0604 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0604.0A.

LD_0604.0A demonstrated arrest of developmental milestones as a toddler and progressive ataxia. She has had notably normal puberty and also normal dentition. MRI at ten years of age shows diffuse hypomyelination with hypointensity of the lateral thalami and globus pallidus. There was thinning of the cerebellar folia.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*POLR3B*	Het	chr12:106826199T>A	ENST00000228347	c.1568T>A	p.Val523Glu
#2	*POLR3B*	Het	chr12:106786897AGTGCCAG>A	ENST00000228347	c.813_819del	p.Cys272fs

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs138249161	0.000280	0.000495	Damaging	Benign	DC
#2	-	-	-	-	-	-

[-] indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

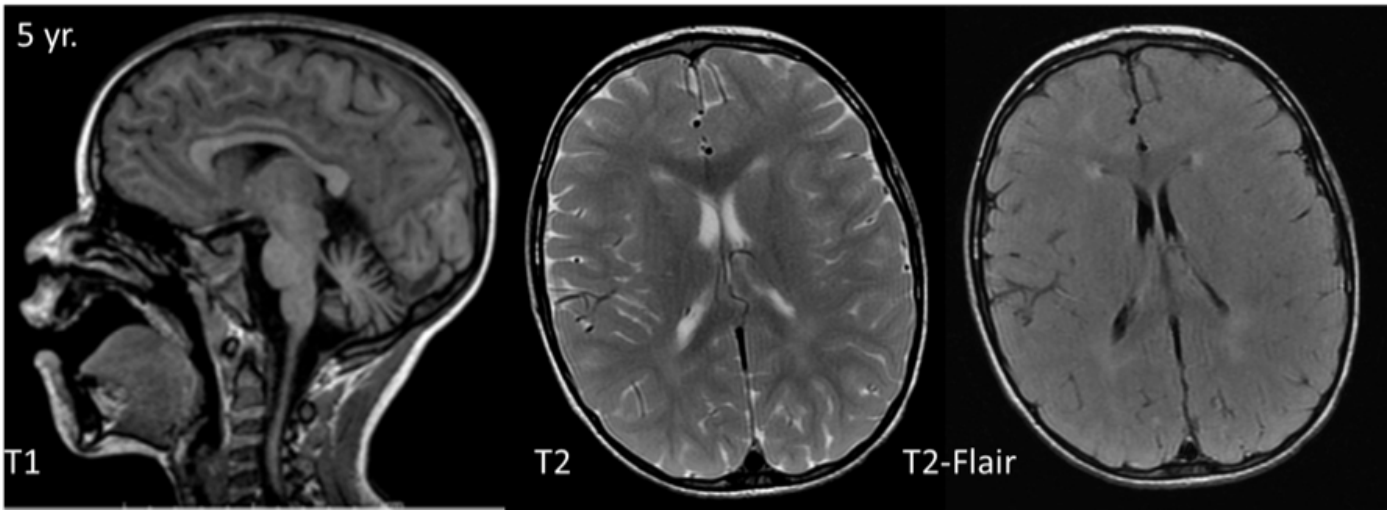
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS1, PM2, PM3, PP2, PP3, PP4,
#2	Pathogenic	PVS1, PM2, PM3, PP2, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism (MIM: 614381).

LD_0607 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0607.0A.

LD_0607.0A is a seven year old male of mixed European descent with a multisystem disorder characterized by elevated creatine kinase, recurrent infection with hypogammaglobulinemia, dyskertosis congenita, and mild transaminase abnormalities. The patient came to medical attention at two years with speech and fine motor delays. MRI of the brain at five years of age revealed moderate cerebellar atrophy and diffuse multifocal white matter changes. Follow-up MRI one year later showed unchanged T2 hyperintensities. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*TERT*	Het	chr5:1279546C>T	ENST00000310581	c.1990G>A	p.Val664Met
#2	*TERT*	Het	chr5:1271247G>A	ENST00000310581	c.2455C>T	p.Arg819Cys

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Tolerated	Benign	DC
#2	-	-	-	Damaging	Damaging	Polymorphism

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

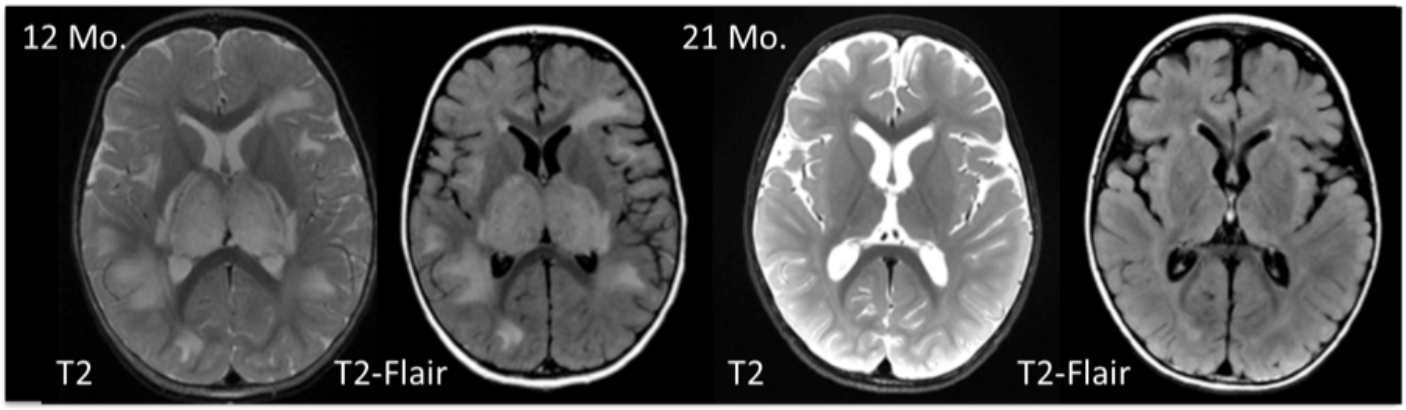
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS3, PM2, PM3, PP2, PP3, PP4,
#2	Pathogenic	PS3, PM2, PM3, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Dyskeratosis congenita, autosomal recessive 4 (MIM:613989).

LD_0611 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0611.0A.

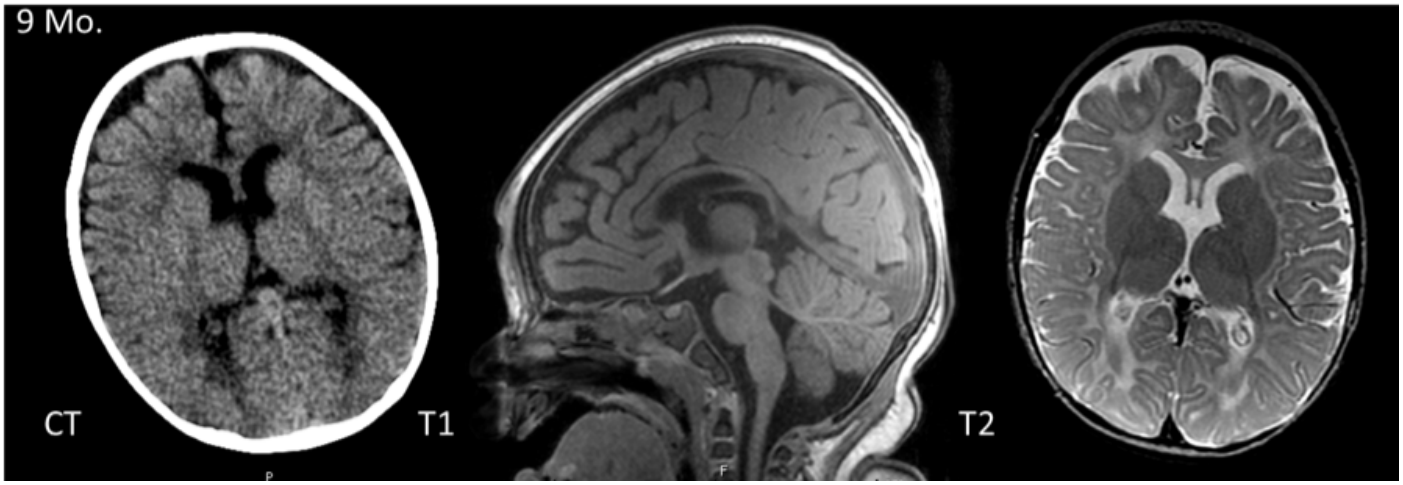
LD_0611.0A is a three year old male of Northern European descent with unsolved leukoencephalopathy with thalamic involvement in the context of CSF pleocytosis and febrile prodrome. He had unexplained facial weakness at eight months. He underwent a period of neurologic regression at one year of age with dystonia. MRI at 13 months of age was significant for multifocal patchy T2 signal abnormality and restricted diffusion within the brainstem and bilateral cerebral hemispheres, prominent in the thalami. Follow-up at 22 months showed significant atrophy of the thalami bilaterally and decreased size of the ventricles and sulci. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0616 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0616.0A.

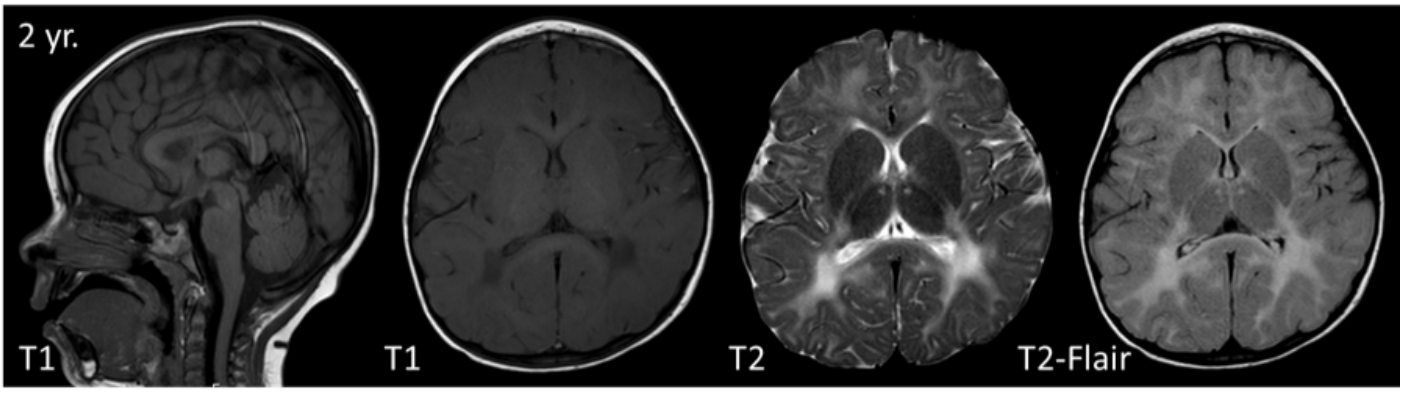
LD_0616.0A is a two year old male of Hispanic descent seen in the context of a primary progressive neurologic disorder. The patient came to attention at two - three months of age due to concerns of developmental delays and inability to make eye contact. He has a history of developmental delay, hypotonia, microcephaly and myoclonic epilepsy. Birth history is significant for bleeding at six months gestation and the possibility of shingles in the first trimester. MRI at nine months of age was significant for significant cerebral atrophy and delayed myelination. CT ruled out the presence of calcifications. Follow-up imaging has not been performed. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0617 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0617.0A.

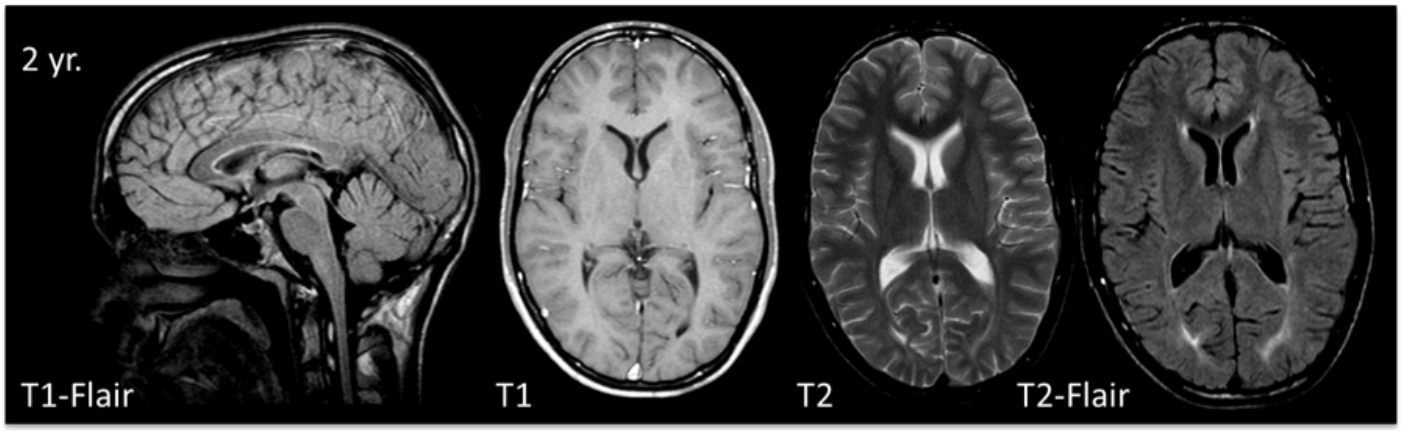
LD_0617.0A is a five year old female of unknown ethnicity who presented to medical attention due to congenital nystagmus and delayed development. She also developed ataxia, hyperreflexia, and spasticity in the lower extremities. She had two episodes of regression following fevers but returned to baseline within a week, otherwise has made slow gains. MRI imaging at two years of age demonstrated bilateral white matter signal abnormalities more prominent within the parietooccipital regions, and small thalamic hyperintensities. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0622 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0622.0A.

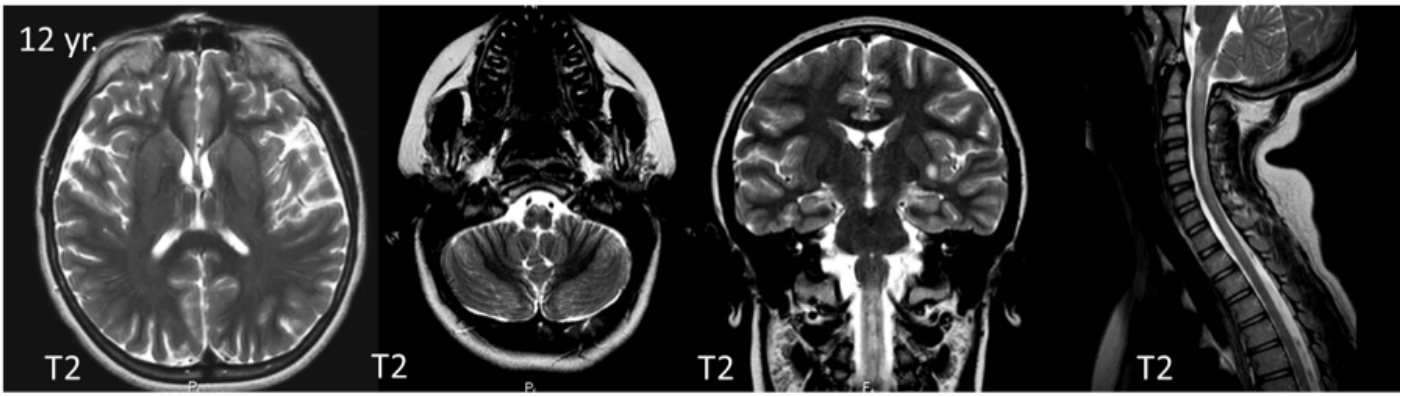
LD_0622.0A is a 24 year old male of Northern European descent seen in the context of progressive gait disturbance and increasing clumsiness. Gait abnormality became apparent at 14 years of age after uneventful childhood with the exception of mild speech delay. MRI of the brain at 20 years of age showed multiple periventricular and deep WM lesions while atrophy of the spinal cord was noted but without signal abnormality. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0646 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0646.0A.

LD_0646.0A is a 15 year old male of Indian descent. He came to medical attention for intellectual disability and toe-walking. He had neck pain for four – five years and imaging was suggestive of a cervicomedullary lesion. At age 12 he experienced regression with worsening of his gait and developed bilateral lower extremity weakness. Further imaging studies identified involvement of the corticospinal tracts in the medulla and cervical spine, with normal supratentorial white matter. Mitochondrial dysfunction confirmed on muscle biopsy (see Fogel et al. 2014[6]). There was no other relevant family history.

This individual was also reported as ATX58 in Fogel et al. 2014[6].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*NDUFS7*	Hom	chr19:1390954C>T	ENST00000414651	c.403C>T	p.Arg135Cys

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

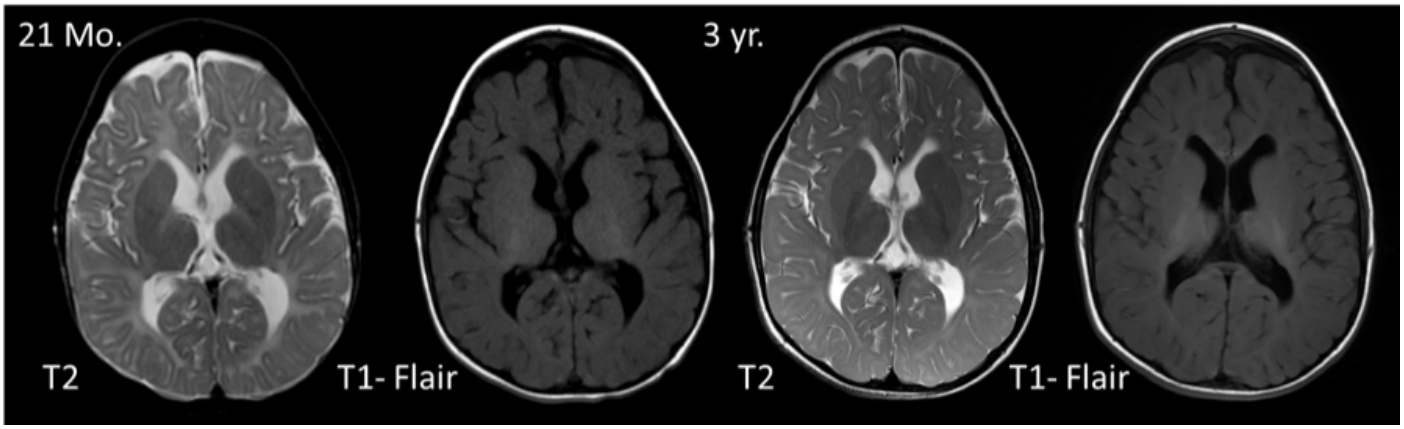
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PS3, PM2, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Leigh Syndrome (MIM:256000).

LD_0664 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0664.0A.

LD_0664.0A is a four year old male of Caucasian descent. He first came to medical attention at birth with left-sided club foot and again at two months with nystagmus. He has a history of hypotonia, developmental delay, optic nerve hypoplasia, and gastrointestinal issues. MRI at 21 months was significant for thinning of the corpus callosum, and diffuse signal abnormalities most consistent with hypomyelination. Follow up MRI at three years was unchanged except for progressive cortical atrophy and arrested myelination. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*FUS*	Het, *de novo*	chr16:31202382CGGGGTGGT>C	ENST00000568685	c.1500_1507del	p.Gly501fs

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	-	-	-

[-] indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PVS1, PS2, PM1, PM2,

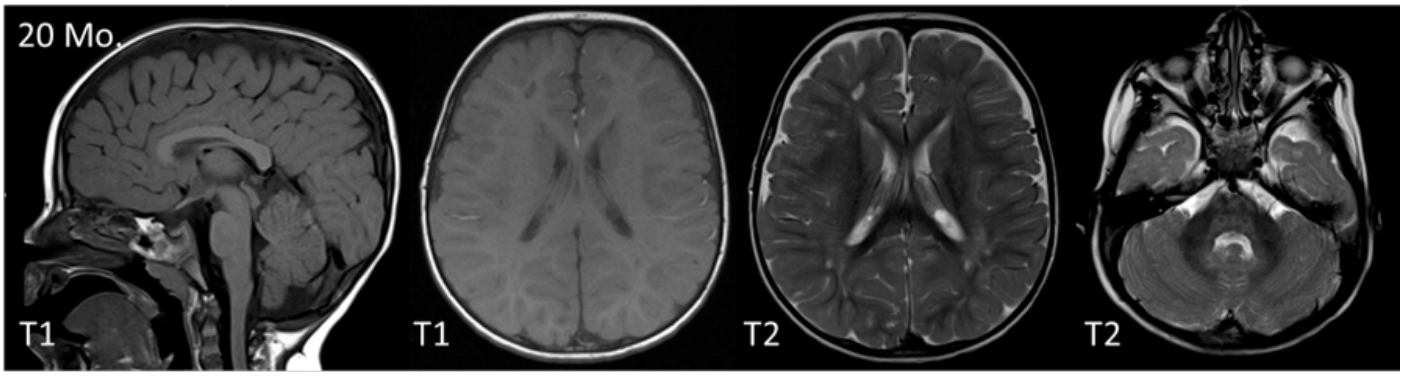
[a] ACMG criteria upon which classification is based[1].

Clinical Interpretation
Previously reported cases of FUS mutations have been associated with a phenotype of amyotrophic lateral sclerosis (ALS) with or without fronto-temporal dementia. Although ALS caused by FUS mutations demonstrate earlier disease onset compared to ALS with mutations in other genes, no infantile onset cases have been previously reported. This variant was classified as Pathogenic by ACMG criteria, this is clinically thought to be consistent with an early-onset variant as seen in other ALS related genes (see LD_0463.0A and LD_0463.0B).

Final Diagnosis
Clinically Resolved: Amyotrophic lateral sclerosis 6 (MIM:608030).

LD_0671 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0671.0A.

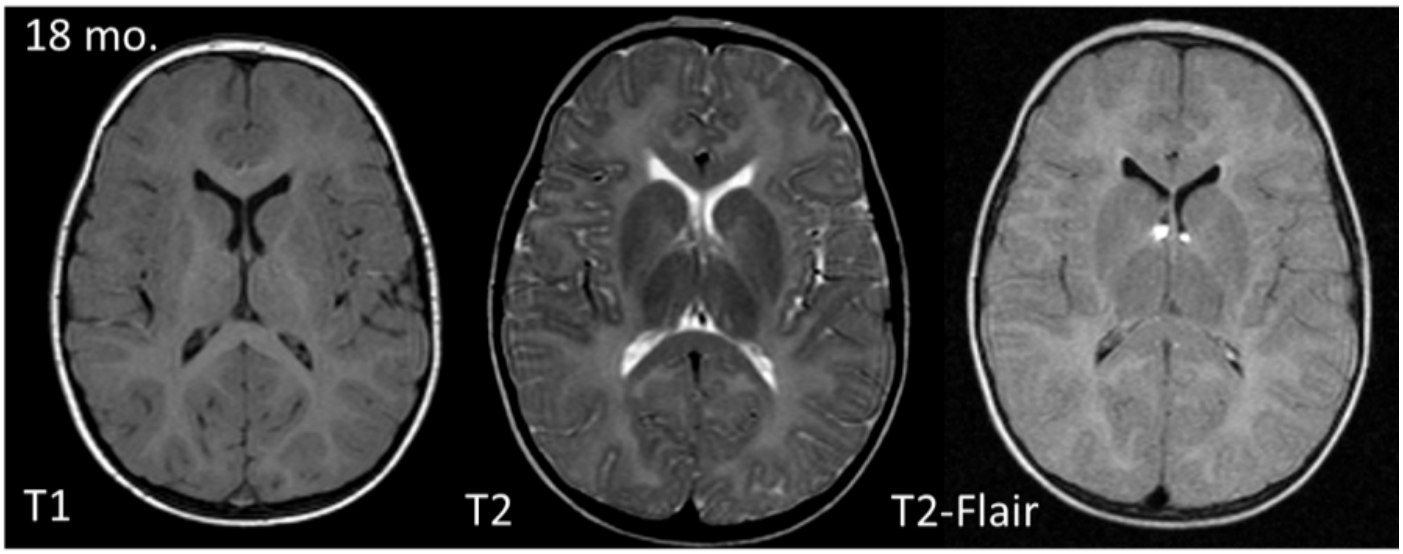
LD_0671.0A is a three year old male of Northern European descent. He has a history of dental abnormalities, strabismus, febrile seizures and developmental delay noticed at about eight months of age. Initial MRI at 18 months showed multifocal T2 signal abnormalities. MRI at three years of age showed progression of myelination with prominent perivascular spaces. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0672 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0672.0A.

LD_0672.0A is a seven year old female of Hispanic descent seen in the context of unsolved hypomyelination. She came to medical attention in the first year of life with motor difficulties and delayed acquisition in skills. MRI at two years of age was significant for diffuse hypomyelination, and was unchanged in follow-up studies. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*TUBB4A*	Het, *de novo*	chr19:6495971A>C	ENST00000264071	c.539T>G	p.Val180Gly

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	-	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

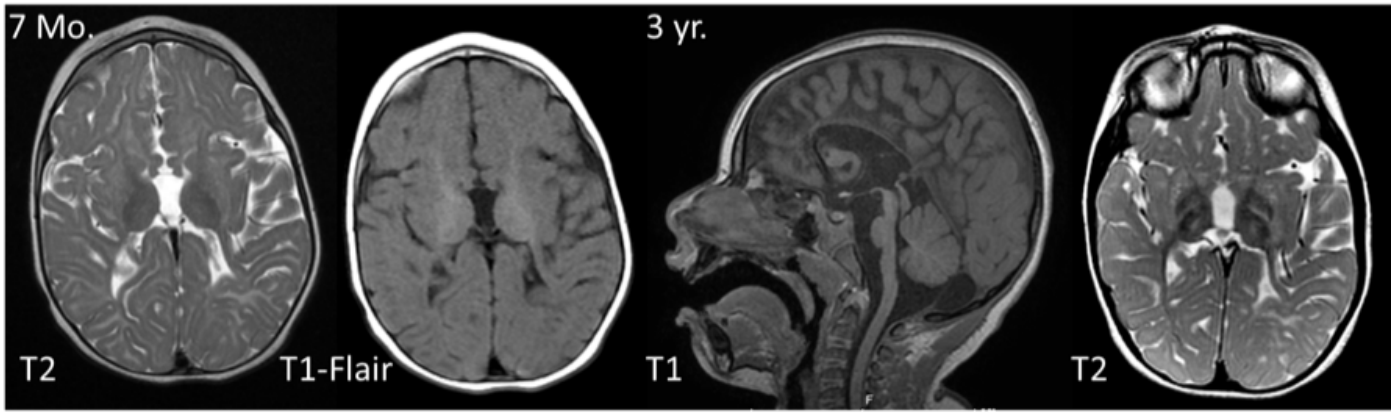
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PS2, PM2, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Leukodystrophy, hypomyelinating, 6 (MIM:612438).

LD_0673 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0673.0A.

LD_0673.0A is a four year old female of Pakistani descent with family history significant for consanguinity. She is seen in the context of microcephaly, hypomyelination, myoclonic epilepsy, and global developmental delay. She first came to attention in the first 6-8 months of life due to severe hypotonia and lack of acquisition of motor milestones. MRI at eight months of age was significant for a dysgenetic appearing brain and abnormal myelin signal. Further studies at three years of age showed volume loss of the brainstem, cerebellar hemispheres and atrophy of the deep gray nuclei, and increased signal within the thalami, caudate, and putamen. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*AMPD2*	Hom	chr1:110173662G>A	ENST00000256578	c.2528G>A	p.Arg843His

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs774256040	0.000009	0.000063	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

Variant	Classification	ACMG Criteria[a]
#1	VUS	PM2, PP2, PP3,

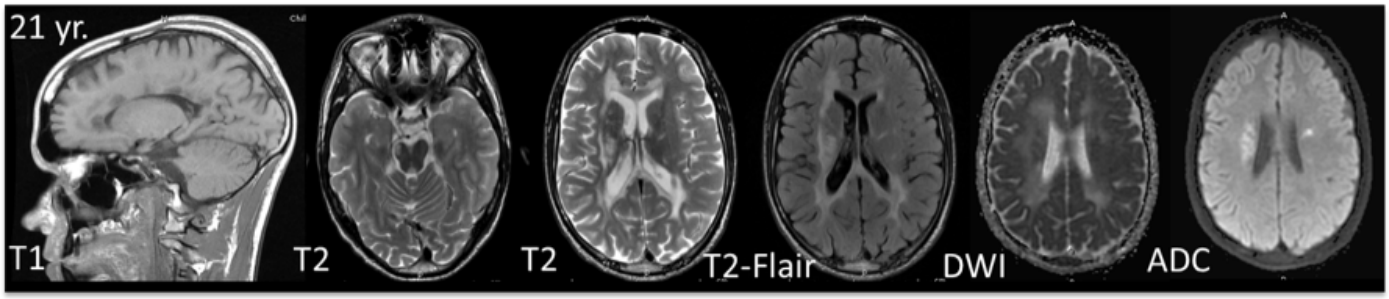
[a] ACMG criteria upon which classification is based[1].

Clinical Interpretation
Although ACMG criteria classify this as a VUS, clinical and neuroradiological features were consistent with recent publications of individuals with these mutations and as such we found it to be clinically consistent with a pathogenic variant.

Final Diagnosis
Clinically Resolved: Spastic paraplegia 63 (MIM:615686).

LD_0675 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0675.0A.

LD_0675.0A is a 22 year old male of mixed European descent with history of motor and cognitive disabilities. He first came to medical attention in infancy due to congenital nystagmus, poor tracking, and leg tremor. Medical history is notable for mild clumsiness, right sided hemiparesis, and ataxia followed by a period of static findings that have more recently been notable for deteriorating motor skills and speech. MRI findings at 14 years of age were significant for mild periventricular white matter changes. Repeat imaging at 21 years of age showed diffuse white matter abnormalities, significantly worse on the right side with signal abnormality involving the corpus callosum and the brainstem. Restricted diffusion evident in the cortical spinal tracts and within the centrum semiovale bilaterally. There was no other relevant family history.

LD_0675.0A was previously reported in[7].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*AARS2*	Het	chr6:44268349C>T	ENST00000244571	c.2893G>A	p.Gly965Arg
#2	*AARS2*	Het	chr6:44274104C>T	ENST00000244571	c.1213G>A	p.Glu405Lys

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs543267101	0.000049	0.000346	Damaging	Damaging	DC
#2	rs587777592	0.000016	0.000086	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PM2, PM3, PP2, PP3, PP4,
#2	VUS	PM3, PP2, PP3, PP4,

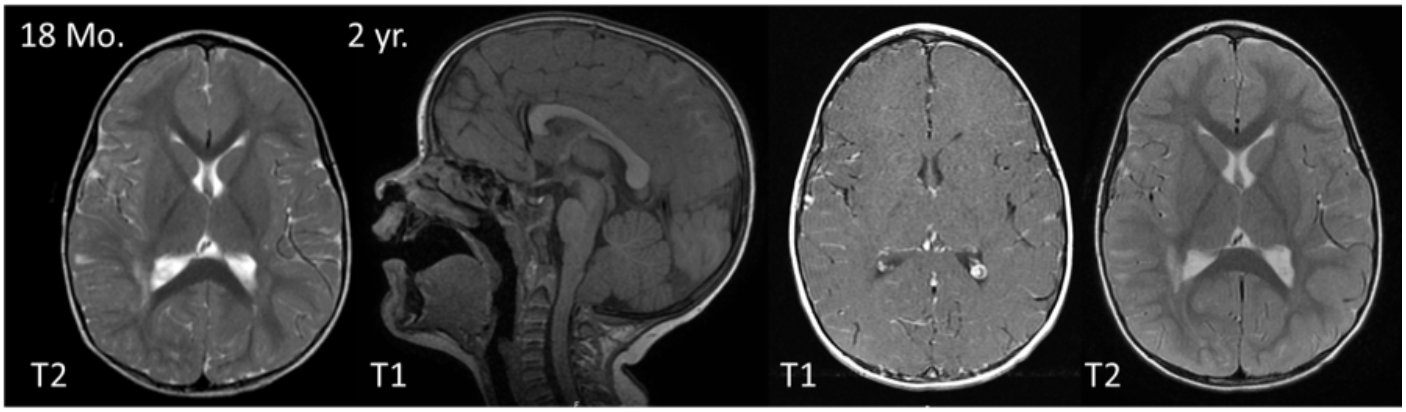
[a] ACMG criteria upon which classification is based[1].

Clinical Interpretation
Although ACMG criteria classify Variant #2 as a VUS, this individual had a clinical course and MRI consistent with a cohort of patients with AARS2 related leukoencephalopathy and as such we found it to be clinically consistent with a pathogenic variant.

Final Diagnosis
Clinically Resolved: Leukoencephalopathy, progressive, with ovarian failure (MIM:615889).

LD_0678 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0678.0A.

LD_0678.0A is a three year old male of mixed European and Native American descent. He has a history of spastic ataxia and came to medical attention at 14 months due to excessive clumsiness noted after the patient learned to walk. He appears to have minor motor regression but has made cognitive gains. MRI at 18 months was significant for white matter abnormality involving the supratentorial white matter (right more than left) and also the deep periventricular white matter. Follow-up MRI of the brain and spine at two years of age was unchanged. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*ATM*	Het	chr11:108206686A>T	ENST00000278616	c.8266A>T	p.Lys2756*
#2	*ATM*	Het	chr11:108115673CT>C	ENST00000278616	c.824del	p.Leu275fs

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs371638537	0.000008	0.000116	-	-	DA
#2	-	-	-	-	-	-

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

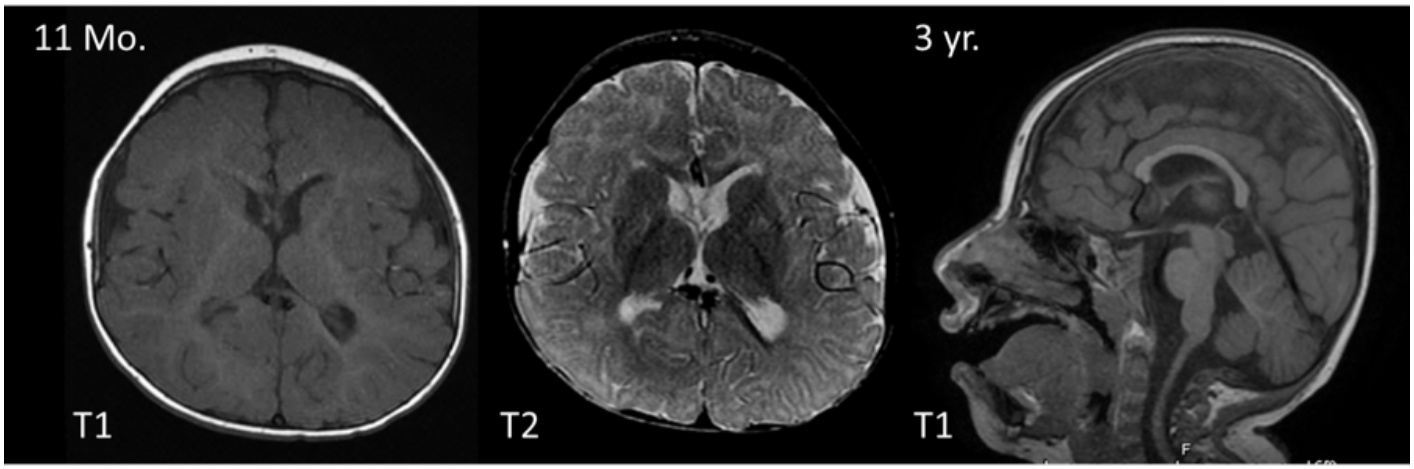
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PVS1, PS3, PM2, PM3, PP4,
#2	Pathogenic	PVS1, PS3, PM2, PM3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Ataxia-telangiectasia (MIM:208900).

LD_0695 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0695.0A.

LD_0695.0A is a four year old male of Middle Eastern descent who came to medical attention at four months of age with concerns for global developmental delay. He is seen in the context of microcephaly, developmental delay, and hypotonia. MRI at one year of age revealed low volume of the corpus callosum, small brainstem, with bilateral periventricular and corona radiate signal abnormality. Follow-up MRI at three years of age showed improved myelination and volume in the corpus callosum with unchanged gliosis. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0725 Case Summary

MR imaging and clinical summary

No MR imaging is avalible for this case.

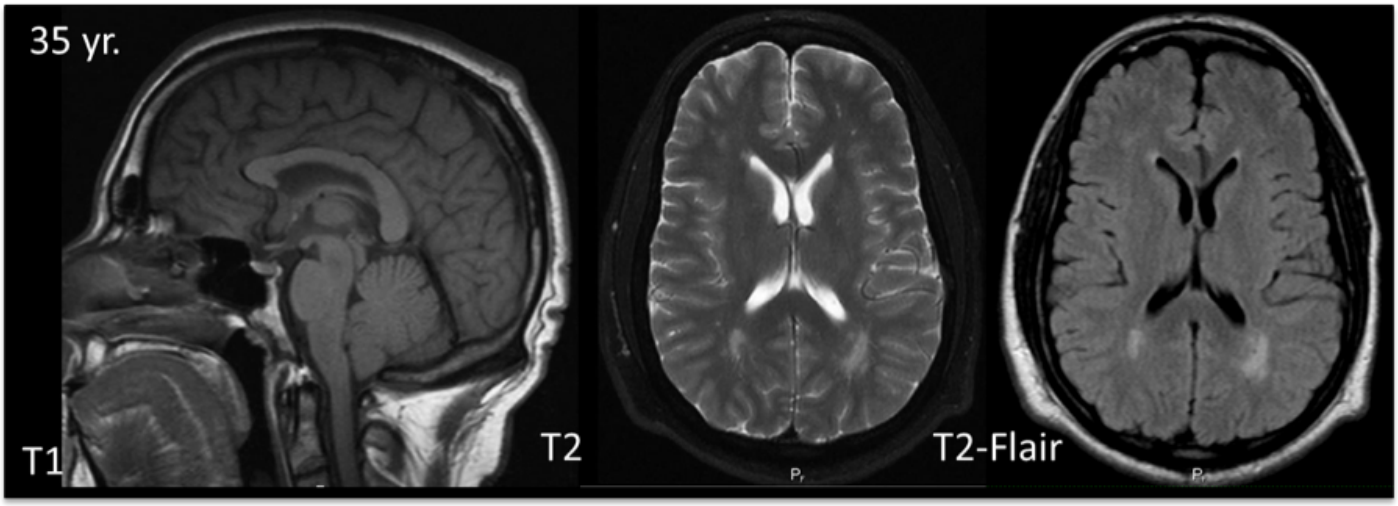
LD_0725.0A is a 19 year old female of Northern European descent. She has a medical history remarkable for choreoathetoid cerebral palsy (diagnosed at one year of age), preterm delivery after prolonged rupture of membranes at 32 weeks, and seizure disorder (diagnosed at age four). MRI at one year of age was notable for thinning of the corpus callosum and enlarged lateral ventricle ventricles as well as non-specific areas of signal abnormality. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0748 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0748.0A.

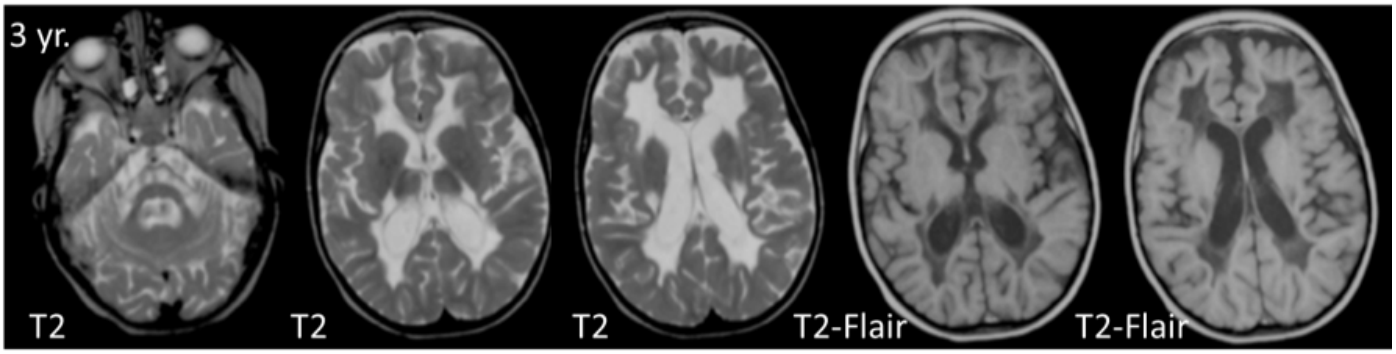
LD_0748.0A is a 36 year old male of unknown ethnicity. He presented in adulthood with psychiatric changes. MRI at 35 years of age demonstrated enlarged perivascular spaces and periventricular white matter signal abnormality. There was no other relevant family history

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0755 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0755.0A.

LD_0755.0A is a patient with family history significant for consanguinity. No clinical information was obtained.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*SDHAF1*	Hom	chr19:36486340G>C	ENST00000378887	c.164G>C	p.Arg55Pro

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs137853193	-	-	Damaging	Damaging	DA

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

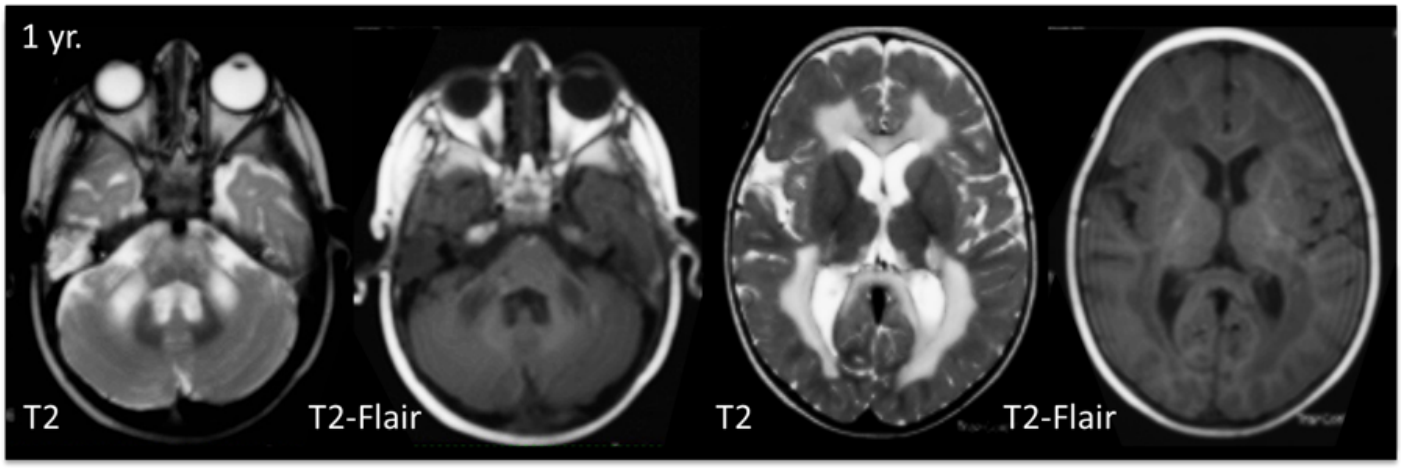
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS1, PM2, PM3, PP1, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Mitochondrial complex II deficiency (MIM: 252011).

LD_0756 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0756.0A.

LD_0756.0A is a young male of Turkish descent with family history significant for consanguinity. Motor delays were noted at birth and this patient had an abrupt decompensation at seven months of age, and a history of ataxia, hypotonia, and spasticity. MRI at three years and six months of of age was significant for signal abnormality of the supratentorial white matter with sparing of the U fibers, a swollen appearance to the corpus callosum, involvement of the cerebellar white matter, and the brain stem. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*SDHB*	Hom	chr1:17371313T>A	ENST00000375499	c.143A>T	p.Asp48Val

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs202101384	0.000049	0.000363	Damaging	Probably Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

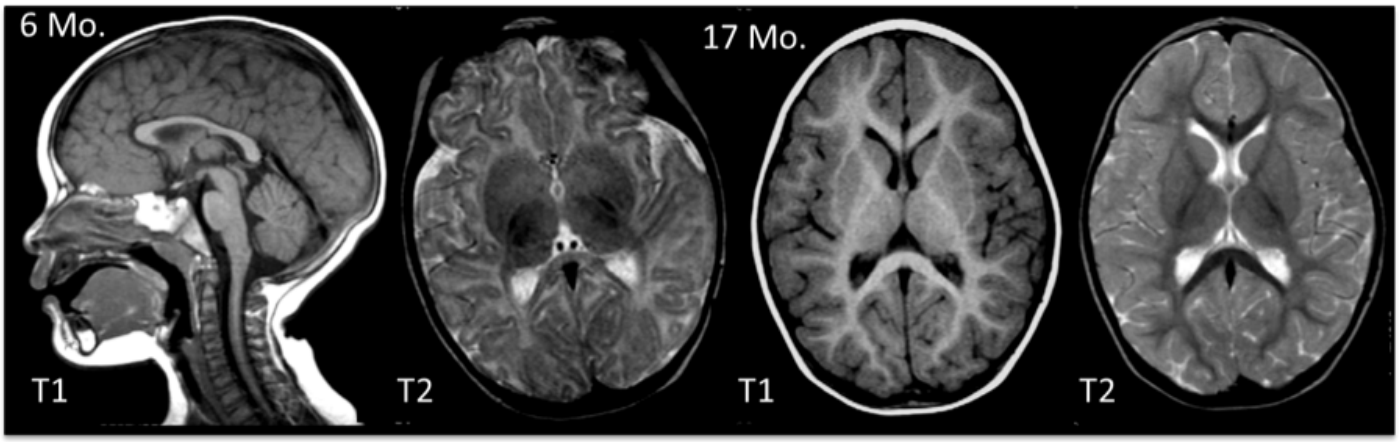
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS1, PS3, PM2, PM3, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Mitochondrial complex II deficiency (MIM: 252011).

LD_0760 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0760.0A.

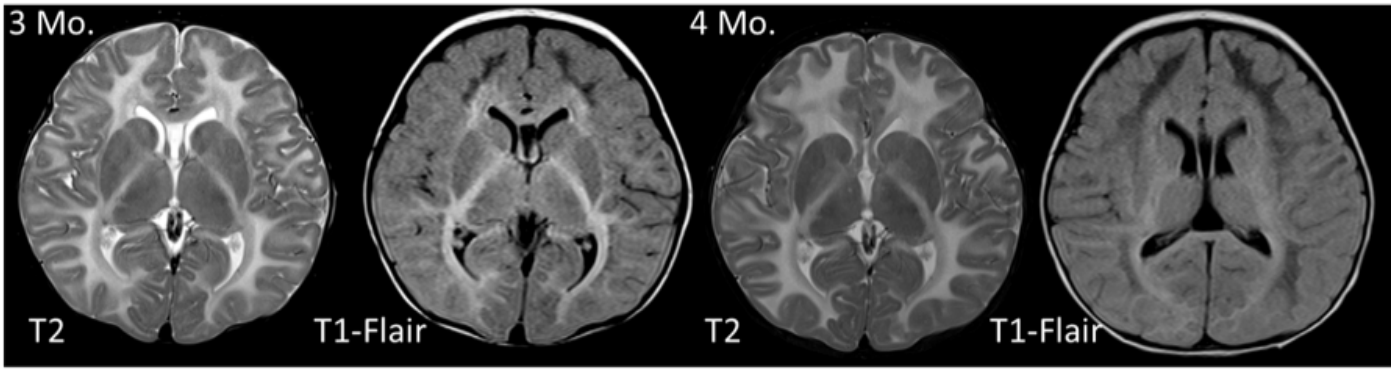
LD_0760.0A is a 12 year old female of German with Ashkenazi Jewish heritage. She has a progressive myoclonic epileptic encephalopathy and autism spectrum disorder. MRIs revealed myelination delay but subsequent studies at 12 years of age showed resolution of myelin deficits but mild cerebellar and cerebral atrophy. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0764 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0764.0A.

LD_0764.0A is a female who died at unexpectedly at seven months after presenting at 5 months with lethargy after an upper respiratory infection. She developed progressive seizures, hypotonia, apnea, and failure to thrive. MRI at two and four months of age showed progressive myelin rarefaction on T2 FLAIR. No diagnosis was made before death. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*EIF2B5*	Het	chr3:183858377C>T	ENST00000273783	c.1015C>T	p.Arg339Trp
#2	*EIF2B5*	Het	chr3:183860869C>T	ENST00000273783	c.1684C>T	p.Gln562*

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs113994068	0.000041	0.000075	Damaging	Damaging	DA
#2	-	-	-	-	-	DA

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

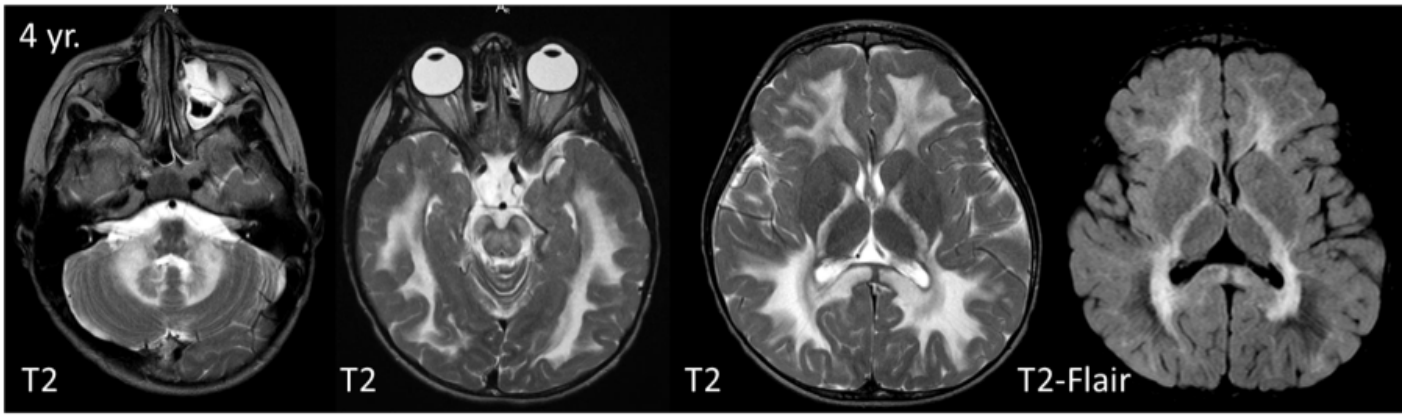
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS1, PM2, PM3, PM5, PP2, PP3, PP4,
#2	Pathogenic	PVS1, PM2, PM3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Leukoencephalopathy with vanishing white matter (MIM:603896).

LD_0765 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0765.0A.

LD_0765.0A is a five year old male of unknown ethnicity who presented gait deterioration, and febrile episodes after receiving the flu shot at four years of age. Prior to this, there were no concerns with health or development. MRI at five years of age was significant for diffuse cerebral T2 weighted signal abnormalities diffusely, with T2 FLAIR rarefaction and signal abnormality of the brainstem including the bilateral cerebral peduncles. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0774 Case Summary

MR imaging and clinical summary

No MR imaging is avalible for this case.

LD_0774.0A is a seven year old male of Chinese descent. He first came to medical attention at 12 months of age with failure to thrive and developmental delay. On examination he had subtle dysmorphisms including low set ears and epicanthic folds, truncal hypotonia, increased tone in all extremities and nystagmus. MRI performed at 18 months was significant for diffuse hypomyelination in all structures with no cerebellar involvement. Hypomyelination was confirmed on follow-up MRI at 3 and 4 years of age. There was no other relevant family history or consanguinity.

This individual was previously reported in[8].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*POLR1C*	Het	chr6:43487857T>C	ENST00000372389	c.436T>C	p.Cys146Arg
#2	*POLR1C*	Het	chr6:43488743AAAG>A	ENST00000372389	c.883_885del	p.Lys295del

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	-	-	-	Damaging	Damaging	DC
#2	rs768468779	-	-	-	-	-

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

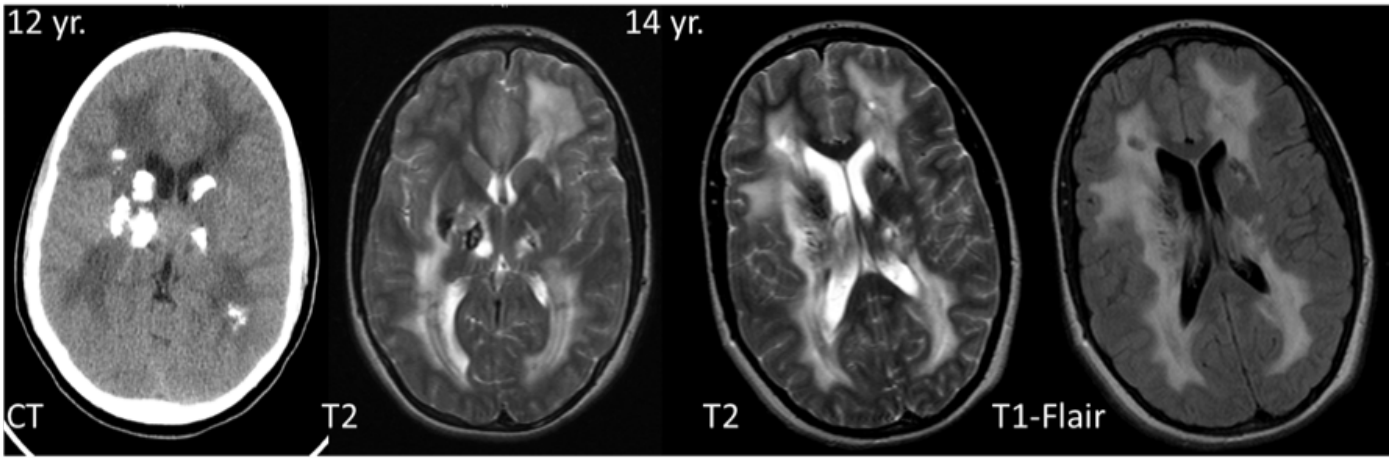
Variant	Classification	ACMG Criteria[a]
#1	Likely pathogenic	PM2, PM3, PP2, PP3, PP4,
#2	Likely pathogenic	PM2, PM4, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: POLR1C related hypomyelination

LD_0807 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0807.0A.

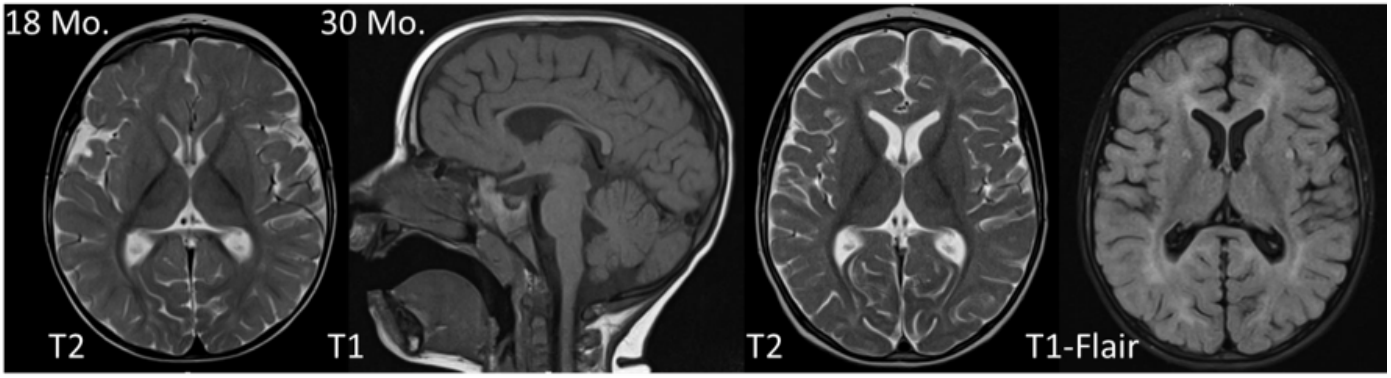
LD_0807.0A is a 15 year old female of German/Irish descent clinically diagnosed with leukoencephalopathy with calcifications and cysts. She has a history of dystonia, extrapyramidal function, left sided gait abnormality, left-sided arm weakness, and seizures with onset at 12 years of age. She also mild cognitive delays. MRI at 13 years of age was significant for extensive white matter signal abnormalities, basal ganglia and parenchymal calcifications and multiple other cystic lesions within the deep white matter of both cerebral hemispheres. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0808 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0808.0A.

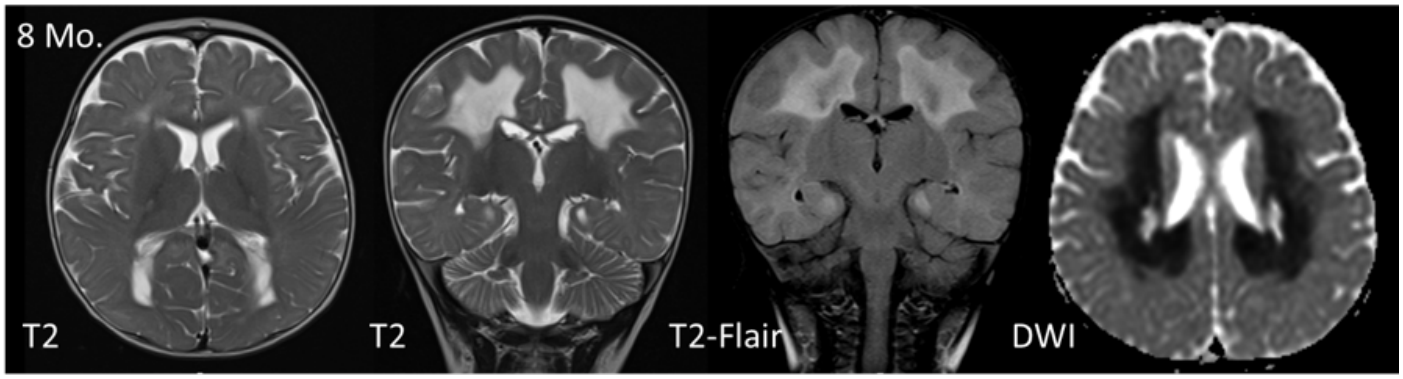
LD_0808.0A is a four year old male of mixed European descent. He presents with acquired microcephaly, developmental delay, congenital bilateral hearing loss, cortical blindness, and severe myoclonic epilepsy with onset around 15 months. He is also hypertonic with opisthotonic posturing since infancy. MRI at three years of age showed stable multifocal white matter abnormalities present as early as 18 months. There was also mild central white matter volume loss. There was no other relevant family history.

No candidate variants were identified in this case.

Final Diagnosis
Unresolved.

LD_0821 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0821.0A.

LD_0821.0A is a one year old female of Asian Indian ethnicity. She has a history of inability to feed, failure to thrive, irritability, and developmental regression. MRI at one year of age showed progressive white matter demyelination in the supratentorial white matter and extending peripherally to involve the subarcuate fibers and deep white matter, as well as inferiorly involving the brainstem along the descending pyramidal tracts. MRI also revealed enlargened ventricles and extra-axial fluid spaces. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*NDUFA2*	Het	chr5:140026915T>G	ENST00000252102	c.134A>C	p.Lys45Thr
#2	*NDUFA2*	Het	chr5:140025246TC>T	ENST00000252102	c.225del	p.Asn76fs

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs757982865	0.000009	0.000080	Damaging	Damaging	DC
#2	-	-	-	-	-	-

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

Variant	Classification	ACMG Criteria[a]
#1	VUS	PM2, PP3, PP4,
#2	VUS	PM4, PP4,

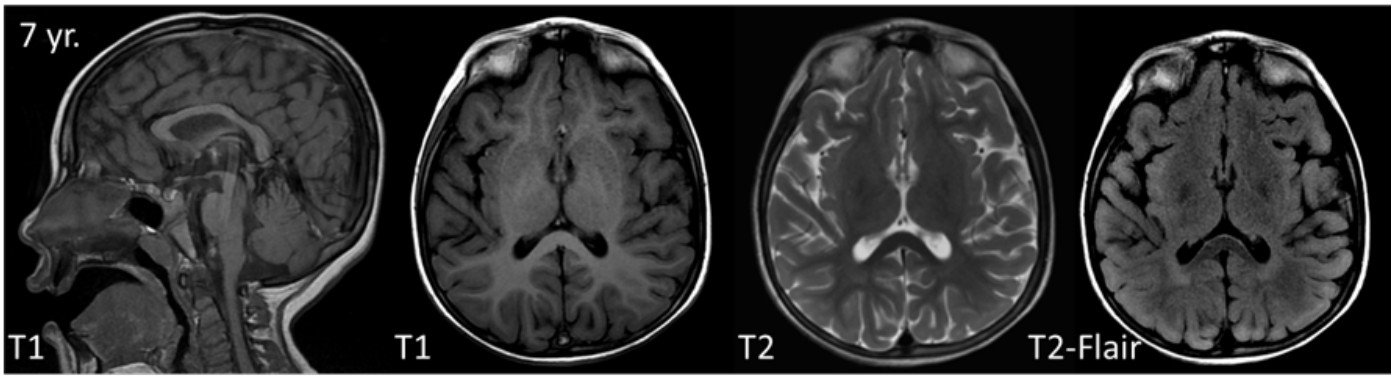
[a] ACMG criteria upon which classification is based[1].

Clinical Interpretation
Although ACMG criteria classify this as a VUS, the MRI features involving selective brainstem tracts is highly suggestive of a mitochondrial leukoencephalopathy and therefore we found it to be clinically consistent with a pathogenic variant.

Final Diagnosis
Clinically Resolved: Leigh syndrome due to mitochondrial complex I deficiency (MIM: 256000).

LD_0846 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0846.0A.

LD_0846.0A is a ten year old female of mixed Northern European and Korean descent. She has a history of complex neurologic disorder manifesting in gait abnormalities, speech abnormalities including dysarthria and apraxia, sensory and cerebellar ataxia, and spondyloepimetaphyseal dysplasia. MRI is significant for signal abnormality in the periventricular white matter in the parietal and occipital regions. Volume loss is noted globally. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*GLB1*	Het	chr3:33109737G>T	ENST00000445488	c.586C>A	p.Arg196Ser
#2	*GLB1*	Het	chr3:33099740A>G	ENST00000445488	c.718T>C	p.Tyr240His

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs192732174	0.000033	0.001319	Damaging	Damaging	DC
#2	-	-	-	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

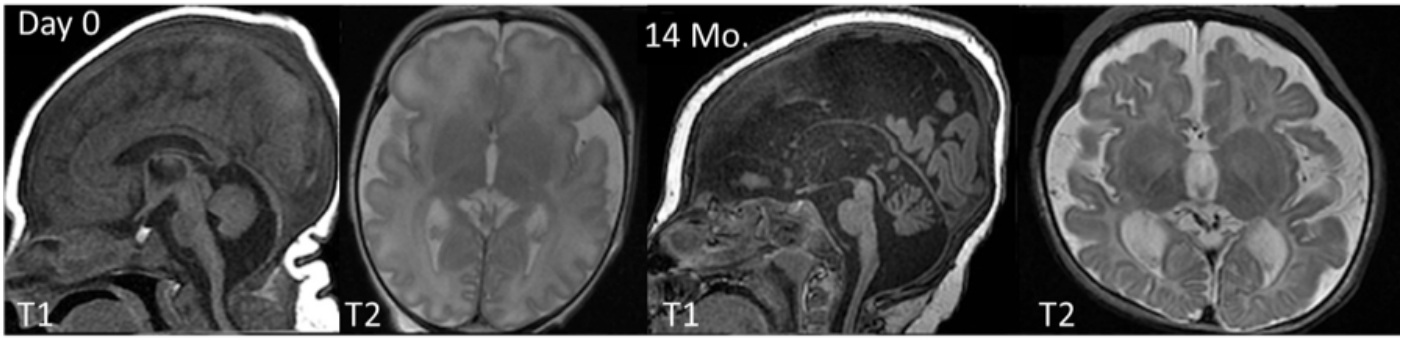
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS1, PM2, PP2, PP3, PP4, PP5,
#2	Pathogenic	PS3, PM2, PM3, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: GM1-gangliosidosis, type III (MIM:230650).

LD_0857 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0857.0A.

LD_0857.0A is a one year old male of Northern European and Irish descent. Since birth he has had a history of abnormal movements and bilateral equinus varus. He later developed refractory epilepsy, blepharospasm, progressive microcephaly, and failure to thrive. MRI at five months of age showed hypomyelination and abnormal diffusion signal, consistent with edema, through the corticospinal tracts, superior cerebellar peduncles and its decussation. This signal was also seen in the proximal peri-atrial fibers bilaterally and symmetrically. Repeat MRI at one year of age showed persistent unchanged restricted diffusion, as well as parenchymal atrophy. There was no other relevant family history.

LD_0857.0A was previously reported in[2].

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*AARS*	Hom	chr16:70289666T>C	ENST00000261772	c.2251A>G	p.Arg751Gly

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs143370729	0.000050	0.000116	Damaging	Damaging	DC

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

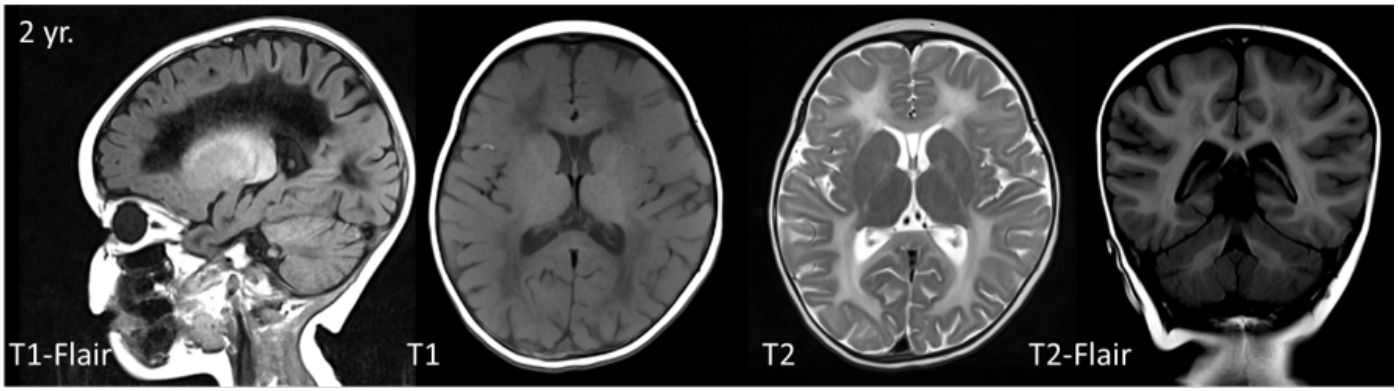
Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS3, PM1, PM2, PM3, PP1, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Epileptic encephalopathy, early infantile, 29 (MIM:616339).

LD_0869 Case Summary

MR imaging and clinical summary



MR imaging of individual LD_0869.0A.

LD_0869.0A is a two year old female of Caucasian descent seen at 20 months in the context of a viral infection with history of slow development and at the time of infection, evidence of regression. Elevated CSF glycine and copy number gain of 1q21.1 on CGH-array were found in the diagnostic workup. MRI was significant for diffuse leukoencephalopathy. There was no other relevant family history.

Variant description

Variant	Gene	Zygosity	Genome	Transcript	CDS	Protein
#1	*EIF2B2*	Het	chr14:75472570G>T	ENST00000266126	c.599G>T	p.Gly200Val
#2	*EIF2B2*	Het	chr14:75472609A>G	ENST00000266126	c.638A>G	p.Glu213Gly

Allele frequency and predicted impact

Variant	rsID	ExAC AF[a]	Max AF[b]	SIFT	Polyphen	MutationTaster[c]
#1	rs113994012	0.000198	0.000581	Damaging	Damaging	DC
#2	rs104894425	0.000033	0.000060	Damaging	Probably Damaging	DA

- indicates allele not present in database.
[a] Total allele frequency in Exome Aggregation Consortium (ExAC) dataset.
[b] Maximum reported allele frequency for any single sub-population represented in ExAC, 1000 Genomes or Exome Variant Server datasets.
[c] DC - Disease Causing; DA - Disease Causing Automatic.

Variant interpretation

Variant	Classification	ACMG Criteria[a]
#1	Pathogenic	PS1, PM2, PM3, PP2, PP3, PP4,
#2	Pathogenic	PS1, PM2, PM3, PP2, PP3, PP4,

[a] ACMG criteria upon which classification is based[1].

Final Diagnosis
Resolved: Leukoencephalopathy with vanishing white matter (MIM:603896).

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