Supplementary Table S1. Molecular, clinical, and paraclinical features of all patients with *RNASEH2B* mutations

Reference	# of patient	Gender	Origin	Consanguinity	Age at onset (year)	Zygosity	Variant	Protein	Exon	Type of variant	Para-clinical findings			Clinical findings
											CT scan	Magnetic Resonance Imaging (MRI)	Laboratory tests	
Leung et al. (2023)	1	Female	European	Not Available (NA)	NA	Com Het	c.529G>A	p.(Ala177Thr)	7	Missense	NA	T2 FLAIR: multiple, scattered, patchy white matter hyperintensities. SWI: a few punctate and linear dark foci	↑ Neopterin (78 nmol/L)	Abnormal gait, decreased left ankle range of motion, speech delay
							c.322-17A>G	p.Gly108Leufs*12	Intron 4					
De Barcelos et al. (2023)	2	Male	NA	NO	20 months	Com Het	c.172C>T	p.(Gln58*)	3		Normal	FLAIR image: bilaterally confluent hyperintensity involving periventricular and subcortical white matter. Axial T2-weighted image: hyperintensity foci in the pons. Mild brain atrophy	NA	Ataxia, drowsiness, motor regression, spastic diplegia, loss of head control, dysarthria, walk with support
							c.529G>A	p.(Ala177Thr)	7	Missense				
	3	Female	NA	Yes	14 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	FLAIR image: frontoparietal patchy and asymmetric distribution of signal hyperintensity at the cerebral white matter.	NA	Motor and language regression, spastic diplegia, loss of head control, speech loss, dysarthria, walk with support
	4	Male	NA	NO	17 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcification	T2 image: bilateral frontoparietal asymmetric areas of signal hyperintensity	NA	Motor and language regression, spastic diplegia, loss of head control, speech loss, dysarthria, walk with support
	5	Male	NA	NO	16 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	WM lesions with patchy asymmetric T2/FLAIR hyperintense lesions involving subcortical and periventricular	NA	Motor and language regression, spastic diplegia, loss of head control, speech loss, dysarthria
Ostrem et al. (2023)	6	Female	NA	NA	13 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	T2/FLAIR hyperintensities in the bifrontal and parietal white matter and corpus callosum and two small aneurysms in the proximal left anterior cerebral artery	NA	Motor regression, spastic quadriparesis, alopecia, constipation, depression, asthma
Gippert et al. (2023)	7	NA	NA	NA	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Myelination delay, and onset of signaling changes in the periventricular white substance	Normal neopterin, normal IFN signature CSF	Primary congenital hypothyroidism, persistent foramen ovale, age-appropriate development, decent abnormalities with white substance deficit
Agarwal et al. (2023)	8	Female	Indian	NO	NA	Com Het	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Normal	Normal	Spastic paraparesis involving both lower limbs, urinary urgency and occasional urge incontinence
							c.617-3C>G	-						
Cadi et al. (2023)	9	Female	Moroccan	YES	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Normal	NA	Motor development delay, dysarthria, walking and standing with assistance, spastic paraplegia, hyperreflexia in the four limbs, pyramidal signs, bilateral Babinski sign, scoliosis
Galli et al. (2023)	10	Female	Moroccan	NO	16 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	Signal abnormalities in the brainstem and in the supratentorial white matter, hyperintense on T2-weighted images, with no diffusion restriction nor contrast enhancement after contrast medium administration	Increased IFN signature	Gait disturbances, left pyramidal signs including hypertonia, weakness, hyperreflexia, and positive Babinski. Irritability, spastic tetraplegia, developmental delay, loss of words production
Garau et al. (2023)	11	Female	European	NA	Late!!	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Hemiplegia, walks with limitations
	12	Female	African	NA	Late!!	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic-dystonic tetraparesis, transported in a manual wheelchair, handles objects with difficulty
	13	Male	European	NA	Neonatal	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Hemiplegia, walks with limitations
	14	Female	African	NA	Late!!	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic diplegia, walks using a held-mobility device, handles most objects, but with somewhat reduced quality
	15	Female	European	NA	Infantile	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic diplegia, walks with limitations
	16	Female	European	NA	Infantile	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic-dystonic tetraparesis, transported in a manual wheelchair, does not handle objects, seldom effective, even with familial partners
	17	Male	European	NA	Infantile	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic-dystonic tetraparesis, transported in a manual wheelchair, does not handle objects, seldom effective, even with familial partners
	18	Male	European	NA	Infantile	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic-dystonic tetraparesis, transported in a manual wheelchair, does not handle objects, seldom effective, even with familial partners
	19	Female	European	NA	Infantile	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic-dystonic tetraparesis, transported in a manual wheelchair, does not handle objects, seldom effective, even with familial partners
	20	Male	European	NA	Infantile	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Spastic-dystonic tetraparesis, transported in a manual wheelchair, handles a limited selection of easily managed objects in adapted situation, inconsistent with familial partners
Mir et al. (2022)	21	Male	NA	NA	NA	Hom	SLC25A12 gene: c.832T>C	p.(Tyr278His)			NA	Severe supratentorial volume loss, thin corpus callosum, bilateral thalamic hyperintensity, hypomyelination	NA	Microcephaly. hypertonic, spastic, global developmental delay, non-verbal, seizures, intermittent episodes of crying, irritability and opisthotonus, jerky movements of the eyes and twitching,
						Hom	RNASEH2B gene: c.356A>G	p.(Asp119Gly)	5	Missense				
Schluter et al. (2022)	22	Female	NA	NO	10 months	Com Het	c.445G>T	p.(Glu149Ter)		Stop-gain	NA	Hypomyelinationm, white matter atrophy, colpocephaly	↑ Neopterin	Spastic-dystonic tetraparesis, global developmental delay; intellectual disability, startle response. irritability, dysarthria, abnormal somatosensory evoked potentials, abnormal visual evoked potentials
							c.529G>A	p.(Ala177Thr)	7	Missense				
	23	Male	NA	YES	4 months	Com Het	c.485A>C	p.(Lys162Thr)		Missense	NA	Hypomyelination, bilateral hippocampus atrophy	NA	Spastic tetraparesis, global developmental delay, nystagmus, opisthotonus, pondo-statural delay, gastroesophageal reflux, demyelinating PNP
							c.529G>A	p.(Ala177Thr)	7	Missense				
	24	Female	NA	NO	4 months	Com Het	c.476G>T	p.(Ser159Ile)		Missense	NA	Diffuse T2 WM hyperintensity, anterior predominance, white matter atrophy, thin CC	25 leucocytes in CSF (Mononuclear predominance)	Spastic tetraparesis, global developmental delay, intellectual disability, microcephaly, pondo-statural delay
							c.529G>A	p.(Ala177Thr)	7	Missense				
	25	Male	NA	YES	6 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Hypomyelination, thin corpus callosum	NA	Spastic-dystonic tetraparesis, hypokinesia, global developmental delay, insufficient head growth, poor eye contact, upgazed episodes, hypomimia, somnolence episode with fever, frequent febrile episodes
	26	Male	NA	NO	11 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Frontotemporal T2 WM hyperintensity	NA	Spastic-dystonic tetraparesis, global developmental delay, intellectual disability, language developmental delay, epilepsy, oxidative phosphorylation, complex II and III deficiency
	27	Female	NA	NO	12 months	Com Het	c.655T>C	p.(Tyr219His)		Missense	NA	Periventricular T2 WM hyperintensity	NA	Pyramidal, abnormal somatosensory evoked potentials
							c.529G>A	p.(Ala177Thr)	7	Missense				
Alburaiky et al. (2021)	28	Female	NA	NO	4 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Periventricular calcifications	Delayed myelination, WM abnormality	↑ Neopterin	Opsoclonus, encephalopathy, transient non-epileptic myoclonus, microcephaly, truncal hypotonia
	29	Male	French	NO	3 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Delayed myelination	↑ Neopterin ↑ Biopterin IFN-α (CSF): 75 UI/L IFN-α (Serum): 5 UI/L	Global development delay, non-epileptic opsoclonus and myoclonus, truncal hypotonia, irritability and neurodevelopmental regression, hypotonia, dystonia, pyramidal signs
Beysen et al. (2021)	30	Female	North-African	YES	10 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Posterior thinning of the corpus callosum	NA	Chilblain, developmental delay, spastic and dyskinetic quadriplegia, mild intellectual disability, speech difficulty, motor delay, scoliosis, joint contractures, hip luxation, fever
	31	Female	Moroccan	NO	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Bilateral frontal periventricular microcysts and diffuse white matter hyperintensities	Hyperammonaemia ↑ Lactic acid	Developmental delay, spastic diplegic cerebral palsy with hyperreflexia, intellectual disability, epileptic seizure, speech difficulty, motor delay, fever, feeding difficulties
He et al. (2021)	32	Female	NA	NO	2	Hom	c.859G>T	p.(Ala287Ser)	11	Missense	Intracranial calcification at basal ganglia and cerebellum	Cerebral atrophy WM abnormalities Knee MRI: thickness of the synovial capsule	Lymphopenia (Blood) ↓ Complement levels ↑Acute-phase reactants ↑ Inflammatory cytokines ↑ IFN-stimulated cytokine genes (ISGs) Positive autoantibodies ↓IFN-α (CSF) ↑ IFN-α (Serum)	Chilblains, Recurrent fever, arthritis, macrocephaly, mild hearing loss, systemic inflammation, movement limitation, growth retardation, failure to thrive, CKD Kidney biopsy: glomerular sclerosis, infiltration of lymphocytes and mononuclear cells, granule degeneration, and calcium deposition in renal tubules.
						Het	c.269C>T	p.(Pro90Leu)	4	Missense				
Garau et al. (2021)	33	Male	NA	NO	1	Com Het	c.65-13G>A	-	Intron 1	Splice site	Normal	Cerebral WM abnormalities Cerebral atrophy	CSF analysis: Pleocytosis IFN-α (CSF): normal Positive blood IFN signature	Encephalopathy, psychomotor delay, spasticity, pyramidal and extrapyramidal signs, microcephaly, irritability, feeding and sleeping difficulties, fever
							c.253C>G	p.(Leu85Val)	4	Missense				
Fenaroli et al. (2021)	34	Female	NA	YES	21 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	T2-hyperintense abnormalities of the lobar and peritrigonal WM	Proteinuria Microhematuria ↓GFR ISGs: normal Positive P-ANCA	Chilblains, spastic paraparesis, hemiparesis, speech disturbance, recurrent fever, maculopapular exanthema, Hashimoto thyroiditis, lower-limb spasticity, hearing loss, articular deformity Kidney biopsy: collapsing glomerulopathy, tubular atrophy, glomerular sclerosis, hyperplasia of parietal epithelial cells, visceral epithelial cell hypertrophy, hyaline resorption droplets, capillary tuft collapsing
Cinotti et al. (2021)	35	Male	NA	NA	NA	Com Het	c.184G>A	p.(Glu62Lys)	3	Missense	Basal ganglia calcification	Leukodystrophy	↑ IFN-α (serum) ↑ IFN-α (CSF)	Spastic paraparesis, Babinski-like response, microcephaly, trophic lesions, acrocyanosis, ulcerations of distal phalanges, punctate, millimetric dark red papules on the feet Skin biopsy: angiokeratomas (Mibelli type), thrombotic lymphocyte vasculitis of small vessels
							c.529G>A	p.(Ala177Thr)	7	Missense				

Supplementary Table S1. Molecular, clinical, and paraclinical features of all patients with *RNASEH2B* mutations (continue)

Reference	# of patient	Gender	Origin	Consanguinity	Age at onset (year)	Zygosity	Variant	Protein	Exon	Type of variant	Para-clinical findings			Clinical findings
											CT scan	Magnetic Resonance Imaging (MRI)	Laboratory tests	
Gall et al. (2021)	36	Male	NA	NA	3	Hom	c.554T>G	p.(Val185Gly)	7	Missense	NA	Abnormal (Details were not available)	NA	Developmental delay, seizure, regression, optic atrophy
Pereira et al. (2020)	37	Female	Brazilian	NO	3	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Linear and "spot-like" calcifications in the bilateral lentiform nucleus	Cerebral atrophy and cavum septum pellucidum.	NA	Spastic paraplegia, epilepsy, generalized tonic-clonic seizures
	38	Female	Brazilian	NO	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Neuromotor development delay, generalized dystonia, mental retardation, refractory epilepsy, unable to walk
Ayrolles et al. (2020)	39	Female	NA	NO	8 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Brain CT scan: Basal ganglia calcification, bilateral lentiform nuclei calcifications Chest CT scan: basal ground glass opacities and moderate bilateral pleural effusion	Periventricular and frontal WM abnormalities with nodular FLAIR signals with restricted diffusion	↑ IFN-α (CSF) ↑ Neopterin ↓ Biopterin ↓ Homovanillic acid	Hyperkinetic catatonia, interstitial lung disease, psychomotor regression, chilblains, pericarditis, arthritis, asthenia, fever, proteinuria, sudden loss of motor abilities and increased spasticity, pyramidal syndrome (spasticity, reflex hyperexcitability and tetraparesis), staring, mannerisms, grasping, echopraxia, echolalia, negativism, restlessness and emotional lability
Videira et al. (2020)	40	Male	NA	NO	5 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcifications	Normal	Normal	Chilblains, generalized dystonia, spastic tetraparesis, encephalopathy, pyramidal signs
	41	Female	NA	NO	---	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Normal
	42	Female	NA	NO	Birth	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcifications	T2 hyperintensity on lenticular nuclei	CSF analysis: mild pleocytosis	Chilblains, encephalopathy, cognitive dysfunction, cerebral palsy, generalized dystonia, spastic tetraparesis, pyramidal signs, epilepsy, autoaggressive behavior, restlessness, delayed psychomotor development
	43	Female	NA	NO	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	NA	NA	Chilblains, dystonic posturing of both hands
	44	Female	NA	NO	Birth	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Lenticular calcifications	Lenticular calcifications	Normal	Chilblains, encephalopathy, cognitive dysfunction, cerebral palsy, jitteriness, hypotonia, generalized dystonia, pyramidal signs, loss of language skills
Lambe et al. (2020)	45	Female	European	NO	1	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	T2 hyperintensity	Normal	Recurrent fever, dragging leg, spasticity and weakness in legs and arms, dysarthria, dysphagia, loss of language skills
Portale et al. (2020)	46	Male	Italian	NO	1 week	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	calcification in the basal ganglia (putamen and globus pallidus)	Hyperintense alterations of the deep and subcortical WM	Positive INF signature	Erythematous lesion, microcephaly, psychomotor delay, recurrent fever, feeding difficulties, upper limbs hypertonia
	47	Female	Italian	NO	2 months	Hom	c.554T>G	p.(Val185Gly)	7	Missense	NA	Modest expansion of encephalic liquoral spaces Slight asymmetry of the ventricles Bilateral subcortical WM hyperintensity	Positive INF signature CSF analysis revealed oligoclonal bands	Psychomotor delay, spastic tetraparesis, axial hypotonia, irritability, feeding difficulties, ataxic gait, steppage gait, trunk hypotonia
Rosello et al. (2020)	48	Female	NA	NA	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	WM abnormalities	NA	Neurodevelopmental delay, spastic tetraparesis, epileptic encephalopathy
Saini et al. (2019)	49	Male	NA	NA	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Intracranial calcifications	Leukoencephalopathy, Periventricular hyperintensities	NA	Developmental delay, excessive startle and motor regression, lethargy following routine vaccination, nasal twang, upper limb dystonia, lower limb spasticity, brisk muscle stretch reflexes, bilateral ankle contractures, Babinski's sign
Briggs et al. (2019)	50	Female	Indian	NO	19	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	↑ ISG score	Purple discoloration of the skin and ulcerations, digital ischemia, erythematous lesions, depression, mood swings, early-morning joint stiffness, generalized muscular pain, fibromyalgia, dry eyes, hair loss, dry mouth Toe X-Rays: acro-osteolysis
Tonduti et al. (2019)	51	Female	Roma	YES	13 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Putamina calcification	WM hyperintensity T2 hyperintensity in the deep and periventricular posterior WM of both hemispheres	↑ IFN-α (CSF)	Spastic-dystonic tetraplegia, irritability, diurnal hypersomnia, feeding difficulties, neuromotor regression, pyramidal and extrapyramidal signs
	52	Male	Italian	NO	11 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	Supratentorial atrophy WM T2 hyperintensity	IFN-α (CSF): normal Folate: normal Pterin: normal Plasma interferon signature: normal	Spastic diplegia, recurrent sterile pyrexias, pyramidal signs
	53	Female	Italian	NA	13 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Putamina calcification	WM T2 hyperintensity	↑ INF signature	Acute fever, hemiparesis, gait, hyporeactivity, daytime somnolence, apathy, dragging leg, reduced appetite
Mahler et al. (2019)	54	NA	NA	NO	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	NA	NA	Severe global developmental delay, spastic tetraplegic cerebral palsy, microcephaly
Medinilla et al. (2019)	55	Male	Romania	NA	10 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	WM abnormalities, hyperintense on T2.	CSF analysis: ↑ protein, ↓Neopterin (1.102), Normal Biopterin (66), ↑INF-α (25)	Spastic tetraplegia, psychomotor retardation, intellectual disability, irritability, microcephaly
Tonduti et al. (2018)	56	Male	NA	NA	9 months	Hom.	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcification	WM abnormalities	INF-α (Serum): normal ISGs: normal	Neurodevelopmental regression, pyramidal and extrapyramidal sign, spastic-dystonic tetraplegia, global hypokinesia
Cortes-Saladelafont et al. (2018)	57	Female	NA	NA	NA	Com Het	c.272T>C c.529G>A	p.(Val91Ala) p.(Ala177Thr)	4 7	Missense Missense	Lenticulostriatal calcifications	Global atrophy, especially in cerebellar vermis	Low level of gamma-aminobutyric acid (GABA)	Global developmental delay (psychomotor stagnation)
Travaglini et al. (2018)	58	Female	NA	NA	1	Hom	c.529G > A	p.(Ala177Thr)	7	Missense	NA	Normal	NA	Toe walking, pyramidal signs of the lower limbs
Spagnoli et al. (2018)	59	Male	NA	NO	Infancy	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	Normal	Normal	Motor delay, pyramidal signs of the lower limbs
Dobrescu et al. (2017)	60	Female	NA	NA	10 months	Com Het	c.529G>A c.554T>G	p.(Ala177Thr) p.(Val185Gly)	7 7	Missense Missense	NA	Leukoencephalopathy	Normal serum ammonia and lactate Normal urine organic amino acid	Hemiparesis, generalized hypertonia
Abdel-Salam et al. (2017)	61	Female	Egyptian	YES	NA	Hom	c.554T>G	p.(Val185Gly)	7	Missense	Periventricular calcification, dilated ventricles, unilateral cerebellar hypoplasia	Ventricular dilatation, leukoencephalopathy, WM loss, unilateral cerebellar hypoplasia, atrophic brainstem	Serological and immunological assessments: normal IFN-α (CSF) and ISGs were not assessed.	Chilblains, limb spasticity, irritability, poor suckling, generalized tonic-clonic convulsions, truncal hypotonia, hyperreflexia Electroencephalogram (EEG) records: slow delta-theta waves and infrequent sharp waves
	62	Female	Egyptian	YES	6 months	Hom	c.554T>G	p.(Val185Gly)	7	Missense	Brain atrophy, periventricular and basal ganglia calcification, WM & cerebellum calcification	Atrophic changes in the cortex, cerebellum, and brainstem Mild ventriculomegaly WM loss	NA	Chilblains, spastic dystonic tetraparesis, seizure, sterile pyrexia, irritability EEG records: slow delta-theta waves and infrequent sharp waves
Bourchany et al. (2017)	63	Male	NA	YES	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcifications	Mild cerebellar hypoplasia	NA	Epileptic encephalopathy, global developmental delay, discreet cerebellar hypoplasia
Al Mutairi et al. (2017)	64	Male	Arab	NA	2 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity
	65	Male	Arab	NA	6 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
	66	Male	Arab	NA	In Utero	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity
	67	Female	Arab	NA	4 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
	68	Male	Arab	NA	1 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	Normal	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
	69	Male	Arab	NA	2 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
	70	Male	Arab	NA	4 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
	71	Male	Arab	NA	7 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
	72	Male	Arab	NA	3 months	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
	73	Male	Arab	NA	Neonatal	Hom	c.356A>G	p.(Asp119Gly)	5	Missense	CNS calcification	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity
	74	Male	Arab	NA	6 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	White matter disease (Improved)	NA	Developmental delay, Spasticity
	75	Male	Arab	NA	3 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity
	76	Female	Arab	NA	4 months	Hom	c.554T>G	p.(Val185Gly)	7	Missense	Normal	Brain atrophy, White matter disease	NA	Microcephaly, Developmental delay, Intellectual disability, Spasticity, Seizures
Svingen et al. (2017)	77	Female	NA	NO	10 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	T2 hyperintensity, hypointensity of globus pallidus on T2, T2-fluid-attentuated inversion recovery, and T2-* images consistent with iron deposition	CSF analyses: Normal	Chilblains, spastic quadriplegia and anarthria, seizure, low axial tone, distal spasticity, exaggerated startle response, scoliosis, language difficulties
	78	Male	NA	NO	9 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	WM lesions, globus pallidus hypointensity on T2* and T2-FLAIR consistent with abnormal metal deposition, red nucleus and substantia nigra in axial FLAIR images	CSF analyses: Normal	Spasticity, exaggerated auditory startle and reflux

Supplementary Table S1. Molecular, clinical, and paraclinical features of all patients with *RNASEH2B* mutations (continue)

Reference	# of patient	Gender	Origin	Consanguinity	Age at onset (year)	Zygosity	Variant	Protein	Exon	Type of variant	Para-clinical findings			Clinical findings
											CT scan	Magnetic Resonance Imaging (MRI)	Laboratory tests	
Dugan et al. (2017)	79	Female	NA	NA	4 months	Com Het	c.128C>A c.529G>A	p.(Pro43His) p.(Ala177Thr)	2 7	Missense Missense	Basal ganglia calcifications	Mildly delayed myelination Incomplete myelination of the centrum semiovale and corona radiate Brain magnetic resonance angiography: developmental vascular variants of the right posterior communicating and left posterior cerebral arteries	Mild ketonuria Low CSF glucose	Global developmental delay, jaundice at birth, head lag, truncal hypotonia, hypertonia with hyperreflexia in both arms and legs, spontaneous myoclonus and staring
Rump et al. (2016)	80	Female	NA	NO	NA	Com Het	c.529G>A c.554T>G	p.(Ala177Thr) p.(Val185Gly)	7 7	Missense Missense	Multiple intra cerebral calcifications	NA	NA	Intellectual disability, microcephaly, feeding problems, short stature, seizures, spasticity, severe developmental delay
La Piana et al. (2014)	81	Female	French Canadian	NO	2	Com Het	c.529G>A c.412C>T	p.(Ala177Thr) p.(Leu138Phe)	7 5	Missense Missense	Lentiform nucleus calcification	Bilateral leukoencephalopathy, involving the deep white matter of the frontoparietal lobes (WM abnormalities) Mild cerebral atrophy	CSF analysis: Normal IFNα (CSF) was not assessed.	Developmental regression, slowed head circumference growth, feeding difficulties, otitis, limb spasticity, hyperreflexia, axial hypotonia, spastic paraparesis, dysarthria
Crow et al. (2014)	82	Female	Egyptian	YES	1	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	Normal	Normal ISGs score	Scissoring gait, recurrent fall, LL weakness, undetected blindness of the left eye, Babinski sign
	83	Female	Egyptian	YES	2	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	Normal	↑ ISGs score (3.0)	Scissoring gait, recurrent fall, Babinski sign
	84	Male	North African	NO	23 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Normal	Nonspecific high signal on T2-weighted imaging Dilatation of lateral ventricles	CSF analysis: Lymphocytosis Normal ISGs score	Scissoring gait, Babinski sign
Tüngler et al. (2014)	85	Male	Moroccan	YES	11 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Ventricular enlargement, symmetrical hyper-intensive (T2w) signals of the WM, progressive demyelination of the posterior limb of the capsula interna, cerebellum and subcortical regions	CSF analysis: pleocytosis, ↑ Neopterin, ↑ IFN-α (CSF) IFT: ANA titer of 1:160 with a dense fine speckled pattern	Global developmental delay, truncal hypotonia and reappearance of primitive reflexes, irritability, jerky movements, mild intracranial hemorrhage, frequent febrile episodes
	86	Female	Moroccan	YES	21 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	NA	Normal	IFT: ANA titer of 1:320 with centromere pattern Positive for auto-antibodies against U1-RNP/O and CENP-B	Weakness of the ipsilateral leg following MMR vaccination, spastic paralysis of both legs
Abe et al. (2013)	87	Female	Japanese	NO	3 months	Het	c.[155T>G];[=]	p.[Leu52Trp];[=]	3	Missense	Calcifications in the bilateral basal ganglia	Brain atrophy, WM abnormalities	CSF lymphocytosis ↑ IFN-α (CSF) ↑ IFN-α (serum)	Eye movement disorder, severe developmental delay, dystonia, microcephaly, abnormal liver function
Ostergaard et al. (2012)	88	Male	Faroese	NO	Birth	Hom	c.322-3C>G		Intron4	Splice site	Periventricular calcifications	Severe atrophy, hypoplasia of corpus callosum, periventricular hyperintensity, high signal changes in the basal ganglia, and dysmyelination	NA	Chilblains, spasticity, microcephaly, psychomotor retarded, IUGR, feeding and language difficulties
	89	Female	Faroese	NO	Fetal	Hom	c.322-3C>G		Intron4	Splice site	NA	NA	Cordocentesis: reticulocytosis and thrombocytopenia Neuropathological examination: multiple calcifications, micro- and macrogliosis, and tissue decay	Decreased foetal movements, ventriculomegaly, oligohydramnios, Intrauterine foetal death (week 35) Ultrasound: foetal hydrops, heart failure, ascites, subcutaneous oedema, hyperperfusion of the brain
	90	Female	Faroese	NA	1 months	Hom	c.322-3C>G		Intron4	Splice site	Cerebral atrophy, periventricular calcifications in the basal ganglia, central pons, medulla oblongata and cerebellum	NA	CSF analysis: Lymphocytosis ↑ neopterin ↑ IFN-α	Microcephaly, nystagmus, irritability, apnoea, inverted mammary papillas, enlarged liver, hypertonic She died 8 months old.
	91	Male	Faroese	NA	4 months	Hom	c.322-3C>G		Intron4	Splice site	NA	Leukodystrophy General atrophy Hypoplasia of corpus callosum ↓ grey matter	NA	Developmental regression, microcephaly, dystonia, hypertonia, psychomotor retarded, feeding difficulties, seizures, decreased vision and nystagmus, decreased spontaneous movement, frequent episodes of vomiting
Taipa et al. (2010)	92	Female	NA	NO	7 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Bilateral basal ganglia calcifications Mild calcifications in both putamen	Normal	Normal	Chilblains, spastic diplegia, slight mental delay, generalized dystonia, spastic tetraparesis, cerebral palsy, pyramidal signs, encephalopathy, brisk reflexes and flexor plantar response
	94	Female	Portugal	YES	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcification	WM defects, Brain atrophy	NA	Dystonia, severe, moderate developmental delay, microcephaly
	95	Female	Sinti	YES	NA	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcification	WM defects, Brain atrophy	CSF lymphocytosis, normal IFN-α and PT levels in CSF, leukocytopenia, anticardiolipin IgM	Recurrent fever, dystonia, microcephaly, seizures, status epilepticus, moderate developmental delay (evident after vaccination)
	96	Male	German	NO	NA	Het	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcification	WM defects, Brain atrophy	NA	Dystonia, severe developmental delay, microcephaly
	97	Female	German	NO	NA	Het	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcification	WM defects, Brain atrophy	NA	Dystonia, severe developmental delay, microcephaly
	98	Male	European American	NO	NA	Het	c.529G>A	p.(Ala177Thr)	7	Missense	Basal ganglia calcification	WM defects, Brain atrophy	NA	Dystonia, severe developmental delay
	99	Male	European Canadian	NO	NA	Com Het	c.529G>A c.685T>C	p.(Ala177Thr) p.(Ser229Pro)	7 8	Missense Missense	Basal ganglia calcification	WM defects, Brain atrophy	NA	Seizures, spastic quadriparesis
Wassmer et al. (2009)	100	Female	Caucasian	NO	4 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Punctate periventricular calcification	Hypomyelination with dysmyelination	↑ Neopterin ↑ Biopterin ↑Dihydrobiopterin Normal CSF IFN-α	Encephalopathy, microcephaly, truncal hypotonia, transient myoclonus, regression, language difficulty
Orcesia et al. (2008)	101	Female	Italian	NO	14 months	Hom	c.529G>A	p.(Ala177Thr)	7	Missense	Bilateral calcifications in the lentiform nuclei	Bilateral WM hyperintensities	CSF analysis: Pleiocytosis ↓ Folates ↑ Biopterin ↑ Neopterin ↑ IFN-α	Gastro-oesophageal reflux, severe fever, otitis media, spastic tetraplegia, hypersomnia, generalised asthenia, irritability, drowsiness, truncal and neck hypotonia, pyramidal and extrapyramidal tract signs (dystonia, buccal-lingual dyskinesia and 'startle reactions'), absent verbal function EEG: diffuse slowing of background activity
D'Arrigo et al. (2008)	102	Female	Italian	NO	4 months	Com Het	c.529G>A c.218G>T	p.(Ala177Thr) p.(Trp73Leu)	7 3	Missense Missense	Normal	Leukodystrophy WM hyperintensity, cerebral atrophy, dilated ventricles and diffuse widening of the cortical sulci	Mild hypertransaminasaemia CSF analysis: Pleocytosis ↑ IFN-α	Chilblains, progressive gait disorder, spastic paraparesis with lower limb weakness and spasticity, an episode of bronchitis, spastic tetraparesis, recurrent fever
	103	Male	Italian	NO	8.5 months	Com Het	c.529G>A c.218G>T	p.(Ala177Thr) p.(Trp73Leu)	7 3	Missense Missense	Calcifications in the frontal regions and putamen	'Patchy' signal abnormalities of the WM	↓ C3 & C4 CSF analysis: ↑ IFN-α	Chilblains, spastic paraparesis, lower limb weakness and spasticity, febrile episodes

NA: not available; Hom: Homozygous; Het: Heterozygous; Com Het: Compound heterozygous; CSF: Cerebrospinal fluid; INF-α: Interferon-α; ISGs: Interferon-stimulated genes; IFT: Immunofluorescence test; EEG: Electroencephalogram; WM: White matter; C3: Complement component 3; C4: Complement component 4; SWI: Susceptibility Weighted Imaging; FLAIR: Fluid-Attenuated Inversion Recovery; PNP: Peripheral neuropathy; CKD: Chronic kidney disease; IUGR: Intra-uterine growth retardation; CT Scan: Computed tomography scan

CSF neopterin: A useful marker of inflammation in a broad range of acute and chronic cerebrospinal fluid disorders (reference range: 7–65 nmol/L).

Biopterin: A cofactor required for the production of certain neurotransmitters and abnormal levels of biopterin in cerebrospinal fluid can be indicative of certain neurological disorders.

↑: high, ↓: low