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Supplemental Data

Mutations in *SPATA5* Are Associated with Microcephaly, Intellectual Disability, Seizures, and Hearing Loss

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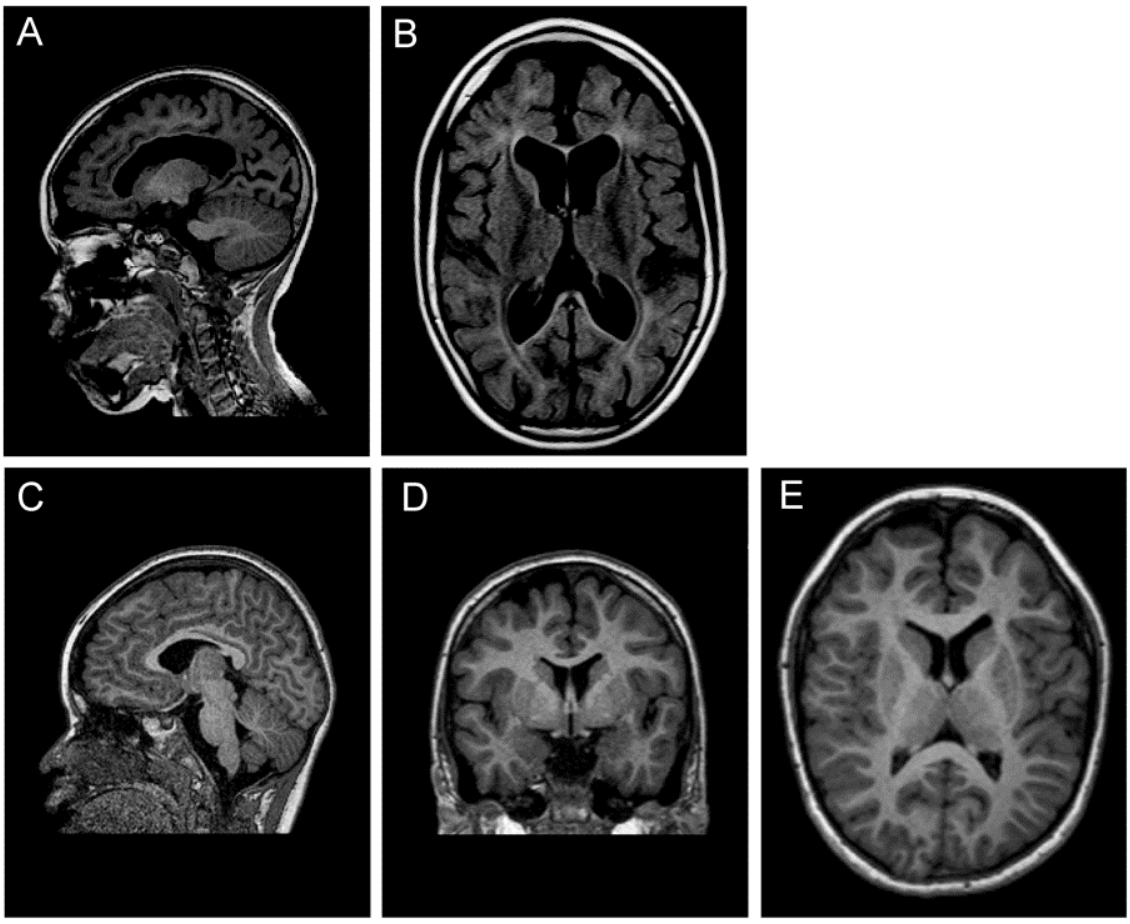

Figure S1. Brain imaging data for individuals with *SPATA5* variants. (A) Sagittal and (B) axial images of Individual 1 at 5 years of age show hypoplasia of the corpus callosum and prominence of bilateral ventricles and subarachnoid spaces with paucity of the white matter. (C) Sagittal (D) coronal and (E) axial images of Individual 6 at 7 years of age with progressive diffuse atrophy and extra-axial arachnoid collections.

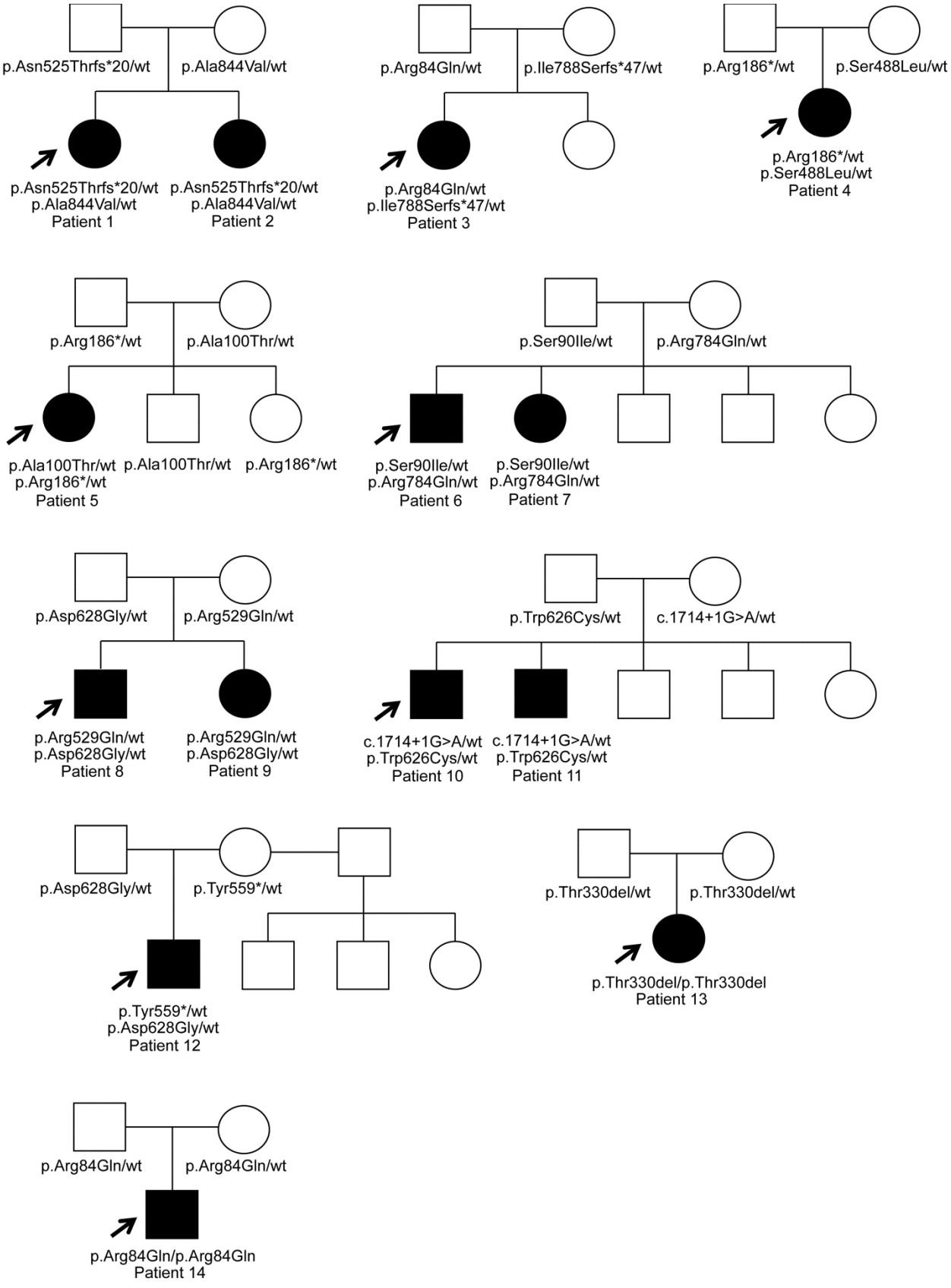

Figure S2. Family pedigrees and genotypes. The affected individuals are represented by filled symbols, and the proband individuals are indicated by arrows. Genotype of the respective mutations is indicated below the symbols of the available individuals.

Table S1. Variants identified from WES of seven families

	Filtering results	Manual review	Resulting genes of interest
Homozygous (# seq changes)	82 (89)	1 (1)	1 (1)
Compound Heterozygous (# seq changes)	276 (684)	1 (2)	1 (2)
De novo (# seq changes)	149 (157)	1 (1)	0 (0)
X-linked genes (# seq changes)	41 (44)	5 (5)	0 (0)
Total genes (# seq changes)	548 (974)	8 (9)	1 (3)

Table S2. Detailed clinical features of patients with mutations in *SPATA5*

Patient	Age	Sex	Proband/ sibling	Mutation	Muscle Tonicity	Spasticity	DD	Head Circumference	Age at Sitting	Age at Walking	Verbal Skills	Vision	Hearing	Brain MRI	Seizure	EEG	GI	Immunodeficiency	Thrombocytopenia
1	6 yo	F	P	p.Ala844Val, p.Asn525Thrfs*20	Hypotonia in early infancy; spasticity, opisthotonus	Spastic quadriplegia	Y	Congenital Microcephaly (<3 %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	CVI	Congenital moderate SNHL (BL)	Progressive atrophy and hypoplasia of corpus callosum	None	Abnormal	FTT, constipation	Y	N
2	9 yo	F	S of 1	p.Ala844Val, p.Asn525Thrfs*20	Spasiticity requiring baclofen pump	Spastic quadriplegia	Y	Congenital Microcephaly (<3 %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	CVI	Congenital moderate-severe SNHL (BL)	Thin corpus callosum, small neonatal subdural hematoma	Neonatal seizures only	Abnormal	FTT	Y	N
3	5 yo	F	P	p.Ile788Serfs*47, p.Arg84Gln	Axial hypotonia; Peripheral hypertonia	Spastic	Y	Congenital Microcephaly (<1%ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	Strabismus	Congenital SNHL (BL)	Delayed myelination and possibly dysmyelination	Infantile spasms starting at 3 mos, epilepsy until 1 yo, currently none	Abnormal (Multifocal spikes)	FTT, G-tube	Y	N
4	4 yo	F	P	p.Ser448Leu, p.Arg186*	Hypotonia	None	Y	Acquired Microcephaly (2nd %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	Discoordinated eye movements, exotropia, possible refractive amblyopia, small optic disc	Congenital moderate SNHL (BL)	Normal	Seizures started at <2 yo (5-6 per day)	Abnormal (Generalized epilepsy)	FTT, GERD, constipation, vomiting	N	N
5	2 yo	F	P	p.Ala100Thr, p.Arg186*	Hypotonia; dystonia	Dystonic spasms, opisthotonus	Y	Acquired Microcephaly (<3rd %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	CVI	Congenital severe SNHL (BL)	Hypomyelination	Epileptic spasms (10-12 per day), started at 3 mos	Abnormal	FTT, G-tube, GERD	Not tested	Not tested
6	11 yo	M	P	p.Arg784Gln, p.Ser90Ile	Hypotonia	Spastic quadriplegia	Y	Acquired Microcephaly (1st %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	CVI, nystagmus	Acquired mild SNHL (BL)	Progressive diffuse atrophy; extra-axial arachnoid collections	Intractable seizures started at 9 mos	Abnormal (Generalized epilepsy, slow background and high voltage epileptiform discharges with frontal predominance)	Does not eat solid food	N	Severe chronic autoimmune thrombocytopenia noted at birth, platelet counts ranging ~20,000-55,000
7	6 yo	F	S of 6	p.Arg784Gln, p.Ser90Ile	Hypotonia	None	Y	Acquired Microcephaly (<3rd %ile)	3 yo	Unknown	Has one word	Unknown	Acquired mild-moderate SNHL (BL)	Normal	One "seizure-like" episode at 2 mos	Abormal (Fragmented generalized discharges up to 2 seconds, no clinical events)	Constipation	N	Platelet counts ranging ~20,000-55,000
8	19 yo	M	P	p.Asp628Gly, p.Arg529Gln	Peripheral hypertonia	Spastic quadriplegia, retrocollis	Y	Unknown	Unknown	Non-ambulatory	Nonverbal	CVI, nystagmus	SNHL (BL)	Cortical atrophy; Immature myelination in occipital and frontal regions; Possible coronal suture	Seizures	Abnormal (Epileptic encephalopathy)	G-tube	Y	Y
9	14 yo	F	S of 8	p.Asp628Gly, p.Arg529Gln	Axial hypotonia	None	Y	Microcephaly	Unknown	Unknown	Unknown	CVI, nystagmus	SNHL (BL)	N/A	Absence, myoclonic, and tonic seizures	Abnormal	None	Unknown	Unknown
10	8 yo	M	P	p.Trp626Cys, c.1714+1G>A	Hypertonia	Spastic	Y	Microcephaly (<3rd %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	CVI	Congenital profound SNHL (BL) cochlear implant and hearing aids	Normal	Infantile spasms, tonic seizures started at 7 mos	Abnormal (Multifocal spikes)	GERD, G-tube	N	N
11	3 yo	M	S of 10	p.Trp626Cys, c.1714+1G>A	Hypotonia	None	Y	Microcephaly (<3rd %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	CVI	Congenital severe SNHL (BL)	N/A	Infanitle spasms, myoclonic seizures, cluster spasms started at 5 mos	Abnormal (Multifocal spikes)	G-tube, GERD	N	N
12	5 yo	M	P	p.Asp628Gly, p.Tyr559*	Hypotonia	Tonus dysregulation	Y	Normal (70th %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	Strabismus	Acquired moderate SNHL (BL), diagnosed at 3 mos	Enlarged cerebrospinal fluid spaces, probable brain atrophy	History of infantile spasms; tonic seizures, seizures with eye deviation (10-15/week) started at 11 mos	Abnormal (Slow background and bilateral occipital spike-and-wave complexes)	Severe constipation, PEG tube feedings	N	N
13	11 yo	F	P	p.Thr330del	Axial hypotonia; hypertonia in extremeties	None	Y	Microcephaly (<1st %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	CVI, exotropia, mildly speckled aspect of retina	Congenital severe SNHL (BL)	Normal	History of infantile spasms starting at 5 mos; tonic seizures	Abnormal (Hypsarrhythmia)	Trouble eating solid food	N	N
14	4 yo	M	P	p.Arg84Gln	Hypotonia	Truncal hypotonia, peripheral spasticity	Y	Congenital Microcephaly (<3rd %ile)	Cannot sit unassisted	Non-ambulatory	Nonverbal	Myopia, astigmatism, visual disinterest	Congenital severe SNHL (BL)	Normal	Seizures started at 1 yo	Abnormal (Frequent brief generalized error bursts of irregular spike and slow-wave activity)	FTT	N	N

Abbreviations are as follows: DD, developmental delay; EEG, electroencephalogram; FTT, failure to thrive; CVI, cortical visual impairment; GI, gastrointestinal issues; GERD, gastroesophogeal reflux disease; SNHL (BL), sensorineural hearing loss (bilateral); ADHD, attention deficit/hyperactivity disorder