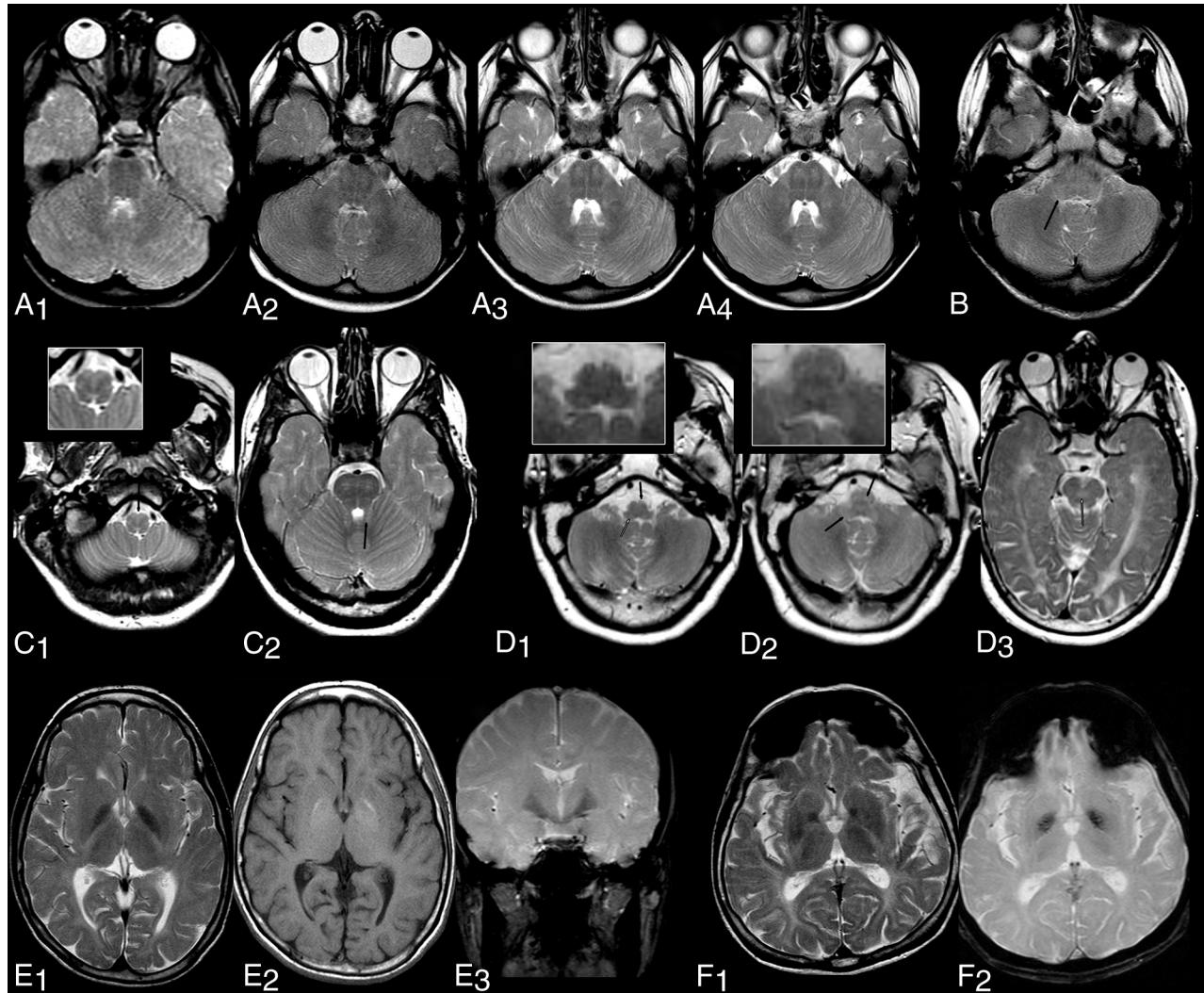


**ON-LINE FIG 1.** Overview of MR imaging changes of all patients. Representative T2WI at the level of the pons and middle cerebellar peduncles (*A*), pallidum (*B*), corpus callosum (*C*), Rolandic area (*D*), and midsagittal T1 images (*E*). Each row shows from left to right patients 1–6, with corresponding annotations, eg, *A*<sub>1,2,3</sub>. Field strength is 3T in patient 3 (*A*<sub>3</sub>–*E*<sub>3</sub>); otherwise, it is 1.5T. Images are from the last scan from patients with multiple scans.



**ON-LINE FIG 2.** Additional brain stem tract (*A–D*) and pallidal changes (*E* and *F*). *A*, Initially normal signal at 5 years of age (*A<sub>1</sub>*) and evolving T2 hyperintensity of the pontine pyramidal tract in patient 1 on follow-up at 5.8, 7.5, and 8.9 years of age (*A<sub>2–4</sub>*). *B*, Involvement of the inferior cerebellar peduncle in patient 2 (black arrow). *C*, Involvement of the pyramidal tract and medial lemniscus at the level of the medulla oblongata (black arrow in *C<sub>1</sub>*) and the superior cerebellar peduncle (black arrow in *C<sub>2</sub>*) in patient 3. *D*, T2 hyperintensity of the pyramidal tract and inferior cerebellar peduncle at the level of the medulla (*D<sub>1</sub>*) and pontomedullary junction (*D<sub>2</sub>*) as well as of crossing of the superior cerebellar peduncle at the level of the mesencephalon (*D<sub>3</sub>*) in patient 4 (black arrows). *E*, Signal changes of the pallidum in patient 2 (*E*) and patient 6 (*F*) with pronounced hypointensity on T2-weighted and gradient-echo T2\*-weighted images in patient 2 with corresponding abnormal T1 hyperintensity. (T2WI: *A–D*, *E<sub>1</sub>*, *F<sub>1</sub>*; TIWI: *E<sub>2</sub>*; T2\*WI: *E<sub>3</sub>*, *F<sub>2</sub>*).

**On-line Table 1: Overview of patients, mutations, and MR imaging findings, sorted by age at first MRI**

Patient (Sex)	Genetic Variant	Syndactyly	Age at MRI (yr)	Supratent. WM Changes				Involving				↑ T2 Pyramidal Tract at Level of				↑ T2 Brain Stem Tracts Other than Pyramidal				Gray Matter (↓ T2) at Level of				Changes on Sagittal Images	
				Diff.	↑ T2	↑ T2/↓ T1 Foci	CC	ALIC	Subcortical	PLIC	Mesenc.	Pons	Med.	Obl.	MCP	ICP	Cortex	Raph.	Pall.	Dentate Nucleus	Thin CC	Cran. Cerv.jct.			
1 (M) (son of p5)	c.17C>G p.(A6G)	Yes	5.0	Yes	No	No	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	Normal	Normal		
2 (F) <sup>a</sup> (daughter of p6)	(46(C>A) p.(T154N)	Yes	7.5	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	Normal	Normal		
3 (F)	c.443G>A p.(A848Gln)	No	8.9	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	Normal	Normal		
4 (F)	c.460A>G p.(Thr154Ala)	Yes	15.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	Normal	Normal		
5 (M) (father of p1)	c.17C>G p.(A6G)	Yes	18.2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Normal		
6 <sup>b</sup> (F) (mother of p2)	(46(C>A) p.(T154N)	Yes	43.7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Normal		
				Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Normal		
				51.9																					

**Note:** ALIC indicates the anterior limb of internal capsule; p, patient; CC, corpus callosum; Diff., diffuse; Cran. Cerv.jct., craniocervical junction; ICP, middle cerebellar peduncle; Med. Lemn., medial lemniscus; Med. Obl., medulla oblongata; Mesenc., mesencephalon; Pall., pallidum; PLIC, posterior limb of internal capsule; Suprant., supratentorial; WM, white matter; ↑, direction of signal alteration on T2WI; ↓, direction of signal alteration on T2WI; –, sagittal images were not acquired.

<sup>a</sup> Clinical and genetic findings have been previously published.<sup>11,12</sup>

<sup>b,c</sup> Corresponding T1 hyperintensity/T2\* hypointensity.

**On-line Table 2: Metabolite changes in white matter  $^1\text{H}$ -MRS**

Patient (Sex)	Age (yr)	NAA	Cho	Cr	mIns	NAA/Cr	Cho/Cr	mIns/Cr	Lac
1 (M)	8.9	~	~	(↑)	~	(↓)	(↓)	(↓)	ND
2 (F)	18.2	~	~	↑	(↑)	↓	↓	~	ND
3 (F)	19.2	~	~	~	~	~	~	~	ND
4 (F)	40.8	(↓)	(↓)	↑	~	↓	↓	↓	ND
5 (M)	43.7	~	~	↑	↑	(↓)	↓	~	ND
6 (F)	51.9	~	↓	↑	↑	(↓)	↓	(↑)	ND

**Note:**—ND indicates not detected; Lac, lactate; ~, metabolite values within the mean  $\pm 1$  SD; (↑)/(↓), values differing between 1 and 2 SDs from the mean; ↑/↓, values differing  $>2$  SDs from the mean.