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Letter to the Editor

The "broken wishbone" splenial sign: A diagnostic hallmark for SPG54 spastic ataxia

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Dear Editor,

Hereditary spastic paraplegias (HSP) are a heterogeneous group of inherited neurodegenerative disorders characterized by genetic mutations that cause degeneration of the corticospinal tracts, manifesting as progressive spasticity and weakness of the lower extremities in isolation (pure HSP) or in combination with other neurological features (complicated HSP). More than 70 genetic loci and around about 60 genes associated with distinct types of pure and complicated HSP have been identified [1]. Autosomal recessive spastic paraplegia type 54 (SPG54) is a rare complicated HSP caused by mutations in the *DDHD2* gene, encoding an intracellular phospholipase involved in organelle biosynthesis, membrane trafficking, and brain triglycerides regulation [2,3]. Homozygous and compound heterozygous pathogenic *DDHD2* variants have been previously reported [4–8]. Affected individuals exhibit delayed psychomotor development, cognitive impairment and early-onset progressive spasticity. MRI typically shows a form of thinning of the callosal splenium that is distinctive from other HSP and possibly a diagnostic hallmark for SPG54.

We have encountered a patient with childhood onset progressive spastic ataxia and dystonia associated with a novel pathogenic *DDHD2* mutation in whom the brain MRI showed a thin corpus callosum with configuration similar to that of other SPG54 cases, mimicking the "broken wishbone", a neuroimaging finding we suspect may represent a pointer for the clinician to suspect this genetic disorder. This finding was confirmed in our review of images available from previously reported cases.

1. Case report

This 44-year-old woman presented for evaluation of ataxia. She had a history of delayed motor developmental milestones, strabismus of the left eye, and gait difficulties since childhood. In her 20s, she experienced worsening of her limb incoordination and gait ataxia with increasing frequency of falls. She became aware of head titubation and had tremor at the age of 35. Over time, she developed cognitive impairment and what appears to have been dystonia of her neck and right shoulder. Family history revealed a maternal cousin with young onset ataxia, and a maternal grandmother with parkinsonism.

Her neurological examination showed cerebellar abnormalities (dysmetria, horizontal gaze evoked nystagmus, dysdiadochokinesis, intention tremor, head titubation, and gait ataxia), hyperreflexia and spasticity in the lower extremities, bilateral Babinski sign, position-sensitive dystonic hand tremor and cervical and right-arm dystonia (Video S1). She had marked cognitive impairment as measured by the Montreal Cognitive Assessment scale (score 6/30). Brain MRI showed mild atrophy of the superior cerebellar vermis and thinning of the corpus callosum, most marked in the splenium, with a unique "broken wishbone" appearance (Fig. 1).

Laboratory investigations were unremarkable for common reversible causes of ataxia. Testing for mutations in DYT1, FRDA1 and spinocerebellar ataxias was negative.

Whole genome sequencing was performed on her DNA and that of her parents (GeneDx Laboratory, Gaithersburg, Maryland). Testing revealed a homozygous c.724C > T (exon 7), pR242C variant in the *DDHD2* gene. Her mother and father were each heterozygous for the same variant. This variant has not been reported in the ClinVar database. (https://www.ncbi.nlm.nih.gov/clinvar/?term=DDHD2%5Bgene%5D).

2. Discussion

The wishbone is the cooked forked bone, or *furcula*, between the neck and breast of a bird; a popular custom holds that when each arm of the furcula is pulled away from the other to a breaking point by two people, the holder of the longer portion is entitled to make a wish. Since both arms of the bird's furcula are similarly thin, it is impossible to predict which arm will remain attached to the longer bone portion when both are pulled at the same time. Although the thinning of the splenium of corpus callosum, best demonstrated on midsagittal brain MRI, has been previously reported in SPG54 [4–6] (Fig. 1B, C, and D), we suggest it is its similar width to the fornix (the "lower" bone of the "furcula") which gives the callosum-fornix combination a striking resemblance to a "broken wishbone" in the callosum. This imaging finding may in part be related to abnormal myelination, since MRI spectroscopy in previous SPG54 cases (not performed in our case) has shown an abnormal lipid peak in the basal ganglia and thalamus [4]. Given that the broken wishbone appearance seems to exclusively apply to SPG54 cases (reported to date), it may represent a diagnostic hallmark in *DDHD2*-associated spastic ataxia, and serve therefore as a

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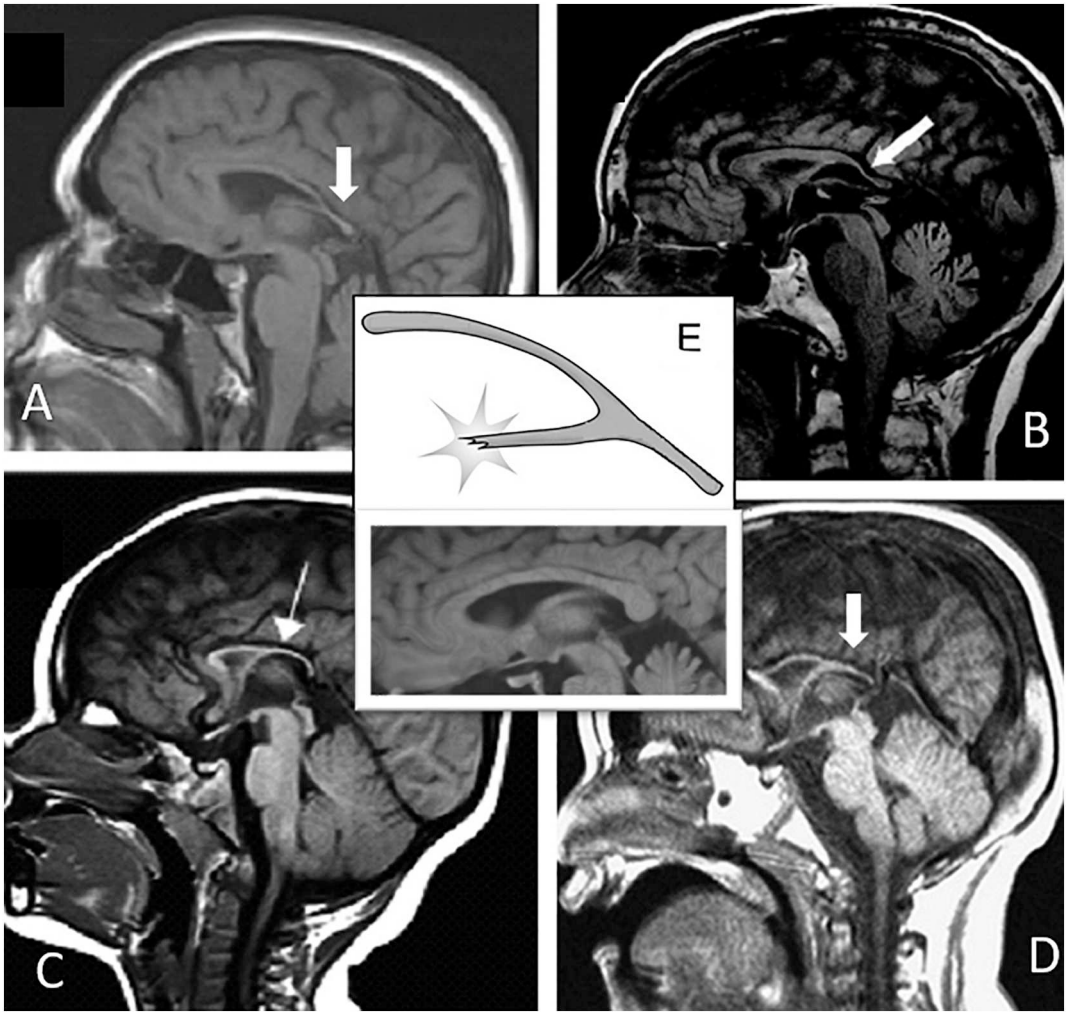

Fig. 1. Thin corpus callosum with "broken wishbone" appearance in mid-sagittal brain MRIs from our patient and three previously published cases with DDHD2 gene mutation. (A) Our patient with a c.724 C > T [p.Arg242Cys] mutation in the *DDHD2* gene; (B) a previously reported patient with c.658G > T [p.Val220phe] mutation [4]; (C) another patient with c.1804_1805insT/c.2057delA [p.Thr602llefs*18/p.Glu686Glyfs*35] mutations [5]; (D) another patient with c.1982_1983delAT [p.Tyr661Cysfs*8] mutation [6]. (E): Illustrative image of a "broken wishbone" above a normal midsagittal callosum. The "wishbone" may appear "broken" at the splenial base rather than at the fornix "arm".

potentially useful clue for the clinician to suspect this disorder.

The brain MRI finding of a thin corpus callosum has been consistently reported in selected forms of HSP, most commonly in mutations in the *KIAA1840* (SPG11) and *ZFYVE26* genes (SPG15) [10], but less commonly in mutations in the *FA2H* (SPG35), *AP5Z1* (SPG48) [10], *ACP33 (SPG21)* [11], *and AP4B1(SPG47)* [12] genes.

The association of *DDHD2* mutations with SPG54 is well recognized. The R242C variant, a novel mutation, is a non-conservative amino acid substitution likely damaging to protein structure and function [9]. While ataxia has been previously reported in Japanese siblings with homozygous *DDHD2* mutations [4], dystonia has not. Our case extends both the genotype and phenotype of *DDHD2* mutations/SPG54, suggesting it should be considered in cases of spastic ataxia with dystonic features.

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Author roles

1. Research project: A. Conception, B. Organization, C. Execution 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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H.M.S.: 1C, 3B
A.J.E.: 1C, 3B
A.P.D.: 1A, 1B, 1C, 3B

Declarations of Competing Interest
None.

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The authors declare that there are no additional disclosures to report.

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