

LETTER TO THE EDITOR

A novel *TUBB4A* mutation suggests that genotype-phenotype correlation of H-ABC syndrome needs to be revisited

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Sir,

We read with great interest the article on the rare childhood syndrome associated with *TUBB4A* and termed hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) (Hamilton *et al.*, 2014a), the commentary by Carvalho and colleagues (2014), and the subsequent reply by Hamilton *et al.* (2014b).

In their seminal paper on 42 unrelated H-ABC patients, Hamilton *et al.* (2014a) suggested the presence of genotype-phenotype correlation, arguing that a more benign phenotype is usually observed in patients with the common c.745G>A than in patients carrying other types of mutations. Carvalho *et al.* (2014) then reported two further patients, one carrying the c.745G>A mutation and the other carrying the novel c.1181T>G mutation, reinforcing the notion that there might exist a genotype-phenotype correlation of H-ABC syndrome. We wished to enter this debate giving examples of our experience, as we feel that sharing information and opinions will further enhance our understanding of this rare disorder.

We have recently come across three patients with a radiological pattern suggestive of H-ABC syndrome (Erro *et al.*, 2014), of whom one carries the previously unreported mutation c.941C>T (p.Ala314Val) in the *TUBB4A* gene. This mutation was proven to be *de novo*, as it was not detected in the parents. It is predicted to be damaging/disease-causing by different software tools (Provean, SIFT, Mutation Taster, SNAP and PhD-SNP) and is not present

in ~5000 Caucasian individuals listed in the NHLBI ESP Exome Variant Server (<http://evs.gs.washington.edu/EVS/>) and in the 1000genome project (<http://browser.1000genomes.org/index.html>) databases.

This female patient had a more benign phenotype and radiological abnormalities than the two patients carrying the classic c.745G>A mutation. She in fact had a normal birth and achievement of early milestones. From the age of 2 years she was noted to be clumsy and unsteady, several falls having occurred. By the age of 4 years, she started developing dystonic symptoms of her right arm upon writing. Her clinical condition progressed over time and she developed speech problems, sounding her voice 'whispering' with increased tension on phonation. Examination at the age of 10 years showed a generalized dystonic syndrome, whereas there were no pyramidal signs or appendicular ataxia. A brain MRI demonstrated mild hypomyelination with atrophy of putamen, while cerebellar volume was relatively preserved (Fig. 1). By the age of 21 years, her gait had worsened such that she had to use a wheelchair. Furthermore, she became virtually aphonic by the age of 24.

The other two patients carrying the classic c.745G>A mutation has a more severe phenotype. They shared most of the clinical characteristics with previously reported H-ABC syndrome, with delayed motor milestones and progressive walking difficulties, leading to wheelchair dependence between ages 5 and 16, and superimposed cerebellar

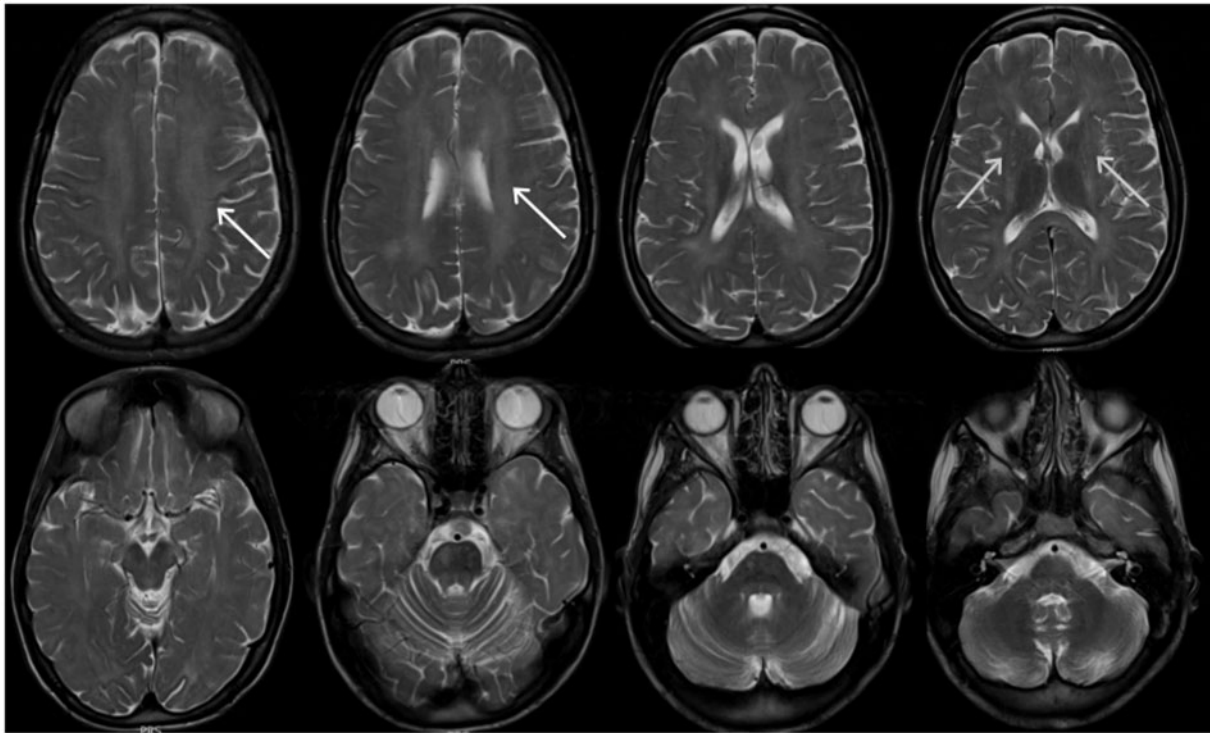


Figure 1 Genotype-phenotype correlation in H-ABC syndrome. Axial T₂ weighted magnetic resonance images showing diffuse supratentorial hypomyelination (white arrows) and bilateral putaminal atrophy (light grey arrows) with preservation of cerebellar volume.

and pyramidal features. Hence, the phenotype was much more severe in these cases than in the patient carrying the novel c.941C>T mutation. Our cases, along with other H-ABC patients who have been more recently described, confirm the idea that there might exist some mutations leading to a more benign phenotype than observed in patients with the common c.745G>A mutation.

We do agree that the genotype influences the phenotype and probably also the radiological appearance of H-ABC syndrome, as suggested by the informative table in the reply by Hamilton *et al.* (2014b). However, when Hamilton *et al.* first suggested the presence of genotype-phenotype correlation of H-ABC syndrome, they compared groups consisting of more than two patients with the same *TUBB4A* mutation, thus excluding groups of single patients, and this might have limited their conclusions. Probably, the more challenging issue in this context is with regard to different heterozygous changes at the same residue, namely c.4C>G and c.4C>T, which result in DYT4 (dystonia type 4; hereditary whispering dysphonia) and H-ABC syndrome, respectively (Hersheshon *et al.*, 2013; Lohmann *et al.*, 2013; Simons *et al.*, 2013). Until now, this has remained unexplained because both mutations are predicted to perturb the autoregulated instability of *TUBB4A* messenger RNA (Yen *et al.*, 1988; Hamilton *et al.*, 2014a; Miyatake *et al.*, 2014).

Functional studies are now more than warranted to understand how specific *TUBB4A* mutations produce both the radiological abnormalities and the clinical phenotype.

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