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Letter to the Editor

Mutations in *FA2H* in three Arab families with a clinical spectrum of neurodegeneration and hereditary spastic paraparesis

To the Editor

FA2H encodes fatty acid 2-hydroxylase, involved in the alpha-hydroxylation of the N-acyl ceramide moiety of sphingolipid fatty acids, essential components of myelin (1). Mutations in *FA2H* were identified in patients with recessive childhood onset spasticity, dystonia, cognitive dysfunction and periventricular white matter disease (2) and later extended to include neurodegeneration with brain iron accumulation (NBIA) (3), as well as in a recessive complicated form of hereditary spastic paraplegia (SPG35, MIM#612319) (4, 5).

We report seven patients from three unrelated consanguineous Arab families each with a novel homozygous *FA2H* gene mutation presenting with progressive spastic paraparesis and features of NBIA, highlighting the age-dependent neuropathy. The disease began with cerebellar manifestations including ataxia, nystagmus, intention tremors and dysarthia while infrequent limb dystonic movements were obvious with disease progression. Spastic quadriparesis and bulbar manifestations were evident with age. Magnetic resonance imaging revealed cerebellar atrophy, high white matter signal especially around occipital horns and low signal in basal ganglia consistent with NBIA. Interestingly, nerve conduction velocity revealed motor and sensory axonal neuropathy in all affecteds tested; a finding recently correlated with Fatty Acid Hydroxylase-associated Neurodegeneration (FAHN) (Table 1).

Whole exome sequencing from DNA from two affected members from each family were generated as

Table 1. Features of the described families with *FA2H* mutations compared with patients of the study by Donkervoort et al. (5)

	Family HSP-1284		Family HSP-1334		Family HSP-1528			Donkervoort et al.
Findings	IV-1	IV-3	IV-5	IV-6	IV-2	IV-3	IV-4	
Ethnicity	Egypt	Egypt	Sudan	Sudan	Yemen	Yemen	Yemen	Montenegro
Age at onset (y)	3	3	4.8	4.5	5	4.8	5	5 and 13 years
Age at last examination (y)	14	8.5	11	6	14	11	9	5 and 13 years
Cognitive impairment	Mild	–	–	–	Mild	–	–	–
Speech	Dysarthria/ anarthria	Dysarthria, bradylalia	Dysarthria/ bradylalia	Dysarthria	Dysarthria/ anarthria	Dysarthria	Dysarthria	Dysarthria
Pseudobulbar manifestations	Mild	–	–	–	+	–	–	–
Spastic parparesis	+	+	+	+	+	+	+	+
Ataxia	+	+	+	+	+	+	+	+
Nystagmus	+	+	+	+	+	+/Mild	–	+
Intention tremors	+	–	+	+	+	+	+	+
Dystonia	+	+	+	–	+	+	–	–
Seizures	+	–	–	–	–	–	–	+_
Sphincter disturbance	+	–	–	–	+	–	–	N/A
Optic atrophy	+	+	–	–	–	–	–	+
Leukodystrophy	+	+	Minimal	Minimal	+	+	+	Minimum
Cerebellar atrophy	+	Mild in the first scan	+	+	+	+	+	+
Hypointensity of basal ganglia	+	Mild	+	+	+	+	+	Mild
Thin corpus callosum	+	+	+	+	+	+	+	+
Nerve conduction velocity	Abnormal	Abnormal	Abnormal	–	Abnormal	Abnormal	–	–
Mutation in *FA2H* gene	p.Gln89stop	p.Gln89stop	p.Trp176Cys	p.Trp176Cys	p.Arg269Leu	p.Arg269Leu	p.Arg269Leu	p.Tyr170Stop

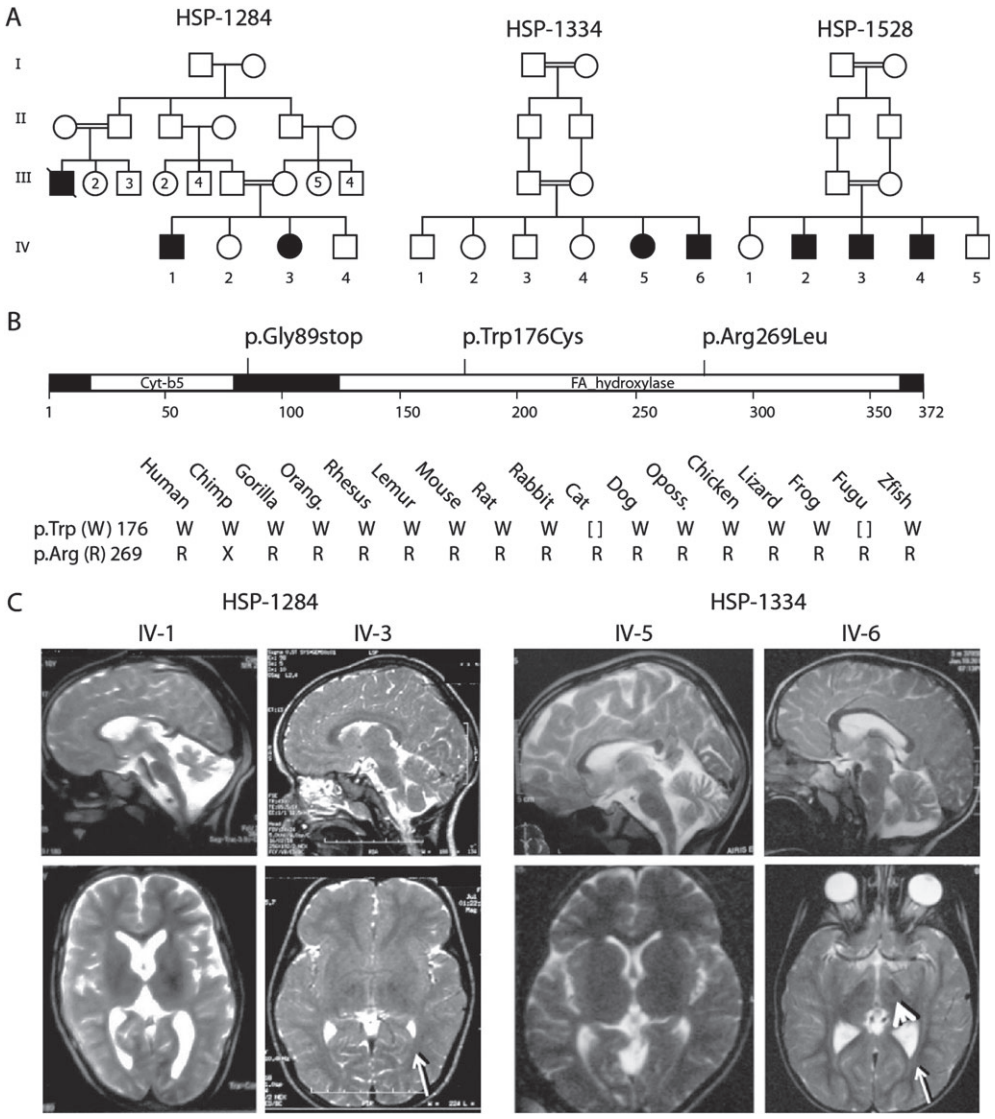

Fig. 1. (**a**) Pedigrees indicating affectation by black shading and number of siblings with a number within the symbol. A total of seven affected individuals are reported. (**b**) Location of protein changes against the FA2H domains. Sequence conservation across evolution of mutated missense amino acids. Cyt-b5, cytochrome b5-like heme/steroid-binding domain; FA_hydroxylase, fatty acid hydroxylase superfamily domain. (**c**) Brain magnetic resonance imaging. Row 1 (midline sagittal T2) showing prominent cerebellar atrophy and thin corpus callosum. Row 2 (axial T2) showing bilateral hypointensity of basal ganglia (arrowheads) and deep white matter hyperintensity around occipital horns (arrows).

part of a larger study of Hereditary Spastic Paraplegia (HSP) (6), approved by the institutional review board, and consented by the family. Homozygous mutations in *FA2H* were identified in all three families including a premature stop codon (chr16:74808389G>A, p.Gln89*) in family HSP-1284 and two nonsynonymous missense mutations (chr16:74760208C>G, p.Trp176Cys and chr16:74750478C>A, p.Arg269Leu) in families HSP-1334 and HSP-1528, respectively. These occurred at highly conserved residues (Fig. 1b) within the fatty acid hydroxylase superfamily transmembrane helical enzymatic domain (http://www.uniprot.org/uniprot/Q7L5A8), suggesting loss of function as the disease mechanism.

Our findings suggest that *FA2H* mutations result in clinical spectrum with a combined presentation of HSP, NBIA and axonal motor and sensory neuropathy, a triad unique in clinical genetics (2–5). We propose that *FA2H*-associated neurodegeneration is an under-diagnosed condition and is an important diagnostic consideration in recessive HSP of all ethnicities. *FA2H* encodes fatty acid 2-hydroxylase, involved in the synthesis of 2-hydroxy fatty acid galactolipids, major components of the myelin sheath and necessary for the production of myelin. A constitutive murine knockout line showed the same central nervous system dysfunction as a conditional Cnp1-Cre driven line (expressed in oligodendrocytes), suggesting a role in myelin (7).

Recently, several single genes responsible for myelination have been implicated in more than a single disease. Mutations in the proteolipid protein gene (*PLP1*) have been associated with two different X-linked recessive

diseases: pure and complicated forms of HSP (SPG2), and the more severe Pelizaeus–Merzbacher disease (8), amongst many other examples. Presumably, allelic diversity, modifiers and environment drive phenotypic diversity in HSP are yet to be fully explained.

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