LETTER TO THE EDITOR

To The Editor

FA2H Mutations in a Young Adult Presenting as an Isolated Cognitive Impairment Syndrome

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Fatty acid 2-hydroxylase (*FA2H*) gene mutations have been associated to a number of clinical phenotypes. These can range from a subtype of neurodegeneration with brain iron accumulation (NBIA) called fatty acid hydroxylase-associated neurodegeneration,[1–3] hereditary spastic paraparesis type 35,[1,4] and leukodystrophy with spasticity and dystonia.[1,5] The phenotypic features are characterized by corticospinal tract involvement with truncal instability, movement disorders, supratentorial and infratentorial atrophy, ophthalmological findings, seizures and leucodystrophy leading to early intellectual decline.[1–5] Its inheritance is autosomal recessive. We hereby report the case of a patient harboring 2 likely pathogenic variants in the *FA2H* gene who presented with isolated early-onset neurocognitive impairment.

A 43-year-old woman was referred for progressive neurocognitive decline over a 5-year period. Her medical history included a concussion in childhood and a diagnosis of attention-deficit disorder in her 30s. She had no history of psychiatric disorder or drug abuse. Family history was negative for any neurodegenerative condition. In terms of educational achievement, the patient completed postgraduate studies in toxicology. In the 2 years prior to initial assessment, she struggled to keep a job because of increasing cognitive difficulties in learning new tasks forcing her to move back with her parents. She scored 29/30 on her mini-mental status examination and 23/30 on her Montreal Cognitive Assessment test revealing deficits in attention span, episodic memory, language, and executive functions. The Frontal Assessment Battery test was also abnormal (12/18). Complete extensive neuropsychological evaluation revealed particularly marked deficits in episodic memory, semantic fluency, verbal memory, and visual gnosia all proving to be progressive upon subsequent analysis. Aside from her cognitive impairment, her neurological examination was negative for focal deficits or localizing signs.

Brain MRI showed moderate cerebellar atrophy and milder diffuse cortical and subcortical atrophy without any significant white matter lesions or brain iron accumulation on susceptibility-weighted imaging. Brain positron emission tomography (PET) scan showed severe cerebellar hypometabolism (Figure 1). Lumbar puncture showed no significant abnormalities including negative biomarkers for Alzheimer. Further investigations, including a complete metabolic workup (electrolytes, renal, and hepatic function, thyroid stimulating hormone, B12, B9, serum protein electrophoresis, iron profile, lipid profile, and inflammatory markers), search for inborn errors of metabolism (plasma amino acids, urinary organic acids, very long-chain fatty acids, acylcarnitines profile, and sterols analysis), infectious etiologies (including HIV and syphillis), and polysomnography were negative.

With alternative diagnostics excluded, a comprehensive neurogenetics gene panel was performed, targeting 36 genes associated with autosomal dominant adult-onset dementia and 109 genes causing recessive disorders associated with developmental regression in children or cognitive decline in adults (see supplementary information for complete genes list). Analysis revealed two rare variations in the *FA2H* gene (RefSeq NM_024306.4): c.366_367delCC (p. Leu123GlyfsTer20) and c.94C > G (p. Arg32Gly). The c.366_367delCC variant has not been reported in patients or as a polymorphism. However, it is expected to be deleterious as it introduces a change in the reading frame of exon 3, which is predicted to lead to a premature stop codon, nonsense-mediated mRNA decay, and absence of the FA2H protein. Loss of function variants are known to be pathogenic.[1] This variant has been classified as likely pathogenic (American College of Medical Genetics and Genomics [ACMG] criteria: PVS1, PM2). The c.94C > G variant has been reported in an affected patient in the ClinVar database by one clinical laboratory, but phenotypic details were not provided. It has only been observed 3 times in the gnomAD database (gnomad.broadinstitute.org) for a low population allele frequency of 3.046e-5. REVEL, an ensemble method to predict pathogenicity of missense variant based on 13 independent tools,[6] yielded a score of 0.53. When using a threshold of ≥0.5 to predict pathogenicity, REVEL has a sensitivity of 0.754 and a specificity of 0.891. However, others bioinformatics predictions tools gave conflicting results about the pathogenicity of this variant. The variation introduces an amino change in the cytochrome b5 heme-binding domain of the FA2H protein. This domain is important for the function of the protein, and other pathogenic changes have been reported in adjacent amino acids, including the p. Asp35Tyr variant. Cells transfection suggested that this variant inactivates FA2H activity.[2] Finally, genetic analysis of her parents revealed that the two variants were inherited in a *trans* pattern, supporting their pathogenicity and the causative role of *FA2H*. This variant was classified as likely pathogenic (ACMG criteria PM2, PM1, PM3).

We present a patient with isolated early-onset neurocognitive impairment and harboring two likely pathogenic variants in the *FA2H* gene. Although the literature remains scarce, the recognized clinical phenotypes have been ever expanding. Current literature suggests the signs and symptoms to be limited to the central nervous system including corticospinal tract involvement, movement disorders, seizures, ophthalmological findings, NBIA, MRI abnormalities,[4] and intellectual deterioration. This disease mainly affects patients in their first or second decade of life and, to our knowledge, only two adult cases have been reported.[7] Follow-up remains crucial for this patient as other symptoms or MRI changes related to *FA2H* mutations may arise over time.

This patient displayed none of the known phenotypic features of the recessive *FA2H* gene mutations. We propose that isolated neurocognitive impairment in the young adult, defined as onset prior to the age of 65, could represent a novel phenotype associated with the *FA2H* gene. Such a clinical presentation has a relatively broad differential diagnosis. It can be dichotomized as early-onset neurodegenerative conditions associated with aging or late-onset forms of childhood neurodegenerative conditions. The most common neurodegenerative etiology remains young-onset Alzheimer's

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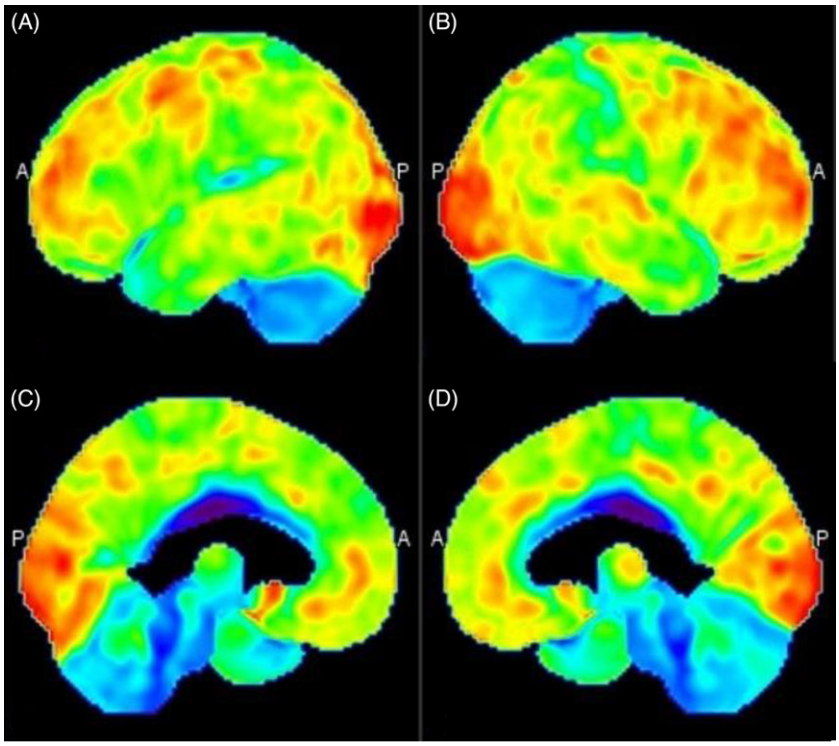

Figure 1: *(A) and (B) fluorodeoxyglucose–PET scan showing severe diffuse hypometabolism of the cerebellum. There is also a slight hypometabolism of the temporoparietal regions. There is no hypometabolism of the posterior cingulate gyrus or the precuneus; (C,D) Sagittal plane showing, once again, the severe and diffuse hypometabolism of the cerebellum.*

disease, which should be thoroughly excluded with appropriate neuroimaging and biochemical studies.[8] When these investigations are inconclusive, genetic testing can be selectively prescribed and should be preceded by proper genetic counseling.

Although *FA2H* gene mutations are associated with intellectual deterioration, it has never been reported as an isolated clinical feature, thus expanding its phenotype. Furthermore, our case highlights the importance of next-generation gene sequencing in the diagnosis of young-onset cognitive impairment. Although the treatment remains, to this day, supportive, such recognition of pathogenic genes can lead to better genetic counseling, prevention of potential complications and improves medical knowledge, hopefully for potential future therapeutic venues.

Disclosures

None of the authors has financial or proprietary interests in any of the material or method mentioned.

Statement of Authorship

LALF: study concept and design, acquisition of data; ML: study concept and design, acquisition of data; SL: revision of manuscript; CB: revision of manuscript.

Supplementary material

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