Fever-Induced Paroxysmal Weakness and Encephalopathy (FIPWE)-Part of a Phenotypic Continuum in Patients With ATP1A3 Mutations?

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Fever-Induced Paroxysmal Weakness and Encephalopathy (FIPWE)—Part of a Phenotypic Continuum in Patients With *ATP1A3* Mutations?

We read with interest the article by Yano et al,[1] identifying a new phenotype of patients with a heterozygous mutation in the gene encoding the sodium-potassium ATPase alpha-3 subunit (*ATP1A3*) at c.2267G>A (residue 756). Previously, specific *ATP1A3* gene mutations were associated with unique phenotypes, including alternating hemiplegia of childhood (AHC), rapid-onset dystonia-parkinsonism (RDP/DYT12), and cerebellar ataxia, pes cavus, optic atrophy, sensorineural hearing loss.[2] In children with *ATP1A3* gene mutations, Yano et al. described a group of patients with another phenotype, presenting with fever-induced paroxysmal muscle weakness and encephalopathy (FIPWE). The authors allocate this specific clinical presentation to a mutation at a single residue 756 (p.(Arg756Leu), p.(Arg756His), or p.(Arg756Cys)).[1]

In addition to recognition of separate genotype-phenotype relationships, awareness of the phenotypic continuum of *ATP1A3* mutations is necessary.[3] This is illustrated by three of our patients with FIPWE-like features, who were reported with different *de novo ATP1A3* gene mutations. The first two (unrelated) children were both diagnosed with an identical *de novo ATP1A3* gene mutation at c.2266C>T, p.(Arg756Cys) (NM_152296.4). These two children suffered from fever-induced attacks with paroxysmal muscle weakness, encephalopathy, ataxia, chorea, dystonia, and mutism. The third child was diagnosed with a *de novo ATP1A3* gene mutation at c. 2232C>A, p.(Asn744Lys) (NM_152296.4). He suffered from three severe fever- and stress-induced attacks with paroxysmal muscle weakness, asymmetrical dystonia, mutism, electroencephalographic seizure activity, and encephalopathy. All three children recovered in between attacks, albeit incomplete and slowly. In the first two children, the FIPWE phenotype-genotype relationship was established. The symptoms of the third patient, however, were attributed to a spectrum of overlapping acronyms (AHC, RPD, and FIPWE).

Although genetically different, these three patients with *ATP1A3*-related disorders may illustrate that the symptoms associated with the FIPWE phenotype[1,4] are encompassed within a broader phenotypic continuum of *ATP1A3* gene mutations. Assigning overly exact phenotype-genotype relationships could promote inaccurate interpretation of the overlapping phenotypes within the broad phenotypic spectrum of *ATP1A3*-related disorders. Furthermore, clinicians need to be aware that laboratories may report specific mutations differently, and therefore we advise that publications on the association between a new acronym and a specific gene mutation also mention the reference sequence accession number (NM_number). This could alert clinicians that their previous patients with similar phenotypes could have been reported differently by another genetic reference sequencing, in the past.

Until now, it remains unclear whether, and if so, which molecular mechanisms underlie these disease presentations. In patients with *ATP1A3* gene mutations, we hope that future insight in the spectrum of genotype-phenotype relationships will add to our understanding of the pathogenesis and to potential therapeutic strategies to prevent these devastating attacks.

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