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Genetics of migraine and related syndromes

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CHAPTER 5

FAMILIAL HEMIPLEGIC MIGRAINE IS ASSOCIATED WITH FEBRILE SEIZURES IN AN FHM2 FAMILY WITH A NOVEL DE NOVO *ATP1A2* MUTATION

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INTRODUCTION

Febrile seizures are the most common form of convulsions between the age of 6 months and 5 years,¹ but genetic factors have not been identified. Here we investigated the molecular basis of febrile seizures in a small family with co-occurring hemiplegic migraine² and febrile seizures (Fig. 1). Intermittent ataxia and diffuse encephalopathic episodes are also present in this family.

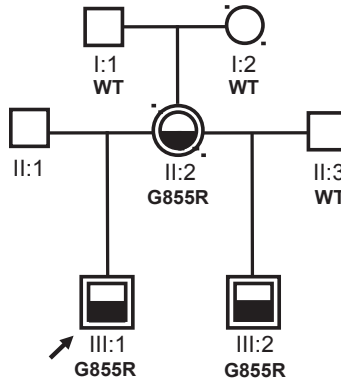


Figure 1. Pedigree of the FHM2 family. The arrow indicates the proband. Squares indicate male subjects and circles indicate female subjects. To indicate clinical diagnosis; with lower-half-filled symbols represent FHM and double-lined symbols represent febrile seizures. Individuals heterozygous for the *ATP1A2* mutation are indicated by G855R. Wild-type (WT) indicates that the individual does not have the mutation.

RESULTS

Using direct sequencing (see Vanmolkot et al., 2003³), we identified a novel de novo heterozygous 2563 G>A substitution in exon 18 resulting in an amino acid change from a glycine to an arginine at position 855 in the *ATP1A2* FHM2 gene⁴ that encodes the $\alpha 2$ subunit of Na⁺, K⁺-ATPase pumps. Only, the proband (III-1), the affected mother (II-2), and affected brother (III-2) carry this *ATP1A2* mutation. Gly855 is evolutionary conserved (Fig. 2A), and the mutation was not identified in 300 control chromosomes.

An ouabain challenge assay⁵ for the mutant p.Gly855Arg construct, unlike wildtype, showed complete loss of cell survival, indicating that the mutation has functional consequences at the protein level (Fig. 2B).

CLINICAL DESCRIPTIONS

This now 13-year-old proband (III-1) (Fig. 1) experienced, from the age of 9 months to 3 years, five complex febrile seizures and one simple febrile seizure. The complex seizures either lasted more than 15 min or started focally. There were also episodes of several seizures occurring

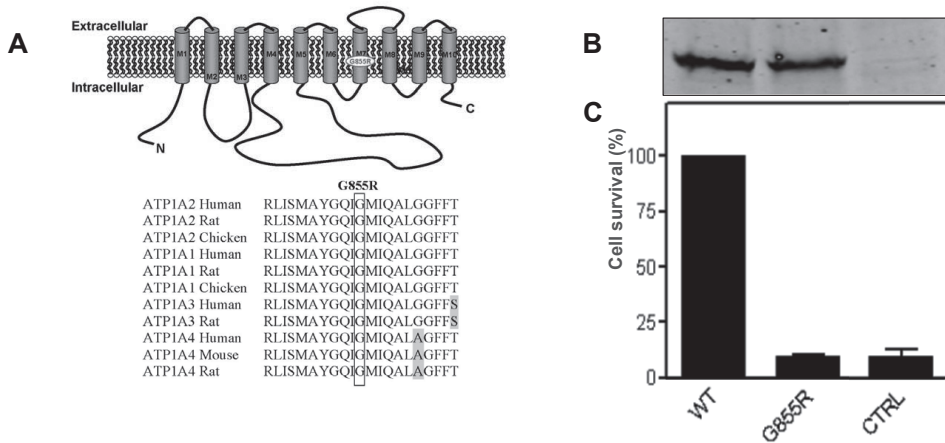


Figure 2. Genetic and functional data on mutant p.Gly855Arg. **(A)** Alignment of amino acid sequences of several vertebrate sodium-potassium ATPase α -subunits; Gly855 is represented as a black box. **(B)** Upper panel shows Western blot analysis of transfected HeLa cells. Lower panel shows graphic representation of ouabain cell survival assay. Bars represent cell survival after 5 days of ouabain treatment [error bars indicate standard error of the mean (SEM)].

sequentially. From the age of 7 months to 5 years, he also experienced several nonfebrile seizures, which typically had a focal onset and were secondary generalized. These seizures usually lasted up to 5 min, but sometimes were prolonged (up to 40 min), and at times occurred in clusters. Seizures stopped at age 5.

From age 2.5, he experienced headache attacks accompanied by transient hemiparesis as well as frequent unprovoked episodes of ataxia lasting a few minutes to days. In addition, he had episodes of rapidly progressive drowsiness down to Glasgow Coma scale (GCS) 6–7, without any focal neurologic deficits or epilepsy. The patient has ongoing behavioral problems and mild learning difficulties.

His now 3-year-old half-brother (III-2) had one complex (focal) febrile seizure lasting 15 min when he was 7 months old. Since the age of 21 months he had episodes of hemiplegia, and recurrent encephalopathic episodes often preceded by headache and hemiplegia, and one episode of unsteadiness after minor head injury. The mother (II-2), now age 31 years, had two simple febrile seizures at age 2 and also had attacks of hemiplegic migraine. The father of the proband (II-1) and the father (II-3) of his half-brother and their grandparents (I-1 and I-2) never had hemiplegic migraine, ataxia, or seizures.

CONCLUSION

We feel that the *ATPIA2* p.Gly855Arg mutation is the causal mutation in this family for a number of reasons: (1) FHM and febrile convulsions were present only in the three mutation carriers and not in non-mutation carriers; (2) the mutation was not identified in a panel of 150 healthy control individuals, and (3) functional studies revealed that the mutant has a

deleterious effect on cell survival. Febrile seizures are reported in only some mutation carriers of three FHM2 families.^{3,6,7} Future identification of additional families with co-occurring hemiplegic migraine and febrile seizures may shed light on the association between *ATP1A2* gene mutations and febrile seizures. We, therefore, recommend genetic analysis of the *ATP1A2* gene in patients with febrile seizures.

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DISCLOSURE

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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