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CASE REPORT

Recessive *ARFGEF2* mutation causes progressive microcephaly, epilepsy, and a distinct MRI pattern

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ABSTRACT

Background: Periventricular nodular heterotopia, a common form of neuronal heterotopia, is heterogeneous in etiology. Recessive mutations in *ARFGEF2* causing microcephaly and periventricular heterotopia have rarely been reported.

Case Presentation: We report two Saudi siblings with a homozygous *ARFGEF2* mutation (c.958 + 1G > A) presenting with microcephaly, dyskinetic movements, seizures, and a distinct brain magnetic resonance imaging pattern, describing the genotype and radiology phenotype correlation.

Conclusion: We speculate that the involvement of the putamen may be a key under recognized feature of *ARFGEF2* mutations.

Keywords: Case report, *ARFGEF2* gene, microcephaly, periventricular nodular heterotopia, putamen.

Introduction

Periventricular nodular heterotopia (PNH) is by far the most frequent form of neuronal heterotopia. Numerous causes, both genetic and nongenetic, have been associated with PNH (1). Genetic causes include mainly X-linked *FLNA* gene mutation (1), and less commonly recessive ADP-RIBOSYLATION FACTOR GUANINE NUCLEOTIDE EXCHANGE FACTOR (*ARFGEF2)* mutation (2), and 6q27 deletion (3).

To further characterize the *ARFGEF2*-related neurological phenotype and neuroradiological features, we report two children from a consanguineous family presenting with progressive microcephaly, early onset refractory seizures, and a distinct brain magnetic resonance imaging (MRI) pattern.

Case Presentation

We report two patients from a consanguineous Saudi family (Figure 1), with an identical presentation.

The patient II-3 had a normal delivery; and normal neonatal parameters (head circumference at birth: 34 cm). Developmental delay became apparent during the first y ear. S he h ad f eeding d ifficulties, re current chest infections, and developed epilepsy in the form of generalized tonic–clonic seizures at 6 months of age. On examination at 3 and 5 years old, she has severe microcephaly head circumference < −4 standard deviation (SD), has no clear eye contact or interaction, is hypotonic, dyskinetic in upper and lower extremities, and has failure to thrive (weight: 8 kg, length: 80 cm; both parameters are less than the 3rd percentile). electroencephalogram (EEG) showed slowing over the right posterior region, with sharp waves over the right occipital area. The ophthalmologic examination was normal, as was the electroretinogram.

Neuro-imaging revealed multiple brain abnormalities. Brain MRI showed subependymal bilateral periventricular heterotopias with the evidence of cobble-stone appearance, hyperintensity in the putamen bilaterally, thin corpus callosum, particularly in the body and the splenium, ventriculomegaly, and paucity of the white matter (Figure 2).

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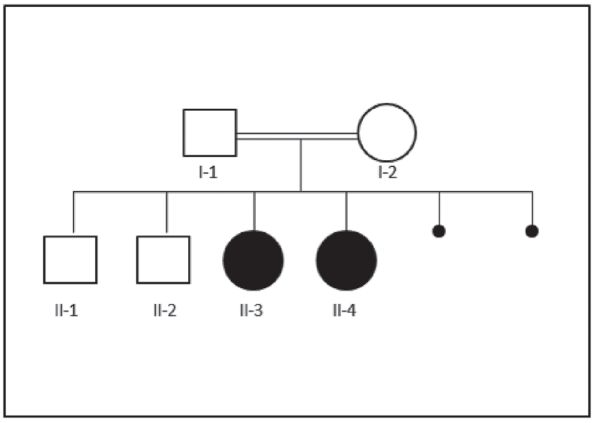

Figure 1. *Pedigree of the study family showing the degree of consanguinity between the parents and the affected patients.*

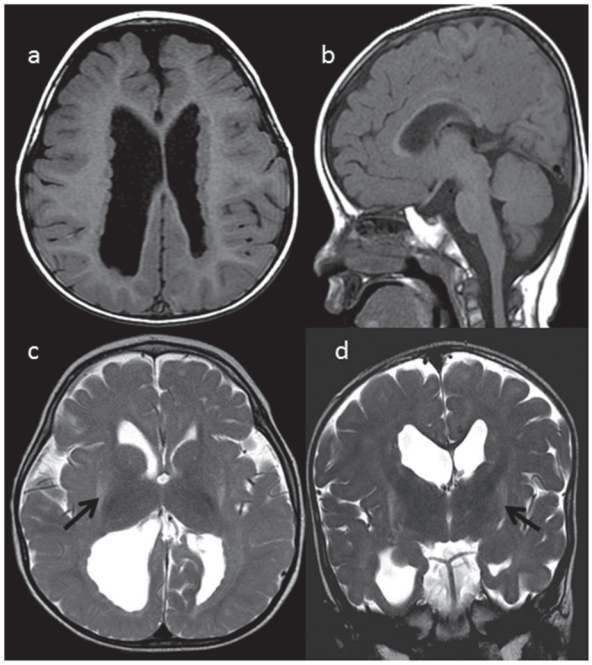

Figure 2. *(a) Axial T1-weighted image shows periventricular heterotopia (white arrow). (b) Sagittal T1-weighted images show thinning of the corpus callosum. (c and d) Axial and coronal T2-weighted images show asymmetrical ventriculomegaly, white matter paucity, and symmetric atrophy of both putamina with T2 high signal at their posterior aspect (black arrow).*

The patient II-4, her young sister, presented more or less with the same complaints, physical and neuroimaging findings.

The genetic study with a gene-panel testing showed a homozygous mutation in the *ARFGEF2* gene: c.1958 + 1G > A, in both patients; confirmed by Sanger sequencing, and heterozygous in their parents.

Discussion

This report describes an *ARFGEF2* mutation causing progressive microcephaly, epilepsy, dyskinetic movements, and profound developmental delay. According to previous reports, all patients harbored homozygous mutations in *ARFGEF2*, and brain MRI showed characteristic findings including PNH, abnormal putamen, and thin corpus callosum (4–8). Banne et al. reported five patients from a consanguineous Palestinian family with the same mutation c.1958 + 1G > A found in our patients. All patients share the same phenotype with refractory epilepsy, severe developmental delay, microcephaly, and the brain MRI showed diffuse periventricular heterotopia with a thin corpus callosum but exhibit difference in the epilepsy phenotype in the form of West syndrome, and lack of the putamen involvement on the neuroimaging (8).

PNH is caused by defective neuronal migration that results in heterotopic neuronal nodules lining the lateral ventricles. It is expressed clinically with epilepsy and developmental delay, mainly intellectual disability. Genetic causes include mainly an X-linked filamin A (*FLNA)* gene mutation, and less commonly a recessive *ARFGEF2* mutation or 6q27 deletion.

In mice, *ARFGEF2* is expressed at high levels during the embryonic periods of ongoing neuronal proliferation and migration and is found to be widely distributed throughout the embryonic central nervous system (9). *ARFGEF2* encodes the brefeldin A-inhibited GEF2 protein (BIG2), which is required, along with *FLNA*, for vesicle and membrane trafficking from the trans-Golgi network. Inhibition of BIG2 decreases cell proliferation suggesting a cell-autonomous regulation of neural expansion. Inhibition of BIG2 also disturbs the intracellular localization of several molecules such as E-cadherin and catenin by preventing their transport from the Golgi apparatus to the cell surface (10,11). As both *FLNA* and BIG2 are implicated in vesicle trafficking, it has been proposed that an overriding defect in the vesicle trafficking machinery may contribute to PNH formation.

The pattern of brain malformation in *ARFGEF2*-PNH patients differs from that observed in association with *FLNA* mutations, and in 6q27 deletion. *FLNA* is the most commonly reported genetic cause of PNH. Although X-linked, the disease affects girls, the clinical phenotype is usually less severe compared with *ARFGEF2*. On MRI, there is bilateral, nearly contiguous PNH that, can be associated with thinning of the corpus callosum and malformations of the posterior fossa, the putamen are constantly normal (1).

In 6q27 deletion, MRI shows various developmental brain abnormalities including PNH, corpus callosum dysgenesis, colpocephaly, cerebellar hypoplasia, and polymicrogyria. The thalami and other basal ganglia appear normal (3). It appears that the main neuroradiological specificity of

ARFGEF2-PHN is the abnormality of the putamen. The mechanism by which there is specific involvement of the putamen in the presence of mutations in the *ARFGEF2* gene remains unknown.

Conclusion

In conclusion, we speculate that the involvement of the putamen may be the key feature of *ARFGEF2* mutations. For infants presenting with progressive microcephaly, dyskinetic movements, and neuroimaging showing PNH, putaminal involvement, and thin corpus callosum, *ARFGEF2* mutations should be considered as a differential diagnosis.

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None.

List of abbreviations

EEG	electroencephalogram
MRI	magnetic resonance imaging
PNH	periventricular nodular heterotopia
SD	standard deviation

Consent for publication
Written informed consent was obtained from the parents of the patients for publication of this paper and any accompanying images.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

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Declaration of conflicting interests
The authors declare that there is no conflict of interests.

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