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Autosomal recessive form of periventricular heterotopia

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Abstract—*Background:* Familial periventricular heterotopia (PH) represents a disorder of neuronal migration resulting in multiple gray matter nodules along the lateral ventricular walls. Prior studies have shown that mutations in the filamin A (*FLNA*) gene can cause PH through an X-linked dominant inheritance pattern. *Objective:* To classify cortical malformation syndromes associated with PH. *Methods:* Analyses using microsatellite markers directed toward genomic regions of *FLNA* and to a highly homologous autosomal gene, *FLNB*, were performed on two pedigrees to evaluate for linkage with either filamin gene. *Results:* Two consanguineous pedigrees with PH that suggest an autosomal recessive inheritance pattern are reported. MRI of the brain revealed periventricular nodules of cerebral gray matter intensity, typical for PH. Seizures or developmental delay appeared to be a common presenting feature. Microsatellite analysis suggested no linkage to *FLNA* or *FLNB*. *Conclusions:* Autosomal recessive PH is another syndromic migrational disorder, distinct from X-linked dominant PH. Further classification of these different syndromes will provide an approach for genetic evaluation.

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Human cortical malformations often are the underlying cause for the development of epilepsy, with many of these disorders having a genetic basis. Familial periventricular heterotopia (PH) represents such an inheritable disorder of neuronal migration and is characterized by aberrant nodules, composed of neurons that line the ventricle and lie beneath an otherwise normal-appearing cortex.¹⁻⁵ Affected individuals often present with seizures.^{6,7} Prior studies have also shown that some individuals with PH have mutations in the X-linked gene, filamin A (*FLNA*).^{8,9} Further classification of other syndromes associated with PH will provide a clearer means with which to identify genes, perhaps related to *FLNA* and involved in cortical development.

Recent studies suggest that additional genes are likely to be involved in causing PH, not linked to *FLNA*.¹⁰ Mutational analysis has shown that within familial PH, >80% of affected families have a detectable *FLNA* mutation. On the other hand, only 20% of individuals with spontaneous PH (i.e., without a family history) have detectable *FLNA* mutations, when evaluated by single-stranded conformational polymorphism analysis. Furthermore, PH has been reported to coexist with multiple pterygium syn-

drome,¹¹ Allgrove's syndrome,¹² celiac disease and palatoschisis,¹³ megalencephaly,¹⁴ and mental retardation.¹⁵ Such observations would suggest additional heterogeneous causes of PH.

Here we describe five individuals from two consanguineous kindreds with PH that suggest an autosomal recessive mode of inheritance.

Patients and methods. Analysis was performed on two pedigrees. Individuals studied by linkage analysis in Family 1 include two affected individuals, an unaffected sibling, and their parents. In Family 2, three affected probands and their parents were studied for linkage to the *FLNA* gene.

DNA was isolated from peripheral whole blood using previously described protocols (Qiagen). Human MapPairs with fluorescent labels were obtained within genomic regions flanking the *FLNA* and *FLNB* gene (ResGen, Invitrogen Corp., Carlsbad, CA; Applied Biosystems, Weiterstadt, Germany). PCR was performed on the previously isolated DNA using the selected markers. The samples were run on an ABI Prism 3100 genetic analyzer, and alleles were determined using standard software package (Genotyper Analysis). Multipoint and two-point logarithm of the odds (lod) scores were calculated with the GeneHunter statistical program.¹⁶

For analysis of linkage to *FLNB*, the disorder was assumed to be X-linked with a penetrance of 90% in men and women and a disease allele frequency of 1 in 10,000. For analysis of linkage to *FLNB*, the disorder was considered to be autosomal recessive with penetrance of 100% in men and women and a disease allele frequency of 1 in 1,000. In all families, we assumed eight alleles per marker at an equal allele frequency (0.125). For the purpose of

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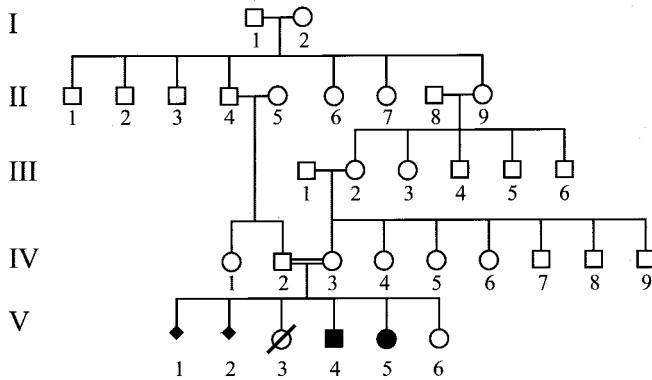
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Family 1



Family 2

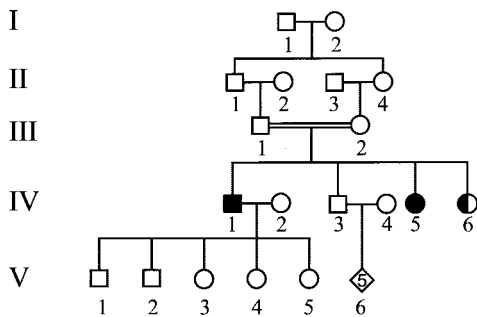


Figure 1. Pedigrees of the two families. Black symbols = affected individuals; black-and-white symbols = probably affected individuals; diagonal lines = deceased individuals; black diamonds = miscarriages; diamonds with numbers = number of offspring of either gender; double bars = consanguinity; Family 1 = Turkish family; Family 2 = Israeli family.

statistical evaluation, the woman (IV-6) from Family 2 was considered to be an affected individual based on clinical presentation.

Results. PH pedigrees. **Family 1.** This consanguineous Turkish family (figure 1) has two affected siblings. The 2.5-year-old boy (V-4) had a history of persistent feeding difficulties and respiratory problems during early infancy. At 2.5 months of age, he developed urticaria pigmentosa, and at 4.5 months he was noted to have developmental delay with inability to control his head in an upright position. By age 7.5 months, he contracted a pulmonary infection, requiring hospitalization. He has no history of seizures. On examination, he has growth retardation (head circumference and weight below 5th percentile, height 10 to 25th percentile) but is able to tolerate only a liquid diet given difficulties arising from esophageal reflux. No heart murmurs are appreciated on auscultation. Neurologically, he has severe mental retardation and is unable to talk or to follow objects. He is bedridden with quadriplegia. He has diffuse hypotonia and only recently is able to keep his head upright. Deep tendon reflexes are diminished. Chest radiograph showed bilateral chronic changes. EEG was notable for background slowing and paroxysmal theta activity. Muscle biopsy showed minimal diameter changes in the muscle fibers but normal oxidative staining. The child underwent a metabolic workup, which included normal biotinidase activity, mild elevation of blood lactic acid (29.3 mg/dL, normal range 10 to 14 mg/dL), and normal pyruvic acid (0.38 mg/dL, normal range 0.5 to 1.0 mg/dL). Urine organic acid analysis, blood creatinine, serum IgE, IgA, IgG, and IgM, and blood gases were normal. MRI revealed focal periventricular heterotopia in the body of the ventricles bilaterally with increased symmetric signal intensity in the putamen bilaterally (figure 2, A and B).

The 16-month-old girl (V-5) has a history notable for a failure to thrive with frequent vomiting at 3 months of age and recurrent pulmonary infections. She has severe developmental delay. At 5 months, she was able to roll over and by 6 months recognized her mother. At 9 months, she was able to smile to environmental stimuli but was not following objects. At 11 months, she could maintain her head in an upright position. She has gastroesophageal reflux and swallowing dysfunction. On physical examination, she has growth retardation (weight and head circumference below 5th percentile, height 25th to 50th percentile). No murmurs were appreciated on auscultation. Neurologically, she recognizes her mother and smiles to stimuli. Her pupils are reactive to light bilaterally. She has generalized weakness and hypotonia. She is unable to hold objects and cannot sit alone. Deep tendon reflexes are normoactive in the upper extremities but hyperactive on the lower extremities. Although no overt clinical seizures were observed, EEG demonstrated background dysrhythmia with occasional spike and wave activity, consistent with a seizure disorder. MRI was notable for malformation of the posterior fossa, delayed myelination, and a thin corpus callosum. Heterotopic gray matter was localized to the body of the lateral ventricles, trigone, and right occipital horn (see figure 2C).

MRI scan of the father (IV-2) was normal. MRI scan of the mother (IV-3) was notable for encephalomalacia in the right paracentral region with an osseous defect in the right parietal bone consistent with known past head trauma but showing no heterotopia. The deceased siblings were either a result of spontaneous abortions (V-1, 3.5 months' gestation; V-2, 5.5 months' gestation) or failed to survive during the early postnatal period because of unknown causes (V-3).

Family 2. The consanguineous Israeli family of Yemenite ethnicity (see figure 1) consists of three affected individuals. The 41-year-old man employed as a metal worker (IV-1) has a history of seizures but otherwise is in good health. He attended school until 17 years of age and then went into the Israeli Army. Onset of seizures was at 13 years of age and involved an aura of colored spots centrally, occasional blurry vision, but no formed hallucinations. Horizontal roving eye movements were followed by oral automatisms and a staring gaze. Episodes would persist over periods of up to 3 weeks, and the patient would then be seizure-free for up to 6 weeks. He would also experience up to two generalized tonic-clonic seizures per year. Seizures are controlled with carbamazepine and topiramate. EEG showed bitemporal slowing but no epileptiform activity. MRI was notable for bilateral periventricular heterotopia, symmetric but more prominent posteriorly (see figure 2D). There was also a question of right hippocampal atrophy.

The 60-year-old woman employed as a factory worker (IV-5) has a history of seizures but otherwise is in good health. She continues to reside with her parents. She went to school until the eighth grade and left owing to seizures. Onset of seizures was at 5 years of age and involved an aura of vertigo, blurred vision, and colored spots. At 17 years old, she had her first generalized tonic-clonic seizure, which progressed to include daily complex partial seizures. At age 29, she underwent a right temporal lobectomy with significant improvement in seizure frequency. She remains on carbamazepine. No abnormalities were noted on physical examination. She appeared to be of normal intellect but did not undergo formal psychometric evaluation. Her prior EEG had shown right temporal theta activity. Angiography of the intracranial vessels was normal. Skin biopsy was unremarkable. MRI revealed a few noncontiguous heterotopia on the posterior aspect of the right lateral ventricle but none on the left side (see figure 2, E and F).

The 65-year-old woman (IV-6) has a history of seizures but is otherwise well. She did not go to school but is intelligent according to her sister. Onset of seizures was at 14 years of age and involved a visual aura with lights. She was felt to have generalized tonic-clonic seizures. These episodes have apparently stopped for the last 10 years. She remains on carbamazepine. The patient refused MRI.

Analysis of filamin A and filamin B linkage. Only two filamin proteins, A and B, are known to be expressed in the CNS. They share >70% sequence identity, they physically interact, and they are co-expressed within neurons during development.¹⁷ The X-linked *FLNA* gene can cause PH. Located on human chromosome 3, *FLNB* represents a potential candidate gene for an auto-

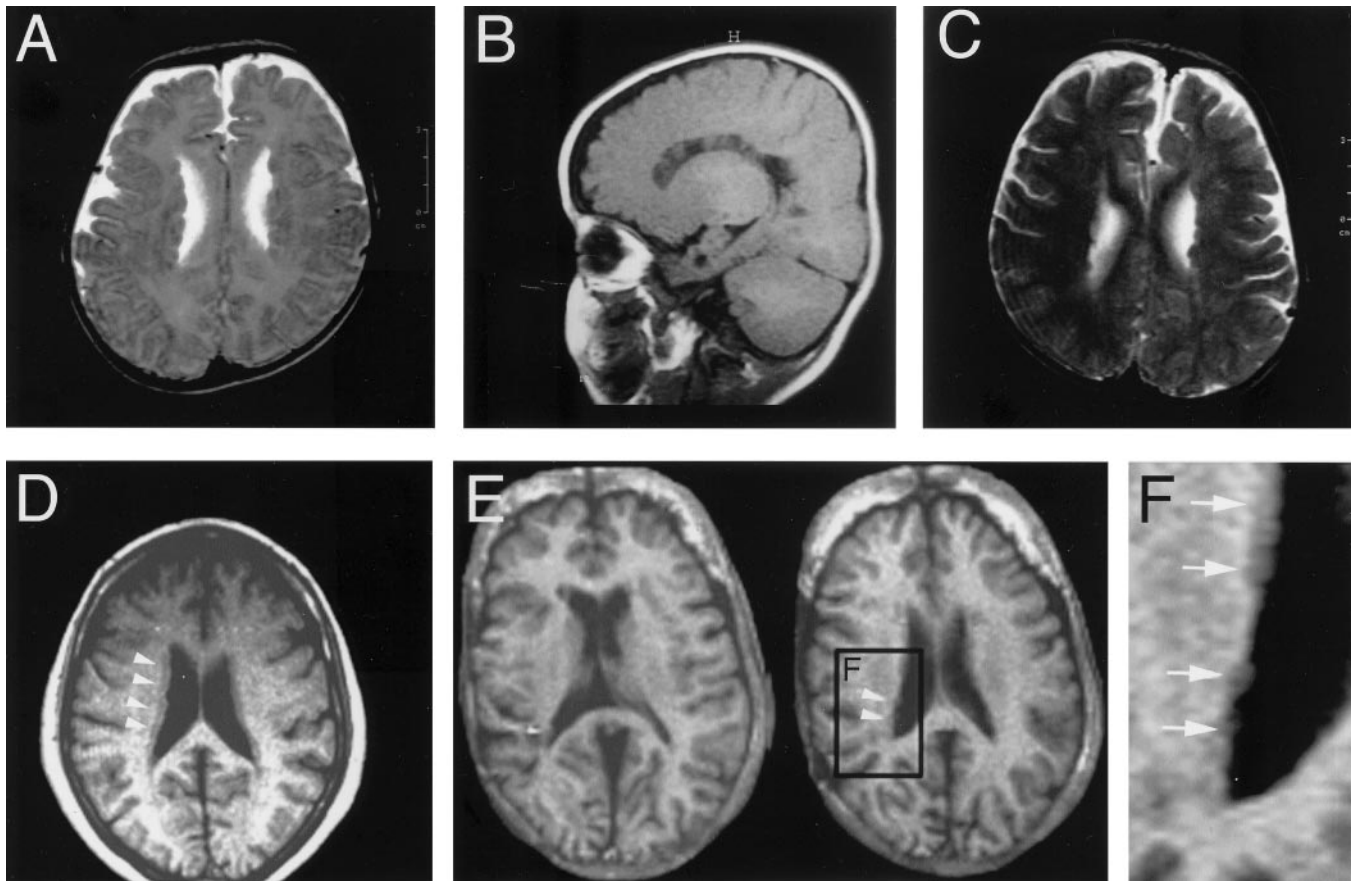


Figure 2. Brain MRI appearance of affected individuals with autosomal recessive periventricular heterotopia (PH). (A) Axial T2-weighted image of the patient (Family 1, V-4) demonstrates bilateral near-contiguous periventricular nodules. (B) Sagittal T1-weighted image of same patient in (A) shows a widespread rostral and caudal distribution of neuronal heterotopia. (C) Axial T2-weighted image of the affected female sibling (Family 1, V-5) similarly displays the characteristic radiographic findings of PH. (D) Axial T1-weighted image of the patient (Family 2, IV-1) demonstrates bilateral contiguous PH. (E) Axial T1-weighted images of an affected sibling (Family 2, IV-5) show nodular heterotopia (arrowheads) along the posterior aspect of the right lateral ventricle. (F) Higher-magnification MRI image of (E) better illustrates the periventricular nodules (arrows).

somal recessive form of PH. We therefore sought to exclude both filamin genes as potential causes of PH.

Direct evaluation of the *FLNA* locus on the X chromosome was performed initially using microsatellite markers (DXS1200, DXS8069, DXS1073), which flank the gene (figure 3A). Two-point analyses revealed a maximal lod score of 0 for Family 1 and 0.6 for Family 2. To further confirm the improbability of linkage, an additional three markers (DXS8045, DXS 998, DXS1193), all within 8 cM of the *FLNA* gene, were analyzed in these families. These studies revealed an lod score ranging from 0 to -5.21 (Family 2) and from 0 to -0.44 (Family 1) by two-point analyses (see figure 3B).

A similar evaluation was performed on the *FLNB* gene in the two pedigrees (see figure 3C). Multipoint analyses on chromosome 3 with microsatellite markers close to the *FLNB* locus (D3S1289, D3S3616, D3S1514, D3S1259, D3S2402, D3S2452, D3S1287, D3S1285) revealed a maximal lod score of -1.0 for Family 1 and -2.0 for Family 2 (see figure 3D).

Discussion. The current report describes two kindreds with PH, suggestive of an autosomal recessive mode of inheritance. The probands have characteristic MRI findings of bilateral PH, which is radiographically indistinguishable from the X-linked dominant PH, associated with *FLNA* mutations.¹⁸ Furthermore, linkage analysis suggested no associa-

tion with either *FLNA* or *FLNB* as causal genes for the patients in the two pedigrees. These results suggest that the affected individuals within these two pedigrees have a new PH syndrome.

Familial autosomal recessive PH (ARPH) represents a new syndrome distinct from PH caused by *FLNA* mutations. Both families in the current study have an autosomal recessive mode of inheritance with unaffected parents and affected offspring of each sex. PH from *FLNA* mutations is X-linked dominant with affected women and fetal lethality in men. The penetrance for PH from *FLNA* mutations appears fairly high, and the clinical phenotype of the affected children in at least one of the reported families is severe, thereby arguing against a parental nonpenetrant carrier. Mosaicism has not yet been detected in the X-linked PH disorder and again represents an unlikely cause for the mode of inheritance seen in the two pedigrees. Last, linkage analysis performed using microsatellite markers closely linked to the *FLNA* or *FLNB* locus showed no evidence of close linkage between the mutant trait and the *FLNA* or

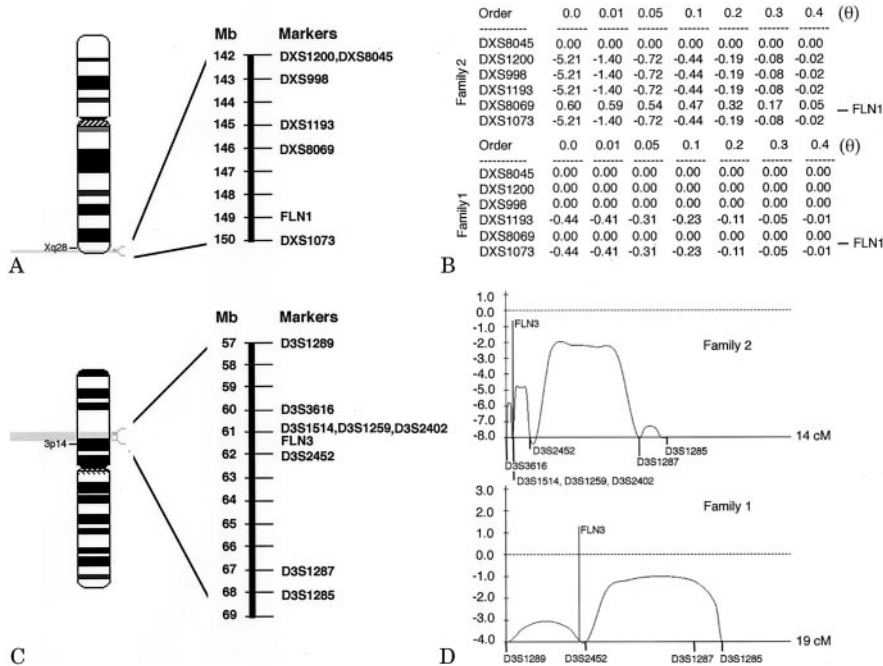


Figure 3. Analysis of linkage of autosomal recessive periventricular heterotopia to filamin A and filamin B. (A, C) Microsatellite markers used in evaluation of homozygosity and linkage for FLNA and FLNB. (B) Two-point analyses performed on FLNA. (D) Multipoint analyses performed on FLNB. θ = recombination fraction.

FLNB gene. Taken in this context, ARPH likely represents a new recessive syndrome within the classification of PH disorders.

The radiographic characteristics seen in the two PH syndromes are virtually indistinguishable. MRI studies within individuals with confirmed *FLNA* mutations typically show bilateral near-contiguous periventricular nodular heterotopia.¹⁸ Three of the four individuals presented within this study have bilateral contiguous or near-contiguous nodules. The one remaining individual had a few noncontiguous heterotopia on the posterior aspect of the right lateral ventricle; this same pattern has previously been appreciated in *FLNA* mutations as well.¹⁰ Last, thinning of the corpus callosum and malformations within the posterior fossa can also be associated with either PH syndrome.^{5,8} The signal intensity changes within the putamen bilaterally and the report of possible hippocampal atrophy in two of the affected patients from these ARPH pedigrees have not been previously seen in the X-linked pedigrees. Whether these observations reflect alteration of other gray matter structures secondary to a dysfunctional gene or merely represent nonspecific radiographic findings or findings secondary to chronic seizure activity remains to be seen.

Certain cardinal features seen in PH associated with *FLNA* mutations are also seen in the currently reported families. Approximately 88% of PH patients with *FLNA* mutations have focal epilepsy.¹⁹ All three affected individuals from Pedigree 2 and likely one individual from Pedigree 1 had epilepsy. Each of the three Israeli members had visual symptoms suggesting focal seizures localizing to the occipital cortex, whereas the Turkish woman had an abnormal EEG with no clear clinical seizure identified. The clinical presentation of seizures may arise from aberrant

neuronal activity from the nodules,⁷ although clearly the nature of the epilepsy origin in these patients is unknown. More variably, affected individuals with *FLNA* mutations can have cardiac abnormalities (patent ductus arteriosus), gastric dysmotility, and vasculopathy or coagulopathy, leading to stroke or ruptured vessels,⁸ but none of these findings is present in the two pedigrees reported here.

The patients in these two kindreds differ in some of their clinical and radiographic features. Aside from seizures, the Israeli family members appear to be mildly affected with normal cognition and no other medically related problems. The probands within the Turkish family, however, have shared features of recurrent infection and gastric reflux with consequent failure to thrive and developmental delay. Microcephaly also appears to be a distinguishing characteristic for both affected individuals from the Turkish family, which is not seen in the Israeli family. As the affected Turkish individuals have more severe neurologic deficits, their radiographic scans correspondingly depict additional structural abnormalities in the corpus callosum, putamen, and posterior fossa. These differences in presentation raise the question of genetic or allelic heterogeneity in ARPH. Thus, whether these two families represent the same autosomal recessive form of PH remains to be determined.

Classification of different syndromes, both by clinical history and by radiographic findings, will provide a clearer means with which to identify specific genes responsible for various neurologic disorders such as PH. The ARPH syndrome shares many of the clinical and radiographic phenotypes associated with X-linked dominant PH, suggesting that this disorder is also caused by genes within the same molecular pathway. Identification of these underlying genes will,

it is hoped, not only provide an understanding of the pathophysiology of ARPH but also elucidate normal mechanisms involved in cortical development.

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