SHORT REPORT

Ehlers-Danlos syndrome and periventricular nodular heterotopia in a Spanish family with a single *FLNA* mutation

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Background: The Ehlers-Danlos syndrome (EDS) comprises a group of hereditary connective tissue disorders. Periventricular nodular heterotopia (PNH) is a human neuronal migration disorder characterised by seizures and conglomerates of neural cells around the lateral ventricles of the brain, caused by *FLNA* mutations. *FLNA* encodes filamin A, an actin binding protein involved in cytoskeletal organisation. The amino-terminal actin binding domain (ABD) of filamins contains two tandem calponin homology domains, CHD1 and CHD2.

Objective: To report clinical and genetic analyses in a Spanish family affected by a connective tissue disorder suggestive of EDS type III and PNH.

Methods: A clinical and molecular study was undertaken in the three affected women. Clinical histories, physical and neurological examinations, brain magnetic resonance imaging studies, and skin biopsies were done. Genetic analysis of the *FLNA* gene was undertaken by direct sequencing and restriction fragment length polymorphism analysis.

Results: Mutation analysis of the *FLNA* gene resulted in the identification of a novel mutation in exon 3 (c.383C→T) segregating with the combination of both syndromes. This mutation results in a substitution of an alanine residue (A128V) in CHD1.

Conclusions: The findings suggest that the Ala128Val mutation causes the dual EDS-PNH phenotype. This association constitutes a new variant within the EDS spectrum. This is the first description of a familial EDS-PNH association with a mutation in *FLNA*.

The Ehlers-Danlos syndrome (EDS) constitutes a heterogeneous group of heritable connective tissue disorders mainly characterised by hyperextensible skin, joint hypermobility, and tissue fragility. At least six types of EDS are recognised on the basis of their clinical manifestations and mode of inheritance.[1 2] However, many patients remain unclassified as some subtypes are not clearly defined and overlapping among phenotypes is common. Periventricular nodular heterotopia (PNH) is an X linked dominant neuronal migration disorder characterised by subependymal grey matter nodules lining the ventricular walls where cerebral cortex neurones are generated during fetal development. In this disorder heterozygous females are affected by the migrational disorder and present with epilepsy, whereas hemizygous males die embryonically.[3] Familial PNH is caused by mutations in the *FLNA* gene. *FLNA* is a widely expressed gene in all brain cortical layers as well as in many other tissues and encodes filamin A (FLNA).[4 5] An autosomal recessive form and forms associated with chromosomal anomalies have recently been reported, thus proving that PNH is a genetically heterogeneous disease.[6–8]

Filamin A is a large (280 kDa) ubiquitous protein that interacts directly with filamentous actin and a large number of cellular proteins with a high functional diversity.[9] From a structural standpoint, filamins are large dimeric phosphoproteins with three functional domains: an amino-terminal actin binding domain (ABD), a long rod-like domain with two flexible hinge structures and a carboxyl-terminal self association domain. The ABD is composed of two tandem calponin homology domains (CHD1 and CHD2) similar to many other actin binding proteins. ABD allows filamins to bind to filamentous actin. The rod-like domain consists of 24 repeats of anti-parallel β sheets which interact with themselves, mediating the dimerisation of the protein, and with several membrane receptors. *FLNA* mutations result not only in PNH but also in other human congenital malformation disorders—frontometaphyseal dysplasia, otopalatodigital syndromes type 1 (OPD1) and type 2 (OPD2), and Melnick-Needles syndrome. These human congenital malformation syndromes constitute allelic conditions with overlapping phenotypes.[10]

Here we report the clinical and genetic analysis of a Spanish family in which three females diagnosed with a connective tissue disorder suggestive of EDS type III and PNH have a novel single mutation in *FLNA*. This is the first report of the familial association of these two diseases with a mutation in *FLNA*.

METHODS

Human subjects and diagnostic criteria

We obtained detailed clinical information and carried out physical and neurological examinations and brain magnetic resonance imaging (MRI) studies in three affected female patients from a four generation Spanish family (fig 1A).

Clinical data were collected by direct interview of the patients and their relatives. Typical clinical features and physical examination were used to diagnose EDS. PNH was diagnosed by magnetic resonance imaging. A skin biopsy and electron microscopy study were carried out in one affected female. The study was approved by the ethics committee of the Fundación Jiménez Díaz, and informed consent was obtained from each participating individual.

Genetic analysis

Genomic DNA was isolated from blood samples using standard protocols. *FLNA* gene exons were analysed by direct sequencing in the three clinically affected relatives (individuals II-2, III-2, and IV-1). Genomic DNA was amplified with

Abbreviations: ABD, actin binding domain; EDS, Ehlers-Danlos syndrome; FLNA, filamin A; PNH, periventricular nodular heterotopia

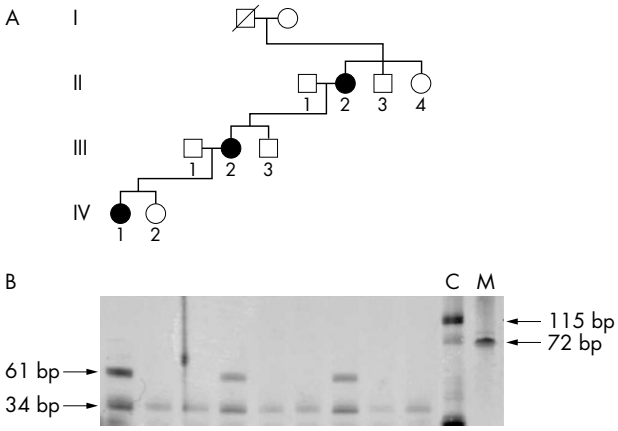

Figure 1 Pedigree of the three generation Ehlers-Danlos syndrome/periventricular nodular heterotopia (EDS-PNH) family showing an abnormal digestion pattern segregating with the phenotype. (A) Family pedigree. Black symbols indicate individuals with EDS-PNH. (B) Polyacrylamide gel showing amplified genomic DNA from members of the family whose DNA was digested with HaeIII. The mutation c.383C→T abolishes an HaeIII restriction site. Affected individuals have lost an HaeIII site and therefore show a larger fragment of 61 base pairs. *C*, control fragment of undigested polymerase chain reaction; M, size marker.

specific primers using standard methods. The corresponding polymerase chain reaction (PCR) products were purified by agarose gel electrophoresis and extracted with the Qiaquick gel extraction kit (Qiagen Inc, Valencia, California, USA). Direct sequencing of PCR products was carried out with a dye-terminator cycle sequencing kit (Perkin-Elmer, Norwalk, Connecticut, USA) using Taq FS DNA polymerase. Sequences were resolved on an ABI PRISM 377 automatic sequencer, and the results analysed with the ABI Analysis software (version 3.1). Screening for *FLNA* gene mutations was subsequently carried out in clinically affected as well as unaffected members of the pedigree by restriction fragment length polymorphism analysis of exon 3 using Hae III.

SSCP analysis[11] was done by PCR, using total genomic DNA to test 92 control individuals and the GenePhor DNA electrophoresis system (Amersham Pharmacia Biotech, Piscataway, New Jersey, USA). Amplification was carried out in a total volume of 10 µl containing 60 ng of genomic DNA, 12.5 pmol of each primer, 1 U of Taq polymerase (Promega, Madison, Wisconsin, USA), 200 µM each dATP, dCTP, dGTP, and dTTP, and 1.5 mM $MgCl_2$. PCR conditions were one cycle at 94°C for two minutes, followed by 30 cycles of 94°C for 30 seconds, 60°C for one minute, and 74°C for 30 seconds, one cycle of 74°C for three minutes, and one last cycle of 25°C for two minutes. Samples were resolved on 12.5% non-denaturing polyacrylamide gels with the GeneGel Excel 12.5/24 kit (Amersham Pharmacia Biotech) and silver stained using the PlusOneTM DNA silver staining kit (Amersham Pharmacia Biotech).

RESULTS

Clinical findings

Patient II-2

This affected women was 68 years old and had a history of frequent spontaneous luxations affecting both elbows particularly since early childhood. Luxations recurred with variable frequency, but at least once or twice a year. Since the age of 40 years, luxations also affected the scapulohumeral joints. Complex partial seizures followed by secondarily generalised tonic–clonic seizures appeared at the age of 20 years. In addition, she was diagnosed with a hiatus hernia.

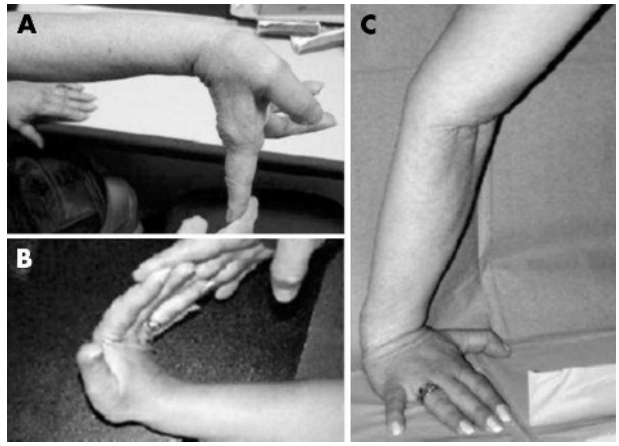

Figure 2 Joint hypermobility in individuals II-2 (A) and III-2 (B, C).

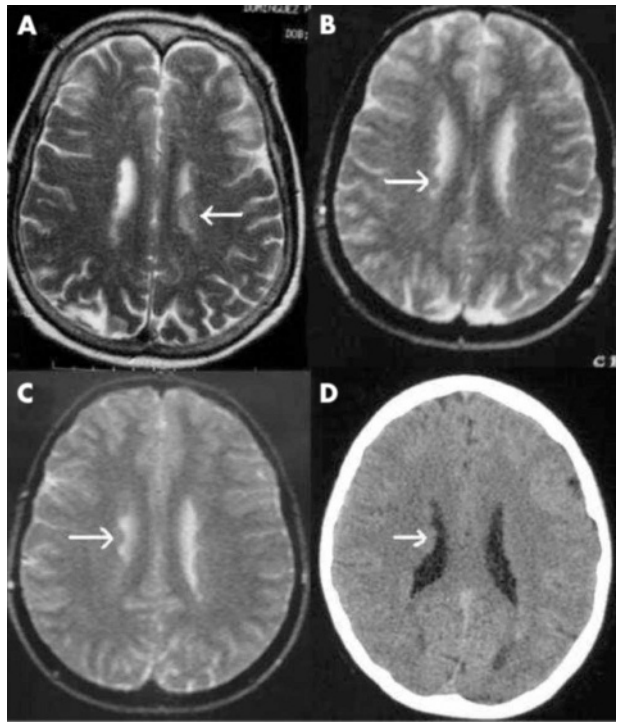

Figure 3 Brain magnetic resonance imaging and computed tomography (CT) showing periventricular nodular heterotopia (PNH). T2 weighted images of patient II-2 (A), III-2 (B), and IV-1 (C) show bilateral PNH. (D) Non-enhanced CT in patient III-2 demonstrates PNH. The presence of typical nodules is indicated by arrows.

At the age of 65 years she developed a subarachnoid haemorrhage. A brain magnetic resonance angiogram and catheter brain angiography were both normal. Physical examination showed an abnormal and striking rubbery consistency of the skin with very flexible joints (fig 2A). Neurological examination was normal. Surface EEG recordings showed slowing over both temporal regions. Brain MRI showed bilateral nodular heterotopia (fig 3A). Cross sectional echocardiography revealed a mild mitral valve prolapse, and coagulation studies showed a marked increased in antiphospholipid antibody levels. An ultrastructural study of a skin biopsy showed abnormal collagen fibrils in the dermis. These were irregular in size (some of them with increased diameters) and morphology. No abnormalities of the elastic fibrils were observed (fig 4A).

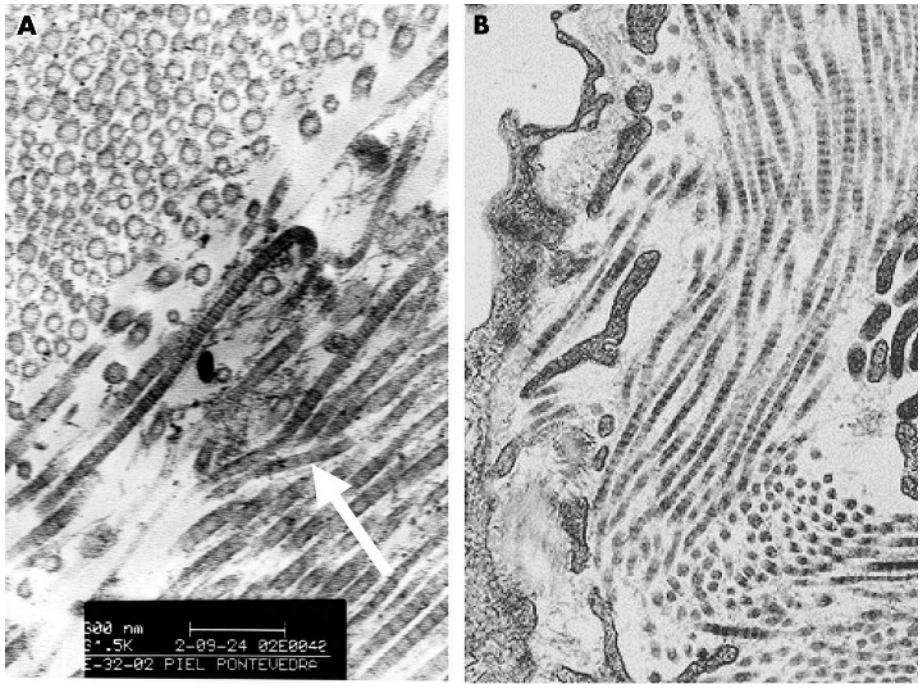

Figure 4 Ultrastructural study of the dermis showing minor variations in size and focal distorted arrangement of collagen fibrils (arrow) and amorphous material corresponding to normal elastic fibres in affected individual II-2 (A) and in a control individual (B).

This patient had four pregnancies. One resulted in a spontaneous abortion during the fourth month and another one in a child who died suddenly a few hours after birth and had a cleft palate and cardiac and testicular malformations. Both probably represented affected males.

Patient III-2

This affected woman was 40 years old. From the age of 14 or 15 years, she had had recurrent knee dislocations, especially affecting the right knee; these appeared with minor trauma but not spontaneously and recurred at a frequency of at least twice a year. On occasion, the dislocations also affected the shoulders. She was evaluated in 2001 because of non-specific dizziness. She had no history of seizures. On examination she had a remarkable soft, rubbery consistency of the skin, joint hypermobility (fig 2, panels B and C), and skeletal abnormalities including a high arched palate, pectum excavatum, scoliosis, and lumbar hyperlordosis. She was diagnosed as having EDS. Neurological examination was normal. Serum biochemical, haematological, cardiac, and electroencephalographic studies were normal. Brain MRI showed bilateral nodular heterotopia (fig 3B), megacisterna magna, and a linear structure, hypointense in T1 weighted and hyperintense in T2 weighted images, located in the right parietal area, suggestive of an abnormal dilated vein (fig 3D).

Patient IV-1

This affected woman was 19 years old. Since infancy, she had had recurrent patellar dislocations, especially affecting the right knee. These appeared at a variable frequency and sometimes on a weekly basis, both spontaneously and after minor trauma. She had been surgically treated for pyloric stenosis and bilateral inguinal hernias during infancy. She was referred for investigation of epileptic seizures at age 18 years. She had had various episodes of arreactivity and loss of consciousness followed by generalised convulsions. Physical examination revealed a high arched palate, lumbar hyperlordosis, joint hypermobility, and a soft rubbery skin. Serum biochemistry, haematological studies, and cardiac examination were normal. Mental and neurological tests were normal. Brain MRI revealed bilateral nodular heterotopia and megacisterna magna (fig 3C).

Clinical features of the affected women are summarised in table 1.

Genetic analysis

The inheritance in this family follows an X linked dominant pattern, as has been described previously for familial PNH. The karyotype from patients III-2 and IV-1 was normal. Mutation analysis of the *FLNA* gene resulted in the identification of a new mutation, a c.383C→T change (Ala128Val) in exon 3, segregating with the combination of EDS and PNH (fig 5). This mutation abolishes a HaeIII restriction site. Genomic DNA was amplified with specific primers and the resulting 115 bp product was digested with HaeIII and analysed on a polyacrylamide gel (fig 1B). Normal individuals had four fragments (8, 27, 34, and 46 bp). A restriction site was not present in mutation carriers, producing a novel fragment of 61 bp (27+34 bp). This change was not observed in unaffected members of this family or in 184 chromosomes from normal controls. Moreover, residue Ala128 is highly conserved in filamin isoforms throughout higher eukaryotes (fig 6).

We analysed the actin binding domain sequence using the ScanProsite tool (Swiss Institute of Bioinformatics). This analysis allows to scan protein sequences for the occurrence of patterns and profiles stored in the PROSITE database, or search protein databases for hits by specifics motifs. When the Ala128Val change was introduced, the analysis failed to recognise the pattern for the actinin-type actin binding domain signature 2 (PS00020). This pattern appeared when the normal sequence was used.

These results exclude the variation being a common polymorphism and suggest that it is a causative mutation for the phenotype.

Table 1 Clinical characteristics of the three affected women

Case	Skin hyperelasticity	Joint hypermobility	Internal haemorrhages	Visceral anomalies	Cardiovascular anomalies	Skeletal anomalies
II-2	+	+ Elbow and scapulo-humeral dislocations	Subarachnoid haemorrhage	Hiatus hernia	Mitral prolapse	–
III-2	+	+ Shoulder and knee dislocations	–	–	–	High arched palate Lumbar scoliosis Pectus excavatum
IV-1	+	+ Knee dislocations	–	Bilateral inguinal hernias Pyloric stenosis	–	High arched palate Lumbar hyperlordosis

DISCUSSION

The association of EDS and PNH has previously been described only in two sporadic patients. In 1981, Cupo *et al* reported a 30 year old woman with a form of the EDS characterised by hyperextensible skin, joint hypermobility, progressive lung disease from panacinar emphysema, aneurysms of the sinuses of Valsalva, myocardial infarction, and seizures. The patient died of intractable ventricular fibrillation and necropsy examination revealed bilateral subependymal PNH. Her twin sister had less striking joint hypermobility, although diagnosis of EDS was not confirmed. These investigators hypothesised that this patient had a form of EDS different from the 10 distinct variants previously described.[12] Subsequently, in 1996 Thomas *et al* described a 24 year old woman with an EDS associated with complex partial and right sensorimotor seizures. EDS was clinically characterised by hyperextensible skin and marked hypermobility of small joints. In addition, dilatation of the non-coronary sinuses of Valsalva with an enlarged diameter of the initial segment of the thoracic aorta was detected in cross sectional echocardiography and MRI studies of the heart. Brain MRI showed PNH, megacisterna magna, and agenesis of the posterior part of the corpus callosum. Interestingly, this patient had two successive pregnancies (two male fetuses) resulting in miscarriages. The investigators suggested that this might constitute a new subtype of EDS characterised by X linked PNH and epilepsy.[13] Association of EDS with other types of cortical cerebral malformations has also been described. A 22 year old woman with type I EDS and a chronic focal seizure disorder was reported by Pretorius *et al* in 1983; in this case epilepsy was associated with left sylvian ectopic grey matter heterotopia and an associated vascular malformation.[14] Two more patients with EDS and bilateral polymicrogyria have been described recently.[15] However, only non-familial associations of cortical brain malformations and EDS have been described to date.

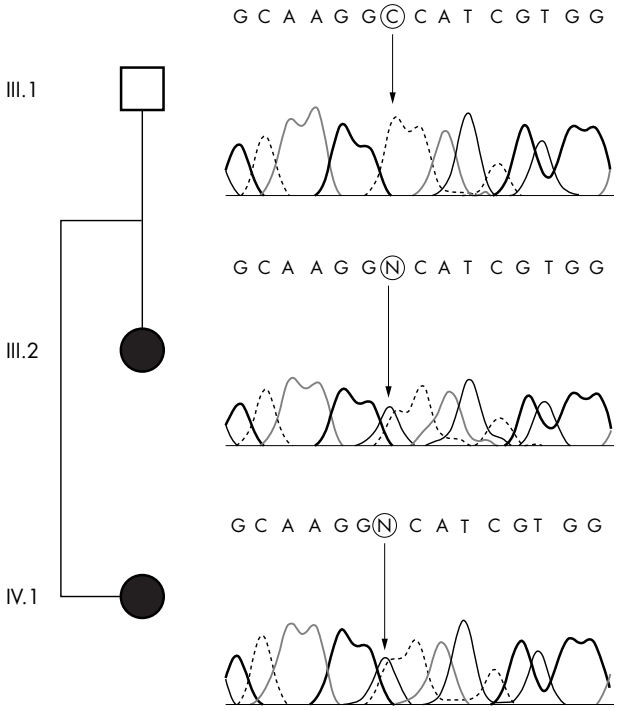

Figure 5 Mutation in *FLNA*. Sequence analysis of *FLNA* identified a c.383C→T change in exon 3. Affected individuals are identified with filled symbols. Relevant portions of the sequencing chromatograms are shown to illustrate segregation of the mutated allele. The C→T change, present in heterozygosity in affected individuals, is indicated with an arrow.

This is the first report on a familial association of PNH and the EDS. The family reported presents a form of the EDS different from previously described variants. Hyperextensible skin and joint hypermobility were the main clinical features and initially suggested a diagnosis of EDS type III. However, additional clinical findings (skeletal anomalies such as scoliosis, hyperlordosis or pectum excavatum, high arched palate, and subarachnoid haemorrhage in individual II-2, and visceral hernias present in two relatives) exceeded the typical features of EDS type III. The X dominant pattern of inheritance observed in this family does not fit well into any of the subtypes of EDS described to date.

PNH has not only been described as an isolated disorder. Heterozygous females with PNH have been shown to present with other clinical signs including patent ductus arteriosus and coagulopathy.[16] Several dysmorphic features, midline skeletal abnormalities, and other skeletal or visceral malformations have also been reported associated with PNH[17–19]. Three unrelated boys with a new multiple congenital anomaly-mental retardation syndrome consisting of PNH, cerebellar hypoplasia, severe mental retardation, epilepsy, and syndactyly have been described recently.[20] PNH with regional cortical dysplasia, frontonasal malformation, and mild mental retardation has been reported in two patients.[21] However, mutation screening of the *FLNA* gene in these two boys was negative.[22]

Mutation analysis of the *FLNA* gene in this family revealed a novel single mutation segregating with PNH and EDS. This mutation affects a highly conserved alanine residue located on the first calponin homology domain of the amino-terminal actin binding domain (ABD). This domain is involved in the interaction of filamin with filamentous actin, inducing the crosslinking of these filaments in order to form the orthogonal networks in cortical cytoplasm.[9 23 24]

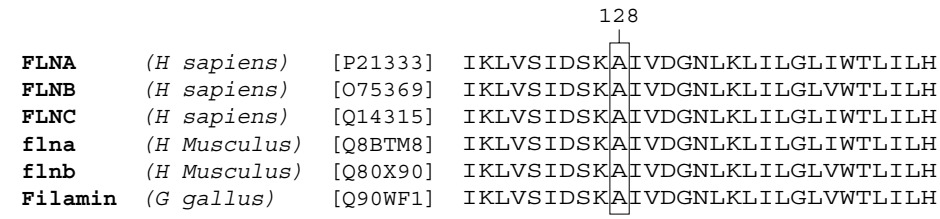

Figure 6 Alignment of the amino acid sequence of human filamin A and paralogue and homologue filamins from various species. The mutated alanine residue is indicated with a vertical box. The number indicates amino acid position in the protein.

Three potential actin binding sites (ABS) within the FLNA ABD have been described. One of them (ABS-2)—a conserved region included in the CHD1—has been shown to be essential for actin binding.[25] Substitution of alanine for valine at position 128 within ABS-2 results in loss of the consensus pattern for this site. Actin binding proteins present differences in binding characteristics probably resulting from amino acid substitutions and differences in molecular interactions. Therefore, the altered ABD–actin interaction may result in structural rearrangements which could affect the shape and flexibility of F-actin, leading to impaired cellular adhesion and as a result to both the migration disorder and the abnormally elastic connective tissue present in the EDS phenotype.

Additional features observed in one affected male who died after birth, including cleft palate and craniofacial and cardiac malformations, bring to mind the spectrum of otopalatodigital (OPD) syndromes, which have been also associated with mutations in the *FLNA* gene. Both syndromes appear to constitute allelic conditions of the same genetic disorder.

Although the precise role of filamin in the pathogenesis of EDS is uncertain, the study of these families and the family presented here suggests that filamin is not only necessary for neuronal migration to the cortex but also for organogenesis and development of diverse tissues, playing an essential role in embryogenesis.

The familial clinical association of PNH and EDS, together with the evidence of a *FLNA* mutation segregating with both diseases in the same pedigree, clearly supports the view that filamin A is responsible for both phenotypes, and suggests that this clinical–genetic association is a new subtype within the spectrum of EDS and connective tissue disorders.

NOTE ADDED IN PROOF

While this manuscript was under review, Sheen *et al* (*Neurology* 2005;**64**:254–62) reported two familial and nine sporadic cases of the EDS variant of PH. Genetic analysis of FLNA revealed three mutations in three sporadic cases.

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