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TITLE OF CASE

Phenotypic manifestations in FLNA-related periventricular nodular heterotopia – a case report and review of the literature

SUMMARY

Periventricular nodular heterotopia (PVNH) is an X-linked disease caused by loss-of-function variants in the filamin A (FLNA) gene. FLNA-PVNH is a heterogeneous disorder, and the phenotype is associated with neurological and non-neurological features including cardiovascular, gastrointestinal, pulmonary, haematological, cutaneous, and skeletal manifestations. No clear definition of the FLNA-PVNH phenotype has been established, but the patients are predominantly females with seizures, cardiovascular manifestations, and normal intelligence or mild intellectual disability. Herein, we describe a PVNH patient diagnosed with a novel heterozygous missense variant in FLNA after an atypical presentation of deep vein thrombosis and thrombocytopenia. Clinical evaluation found hypermobility, cardiovascular, and skin manifestations. Moreover, we conducted a literature review of 186 FLNA-PVNH patients to describe the phenotypic spectrum. In conclusion, our patient highlights the importance of thorough clinical evaluation to identify manifestations in this very heterogeneous disorder. The phenotypic review may guide clinicians in the assessment and follow-up of FLNA-PVNH patients.

Key words: Filamin A, FLNA, filaminopathy, periventricular nodular heterotopia

BACKGROUND

Filamin A (FLNA) is a large ubiquitous actin-binding protein involved in cytoskeletal reorganisation.[1,2] FLNA interacts with several cytoplasmatic and membrane-bound proteins of varying function and is involved in cell migration, signalling, and adhesion.[1,3,4] The protein is widely distributed in the body and it is essential during embryogenesis.[5,6] The FLNA protein is encoded by the FLNA gene (MIM* 300017) located on Xq28.[7] Pathogenic variants in FLNA lead to X-linked filaminopathies covering eight syndromes: X-linked cardiac
valvular dysplasia, congenital short bowel syndrome, frontometaphyseal dysplasia type 1, Melnick-Needles syndrome, otopalatodigital syndrome type 1 (OPD1) and type 2 (OPD2), terminal osseous dysplasia (and pigmentary defects), and periventricular nodular heterotopia (PVNH). Some authors have suggested isolated thrombocytopenia and a disorder characterised by keloid scarring, joint contractures and cardiac valvulopathy as a part of the X-linked filaminopathies.[3,8-10]

FLNA-PVNH is an X-linked dominant neuronal migration disorder caused by loss-of-function mutations in FLNA.[11] It is characterised by subependymal nodules of gray matter ectopically lining the lateral ventricles.[3] Most FLNA-PVNH patients are female, and there is a high lethality among hemizygous males.[12] FLNA-PVNH is a heterogeneous disorder associated with seizures, learning difficulties and structural cerebral manifestations such as enlarged cisterna magna.[13-15] Extrakerebral manifestations include various cardiovascular anomalies (patent ductus arteriosus, atrial or ventricular septal defect, cardiac valve disease, dilatation of the sinuses of Valsalva or the thoracic aorta, stroke, and aneurysm formation), thrombocytopenia, gastric immotility, and pulmonary disease.[5,13,16] Moreover, connective tissue and vascular anomalies of classic Ehlers-Danlos syndrome (EDS) have been reported in some FLNA-PVNH patients.[12,13,17-19] The great variability in the phenotypic spectrum observed in PVNH patients with a FLNA variant is not fully clarified nor described.[14]

We present a case of a female in her 20s, who was diagnosed with FLNA-related PVNH with thrombocytopenia, cardiac, and connective tissue manifestations, and we provide a review of previously published cases to elucidate the FLNA-PVNH phenotype. To our knowledge, this is the first literature review of all the phenotypic manifestations in FLNA-PVNH patients.

CASE PRESENTATION

The proband was a female in her 20s, the third child of non-consanguineous healthy parents. She was born at term after an unremarkable prenatal period and birth. She presented after birth with hip dysplasia and severe hypermobility requiring orthopaedic casts and physiotherapy during infancy. She also had failure to thrive due to restrictive eating necessitating hospital admissions and dietary supplementation up to school age. Motor development was delayed, and independent walking was not achieved until the age of 3 years. The patient later reported impaired balance, clumsiness, and multiple episodes of falling without any apparent reason, as well as sudden inability to hold on to things. Her finger- and toe-joints were often painful. She also reported dislocation of her patella twice after minor preceding trauma. Her speech and language development were normal. She had normal hearing and vision and no history of seizures. She
passed an ordinary school and high school programme, and currently attends classes at university level.

In her early 20s, she was referred from the Department of Hematology to genetic testing and counselling due to an episode of deep vein thrombosis and unexplained thrombocytopenia. Clinical examination revealed a normal proportionate stature with a height of 166.5 cm, weight 56 kg, and head circumference 56 cm.

Her lips were red violet to blue, and her nails often had a blue discoloration. She also presented a slight hypotrichosis. Her skin was soft, doughy, and stretchable 1-1.5 cm on the volar aspect of the forearms. The skin was slightly translucent with visible blood vessels on her cheeks, elbows and feet. There were no signs of purpura. She also had pes planus, short toes and increased bilateral gap between her 2nd and 3rd toes bilateral. Cutis marmorata was present on both legs (Figure 1). Moreover, she presented general joint hypermobility with a Beighton score of 7/9.

**INVESTIGATIONS**

The investigations included cytogenetic studies on bone marrow revealing a normal female karyotype. Flow cytometry of bone marrow cells and chest X-ray were both unremarkable. In a blood sample, platelet level was measured to be 80 (reference: 165-400 x 10^9/L), and a thrombophilia investigation was unremarkable. Later measurements revealed persistent thrombocytopenia with platelet levels around 80 to 99. Thorough investigation did not reveal any sign of infection.

Later investigations included an echocardiography due to a diastolic murmur, which revealed an aorta ectasia >4 cm at the sinuses of Valsalva and severe aortic valve insufficiency.

Genomic DNA of the proband was screened for mutations with a commercial Comprehensive Haematology Panel including sequence analysis and copy number variation analysis of 253 disease causing genes. The analysis led to the identification of a novel heterozygous missense variant in exon 2 in *FLNA* (NM_001456.3: c.332T>C, p.(Leu111Pro)). This variant was initially classified with unknown significance. Genotyping of the proband’s parents revealed that the variant arose de novo (Figure 2). Pathogenicity of the variant was strongly supported by *in silico* analysis. The variant was absent in the Genome Aggregation Database (gnomAD) including more than 120.000 exomes and 15.000 genomes. The variant was also absent in the medical literature and in disease-related databases such as ClinVar and HGMD. Prediction programs SIFT, MutationTaster and CADD: 24.8, predicted a damaging effect on protein structure and function. In addition, both the nucleotide and amino acid positions were evolutionary highly conserved down to zebrafish.
Based on the results of the segregation analysis and the additional clinical and molecular results suggesting pathogenicity of p.(Leu111Pro), the FLNA missense variant was re-classified as likely pathogenic.

The genetic analysis also detected a small heterozygous deletion of 94.7 kb at chromosome 1q21.1 that was reported as an additional finding. The estimated genomic region of the deletion covered chr1:145415463-145509308 (Human Genome Build 37). The 1q21.1 deletion included the RBM8A-gene and was classified as pathogenic. Biallelic variants in RBM8A is associated with Thrombocytopenia Absent Radius (TAR) syndrome. No other sequence variants, deletions or duplications were detected in the proband.

After the identification of the missense variant in the FLNA gene, a brain MRI was conducted and showed bilateral PVNH and further identified a retrovermian arachnoid cyst (Figure 3).

**TREATMENT**

Based on the aorta ectasia and aorta valve insufficiency, the patient underwent subacute heart surgery. She had a mechanical aorta valve prosthesis and a composite graft at the ascending aorta inserted as well as left ventricular repair.

**OUTCOME AND FOLLOW-UP**

The heart surgery was successful, and the patient is now followed-up yearly with echocardiography in the outpatient clinic of Cardiology. Furthermore, she is followed in the benign haematological outpatient clinic once a year with blood tests every three months to check for eventual later development of bone marrow disease. She has not developed seizures and she is continuing her university studies.

**DISCUSSION**

We described a FLNA-PVNH patient with thrombocytopenia, deep vein thrombosis, hypermobility, cutaneous and cardiovascular manifestations. After the identification of a de novo variant in the FLNA-gene, PVNH was identified by a brain MRI scan. We conducted a literature search using PubMed, which generated 56 publications with 186 cases excluding our patient (Figure 4). Data extraction was done, and the following categories were registered: sex, age, family history, phenotype, FLNA variation, and manifestations (Table S1, S2, and S3).
PVNH is phenotypically a very heterogenous disorder. Several manifestations have been described in published cases having a broad spectrum of neurological and non-neurological manifestations.[5] Most FLNA-PVNH patients are female with seizures, normal intelligence to mild intellectual disability, and cardiovascular anomalies.[20] The complex FLNA protein structure and interaction with numerous membrane receptors is suggested to contribute to the broad phenotypical spectrum.[2]

Skin manifestations are not frequently reported but are interesting in the FLNA-PVNH phenotype, since they may be a differential diagnosis to EDS.[12] Overall, skin manifestations are reported in 16.6 % of FLNA-PVNH patients (Table 1). In our literature review, the most common skin manifestation is hyperextensible skin reported in 7 % of FLNA-PVNH patients. Thin, soft skin and easy bruising occur with a frequency of 3.2 % (Table S1). Our patient presented with various cutaneous manifestations including soft, doughy, and slightly translucent skin with visible blood vessels on the cheeks, elbows and ankles. The translucency of her skin gave her lips a purple hue. Reinstein and colleagues (2013) reported a cohort of 11 FLNA-PVNH patients with vascular and connective tissue anomalies. They described various skin findings in all the patients including easy bruising, soft, thin, translucent, or hyperelastic skin, indicating heterogeneity in the cutaneous manifestations.[12] Other PVNH patients have also been reported with an EDS-like phenotype characterised by joint hypermobility, recurrent dislocations, skin anomalies and aorta aneurysms.[11,18,21-24] The EDS-PVNH phenotype is proposed to be regarded as a part of the clinical FLNA-PVNH spectrum, and not as a separate subtype.[12]

Neurological symptoms are the most frequent manifestations in FLNA-PVNH patients. Our review found that 72.7 % of the patients presented with a neurological manifestation other than PVNH (Table 1). Of these, seizures are the most frequently reported (45.5 %) (Table S1). In fact, most female patients are diagnosed with FLNA-PVNH based on seizures. The seizures vary greatly in severity and age of onset but most often develop in the second decade of life.[15,25-27] Our patient did not have a history of seizures, but she was informed about the potential risk of developing seizures later in life. Another notable neurological manifestation is enlarged cisterna magna, which is reported in 20.3 % of the patients in the literature. Intelligence levels have been reported to range from normal to intellectual disability of variable severity.[15,28] In the reviewed literature 10.2 % presented with mild to severe intellectual disability.

Cardiovascular anomalies are also common and present in almost half of the reported patients (Table 1). The most frequent anomaly is patent ductus arteriosus (18.2 %) (Table S1). Our patient presented with severe aortic valve insufficiency which is reported in 12.3 % of the FLNA-PVNH patients in the literature. Other frequent cardiovascular anomalies include dilatation of aorta,
pulmonary hypertension, and atrial/ventricular septal defect. The association between PVNH and cardiovascular abnormalities is well-documented,[13,21,29] and in some instances, the cardiologist may be the first to suspect the syndromic nature of the patients’ manifestations.[22] Pulmonary manifestations are reported in 18.2 % of the reviewed FLNA-PVNH patients (Table 1). Respiratory distress (7 %), hyperinflation (7 %), and atelectasis (6.4 %) are the most frequent clinical signs (Table S1). The lung involvement can vary from multiple pulmonary infections to progressive severe pulmonary disease.[30] These patients develop respiratory failure neonatally or in early infancy with a median age of 1 month.[26,30]

About a quarter of the FLNA-PVNH patients presents with a skeletal manifestation (Table 1). Our patient had general joint hypermobility which is seen in 17.6 % of the reviewed cases. Interestingly, our patient was initially referred from the Haematological Department with deep vein thrombosis and unexplained thrombocytopenia. Haematological manifestations are seen in 7.5 % of the FLNA-PVNH patients (Table 1). The most common is thrombocytopenia reported in 4.8 % with a subset having giant platelets (Table S1). No previous publications have reported deep vein thrombosis.

Gastrointestinal involvement is seen in 10.7 % of the patients. Jenkins and colleagues (2018) reported six patients with FLNA variants and two of these presented with PVNH and congenital intestinal pseudo-obstruction (CIPO). CIPO is characterised by intestinal dysmotility and obstruction and manifest as a short, dilated, malrotated small intestine.[14] Intestinal malrotation and intestinal pseudo-obstruction, seen in 4.8 % and 2.7 %, respectively, are differential diagnoses to acute abdomen in FLNA patients. Short small intestine is reported in 3.7 % of FLNA-PVNH patients and results in more chronic abdominal complaints (Table S1).[31]

Various craniofacial features have also been described. Some of the more frequently reported are hypertelorism (3.7 %), low-set ears (4.3 %), micrognathia (3.2 %), and anteverted nares (3.2 %). Ophthalmological manifestations are very rare in FLNA-PVNH patients but may include strabismus or orbital fullness (Table S1).

Motor development was delayed in our patient, and she had been failing to thrive in childhood. In the literature, 16 cases presented with developmental delay and seven experienced failure to thrive. FLNA-PVNH patients may also present with a variety of other manifestations such as hernia and spontaneous miscarriages (Table S1). Furthermore, neuropsychiatric diseases have been linked to the FLNA-PVNH phenotype. This association is not well established and may be coincidental, but clinicians should be aware of the potential psychiatric comorbidities in PVNH patients.[32]

In the literature review, we found a male/female ratio of 39/148 (79 % females) (Table S2). This is in line with the X-linked inheritance of FLNA-PVNH where the vast majority of reported patients
are female.[12,17] In most hemizygous males the condition is lethal either prenatally or during the neonatal period.[12,14,33] When surviving males are reported with FLNA-PVNH, it is due to residual or partial expression of the FLNA protein related to missense, splice site or distal truncating variants or somatic mosaicism.[31,34,35]

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Neurological</td>
<td>72.7 %</td>
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<tr>
<td>Cardiovascular</td>
<td>48.1 %</td>
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<tr>
<td>Skeletal</td>
<td>26.7 %</td>
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<tr>
<td>Pulmonary</td>
<td>18.2 %</td>
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<tr>
<td>Skin</td>
<td>16.6 %</td>
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<tr>
<td>Craniofacial</td>
<td>15 %</td>
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<tr>
<td>Gastrointestinal</td>
<td>10.7 %</td>
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<tr>
<td>Ophthalmological</td>
<td>10.2 %</td>
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<tr>
<td>Haematological</td>
<td>7.5 %</td>
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Table 1: Frequency of clinical manifestations in various organ systems described in 187 FLNA-PVNH literature patients and this case. Neurological manifestations do not include PVNH. FLNA = Filamin A, PVNH = periventricular nodular heterotopia.

Pathogenic variants have been shown to be distributed throughout the FLNA gene. Especially loss of function variants are a major cause of the FLNA-PVNH phenotype.[13] In a review of 92 patients, frameshift and missense variants were identified as the most common variant types (n=34 and n=20, respectively).[24] Interestingly, the actin-binding domain of FLNA was shown to be significantly enriched in pathogenic missense variants,[24] which is where we also detected the novel missense variant in our patient. Although no functional studies were conducted, the novel missense variant in our patient was re-classified as likely pathogenic based on the convincing clinical findings (PVNH), the de novo occurrence, the rarity of the variant in control populations (gnomAD), and in silico predicted pathogenicity. A heterozygous deletion in the RBM8A-gene was further identified, but beside thrombocytopenia, the patient did not present symptoms suggestive of TAR syndrome. This was in line with the genetic results that only identified a heterozygous deletion and no second variant in the patient.

When a proband is diagnosed with PVNH, genetic counselling is important. In approximately half of the patients the pathogenic variant arises de novo while in the other half it is passed on by the mother. Molecular genetic testing of the mother is therefore recommended. As FLNA-PVNH is
inherited in an X-linked dominant manner, the risk of transmitting the pathogenic variant is 50% for affected women.[16] If the pathogenic variant has been identified in the family, prenatal testing is possible. However, the difficulty in predicting the phenotypic outcome represents a challenge in the prenatal counselling.[25] Ultrasound or MRI may detect PVNH in a fetus from gestational week 24.[16]

A thorough clinical exam and follow-up is important to identify all symptoms in the FLNA-PVNH patients. Monitoring and screening for cardiovascular disease is essential given the increased risk, even in asymptomatic carriers.[12,17,23,36] Skin, joints, and vasculature may also be affected, and a complete evaluation is recommended.[12] Seizures often develop in adolescence and sometimes in adulthood why awareness and a long follow-up period could be necessary.[17] If seizures are present, an evaluation by a neurologist is recommended.[16]

In conclusion, our case presented with hypermobility, cardiovascular, and cutaneous manifestations and contributes to the number of cases reported with a phenotype resembling EDS in the FLNA-PVNH phenotypic spectrum. She is the first FLNA-PVNH patient reported with a deep vein thrombosis. The literature review of the phenotypic expressions in FLNA-PVNH patients describe the frequencies and the wide spectrum of manifestations associated with this condition. This review may guide clinicians in the clinical evaluation and follow-up in PVNH patients with a pathogenic FLNA variant.

**LEARNING POINTS/TAKE HOME MESSAGES**

1. Loss-of-function variants in the filamin A (*FLNA*) gene cause X-linked periventricular nodular heterotopia (PVNH), but missense variants are also repeatedly being identified, especially in the actin-binding domain of the gene.
2. No clear definition of the FLNA-PVNH phenotype is established.
3. The phenotype of FLNA-PVNH patients varies greatly and common manifestations are seen in the cardiovascular, neurological, pulmonary, haematological, skeletal, cutaneous, and gastrointestinal systems.
4. FLNA-PVNH may mimic Ehlers-Danlos syndrome due to hypermobility, cardiovascular, and cutaneous manifestations.
5. A thorough genetic and clinical evaluation and follow-up is recommended due to the potentially severe manifestations especially in the cardiovascular system.
REFERENCES


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**Figure 1:** Photos demonstrating phenotypic features of the proband. 

**A.** The proband’s elbow with a violaceous hue due to visible blood vessels. 

**B.** The proband’s skin is translucent with telangiectasia on her cheeks and violet lips. 

**C.** The hands of the proband with bluish discoloration and blue nails. 

**D, E.** The feet of the proband with phlebectasias, pes planus, short toes, and sandal gap.

**Figure 2:** Pedigree of the family. Squares represent male family members, and circles female family members. Filled symbols represent affected family members, and open symbols represent unaffected family members. The arrow indicates the proband (II-3) with PVNH, skin manifestations, cardiovascular anomalies, hypermobility, and thrombocytopenia, and a novel missense *FLNA* variant. The figure is drawn by the authors. FLNA = Filamin A, PVNH = periventricular nodular heterotopia.

**Figure 3:** Axial T2-image shows small nodules of grey matter along the ventricular walls consistent with typical findings in periventricular nodular heterotopia.

**Figure 4:** A PubMed search was conducted on 14-04-2021 with the following terms: periventricular nodular heterotopia, PVNH, FLNA, filamin A, FLN1, filamin 1, filaminopathy, and Ehlers-Danlos syndrome. The latter was included to identify patients similar to our case. Our inclusion criteria were: 1) MRI-confirmed PVNH, and 2) genetically confirmed *FLNA* variant. Papers were excluded if they were not in English, and if they contained cohorts with aggregated data to eliminate the risk of duplicates. This method generated 53 articles with patients who met the inclusion criteria. Furthermore, we reviewed the references in the articles for original literature potentially missed in the main search. Duplicates were excluded. In total, 56 articles were included reporting a total of 186 FLNA-PVNH patients. The figure is drawn by the authors. PVNH = periventricular nodular heterotopia, FLNA = Filamin A, FLN1 = Filamin 1.

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