

FLNA-related periventricular nodular heterotopia with multisystem involvement: a case report

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Case Report

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Abstract

Background

FLNA-related periventricular nodular heterotopia (PVNH) is an X-linked neuronal migration disorder classically associated with epilepsy. Accumulating evidence indicates that it is a multisystem disorder involving cardiac valvular, pulmonary, and ophthalmologic manifestations. We report a patient with an unusually comprehensive multisystem phenotype to emphasize the need for systematic extracranial evaluation in FLNA-related PVNH.

Case presentation:

A 33-year-old woman presented with two decades of headache and palpitations. Physical examination revealed digital clubbing and prominently dilated cardiac valves. Brain MRI demonstrated bilateral periventricular heterotopia. Enhanced whole-exome sequencing identified a heterozygous pathogenic nonsense variant in FLNA (NM_001110556.2:c.2193C > G, p.Tyr731Ter). Multisystem involvement comprised focal epilepsy, polyvalvular regurgitation, interstitial lung disease, and ophthalmologic abnormalities. Seizures were controlled with oxcarbazepine and lamotrigine, and the patient was referred for coordinated cardiologic, pulmonary, and ophthalmologic follow-up.

Conclusions

FLNA-related PVNH should be managed as a multisystem disorder rather than isolated epilepsy. Routine cardiovascular, pulmonary, and ophthalmologic screening, combined with genetic counseling for X-linked dominant transmission, should be integrated into standard care.

Background

Periventricular nodular heterotopia (PVNH) is an X-linked neuronal migration disorder caused by loss-of-function FLNA variants, typically presenting with epilepsy in heterozygous females (1, 2). Beyond the brain, FLNA deficiency produces a multisystem phenotype encompassing cardiovascular valvular disease, pulmonary involvement, connective-tissue and skeletal anomalies, and posterior fossa malformations such as mega cisterna magna (3–6). The pulmonary component may be severe and is often under-recognized. We report a 33-year-old woman whose FLNA-related PVNH coexisted with a multisystem phenotype that included an unusually severe, smoking-independent pulmonary disease, raising the possibility of an additional genetic contributor.

Case presentation

The patient's demographics, clinical manifestations across systems, and key diagnostic evidence are summarized in Table 1.

Table 1
Summary of the patient's multisystem manifestations and key diagnostic evidence.

System / domain	Manifestation	Key diagnostic evidence
Demographic	33-year-old woman; lifelong non-smoker	Clinical history
Neurological	Headache/palpitations since adolescence; focal seizures with impaired awareness	EEG: right frontopolar discharges
Brain MRI	Bilateral periventricular nodular heterotopia; mega cisterna magna	T2WI / T1-FLAIR
Cardiovascular	Polyvalvular regurgitation (mitral, tricuspid, aortic); right subclavian plaque	Echocardiography; MRA
Pulmonary	Emphysema, bullae, interstitial change; severe obstruction	HRCT chest; PFT
Skeletal / ocular	Thoracic scoliosis; proliferative retinopathy; digital clubbing	Exam; imaging
Genetic	FLNA c.2193C > G (p.Tyr731Ter), maternal, pathogenic; SERPINA1 c.918G > A	WES + Sanger

History

A 33-year-old woman from Guangzhou was admitted to Nanfang Hospital in March 2023 for two decades of headache and palpitations. Episodic headaches with nausea began around age 13, followed by a single generalized seizure at 14 and subsequently frequent focal seizures with impaired awareness, paroxysmal palpitations, dyspnoea, and transient blackouts. She was a lifelong non-smoker with regular menses and no children. Prior work-up (2000–2021) had documented a pituitary lesion with mild hyperprolactinemia, progressive polyvalvular regurgitation, emphysema with bullae, positive rheumatoid factor and anticentromere/anti-CCP antibodies, vitamin D insufficiency, and a SERPINA1 c.918G > A variant, leading to a diagnosis of COPD attributed to alpha-1 antitrypsin deficiency.

Physical examination

On admission she was alert and cooperative with normal vital signs. Notable findings included digital clubbing and prominent, abnormally dilated dorsal hand veins without ulceration. Neurologic examination was unremarkable.

Investigations

Brain MRI (3T) showed bilateral symmetrical subependymal nodules isointense to cortical grey matter on all sequences with homogeneous enhancement, and an enlarged cisterna magna without mass effect (Fig. 1); the corpus callosum was intact. Chest CT revealed emphysema with bullae, micronodules and interstitial change; pulmonary function testing showed a severe obstructive defect. Echocardiography demonstrated polyvalvular regurgitation (mitral, tricuspid, aortic; mild-moderate) and a right subclavian artery plaque. EEG localized epileptiform activity to the right frontopolar region. Laboratory studies showed elevated rheumatoid factor (57–157 IU/mL), positive anticentromere and anti-CCP antibodies, low vitamin D, and mild leucocytosis.

Enhanced whole-exome sequencing identified a heterozygous pathogenic nonsense variant in FLNA, NM_001110556.2:c.2193C > G (p.Tyr731Ter), in exon 15. This variant introduces a premature stop codon at tyrosine 731, within the N-terminal immunoglobulin-like (rod) domain – the region where PVNH-causing FLNA variants predominantly cluster (6, 7), in contrast to C-terminal FLNA variants that produce the skeletal dysplasias of the otopalatodigital spectrum (OPD/FMD/MNS) (5); it is predicted to generate a truncated, non-functional filamin A (a loss-of-function / haploinsufficiency allele). The variant is absent from population databases (gnomAD allele frequency 0) and, as of 2026, is catalogued in ClinVar (Variation ID VCV004294528) as Likely pathogenic, with recorded associations to both X-linked cardiac valvular dysplasia (OMIM 314400) and PVNH (OMIM 300049); the ClinVar record explicitly lists valvular abnormalities among the variant's clinical features, directly supporting the patient's polyvalvular regurgitation as an intrinsic component of the FLNA genotype rather than an incidental finding. The diagnostic laboratory classified the variant as pathogenic under ACMG criteria (PVS1 + PS4_Supporting + PM2_Supporting), and maternal inheritance was confirmed (asymptomatic carrier mother; wild-type father) (8, 9). A heterozygous SERPINA1 c.918G > A (p.Arg306=) synonymous variant of uncertain significance—previously linked to alpha-1 antitrypsin deficiency (10, 11)—was also detected.

Clinical course and treatment

She was transferred to neurology and started on levetiracetam, which was stopped for intolerance; oxcarbazepine and lamotrigine were better tolerated. Inhaled triple therapy (fluticasone furoate/vilanterol/umeclidinium) and oral N-acetylcysteine were given for COPD/ILD. At discharge after 21 days she was symptom-free for three consecutive days. Discharge diagnoses included FLNA-related PVNH, symptomatic focal epilepsy, polyvalvular heart disease, COPD with emphysema/ILD, proliferative retinopathy, right subclavian plaque, scoliosis, and mega cisterna magna. Multidisciplinary follow-up was arranged.

Discussion

This case illustrates the full multisystem expression of FLNA-related PVNH in an adult woman—neurological (PVNH with focal epilepsy), cardiovascular (polyvalvular regurgitation, subclavian plaque), pulmonary (COPD/emphysema/ILD), and posterior fossa (mega cisterna magna)—together with scoliosis and proliferative retinopathy (3–6). The pulmonary disease is striking: emphysema, bullae and severe obstruction in a lifelong non-smoker. FLNA deficiency has been linked to severe congenital and interstitial lung disease (3, 5), but the extent here exceeds typical descriptions. The patient also carried a SERPINA1 c.918G > A synonymous variant implicated in alpha-1 antitrypsin deficiency (10, 11), an autosomal codominant disorder causing early emphysema even without smoking through unopposed neutrophil elastase. We hypothesize a 'dual-hit' contribution—FLNA haploinsufficiency predisposing to airway/parenchymal abnormality, compounded by AATD-mediated protease imbalance. Because p.Arg306 = is a synonymous variant of uncertain significance, this remains hypothetical without biochemical confirmation (e.g., serum alpha-1 antitrypsin level or Pi typing). The presentation nonetheless parallels reported Chinese families with FLNA frameshift variants and similar multiorgan involvement (12), and aligns with reviews emphasizing under-recognized extraneural features in FLNA-PVNH (13). The neuroradiologic spectrum of gray-matter heterotopia that defines this imaging phenotype has been well characterized, and PVNH phenotypic heterogeneity has been linked to FLNA genotype by Parrini et al. (7). Earlier recognition of the multisystem nature could direct proactive screening and counseling.

Genotype–phenotype correlation

The p.Tyr731Ter variant belongs to the class of N-terminal truncating FLNA alleles that reliably produce the multisystem, connective-tissue and cardiovascular phenotype of FLNA deficiency, distinct from the isolated PVNH seen with some C-terminal variants (6, 7). Consistent with this, cardiac and valvular involvement is now a well-recognised feature of FLNA-related PVNH, reported across individual cases and family series (4, 6, 14, 15). Our patient's polyvalvular regurgitation (mitral, tricuspid and aortic), together with the right subclavian artery plaque, extends this cardiovascular spectrum, while the severe smoking-independent pulmonary disease and proliferative retinopathy further broaden the recognised extraneural manifestations. The coexistence of a SERPINA1 synonymous variant of uncertain significance raises the possibility of a modifying 'second hit' for the pulmonary phenotype, as discussed above.

Table 2 compares the present case with previously reported FLNA-related PVNH cases exhibiting cardiac/valvular involvement.

Table 2

Reported FLNA-related PVNH cases with cardiac/valvular involvement. (data compiled from the cited references).

Report (year)	FLNA variant	PVNH	Cardiac / valvular manifestation	Other multisystem features	Ref.
Reinstein et al. (2013)	c.883_890del8 (p.Asn296Glufs*38), exon 6	Yes	Sinus of Valsalva aneurysm + aortic root repair (F1); right subclavian artery aneurysm (F2); pulmonary artery/branch dilatation, dysplastic pulmonary/tricuspid/aortic valves, PDA, pulmonary hypertension (F3)	Joint hypermobility, easy bruising, aortic branch ectasia	(6)
Jefferies et al. (2010)	c.7896G > A (p.Trp2632Ter)	Yes	Redundant pulmonary valve, cleft anterior mitral leaflet + mitral regurgitation, patent foramen ovale	—	(15)
Kyndt et al. (2007)	Various FLNA	Yes (subset)	Mitral/tricuspid/aortic valvular dystrophy and prolapse; aortic root dilation	Familial cardiac valvular dystrophy	(4)
Zhou et al. (2016)	c.7539_7540insA (frameshift), exon 46	Yes	Partial anomalous pulmonary venous connection; bicuspid + tricuspid regurgitation	Enlarged cisterna magna	(12)
Present case (2026)	c.2193C > G (p.Tyr731Ter), exon 15	Yes	Polyvalvular regurgitation (mitral, tricuspid, aortic); right subclavian plaque	COPD/emphysema/ILD, scoliosis, proliferative retinopathy, mega cisterna magna	—

Conclusion

FLNA-related PVNH is a multisystem disorder extending well beyond epilepsy. Comprehensive cardiovascular, pulmonary, and ophthalmologic assessment—and consideration of coexisting alpha-1 antitrypsin deficiency when

lung disease is disproportionate to smoking history—should accompany genetic diagnosis and guide long-term surveillance.

Practical Implications

- FLNA-related PVNH should be managed as a multisystem disorder, not solely an epilepsy diagnosis.
- Adults with PVNH and severe, smoking-independent lung disease warrant evaluation for coexisting alpha-1 antitrypsin deficiency (serum AAT level or Pi typing).
- Baseline and serial cardiologic, pulmonary, and ophthalmologic screening should be integrated into routine care.
- Genetic counseling for X-linked dominant transmission (50% risk per pregnancy) is essential and enables familial cascade testing.
- FLNA genotyping is indicated in any PVNH patient with cardiac/valvular disease, enabling cascade screening of female relatives for X-linked cardiac valvular dysplasia (OMIM 314400).

Declarations

Ethics approval: The requirement for ethical approval was waived by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University for this single-case report, which was conducted in accordance with the Declaration of Helsinki and with written informed consent for publication obtained from the patient.

Consent to participate: Written informed consent was obtained from the patient for participation in the study.

Consent to publish: Written informed consent was obtained from the patient for publication of this case report and the accompanying de-identified images. This case report is reported in accordance with the CARE guidelines, and the CARE checklist is provided as supplementary material.

Competing interests: The authors report no disclosures relevant to the manuscript.

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Data availability: The FLNA variant identified in this study (NM_001110556.2:c.2193C>G, p.Tyr731Ter) is publicly available in the ClinVar database (Variation ID: VCV004294528; <https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV004294528>). All de-identified clinical, imaging, electrophysiological, and phenotypic data supporting the findings of this case report are included within the manuscript and its supplementary files (Tables 1 and 2, Fig. 1). Individual-level whole-exome sequencing data are not publicly deposited to protect patient privacy in accordance with the approved consent; these data are available from the corresponding author upon reasonable request.

Authors' contributions: LW and PS conceptualized and designed the case report; LW collected the clinical data and drafted the manuscript; CY and PS critically revised the manuscript for important intellectual content; PS and CY supervised the work; all authors read and approved the final manuscript.

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Figures

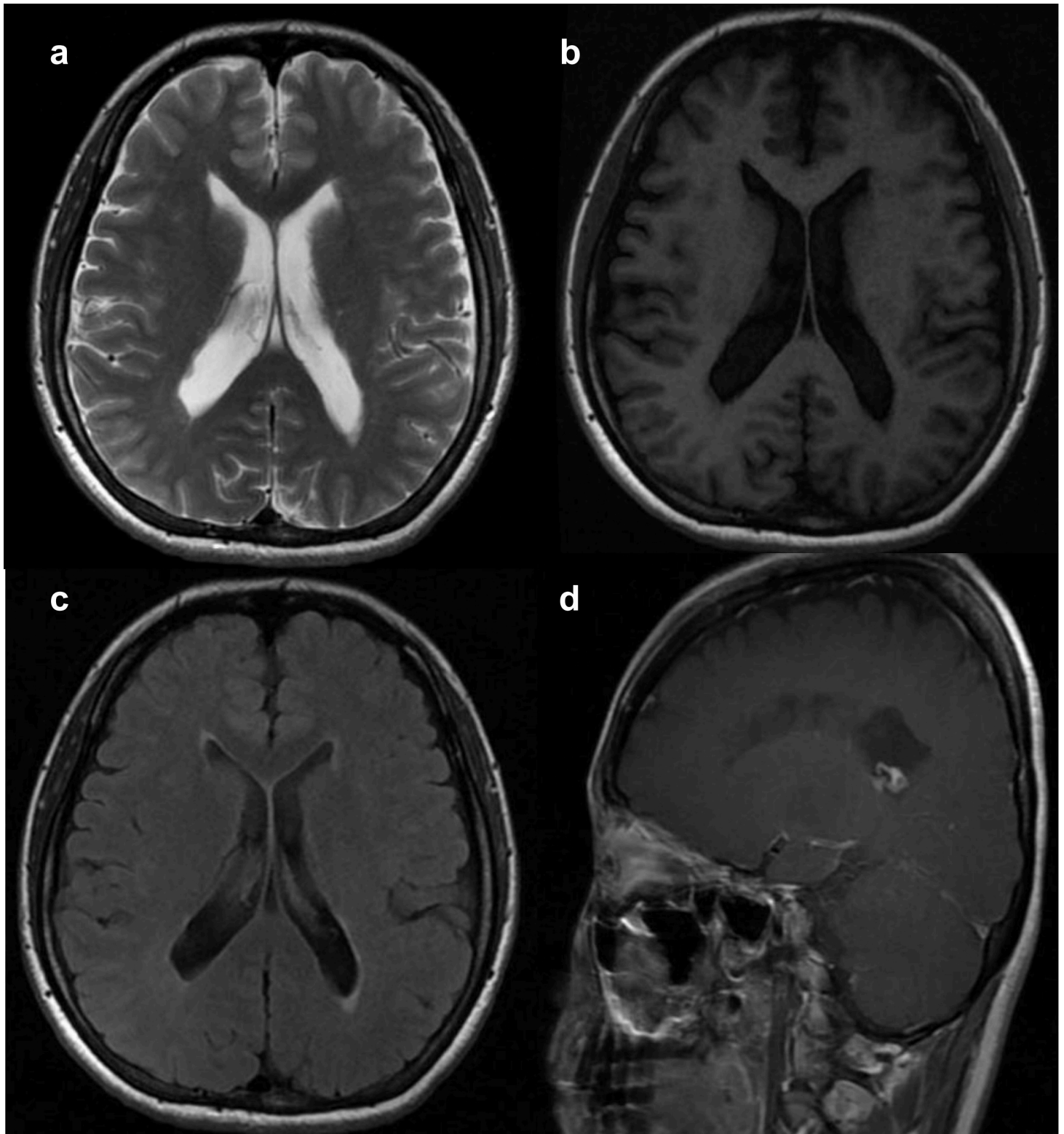


Figure 1

De-identified brain MRI of the patient. (a) Axial T2-weighted image showing bilateral periventricular nodules isointense to gray matter along the lateral ventricles. (b) Axial T1-FLAIR image at the same level demonstrating the nodules are isointense to cortex. (c) Axial T2-FLAIR image confirming the heterotopic nodules without surrounding edema. (d) Sagittal post-contrast T1-weighted image showing an intact corpus callosum