Citation: Murugan A, Babiker MOE, Newbury-Ecob R. An FLNA gene variant causing congenital cardiac defects, persistent thrombocytopenia and an 'incidental' periventricular nodular heterotopia: a case report. European Journal of Medical Case Reports. 2017;1:10-13. https://doi.org/10.24911/ejmcr/1/3

European Journal of Medical Case Reports

CASE REPORT

An FLNA gene variant causing congenital cardiac defects, persistent thrombocytopenia and an 'incidental' periventricular nodular heterotopia: a case report

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ABSTRACT

Background: Many children with multiple congenital organ defects have a genetic etiological basis. Periventricular nodular heterotopia (PVNH) is a neuronal migrational disorder that can be seen in isolation or in association with other neurological and non-neurological features. Mutations in the FLNA gene may result in X-linked dominant bilateral PVNH, a condition that is predominately seen in females due to its in-utero lethality for males. Associated features may include cardiovascular defects and thrombocytopenia.

Case presentation: We present an 8 year old girl with multiple congenital heart defects and longstanding unexplained low platelets counts. There were no neurodevelopmental concerns but she was incidentally found to have bilateral PVNH. Targeted genetic testing confirmed a mutation in the FLNA gene.

Conclusion: Testing for mutations in this gene in any child with bilateral symmetrical PVNH is recommended. If mutations are found, then other associations should be searched for if not already evident.

Keywords: FLNA gene, cardiac defects, periventricular heterotopia, thrombocytopenia, case report.

Background

Whether the link between congenital cardiac defects and brain disorders is genetic or environmental has long been debated. However, recent research has shown that pathogenic de novo genes mutations exist in 20% of the patients who have congenital heart defects, extra-cardiac anomalies and neurodevelopmental disorders [1].

The FLNA gene encodes for the protein filamin A. This is an action-binding protein which is involved in remodeling the cytoskeleton to effect changes in cell shape and migration. It is located on the long arm of X chromosome in position 28 [2]. Mutations of this gene may result in X-linked dominant bilateral periventricular nodular heterotopia (PVNH), a condition that is predominately seen in females due to its in-utero lethality for males [2]. Associated features may include cardiac defects, thrombocytopenia and skeletal defects [3,4].

We hereby describe a pediatric case in which the incidental finding of bilateral PVNH led to diagnosing a genetic variant of the FLNA gene.

Case presentation

This 8-year-old girl was regularly followed up for multiple congenital heart defects including severe sub-aortic stenosis, interrupted aortic arch, a ventricular septal defect and an aberrant right subclavian artery. Antenatally, a foetal ultrasound scan demonstrated 'small-sized brain ventricles' however, this was not followed through. Of note, her healthy mother had two miscarriages at 6 and

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9 weeks' gestation. This girl had a younger brother who was well. Her motor and cognitive development had been normal. There had been a history of easy bruising secondary to a persistently moderately low platelet count ranging between 64 to 142 x109 (reference range: 150-450 x 109/L). Despite extensive investigations, no hematological explanation was found.

She presented with an acute headache that was retrospectively attributed to a stressful life event at the time. However, and in view of the history of thrombocytopenia, she underwent a head CT scan which, incidentally, revealed bilateral periventricular grey matter heterotopia (figure 1). A brain MRI scan confirmed this (figure 2). On follow up, she continued to have no neurological concerns or deficits on examination. Of note, musculoskeletal examination and renal ultrasound scans were also normal.

Sequencing of FLNA gene using genomic DNA from this patient was carried out using Agilent's Focussed Exome custom target enrichment system and next generation sequencing. Analysis revealed that she was heterozygous for a pathogenic nonsense variant in the X-linked FLNA gene: c.5577T>G p.(Tyrl859Ter).

Discussion

Bilateral symmetrical PVNH is usually secondary to genetic causes as opposed to unilateral cases whereby a perinatal vascular event is a likely cause. Congenital vascular abnormalities, such as those described in this case, have been described in association with FLNA gene mutations [3]. Maternal history of miscarriage, in this case, may suggest maternal inheritance although 50% of the mutations arise de novo. Despite the extensive neuroimaging changes, patients tend to have normal cognition with the normal motor examination. Epilepsy is the presenting feature in 88% of these individuals, usually within the second decade of life [5].

Thrombocytopenia has been described in association with FLNA gene mutations [4,6]. This is postulated to result from abnormal platelet production, morphology and function in these patients [4].

FLNA gene mutations lead to varied clinical phenotypes. Nonsense variants are commonly associated with neuronal migration disorders, vascular anomalies, and disorders of connective tissue integrity. On the other hand, missense variants lead to skeletal disorders [7]. It is thus not surprising that our case, who had a nonsense mutation, had the former features.

Conclusion

In this case, genetic testing provided an explanation for her constellation of clinical features. We recommend testing for FLNA gene mutations in any child with bilateral symmetrical PVNH and if found, other associations should be searched for if not already evident.

Acknowledgements
None

List of Abbreviations

CT	Computed Tomography
FLNA	Filamin A, alpha
PVNH	Periventricular Nodular Heterotopia

Conflict of Interests
None

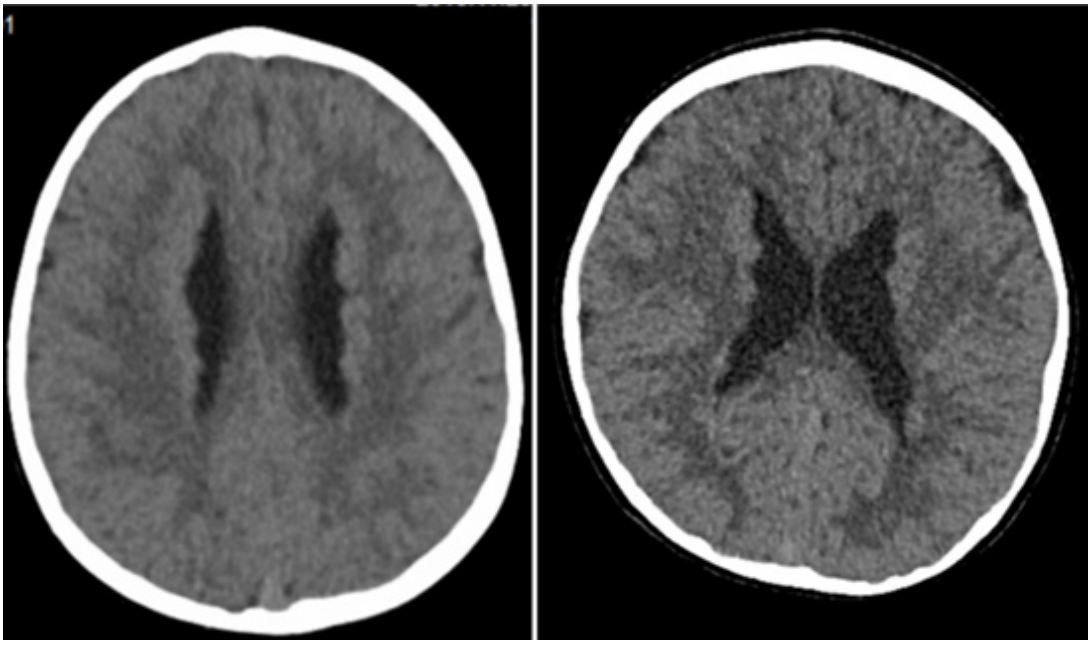

Figure 1: *Brain CT scan revealing the nodular heterotopic grey matter along the lateral ventricles giving them a ragged appearance.*

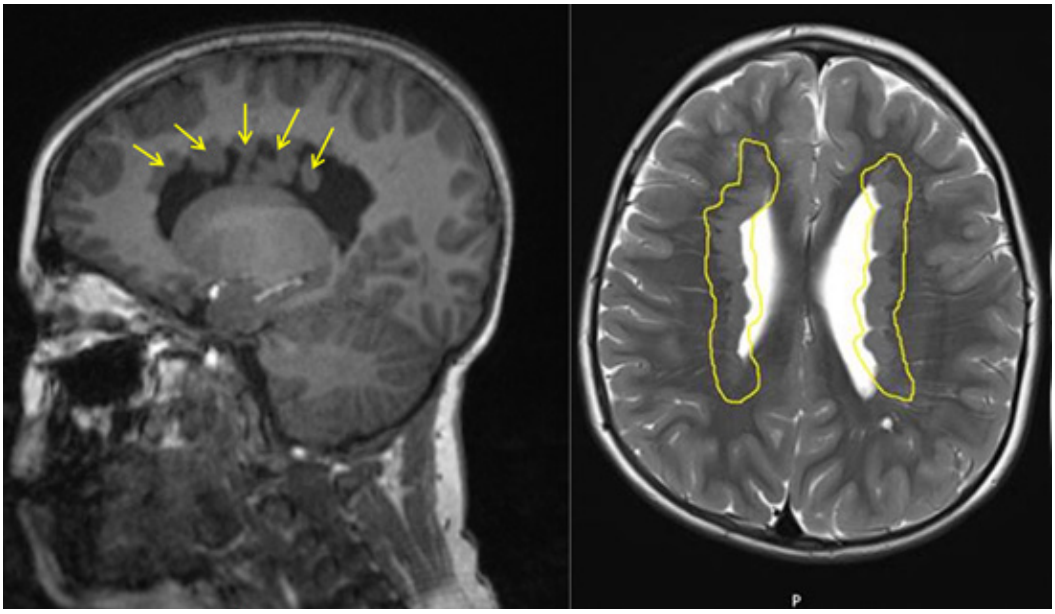

Figure 2: *Sagittal T1-weighted MRI on the left shows periventricular heterotopias (yellow arrows) extending into the lateral ventricle. Coronal T2-weighted image on the right demonstrating the nodular heterotopias along the surface of the lateral ventricle in a symmetrical bilateral distribution (outlined in yellow). Note that the nodules are isointense to cortical grey matter in all sequences.*

Funding
None

Consent for publication
Informed consent has been obtained from parents to present and publish this case.

Ethical approval
Ethical approval is not required at our institution for publishing a case report in a medical journal.

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Authors' contribution
All authors contributed to the management of the patient. All authors participated in drafting, revising and final editing of the manuscript.

Received: 21 November 2016
Accepted: 3 January 2017
Published online: 6 January 2017

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Summary of the case

Patient (gender, age)	1	Female, 8 year old
Final Diagnosis	2	An FLNA gene variant causing congenital cardiac defects, persistent thrombocytopenia and periventricular nodular heterotopia
Symptoms	3	Congenital cardiac defects and thrombocytopenia
Medications (Generic)	4	N/A
Clinical Procedure	5	Neuroimaging/ Genetic testing
Specialty	6	Pediatrics, Genetics, Cardiology, Neurology
Objective	7	Highlight importance of genetic testing in similar cases
Background	8	The FLNA gene encodes for the protein filamin A. This is an actin-binding protein involved in remodeling the cytoskeleton to effect changes in cell shape and migration. It is located on the long arm of X chromosome in position 28. Mutations of this gene may result in X-linked dominant bilateral periventricular nodular heterotopia (PVNH), a condition that is predominately seen in females due to its in-utero lethality for males. Associated features may include cardiac defects, thrombocytopenia, and skeletal defects.
Case Report	9	A pediatric case in which the incidental finding of bilateral PVNH led to diagnosing a genetic variant of the FLNA gene
Conclusions	10	Genetic testing provided an explanation for her constellation of clinical features. We recommend testing for FLNA gene mutations in any child with bilateral symmetrical PVNH and if found, other associations should be searched for if not already evident.
MeSH Keywords	11	FLNA gene, cardiac defects, periventricular heterotopia, thrombocytopenia, case report.