LETTER

Update on a previously reported male with a *FLNA* missense mutation

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We read with interest the article by Oda *et al*¹ expanding the phenotypic and mutation spectrum of *FLNA* mutations in surviving males. In this regard, we would like to provide an update on a now adult male with an *FLNA* variant who was originally reported in this journal by Reinstein *et al*² (Case M3) in 2013 but whose clinical phenotype has evolved significantly since publication.

At the time of original report, Case M3 was 16 years. He had been diagnosed clinically with a connective tissue disorder – Ehlers Danlos syndrome – in the neonatal period after he was noted to have soft skin with increased elasticity and hypotonia. He was subsequently found to have diaphragmatic eventration and when on to develop spontaneous pneumothoraces, joint hypermobility and mild aortic root dilatation.² At 14 years, a MRI brain to investigate a history of headaches demonstrated bilateral periventricular nodular heterotopia. Sequencing of the *FLNA* locus revealed a novel maternally inherited hypomorphic missense variant, (NM_001456.1:c.381G>C, NP_001447.2 p.(Lys127Asn)). This is listed on the gene variant database at www.lovd.nl/*FLNA* (individual ID 00074612). His mother had mild joint hypermobility (Beighton hypermobility score 4/9). He was intellectually normal and attending mainstream school, with no history of seizures. He has no dysmorphic or bone features suggestive of an OPD spectrum disorder.

Since then, at age of 17, he required gastroplexy for gastric volvulus and malrotation on a background of recurrent abdominal pain and vomiting likely secondary to small bowel obstruction. During the laparotomy, he was found to have a ‘wandering spleen’ and a stretched gastocolic omentum with multiple openings that were facilitating internal hernias. These were managed surgically with excision of the greater omentum and splenic tethering. Following the operation, he developed incisional hernias that required surgical repair. He also had surgery for a left-sided testicular torsion and had a right-sided orchidopexy at the age of 19.

Recently aged 20, he has required a prolonged hospital admission of 5 months. He presented initially with a right-sided pneumothorax, and then developed a recurrent mid-gut volvulus. He has undergone three laparotomies including a bowel resection and eventually a total colectomy with stoma formation. He currently requires nasogastric feeding having previously had a period of time on total parenteral nutrition. He developed marked splenomegaly and portal hypertension with associated gastric varices secondary to splenic vein thrombosis, which ultimately led to a splenectomy. He has been admitted to intensive care on three occasions. This hospital admission occurred on a background of a 4 year history of severe chronic bilateral flank pain of unknown origin for which he attends a chronic pain clinic. As a result of the burden of his illness and hospital commitments, he left

school at age 17 and completed year 11 and year 12 English by distance education.

Males with PNH-associated *FLNA* variants who survive past infancy are rare with <30 cases described in the literature and even fewer reported cases surviving into adulthood. The intestinal manifestations in our patient are particularly marked and based on the paper by Kapur *et al* may relate to an underlying myopathic process.³ The features seen in our patient including his wandering spleen, recurrent bowel obstruction and hernias have been previously reported individually in other patients.^{1–5} However to our knowledge, this is the first reported case of these features developing later in life after a relatively stable neonatal period and childhood.

The majority of patients with *FLNA*-associated PVNH are females with most variants that affect function being lethal in males.⁵ Surviving males usually have missense or distal truncating variants that are associated with some residual protein function^{6–9} and this extends to males with other *FLNA*-related phenotypes.⁵ Hehr *et al* described a male with splice site mutation in *FLNA* who had PVNH, severe constipation and facial dysmorphism.⁹ They showed that the splice site resulted in both normal and aberrant mRNA transcripts and they attributed his non-lethal phenotype to him retaining some normal Filamin A function.⁹ Oda *et al* proposed that in-frame exon skipping of a 4 bp deletion in *FLNA* in two boys was associated with a milder phenotype. Our patient has a missense variant in the CH1 domain of *FLNA*, where the majority of PVNH variants are reported, and is predicted to interfere with the actin binding site.² This update on our patient provides further insight into the phenotype of males with PVNH and *FLNA* variants that affect protein function and demonstrates that even those that appear mildly affected in early childhood and adolescence should be actively monitored for complications later in life. It also highlights the psychological and physical burden of this condition on the patient, and difficulty in counselling and managing patients with novel *FLNA* missense variants.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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