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CASE REPORT

Further characterization of *NFIB*-associated phenotypes: Report of two new individuals

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Abstract

Nuclear Factor I B (*NFIB*) haploinsufficiency has recently been identified as a cause of intellectual disability (ID) and macrocephaly. Here we report on two new individuals carrying a microdeletion in the chromosomal region 9p23-p22.3 containing *NFIB*. The first is a 7-year 9-month old boy with developmental delays, ID, definite facial anomalies, and brain and spinal cord magnetic resonance imaging findings including periventricular nodular heterotopia, hypoplasia of the corpus callosum, arachnoid cyst in the left middle cranial fossa, syringomyelia in the thoracic spinal cord and distal tract of the conus medullaris, and a stretched appearance of the filum terminale. The second is a 32-year-old lady (the proband' mother) with dysmorphic features, and a history of learning disability, hypothyroidism, poor growth, left inguinal hernia, and panic attacks. Her brain magnetic resonance imaging findings include a dysmorphic corpus callosum, and a small cyst in the left choroidal fissure that marks the hippocampal head. Array-based comparative genomic hybridization identified, in both, a 232 Kb interstitial deletion at 9p23p22.3 including several exons of *NFIB* and no other known genes. Our two individuals add to the knowledge of this rare disorder through the addition of new brain and spinal cord MRI findings and dysmorphic features. We propose that *NFIB* haploinsufficiency causes a clinically recognizable malformation-ID syndrome.

KEYWORDS
brain/spinal cord malformation, developmental delay, intellectual disability, *NFIB*, periventricular nodular heterotopia, syringomyelia

1 | INTRODUCTION

The Nuclear Factor I (NFI) family of transcription factors play an important role in normal development of several organs. Three NFI family members (*NFIA*, *NFIX*, *NFIB*) are highly expressed in the brain, and deletions and sequence variations in all of them have been associated with intellectual disability (ID) and variable structural brain anomalies (Betancourt et al., 2014; Chen et al., 2017; Gronostajski, 2000; Mason et al., 2009; Murtagh et al., 2003).

Deletions of chromosome 1p32-p31 (MIM: 613735) as well as deletions or sequence variations of *NFIA* lead to a variable phenotype characterized by global developmental delay, ID, central nervous

system malformations (loss of white matter, polymicrogyria and hypoplastic falx cerebri, partial inversion of the hippocampi), macrocephaly, and craniofacial dysmorphisms (Bayat et al., 2017; Campbell et al., 2002; Koehler et al., 2010; Labonne et al., 2016; Lu et al., 2007; Negishi et al., 2015; Nyboe et al., 2015; Rao et al., 2014; Shanske et al., 2004; Zinner & Batanian, 2003). Mutations leading to haploinsufficiency of *NFIX* cause the autosomal dominant Malan syndrome (MIM: 614753), whereas dominant-negative mutations in *NFIX* cause the autosomal dominant Marshall–Smith syndrome (MIM: 602535). Marshall–Smith syndrome is due to exon deletions, indels and splice site variants leading to frameshift downstream of Exon 5; the mutant NFIX protein has a preserved DNA binding and dimerization domain, and therefore likely acts in a dominant negative manner. The syndrome is characterized by prenatal overgrowth, advanced bone age, "Bullet"-shaped middle phalanges, failure to thrive, high neonatal mortality, thick eyebrows, prominent eyes, depressed nasal bridge, anteverted nares, choanal atresia, overfolded helix, and micrognathia (Adam et al., 2005; Aggarwal et al., 2017; Malan et al., 2010; Martinez et al., 2015; Schanze et al., 2014). Malan syndrome is characterized by postnatal overgrowth, decrease in height, overgrowth with age, persistent macrocephaly, learning disability, autism and anxiety, hypotonia, brain anomalies, and dysmorphic features (Malan et al., 2010; Yoneda et al., 2012). *NFIX* duplication has also been observed in a few individuals presenting ID, short stature, small head circumference, and minor dysmorphic features (Dolan et al., 2010; Trimouille et al., 2018). Recently, haploinsufficiency of *NFIB* (caused by either deletions of 9p23-p22.2 or *NFIB* sequence variations), has been shown to cause ID with macrocephaly, along with motor delay, hypotonia, behavioral abnormalities, and variable structural brain anomalies mainly involving the corpus callosum (Barrus et al., 2020; Schanze et al., 2018).

Herein we report two individuals (the proband and his mother) carrying a microdeletion in the chromosomal region 9p23-p22.3 containing *NFIB*, assessed at the IRCCS Stella Maris Foundation (Scientific Institute for Research, Hospitalization and Healthcare Stella Maris Foundation), Pisa, Italy. We describe new imaging data and clinical findings that have not been previously reported.

2 | CASE REPORTS

Patient 1 is a 7-year 9-month old boy born by caesarean for breech presentation at 37 + 3 weeks of gestation. Apgar was 7/8. His birth weight was 1800 g. (<10th centile), length 48 cm (50th centile), OFC 33.5 cm (50th centile). He was found to have a ventricular septal defect (VSD), a patent foramen ovale (PFO), and jaundice which was treated with phototherapy. Developmental delay was obvious from early on; he held his head at 9 months, sat unsupported at 18 months, and walked alone at 26 months; babbling appeared at around 2 years, and first bisyllabic words at 3 years. Presently, at age 7-year 9-month, he pronounces both simple and complex sentences with some phono-articulatory alterations.

VSD and PFO spontaneously resolved. At age 3 months he underwent surgery for a right inguinal hernia, and at age 3 years 7 months for a left congenital hydrocele. With time, his growth remained between 10th and 25th centile. Frequent, severe urinary tract infections were reported from early on.

Array-comparative genomic hybridization (Array-CGH) CytoSure Oligo Arrays OGT-Oxford Gene Technology), performed elsewhere, showed a deletion of the short arm of a Chromosome 9 in the p23p22.3 region sizing ~232 Kb, starting at 14.107.008 pb and ending at 14.339.185 pb (hg19) including most of the gene *NFIB* (Nuclear Factor I/B; NFIB, *600728). The rearrangement was confirmed by fluorescence in situ hybridization (FISH) using bac RP11-1147E20 which maps in 9p23p22.3. Array-CGH on both parents showed the same deletion in the proband's mother.

The child was referred to our institute at 7 years due to psychomotor developmental delay and dysmorphic features. Physical examination showed height 115 cm (10–25th centile), weight 18.8 kg (3rd–10th centile), occipitofrontal circumference (OFC) 53.5 cm (50–98th centile). There were frontal bossing, broad forehead, high anterior hairline, sparse eyebrows, palpebral fissures length of 2.2 cm, anteverted nares, long and smooth philtrum (lip/philtrum 5), thin vermilion of the upper lip, micro-retrognathia, prominent digit pads, winged scapulae, and cervico-dorsal left convex scoliosis (Figure 1). Neuropsychological evaluation showed a receptive and expressive language disorder, emotional behavioral immaturity, learning disability, and borderline intellectual functioning (Wechsler Preschool and Primary Scale of Intelligence-WPPSI III test total intelligence quotient-QIT 77; performance intelligence quotient-PIQ 85; performance intelligence quotient-VIQ 80) (Luiselli et al., 2013). Fragile X testing and a polygraphic video-electroencephalography (video-EEG) recording (performed while the patient was awake and asleep) were normal. Brain and spinal cord magnetic resonance imaging (MRI) at 7 years of age showed two heterotopic nodules beneath the frontal horn of the left and right lateral ventricles, slight hypoplasia of the rostrum and the splenium of the corpus callosum, a small arachnoid cyst in the left middle cranial fossa, and syringomyelia in the thoracic spinal cord and distal tract of the conus medullaris and slightly stretched appearance of the "filum terminale" (Figure 2A–D). On this basis and given the suspected bladder dysfunction, the child underwent a spinal cord detethering by release of filum terminalis.

Patient 2, the proband's mother, is a 32-year-old lady with a history of learning disability, hypothyroidism, poor growth, left inguinal hernia, and panic attacks. Her cranio-facial features were very similar to those observed in the proband (Figure 3). In addition, she showed bilateral short fourth metatarsal with nail dysplasia, and widely spaced toes (Figure 4). Her weight was 61 kg (50–75th centile), height 148.4 cm (<3rd centile), OFC 55.5 cm (50–98th centile). Brain MRI at the age of 32 years showed a dysmorphic corpus callosum, and a small cyst in the left choroidal fissure that marks the hippocampal head (Figure 2E,F). She has a mild ID (total intelligence quotient-QIT 55; verbal comprehension index-VCI 61; perceptual reasoning index-PRI 67; working memory index-WMI 69; processing speed index-PSI

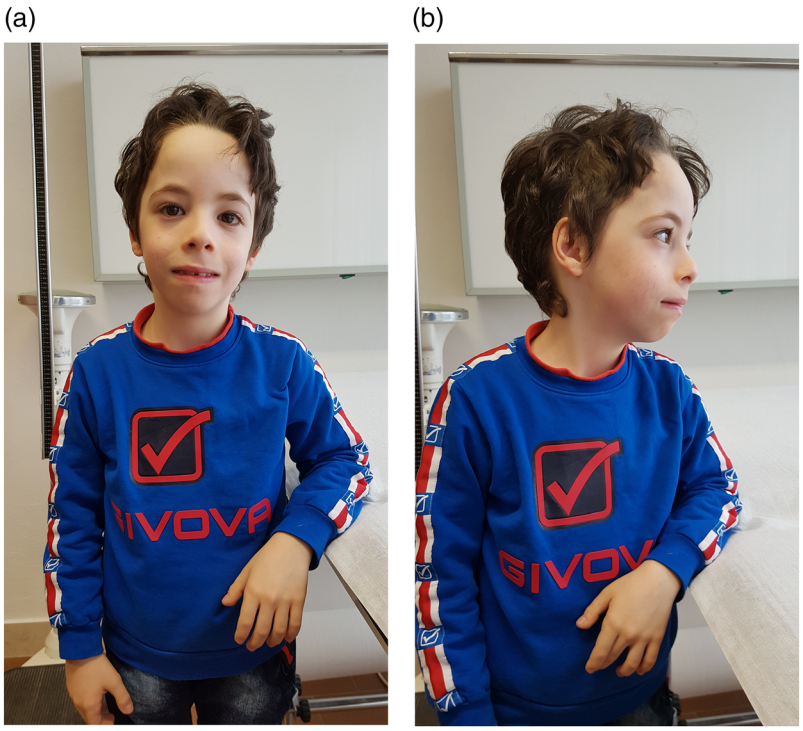

FIGURE 1 Front (a) and side (b) view of Patient 1 displaying a definite and well recognizable craniofacial phenotype

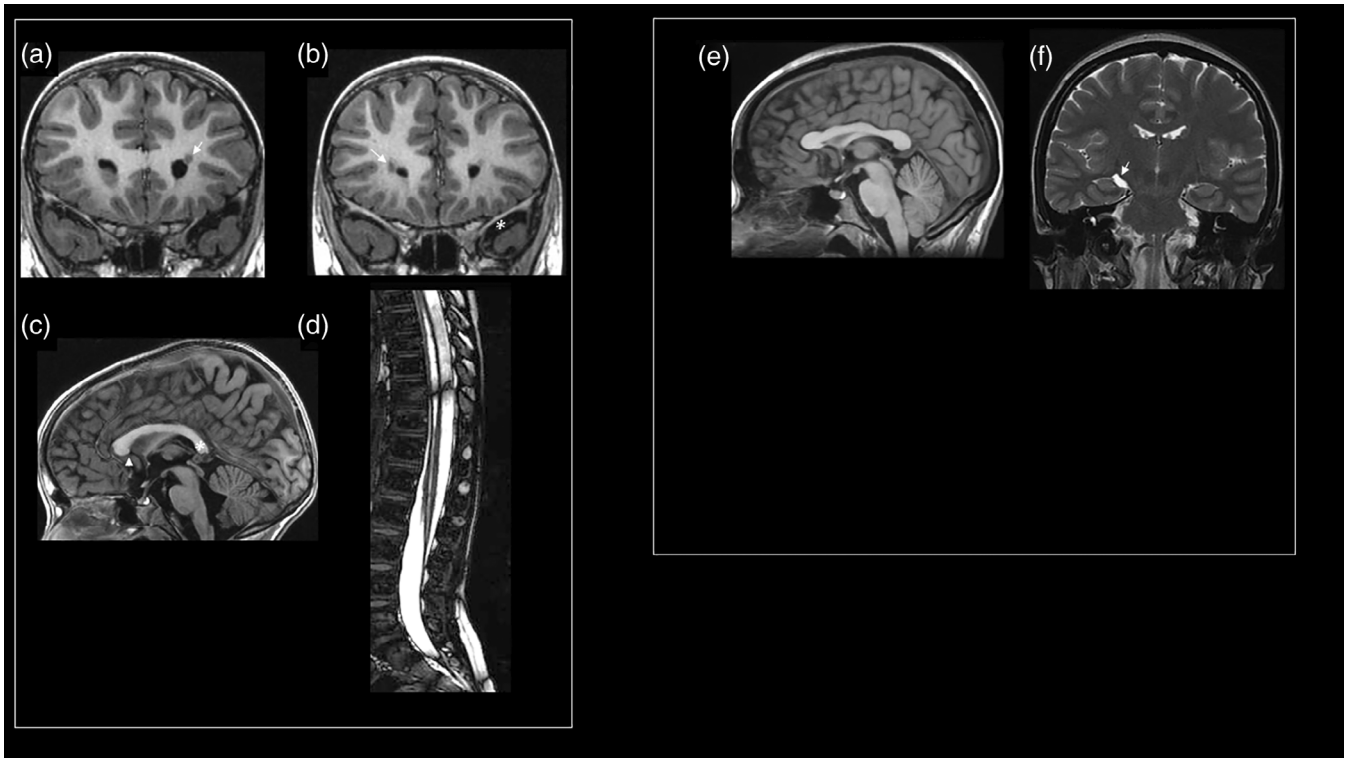

FIGURE 2 Patient 1: (a,b) Coronal T1-weighted image shows periventricular nodular heterotopia confined to the walls of the frontal horns bilaterally (white arrow) and a small arachnoid cyst in the left middle cranial fossa (*). (c) Sagittal T1-weighted image shows slight hypoplasia of the rostrum (head arrow) and the splenium (*) of the corpus callosum. (d) Sagittal T2 FIESTA shows syringomyelia in the thoracic spinal cord and distal tract of the conus medullaris and slightly stretched appearance of the small terminal. Patient 2: (e) Sagittal T1-weighted image shows a dysmorphic corpus callosum. (f) Coronal T2-weighted image shows a small cyst in the left choroidal fissure (white arrow) that marks the hippocampal head

FIGURE 3 Front view of Patient 2, the proband's mother

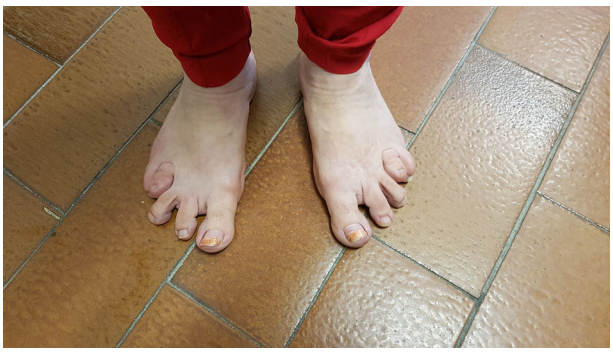

FIGURE 4 Feet of Patient 2, showing bilateral short fourth metatarsal with nail dysplasia, and widely spaced toes

67, assessed with the Wechsler Adult Intelligence Scale psychometric test).

3 | DISCUSSION

We report on two individuals with ID, abnormal brain and spinal cord MRI findings, and dysmorphic features who both had a heterozygous microdeletion of a Chromosome 9 in the p23p22.3 region, sizing ~232 Kb, including most of the gene *NFIB* (*MIM:618286*). The most distinct dysmorphic features in these individuals include broad forehead, high anterior hairline, sparse eyebrows, anteverted nares, long and smooth philtrum, and thin vermilion of the upper lip. Such clinical features are highly similar to those observed in individuals previously reported by Schanze et al. (2018), and seem to be distinctive enough to allow a clinical recognition of the *NFIB* haploinsufficiency even before the cytogenomic confirmation.

Contrary to what previously observed, our proband did not have macrocephaly and showed poor growth (Schanze et al., 2018). Both had a dysmorphic corpus callosum and small arachnoid cysts, consistent with previously reported MRI findings (Barrus et al., 2020; Schanze et al., 2018). The periventricular nodular heterotopias (PNH) along the frontal horns of the lateral ventricles observed in Proband 1 appear to be very similar to those found in Patient 7 described by Schanze et al. (2018). PNH, most often bilateral and symmetric, have been observed in several conditions. They are thought to result from loss of radial glial cell attachment to disrupted neuroependyma (Ferland et al., 2009). Classic PNH, occurring near or in the ventricular walls, are associated with mutations in *FLNA* and *ARFGEF2*, and are probably associated with vesicle trafficking and neuroependymal repair during neuron proliferation and intracellular transport (Ferland et al., 2009). They can occur in isolation or associated with other central nervous system (CNS) anomalies. It might well be that such PNH will prove more common than presently reported, as a number of described individuals have not undergone brain imaging. *NFIB* haploinsufficiency should be considered in the differential diagnosis of individuals with PNH, particularly bearing in mind the low penetrance of the phenotype.

Our Proband 1 also showed previously unreported spinal cord anomalies on MRI, including syringomyelia in the thoracic spinal cord and distal tract of the conus medullaris and slightly stretched appearance of the "filum terminale." Seemingly, bilateral short fourth metatarsal with nail dysplasia, and widely spaced toes, observed in Proband 2, have not been previously reported, although such features might well be secondary to an associated autosomal dominant disorder. As far as we know, no other family members were reported to have similar anomalies.

All reported findings expand the spectrum of structural brain/spinal cord and physical anomalies associated with *NFIB* haploinsufficiency and highlight the value of performing MRI in such individuals.

Minor heart defects similar to those observed in our Proband 1 have also been reported in 5 out of the 17 individuals reported by Schanze et al. (2018).

The Proband 2's milder MRI anomalies may represent the disorder's variable expressivity in this family.

The clinical spectrum of *NFIB*-related conditions will continue to evolve as new individuals are properly studied. Special attention should be given to the neuropsychological data, and brain/spinal MRI findings, including malformations of cortical and spinal cord development. Thereafter, genotype–phenotype correlations can be developed to help physicians provide anticipatory guidance to both the affected individuals and their families in the future.

In conclusion, the reported family adds to the knowledge of this rare disorder through the addition of new brain and spinal cord MRI findings and dysmorphic features, and showing its variable expressivity.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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