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Letter to the editor

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BPTF-associated Neurodevelopmental Disorder Masquerading as Leukodystrophy

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Nucleosome remodeling factor (NURF), the largest subunit of which is bromodomain PHD finger transcription factor (BPTF), is part of the imitation switch chromatin remodeling complex. NURF complexes have been shown to catalyze adenosine triphosphate-dependent nucleosome sliding, promoting chromatin transcription and impacting various genes [1]. BPTF plays a role in both cancer development and T-cell function, and its involvement in multiple pathways has been extensively documented [2,3]. In humans, *BPTF* haploinsufficiency results in a neurodevelopmental disorder that presents with dysmorphism and abnormalities of the distal limb. This syndrome is known as neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (NEDDFL). Additional clinical features commonly observed include postnatal microcephaly, speech delay, seizures, and scoliosis [4]. In this report, we present a case involving a novel variant of the *BPTF* gene, marked by developmental delay, dysmorphism, and a leukodystrophy-like pattern on neuroimaging.

A 2-year-old boy presented with global developmental delay. He was born to a non-consanguineous couple, and the antenatal and postnatal courses were uneventful. The patient had no history of seizures, regression of milestones, or family history of similar conditions. He achieved neck control at 5 months, sat with support at 9 months, and stood with support at 14 months. At present, he can scribble. However, he has not yet developed a pincer grasp and can speak only in monosyllables. Stranger anxiety developed at 8 months, and he began to wave goodbye by 9 months. Anthropometric measurements indicated growth faltering, with weight, height, and weight-for-height all below the −2 standard deviation (SD) mark, and head circumference below −3 SD. The child exhibited facial dysmorphism, including a prominent nasal bridge, bulbous nasal tip, and clinodactyly of the fifth toe (Supplementary Fig. 1A-C). Neurological examination revealed strabismus, drooling, increased muscle tone in the bilateral upper and lower limbs, and brisk deep tendon reflexes. No skeletal abnormalities were apparent. The general physical examination of the child's parents was unremarkable, except for a sandal gap deformity noted in the mother (Supplementary Fig. 1D). The written informed consent was obtained from his parents. The parents exhibited no dysmorphic features, and their neurological examinations were normal. The patient's mother, a 30-year-old woman with an average

build, had unremarkable birth, developmental, and obstetric histories. Bilaterally, her muscle tone, deep tendon reflexes, and muscle power (for all muscle groups) were normal. The mother's pedigree is shown here .

Brain magnetic resonance imaging (MRI) of the child showed bilateral symmetrical T2 hyperintensity in the periventricular and deep white matter, as well as in the centrum semiovale. The corpus callosum, basal ganglia, and infratentorial structures were not affected (Fig. 1). Given these MRI findings, the possibility of leukodystrophy or neurometabolic disorder was considered. Subsequent next-generation sequencing (whole exome and whole mitochondrial genome) identified a heterozygous variant c.7178C>T (p.Ser2393Leu) in exon 21 of the *BPTF* gene, with transcript number ENST00000306378.11. This novel variant is classified as a variant of uncertain significance according to American College of Medical Genetics guidelines. It has not been previously reported in the 1000 Genomes Project, gnomAD v3.1, gnomAD v2.1, or TOPMed databases.

Haploinsufficiency due to variants in *BPTF* has been suggested as the underlying cause of NEDDFL. Stankiewicz et al. [5] were the first to describe this syndrome, establishing its autosomal dominant pattern of inheritance. The condition affects the central nervous system, bones, eyes, and craniofacial structures and is associated with growth impairment. Key characteristics include developmental delay across all domains, intellectual disability, seizures, and various skeletal abnormalities. These skeletal issues encompass scoliosis, distal limb defects, spinal anomalies, limb length discrepancies, and delayed bone age [5]. In one report, Midro et al. [6] reported vertebral abnormalities, including scoliosis, as well as limb defects. Ophthalmological features, such as strabismus and myopia, are observed in approximately 57% of cases, with one patient also presenting with cataracts and hypertropia. Reported craniofacial anomalies include microcephaly, micrognathia, and prominent nose. Some research indicates that *BPTF* is involved in the formation of mesoderm, endoderm, and differentiated ectoderm lineages, as well as in establishing the antero-posterior axis during early development, which may explain the skeletal abnormalities [7]. *BPTF* haploinsufficiency is associated with neuronal death, which results in microcephaly and neurological abnormalities [5,8]. *BPTF* also plays a crucial role in regulating progenitor differentiation and activating determinants for key cortical neuron subtypes [9]. The mechanisms underlying the observed growth delay and skeletal abnormalities remain unclear. Wu and Chen [10] noted a positive response to recombinant human growth hormone treatment in patients with short stature due to *BPTF* mutation.

To our knowledge, only 38 cases of *BPTF* variants have been reported worldwide. Our case involved a patient presenting with global developmental delay and dysmorphism. The literature describes various MRI brain changes associated with this condition, including thickening of the sella turcica, hyperintensities in the periventricular white matter, and asymmetry of the lateral horn of the right ventricle. In the present case, brain MRI performed during the diagnostic examination raised suspicion of leukodystrophy. Next-generation sequencing revealed a novel variant in the *BPTF* gene, which has not been previously reported. This variant has been documented as displaying incomplete penetrance [4]. In our case, the novel variant—c.7178C>T (p.Ser2393Leu) in exon 21 of the *BPTF* gene—was detected in the mother, but no variant was identified in the father. Distal limb deformities, including a sandal gap, have been previously reported and were observed in both the index case and the mother. Notably, the neurodevelopmental delay associated with *BPTF* mutation can present with a neuroimaging pattern that resembles leukodystrophy. This case highlights the importance of genetic studies and maintaining a high index of suspicion for such variants in cases of dysmorphism with developmental delay.

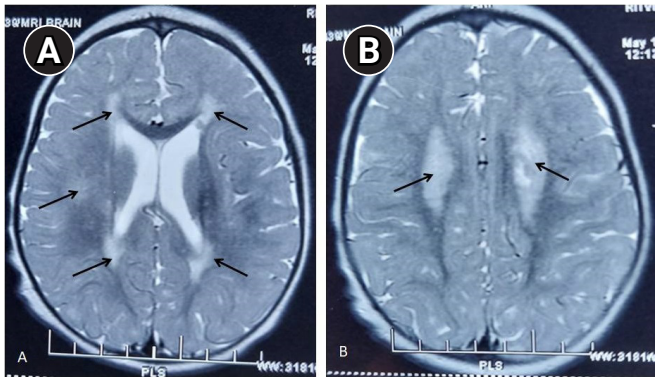

Fig. 1. Magnetic resonance imaging features associated with bromodomain PHD finger transcription factor (*BPTF*) mutation. A T2-weighted axial image displays symmetrical hyperintense signals (arrows) involving the bilateral periventricular and deep white matter at the level of the lateral ventricles (A), as well as symmetrical hyperintense signals (arrows) in the bilateral centrum semiovale (B).

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2023.00402.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contribution

Conceptualization: AW. Data curation: AB, AW, AKM, SP, and PKC. Formal analysis: AKM. Project administration: AW and AKM. Visualization: AKM and PKC. Writing - original draft: AB. Writing - review & editing: SP.

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