Letter to Editor

Trinucleotide repeat containing adaptor 6B protein deficiency syndrome – A rare cause for language delay and attention deficit hyperactivity disorder

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To the Editor,

Trinucleotide repeat containing adaptor 6B protein (TNRC6B) deficiency syndrome, caused by a mutation in the *TNRC6B* gene, is a very rare autosomal dominant neurodevelopmental disorder with a broad spectrum of clinical features. The *TNRC6B* gene encodes a protein involved in gene silencing through the microRNA pathway, which is crucial for regulating gene expression during development. Key clinical features are global developmental delay, intellectual disability, autism spectrum disorders (ASD), and attention-deficit hyperactivity disorder (ADHD). Speech and language delays are particularly prominent, ranging from mild impairment to severe expressive and receptive language difficulties.

A 15-year-old girl presented to the neurology outpatient department with global developmental delay, subnormal intelligence, ADHD, expressive language disorder, and learning disorder. She had a few episodes of generalized tonic-clonic seizures in childhood and was responsive to anti-seizure medication and was successfully tapered off after 3 years of seizure freedom. On examination, a mild level of intellectual disability (50% disability, predicted IQ score – 57, Binet–Kamat intelligence scale IQ – 46 [1], Vineland social maturity scale score – 63 [2] was observed. There was no facial dysmorphism. There were no neurocutaneous markers. Her basic workup, including thyroid function tests, urine, and serum aminogram, was normal. Her electroencephalogram and magnetic resonance imaging of the brain were normal. In view of a significant language disorder, clinical exome sequencing was ordered, which showed a heterozygous missense variant in exon 5 of the *TNRC6B* gene (chr22:g.40266716C>T; Depth: ×150) that results in the amino acid substitution of leucine for proline at codon 829 (p.Pro829Leu; ENST00000454349.7). This mutation has not been reported so far in the available literature.

Key clinical features are global developmental delay, noticeable in infancy or childhood. Most affected individuals have mild-to-moderate intellectual disability. Learning difficulties are prominent and persist into adolescence and adulthood. ASD traits, including poor social interaction and repetitive behaviors, are frequently observed. Hyperactivity, attention deficits, and anxiety may also be present. Epilepsy has been reported in a few patients and often responds to standard anti-seizure medications. Some affected individuals may have subtle facial dysmorphisms, which include a high forehead, flat nasal bridge, or thin upper lip. Mild skeletal anomalies or joint hypermobility are seen in some cases. Some patients can have gastrointestinal symptoms such as constipation and reflux. Magnetic resonance imaging findings can include delayed myelination, enlarged ventricles or cortical atrophy, though some individuals have normal imaging [3,4].

In a series of 506 patients with neurodevelopmental disorders, 197 (38.9%) had positive molecular testing. Of these 69 patients (35%) had autosomal dominant inheritance [5]. To date, only 19 variants in the TNRC6B gene have been reported in patients with TNRC6B deficiency syndrome. The 19 variants identified include two large exons deletions, nine nonsense variants, four frameshift variants, two splicing variants, and two missense variants. There are only 23 cases reported to date, and clinical features will evolve as more and more cases are reported [6]. TNRC6B deficiency syndrome is probably under-detected, and it is suggested to do next-generation sequencing in cases of primary global developmental delay with ASD or ADHD, especially with significant language disorders [7].

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