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Letter to the Editor

Comments on: Novel Variant in the MYT1L Gene Shared by Three Individuals with Neuropsychiatric and Neurodevelopmental Manifestations in a Family

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Letter to the Editor

We read with interest the article by Varghese *et al.* on a case study of three patients with MYT1L syndrome (Patient 1: 50-year-old man, Patient 2: 22-year-old woman, Patient 3: 17-year-old woman) due to the homozygous c.2612A>C variant in the MYT1L gene [1]. All three patients only partially met the diagnostic criteria for MYT1L syndrome (Table 1). Furthermore, they exhibited marked phenotypic heterogeneity, resulting in a low genotype-phenotype correlation [1]. The study is promising, but several points should be discussed.

Table 1: Clinical presentation of the three reported patients with MYT1L syndrome

Core phenotype of MYT1L syndrome	Patient 1	Patient 2	Patient 3
Neurodevelopmental delay	no	yes	no
Cognitive impairment	yes	yes	no
Behavioural abnormalities (ASD, ADHD, aggression, impulsivity)	yes	yes	yes
Obesity, hyperphagia	no	no	no
Epilepsy	yes	no	no
Hypotonia	no	no	no
Microcephaly	no	no	no
Facial dysmorphism	no	no	no
Feature atypical for MYT1L syndrome	Parkinsonism, episodes of fever, confusion, stiffness, incontinence, hallucinations, presumed MNS	Tracheo-esophageal fistula, lithium induced hypothyroidism, presumed MNS	catatonia

First, it was not explained why all three patients presented with clinical features that are not usually typical of MYT1L syndrome [1]. MYT1L syndrome is typically characterized by developmental delays, particularly in speech and motor development, severe learning disabilities, cognitive impairment, autism spectrum disorder (ASD), ADHD, emotional instability, aggression, extreme impulsivity, premature weight gain, hyperphagia, compulsive eating, seizures, hypotonia, microcephaly, strabismus, cortical visual impairment, and facial dysmorphism (long chin, upward-pointing eyes, broad nasal tip) (Table 1) [2]. Was the parkinsonism in Patient 1 a consequence of long-term neuroleptic therapy? Was the DATSCAN scan indicative of Parkinson's disease? Did the patient require L-Dopa and respond to this medication?

The second point is that the phenotypic heterogeneity was not sufficiently explained [1]. The apparent phenotypic heterogeneity among the three patients could be explained by: the presence of polymorphic genes that enhance, suppress, or completely alter the effect of the primary mutation; DNA methylation or histone acetylation, which can regulate gene expression without altering the DNA sequence; microecological factors such as local pH, temperature, nutrition, and exposure to the host's immune response; random variations in the timing and rate of transcription and translation; metabolic state, cell cycle phase, and individual cell history [3].

The third point is that none of the three patients underwent testing for a second genetic disorder. Since there was consanguinity between the parents of Patient 1, chromosome analysis would also have been appropriate. Furthermore, the diagnosis of a tracheoesophageal fistula in Patient 2 suggests that they have an additional chromosomal defect.

The fourth point concerns the lack of in-depth investigations to confirm the pathogenicity of the identified MYT1L variant [1].

Confirming the pathogenicity of a genetic variant requires a standardized, evidence-based approach that combines population data, computational predictions, medical history, and functional assays. Clinical laboratories and geneticists typically follow the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology^[4].

The fifth point concerns the elevated serum creatine kinase in patient 2 (1983 U/L), which was not adequately explained. It should be clarified whether this patient suffered from seizures, neuroleptic malignant syndrome, rhabdomyolysis, myopathy, trauma, or ADHD. Was the creatine kinase level repeatedly elevated or only once?

In conclusion, patients with an atypical MYT1L syndrome phenotype require further genetic testing. Similarly, the pathogenicity of a MYT1L variant must be confirmed by functional assays before it can be identified as the cause of MYT1L syndrome. Furthermore, the phenotypic heterogeneity of the three family members should be explained.

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