The first siblings with TRAPPC6B mutation

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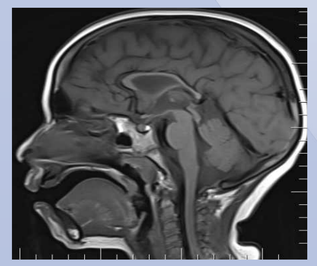
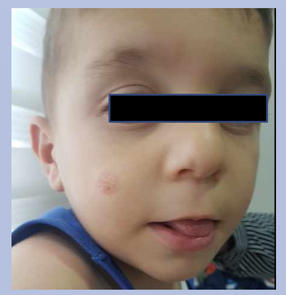
INTRODUCTION

Intellectual disability (ID) is a clinically diverse and genetically heterogeneous group of disorders with a total prevalence of 1–3%, around the global population. Although the identification of the genetic etiology underlying autosomal dominant ID still remains elusive. The diagnosis yield of ID-causing genes in consanguineous families is higher.

OBJECTIVES

Herein, we report two Turkish siblings from consanguineous parents with homozygous nonsense mutation of the TRAPPC6B gene.





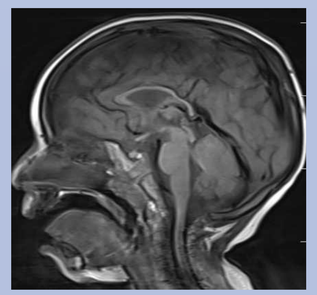


Figure 1

Figure 2

MATERIALS & METHODS

Case 1

A Turkish boy was presented with autistic features and developmental delay at the age of 1 year and 10 months. Pregnancy and delivery were unremarkable, and his family history is remarkable with a cousin's marriage between his parents and developmental delay in one of her sisters and cousins. A physical and neurologic examination revealed minor dysmorphic features as including low-set ears, broad nasal bridge and down-slanted eyes with gait disturbance. Significant developmental delay was detected in speech and motor skills in Denver Developmental Screening Test-II (DDST-II). Laboratory analysis revealed no abnormalities in blood chemistry, including normal levels of ammonia, and tandem mass spectrometry of the blood produced negative results for organic acid and revealed no acylcarnitine profile abnormalities. Similarly, her blood lactate and pyruvate, plasma carnitine, blood and urine amino acids, and urine organic acids were all normal. Cranial magnetic resonance imaging revealed white matter volume loss, thin corpus callosum and and periventricular millimetric calcifications. The patient was initially tested for interferonopathies, but no mutations were identified. Whole exome analysis revealed a homozygous mutation c.32A>G pH11R (NM001079537.1) in the *TRAPPC6B* gene. His parents were also carriers for the same mutation.

Case 2

A homozygous mutation in the *TRAPPC6B* gene was encountered in a *TRAPPC6B* gene sequencing that was performed since the index case's 5-year-old sister had a similar history.

Discussion:

The TRAPP (transport protein particle) protein family is involved in membrane trafficking, autophagy and mitosis and was recently reported as a cause of ID. The common features of the cases are global developmental delay, microcephaly, epilepsy, brain atrophy, autistic features and early onset generalized epilepsy. Although TRAPP mutations have been reported in patients with mutations in TRAPPC9, TRAPPC6A, TRAPPC6B and TRAPPC2L genes. Mutations in the TRAPPC6B gene have so far been reported in only a handful of families worldwide (8 cases). This is an extremely rare autosomal recessive disorder characterized by global developmental delay, severe intellectual disability and speech delay, microcephaly, stereotypic autistic traits, early-onset generalized seizures and thin corpus callosum on MRI.

Conclusion

The reported siblings show a phenotype of global developmental delay, intellectual disability with severe speech delay, volume loss in the white matter with periventricular millimetric calcifications and thin corpus callosum on MRI. Interestingly, our patient did not show any seizures and microcephaly which expands the clinical spectrum of TRAPPC6B related ID.