Two Turkish siblings with intellectual disability associated with TUSC3 mutation

İlknur Erol[1], Gökçe Yegül Gülnar[2], Elif Perihan Öncel[1] , Şeyda Beşen[1], Leman Tekin Orgun[1], Yavuz Şahin[3]

[1]Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Application and Research Center, Department of Pediatric Neurology, Adana, Turkey
[2]Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Application and Research Center, Department of Pediatrics, Adana, Turkey
[3]Genoks Genetic Diagnostic Center, Ankara, Turkey

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INTRODUCTION

Tumor suppressor candidate 3 (TUSC3) was first described in humans in 1996. TUSC3 constitutes a major component in cellular magnesium transport, which plays an important role in learning and memory. In recent years, homozygous mutations of TUSC3 gene which is a tumor suppressor gene, have been reported to be associated with autosomal recessive (AR) non-syndromic intellectual disability (ID) and behavioral disorders. With the advanced genetic techniques, disorders underlying the non-syndromic intellectual disability are more frequently identified. TUSC3 gene is a recently identified gene which is associated with ID.

As research data accumulates, hope for therapeutic targeting of TUSC3 protein to treat psychiatric and oncological diseases may be on the horizon. Therapeutic strategies may include recombinant gene therapy, targeting negative regulators of TUSC3, and targeting destabilized pro-oncogenic TUSC3 mutant.

OBJECTIVES

TUSC3 gene mutation related non-syndromic ID is inherited autosomal recessively and very rare. In this article, two siblings from Turkey are presented to emphasize that the effective use of new genetic diagnostic methods will prevent family relapses in societies like our country where consanguineous marriages are common.

CONTACT

Prof. Dr. İlknur EROL
e-mail: ilknur_erol@yahoo.com
Phone: +905053837661

CASE

9-year-old,male

Complaint:

- Developmental delay , speech delay

History: .

- Prenatal and natal history were unremarkable
- Consanguineous parents
- 10-year-old brother has similar developmental and clinical profile

Examination:

- He was able to follow only simple commands
- His attention was very scattered
- Other neurological examination was normal

Investigations:

- Normal serum lactate ,pyruvate, acylcarnitine, amino acid levels and urine organic acid analyses were normal
- Brain MRI : Retrovermian arachnoid cyst and vermian hypoplasia.
- EEG: Bilateral centrotemporal epileptic abnormality
- Karyotype : 46 XY , aCGH: Normal.
- WES: *c.426G>A(p.Gln142Gln) homozygous mutation in the TUSC3 gene*
- Heterozygous mutations in the TUSC3 gene were found in his parents, and homozygous in his brother.

DISCUSSION

Defects in the tumor suppressor candidate 3 (TUSC3) gene have been identified in individuals with autosomal recessive intellectual disability, resently. These cases presented with non-syndromic ID and psychiatric problems such as obsessions, anxiety, sleep and eating disorders have been reported. TUSC3 gene mutation-associated ID has been described in a small number of cases in the literature, Previous reports have shown that patients with biallelic TUSC3 mutations have moderate to severe ID with speech delay as the prominent features. These findings are consistent with the patients described in this report. Congenital anomalies, including syndactyly and undescended testis were observed in some of the reported cases. No congenital anomaly was observed in our patients. McSherry et al., reported first Turkish case with ID and TUSC3 mutations in 2018. In addition, Ozmansur et al., reported homozygous frameshift mutation in the TUSC3 gene identified in Turkish two sibling in 2022. Our cases are the fourth and fifth cases with TUSC3 mutation who have been reported from Turkey.

TUSC3 gene is also related to malinancies. Although at the time of assessment, there is no evidence of malignancy in our patients, we recommend the patient may be followed-up in later stages of his life. Since this effect is only observed in the homozygous case, his brother also need to be included in the follow-up program.

CONCLUSION

The protein encoded by TUSC3 localized to the endoplasmic reticulum, where it forms part of the multimeric oligosaccharyl transferase complex that is likely to be involved in post-translational glycosylation of selected proteins which are essential for normal brain development. Patients with homozygous TUSC3 mutations have moderate to severe ID with speech delay. Cases presented with psychiatric problems such as obsessions, anxiety, sleep and eating disorders have been reported. TUSC3 gene mutation-associated ID has been described in a small number of cases in the literature, and only two siblings has been reported from Turkey.

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