TRAPPC9-related intellectual disability: report of two new cases

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INTRODUCTION

Intellectual disability (ID) affects approximately 1-3% of the general population and is a major socioeconomic problem. In countries such as Turkey where parental consanguinity is common, autosomal recessive gene defects are the most common form of ID. However, very little is revealed about causative genes and genotype–phenotype associations in autosomal recessive ID (AR-ID).

Hence, only up to 60% of patients get a precise genetic diagnosis due to this genetic heterogeneity and the lack of specific phenotypic features Trafficking protein particle complex subunit 9 gene (TRAPPC9; OMIM# 611966) plays a critical role in the neuronal NF-kB signaling pathways and is one of the numerous genes involved in the AR-ID. Patients with pathogenic biallelic mutations of TRAPPC9 have been manifested as ID, developmental delay (DD), microcephaly, autistic features and brain abnormalities on MRI investigations.

OBJECTIVE

Here, we described two unrelated patients with ID, microcephaly, autistic features, and identified three novel mutations in TRAPPC9. Also, we reviewed the clinical findings and mutation spectrum of the reported patients with TRAPPC9-related ID so far.

METHODS

Karyotyping and Array-CGH Analyses

Cytogenetic analysis was performed on GTG-banded chromosomes from circulating leukocytes using a standard protocol. Array-CGH was performed using a 60 K whole-genome oligonucleotide microarray following the manufacturer's protocol (Human Genom CGH Microarray, 60K, Agilent Inc.).

Whole-exome sequencing (WES) Studies

WES for the patient was performed for Case 2. Twist® Human Core Exome kit was used for enrichment. ACMG 2015 guideline was used for variant evaluation

Sanger Sequencing

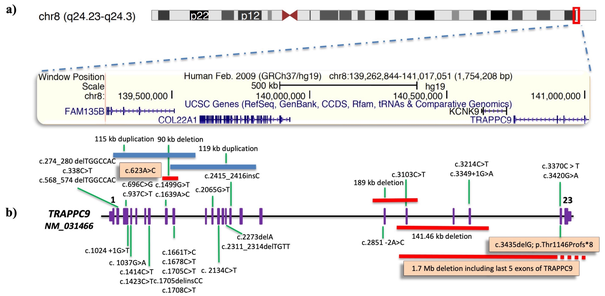
All coding exons and flanking intronic sequences of TRAPPC9 gene were sequenced by Sanger sequencing for case 1. Parental segregation of the homozygous mutation in the case 2 was confirmed by sanger sequencing.

RESULTS

Case 1: 9 years-old female patient, was admitted to our clinic with complaints of microcephalia , mental and motor retardation. Her head control was at 3 months of age, and she could sit without support at 7 months-old, walked without support at 5 years old and could only say 4-5 single words. Brain MRI showed thinning of posterior body part of the corpus callosum and several areas of T2 hyperintensity in the periventricular white matter .

Case 2: 11 years old girl admitted with autistic features, and ID. She had normal mental and motor development until 7 months-old of age. At 7 months old, there was a seizure history following. At the 15th month, the family noticed that the child still couldn't walk, and add new words as well as inattentive behavior.

Brain MRI showed thin corpus callosum, widened lateral ventricles seconder to central cerebral atrophy and periventricular ischemic white matter changes.



First case has a microdeletion on chromosome 8q24.23-q24.3 region which is 1.7 Mb in length and included the last 5 exons of TRAPPC9 , and c.3435delG [p.Thr1146Profs*8] deletion. Second case has a homozygous missense c.623A>C (p.His208Pro) variant in TRAPPC9 gene which is detected by means of whole exome sequencing study of the proband. We also reviewed the clinical findings and mutation spectrum of the all patients with TRAPPC9-related ID reported so far (**Figure**).

CONCLUSION

We described two cases three novel mutations in TRAPPC9 gene and reviewed the clinical findings and mutation spectrum of the all 60 patients reported so far. It is showed that most consistent clinical findings for TRAPPC9-related ID are ID/DD, microcephalia, and brain MRI abnormalities such as thin corpus callosum and white matter signal changes. The mutation in the TRAPPC9 gene are scattered throughout the all exons of TRAPPC9 gene indicating there is no hot spot mutation region in this gene and every exon have critical role for properly functioning of TRAPPC9 gene.

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