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ORIGINAL ARTICLE

Identification of two novel homozygous nonsense mutations in *TRAPPC9* in two unrelated consanguineous families with intellectual Disability from Iran

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ABSTRACT

Background: Pathogenic mutations in *TRAPPC9* are associated with autosomal recessive Intellectual Disability (ID), a major public health issue that affects about 1–3% of children worldwide.

Method: Clinical evaluation, magnetic resonance imaging, peripheral blood karyotype, Multiplex ligation-dependent probe amplification (MLPA), array CGH, and whole-exome sequencing were used to characterize etiology in three patients from two unrelated consanguineous families of Iranian descent with intellectual disability.

Results: Whole-exome sequencing showed two novel homozygous nonsense mutations (c.937C>T) in exon 3 and (c.3103C>T) in exon 19 of *TRAPPC9* (NM_031466.7) in two unrelated consanguineous families.

Conclusion: The two novel variants found in *TRAPPC9* caused truncated protein and clinical manifestations such as ID, developmental delay, microcephaly, and brain abnormalities in three patients.

KEYWORDS

intellectual disability, Iran, nonsense mutation, *TRAPPC9*

1 | INTRODUCTION

Intellectual disability (ID) is a neurodevelopmental disorder, characterized by considerable limitation of intellectual functioning, adaptive behavior, or daily living skills, and with an onset before 18 years of age (Heidari et al., 2015). It is one of the most important challenges in health care, with significant life-long socioeconomic burden. ID is genetically heterogeneous and may result from chromosomal aberrations, or from either autosomal recessive (AR), autosomal dominant, X-linked, or mitochondrial mutations. With the prevalence of ~1% of children worldwide (Maulik et al., 2011; Musante & Ropers, 2014), ID can be divided into two main groups: nonsyndromic (NS) ID, where it might display the sole clinical feature, and syndromic ID, where additional clinical or dysmorphological features may also be present. Over the past few years, next-generation sequencing technologies have led to the identification of a number of ID-associated genes, emphasizing the considerable genetic heterogeneity of ID.

Trafficking protein particle complex subunit 9 gene (*TRAPPC9*; OMIM# 611966) plays an important role in the neuronal NF-kB signaling pathways and is one of the numerous genes involved in the nonsyndromic form of ID (MIM