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Two adult Moroccan women with phenotypes suggestive of TRRAP-related neurodevelopmental disorder carrying TRRAP variants of uncertain significance: a case report of two patients

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ABSTRACT

Background: Heterozygous TRRAP variants have been associated with a neurodevelopmental disorder characterized by developmental delay or intellectual disability, epilepsy, dysmorphic features, and variable congenital anomalies. Most established cases involve de novo missense variants, whereas the contribution of truncating variants remains uncertain. We describe two adult Moroccan women with suggestive phenotypes and TRRAP variants of uncertain significance (VUS).

Case presentation: Patient 1, aged 21 years, had syndromic intellectual disability, attention-deficit/hyperactivity disorder (ADHD), facial dysmorphism, digital anomalies, white-matter abnormalities, renal malrotation with hydronephrosis, and a bicornuate bicervical uterus. Exome sequencing identified a novel heterozygous frameshift variant, c.4796dup, p.(Leu1599PhefsTer63). Patient 2, aged 30 years, had syndromic intellectual disability, epilepsy controlled with sodium valproate, congenital atrial and ventricular septal defects, facial dysmorphism, and mild ventriculomegaly. Exome reanalysis identified the heterozygous missense variant c.2686G>A, p.(Gly896Ser). Both variants were classified as VUS, and parental testing was unavailable.

Conclusion: The phenotypic overlap supports considering these variants as candidate contributors but does not establish TRRAP-related disease. Segregation and functional studies are required. The second case also illustrates the value of exome reanalysis.

Keywords: TRRAP, neurodevelopmental disorder, frameshift, whole exome sequencing, intellectual disability, case report

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Introduction

The TRRAP gene encodes transformation/transcription domain-associated protein, a large pseudokinase scaffold involved in histone-acetyltransferase complexes and transcriptional regulation. Heterozygous TRRAP variants have been associated with an autosomal dominant neurodevelopmental disorder characterized by developmental delay or intellectual disability, autism spectrum disorder, epilepsy, dysmorphic features, and, in some individuals, congenital anomalies. Most established cases involve de novo missense variants, and the contribution of truncating variants remains uncertain [1–4]. We describe two unrelated adult Moroccan women with syndromic intellectual disability and TRRAP variants classified as variants of uncertain significance (VUS), including a novel frameshift variant and a missense variant identified through exome reanalysis.

Case presentation 1

A 21-year-old woman born at term to non-consanguineous parents after an uneventful pregnancy was referred for syndromic intellectual disability, learning difficulties, and ADHD. Examination showed hypertelorism, upslanting palpebral fissures, a broad nasal bridge, long philtrum, thin upper lip, wide mouth, micrognathia, prominent forehead, fifth-finger clinodactyly, brachydactyly, digital clubbing, and flat feet. She had no seizures or family history of a similar condition.

Brain magnetic resonance imaging (MRI) showed a few small, predominantly left frontoparietal white-matter lacunar defects. Abdominopelvic ultrasonography demonstrated moderate right hydronephrosis in a malrotated kidney without an identified obstruction and a bicornuate bicervical uterus. Echocardiography, macular optical coherence tomography, and auditory evoked potentials

were normal. Karyotyping and chromosomal microarray were non-diagnostic.

The combination of syndromic intellectual disability, dysmorphic features, and renal and Müllerian anomalies, together with non-diagnostic karyotyping and chromosomal microarray, prompted investigation for a monogenic disorder using whole-exome sequencing (WES).

WES, aligned to Genome Reference Consortium Human Build 37 (GRCh37)/hg19 with 98% of targeted regions covered at least 20×, identified the heterozygous TRRAP variant NM_001375524.1:c.4796dup, p.(Leu1599PhefsTer63), which was confirmed by Sanger sequencing. The variant was absent from gnomAD v4.1.0, ClinVar, and DECIPHER v11.36 and was classified as a VUS. Parental samples were unavailable; therefore, inheritance and de novo status could not be determined.

Case presentation 2

A 30-year-old woman was born at term to non-consanguineous parents after a pregnancy complicated by fetal growth restriction. Her birth weight was 2,200 g. Neonatal distress and transient generalized hypotonia were reported. Congenital atrial and ventricular septal defects were diagnosed. Psychomotor delay and intellectual disability were subsequently recognized. Epileptic seizures began at 14 months and were satisfactorily controlled with sodium valproate.

Examination showed external-ear malformations, a long philtrum, downslanting palpebral fissures, hooded eyelids, and strabismus. There was no family history of a similar phenotype. Electroencephalography showed rare diffuse, synchronous, sporadic multifocal slow spikes. Childhood neuroimaging demonstrated mild ventriculomegaly. MRI at 28 years showed a 16-mm Rathke cleft cyst, and spinal radiographs showed lumbosacral transitional anatomy; the clinical relevance of these additional findings is uncertain. Thyroid function, plasma phenylalanine, and karyotyping were normal.

The combination of intellectual disability, early-onset epilepsy, dysmorphic features, and congenital heart defects, together with non-diagnostic biochemical and cytogenetic investigations, prompted WES. Because the initial analysis was non-diagnostic, subsequent reanalysis was undertaken.

WES, aligned to GRCh37/hg19 with more than 98% of targeted bases covered at least 30×, was initially non-diagnostic. Reanalysis two years later identified the heterozygous TRRAP missense variant NM_001375524.1:c.2686G>A, p.(Gly896Ser), which was confirmed by Sanger sequencing and classified as a VUS. Parental samples were unavailable; therefore, inheritance and de novo status could not be established.

No disorder-specific treatment was initiated for Patient 1. Patient 2 remained on sodium valproate, initiated after seizure onset at 14 months of age, with satisfactory seizure control and no reported treatment-related adverse effects. No variant-directed treatment was initiated in either patient.

Variant interpretation

The diagnostic laboratory reports classified both variants as variants of uncertain significance but did not provide the underlying ACMG/AMP evidence codes. We therefore reassessed the available evidence using the ACMG/AMP framework [5]. For the c.4796dup, p.(Leu1599PhefsTer63) variant, PM2_Supporting was applied because the variant was absent from population databases. PVS1 was not applied because loss of function and haploinsufficiency are not currently established disease mechanisms for TRRAP, for which ClinGen reports limited evidence of haploinsufficiency [4]. For the c.2686G>A, p.(Gly896Ser) variant, PM2_Supporting was applied because of its extreme rarity in population databases [6]. Although computational predictions suggest a deleterious effect, this evidence was not considered sufficient to support pathogenicity. For both variants, de novo criteria (PS2/PM6), segregation evidence (PP1), and functional evidence (PS3) were unavailable; PP4 was not applied because the clinical phenotypes were not sufficiently specific. Consequently, each variant meets only PM2_Supporting and remains classified as a VUS.

Clinical timeline

Patient 1: Uneventful term birth → childhood learning difficulties, intellectual disability, and ADHD → syndromic evaluation at 21 years → non-diagnostic karyotype and chromosomal microarray → WES identification of TRRAP c.4796dup, p.(Leu1599PhefsTer63), confirmed by Sanger sequencing and classified as a VUS.

Patient 2: Prenatal growth restriction and congenital heart defects → epilepsy onset at 14 months → mild ventriculomegaly identified at 7 years → adult genetic evaluation → initially non-diagnostic WES → reanalysis two years later identifying TRRAP c.2686G>A, p.(Gly896Ser), confirmed by Sanger sequencing and classified as a VUS.

Discussion

TRRAP-associated neurodevelopmental disorder was initially delineated mainly through de novo missense variants. Reported manifestations include developmental delay or intellectual disability, autism spectrum disorder, epilepsy, facial dysmorphism, and variable brain, cardiac, renal, and genitourinary anomalies. Two broad patterns have been proposed: a multisystem presentation and a predominantly neurodevelopmental or epilepsy-associated presentation. However, phenotypic overlap occurs, and the evidence supporting individual variants must be evaluated independently [2].

Patient 1 shares neurodevelopmental, craniofacial, renal, and Müllerian features with the reported multisystem phenotype. Her novel frameshift variant is predicted to introduce a premature termination codon; however, its effect on TRRAP transcript stability or protein expression has not been experimentally assessed. Furthermore, ClinGen reports only limited evidence for TRRAP haploinsufficiency, and the established disease association is based predominantly on missense variants. In addition, segregation and functional studies were unavailable. The frameshift variant must therefore remain a VUS and should be regarded only as a candidate contributor to the phenotype [2,4,5].

Patient 2 shares intellectual disability, epilepsy, facial dysmorphism, and congenital cardiac defects with previously reported TRRAP-associated phenotypes. The p.(Gly896Ser) variant is rare, and computational predictions suggest a deleterious effect. However, computational evidence and phenotypic similarity alone are insufficient to establish pathogenicity. The variant therefore remains a VUS [5,6]. The Rathke cleft cyst and lumbosacral transitional anatomy may be incidental and should not currently be considered extensions of the TRRAP-associated spectrum. This case also illustrates the value of periodic exome reanalysis in individuals with unresolved syndromic intellectual disability.

The most important limitation of this report is the absence of parental testing in both families. Parental samples were unavailable, preventing assessment of segregation and confirmation or exclusion of de novo occurrence. This limitation is particularly important because TRRAP-associated neurodevelopmental disease is generally inherited in an autosomal dominant manner, and many reported disease-associated variants have occurred de novo. Phenotypic similarity alone cannot establish the pathogenicity of either variant. Furthermore, no functional studies were performed, and in silico predictions cannot substitute for genetic or experimental evidence. Both variants therefore remain VUS. Functional studies assessing transcript stability and TRRAP expression could test whether the c.4796dup variant results in nonsense-mediated decay [2,5].

Conclusion

These two patients have phenotypes suggestive of TRRAP-related neurodevelopmental disorder and carry TRRAP VUS. The novel frameshift variant identified in Patient 1 may be a candidate contributor to her multisystem phenotype, while the identification of the missense variant in Patient 2 illustrates the value of exome reanalysis for detecting candidate variants. However, neither finding establishes a molecular diagnosis. Parental segregation and functional studies are required before either variant can be considered disease-causing.

A formal patient perspective was not obtained from either patient.

What is new?

This report describes two adult Moroccan women with phenotypes suggestive of TRRAP-related neurodevelopmental disorder who carry TRRAP variants of uncertain significance. It highlights a novel frameshift variant as a candidate contributor to a multisystem phenotype and illustrates the value of exome reanalysis, while emphasizing the need for segregation and functional studies.

List of Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ClinGen	Clinical Genome Resource
DECIPHER	Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources
gnomAD	Genome Aggregation Database
GRCh37	Genome Reference Consortium Human Build 37
hg19	human genome build 19
MRI	Magnetic resonance imaging
TRRAP	Transformation/transcription domain-associated protein
VUS	Variant of uncertain significance
WES	Whole-exome sequencing
ACMG/AMP	American College of Medical Genetics and Genomics/Association for Molecular Pathology

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent was obtained from the patients for anonymized patient information to be published in this article.

Ethical approval

Written informed consent was obtained from the patients for their anonymized information to be published in this article. This case report contains no identifiable information about the patients. Our institution does not require ethical approval for reporting individual cases or case series.

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Summary of the case

		Case 1	Case 2
1	Patient (gender, age)	21-year-old woman	30-year-old woman
2	Clinical diagnosis	Syndromic intellectual disability with dysmorphic, digital, renal, and Müllerian anomalies; heterozygous TRRAP VUS identified.	Syndromic intellectual disability with epilepsy, dysmorphic features, and congenital heart defects; heterozygous TRRAP VUS identified
3	Main findings	Intellectual disability, ADHD, facial dysmorphism, digital anomalies, hydronephrosis in a malrotated kidney, and bicornuate bicervical uterus	Intellectual disability, epilepsy, transient neonatal hypotonia, atrial and ventricular septal defects, facial dysmorphism, and mild ventriculomegaly
4	Medications	No disorder-specific treatment	Sodium valproate since seizure onset, with satisfactory seizure control and no reported adverse effects
5	Diagnostic procedures	Karyotyping, chromosomal microarray, WES, and Sanger confirmation	Karyotyping, biochemical investigations, WES with reanalysis after two years, and Sanger confirmation
6	Specialty	Medical genetics; multidisciplinary care as clinically indicated	Medical genetics, neurology, and multidisciplinary care as clinically indicated