Cureus
Part of SPRINGER NATURE

Open Access Case Report

A Novel Variant in Transformation/Transcription Mediator-Associated Protein (TRRAP) at a Known Hot Spot Causing a Blended Phenotype: Implications for Further Research

Review began 10/15/2026
Review ended 11/04/2026
Published 11/10/2026

© **Copyright** 2026
Patel et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.119423

Devanshi Patel [1], Richard Sidlow [2]

1. Medical School, University of Missouri School of Medicine, Columbia, USA 2. Medical Genetics and Metabolism, Valley Children's Hospital, Madera, USA

Corresponding author: Devanshi Patel, dnp7nr@umsystem.edu

Abstract

The transformation/transcription mediator-associated protein, or TRRAP, is a crucial component of gene expression regulation and transcription. This protein acts as a cofactor for histone acetyltransferases, allowing the regulated progression of the cell cycle, which is crucial for early neural development. We report on a young male patient with a previously unreported variant in the TRRAP gene whose phenotype is similar to that of patients with other previously reported TRRAP-related neurodevelopmental disorders. We compare and contrast this patient's presentation with other reported cases and argue for the pathogenicity of this variant of uncertain significance. This variant may also support the pathogenicity of a hotspot region within the TRRAP gene, and we argue for adding this variant to the list of syndrome-causing variants.

Categories: Neurology, Genetics, Pediatrics
Keywords: autism spectrum disorder (asd), chromatinopathy, intellectual disability (id), neurodevelopmental disorder, pediatric genetics

Introduction

The transformation/transcription mediator-associated protein (TRRAP), a member of the ataxia-telangiectasia mutated superfamily, is crucial for the regulation of gene expression and transcriptional activation [1]. As a cofactor for histone acetyltransferase (HAT), TRRAP helps control cell cycle progression through interactions with other proteins, such as c-MYC and E2F [2]. TRRAP recruits the HAT complex to acetylate histone proteins around transcription factors, allowing selected genes to be transcribed [2]. This process is essential for early neural development [2].

TRRAP is among the most conserved gene sequences, with little tolerance for variation, and is broadly expressed [3,4]. Null mutations in TRRAP-knockout mice resulted in peri-implantation lethality because the blastocysts were unable to proliferate correctly [5]. Cell cycle errors and failure to stop at mitotic checkpoints underlie this lethality [6]. TRRAP knockout in zebrafish resulted in similar malformations, including a reduced number of hair cells per neuromast, abnormal stereocilia on the hair cells, and fewer lateral neuromasts [6].

Similar profound embryonic-stage anomalies have also been observed in humans, with mutations in TRRAP tending to affect brain, facial, and skeletal development [1,7]. Embryos examined at approximately 18 days of embryonic age with biallelic TRRAP mutations show poor growth of the trophoblast layer and absence of the inner cell mass [5].

Heterozygous pathogenic or likely pathogenic variants in the TRRAP gene are associated with epilepsy, schizophrenia, and childhood disintegrative disorder, with two main disease spectra: one characterized by greater multiorgan dysfunction and intellectual disability, and the other by autism spectrum disorder with epilepsy. Both are associated with neurocognitive delays and facial dysmorphisms [3,5]. We present a patient with a blended phenotype who harbors a novel genetic variant within a previously identified hotspot in TRRAP.

Case Presentation

The patient was born at 41 weeks' gestation via vaginal delivery, with no birthing complications, weighing 7 lb 10 oz. Fetal movements were detected at 16 weeks but were reduced, with no other complications noted during pregnancy. Development was normal, with walking beginning around 14 months of age and first words spoken around 18 months of age.

Concerns about attention-deficit/hyperactivity disorder (ADHD), intellectual disability, and autism were raised when the patient was around six years of age. These included aggressive behaviors at home, the need

for frequent reminders to maintain a schedule, and episodes of feeling overwhelmed three to four times daily, lasting 15-60 minutes. Other concerns included repetitive behaviors, sensory seeking with water but sensory avoidance with food, ritualization of some activities, and anxiety. The caregiver reported that the patient was at constant risk of elopement.

Before formal assessment, the patient was trialed on dexmethylphenidate hydrochloride extended-release, methylphenidate hydrochloride extended-release (oral suspension and pill forms), and amphetamine-dextroamphetamine, which caused unwanted side effects and appetite suppression. After the caregiver expressed a lack of interest in further pharmacotherapy, social, psychomotor, and cognitive tests were administered before referral to genetics.

The caregiver reported concerns about hyperactivity, difficulty focusing, dislike of loud noises, lack of understanding of personal space, aversion to certain textures in food and textiles, and difficulty articulating his own emotions or understanding others. The caregiver also reported difficulties with activities of daily living. Although the patient was independent with dressing, feeding, and brushing his teeth, he needed help staying on task and ensuring that his clothing was not on backward. The patient was estimated to be 20% independent in activities of daily living without reminders. He communicated in full sentences but had difficulty focusing and following commands.

Based on these observations, the patient was transferred to homeschooling at his mother's request. He was also diagnosed with ADHD, combined type, learning difficulty, fine motor delay, and suspected autism. Fine motor delays were addressed with occupational therapy.

The patient had failure to thrive due to appetite suppression from his ADHD medication and aversions to the textures of certain foods. He was prescribed one can of PediaSure per day and gained 1.9 kg over three months. At the next clinic visit, the prescription was increased to two cans per day, but he subsequently began refusing it. He was also prescribed cyproheptadine to improve his appetite, but it induced mood swings. Over the year between his initial visit and the subsequent two visits, his weight and height were at the 1st and 3rd percentiles, respectively.

The patient was initially evaluated by the genetics team at approximately seven years and nine months of age for dysmorphic features, poor growth, and ADHD. The dysmorphic features identified on physical examination included a tall, bossed forehead, mild hypertelorism, a wide, upturned nasal tip, hypoplastic malar configuration, protuberant abdomen, hyperlordosis, flat feet, and global hypotonia that was more marked in the lower half of the body. Whole-genome sequencing revealed a heterozygous de novo variant of uncertain significance in the TRRAP gene (c.3304T>G, p.Tyr1102Asp), as well as an X-linked syndromic Turner type variant of uncertain significance in the HUWE1 gene (c.2317G>A, p.Val773Met) (Table *1*). Given the phenotypic dissimilarity between our patient and his mother and the reported HUWE1-related syndrome, further investigation focused on the TRRAP variant.

Findings	Location	Variant	Mode of inheritance/disease	Classification
Primary	TRRAP NM_001375524.1	c.3304T>G p.Tyr1102Asp heterogenous in proband; not detected in father; not detected in mother	Autosomal dominant developmental delay with or without dysmorphic facies and autism	Uncertain Significance PS2_Supporting, PM2_Supporting
Other variants	HUWE1 NM_031407.7	c.2317G>A p.Val773Met hemizygous in proband; not detected in father; heterozygous in mother	X-linked syndromic Turner-type intellectual developmental disorder	Uncertain Significance BP4, PM2_Supporting

TABLE 1: Results of whole-genome sequencing

TRRAP, transformation/transcription mediator-associated protein

Deep phenotyping revealed a 16-degree lumbar levocurvature, mild lumbar lordosis (Figure *1*), and slightly decreased height of the left aspects of T9-T10 and T9 on spinal X-rays (Figure *1*). MRI of the head without contrast also showed a small cyst near the ependymal surface of the frontal horn of the right lateral ventricle (Figure *2*).



FIGURE 1: Spinal X-ray highlighting a 16-degree levolumbar curvature

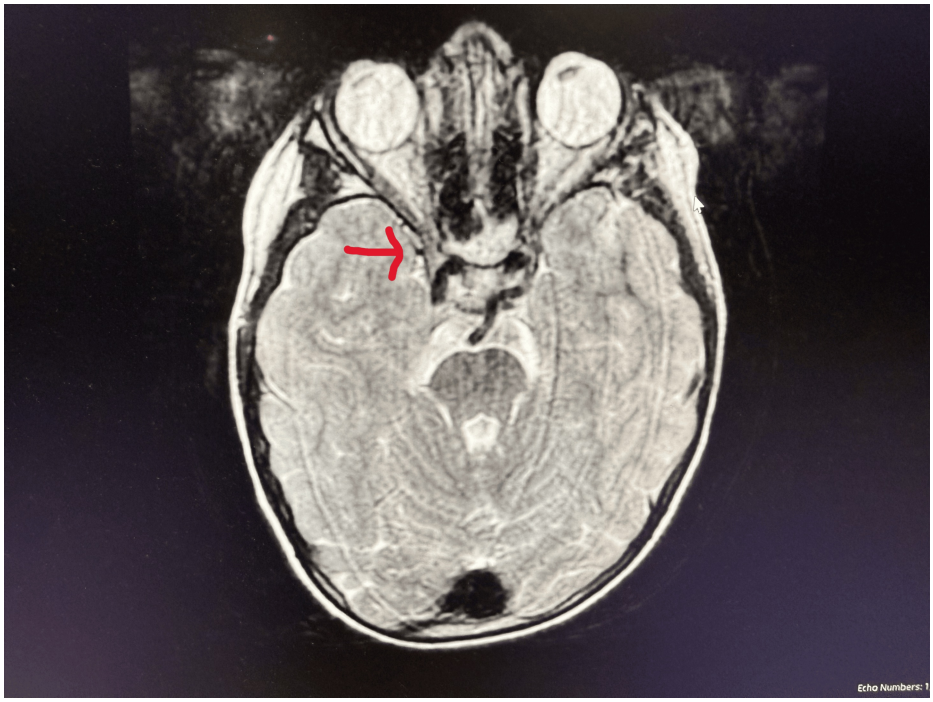


FIGURE 2: Small cyst seen on MRI

Discussion

Two spectra of TRRAP-related disease have been identified: one is a multisystemic syndrome with malformations of various organs and intellectual disability, and the other is autism spectrum disorder associated with intellectual disability and/or epilepsy [4]. These spectra are broad. In one patient, the TRRAP variant was associated with autosomal dominant nonsyndromic hearing loss resulting from a lysine-to-arginine substitution at position 1787 [6]. A patient with a p.Asp3715Asn variant had facial morphological differences, including a broad forehead and high-arched palate, as well as a ventricular septal defect, hypospadias, syndactyly, and polydactyly [1]. TRRAP variants have also been implicated in melanoma, glioblastoma multiforme, pancreatic adenocarcinoma, and lymphoma [4]. A review of the literature on pathogenic variants in TRRAP revealed a varied clinical presentation and disease spectrum (Table *2*).

Case study	Disease	Variant	Zygosity	Inheritance
Mavros et al. [3]	Early-onset major depression with psychotic episode with nonverbal learning disability and OCD	c.5957G>A p.(ARG1986Gln)	Heterozygous	De novo
Acharya et al. [1]	Developmental delay, dysmorphic facies, congenital malformations	c.11143G>A p.(Asp3715Asn)	Heterozygous	De novo
Nagy et al. [6]	Autosomal dominant non-syndromic hearing loss	c.5360A>G p.(Lys1787Arg)	Heterozygous	De novo, autosomal dominant
Clay et al. [8]	Intellectual disability, facial dysmorphisms, multiorgan dysfunction	c.3475G>C p.(G1159R)	Heterozygous	De novo, autosomal dominant

TABLE 2: Review of the literature on pathogenic variants in TRRAP revealed a varied clinical presentation and disease spectrum

OCD, obsessive-compulsive disorder; TRRAP, transformation/transcription mediator-associated protein

Cogne et al. conducted a study of pathogenic TRRAP variants involving 24 patients with neurodevelopmental disorders and 17 distinct missense mutations (see Table *3*) [4].

Study	cDNA	Protein	Inheritance	CpG	gnomAD	CADD Phred Score	SIFT	PolyPhen2 HVAR	Number of individuals
Cogne et al. [4]	c.2413C>T	p.Leu805Phe	De novo	No	Absent	28.2	Deleterious (0)	Probably damaging (0.998)	1
Cogne et al. [4]	c.2580C>G	p.Phe860Leu	De novo	No	Absent	27.6	Deleterious (0.03)	Possibly damaging (0.867)	1
Cogne et al. [4]	c.2678G>T	p.Arg893Leu	Apparently de novo	Yes	Absent	34	Deleterious (0)	Probably damaging (0.986)	1
Cogne et al. [4]	c.3093T>G	p.Ile1031Met	De novo	No	Absent	23.4	Deleterious (0.02)	Benign (0.308)	1
Cogne et al. [4]	c.3104G>A	p.Arg1035Gln	De novo	Yes	Absent	23.9	Tolerated (0.09)	Benign (0.404)	1
Cogne et al. [4]	c.3111C>A	p.Ser1037Arg	De novo	Yes	Absent	23.7	Tolerated (0.14)	Possibly damaging (0.656)	1
Cogne et al. [4]	c.3127G>A	p.Ala1043Thr	De novo	Yes	Absent	23.2	Tolerated (0.27)	Benign (0.066)	5
Cogne et al. [4]	c.3311A>G	p.Glu1104Gly	De novo	No	Absent	24.6	Deleterious (0.04)	Probably damaging (0.91)	1
Cogne et al. [4]	c.3316G>A	p.Glu1106Lys	De novo	No	Absent	27.7	Deleterious (0)	Possibly damaging (0.816)	2
Cogne et al. [4]	c.3331G>T	p.Gly1111Trp	Apparently de novo	Yes	Absent	34	Deleterious (0)	Probably damaging (0.999)	1
Cogne et al. [4]	c.3475G>A	p.Gly1159Arg	De novo	No	Absent	33	Deleterious (0)	Probably damaging (0.999)	1
Cogne et al. [4]	c.5575C>T	p.Arg1859Cys	De novo	Yes	Absent	34	Deleterious (0)	Probably damaging (0.997)	1
Cogne et al. [4]	c.5596T>A	p.Trp1866Arg	De novo	No	Absent	28.7	Deleterious (0)	Probably damaging (0.999)	1
Cogne et al. [4]	c.5598G>T	p.Trp1866Cys	De novo	No	Absent	33	Deleterious (0)	Probably damaging (0.999)	1
Cogne et al. [4]	c.5647G>A	p.Gly1883Arg	De novo	Yes	Absent	33	Deleterious (0)	Probably damaging (1)	2
Cogne et al. [4]	c.5795C>T	p.Pro1932Leu	Germline mosaicism	Yes	Absent	35	Deleterious (0)	Probably damaging (0.997)	2
Cogne et al. [4]	c.11270G>A	p.Arg3757Gln	De novo	Yes	Absent	28.6	Deleterious (0.01)	Benign (0.296)	1
Our patient	c.3304T>G	p.Tyr1102Asp	De novo	-	-	-	-	-	1

TABLE 3: Comparison of the case study patient with 17 previously identified missense mutations reported in the literature

cDNA, complementary DNA; CpG, cytosine-phosphate-guanine; gnomAD, Genome Aggregation Database; CADD, Combined Annotation Dependent Depletion; SIFT, Sorting Intolerant From Tolerant; PolyPhen-2 HVAR, Polymorphism Phenotyping v2 (HumVar); HVAR, HumVar

Cogne et al. identified a cluster of variants between codons 1030 and 1159 of the TRRAP gene in 13 of the 24 patients. When examined in a 3D model of the TRRAP protein, these variants were found to localize near one another [4]. Our patient also presented with a variant within this cluster (see Table *3*). Similar to our patient, 19 patients in their study had various dysmorphic facial features, including a wide nasal bridge, upslanted palpebral fissures, epicanthus, telecanthus, a broad and smooth philtrum, and a thin upper lip. Eleven of the 13 patients harboring variants in the codon 1030-1159 cluster also had facial dysmorphisms

[4]. Furthermore, all patients in the aforementioned study had some degree of intellectual disability, ranging from marked impairment in daily activities to minimal intellectual disability. Intellectual disability and global developmental delay were identified in all patients with variants in the codon 1030-1159 cluster of the TRRAP gene, as in our patient [4]. Marked hypotonia, which was also observed in our patient, was noted in eight of the 24 patients in the previous study, four of whom harbored variants in the codon 1030-1159 cluster [4].

In summary, our patient's phenotype incorporates significant features of both previously identified TRRAP-related disease spectra and, more specifically, those observed in patients with variants in a previously identified hotspot within this gene. Although functional studies are lacking to explain the significance of the codon 1030-1159 cluster, in silico tools most often support the pathogenicity of variants in this domain (see Table *3*). This may be because this domain binds to HAT, affecting its downstream function as a chromatin modifier and potentially explaining the protean phenotypic manifestations of variants within this genetic domain. In addition to studies of TRRAP-HAT binding, studies focusing on acetylation patterns and/or other epigenetic modifications to the genome using saturation mutagenesis of this domain could be particularly revealing.

Conclusions

This case describes a novel TRRAP variant within a previously identified hotspot in the gene in a patient presenting with a blended TRRAP phenotype involving neurodevelopmental and multisystem features. The genotype-phenotype correlation is very strong, supporting the pathogenicity of this variant despite its classification as a variant of uncertain significance. Further investigation of this region will help elucidate the reason for the clustering of pathogenic variants within the codon 1030-1159 domain, in which our variant lies, and determine whether the mechanism underlying their pathogenicity involves altered chromatin acetylation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Devanshi Patel, Richard Sidlow

Acquisition, analysis, or interpretation of data: Devanshi Patel, Richard Sidlow

Drafting of the manuscript: Devanshi Patel

Critical review of the manuscript for important intellectual content: Devanshi Patel, Richard Sidlow

Supervision: Richard Sidlow

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Acharya R, Bhalla K, Gathwala G: A rare mutation in TRRAP gene and the expanded new phenotype . Indian J Pediatr. 2024, 91:987. 10.1007/s12098-024-05115-z
2. Transformation/transcription domain-associated protein; TRRAP . (2018). Accessed: November 9, 2026: https://omim.org/entry/603015.
3. Mavros CF, Brownstein CA, Thyagrajan R, et al.: De novo variant of TRRAP in a patient with very early onset psychosis in the context of non-verbal learning disability and obsessive-compulsive disorder: a case report. BMC Med Genet. 2018, 19:197. 10.1186/s12881-018-0711-9
4. Cogné B, Ehresmann S, Beauregard-Lacroix E, et al.: Missense variants in the histone acetyltransferase complex component gene TRRAP cause autism and syndromic intellectual disability. Am J Hum Genet. 2019, 104:530-41. 10.1016/j.ajhg.2019.01.010
5. Herceg Z, Hulla W, Gell D, Cuenin C, Lleonart M, Jackson S, Wang ZQ: Disruption of TRRAP causes early embryonic lethality and defects in cell cycle progression. Nat Genet. 2001, 29:206-11. 10.1038/ng725
6. Nagy N, Szalenko-Tőkés Á, Pál M, et al.: Novel pathogenic variant of the TRRAP gene detected in a

Hungarian family with autosomal dominant non-syndromic hearing loss. Int J Mol Sci. 2025, 26:1583. 10.3390/ijms26041583

7. Tapias A, Zhou ZW, Shi Y, et al.: Trrap-dependent histone acetylation specifically regulates cell-cycle gene transcription to control neural progenitor fate decisions. Cell Stem Cell. 2014, 14:632-43. 10.1016/j.stem.2014.04.001
8. Clay S, Zambrano R. TRRAP associated neurodevelopmental disorder: a case report . (2023). Accessed: September 10, 2026: https://digitalscholar.lsuhsc.edu/cgi/viewcontent.cgi?article=1236&context=sommrd.