"TRRAP Associated Neurodevelopmental Disorder: A Case Report"

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Introduction

Transformation/transcription domain associated protein (TRRAP) is a large multidomain protein of the phosphoinositide 3-kinase-related kinases (PIKK) family, which is a component of many histone acetylation complexes (HATs).

The exact physiologic role of this gene is not well described, however, patients with pathogenic *TRRAP* variants, inherited in an autosomal dominant manner, exhibit a multitude of abnormalities including:

- developmental delay
- intellectual disabilities
- dysmorphic facies
- autism spectrum disorder
- multisystem organ anomalies

Cogné et. al. recently described a strong genotype-phenotype correlation between patients carrying variants within the codons 1031-1159. These patients mainly present with multi-system organ defects. Variants outside this regions produce a behavior/neurological disorder phenotype: autism, seizures, schizophrenia, etc.

We present the case of a pediatric patient with a *de-novo*, pathogenic *TRRAP* variant located within the 1031-1159 codon region and compare his presentation to a previously published case. His presentation is consistent with the phenotype "Developmental Delay With or Without Dysmorphic Facies and Autism" (OMIM #618454).

Case

A 9-year-old African American male presented to the Multi-disciplinary Craniofacial Clinic at Children's Hospital of New Orleans (CHNOLA) for initiation of care.

He had been previously evaluated at two other institutions in different states. His past medical history and physical are significant for the features noted in Figures 1A and 1B.

He was seen by genetics at one outside institution as an infant where he had a normal microarray. No further genetic workup was documented.

He has one healthy 13-year-old brother. His parents are healthy and have no family history of genetic disorders.

Whole exome and mitochondrial sequencing via XomeDxPlus (GeneDx) was performed and the report is shown in Figure 2. Parental testing was negative for this variant thus it most likely arose de-novo. However, the possibility of germline mosaicism must be considered.

He later underwent a left cleft alveolar ridge bone graft with palatoplasty and repair of oronasal fistula. He will follow up with the craniofacial clinic for repeat imaging at his 3-month post-op appointment.

Figure 2: GeneDx Report

Causative Variant(s) in Disease Genes Associated with Reported Phenotype:

Gene	Disease	Mode of Inheritance	Variant	Zygosity	Inherited From	Classification
TRRAP	TRRAP-related neurodevelopmental disorder with multiple anomalies	Autosomal Dominant	c.3475 G>C p.(G1159R)	Heterozygous	De Novo	Pathogenic Variant

Figure 1A: Features

Symptoms	Our case	Previously reported case*	Codon Cluster 1031-1159 (N = 13) [1]
Global developmental delay	X	X	100%
Intellectual disability	X	X	100%
Facial dysmorphisms	X	X	85%
ASD			0%
Seizures			8%
Microcephaly	X		46%
Short stature	X	X	33%
Feeding difficulties	X		54%
Cleft lip and palate	X		38%
Cerebellar hypoplasia		X	55%
Cerebral abnormalities		X	55%
Renal malformations	X	X	38%
Genital malformations	X		38%
Hearing impairment		X	23%
Lacrimal duct aplasia		X	18%
Abdominal wall defects	X	X	23%
Hypothyroidism	X		8%**

"X" indicates the patient displays the corresponding symptom.
Right-most column denotes the proportion of Cogné et. al subjects in their "codon cluster" cohort presenting with the corresponding symptom.

Yellow cell = key features shared by both phenotypes
Purple cell = Key features of variants outside the 1031-1159 codon cluster

**Subject is a 2 y/o Caucasian female published in Cogné et. al with the TRRAP variant c.3475G>A(p.G1159R)*
***This value is derived from one deceased individual noted in Cogné et. al.*

Discussion

-The physiologic role of *TRRAP* is not well understood, however, it is theorized that pathogenic variants dysregulate acetylation, a known mechanism of other neurodevelopmental and behavioral disorders, leading to differential gene expression [1,2]. Our comparison to Cogné et. al's case demonstrates this variable phenotype [1].

-*TRRAP* is highly intolerant to mutation (ExAC score 10.5) and knockout mice demonstrate peri-implantation lethality [1,3]. Zebrafish models have shown high expression of *TRRAP* in craniofacial development, and manipulation lead to alterations in eye and head diameter [3].

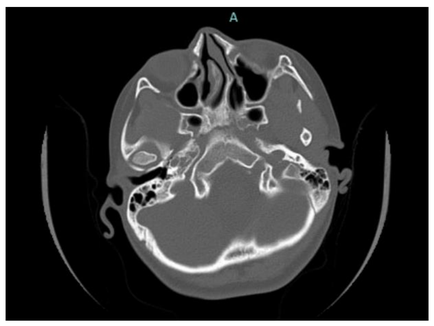
-A *TRRAP* variant in the same position but a different amino acid change was published in Cogné et. al. and was reported as Pathogenic. The variant identified in our case does not have a high frequency in population databases, and in-silico analysis supports a deleterious effect. Parentage was also confirmed, thus altogether leading to the Pathogenic classification [Gene Dx Report].

-No studies to date have compared the gene expression between the two phenotypes described in Cogné et. al. Although our case supports their hypothesis, further studies are required to confirm this genotype-phenotype relationship.

References

1. 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(3):530-541. doi:10.1016/j.ajhg.2019.01.010
2. 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(1):197. Published 2018 Nov 13. doi:10.1186/s12881-018-0711-9
3. Suzuki T, Hirai Y, Uehara T, Ohga R, Kosaki K, Kawahara A. Involvement of the zebrafish trrap gene in craniofacial development. *Sci Rep*. 2021;11(1):24166. Published 2021 Dec 21. doi:10.1038/s41598-021-03123-z

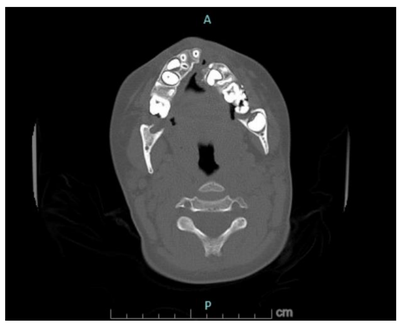
Figure 1B: Images

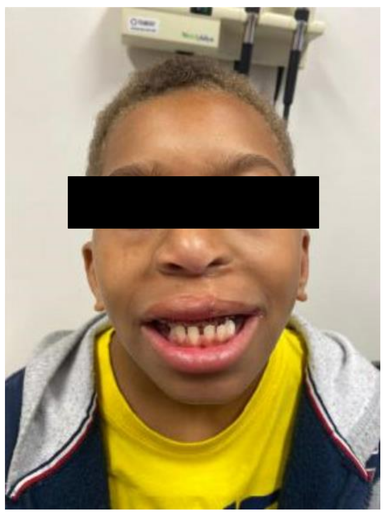


CT images status-post palatoplasty impression:
Soft tissue closure of left central maxillary cleft defect.

Persistent bone defect anterior hard palate and maxilla.

Persistent left nasal septal deviation.



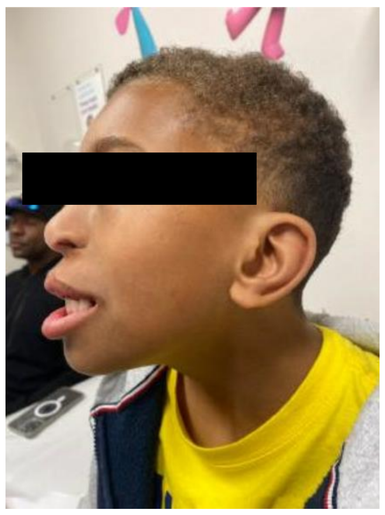


Photos:
Slight microcephaly and facial, orbital, nasal, and lip asymmetry were noted.

His ears were prominent and posteriorly rotated bilaterally.

His right eye deviated nasally at times and his eyes are grey/green in color.

Written consent was obtained for use of photographs for research purposes.



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