Sloane M Clay
L3
LSU Health Sciences Center, New Orleans, LA

Regina Zambrano MD:
Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, Department of Pediatrics, Division of Clinical Genetics, New Orleans, LA, USA

"TRRAP Associated Neurodevelopmental Disorder: A Case Report"

Introduction: *TRRAP* encodes the transformation and transcription domain associated protein, an essential component of many histone acetyltransferase complexes which modify chromatin. Pathogenic variants cause a rare neurodevelopmental disorder with a highly variable clinical presentation; however; almost all cases in the literature report global developmental delay and/or intellectual disabilities as symptoms. Cogné et. al. report a strong genotype/phenotype relationship in individuals whose variant falls within the 1031-1159 codon cluster. These individuals tend to have severe symptoms along with "syndromic" abnormalities such as renal, cardiac, and genital malformations. Individuals with variants outside this region tend to have neurological/behavioral abnormalities, notably autism spectrum disorder and seizures. We present the case of a pediatric patient with a *de-novo*, pathogenic *TRRAP* variant located within the 1031-1159 codon region. We compare him with a case caused by the same amino acid substitution via a different nucleotide change. 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 for initiation of care. He had been previously evaluated at two outside hospitals (OSH) and his past medical history is significant for the following: left cleft lip and palate status-post (s/p) repair and revision, omphalocele s/p repair, poor feeding requiring g-tube supplemental feeds from birth later removed at 1 year, resolved hypothyroidism, short stature, undescended testes bilaterally, malrotation of the left kidney, and learning delay. He was seen by genetics at one OSH as an infant where he had a normal microarray. No further genetic workup was noted. He has one healthy 13-year-old brother. His parents are healthy with no family history of genetic disorders. He underwent genetic testing via GeneDx's XomeDxPlus sequencing whole exome plus mitochondrial DNA. A *de-novo*, pathogenic variant, c.3475 G>C p.(G1159R), was detected. He later underwent a left cleft alveolar ridge bone graft with palatoplasty and repair of oronasal fistula.

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 disorders, leading to differential gene expression. Compared to Cogné et. al.'s case carrying the variant c.3475 G>A (p.G1159R), they share key features of intellectual disability, developmental delay, and facial dysmorphisms; however, they do not share many other phenotypic features, supporting the disorder's previously documented variable presentation. *TRRAP* is highly intolerant to mutations (ExAC z-score 10.1) and *TRRAP* knockout mice exhibit peri-implantation lethality. Although Cogné et. al. report two distinct phenotypes based around the 1031-1159 codon cluster, no studies to date compare gene expression between these two patient groups to verify a molecular basis for this observation. Our case supports the correlation previously described by Cogné et. al. and contributes to the body of knowledge regarding this rare disease.