De Novo CAMK2D Variant in Patient with Down Syndrome

Abigail Doll BS, Isabella Steinbach MS CGC, Abigail Hopkins MD, Tracy Stroud DO

School of Medicine
University of Missouri

Thompson Center for Autism & Neurodevelopment
University of Missouri

INTRODUCTION

CAMK2D variants are associated with neurodevelopmental disorders and dilated cardiomyopathy that may require transplantation. The relationship between CAMK2D and Down syndrome is not directly established in the current medical literature. This is the first reported case to demonstrate a CAMK2D variant in a patient with co-occurring trisomy 21.

CASE PRESENTATION

A 4-year-old female with a history of trisomy 21, congenital hypothyroidism, hypotonia, pulmonary hypertension, chronic lung disease with bronchiectasis, specific antibody deficiency, G-tube dependence, and ASD/VSD/PDA s/p closure presented to a cardiology clinic for elevated NT-proBNP levels with echocardiogram concerning for LV dilation and mildly decreased systolic function of unclear etiology. It was recommended that the patient start enalapril and undergo comprehensive genetic testing to identify possible etiologies that could explain the patient's clinical presentation.

A whole exome sequencing (WES) trio test identified a de novo heterozygous pathogenic variant in CAMK2D c.824G>A.

The patient is currently undergoing additional workup including a skeletal survey and brain MRI to better understand her phenotypic presentation given this CAMK2D variant.

DISCUSSION

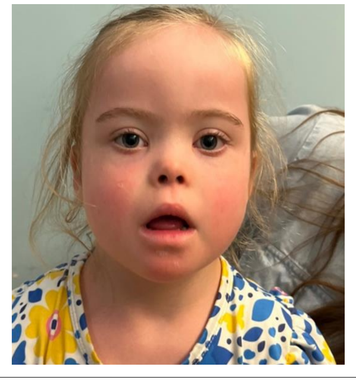
The CAMK2 protein family consists of four isozymes: A, B, G, and D. CAMK2D expression is highest in the heart but also expressed in the brain. Substitution of the amino acid arginine for histidine in this variant destabilizes the normal structure of the CAMK2 protein. This leads to disruptions in excitation-contraction coupling in the heart and neuronal signaling in the brain.

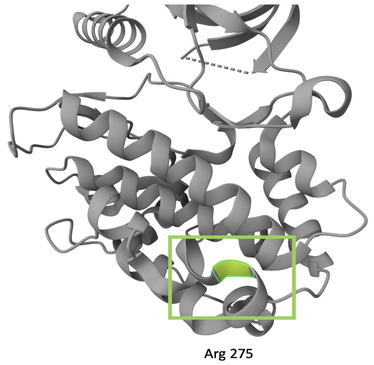
Pathogenic variants in CAMK2D have been previously identified in individuals with intellectual disability, speech delay, behavioral problems, dilated cardiomyopathy, structural brain anomalies, hypotonia, seizures and skeletal anomalies. However, none of the cases currently published have exhibited co-occurring trisomy 21.[1,2]

This case of trisomy 21 co-occurring with a de novo CAMK2D variant highlights the importance of comprehensive genetic testing in the setting of complex medical concerns that may not fully be explained by the natural history of Down syndrome. Health concerns in an individual with Down syndrome that may necessitate comprehensive exome or genome sequencing include cardiomyopathy as well as other heart defects and congenital anomalies atypical for Down syndrome among many others.

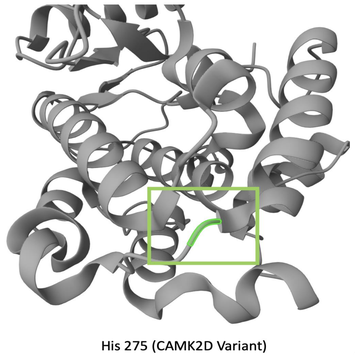
Presence or Prevalence of Health Concerns in Down Syndrome and CAMK2D[1,2,3]

	Seizure	Hypotonia	Congenital Heart Defects	Skeletal Abnormalities
Patient with DS and CAMK2D Variant	-	+	+	Unknown
Prevalence in DS	1-13%	80%	40-50%	1-2% (atlantoaxial instability) 7-9% (scoliosis)
Prevalence in CAMK2D Case Reports	22% (2/9)	67% (6/9)	78% (7/9, all dilated cardiomyopathy)	78% (7/9)





Arg 275



His 275 (CAMK2D Variant)

CONCLUSION

A diagnosis of Down syndrome may not fully explain the entire clinical presentation of a patient, highlighting the importance of whole exome or genome sequencing.

Previously identified patients with CAMK2D variants have demonstrated both cardiac abnormalities and neurodevelopmental disorders.

Further studies into CAMK2D variants are necessary to further understand the associated phenotypic spectrum and guide medical management recommendations.

Additional workup for this patient and future studies that include other patients are required to further evaluate the relationship between CAMK2D variants and Down syndrome.

REFERENCES

1.Rigter, P. M. F., et al (2024). Role of CAMK2D in neurodevelopment and associated conditions. *American journal of human genetics*, *111*(2), 364–382. https://doi.org/10.1016/j.ajhg.2023.12.016

2. Tolmacheva, E. R., et al. (2023). CAMK2D De Novo Missense Variant in Patient with Syndromic Neurodevelopmental Disorder: A Case Report. *Genes*, *14*(6), 1177. https://doi.org/10.3390/genes14061177

3. Marilyn J. Bull, Tracy Trotter, Stephanie L. Santoro, Celanie Christensen, Randall W. Grout, THE COUNCIL ON GENETICS; Health Supervision for Children and Adolescents With Down Syndrome. *Pediatrics* May 2022; 149 (5): e2022057010. 10.1542/peds.2022-057010

4. The 3D structure of CAMK2D (PDB ID: 2VN9) was visualized using Mol* 3D Viewer and the RCSB PDB (RCSB.org). The structure was originally published by Rellos P, Pike AC, Niesen FH, Salah E, Lee WH, von Delft F, Knapp S. Structure of the CaMKIIdelta/calmodulin complex reveals the molecular mechanism of CaMKII kinase activation. PLoS Biol. 2010 Jul 27;8(7):e1000426. doi: 10.1371/journal.pbio.1000426. PMID: 20668654; PMCID: PMC2910593.

ACKNOWLEDGEMENTS

DSMIG-USA® Down Syndrome Medical Interest Group