Evidence for a Pathogenic Variant in a Patient with Generalized Arterial Calcification of Infancy

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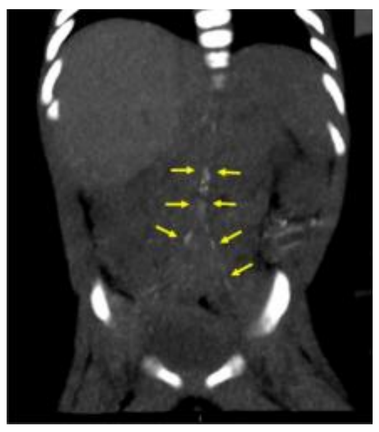
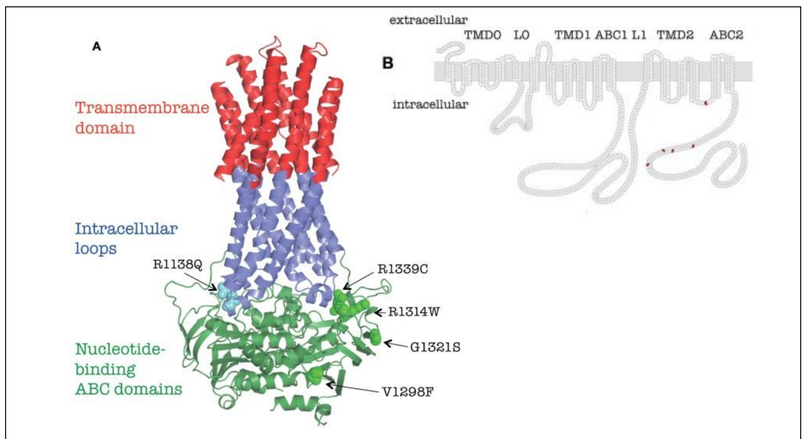
Background:

Generalized Arterial Calcification of Infancy (GACI) is an autosomal recessive disorder characterized by calcifications of the blood vessels early in life. GACI is known to be associated with mutations in two genes, *ENPP1* (OMIM #173335) and *ABCC6* (OMIM #603234).

The ABCC6 (ATP Binding Cassette subfamily C member 6) product is a membrane bound protein found primarily in the liver and kidneys. It is a transport protein, but the substrate it transports across membranes is not known.



Computed Tomography imaging of a patent with GACI demonstrating calcification of abdominal aorta. *From Ferriera et al 2020*



(A) Homology model of human ABCC6. The position of missense mutants studied in *Arayni et al 2013* are indicated. **(B)** Membrane homology model of human ABCC6. The domain structure are indicated on the top, the position of missense mutants are shown in red. *From Aranyi et al 2013*

Clinical Presentation:

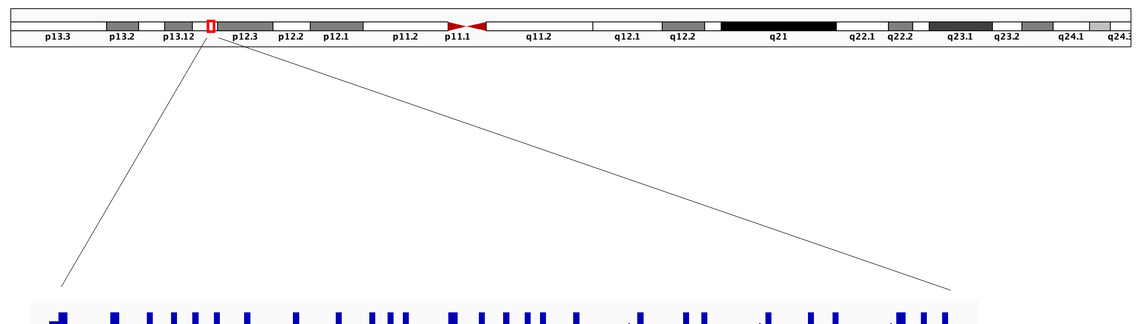
The patient is a male born to a 37-year-old mother (G5P2022>3023) of European ancestry and a 36 year old father of African American ancestry. Delivery was by cesarean section at 37 weeks due to ultrasound discovery of aortic calcification. Fetal ultrasound also showed a pericardial effusion, which resolved spontaneously after delivery. Mild respiratory distress also resolved quickly. He was discharged 10 days after birth.

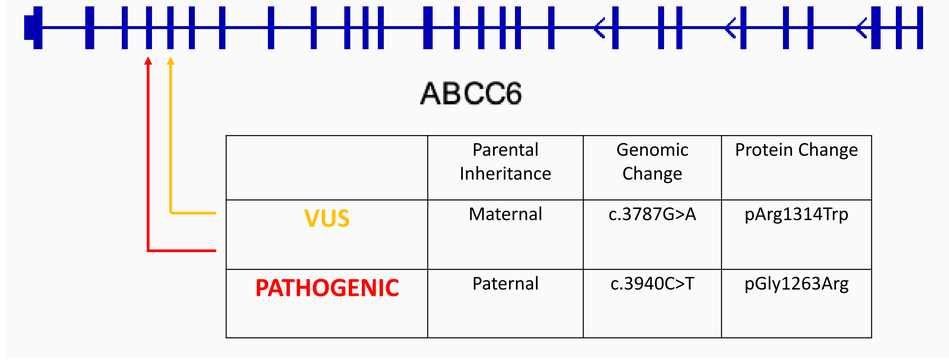
CT scans showed calcification in the aortic arch, descending aorta, pulmonary artery, and carotid and brachial vessels. Echo showed stenosis in the pulmonary artery, consistent with his systolic ejection murmur at the left sternal border. Follow up cardiology at 12 and 18 months and remained free of cardiac symptoms.
Developmental milestones were typical.

The patient was referred for genetic evaluation at age 3 months. Anthropometric measurements were normal and there were no dysmorphic features. At that time, he was observed to be a robust, healthy infant in no acute distress. Prevention Genetics performed molecular analysis of the *ABCC6* and *ENPP1* genes. No variants were found in *ENPP1,* but there was compound heterozygosity in *ABCC6*, with a pathogenic variant c.3940C>T(p.Arg1314Trp) of paternal origin, and a variant of uncertain clinical significance (VUS) c.3787G>A(p.Gly1263Arg) of maternal origin. Theoretical modelling of the VUS was also conducted by Prevention Genetics, which predicted that the mutation of c.3787G>A(p.Gly1263Arg) would damage protein function, but the classification was VUS because of lack of other supporting evidence.

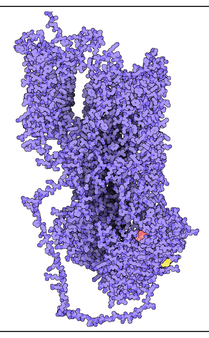
Biochemistry and Genetics

Chromosome 16





	Parental Inheritance	Genomic Change	Protein Change
VUS	Maternal	c.3787G>A	pArg1314Trp
PATHOGENIC	Paternal	c.3940C>T	pGly1263Arg



AlphaFold predicted structure of the *ABCC6* wild-type structure. The Amino Acid labelled red is the location of the pathogenic mutation found in this patient. The amino acid labelled yellow is the location of his Variant of Unknown Significance.

Conclusions

We report a patient presenting with generalized arterial calcification of infancy, a recessive condition, with compound heterozygosity in the *ABCC6* gene, one variant a known pathogenic and the other classified as being of uncertain significance due to lack of reported tracking with clinical pathology. We believe that the phenotype in this patient supports a classification of “pathogenic” or at least “likely pathogenic”.

Citations

Ferreira, C.R., Hackbarth, M.E., Ziegler, S.G. *et al.* Prospective phenotyping of long-term survivors of generalized arterial calcification of infancy (GACI). *Genet Med* **23**, 396–407 (2021).

Arányi T, Bacquet C, de Boussac H, Ratajewski M, Pomozi V, Fülöp K, Brampton CN, Pulaski L, Le Saux O, Váradi A. Transcriptional regulation of the ABCC6 gene and the background of impaired function of missense disease-causing mutations. Front Genet. 2013 Mar 11;4:27.

Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), {date}. World Wide Web URL: https://omim.org/