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Timothy syndrome associated with a novel likely pathogenic CACNA1C variant: A neonatal case report

Ramón Miguel Vargas-Vera, Phd[1*], Lito Danny Campos-Carbo MD[2], Wilson Ramón Solórzano-Loor MD[3], Luis Alberto Rodríguez-Matías MD[4], Julio César Meneses-Garrido MD[5], María Monserrate Ganchozo-Pincay MD[6], Martha Verónica Placencia-Ibadango PhD[7]

[1]Universidad Católica Santiago De Guayaquil, Guayaquil, Ecuador
[1,2,3,4,7]Universidad De Guayaquil, Guayaquil, Ecuador
[5]Universidad de Especialidades Espíritu Santo: Guayaquil, Guayas
[6]Hospital Clínica San Francisco

Abstract

Timothy Syndrome (TS) is a rare multisystem channelopathy caused by pathogenic variants in CACNA1C, classically associated with severe cardiac involvement and neurodevelopmental abnormalities. Variants affecting codon 402 represent a critical functional hotspot of the CaV1.2 L-type calcium channel. We report a preterm male neonate presenting with microcephaly, small anterior fontanelle, mild fetal ventriculomegaly, cardiomyopathy, bradycardia, and neonatal respiratory failure. Whole-exome sequencing identified a heterozygous likely pathogenic variant in CACNA1C (NM_000719.7:c.1205G>A; p.Gly402Asp), not previously reported in the literature but affecting a codon with established pathogenic relevance in Timothy syndrome. This case expands the genotypic and phenotypic spectrum of Timothy syndrome and highlights the importance of early clinical–genetic correlation in neonates with severe cardiac manifestations.

Keywords: Timothy syndrome, CACNA1C, Neonatal cardiomyopathy, Channelopathy, Case report

Introduction

Timothy syndrome (OMIM #601005) is an extremely rare genetic disease, inherited in an autosomal dominant manner, caused by pathogenic variants in the CACNA1C gene, which encodes the α1C subunit of the voltage-dependent L-type calcium channel (CaV1.2) [1–3]. This channel plays a key role in cardiac depolarization, myocardial contractility, and neurological development.

The variants classically associated with the syndrome affect highly conserved domains of the channel, particularly codon 402, causing altered voltage-dependent inactivation and a sustained increase in intracellular calcium influx [2,4,5]. Clinically, the syndrome manifests with severe arrhythmias, cardiomyopathy, neurological abnormalities, craniofacial anomalies, and, in some cases, syndactyly.

Case presentation

Male newborn, product of a pregnancy complicated by fetal hemodynamic alterations evidenced by Doppler echocardiography, who was delivered by emergency cesarean section due to acute fetal distress. He presented with severe respiratory

distress at birth, requiring immediate admission to the neonatal intensive care unit.

On initial physical examination, microcephaly was observed (head circumference below the percentile for gestational age), a small anterior fontanelle, without evident major facial dysmorphisms. The cardiovascular system showed signs of hemodynamic compromise and bradycardia. Imaging studies confirmed cardiomyopathy and mild fetal ventriculomegaly. He developed episodes of neonatal hypoglycemia and suspected neonatal sepsis.

Genetic findings

Whole exome sequencing was performed using genomic DNA obtained from peripheral blood, a methodology widely validated for the diagnosis of rare genetic diseases in the neonatal period [6,7]. The analysis identified a heterozygous variant likely pathogenic in CACNA1C: NM_000719.7:c.1205G>A,

Correspondence: Ramón Miguel Vargas-Vera, Universidad Católica Santiago De Guayaquil, Guayaquil, Ecuador, **e-mail:** dr.ramonvargasvera@hotmail.com,
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resulting in the amino acid change p.Gly402Asp.

This variant has an extremely low frequency in population databases (gnomAD <0.001%) and in silico predictions highly suggest a damaging effect (REVEL 0.95; 3Cnet 0.97). Although it has not been previously reported in patients, other variants at the same codon (p.Gly402Ser and p.Gly402Val) have been described as pathogenic in association with Timothy syndrome, reinforcing the functional relevance of this protein region [4,8].

Figure 1. Neonatal facial appearance showing subtle craniofacial features without major dysmorphisms

Figure 1. Neonatal clinical appearance. Frontal facial view showing subtle craniofacial features without major dysmorphisms. Note the reduced cranial size consistent with microcephaly and a small anterior fontanelle. Images were obtained during the neonatal period in the neonatal intensive care unit, prior to the genetic diagnosis.

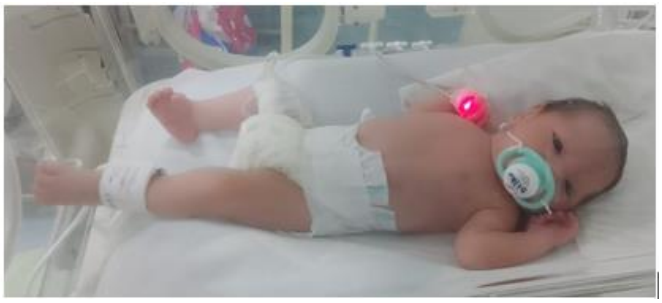

Figure 2. Neonate in the neonatal intensive care unit under cardiorespiratory monitoring

Figure 2. General clinical status in the neonatal intensive care unit. The patient is shown in a neonatal incubator under cardiorespiratory monitoring, illustrating the need for intensive neonatal care due to respiratory distress and cardiovascular instability.

Figure 3. Lower limb and plantar view showing absence of syndactyly, consistent with atypical Timothy syndrome

Figure 3. Lower limb examination. Image shows the plantar aspect of the foot and lower limb with no evidence of classical syndactyly. The absence of limb fusion supports an incomplete or atypical presentation of Timothy syndrome.

Discussion

The identification of a probably pathogenic variant at codon 402 of CACNA1C in a patient with severe neonatal cardiac involvement and early neurological abnormalities is highly suggestive of Timothy syndrome, even in the absence of classic syndactyly [3,9,10]. The absence of syndactyly in this patient supports the existence of incomplete or atypical forms of the syndrome, as previously described in the literature. This case contributes to expanding the mutational spectrum of CACNA1C and reinforces the functional relevance of codon 402 as a critical region for CaV1.2 channel physiology. It also highlights the importance of early genetic diagnosis for clinical

management, prognostic stratification, and family genetic counseling.

Conclusion

A neonatal case compatible with Timothy syndrome associated with a new likely pathogenic variant in CACNA1C is described. The clinical-genetic correlation supports the causal involvement of the p.Gly402Asp variant and emphasizes the need for close cardiac and neurological monitoring in these patients.

Ethics statement

Written informed consent was obtained from the patient's parents for genetic testing and for publication of this case report and any potentially identifiable data/images.

Author contributions

RMVV conceptualized the study, interpreted the genetic findings, and drafted the initial manuscript. MVP-I contributed to clinical data collection, literature review, and critical revision of the manuscript. KSV-S contributed to the cardiology assessment, clinical interpretation, and manuscript revision. IMT-R and MJUB contributed to patient data acquisition, clinical follow-up, and manuscript review. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data availability statement

The data supporting the conclusions of this article are included within the article. Further inquiries can be directed to the corresponding author.

Informed consent was obtained from the parents for the performance of genetic studies and the publication of clinical information in an anonymized manner.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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