HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

Heart Rhythm Society SM

Top Stories: Pediatric

The expanding genetic, mechanistic, and phenotype scope of *CACNA1C*-mediated disease

Andrew P. Landstrom, MD, PhD, FHRS,[1] Susan P. Etheridge, MD, FHRS, CEPS-P[2]

(Heart Rhythm 2025;22:1626–1627)

CACNA1C encodes the alpha-1c subunit of the voltage-gated L-type calcium channel ($Ca_v1.2$), which is expressed across multiple tissues. Classically, disease-associated variants in *CACNA1C* are linked to Timothy syndrome (TS), a multisystem disorder presenting in infancy or childhood with a markedly prolonged QT interval, life-threatening ventricular arrhythmias, and a broad, variable spectrum of noncardiac manifestations. TS is associated with high mortality, particularly early in life. Our understanding of the genetic and molecular mechanisms connecting *CACNA1C* variants with TS and broader disease states is rapidly evolving, with increasing recognition of genetic and phenotypic diversity.

Natural history of TS

CACNA1C undergoes extensive alternative splicing. Exon 8 and the mutually exclusive exon 8A are identically sized but incorporated into distinct transcript isoforms. The most common TS-associated variant, Gly406Arg, localizes to these exons. When present in exon 8A, Gly406Arg causes the classic TS phenotype, designated TS type 1; when present in exon 8, it is associated with TS type 2. Recent data from the international cohort of neonatal TS have advanced our understanding of TS type 1.[1] Of 44 individuals diagnosed clinically with TS type 1 and harboring Gly406Arg, disease onset was uniformly early and severe. Nearly half of all probands exhibited fetal bradycardia, frequently associated with premature delivery before 37 weeks of gestation. This bradycardia often reflected atrioventricular block due to extreme QT prolongation. Syndactyly and QT prolongation were present in ~90% and ~60%, respectively. Mortality rate reached 16% in infancy, and several cases were diagnosed only after cardiac arrest or postmortem genetic testing. TS should be considered in pediatric patients with a long QT and syndactyly. Recognition of TS in the neonatal period allows early intervention to prevent life-threatening arrhythmias.

Expanding genetic subtypes of *CACNA1C*-mediated disease

Although Gly406Arg accounts for ~70% of TS cases, additional pathogenic variants have been identified in exon 8/8A and other exons. Consequently, the phenotype associated with *CACNA1C* variants has expanded beyond TS types 1 and 2 into a broader category, perhaps more accurately referred to as *CACNA1C*-associated disease. Delinière and coworkers[2] recently found a rare de novo Gly402Ser variant in exon 8, which may define a distinct clinical subgroup. In a case series of 4 young, unrelated individuals hosting this variant, all exhibited markedly prolonged QT intervals with prolonged isoelectric ST segment leading to either negative or sharply peaked T waves in the precordial leads. They had a high rate of arrhythmias (2:1 atrioventricular block, T-wave alternans, ventricular fibrillation). These individuals did not have syndactyly and lacked many of the extracardiac manifestations. These cases support the hypothesis that specific *CACNA1C* variants may underlie genetically and clinically distinct subgroups.

Expanding spectrum of cardiac phenotypes

Although once associated with prolonged QT, syndactyly, and hypoglycemia, among other features, recent data suggest an expanding spectrum of cardiac disease for individuals with *CACNA1C* variants. In a recent natural history study by Katherine Timothy, for whom TS is named, *CACNA1C*-associated conditions ranged from classic TS to broader cardiac phenotypes, including cardiomyopathy, congenital heart disease, and isolated long QT syndrome.[3] This phenotypic

From the [1]Division of Cardiology, Department of Pediatrics, and Department of Cell Biology, Duke University School of Medicine, Durham, North Carolina, and [2]St Luke's Children's, Boise Idaho, and Stanford Lucile Packard Children's, Palo Alto, California.

https://doi.org/10.1016/j.hrthm.2025.03.1991
1547-5271/$-see front matter

heterogeneity reflects variable expressivity and incomplete penetrance of *CACNA1C*-associated disease.

Expanding association with neuropsychiatric disease

A cross-sectional study by Levy and coworkers,[4] involving 24 individuals with *CACNA1C* variants, reported neuropsychiatric symptoms or developmental delay in 92% of patients. Additional features, such as hypotonia, poor coordination, and autism spectrum disorder, were observed in most cases. These data underscore the expanding genetic substrate and the broadening phenotypic spectrum of *CACNA1C*-related disease.

Mechanistic insight into *CACNA1C*-mediated hypoglycemia

Despite the initial description of TS 2 decades ago, the mechanisms linking *CACNA1C* variants to tissue-specific disease remain incompletely understood. Recent work has begun to clarify the molecular basis of hypoglycemia, a frequent feature in children with TS and sometimes associated with the fatal event. It was previously postulated that increased calcium influx through mutant $Ca_v1.2$ channels in pancreatic beta cells led to hyperinsulinemia and hypoglycemia. However, Matsui and colleagues,[5] using a *Cacna1c*^{G406R} knock-in mouse model, refuted this hypothesis. These mice did not demonstrate hyperinsulinemia and mutant $Ca_v1.2$ channels did not increase insulin secretion. Instead, their findings suggest possible dysfunction of pancreatic alpha cells.

Since the original description of TS, our understanding of the genetic, phenotypic, and mechanistic dimensions of *CACNA1C*-associated disease has grown substantially. Katherine Timothy has dedicated her considerable energy to this patient population as evidenced by her ongoing participation in most of the publications related to TS in the past decade. She demonstrated how expertise in phenotype characterization, when coupled with basic science research, advanced our understanding of *CACNA1C*-associated disease. Continued investigation of the genetic architecture and cellular mechanisms underlying these disorders holds promise for earlier diagnosis, improved risk stratification, and development of targeted precision therapies.

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: The authors have no conflicts of interest to disclose.

Address reprint requests and correspondence: Dr Susan Etheridge, St Luke's Children's, Boise Idaho, and Stanford Lucile Packard Children's, Palo Alto, California. E-mail address: susan.etheridge12@gmail.com

References

1. Matthews A, Timothy K, Golden A, Gonzalez Corcia MC. International cohort of neonatal Timothy syndrome. Neonatology 2024;121:388–395.
2. Delinière A, Haddad C, Herrera-Siklódy C, et al. Phenotypic characterization of Timothy syndrome caused by the *CACNA1C* p.Gly402Ser variant. Circ Genom Precis Med 2023;16:280–282.
3. Timothy KW, Bauer R, Larkin KA, et al. A natural history study of Timothy syndrome. Orphanet J Rare Dis 2024;19:433.
4. Levy RJ, Timothy KW, Underwood JF, Hall J, Bernstein JA, Paşca SP. A cross-sectional study of the neuropsychiatric phenotype of *CACNA1C*-related disorder. Pediatr Neurol 2023;138:101–106.
5. Matsui M, Lynch LE, Distefano I, et al. Multiple beta cell–independent mechanisms drive hypoglycemia in Timothy syndrome. Nat Commun 2024;15:8980.