Genetic Case Study of TNNC1 Variant in Familial Cardiomyopathy and Coagulopathy

Robell Ephrem[1] [3], Katelyn Ingram[2], Dr. Mahwash Kassi[2]

[1]Dulles High School, Sugar Land, Tx

[2]Houston Methodist Debakey Heart & Vascular Center, Houston, Tx

[3]Gifted and Talented Mentorship Program, Fort Bend ISD, Tx

Abstract

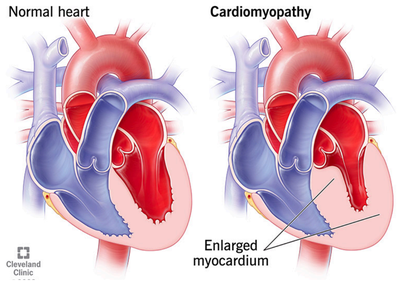
Cardiomyopathy can be hard to understand when it runs in families and is tied to genetic variants we don't fully know how to interpret. This case study looks at a father and son who both developed severe heart failure, needed mechanical support devices, and ultimately received heart transplants. Genetic testing showed they share the same heterozygous variant in the TNNC1 variant, which is a gene involved in helping heart muscles contract. Although this variant is currently labeled as one of uncertain significance, the fact that both patients have it and experienced similar, serious complications, including issues with blood clots, makes it worth studying more closely. Using detailed chart review, we compared their medical histories, hospital courses, and genetic findings to explore possible patterns. While this single-family case cannot confirm causation, it suggests TNNC1 may deserve more attention, particularly in cases with early-onset cardiomyopathy and coagulopathy. Our findings support the value of family-based analysis and point to the need for broader studies to better understand rare gene variants like this one.

Introduction/Summary

Familial heart conditions can be difficult to predict and manage, especially when they involve genetic variants that are not yet well understood. One gene of growing interest is TNNC1, which plays a key role in how the heart muscle contracts. Variants in this gene have been found in patients with cardiomyopathy, but some—like the one discussed here—are still considered Variants of Uncertain Significance (VUS), meaning it's unclear whether they are harmful or not.

This case report looks at a father and son who both developed severe cardiomyopathy and were found to share the same heterozygous TNNC1 variant. The son was diagnosed as a teenager and had a rapidly progressing illness that led to a stroke, blood clots in both ventricles, and ultimately the need for a heart and liver transplant. Years earlier, his father had developed cardiomyopathy as well, requiring a ventricular assist device (VAD), several complications related to clotting and abdominal bleeding, and eventually a heart transplant.

By comparing their clinical histories and complications—especially their overlapping need for advanced therapies and evidence of coagulopathy—this report explores whether the shared TNNC1 variant might be playing a role. While a single-family case cannot prove causation, it raises important questions that could guide future studies, particularly in how we interpret uncertain genetic variants in real-world clinical settings.



Method

This case-based study investigates the clinical trajectory and genetic underpinnings of familial cardiomyopathy in a father-son pair, both harboring the TNNC1 c.400G>A (p.Glu134Lys) variant, classified as a Variant of Uncertain Significance (VUS). Clinical data were extracted from electronic medical records at Houston Methodist and genetic testing performed via the Invitae Arrhythmia and Cardiomyopathy Panel.

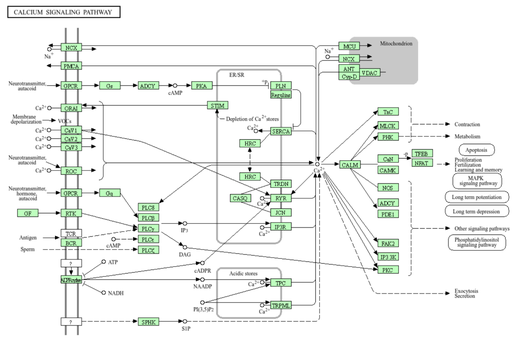
Key variables included:

- Onset of heart failure symptoms
- Progression to advanced heart failure therapies (e.g., temporary MCS, durable VADs)
- Time to transplant and post-operative course
- Documented thrombotic events (e.g., stroke, ventricular clots, hematomas)

Comparative analysis was conducted on:

- Clinical interventions (e.g., number and type of VADs, surgical complications)
- Hematologic manifestations and anticoagulation profiles
- TNNC1 functional implications via literature review and genetic databases (e.g., NCBI, PubMed)

By integrating clinical progression with genomic context, this methodology aims to assess whether the TNNC1 variant contributes to phenotype severity, including both cardiac and coagulopathic complications.



Results

A 44-year-old man, was diagnosed with cardiomyopathy in 2014, progressing to end stage heart failure. He required VAD implantation due to end-stage heart failure. The original device was complicated by suspected infection and bleeding, leading to a replacement within one week. Continued complications required a second VAD exchange approximately six months later. Despite these interventions, his condition remained unstable, and he ultimately underwent heart transplantation nearly three years after his initial diagnosis. His history includes:

- Pericardial hematoma drainage
- Abdominal hematomas and wound evacuations, likely reflective of underlying coagulopathy. These bleeding complications required multiple surgical interventions and may parallel the thrombotic events seen in his son, suggesting a shared vascular or coagulation-related vulnerability alongside their cardiac disease.
- A medication profile reflecting ongoing coagulation management and post-transplant immunosuppression

His 19-year-old son, was hospitalized after rapid onset symptoms and diagnosed with cardiomyopathy ten years after his father.His condition rapidly deteriorated, progressing to severe biventricular heart failure with an LVEF dropping below 20% and reaching as low as 10%. NT-proBNP levels rose to 9,931 pg/mL and eventually 15,957 pg/mL, indicating worsening cardiac strain. Prior to permanent VAD placement on Day 65, he required temporary mechanical circulatory support including right femoral intra-aortic balloon pump (IABP), which was later transitioned to a right axillary Impella, followed by ECMO and Protek Duo cannulation. Given ongoing instability, he ultimately required biventricular assist devices. His treatment course was complicated by:

- Stroke on day 36
- Right and left ventricular clots on day 70
- Repeated abdominal interventions, including a liver transplant on day 87, and multiple washouts
- Heart transplant

The son's case was marked by multiple thrombotic events, confirmed by hematology follow-up, and he remains on long-term anticoagulant and immunosuppressive therapy to prevent his body from rejecting his transplanted heart and liver.

Findings

This case study explored a father and son with shared cardiomyopathy and the TNNC1 (c.400G>A, p.Glu134Lys) variant, classified as a Variant of Uncertain Significance (VUS). Despite limited case numbers, several patterns raise clinical concern:

- Progression: The son experienced rapid-onset, multisystem deterioration requiring biventricular assist devices and dual organ transplant. The father progressed more slowly but needed two VAD exchanges and heart transplantation.
- Complications: Both cases presented with significant coagulopathy—ventricular clots and stroke in the son, hematomas in the father—suggesting a shared vascular vulnerability.
- Genetic Implications: TNNC1 encodes cardiac troponin C, crucial for calcium-mediated muscle contraction. The variant's position in a calcium-regulatory domain may influence sarcomere performance.
- Significance: The shared presentation across generations suggests that TNNC1 may contribute to both cardiac dysfunction and abnormal clotting tendencies in select patients. Further research is needed to clarify its clinical impact.

Discussions

This case study raises clinical suspicion that the TNNC1 variant (c.400G>A, p.Glu134Lys) may play a role in inherited cardiomyopathy. Both the father and son developed severe heart failure, required mechanical support, and ultimately underwent heart transplantation. The consistency of these outcomes, paired with shared complications involving thrombosis and bleeding, suggests the variant may contribute to both cardiac dysfunction and vascular vulnerability.

Although this variant is currently classified as a Variant of Uncertain Significance, its location in a calcium-regulating domain of troponin C1—a protein essential for heart muscle contraction—adds biological plausibility. Disruption in this region could affect sarcomere performance and calcium sensitivity, potentially contributing to disease progression.

References

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