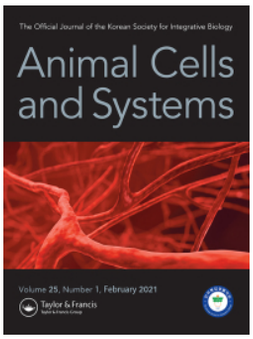

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Troponin I – a comprehensive review of its function, structure, evolution, and role in muscle diseases

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ABSTRACT

The troponin complex is a critical component of thin filaments and plays an essential role in the calcium-mediated regulation of contraction and relaxation in striated muscles, including both cardiac and skeletal muscle. Troponin I, a subunit of this complex, inhibits actomyosin interactions during muscle relaxation. Its function is finely tuned by posttranslational modifications, particularly phosphorylation, which influence calcium sensitivity and actin affinity, thus impacting muscle contraction. Mutations in troponin I are closely associated with various human diseases. Specifically, several mutations in cardiac troponin I have been linked to cardiomyopathies, such as hypertrophic, dilated, and restrictive cardiomyopathies, which affect heart contractility and calcium handling. In this review, we explore the multifaceted aspects of troponin I, including its structure, functional role in muscle contraction, evolution, and the complex interactions between posttranslational modifications and genetic mutations that alter its function and contribute to disease progression.

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KEYWORDS
Troponin I; cardiomyopathy; evolution of troponin I; post-transcriptional modification of troponin I; genetic mutations in troponin I

Introduction

The sarcomere is the fundamental contractile unit of striated muscles, such as cardiac and skeletal muscle. It consists of interlocking thick and thin filaments whose coordinated movement drives muscle contraction and relaxation, regulated by calcium ions that facilitate their sliding past each other (Wang and Raunser 2023). According to the sliding filament model, myosin heads on thick filaments bind to actin on thin filaments and pull the thin filaments toward the center of the sarcomere, thereby shortening the entire structure (Huxley and Hanson 1954). Thick filaments are mainly made up of the motor protein myosin (Rayment et al. 1993a). In muscle cells, myosin II converts the chemical energy stored in adenosine triphosphate (ATP) into mechanical energy, thereby facilitating movement (Sweeney and Houdusse 2010). Each myosin molecule consists of two heavy chains that form a long tail and a globular head. The tails intertwine to create the filament's backbone, while the heads extend outward at regular intervals along its length (Rayment et al. 1993b; Sellers 2000; Dutta et al. 2023). These myosin heads are enzymatically active and possess ATPase activity, enabling them to hydrolyze ATP and produce the energy necessary for contraction (Lymn and Taylor 1971). Driven by ATP hydrolysis, myosin heads interact with actin on thin filaments, pulling the thin filaments toward the center of the sarcomere and thereby shortening the muscle fiber – a fundamental process in muscle contraction (Huxley 1969). Thin filaments, extending from the Z-disc to the sarcomere, are primarily composed of actin. Actin forms a double-helical structure that provides a scaffold for the thin filaments and creates binding sites for myosin during contraction (Holmes et al. 1990). In addition to actin, the thin filament contains regulatory proteins such as tropomyosin and the troponin complex, which play essential roles in contraction regulation. Tropomyosin, a fibrous protein, spirals around the actin filament and initially blocks the myosin-binding sites on actin (Lehman et al. 1994). It resides in the grooves of the actin helix and spans across seven actin monomers, preventing muscle contraction in the relaxed state by obstructing the myosin-binding sites (Parry 2023). The troponin complex, a critical regulatory unit,

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attaches at specific intervals along the actin-tropomyosin structure and consists of three subunits: troponin C, troponin T, and troponin I. Troponin C (TnC) binds calcium ions, troponin T (TnT) anchors the complex to tropomyosin, and troponin I (TnI) inhibits the interaction between actin and myosin (Marston and Zamora 2020). This complex responds to fluctuations in calcium ion levels to regulate muscle contraction. When contraction begins, calcium ions flood the muscle cell cytoplasm and bind to TnC. This interaction triggers a conformational change in the troponin complex, moving tropomyosin on the actin filament and exposing myosin-binding sites on actin. Myosin heads on thick filaments can then bind to actin on thin filaments and initiate contraction through successive power strokes (Solaro and Rarick 1998; Tobacman 2021). In essence, the intricate interplay among sarcomere components – actin, myosin, and regulatory proteins such as tropomyosin and the troponin complex – underlies the molecular mechanisms of muscle movement and force generation. Troponin I (TnI), a subunit of the troponin complex, is a key regulator of muscle contraction and relaxation, playing a vital role in thin filament regulation through its structural and functional properties and its modulation by posttranslational modifications (PTMs). Beyond its essential physiological role, TnI has significant clinical relevance, as mutations and modifications in this protein are closely associated with cardiomyopathies and myopathies, underscoring its significance as a target for studying muscle-related disorders. This review aims to provide a comprehensive exploration of TnI, focusing on its structural framework, evolutionary adaptations, and the influence of PTMs and genetic mutations on its function. By integrating recent discoveries, it highlights the potential for therapeutic strategies targeting TnI to address skeletal and cardiac muscle pathologies. The review is organized to first discuss TnI's function and structural properties, followed by an examination of its mutations and associations with muscle diseases, and concluding with an analysis of how PTMs regulate its activity.

TnI function and structure

TnI has a distinct structural organization characterized by multiple domains, each playing a specific role in its regulatory function. Here, we focus on the structural features and regulatory functions of cardiac troponin I (cTnI) (Figure 1). The cardiac-specific *N*-terminal extension (residues 1–30) includes two serine residues, 23 and 24 (S23 and S24), which can be phosphorylated by protein kinase A (PKA). This phosphorylation modulates calcium sensitivity and influences the timing of Ca^{2+} release from troponin C (TnC), thereby affecting the dynamics of sarcomere contraction. The *N*-terminal conserved region (residues 43–65) is an amphiphilic segment that corresponds to the H1 α-helix and interacts with the *C*-terminal domain of troponin C (TnC) (Takeda et al. 2003). The TnT-binding region (residues 66–136), which encompasses the *C*-terminal portion of H1 and H2 α-helices, forms a coiled-coil interface with TnT, anchoring TnI to the troponin complex. The 'Switch region' (residues 137–160) interacts with troponin C (TnC) when Ca^{2+} binds to it, leading to conformational changes in the troponin complex. Residues 137–148, often referred to as the inhibitory region, contain six positively charged residues and interact with actin-tropomyosin, inhibiting actomyosin ATPase activity at a sub-stoichiometric ratio to actin. Although this region is named for its isolated ability to inhibit actomyosin ATPase, in the context of the entire troponin complex, it functions as a flexible linker between the *N*-terminal domain of TnC, rather than directly inhibiting muscle contraction (Marston and Zamora 2020). In this review, we refer to the 'inhibitory region' as the 'switch region', in line with its actual function. The *C*-terminal mobile domain (residues 163–210) features a protruding α-helix (H4) and exhibits high mobility, facilitating interactions with actin and tropomyosin. Both the 'switch region' (∼137–160) and the *C*-terminal 'mobile region' (∼163–210) of cTnI are intrinsically disordered, allowing them to function as flexible tethers that transmit allosteric signals along the thin filament (Na et al. 2016; Mahmud et al. 2019). In the Ca^{2+}-free state, this region tightly binds to actin and tropomyosin, maintaining the thin filament in an 'off' state that blocks myosin binding and prevents contraction. Upon Ca^{2+} binding to TnC, the 'switch region' of TnI interacts with TnC, causing the *C*-terminal mobile region of TnI to dissociate from actin and tropomyosin. This dissociation allows tropomyosin to shift and expose the myosin binding sites, thereby enabling contraction. A recent cryo-electron microscopy (cryo-EM) analysis revealed that in the Ca^{2+}-free state, the *C*-terminal region of TnI extends along actin and tropomyosin, while this extension is not observed in the Ca^{2+}-bound state, indicating its release (Yamada et al. 2020). These structural changes in TnI facilitated by Ca_2^+ binding are essential for the dynamic regulation of muscle contraction and relaxation cycles, ensuring precise control over muscle function. In native filaments imaged at physiological systolic Ca^{2+} (pCa 5.8), cryo-EM shows that the two actin strands are only partially and stochastically

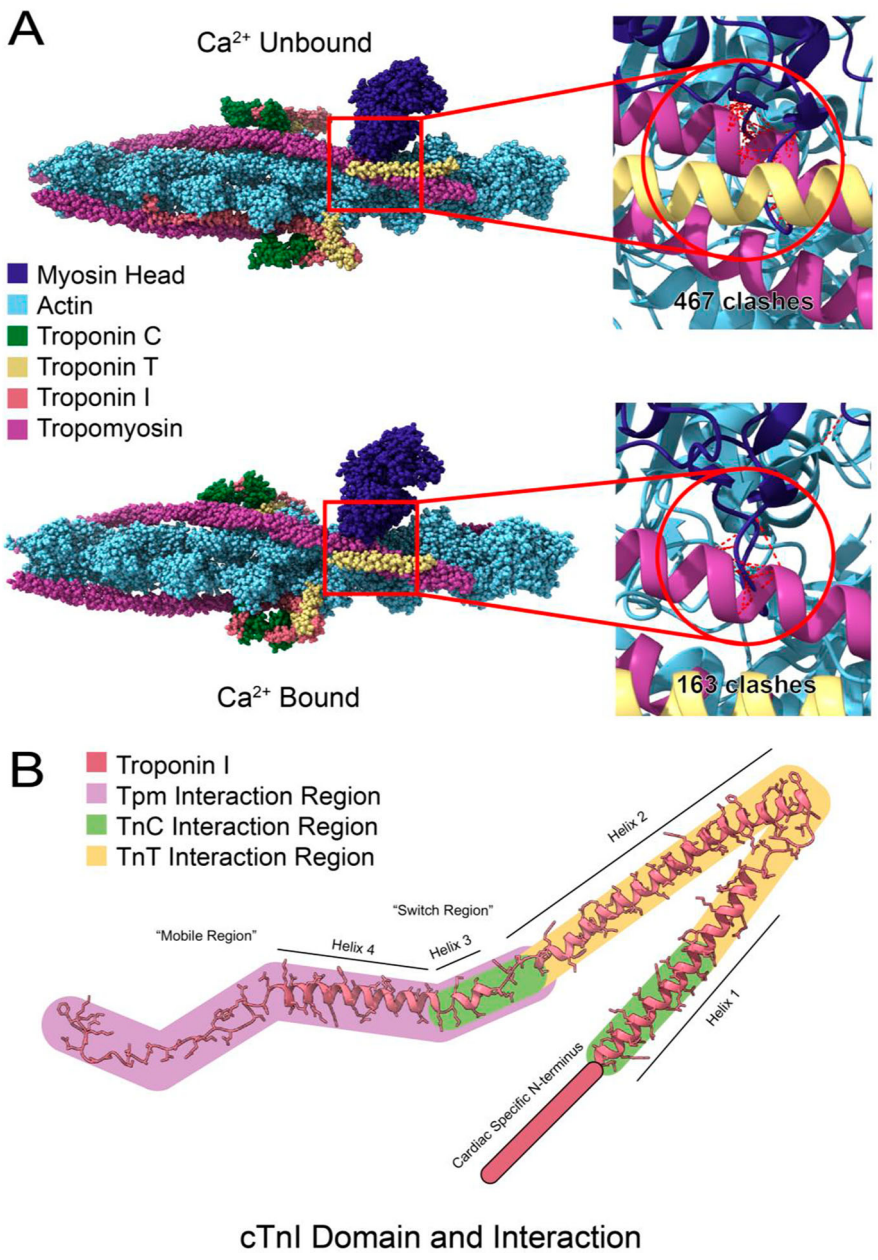

Figure 1. Thin filament and cTnI EM structure. A. Overlay of the relaxed (top, Ca^{2+} Unbound) and excited (bottom, Ca^{2+} Bound) thin filament states, integrating the thin-filament coordinates (PDB: 6KN7/6KN8) (Yamada et al. 2020) with the myosin head (PDB: 8EFI) (Doran et al. 2023). In the red squares, we calculated the number of atomic contacts between the myosin head and tropomyosin, represented by red pseudobonds. Steric clashes between tropomyosin and myosin head are quantified as atom-atom contacts less than 0.6Å (relaxed = 467, active = 163). In the relaxed state (PDB: 6KN7), in which Ca^{2+} is unbound, the tropomyosin (magenta) blocks the myosin-binding sites on the actin filaments (light-blue), preventing interaction between myosin heads (purple) and actin filaments. In this conditions, the 'matchmaker' between myosin head and thin filament yields 467 atom-atom contacts between the myosin head and tropomyosin. In the Ca^{2+} Bound excited state (PDB: 6KN8), calcium ions bind to troponin C, resulting in a conformational shift of the troponin complex. This shift is reflected by a reduced number of 163 atom-atom contacts between the myosin head and tropomyosin, pulling tropomyosin away from the myosin-binding sites on actin and allowing the myosin heads to bind to these exposed sites. It is notable that the contact count does not reach zero because the myosin head and thin-filament structures are derived from independently obtained data sets. As a result of the shift, the myosin heads can now bind to these exposed sites on actin, initiating contraction through their power stroke. **B.** Structural representation of human cardiac troponin I (cTnI) (PDB: 6KN7) (Yamada et al. 2020) highlighting its domain-specific interactions. The cardiac-specific N-terminus (residues 1-30) is unique to cTnI and influences calcium sensitivity through phosphorylation. Helix 1 (residues 42-80) and Helix 2 (residues 89-141) interact with Troponin T(*yellow*). Helix 3 (residues 149-154) and Helix 4 (residues 156-184) form part of the switch and mobile regions, respectively, interacting with troponin C (*green*). The mobile region (residues 163-210) also interacts with tropomyosin (*magenta*). Tropomyosin (Tpm); Troponin T (TnT); Troponin C (TnC).

activated, with short-range cooperativity limited to a single strand – placing the TnI switch region in a dynamic on/off equilibrium during each heartbeat (Risi et al. 2021). Conversely, a 3.8Å structure of the tropomyosin overlap N-terminus of TnT 'junction' in the relaxed filament demonstrates that TnT clamps this region onto actin, rigidly stabilizing the blocked state and thereby complementing the inhibitory grip of TnI's *C*-terminal tail (Risi et al. 2023). Recently, high-resolution maps across multiple Ca^{2+} states show that full activation requires complete disengagement of the TnI C-terminus. This transition can be triggered not only by Ca^{2+} but also by strongly bound cross-bridges or the C1 domain of cMyBP-C – highlighting TnI as a key allosteric hub that integrates signals from Ca^{2+}, myosin, and cMyBP-C (Risi et al. 2024). Vertebrates express specific genes for each troponin subunit depending on the muscle type – cardiac, slow twitch, or fast twitch. The troponin complex consists of different combinations of TnC, TnT, and TnI in each striated muscle type. There are three TnI genes (*TNNI*): slow skeletal Troponin I (ssTnI, *TNNI1*), which is found in slow skeletal muscle and is involved in sustained, endurance-type activities; fast skeletal Troponin I (fsTnI, *TNNI2*), which is present in fast skeletal muscle and facilitates rapid, short-duration activities; and cardiac Troponin I (cTnI, *TNNI3*), which is critical for contraction and relaxation in the heart. Each type

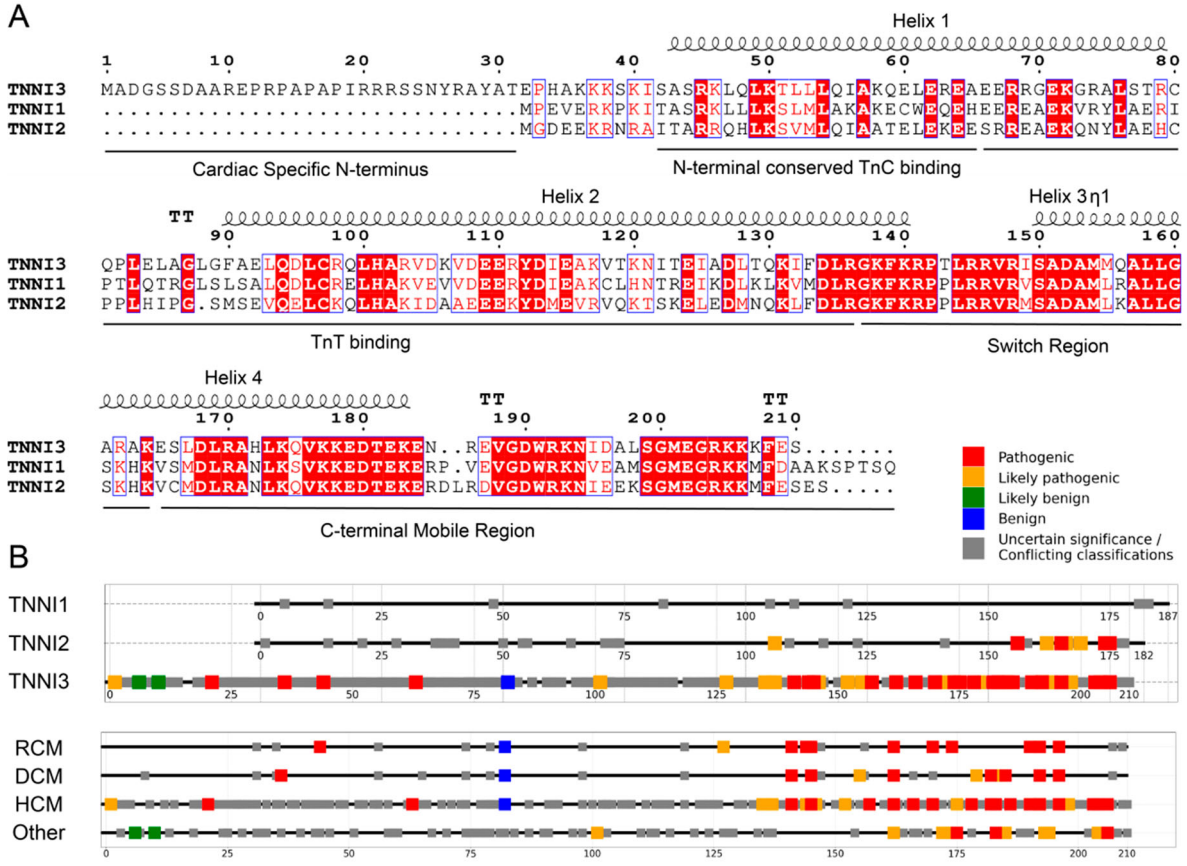

Figure 2. Sequence alignment of troponin I proteins and reported missense and nonsense mutation in ClinVar. A. Sequence alignment of troponin I (TNNI) proteins reveals conserved domains and features across the three isoforms, with the exception of the TNNI3-specific N-terminus. In the alignment, α-helices (3_{10}-helices) and π-helices are represented as squiggles, while the η symbol denotes a 3_{10}-helix. Strict β-turns are marked as 'TT.' (https://espript.ibcp.fr) (Robert and Gouet 2014). **B.** Various mutations including missense and nonsense mutations are reported in ClinVar. The upper and lower panels are schematic representation of missense and nonsense mutations with clinical classification. Each horizontal bar indicates the amino acid sequence of troponin I(TNNI1: 1–187; TNNI2: 1–182; TNNI3: 1–210). The colored and gray boxes indicate individual variants, color-coded by clinical classification (red, pathogenic; orange, likely pathogenic; green, likely benign; blue, benign; and small gray boxes, uncertain significance/conflicting classifications). In lower panel, mutations of TNNI3 are plotted to reported diseases – restrictive cardiomyopathy (RCM), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and other pathogenic phenotype. Clustering of pathogenic and likely pathogenic variants within C-terminus, which is 'mobile regions' highlights the importance of these domains in pathogenesis and function.

of troponin protein shares a common structural framework, which includes a TnT- and TnC-binding region as well as *C*-terminal domains. However, they exhibit unique amino acid sequences that confer specific regulatory properties. These variations influence their interactions with other proteins within the thin filament, their calcium response, and their susceptibility to posttranslational modifications, all of which are critical for the nuanced control of muscle contraction (Figure 2(A)). Notably, cardiac troponin I (cTnI) contains distinct *N*-terminal extensions that are targets of phosphorylation, a modification that plays a vital role in modulating heart muscle contractility in response to adrenergic signals. This type-specific differentiation underscores the evolutionary adaptation of muscle functions and highlight the complex regulatory mechanisms that govern muscle physiology across different tissues within the organism. During human heart development, there is a significant change in the expression of TnI genes. In the fetal heart, *TNNI1* is the predominant isoform, transitioning to *TNNI3* after birth, which becomes the sole detectable TnI by 9 months postnatally (Saggin et al. 1989; Hunkeler et al. 1991; Sasse et al. 1993). This developmental shift is regulated at the gene transcription level, with implications for myocardial contractility in both fetal and postnatal stages.

Troponin I mutation & related diseases

Mutations in *TNNI* can lead to various muscle disorders collectively known as myopathies and cardiomyopathies. These mutations disrupt the normal function of TnI, resulting in abnormal muscle contraction and relaxation. Understanding these mutations is crucial for diagnosing related conditions, developing targeted therapies, and managing patients with genetic disorders (Keyt et al. 2022). While mutations in *TNNI1* and *TNNI2* are less commonly associated with disease than those in *TNNI3*, they can still impact muscle function and lead to myopathies (Sheng and Jin 2016). Although rare, mutations in *TNNI1* can lead to myopathies characterized by muscle weakness and atrophy, predominantly affecting slow-twitch muscle fibers. Symptoms often include difficulty performing activities that require prolonged muscle use. *TNNI1* variants can result in muscle diseases with distinct hypo- or hyper-contractile phenotypes. Identified loss-of-function (R14H/C) and gain-of-function (R174Q and K176del) in *TNNI1* have been linked to specific physiological consequences. Phenotypic changes associated with these variants have been validated in zebrafish studies, highlighting distinct pathological mechanisms associated with hypo- and hypercontractile phenotypes (Donkervoort et al. 2024).

Mutations in *TNNI2* are associated with distal arthrogryposis type 2B (DA2B). Patients with DA2B typically present with congenital contractures of the hands, wrists, and feet, along with facial features, such as down-slanting palpebral fissures, prominent nasolabial folds, and a triangular face. Intelligence remains normal in affected individuals, distinguishing DA2B from other forms of DA associated with cognitive impairments. Several mutations in *TNNI2* related to DA2B have been reported including the F178C (Wang et al. 2016a), K175N (Li et al. 2022), and K175del (Zhu et al. 2014) and those validated in mouse model (Jiang et al. 2006), such as K176del (Kimber et al. 2006), E167del (Shrimpton and Hoo 2006), K168E, R162G (Beck et al. 2013), R156* (Sung et al. 2003; Drera et al. 2006) and R174Q (Sung et al. 2003). These mutations typically affect the *C*-terminal region (mobile region) of the protein, which is essential for its interaction with other components of the troponin complex and actin.

TNNI3 mutations are closely associated with various cardiomyopathies, including hypertrophic, dilated, and restrictive cardiomyopathies (HCM, DCM, and RCM, respectively) (Table 1). The majority of reported pathogenic mutations in *TNNI3* lead to HCM, resulting in a hypercontractile phenotype of the cardiac muscle. Impaired diastolic function caused by abnormal thickening of the heart muscle, leads to obstructed blood flow and impaired cardiac function. This hypercontractility is caused by the disruption of TnI, which inhibits muscle contraction. This results in increased calcium sensitivity of the contractile apparatus, enhancing contractility and leading to muscle hypertrophy. Patients with HCM often present with symptoms such as chest pain, shortness of breath, palpitations, and sudden cardiac death. Histological features of HCM include myocyte hypertrophy, disarray, and fibrosis. In contrast, DCM exhibits a hypocontractile phenotype characterized by the enlargement and dilation of the ventricular chambers, leading to a weakening of the heart's ability to pump blood and impaired systolic function. Multiple mutations in *TNNI3* have been reported to cause DCM, which results in decreased strength of muscle contraction. These mutations can also compromise the structural integrity of the troponin complex, another essential functional protein involved in muscle contraction. Notable mutations include K36Q (Carballo et al. 2009; Vikhorev et al. 2017), E184 K (Lakdawala et al. 2012), and N185 K (Carballo et al. 2009). RCM involves the stiffening of the heart muscle and restricts of proper

Table 1. Featured pathogenic human TNNI3 mutation.

Mutation	Disease type[a]	References
R21C	HCM	Fahed et al. (2020), Marschall et al. (2019), Cheng et al. (2015), Liang et al. (2015), Dweck et al. (2014), Berge and Leren (2014), Wang et al. (2012b), Arad et al. (2005), Gomes et al. (2005a)
K36Q	DCM	Vikhorev et al. (2017), Carballo et al. (2009)
R63* (homozygote)	DCM	Janin et al. (2022), Mehaney et al. (2022), Kühnisch et al. (2019)
L135P	HCM	Jordan et al. (2011)
R141Q	HCM	Landry et al. (2017); Viswanathan et al. (2017), Walsh et al. (2017), Mogensen et al. (2015), Coppini et al. (2014), Kapplinger et al. (2014), Ramachandran et al. (2013), Zou et al. (2013), Rani et al. (2012), Wang et al. (2012a), Curila et al. (2012), Santos et al. (2012), Van Den Wijngaard et al. (2011), Jordan et al. (2011), Curila et al. (2009), Morita et al. (2008), Mogensen et al. (2004), Pi et al. (2003), Van Driest et al. (2003), Richard et al. (2003)
L144Q	RCM	Mogensen et al. (2003); Gomes et al. (2005b), Gomes and Potter (2004a)
R145G	HCM	Walsh et al. (2017), Cheng et al. (2015), Zhao et al. (2015), Zou et al. (2013), Brunet et al. (2012), Van Den Wijngaard et al. (2011), Choi et al. (2010), Wen et al. (2009), Mathur et al. (2009), Reis et al. (2008), Wen et al. (2008), Davis et al. (2008), Robinson et al. (2007), Kobayashi and Solaro (2006), Lindhout et al. (2005), Kruger et al. (2005), Mogensen et al. (2004), Murphy et al. (2004), Barta et al. (2003), Mogensen et al. (2003), Lindhout et al. (2002), Burton et al. (2002), Lang et al. (2002), Takahashi-Yanaga et al. (2001), Deng et al. (2001), James et al. (2000), Elliott et al. (2000), Takahashi-Yanaga et al. (2000), Kimura et al. (1997)
R145W	RCM	Hwang et al. (2017); van Velzen et al. (2018), Walsh et al. (2017), Wang et al. (2014), Berge and Leren (2014), Zou et al. (2013), Maron et al. (2012), Van Den Wijngaard et al. (2011), Fokstuen et al. (2011), Ho et al. (2009), Wen et al. (2009), Mathur et al. (2009), Andersen et al. (2009), Davis et al. (2008), Fokstuen et al. (2008), Wu et al. (2007), Kubo et al. (2007), Kobayashi and Solaro (2006), Yumoto et al. (2005), Moon et al. (2005), Cheng (2005), Gomes et al. (2005b), Mogensen et al. (2004), Mogensen et al. (2003), Takahashi-Yanaga et al. (2001), Kimura et al. (1997)
R145Q	HCM	Al-Shafai et al. (2021); Hathaway et al. (2021), Chung et al. (2021a), Ormondroyd et al. (2020), Kim et al. (2020), Robyns et al. (2020), Marschall et al. (2019), Robyns et al. (2017), Weissler-Snir et al. (2017), Walsh et al. (2017), Wang et al. (2014), Berge and Leren (2014), Lu et al. (2013), Zou et al. (2013), Van Den Wijngaard et al. (2011), Jordan et al. (2011), Choi et al. (2010), Mogensen et al. (2004), Takahashi-Yanaga et al. (2001), Kimura et al. (1997)
A157V	HCM	Fourey et al. (2017), Gomez et al. (2017), Weissler-Snir et al. (2017), Kobayashi et al. (2017), Walsh et al. (2017), Zheng et al. (2016), Lopes et al. (2015), Coppini et al. (2014), Rowin et al. (2014), Captur et al. (2014b), Berge and Leren (2014), Zou et al. (2013), Brito et al. (2012), Kuliev et al. (2012), Van Den Wijngaard et al. (2011), Jordan et al. (2011), Curila et al. (2009), Brito and Madeira (2005), Harada and Morimoto (2004), Mogensen et al. (2004), Gomes and Potter (2004a), Gomes and Potter (2004b), Richard et al. (2003)
R162Q	HCM	Mazzaccara et al. (2022), Smith et al. (2022), Hathaway et al. (2021), VanDyke et al. (2021), Lorenzini et al. (2020), Lahrouchi et al. (2020), Duan et al. (2019), Norrish et al. (2019), Burns et al. (2017), Mademont-Soler et al. (2017), Kobayashi et al. (2017), Alejandra Restrepo-Cordoba et al. (2017), Walsh et al. (2017), Cecconi et al. (2016), Richards et al. (2015), Mouton et al. (2015), Lopes et al. (2015), Kapplinger et al. (2014), Das et al. (2014), Coppini et al. (2014), Captur et al. (2014a), Ramachandran et al. (2013), Gray et al. (2013), Rani et al. (2012), Jordan et al. (2011), Gruner et al. (2011), Bos et al. (2006), Moon et al. (2005), Ingles et al. (2005), Cheng (2005), Doolan et al. (2005), Mogensen et al. (2004), Van Driest et al. (2003), Richard et al. (2003), Takahashi-Yanaga et al. (2001), Elliott et al. (2000), Kimura et al. (1997)
R162P	HCM, RCM	Chung et al. (2021a), Chung et al. (2021b), Asatryan et al. (2019), Ingles et al. (2017), Gomez et al. (2017), Walsh et al. (2017), Alfares et al. (2015), Coppini et al. (2014), Rani et al. (2012), Santos et al. (2012), David et al. (2012), Garcia-Pavia et al. (2011), Kubo et al. (2011), Bos et al. (2006), Ingles et al. (2005), Cheng (2005), Doolan et al. (2005), Mogensen et al. (2004), Richard et al. (2003), Takahashi-Yanaga et al. (2001), Elliott et al. (2000), Kimura et al. (1997)
S166F	HCM	Hartl et al. (2023), Sepp et al. (2022), Resdal Dyssekilde et al. (2022), Alimohamed et al. (2021), Marschall et al. (2019), Zouk et al. (2019), van Lint et al. (2019), Ho et al. (2018), Walsh et al. (2017), Murphy et al. (2016), Mogensen et al. (2015), Kapplinger et al. (2014), Liu et al. (2012), Brion et al. (2012), Maron et al. (2012), Van Den Wijngaard et al. (2011), Ingles et al. (2005), Mogensen et al. (2004), Van Driest et al. (2004), Erdmann et al. (2003), Ward et al. (2001)
R170W	RCM	Mogensen et al. (2015), Zhang et al. (2011a), Galinska et al. (2010), Kaski et al. (2009)
R170Q	RCM	Stava et al. (2022), Marey et al. (2020), Marschall et al. (2019), Ross et al. (2017), Walsh et al. (2017), Mouton et al. (2015), Kaski et al. (2009), Kubo et al. (2007)
R170P	RCM	

(*Continued*)

Table 1. Continued.

(*Continued*)

Table 1. Continued.

Mutation	Disease type[a]	References
		Walsh et al. (2017), Mouton et al. (2015), Kaski et al. (2009)
K178E	RCM	Mogensen et al. (2003)
E182K	DCM	Quiat et al. (2020), Walsh et al. (2017), Pugh et al. (2014), Lakdawala et al. (2012)
K183E	HCM	Van Driest et al. (2003)
K183N	HCM	Coppini et al. (2014), Teirlinck et al. (2012), Van Den Wijngaard et al. (2011), Mogensen et al. (2004)
E184K	DCM	Lakdawala et al. (2012)
N185K	DCM	Carballo et al. (2009)
R186Q	HCM, RCM	Stava et al. (2022), Ware et al. (2021), Sohn et al. (2017), Walsh et al. (2017), Wang et al. (2016b), Lopes et al. (2015), Coppini et al. (2014), Roberts et al. (2013), Zhu Hu et al. (2012), Jordan et al. (2011), Fokstuen et al. (2011), Millat et al. (2010), Moon et al. (2005), Mogensen et al. (2004), Richard et al. (2003)
D190Y	RCM, HCM	Mogensen et al. (2003), (Kapoor et al. 2020)
D190G	RCM, HCM	Mogensen et al. (2003)
R192C	RCM	Hayashi et al. (2018), Alfares et al. (2015), Van Den Wijngaard et al. (2011), Millat et al. (2010), Mogensen et al. (2003)
R192H	RCM	Parrott et al. (2020), Fujino et al. (2002), Hayashi et al. (2018), Ding et al. (2017), Walsh et al. (2017), Kohda et al. (2016), Alfares et al. (2015), Thomas et al. (2015), Chen et al. (2014), Yang et al. (2013), Liu et al. (2012), Van Den Wijngaard et al. (2011), Jordan et al. (2011), Millat et al. (2010), Davis and Metzger (2010), Rai et al. (2009), Mathur et al. (2009), Davis et al. (2008), Du et al. (2008), Davis et al. (2007), Du et al. (2006), Kobayashi and Solaro (2006), Gomes et al. (2005b), Mogensen et al. (2003)
R192P	RCM, HCM	Yang et al. (2013), Liu et al. (2012), Van Den Wijngaard et al. (2011), Millat et al. (2010), Davis and Metzger (2010), Rai et al. (2009), Mathur et al. (2009), Davis et al. (2007), Kobayashi and Solaro (2006), Gomes et al. (2005b), Mogensen et al. (2003)
D196N	HCM	Kasak et al. (2022), Murdock et al. (2021), Norrish et al. (2019), Pantou et al. (2019), Walsh et al. (2017), Murphy et al. (2016), Amendola et al. (2015), Coppini et al. (2014), Berge and Leren (2014), Andreasen et al. (2013), Zhang et al. (2011b), Galinska et al. (2010), Mogensen et al. (2004), Richard et al. (2003), Niimura et al. (2002)
L198V	HCM	Cava et al. (2021), Burstein et al. (2021), Magri et al. (2020), Walsh et al. (2017), Lopes et al. (2015), Arad et al. (2014), Coppini et al. (2014), Lopes et al. (2013), Otsuka et al. (2012), Maron et al. (2012), Lippi et al. (2009), Baudenbacher et al. (2008), Doolan et al. (2005)
G203S	HCM	Kimura et al. (1997), Deng et al. (2003)
R204H	RCM	Parrott et al. (2020), Marschall et al. (2019), Maurizi et al. (2018), Robyns et al. (2017), Ding et al. (2017), Ross et al. (2017), Ingles et al. (2017), Campuzano et al. (2017), Walsh et al. (2017), Nguyen et al. (2016), Yang et al. (2010), Parvatiyar et al. (2010), Gambarin et al. (2008), Ingles et al. (2005), Doolan et al. (2005), Kimura et al. (1997)
K206Q	HCM	Kimura et al. (1997), Deng et al. (2003), Kohler et al. (2003)

(*Continued*)

Table 1. Continued.

[a]HCM, DCM, and RCM indicate hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, respectively.
Data source: https://www.ncbi.nlm.nih.gov/clinvar (Landrum et al. 2018).

blood filling, resulting in reduced cardiac output and symptoms of heart failure. RCM is characterized by rigid ventricular walls that impede filling during diastole, leading to heart failure symptoms. *TNNI3* mutations associated with RCM increase cardiac muscle stiffness, impairing relaxation between beats. Notable mutations include D127Y (Carballo et al. 2009) and L144Q (Mogensen et al. 2003). However, many mutations overlap among the three cardiomyopathy categories and some reported mutations exhibit conflicting pathogenicities.

Most mutations in troponin I occur in the switch or mobile region (Figure 2(B)). These regions are crucial for the inhibitory function of TnI, making mutations in these regions more likely to be pathogenic (Tobacman and Cammarato 2021). Furthermore, experimental deletion of the *C*-terminal 'mobile region' significantly increases thin-filament Ca^{2+} sensitivity and mimics the hypercontractile/diastolic-dysfunction phenotype seen in patients, emphasizing the pathogenic potential of variants in this region (Gilda et al. 2016; Meyer and Chase 2016). Additionally, some mutations have been identified in the cardiac-specific *N*-terminal and *N*-terminal conserved regions, which are important for PTMs; mutations in these sites can interfere with PTMs and downstream signaling. Notably, few mutations have been reported in the TnT-binding region, where a single amino acid change is less significant for the structural integrity of TnI and TnT interactions (Tadros et al. 2020). Functional studies on *TNNI3* mutations have utilized various models, including transgenic mice and induced pluripotent stem cell-derived cardiomyocytes. These studies provide insights into the molecular mechanisms underlying disease phenotypes and may assist in the development of targeted therapies. Continued research and genetic analyses are essential for understanding the full spectrum of mutations and their clinical implications, which will aid in improving diagnosis and developing potential therapeutic strategies for affected individuals.

Troponin I posttranslational modification

Posttranslational modifications (PTMs) of TnI play a critical role in regulating muscle contraction, especially in cardiac muscles, and have been extensively studied to understand their impact on cardiac function (Table 2). Compared to ssTnI and fsTnI, PTMs of cTnI have been more thoroughly investigated. Phosphorylation of cTnI is one of the most widely studied PTMs, involving the addition of phosphate groups to specific amino acid residues, primarily serine and threonine. While S5 and S6 have been less studied than other serine sites on cTnI, phosphorylation of these sites has been identified in wild-type mice. Studies have demonstrated that substituting serine residues at these positions with aspartic acid (S5D and S6D) to mimic phosphorylation and with alanine (S5A and S6A) to prevent phosphorylation has distinct impacts on myofilament function. Specifically, S6 phosphorylation affects ATPase activity without influencing calcium sensitivity. In contrast, preventing S5 phosphorylation affects calcium sensitivity but not ATPase activity (Henze et al. 2013). Additionally, S5/S6 phosphorylation has been observed in human cardiac tissues (Zhang et al. 2012). Phosphorylation at S23 and S24 are well-known phosphorylation sites in cTnI that play crucial roles in regulating cardiac muscle contraction and relaxation. These sites are primarily phosphorylated by protein kinase A (PKA) in response to β-adrenergic stimulation, commonly associated with the

Table 2. Featured human TNNI posttranslational modification.

Isoform	PTM	Position	Enzyme	References
TNNI3	Phosphorylation	S5, S6	Unknown	Zhang et al. (2012)
		S23, S24	AMPK, PKCα, PKCδ, PKD1, PKA, PKG	Sevrieva et al. (2020), Dvornikov et al. (2016), Cheng and Regnier (2016), Bedada et al. (2016), Wu et al. (2014), Wijnker et al. (2014), Cheng et al. (2014), Wijnker et al. (2013), Lang et al. (2013), Kooij et al. (2013), Zhang et al. (2012), Oliveira et al. (2012), Zhang et al. (2011a), Wijnker et al. (2011), Sfichi-Duke et al. (2010), Lu et al. (2010), Kooij et al. (2010), Han et al. (2010), Rybin et al. (2009), Zabrouskov et al. (2008), Sumandea et al. (2008), Howarth et al. (2007), Layland et al. (2005), Ward et al. (2004), Haworth et al. (2004), Deng et al. (2003), Schmidtmann et al. (2002), Ward et al. (2001), Deng et al. (2001), Dong et al. (2000), Keane et al. (1997), Dohet et al. (1995), Mittmann et al. (1990)
		Y26	Unknown	Zhang et al. (2012); Salhi et al. (2014)
		T31	MST1	You et al. (2009)
		S39	PKA	Ward et al. (2001)
		S42, S44	PKCα, PKCβ, PKCε, PKCγ	Layland et al. (2005); Kooij et al. (2013), Ward et al. (2004), Burkart et al. (2003), Noland et al. (1989),
		T51	MST1	You et al. (2009); Zhang et al. (2012)
		S77, T78	Unknown	Zabrouskov et al. (2008); Zhang et al. (2012)
		T129	MST1	You et al. (2009),
		T143	PKCα, PKCβ, PKCδ, MST1	Wijnker et al. (2014); Dvornikov et al. (2016), Kooij et al. (2013), Zhang et al. (2012), Rybin et al. (2009), You et al. (2009), Sumandea et al. (2008), Wang et al. (2006), Noland et al. (1989),
		S150	AMPK, PAK3	Nixon et al. (2012); Oliveira et al. (2012), Layland et al. (2005), Buscemi et al. (2002)
		S166	PKA	Zhang et al. (2012), Van Den Wijngaard et al. (2011), Ward et al. (2001)
		T181	Unknown	Zhang et al. (2012)
		S199	PKCα	Kooij et al. (2013); Wijnker et al. (2015), Zhang et al. (2012)
	Methylation	R74, R79, R146, R148	PRMT1	Onwuli et al. (2019)
	Ubiquitination	Lysines	MuRF1	Kedar et al. (2004)
	SUMOylation	K177	SUMO ligases (E1, E2, E3) (E2: UBC9)	Fertig et al. (2022)
	Glycation	K36, K50, K58, R79, K117, K120, K131, R148, R162, K164, K183, K193, R204	Unknown	Janssens et al. (2018)
	Citrullination	R158, R203	PAD2	Fert-Bober et al. (2015)
TNNI2	S-Nitrosylation	C134	Unknown	Dutka et al. (2017)
	S-glutathionylation	C134	Unknown	Dutka et al. (2017)
TNNI1,2,3	Acetylation	A2	Unknown	Mittmann et al. (1990)

AMPK, AMP-activated protein kinase catalytic subunit alpha-1 (PRKAA1); PKCα, Protein kinase C alpha type (PRKCA); PKCδ, Protein kinase C delta type (PRKCD); PKD1, Protein kinase D1 (PRKD1); PKA, cAMP-dependent protein kinase catalytic subunit alpha (PRKACA); PKG, cGMP-dependent protein kinase 1 (PRKG1); MST1, Serine/threonine-protein kinase 4 (STK4); PKCβ, Protein kinase C beta type (PRKCB)l; PKCγ, Protein kinase C gamma type (PRKCG); PKCε, Protein kinase C epsilon type (PRKCE); PAK3, Serine/threonine-protein kinase 3 (PAK3); PRMT1, Protein-arginine N-methyltransferase 1 (PRMT1); MuRF1, Muscle-specific RING finger protein 1 (TRIM63); UBC9, Ubiquitin-conjugating enzyme E2 I (UBE2I); PAD2 Peptidyl-arginine deiminase type 2 (PADI2).

fight-or-flight response. Phosphorylation at these sites decreases the sensitivity of myofilaments to calcium, thereby accelerating the relaxation phase of cardiac muscle contraction. Studies with transgenic mice expressing a non-phosphorylatable form of cTnI have shown that phosphorylation of these residues is essential for the proper response of cardiac myocytes to β-adrenergic signaling. This phosphorylation facilitates the rapid relaxation necessary for an increased heart rate and enhanced cardiac output during stress responses (Pi et al. 2002). A recent study has reported that phosphorylation of tyrosine 26 (Y26) represents a novel regulatory mechanism of cardiac function in a mouse model, which accelerates myocardial relaxation by decreasing calcium-sensitive force development and hastening calcium dissociation without compromising systolic performance (Salyer et al. 2024). Furthermore, the threonine 31 (T31) residue is phosphorylated by mammalian sterile 20-like kinase 1 (Mst1). This modification alters interactions within the troponin complex, ultimately affecting myofilament function and cardiac contractility. Although the role of T31 phosphorylation is not well understood, it may be relevant to oxidative stress, where Mst1 activation leads to increased phosphorylation of cTnI. T51 and T129 exhibit a similar mechanism of action as T31 (You et al. 2009). S39 is phosphorylated by PKA and, like S23 and S24, this modification significantly reduces the affinity of troponin I for troponin C, resulting in decreased calcium sensitivity and myocardial contractility. One study suggested that this mechanism involves 'overphosphorylation' beyond the usual S22 and S23 sites, further diminishing the affinity of troponin I for troponin C and fine-tuning calcium sensitivity and contractility (Ward et al. 2001). S42 and S44, like S23 and S24, similarly reduce the Ca^{2+} sensitivity of the myofilaments but are phosphorylated by Protein Kinase C alpha (PKCα) (Kooij et al. 2013). S77 and T78 have been identified in several studies; however, their functions and mechanisms remain unclear (Zabrouskov et al. 2008; Zhang et al. 2012). In contrast, phosphorylation of T143 significantly enhances myofilament Ca^{2+} sensitivity and improves muscle contraction. This phosphorylation is particularly important in heart failure, where elevated T143 phosphorylation alters muscle function by increasing Ca^{2+} sensitivity. Although T143 phosphorylation alone affects Ca^{2+} sensitivity, it works in concert with phosphorylation at other sites, such as S23 and S24, to comprehensively regulate cardiac muscle performance (Wijnker et al. 2014). S150 is phosphorylated by the AMP-activated protein kinase (AMPK), which increases myofilament Ca^{2+} sensitivity and enhances cardiac muscle contractility, particularly under ischemic conditions (Oliveira et al. 2012). The roles of S166 and threonine 181 (T181) residues are not well understood; however, a mutation in S166 has been identified as pathogenic in clinical studies (Van Den Wijngaard et al. 2011).

Other PTMs of TnI include methylation (Onwuli et al. 2019), ubiquitination (Kedar et al. 2004), SUMOylation (Fertig et al. 2022), glycation (Janssens et al. 2018), citrullination (Fert-Bober et al. 2015), oxidation (Cuello et al. 2018), S-nitrosylation and S-glutathionylation (Dutka et al. 2017), and acetylation (Mittmann et al. 1990). Although less studied, these modifications are gaining recognition as important regulators of TnI function and stability. Acetylation alters the charge and structure of TnI, potentially affecting its interactions with other myofilament proteins and muscle contraction. Acetylation is often associated with the regulation of protein stability and function. SUMOylation involves the attachment of a small ubiquitin-like modifier (SUMO) to specific lysine residues on TnI, which may play a role in stress response and cardiac protection mechanisms. Glycation, the non-enzymatic attachment of sugar molecules to amino groups in proteins (often due to elevated glucose levels), impairs protein function and is linked to diabetic complications. This modification negatively affects the structural integrity and contractile function of TnI. Methylation may regulate the function of TnI and its interactions within the troponin complex, thereby influencing cardiac contractility. Oxidation involves the addition of oxygen molecules to amino acid residues, often occurring during oxidative stress. This modification has been linked to altered myofilament function and cardiac dysfunction, particularly in heart failure. Citrullination, on the other hand, involves the conversion of arginine residues into citrulline by peptidylarginine deiminases (PADs). Citrullination has been implicated in the pathogenesis of heart failure by modifying the function and stability of proteins, potentially disrupting normal cardiac muscle contractions.

PTMs of cTnI are essential for regulating heart muscle function. Phosphorylation and other modifications modulate TnI activity, stability, and interactions, thereby influencing muscle physiology and pathology. Phosphorylation regulates calcium sensitivity and ATPase activity. Particularly, S23/24 is a great example of this mechanism, which is mediated by the β-adrenergic response, reducing calcium sensitivity and aiding muscle relaxation. Other PTMs, such as acetylation, SUMOylation, glycation, methylation, oxidation, and citrullination, although less explored, are important for cTnI function and stability. Ongoing research into these modifications may uncover novel

therapeutic targets for heart diseases associated with cardiac physiology. Future investigations should aim to elucidate the detailed mechanisms and interactions among these modifications to develop targeted therapies for muscle-related diseases.

Troponin I evolution

The troponin complex originated approximately 700 million years ago, with troponin I evolving as a key regulatory protein in early metazoans. This early emergence is marked by the presence of *TNNI* genes in all invertebrates, except for cnidarians (jellyfish and sponges), highlighting a significant evolutionary advancement in the development of more complex muscle regulation mechanisms. In invertebrates, a single gene encodes TnI, which regulates muscle contraction by interacting with actin and tropomyosin (Cao et al. 2019). The *TNNI* gene family has since diversified into three main types in vertebrates: cardiac *TNNI* (*TNNI3*), skeletal fast *TNNI* (*TNNI2*), and skeletal slow *TNNI* (*TNNI1*). This diversification resulted from gene duplication events, including two rounds of whole-genome duplication (WGD), 1R and 2R, early in the evolution of vertebrates (Figure 3). In mammals, there are three *TNNI* paralogs (*TNNI1*, *TNNI2*, and *TNNI3*) and three *TNNT* paralogs (*TNNT1*, *TNNT2*, and *TNNT3*). The genes encoding TnI and TnT are located on the same chromosome and exhibit tissue-specific expression patterns. The *TNNI* and *TNNT* genes are closely linked within the genome: *TNNI2* (11p15.5) is near *TNNT3* (11p15.5), *TNNI3* (19q13.4) is near *TNNT1* (19q13.4), and *TNNI1* (1q31.3) is near *TNNT2* (1q32). This genomic arrangement suggests that *TNNI* and *TNNT* genes have co-evolved, with tandem duplications and WGDs playing significant roles (Rasmussen and Jin 2021). *TNNI3* and *TNNT2* are specifically adapted for cardiac muscles, while *TNNI2* and *TNNT3*tailored for fast-twitch skeletal muscles. In contrast, *TNNI1* and *TNNT1* are adapted for slow-twitch muscles. Although the core function of TnI is conserved across species, sequence variability is evident, particularly in regions critical for its interaction with other troponin subunits and actin. The conserved regions ensure the fundamental inhibitory function of TnI, whereas the variable regions permit species-specific adaptations. Phylogenetic analyses have shown that *TNNI* sequences cluster according to muscle type rather than species, underscoring the functional specialization of each *TNNI* types (Rasmussen et al. 2022). This conservation of function, along with sequence variability, underscores the evolutionary balance between maintaining essential regulatory roles and adapting to diverse physiological demands. The *N*-terminal extension of cardiac TnI (*TNNI3*) represents a significant adaptation that first appeared in early tetrapods and certain lobe-finned fishes, such as the coelacanth. This extension – absent in ray-finned fish – facilitates PKA-mediated phosphorylation and enhances cardiac muscle relaxation and ventricular filling. This evolution reflects the high selective value placed on efficient cardiac function in air-breathing tetrapods, adapting to the increased metabolic demands of life on land (Joyce et al. 2023). Recent comparative genomic studies show that this extension continues to evolve: in several high-heart-rate mammal groups, the entire exon encoding the Ser23/24 motif has been independently lost or

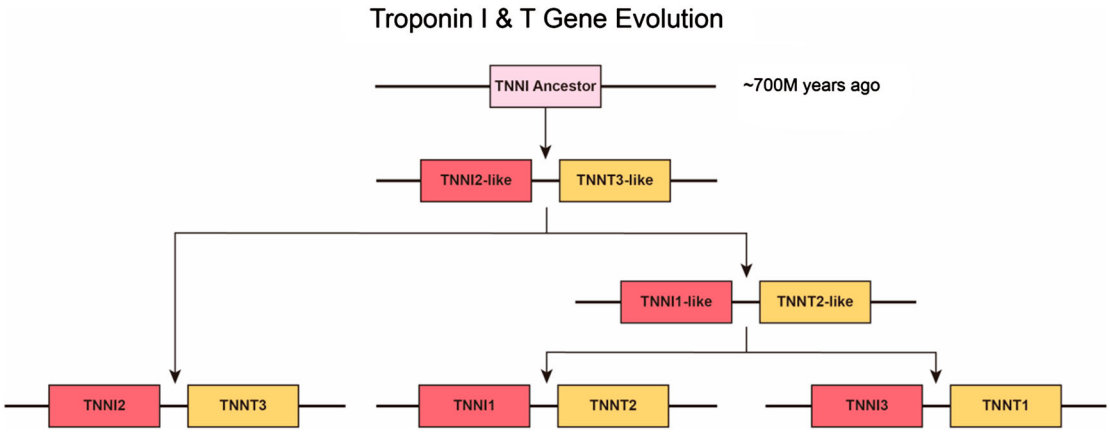

Figure 3. Hypothetical evolutionary pathways of troponin I and troponin T genes. Based on loci and sequence similarities, the evolution of human troponin I (TNNI) and troponin T (TNNT) genes appears to have been shaped by whole-genome duplications (WGDs) and multiple gene duplication events. An ancestral TNNI gene, which gave rise to the TNNI and TNNT gene families, is hypothesized to have first diverged into TNNI2-like and TNNT3-like lineages. Subsequent evolutionary events further differentiated these genes into TNNI1-like, TNNT2-like, and other specific subtypes, ultimately leading to the diversification of the modern TNNI and TNNT gene families.

alternatively spliced, effectively mimicking constitutive phosphorylation and enhancing diastolic function (Joyce et al. 2024). These evolution-guided insights emphasize the importance of studying natural variants to inform precision medicine strategies. For example, therapeutic exon-skipping of TNNI3 exon 3 might provide a new approach for treating diastolic heart failure (Landim-Vieira and Pinto 2024).

Conclusions and perspective

Troponin I, a critical component of the troponin complex in striated muscles, plays a central role in regulating muscle contraction and relaxation through calcium-mediated mechanisms. It serves as a molecular switch for Troponin C, enabling precise control over actomyosin interactions during muscle activity. The three TnI isoforms – encoded by the genes TNNI1, TNNI2, and TNNI3 – are specialized for slow skeletal, fast skeletal, and cardiac muscles, respectively, reflecting tissue-specific adaptations to diverse physiological demands. The function of troponin I is finely tuned by various posttranslational modifications (PTMs), including phosphorylation, acetylation, SUMOylation, glycation, methylation, oxidation, and citrullination. Among these modifications, phosphorylation at serines 23 and 24 in cardiac troponin I (TNNI3) is particularly critical, as it modulates calcium sensitivity and myocardial contractility in response to adrenergic signals. Emerging approximately 700 million years ago, the troponin complex has undergone evolutionary diversification through gene duplication events, resulting in specialized isoforms tailored for distinct muscle functions. Mutations in TNNI3 are strongly associated with various cardiomyopathies, including hypertrophic, dilated, and restrictive cardiomyopathy, which impair heart contractility and calcium handling. In contrast, mutations in TNNI1 and TNNI2, while less common, have been linked to muscle weakness and congenital contractures, reflecting the diverse roles of TnI across muscle types. Understanding the multifaceted regulatory mechanisms and functional roles of troponin I is essential for advancing our knowledge of muscle physiology. Ongoing research into the interplay of PTMs and genetic mutations shows promise for uncovering novel therapeutic strategies for cardiomyopathies and other muscle-related disorders, paving the way for targeted interventions and improved clinical outcomes.

Contributions

DH: Conceptualization; Investigation; Data Curation; Writing-Original Draft. **YL**: Data Curation; Writing-Original Draft. **SL**: Writing-Original Draft; Writing-Review & Editing. **SE**: Conceptualization; Data Curation; Writing-Original Draft.

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