

Mutations in Genes Encoding Fast-Twitch Contractile Proteins Cause Distal Arthrogryposis Syndromes

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The distal arthrogryposes (DAs) are a group of disorders characterized by multiple congenital contractures of the limbs. We previously mapped a locus for DA type 2B (DA2B), the most common of the DAs, to chromosome 11. We now report that DA2B is caused by mutations in *TNNI2* that are predicted to disrupt the carboxy-terminal domain of an isoform of troponin I (TnI) specific to the troponin-tropomyosin (Tc-Tm) complex of fast-twitch myofibers. Because the DAs are genetically heterogeneous, we sought additional candidate genes by examining modifiers of mutant *Drosophila* isoforms of TnI. One of these modifiers, *Tm2*, encodes tropomyosin, another component of the Tc-Tm complex. A human homologue of *Tm2*, *TPM2*, encodes β -tropomyosin and maps to the critical interval of DA type 1 (DA1). We discovered that DA1 is caused by substitution of a highly conserved amino acid residue in β -tropomyosin. These findings suggest that DAs, in general, may be caused by mutations in genes encoding proteins of the contractile apparatus specific to fast-twitch myofibers. This provides a new opportunity to directly study the etiology and pathogenesis of multiple-congenital-contracture syndromes.

Introduction

A child with an isolated congenital contracture (e.g., clubfoot) is born once in every 200–500 live births, and ~1 of every 3,000 children is born with two or more body areas affected by congenital contractures (i.e., arthrogryposis). Nevertheless, the etiology and pathogenesis of congenital contractures in neurologically normal children remains unclear in the majority of cases, most of which are sporadic. However, it is clear that the etiology of clubfoot has a genetic component (Andrade et al. 1998), and autosomal dominant segregation of contractures has been well documented (Hall et al. 1982; Bamshad et al. 1996a; Krakowiak et al. 1998). In the mid-1990s, to facilitate the identification of genes causing contractures, we revised the definition and classification of a group of heritable disorders called the “distal arthrogryposes” (DAs) (Bamshad et al. 1996b). In general, the DAs are characterized by nonprogressive, congenital contractures of two or more different body areas without primary neurological and/or muscle disease that affects limb function. Features common to all DAs in-

clude a consistent pattern of distal joint involvement, limited proximal joint involvement, an autosomal dominant inheritance pattern, and widely variable expressivity. Ten different DAs were recognized and classified hierarchically according to the proportion of features they share with one another (Bamshad et al. 1996b).

The prototypic DA is DA type 1 (DA1 [MIM 108120]), which is primarily characterized by campodactyly and clubfoot, although the shoulders and hips may also be affected. The phenotype of DA1 is similar to that of another DA called “Freeman-Sheldon syndrome” (FSS [MIM 193700]). In contrast to DA1, the phenotype of FSS includes scoliosis, a very small oral orifice (often only a few millimeters in diameter at birth), H-shaped dimpling of the chin, deep nasolabial folds, and blepharophimosis (narrow palpebral fissures) (Freeman and Sheldon 1938). In some individuals, however, distinguishing between the diagnosis of DA1 and FSS can be difficult. Moreover, in some extended families, different individuals have been assigned a diagnosis of either DA1 or FSS (Klemp and Hall 1995).

In 1997, we described individuals with characteristics of both DA1 and FSS (Krakowiak et al. 1997). Their features included a triangular face, downward-slanting palpebral fissures, prominent nasolabial folds, a small mouth, small mandible, cervical webbing, severe campodactyly, ulnar deviation, and clubfoot or calcaneovalgus deformities (fig. 1). We classified this disorder as variant FSS, or DA2B (MIM 601680), whereas indi-

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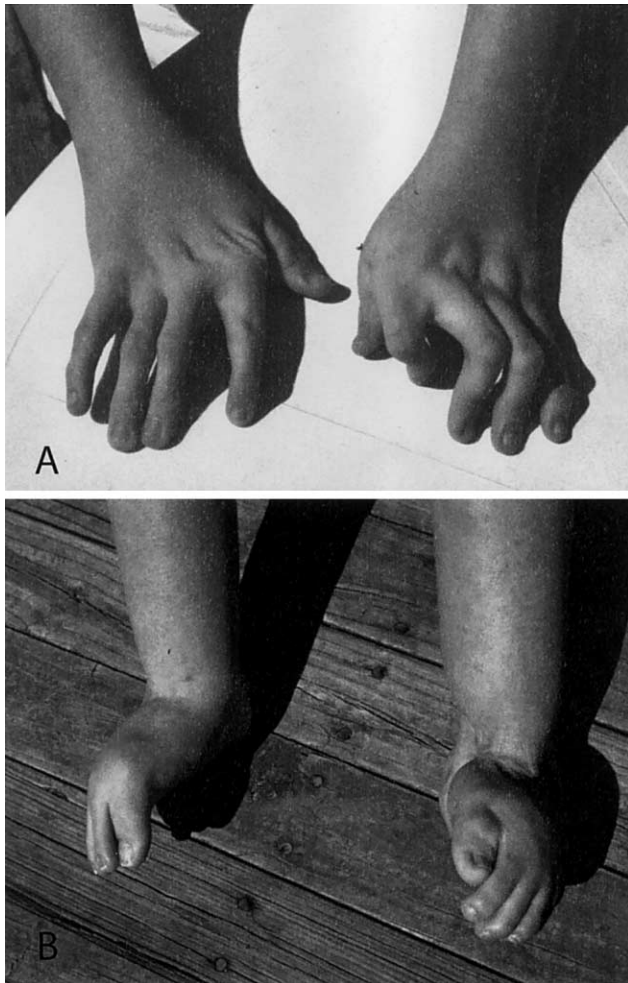


Figure 1 Typical malformations observed in individuals with DA2B. *A*, Hands characterized by camptodactyly and ulnar deviation. *B*, Feet showing camptodactyly accompanied by calcaneovalgus deformities and a vertical talus or clubfoot (not shown).

viduals meeting the full diagnostic criteria for FSS (Bamshad et al. 1996b) were referred to as having classical FSS, or DA2A. Subsequently, we mapped a locus for DA2B to chromosome 11p15.5 within a few hundred kilobases of the telomere (Krakowiak et al. 1997).

We now report that DA2B is caused by mutations in *TNNI2*, encoding an isoform of troponin I (TnI) specific to fast-twitch myofibers. Homologues of *TNNI2* have been studied in a wide variety of model organisms, including *Drosophila*, chick, rabbit, and mouse models (Mullen and Barton 2000). In *Drosophila*, TnI mutants with abnormalities of skeletal muscle architecture causing wing and limb defects have been available for many decades (Vigoreaux 2001). These mutants have hypercontracted intercostal flight muscles (IFM), a condition that causes protracted elevation of the wings, reduced frequency of wing beats, and an awkward, irregular gait

(Beall and Fryberg 1991; Barbas et al. 1993). As a consequence, the TnI locus was named “wings up A” (*wup A*) (Hotta and Benzer 1972), although the name was subsequently changed to “*heldup*” (Deak 1977; Deak et al. 1982).

Because of the indispensability of the IFM for flight, the flightlessness phenotype has been a useful screening device for identification of genes involved in myogenesis. Many of the genes identified encode components of the troponin-tropomyosin-actin complex. This led, in part, to the search for genetic interactions among alleles of these loci, and a handful of dominant suppressors of *heldup* mutants have been identified (Vigoreaux 2001). Recently, a serine-to-phenylalanine substitution at amino acid residue 185 of tropomyosin, encoded by a mutant allele (*D53*) of *tropomyosin-2* (*Tm2*), was found to be a suppressor of *heldup*² (Naimi et al. 2001). Genetic suppressors are often associated with their own mutant phenotype, and *D53* homozygotes are no exception, exhibiting a significant reduction in flight ability in comparison with the wild type. The human homologue of *Tm2* (*TPM2*) maps to chromosome 9p11.3 in the critical interval for DA1 (Bamshad et al. 1994). Moreover, the protein encoded by *TPM2* (β -tropomyosin) interacts directly with TnI. Consequently, we considered *TPM2* a candidate gene for other DAs. Screening of *TPM2* led to the identification of a mutation causing DA1. Thus, mutant alleles encoding TnI and tropomyosin in *Drosophila* are both associated with reduced movement and morphological defects, and they encode proteins that interact with one another. Mutations in both of the human homologues cause multiple-congenital-contraction syndromes.

Material and Methods

Clinical Status

All studies were performed with the approval of the institutional review board of the University of Utah and the General Counsel of the Shriners Hospitals for Children. After informed consent was obtained, living members of each kindred were evaluated by review of their medical history, completion of a questionnaire, and physical examination. An individual was considered to have a diagnosis of DA1 if two or more of the major clinical manifestations were present (Bamshad et al. 1996b). For DA2B, at least two major features plus two minor features were required for diagnosis (Krakowiak et al. 1997). Major diagnostic criteria of the upper limbs included ulnar deviation, camptodactyly, hypoplastic and/or absent flexion creases, and overriding fingers at birth. Major diagnostic criteria of the lower limbs included talipes equinovarus, calcaneovalgus deformities, a vertical talus, and metatarsus varus. Minor diagnostic

criteria include a triangular face, downward-slanting palpebral fissures, attached ear lobules, a small mouth, small mandible, arched palate, cervical webbing, and short stature.

For DA1, a total of 10 patients with familial disease and 4 patients with sporadic disease were tested; for DA2B, 16 patients with familial disease and 18 patients with sporadic disease were examined. Fourteen patients with classical FSS (5 familial and 9 sporadic) were also screened for mutations in *TNNI2* and *TPM2*.

Mutation Analysis of *TNNI2* and *TPM2*

Genomic DNA was prepared from peripheral lymphocytes and/or Epstein-Barr virus-transformed lymphoblastoid cell lines, using standard techniques. Genomic DNA sequences were amplified according to the Qiagen HotStar*Taq* protocol in 1 × buffer (10 mM Tris [pH 8.3], 40 mM KCl, 1.5 mM MgCl₂, and 1 × Q solution). The reaction was performed with 25 ng of template genomic DNA, 200 μM of dNTPs, 10 pmol of each primer, and 0.625 U of HotStar*Taq* DNA polymerase in a total reaction volume of 25 μl. Samples were cycled 30 times in an MJ Research DNA Engine Tetrad, using a standard three-step PCR profile with an initial denaturing step at 94°C for 15 min and a final extension step at 72°C for 10 min. Annealing temperatures and primer sequences can be found in tables A and B (online only). PCR products of *TNNI2* were purified on a 2% agarose gel, and PCR products of *TPM2* were purified using Qiaquick columns (Qiagen). Purified PCR products were sequenced using ABI BigDye Terminator, version 2.0, reagent. Sequenced products were loaded on an ABI 377 automated sequencer and analyzed by Sequencing Analysis 3.4.1 and Sequencher 4.1 software (Genecodes). The forward and reverse strand of exons 1–8 of *TNNI2* and exons 1–9 of *TPM2*, including the flanking splice-recognition sequences, were analyzed.

The presence of each mutation was confirmed in at least one affected individual in each kindred by cloning a PCR-amplified product into pCR2.1 plasmid by use of the TA cloning kit (Invitrogen), according to manufacturer's recommendations. For each individual, 10 transformed clones and 3 control clones were screened. Plasmid DNA was isolated with a Qiaprep miniprep kit (Qiagen) and was subjected to direct sequencing, as described above. In all other family members, mutations were detected by restriction digestion. In *TNNI2*, a G→A mutation at position 521 in exon 8 creates a novel *MspI* restriction site, and the C→T nonsense mutation at bp 466 of *TNNI2* eliminates a *BfuAI* restriction site. A C→G missense mutation at position 271 in exon 3 of *TPM2* destroys a novel *SacII* restriction site. Accordingly, each of these exons—and the regions flanking it—was amplified from affected and unaffected family

members and was then digested, with the appropriate restriction enzyme, and gel fractionated. For each mutation, 140 control chromosomes were also screened. Haplotypes of *TNNI2* were constructed by genotyping each affected individual and his or her parents for three microsatellite markers: D11S1984, D11S4893, and D11S1923.

Results

Two different mutations in *TNNI2* were found in 4 (~10%) of 34 kindreds with DA2B (fig. 2). The first mutation found was a G→A missense mutation at bp 521 that causes an arginine-to-glutamine substitution at amino acid residue 174 (R174Q). Several factors suggest that this mutation is probably disease causing. First, the R174Q mutation results in the substitution of an amino acid residue that is highly conserved in all isoforms of TnI and between mice and humans (fig. 3). Second, this change was found in two unrelated families with DA2B but was not found in 140 control chromosomes. Third, in pedigree K2 (fig. 2), the R174Q missense mutation arises de novo and causes DA2B in all of the children who inherited it (data not shown).

The second mutation found in *TNNI2* was a C→T nonsense mutation at bp 466 that is predicted to encode a mutant TnI lacking 26 amino acid residues of the carboxy-terminus. In kindred K3, this mutation arose de novo in the affected father and was subsequently transmitted to all of his offspring, each of whom is affected and has a different mother (fig. 2). The segregation of this mutation in kindred K4 suggests either that it arose de novo twice or that mosaicism for this mutation exists in one of the phenotypically normal parents. However, the level of mosaicism may be too low to be detected in lymphocytes and/or may exist in cell populations that were not tested (e.g., gonadal tissue). In each of the kindreds in which we found a disease-causing mutation in *TNNI2*, the mutation arose on a different haplotype background (data not shown). In addition, these mutations were found on both maternally and paternally derived chromosomes from different kindreds.

Patients with sporadic DA2B and those belonging to families with only an affected parent-child pair, which are uninformative for linkage studies, were also screened for mutations in *TNNI2* by sequencing all of the exons and one of the known regulatory regions of *TNNI2* (Mullen and Barton 2000). No disease-causing mutations were found. To look for large deletions that may not be detected via sequencing of genomic regions, we screened for allelic dropout, using a battery of microsatellites that bracket *TNNI2*. In addition, we used long-range PCR to amplify genomic regions of ~2–3 kb spanning entire exons and introns, and we looked for

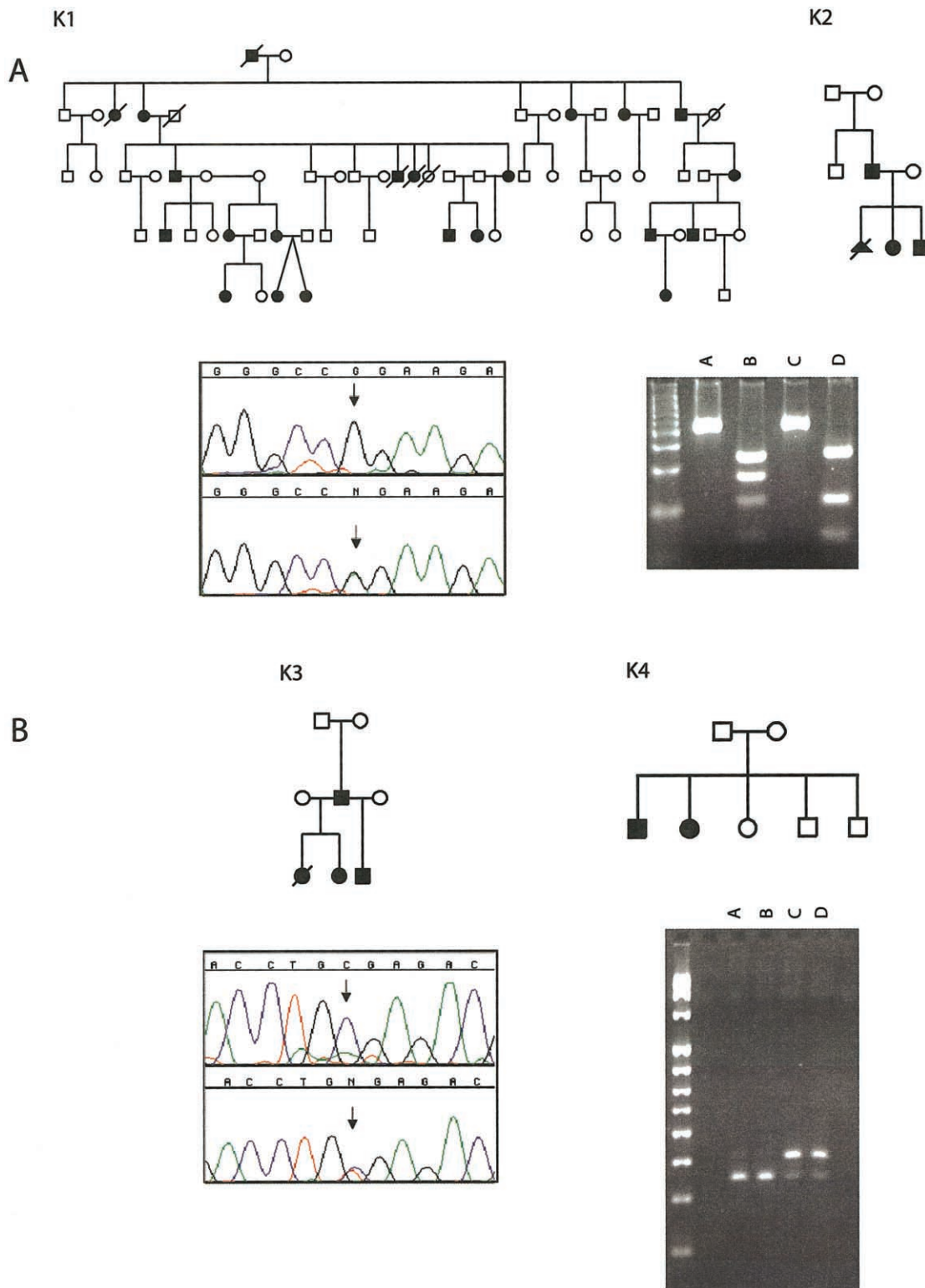


Figure 2 Electropherograms of mutations in exon 8 of *TNNI2*. A, G→A missense mutation at position 521 in exon 8 of *TNNI2* in kindreds K1 and K2. The mutation creates a novel *MspI* restriction site. Digests of *TNNI2* amplicons from an affected individual (lane B) fractionate into four fragments (243 bp, 166 bp, 110 bp, and 56 bp), whereas only three fragments (243 bp, 110 bp, and 56 bp) are observed in an unaffected individual (lane D). Lanes A and C, Undigested control samples. B, C→T nonsense mutation at bp 466 of exon 8 of *TNNI2* in kindreds K3 and K4. The mutation eliminates a *BfuAI* restriction site. Digests of *TNNI2* amplicons from two affected sibs in kindred K4 (lanes C and D) fractionate into two fragments (409 bp and 344 bp), whereas only one fragment (344 bp) is found in the unaffected parents (lanes A and B). The 65-bp product cannot be observed on this gel.

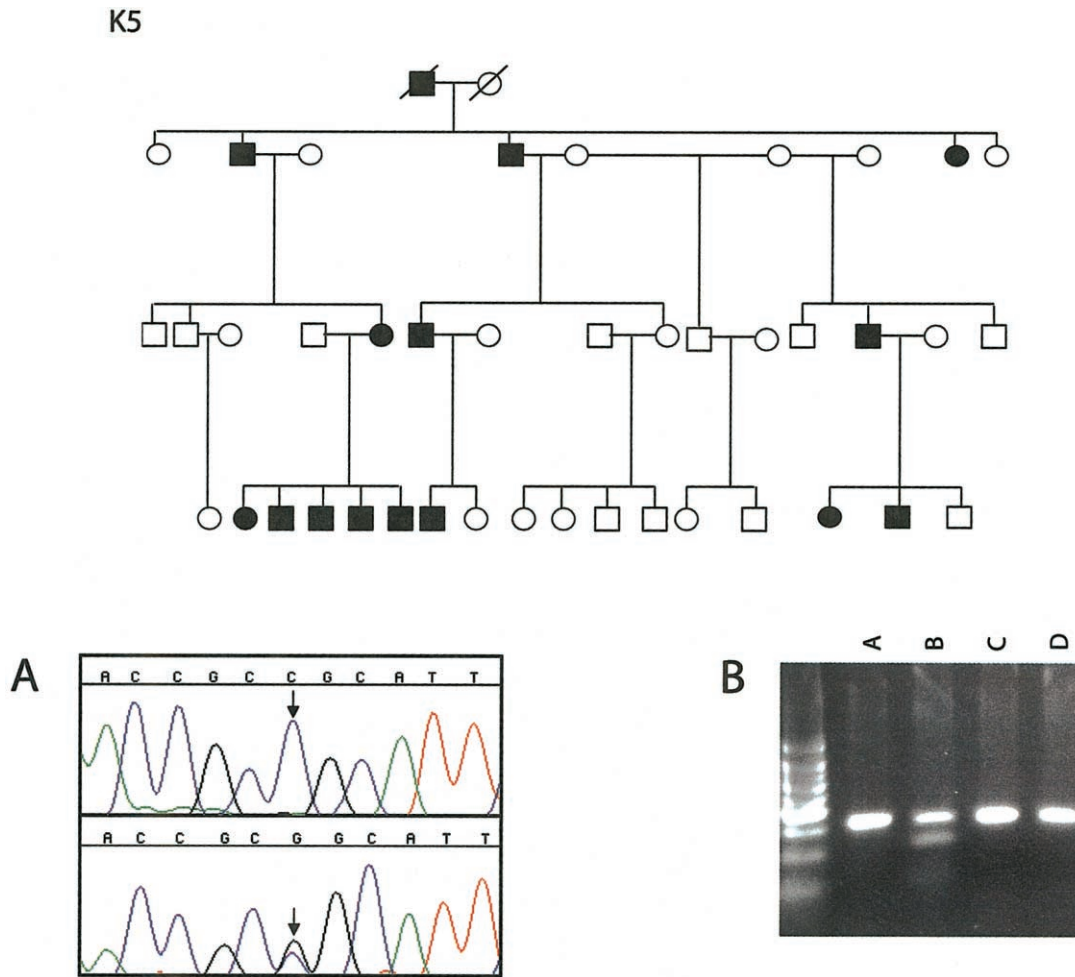


Figure 4 *Top*, Pedigree of family K5. *Bottom*, electropherogram of a mutation on exon 3 and digests of amplicons. *A*, Electropherogram of a C→G missense mutation at position 271 in exon 3 of *TPM2*. The mutation creates a novel *Sac*II restriction site in kindred K5. *B*, Digests of *TPM2* amplicons from an affected individual. The digests from this individual separate into three fragments (320 bp, 218 bp, and 102 bp) (lane B), whereas amplicons from an unaffected individual remain undigested (lane D). Lanes A and C, Undigested control amplicons.

inhibiting actomyosin ATPase activity. TnC binds Ca^{+2} ions, leading to a conformational change that relieves TnI inhibition on actomyosin ATPase activity. Yet, its sensitivity to Ca^{+2} ions appears to be determined, in part, by the carboxy-terminal residues of TnI (Digel et al. 2001; Burton et al. 2002).

Mutations in the *TNNI2* paralogue, *TNNI3*, encoding a cardiac-specific isoform of TnI, can cause a cardiomyopathy by either a dominant-negative effect or haploinsufficiency (Seidman and Seidman 2001). In *TNNI3*, substitution of amino acid residues homologous to those juxtaposed on either side of R174Q in *TNNI2* result in diminished sensitivity to Ca^{+2} ions and a reduction in contractile force leading to the development of a cardiomyopathy (Watkins et al. 1995; Murphy et al. 2001). For example, a glycine-to-serine substitution of amino acid residue 203 results in decreased maximal contractile force and diminished sensitivity to

Ca^{+2} ions (Burton et al. 2002). Similarly, deletion of the 17 carboxy-terminal amino acid residues of TnI, thought to occur in the heart during myocardial stunning, results in diminished sensitivity to Ca^{+2} ions and reduced contractility (McDonough et al. 1999). Transgenic mice expressing a gene encoding this truncated protein also develop diminished responsiveness to Ca^{+2} ions, diminished contractility, and ventricular dilatation—recapitulating the stunned myocardium (Murphy et al. 2000). The R156Ter mutation predicted to delete the 26 carboxy-terminal amino acid residues of TnI specific to fast-twitch myofibers might have a comparable effect. Accordingly, we hypothesize that both substitution and deletion mutants of the carboxy-terminus of fast-twitch-specific TnI result in diminished responsiveness to Ca^{+2} ions, leading to reduced muscle contraction and congenital contractures.

It is also possible that the contractures observed in

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Chicken  ATDAEAEVASLNRRIQ---LVEEELDRAQERLATALQKLEEAKEKADESE-
Frog     ---AEAEEVASLNRRIQ---LVEEELDRAQERLATALQKLEETEKAVIDESE-
Rabbit   ---AEDVASLNRRRTOMIQLVVEEELTPAQERLVTSLQKLEEAKEKADESE-
Rat      ---AEDVASLNRRIQ---LVEEELDRAQERLATALQKLEEAKEKADESER-
Mouse    ---AEDVASLNRRIQ---LVEEELDRAQERLATALQKLEEAKEKADESE-
Human    ----EADVASLNRRIQ---LVEEELDRAQERLATALQKLEEAKEKADESE-
                R91G

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Figure 5 Alignment of isoforms of β -tropomyosin from six animal species. The R91G substitution replaces an arginine residue that is invariant among species.

individuals with DA2B are caused by perturbation of a nontraditional function of TnI. The TnI isoform encoded by *TNNI2* has recently been discovered to bind to bFGF, to inhibit capillary endothelial cell proliferation (Feldman and Rouleau 2002), and to be a potent inhibitor of angiogenesis in human cartilage (Moses et al. 1999). Other proteins of the contractile apparatus (e.g., actin) are also found in cellular compartments that are different from their conventional location, although their function in these compartments is unknown.

β -Tropomyosin is a coiled-coil protein that binds head to tail along the length of the actin filament. It is negatively charged overall, and the R91G substitution is predicted to cause a local reduction in surface charge that may alter both the local conformation of the coiled coil and its flexural rigidity (fig. 6). This could influence its interactions with actin, which are thought to be critical for thin-filament regulation (Squire and Morris 1998). Glycine residues in porcine cardiac and rabbit skeletal α -tropomyosins appear to be compatible with the overall helical character of the protein suggested by low-resolution crystal structures (Whitby and Phillips 2000). A glycine side chain might, however, create an irregularity in the coiled coil, resulting in a region of increased flexibility that affects thin-filament regulation. Interestingly, a missense mutation in *TPM3* that causes nemaline rod myopathy encodes a γ -tropomyosin molecule that folds abnormally and exhibits reduced sensitivity of actomyosin ATPase activity in the presence of Ca^{+2} ions (Moraczewska et al. 2000). Thus, the reduced sensitivity of actomyosin ATPase to Ca^{+2} ions may be the mechanism that causes congenital contractures in individuals with DA1.

The hypothesis that some DA disorders have a myopathic origin has been tendered for two decades (Hall et al. 1982), yet many affected individuals have never undergone a muscle biopsy, and the findings, if any, in those who do undergo biopsy are typically nonspecific. Moreover, the site of the muscle biopsy is commonly chosen for its convenience (e.g., quadriceps) and is usually not a muscle rich in fast-twitch myofibers. Of the existing anecdotal reports of the muscle histology of children affected with various DAs, a single case report is noteworthy. It describes a paucity of fast-twitch myo-

fibers in an individual with a phenotype resembling DA2B (Vanek et al. 1986). Our results suggest that further study of muscles rich in fast-twitch myofibers in children with DA1 and DA2B is warranted.

Although the expression of TnI isoforms is restricted among adult muscle fiber types, the spatial expression patterns of these genes during development is not (Zhu et al. 1995). In the developing skeletal muscle of mice, isoforms of TnI are first expressed in the myotome of somites at 9.5 days post conception (dpc). The slow-twitch isoform is expressed first in all newly formed myotubes, regardless of the future fiber type. As primary myotubes develop into secondary myotubes (14–16 dpc), expression of the fast-twitch isoform of TnI increases. The timing of this switch between isoforms is intriguing, because, in our experience with half a dozen patients for whom a diagnosis of DA2B was established prenatally, the limbs are often normal during the first 18–20 wk of gestation. It is typically over the next 6–8 wk that the contractures of the hands and feet become recognizable via ultrasonography. Although there are no data on the temporal and spatial expression patterns of TnI isoforms in humans, the onset of expression of a mutant *TNNI2* during myogenesis appears to coincide with our ability to detect fetal contractures in DA2B.

In newborn mice, the expression of slow-twitch TnI is stronger in “deep” muscles containing predominately slow-twitch fibers (e.g., soleus), whereas expression of fast-twitch TnI is stronger in more-peripheral muscles (e.g., tibialis anterior and extensor digitorum longus) (Zhu et al. 1995). The homologous peripheral muscles in humans also contain predominately fast-twitch myofibers and control the movements of body areas affected in individuals with DA2B. In contrast, expression of *TPM2* is lower in fast-twitch myofibers than in slow-twitch myofibers. However, the expression of β -tropomyosin protein is higher in fast-twitch myofibers (Pieple and Wiczorek 2000). Thus, the spatial expression pattern of *TPM2* also reflects the peripheral distribution of contractures in individuals with DA1.

In 1991, Beall and Fyrberg discovered that the original *heldup* allele (i.e., *heldup*²), a troponin mutant, was caused by an alanine-to-valine substitution. A variety of *heldup* alleles with phenotypes varying in severity

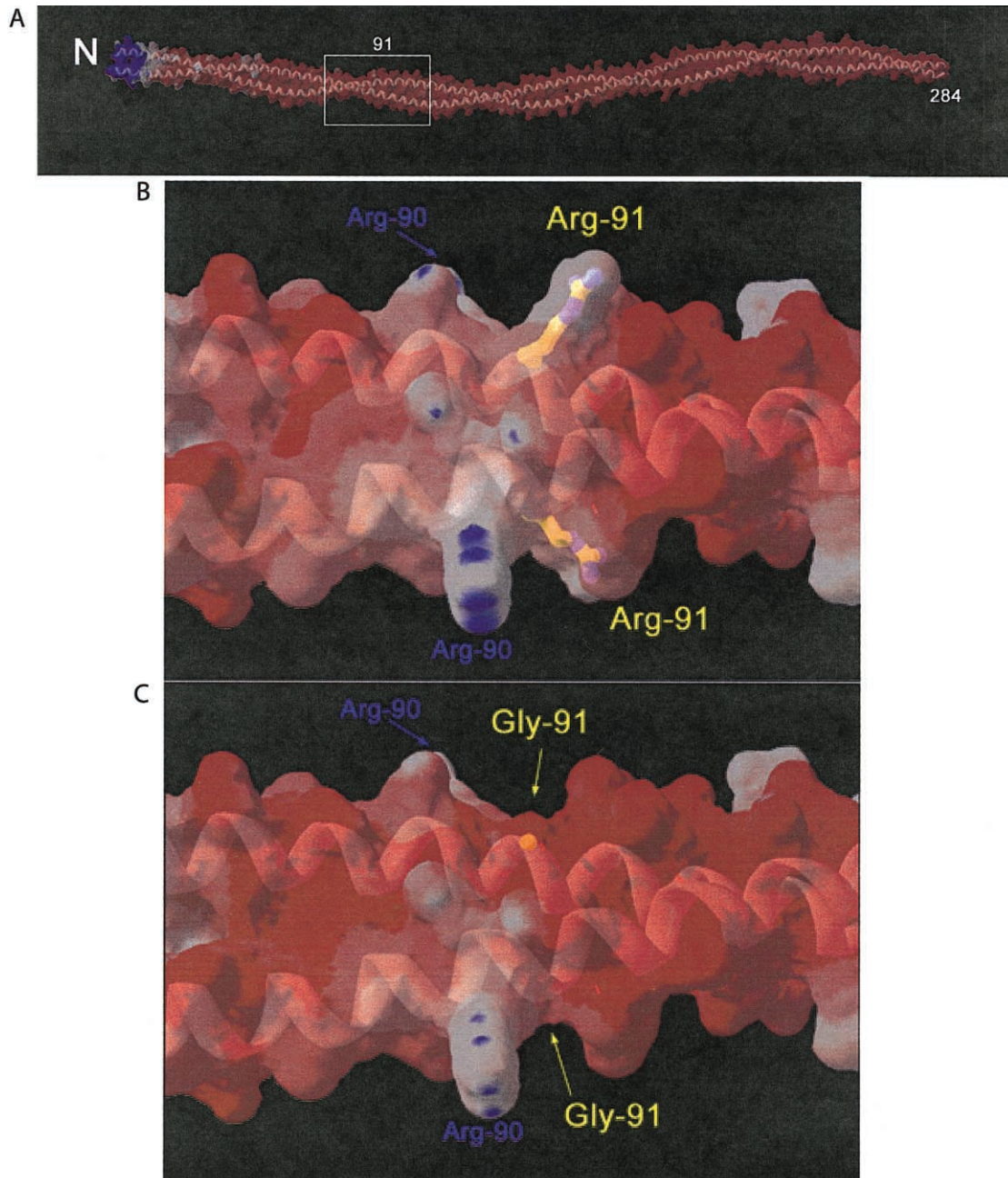


Figure 6 A, Homology model of human β -tropomyosin dimer with a molecular surface colored by relative surface electrostatic charge. The model is based on the 7-Å crystal structure of porcine cardiac α -tropomyosin dimer (Protein Database entry 1C1G). A partially transparent molecular surface is shown colored by electrostatic charge: *red* indicates regions dominated by negative charge; *white* indicates areas that are neutral; *blue* indicates positive charge. Relatively few positively charged arginine and lysine surface amino acid side chains are found outside the N-terminal region. The sparse positively charged amino acids are largely neutralized by the large number of surface negatively charged aspartate and glutamate amino acids, which creates the dominant negatively charged surface character of the molecule. A ribbon model (*gray*) shows the characteristic coiled-coil fold of tropomyosin and is visible through the partially transparent molecular surface. “N” indicates the relatively positively charged N-terminal region, which is important for end-to-end polymerization, and “284” indicates the C-terminus. Box indicates the region of the molecule surrounding residue 91 shown in detail (*panels B and C*). B, Detailed view of the area of surrounding residue 91. A ball-and-stick model of the Arg91 side chain is colored by atom type and is visible through the partially transparent molecular surface. The positive charge provided by Arg90 and Arg91 is flanked by negative charge, characteristic of the molecule as a whole. C, Detailed view of the area surrounding residue 91 with R91G mutation. Mutation to glycine neutralizes the positive charge at that position, leading to an increase in local negatively charged character, seen as an increase in red color in *panel C* relative to *panel B*. Figures were generated with the program Swiss PDB Viewer.

from embryonic lethal to mild abnormalities of flight performance and jump ability have subsequently been described. No substantial differences were noted between the phenotypes of the individuals with different alleles of *TNNI2*, although each of these mutant alleles disrupts the same domain of TnI. The IFM of many *heldup* mutants show nearly normal morphogenesis but subsequently begin to hypercontract, leaving only stumps near their attachment points in newly emerged flies. This recapitulates the reports of misplaced, hypoplastic, or absent tendons in some individuals with DA (Hall et al. 1982), as well as in those in whom we identified mutations in *TNNI2*.

The spatial and temporal expression patterns of genes encoding proteins of the Tc-tropomyosin-actin complex in fast-twitch fibers may not be regulated independently in patients with DA. For example, a lack of TnT in *Drosophila* results in a secondary reduction of tropomyosin and actin (Fyrberg et al. 1990). This indicates that a feedback mechanism tightly coordinates the expression of interrelated genes and proteins. Accordingly, abnormalities of other proteins of the Tc-tropomyosin-actin complex in fast-twitch myofibers may cause other multiple-congenital-contraction disorders. We suspect that the development of DA may be a final common outcome of mutations that alter the function and stoichiometry of any one of the proteins of the Tc-tropomyosin-actin complex in fast-twitch fibers. This would be analogous to the observation that mutations in genes encoding many of the isoforms of the Tc-tropomyosin-actin complex in cardiac muscle can cause a cardiomyopathy.

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Electronic-Database Information

Accession numbers and the URL for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM) <http://www.ncbi.nlm.nih.gov/Omim/> (for DA1 [MIM 108120], DA2B [MIM 601680], and FSS [MIM 193700])

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