Cardiac and skeletal myopathies: can genotype explain phenotype?

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Abstract

The inherited muscle diseases, skeletal muscle nemaline myopathy and cardiac muscle hypertrophic myopathy (HCM) have been recognised for decades. Recently it has become apparent that mutations in almost any protein component of the sarcomere could cause myopathy. Thus changes in many sarcomeric protein genes can produce a common phenotype. Several recent publications indicate the opposite property: mutations in one sarcomeric protein can produce different muscle disease phenotypes. The most dramatic example of this property is actin, mutations in which are associated with hypertrophic cardiomyopathy, dilated cardiomyopathy, nemaline myopathy and actin myopathy.

The inherited muscle diseases, skeletal muscle nemaline myopathy and cardiac muscle hypertrophic myopathy (HCM) have been recognised for decades, however the molecular causes of disease were unknown. The breakthrough came with the discovery that a point mutation at arginine 403 in cardiac muscle β-myosin was responsible for FHC (Perryman et al., 1992). Functional studies followed that indicated slower actin filament sliding in the in vitro motility assay and slower muscle shortening (CUDA et al., 1993). This work provoked an intensive search for other mutations and other genes associated with HCM and it soon became apparent that mutations in every protein component of the sarcomere could cause cardiomyopathy (Bonnie et al., 1998). Recently it has been found that skeletal muscle myopathies can also be caused by mutations in contractile proteins leading to a simple hypothesis that sarcomeric diseases are always due to mutations in sarcomeric proteins. Investigations of the functional consequences of these mutations seemed to produce as many different answers as there were mutations (Redwood et al., 1999); some mutations increase speed of muscle shortening and some decrease it; some increase Ca2+ sensitivity and some decrease it. These results have posed the difficult question of explaining how mutations in different genes and with different functional effects in vitro could lead to the same phenotype (Bonnie et al., 1998; Redwood et al., 1999).

The situation is made even more intriguing by several recent publications which indicate the opposite property: mutations in one sarcomeric protein can produce different muscle disease phenotypes. The most dramatic example of this property is actin, the backbone of the thin filament and one of the most highly conserved proteins in the sarcomere (Figure 1), but mutations in tropomyosin and troponin T have also been shown responsible for either HCM or nemaline myopathy. Mutations R312H and E361G in the ACTC gene were initially identified as being associated with inherited dilated cardiomyopathy (DCM) (Olson et al., 1998). Subsequently a separate set of mutations (E99K, A331P, P164A, A295S) was shown to be associated with HCM. (Mogensen et al., 1999; Olson et al., 2000).

Skeletal muscle myopathies are generally much more severe than cardiomyopathy, presumably because a severe defect in cardiac contractility is not compatible with life. Their genetic origin is correspondingly different; whilst cardiomyopathies are generally dominant mutations, skeletal muscle myopathy mutations are often recessive (presumably the mutant protein is so damaged it cannot compete with wild-type) and many severe mutations are de novo rather than inherited. Tropomyosin (TPM3) (Laiing et al., 1995) was the first gene associated with nemaline myopathy, followed by nebulin (Pelis et al., 1999) and actin (ACTA1) (Nowak et al., 1999). Most recently a mutation in the slow skeletal muscle troponin T gene (TNNT1) has been reported associated with nemaline myopathy (Johnston et al., 2000). Although skeletal muscle myopathies are not as well characterised as cardiomyopathies there are two extreme phenotypes–nemaline myopathy, characterised by accumulations of nemaline bodies (essentially stacked Z-lines) and actin myopathy, characterised by excess thin filaments outside the sarcomeres. Nowak et al. (1999) reported 15 mis-sense mutations in the ACTA1 gene resulting in 14 amino acid changes. The number of ACTA1 mutations currently stands at 35 and growing. It is of great interest that, as with ACTC mutations, a range of phenotypes was observed; of the 15 mutations reported by Nowak et al. three were from patients with congenital myopathy with excess of thin

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myofilaments’, four had ‘mild nemaline myopathy’ and 11 had ‘severe nemaline myopathy’ (seven of the 11 died within the first year of life).

The theme of multiple diseases from mutations in the same protein is also observed with tropomysosin, where D175N and E180G and V95A mutations in the TPM1 gene lead to slightly increased Ca$$^{2+}$$-sensitivity of contraction and are associated with HCM (Bing et al., 2000; Karibe et al., 2001), whilst an M9R mutation in the TPM3 gene associated with nemaline myopathy caused a large decrease in Ca$$^{2+}$$-sensitivity in transfected muscle cells (Michele et al., 1999). The recent series of studies on actin mutations and the four associated disease phenotypes may provide information about the structure–function relationships of the actin molecule. Although the atomic structure of monomeric actin in combination with several actin binding proteins has been determined the structure of polymeric actin is still derived from models. Relatively little is known about the contact sites on f-actin with contractile regulatory proteins and their functional interactions with actin and with each other. Consequently it is very tempting to try and derive structure–function relationships from these mutations. Olson et al. (2000) speculate that the

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<th>HCM</th>
<th>DCM</th>
<th>Severe Nemaline myopathy</th>
<th>Actin myopathy</th>
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Fig. 1. Mutations in actin can produce four different phenotypes. The location of mutations associated with HCM (magenta), DCM (red), nemaline myopathy (green) and actin myopathy (dark blue) are shown. The location of subdomain 1 is indicated.