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Review

Genotype–phenotype correlations in *ACTA1* mutations that cause congenital myopathies

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ABSTRACT

Mutations in the skeletal muscle actin gene, ACTA1 are responsible for up to 20% of congenital myopathies with a variety of pathologies that includes nemaline myopathy, intranuclear rod myopathy, actin myopathy and congenital fibre type disproportion. In their review of 2003, Sparrow et al. considered how these actin mutations might affect muscle function at the molecular level and thus cause the disease. Since then several laboratories have taken up the challenge of investigating genotype–phenotype relationships experimentally. The objective of this review is to assess the current state of our understanding of the molecular mechanisms of skeletal myopathies and the prospects for future therapies based on this knowledge. Thirty congenital myopathy-causing *ACTA1* mutations have been studied using a range of biochemical and *in vitro* approaches. They showed diverse molecular defects, and there is no obvious pattern seen in mutations resulting in the same histopathology.

1. Introduction

Actin is a highly conserved protein of the cytoskeleton and an essential part of the contractile apparatus in muscle. In the human genome there are six actin genes which encode for isoforms with 90% similarity in their sequence. *In vivo*, different isoforms can coexist in the same cell, but are differentially regulated, and tissue-specific [1]. By far the most well studied actin isoform is skeletal muscle α-actin encoded by *ACTA1*. This isoform is the predominant isoform in skeletal muscle, and also accounts for 20% of total actin in adult hearts, while cardiac α-actin, encoded by *ACTC*, constitutes 80% [2]. These two sarcomeric actins differ by only four residues. The contractile filaments of smooth muscle are made up from smooth muscle α-(*ACTA2* gene) and γ-actin (*ACTAG2* gene) whilst the cytoskeletal actin isoforms are cytoplasmic β-(*ACTB* gene) and γ-actin (*ACTG1* gene). Mutations in five of the actin genes have been reported to be disease-causing. Mutations in the *ACTA1* gene lead to a variety of muscle diseases including nemaline myopathy (NM), intranuclear rod myopathy (IRM), actin myopathy (AM) and congenital fibre type disproportion (CFTD) [3,4]. Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) can be consequent upon mutations in *ACTC* gene [5–7], and missense mutations in the γ-cytoplasmic actin gene (*ACTG1*) have been associated with autosomal dominant deafness [8]. Mutations in smooth muscle α-actin (*ACTA2*) cause thoracic aortic aneurysms and dissections [9] and mutation of β-actin (*ACTB*) has been associated with developmental malformations, deafness and dystonia [10].

In their review of 2003, Sparrow et al. considered how the known actin mutations that cause skeletal myopathy might affect muscle function and cause the disease [11,12]. Since then several laboratories have taken up the challenge of investigating genotype–phenotype relationships experimentally. The objective of this review is to assess the current state of our understanding of the molecular mechanisms of skeletal myopathies and the prospects for future therapies based on this knowledge.

2. Structure

Actin is a single chain peptide with 375 residues. The structure of monomeric actin has been determined using X-ray crystallography, most recently by Otterbein et al. [13]. The molecule is divided into two domains of roughly equivalent size (inner domain 3 + 4 and outer domain 1 + 2) by a cleft containing the bound nucleotide and cation. Those two domains are connected by only two strands of the polypeptide chain (the 'hinge' region 137–150 and 333–338) [14], allowing relative movement of the two domains. The core of

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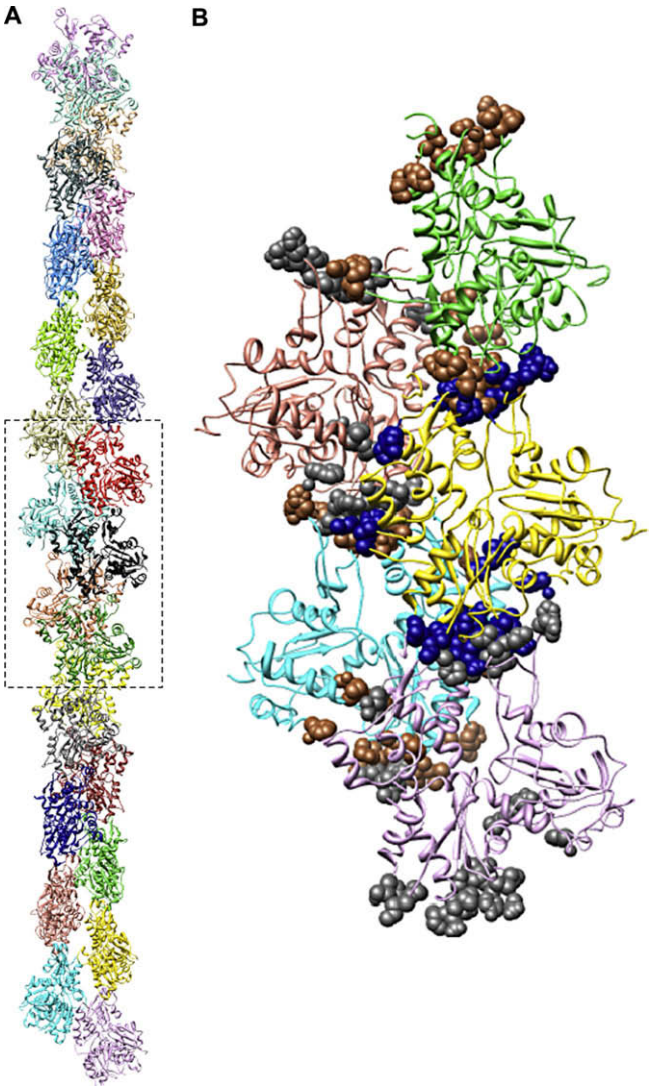

Fig. 1. Molecular model of actin filament. The figure was produced with Chimera software using Actin_Model.pdb file [81] with individual actin monomers differently coloured. The central part of the structure is magnified in (B). Residues that are involved in intermolecular contacts are shown as spheres and are colour coded for different monomers.

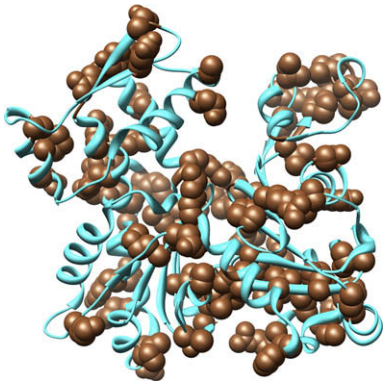

Fig. 2. NM ACTA1 mutations do not cluster on 3D structure of actin molecule. NM actin mutations are spread all over the 3D structure of actin molecule with mutated residues marked as brown spheres. Produced with Chimera software using Actin 1J6Z.pdb file.

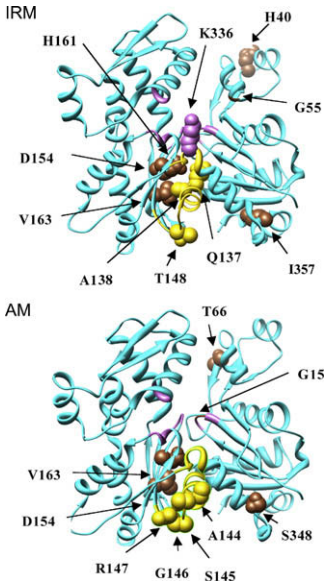

Fig. 3. Location of IRM actin mutations. Mutated residues H40, D154, H161, V163 and I357 are marked as brown spheres. Q137, A138, T148 (yellow sphere) are part of the 'hinge' region (yellow). K336 (purple sphere) sits within the 'hinge' region also at the nucleotide binding site (purple). Produced with Chimera software using Actin 1J6Z.pdb file. Location of AM actin mutations. Mutated residues T66, D154, V163 and S348 are marked as brown spheres. G15 (purple sphere) is part of the nucleotide binding sequence (purple). G146 and R147 (yellow sphere) are in the 'hinge' region (yellow). Produced with Chimera software using Actin 1J6Z.pdb file.

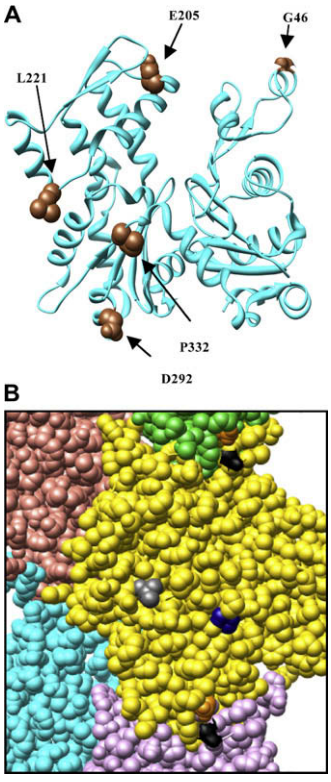

Fig. 4. Location of CFTD mutations in the actin molecule. (A) Location of the mutations in the actin monomer. Peptide backbone in cyan, mutated residues as brown spheres. (B) Location of the mutations in the actin polymer. Except for E205, all the residues mutated (G46-black, L221-grey, D292-orange and P332-navy) in CFTD patients are exposed in the actin polymer. Interestingly, G46 is in contact with residue D292 of the adjacent actin monomer. Produced with Chimera software using Actin 1J6Z.pdb file for (A) and Actin_Model.pdb [81] file for (B).