Genomic organization and single-nucleotide polymorphism map of desmuslin, a novel intermediate filament protein on chromosome 15q26.3

ABSTRACT

No causative mutations were found in the desmuslin gene. However, the single-nucleotide polymorphisms mapped in this study represent a well-mapped group that can be used for disequilibrium studies of this region of chromosome 15q26.3.

INTRODUCTION

Background Dystrophin and its associated proteins are thought to be involved in the anchoring of the muscle cell membrane to the extracellular matrix, and the absence of many of these proteins can lead to the phenotype of muscular dystrophy. The dystrophin-associated protein complex (DAPC) consists of several subgroups of protein complexes, each associated either directly or indirectly with dystrophin. The sarcoglycans are four transmembrane proteins that are organized by a fifth protein called sarcospan. This complex is thought to be involved in signalling at the cell membrane. A second subcomplex, known as the dystroglycan complex, interacts directly with dystrophin in the cytoplasm and laminin in the extracellular matrix, thus providing a structural link between the inside and the outside of the cell. A third subcomplex involves the dystrobrevins and syntrophins which form a complex at the C-terminal region of dystrophin and have an as yet unidentified function. Desmuslin (DMN) was recently identified as an α-dystrobrevin-interacting protein via the yeast two-hybrid method. Both desmuslin mRNA and protein are expressed primarily in cardiac and skeletal muscle and the gene encodes a novel intermediate filament (IF) protein of 1253 amino acids. Electron microscopic analysis shows that desmuslin colocalizes with desmin, another muscle IF protein. Co-immunopreciptation experiments revealed that the desmuslin and α-dystrobrevin interaction involves the region of protein encoded by exons 8-16 of α-dystrobrevin and domains 1A through 2A of the desmuslin rod domain. Desmuslin is hypothesized to function as a mechanical support to the muscle myofibers by making a previously unrecognized linkage between the extracellular matrix via the DAPC and the Z-discs through desmin and plectin. As several IF proteins, including desmin, have been implicated in human genetic disorders such as dominant and recessive congenital and adult onset myopathies, desmuslin becomes a candidate to be involved in myopathies as well. Supporting this is the exclusive expression of DMN in skeletal and cardiac muscle. The DMN gene was analyzed for mutations in 71 patients with various forms of muscular dystrophy and myopathy. In addition to 9 single-nucleotide polymorphisms (SNPs) that do not change the protein sequence, we identified 12 SNPs that do alter the residue they encode. Although examination of controls has shown that none of them is likely to cause the phenotype, our results are useful for future disequilibrium studies of this region of chromosome 15q26.3 and for mutation analysis and association studies in other genetic disorders.

CONCLUSION

Conclusions The characterization of the individual components that form protein complexes in skeletal muscle and heart, especially information concerning genotype-phenotype correlations, will increase our understanding of the pathophysiology of human muscle diseases. We encourage other groups to test for the presence of the C598T DMN

mutation in their human patient samples affected by muscular and cardiac diseases. The generation of desmuslin null animal models will also contribute to the understanding of the role of this protein in muscle and cardiac disease.