

tients who are homozygous for null mutations and did not express adhalin. Missense mutations resulted in milder phenotypes with varying degrees of severity and a pronounced decrease in adhalin expression. Interestingly, a large number of patients have the Arg77Cys mutation, and almost all the mutations have been found in the extracellular domain of adhalin.

How do these missense mutations lead to the loss of adhalin in the sarcolemma and eventually to dystrophic skeletal muscle? First, it is not clear why these missense mutations affect adhalin function or stability. However, missense mutations in other membrane proteins, such as the cystic fibrosis transmembrane conductance regulator, lead to improper protein processing, resulting in a degraded protein. Thus, a reasonable hypothesis is that mutations in adhalin may result in improper processing or improper assembly of adhalin with other components of the dystrophin-glycoprotein complex which, in turn, lead to rapid turnover of mutated adhalin. The reduction of the 35-kd DAG and novel 43-kd DAG (A3b) in patients with adhalin deficiency supports this hypothesis. Interestingly, a similar absence of adhalin and reduction in the 35-kd DAG and 43-kd DAG was observed in the BIO 14.6 cardiomyopathic hamster, which experiences both autosomal recessive cardiomyopathy and myopathy [12]. Biochemical experiments on isolated membranes from skeletal muscle of this hamster have demonstrated that a loss of adhalin can lead to the functional disruption of the dystrophin-glycoprotein complex. Thus, it is likely that the deficiency of adhalin, whether caused by null or missense mutations, will lead to the disruption of the linkage between the sarcolemma and extracellular matrix.

Analysis of adhalin mutations will be important to distinguish genetically heterogenous forms of autosomal recessive muscular dystrophy. Hopefully in the future this will ensure appropriate genetic counseling and possible gene therapy. The small size of the adhalin cDNA (1.5 kb) is encouraging for future adhalin gene therapy approaches. In addition, pharmacological approaches may be developed to allow adhalin with missense mutations to reach the sarcolemma membrane. Finally, the oligomeric structure of the dystrophin-glycoprotein complex [7, 8, 14] raises the intriguing possibility that mutations in the 43-kd DAG (A3b), 35-kd DAG, or 25-kd DAP could also result in autosomal recessive limb-girdle muscular dystrophy.

Kevin P. Campbell, PhD
Howard Hughes Medical Institute
Department of Physiology and Biophysics
University of Iowa College of Medicine
400 EMRB
Iowa City, IA 52242

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