**A MISSENSE MUTATION IN THE CHRM2 GENE IS ASSOCIATED WITH FAMILIAL DILATED CARDIOMYOPATHY**

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Circulating autoantibodies against the M2-muscarinic acetylcholine receptor (CHRM2) have been detected in patients with dilated cardiomyopathy (DCM). However, it has yet to be determined whether the pathogenesis of familial DCM may be linked to the genetic variability of the CHRM2 gene. The coding regions of the CHRM2 gene were examined by direct DNA sequencing. Plasma concentrations of autoantibodies against CHRM2 were determined by ELISA in 7 unrelated DCM families. Linkage analysis demonstrated cosegregation of the microsatellite markers, D7S509 and D7S495 that flank the CHRM2 gene, with the familial form of DCM. A novel missense mutation (C722G) replacing cysteine with tryptophan (Cys176Trp) was identified in the CHRM2 gene in all affected members but was absent in unaffected members. Additionally, 139 sporadic DCM patients and 450 normal volunteers were screened for the same mutation, but none were identified. Among the 12 affected members with familial DCM, 5 patients had died suddenly and 7 experienced ventricular arrhythmia, atrioventricular conduction block, and heart failure. All mutation carriers were positive for autoantibodies against CHRM2. Survival analysis disclosed that prognosis in patients who were mutation carriers with familial DCM was poorer than that seen in patients who were noncarriers with sporadic DCM (P<0.05). We have identified a novel missense mutation (C722G) in the CHRM2 gene associated with familial DCM. We also show that this variant correlates with the presence of autoantibodies against CHRM2. Patients with C722G mutation have more progressive disease, characterized by sudden death, arrhythmia, and heart failure.