Sporadic cases of dilated cardiomyopathies associated with atrioventricular conduction defects are not linked to mutation within the connexins 40 and 43 genes

Dilated cardiomyopathies are common forms of primary myocardial disorders responsible for severe heart failure which may require cardiac transplantation[1]. Viral infection, alcohol, carnitine deficiency or mutation within the dystrophin gene have been recognized as causative for the myopathy[2–4].

Epidemiological studies have shown that approximately 20% of these cardiomyopathies are inherited[5]. A subset of dilated cardiomyopathies are associated with severe atrioventricular conduction defects. This clinical entity is rare and mitochondrial mutations can cause the disease but usually affect other organs besides the myocardium[6]. A large kindred with autosomal dominant transmission of dilated cardiomyopathy associated with atrioventricular conduction defects was carefully studied a few years ago[6]. A genome-wide linkage analysis with this pedigree identified a disease locus mapped to chromosome 1p1-1q1. Several candidate genes are mapped to this region, including the gap junction protein connexin 40 gene[6]. Moreover, the selective disruption of the murine connexin 40 (Cx40) was shown to be responsible for atrioventricular block, supporting the hypothesis that this gene could be a candidate gene to human heart conduction abnormalities[7].

Connexin 43 (Cx43) is the predominant junction protein in the heart and it is thought to modulate the contractility and the electrical coupling of cardiac myocytes[8–10]. In human hypertrophic and ischaemic hearts, Cx43 content in the myocardium was shown to be reduced[11,12]. Based on these functional data observed in humans and animals together with the genetic epidemiological data, we investigated whether mutation within the coding region of the Cx40 and Cx43 genes could be responsible for the very rare sporadic cases of dilated cardiomyopathies with complete heart block.

We report three cases of patients presenting the rare association of congenital heart block and dilated cardiomyopathy. The first case had a congenital Wenckebach A-V block and short episodes of complete atrioventricular block with abnormal left ventricular function. The two other cases had a complete atrioventricular block requiring pacemaker implantation in association with severe left ventricular dysfunction (idopathic dilated cardiomyopathy), leading, in one case, to heart transplantation. The cases were sporadic with no evidence of viral, toxic or gene-associated defects, as observed in mitochondrial gene mutations. DNA was extracted from whole blood from the three cases and from three unrelated healthy subjects. The DNA was amplified by PCR using several oligonucleotides flanking the human Cx40 and Cx43 genes and the PCR products were sequenced using standard conditions. Nucleic acid and amino-acid composition of both genes was shown to be identical in the control and the three identified cases. Several amino acid substitutions were noticed between the previously published Cx40 gene[13] and our three Cx40 control sequences (GenBank accession numbers: Bank1270156, AF151979 for Cx40, Bank1270357, AF151980 for Cx43).

Since the nucleic acid composition of our three cases and the three controls were strictly identical, we concluded that a different genetic background could have resulted in the differences, compared with the previously published human Cx40 gene[13] and/or that this may later have incorporated some sequencing errors. Our study revealed that mutations within the coding regions of the Cx40 and Cx43 genes are not responsible for the very rare forms of sporadic dilated cardiomyopathy associated with atrioventricular conduction defects. However, this study could not exclude the presence of mutations within the regulatory regions of these genes and/or the presence of mutations within trans-acting factors which regulate the expression of these genes.

J.-A. HAEFLIGER
J. J. GOY
G. WAEBER
University Hospital,
Lausanne, Switzerland

References


