Familial Atrial Septal Defect and Atrioventricular Conduction Disturbance Associated With a Point Mutation in the Cardiac Homeobox Gene CSX/NKX2-5 in a Japanese Patient

Toru Hosoda, MD; Issei Komuro, MD; Ichiro Shiojima, MD; Yukio Hiroi, MD; Miki Harada, MD; Yuji Murakawa, MD; Yasunobu Hirata, MD; Yoshio Yazaki, MD

Atrial septal defect (ASD) is the most common form of congenital cardiac defect in humans. Recently, point mutations in the cardiac homeobox gene CSX/NKX2-5 have been reported to cause the autosomal dominant form of familial ASD. Notably, all the affected patients exhibit atrioventricular conduction disturbance and some of them died suddenly. The first case of familial ASD with a mutation of the CSX/NKX2-5 gene in a Japanese patient is reported here. Identification of CSX/NKX2-5 mutations in ASD patients would be very important because the existence of such mutations may predict sudden cardiac death. (Jpn Circ J 1999; 63: 425–426)

Key Words: Atrial septal defect; CSX/NKX2-5; Homeobox; Sudden cardiac death

Congenital cardiovascular diseases account for most human birth defects1,2 and the susceptibility of the heart to developmental anomalies is thought to reflect the complex process of heart formation during embryonic development. Although a growing number of the molecular determinants that govern the process of cardiogenesis have been identified3,4, the role of these molecules in the development of congenital cardiac defects is largely unknown. Recently, however, point mutations in the human cardiac homeobox gene CSX/NKX2-5 were shown to be associated with cases of familial atrial septal defect (ASD) and atrioventricular (AV) conduction disturbances5. Csx/Nkx2-5 is a homeobox-containing gene, which was first isolated from the murine heart6,7. It is predominantly expressed in the heart, and targeted gene disruption revealed its essential role in normal heart development and morphogenesis8, which indicates the critical role of CSX/NKX2-5 not only in the morphogenesis of the heart, but also in the physiological function of the cardiac conduction system. Here we report the first case of familial ASD with AV conduction disturbance associated with a mutation in CSX/NKX2-5 in a Japanese patient.

Case Report

A 59-year-old man was admitted to hospital because of the failure of his pacemaker lead, which was successfully treated by implanting a new pacing lead. At the age of 45, when he exhibited Adam-Stokes syncope due to atrial fibrillation with slow ventricular response, he was diagnosed as having ASD (Fig 1) and he had simultaneous surgical ASD closure and permanent pacemaker implantation. One of his 2 sons also had ASD and exhibited AV block at the age of 10. He too had had surgical ASD closure and permanent pacemaker implantation, but died at the age of 18 due to pneumonia (Fig 2). In order to examine whether a point mutation in CSX/NKX2-5 was associated with this case of familial ASD, we extracted genomic DNA from the whole blood of the 59-year-old patient and determined the sequence of the entire coding region of CSX/NKX2-5. Sequence analysis revealed a C to T transversion at nucleotide 701 in one allele (Fig 3), resulting in the production of a carboxy-terminal truncated protein due to the nonsense mutation at amino acid 198.

Discussion

Three types of point mutations in CSX/NKX2-5 have been reported in 4 big ASD families5. All mutations are situated in or just after the homeodomain5. The mutation in CSX/NKX2-5 is a homeobox-containing gene, which was first isolated from the murine heart6.7. It is predominantly expressed in the heart, and targeted gene disruption revealed its essential role in normal heart development and morphogenesis8, which indicates the critical role of CSX/NKX2-5 not only in the morphogenesis of the heart, but also in the physiological function of the cardiac conduction system. Here we report the first case of familial ASD with AV conduction disturbance associated with a mutation in CSX/NKX2-5 in a Japanese patient.
the present case is the same as one of these 3 mutations and exists just after the homeodomain. The truncation in the carboxy-terminal sequences outside the homeodomain is thought to result in activation of CSX/NKX2-5 due to the production of an activating mutant. In contrast, the other 2 mutations in the homeodomain are thought to cause CSX/NKX2-5 haplo-insufficiency due to the change in the DNA-binding affinity or the sequence specificity of the homeodomain. In this respect, there is an apparent paradox in the pathophysiological nature of the ASD caused by CSX/NKX2-5 mutations. Both partial hyperactivation and inactivation of the function of the CSX/NKX2-5 protein result in the failure of atrial septum formation. In addition, no ASD or AV conduction abnormalities have been reported in mice heterozygous for the Csx/Nkx2-5 null allele. Therefore, the precise molecular mechanisms by which these mutations in CSX/NKX2-5 cause ASD awaits further detailed analysis.

It has been reported that all the affected patients with CSX/NKX2-5 mutations have AV conduction abnormalities and a high incidence of sudden death or pacemaker implantation even after surgical correction of the ASD. Our proband and his son also showed AV conduction abnormalities (Fig 2), which suggest the critical role of CSX/NKX2-5 in the physiological function of the AV conduction system in the adult. Although the precise function of CSX/NKX2-5 in the maintenance of normal AV conduction is unknown at present, the fact that the electrophysiological properties of AV nodal cells are similar to those of embryonic cardiomyocytes may suggest a possible relationship between AV nodal dysfunction and impaired cardiomyocyte differentiation due to CSX/NKX2-5 mutations. The identification of CSX/NKX2-5 mutations in familial ASD patients is, therefore, of practical importance in that the existence of such mutations may predict the risk of sudden cardiac death and the requirement for pacemaker implantation.

In summary, we have identified the first case of familial ASD with AV conduction abnormalities associated with a point mutation in CSX/NKX2-5 in a Japanese patient. Further cumulative information regarding the CSX/NKX2-5 mutations that cause familial ASD will elucidate both the pathological nature of congenital heart diseases and the genetic basis of heart development.

References