Novel NKX2-5 mutations responsible for congenital heart disease

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ABSTRACT. Congenital heart disease (CHD) is the most common birth defect and is the leading cause of infant morbidity and mortality resulting from birth defects. Increasing evidence demonstrates that genetic variation in the NKX2-5 gene, which encodes a homeobox-containing transcription factor crucial to cardiogenesis, is an important molecular determinant for CHD. Nevertheless, the genetic components underlying CHD remain largely unknown. We screened NKX2-5 for potential molecular defects in patients with CHD. The entire coding region of NKX2-5 was initially sequenced in a cohort of 268 unrelated patients with CHD. The relatives of the patients carrying identified mutations and 200 unrelated control individuals were subsequently genotyped. Three novel heterozygous missense NKX2-5 mutations, p.Q22K, p.R36S, and p.E54K, were identified in three families with autosomal dominantly inherited atrial septal defect, ventricular septal defect, and tetralogy of Fallot, respectively. These mutations, absent in 200 control individuals, appear to be highly conserved evolutionarily and co-segregated with...
CHD in the families, with complete penetrance. These findings expand the spectrum of mutations in NKX2-5 associated with CHD and provide new insight into the molecular etiology involved in the pathogenesis of CHD, which signifies potential implications for genetic diagnosis and gene-specific therapy for this common disease in newborns.

**Key words:** Congenital heart disease; Transcription factor; Genetics