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NOVEL NKX2-5 MUTATIONS RESPONSIBLE FOR CONGENITAL HEART DISEASE

Wang Juan,¹ Liu Xingyuan,² Yang Yiqing³ ¹Department of Cardiology, School of Medicine, East Hospital, Tongji University, Shanghai, China; ²Department of Pediatrics, School of Medicine, Tongji Hospital, Tongji University, Shanghai, China; ³Department of Cardiovascular Research, Medical College of Shanghai, Shanghai Chest Hospital, Jiaotong University, Shanghai, China

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Objective Congenital heart disease (CHD) is the most common birth defect and is the leading cause of infant morbidity and mortality resulted from various 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 in a significant portion of patients remain largely unknown. In this study, we sought to screen NKX2-5 for potential molecular defects in patients with CHD.

Methods The entire coding region of NKX2-5 was sequenced initially 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.

Results Three novel heterozygous missense NKX2-5 mutations, p.Q22K, p.R36S, and p.E54K, were identified in 3 families with autosomal dominantly inherited atrial septal defect, ventricular septal defect, and tetralogy of Fallot, respectively. Absent in 200 control individuals, these mutations were highly conserved evolutionarily and co-segregated with CHD in the families with complete penetrance.

Conclusion The findings expand the spectrum of mutations in NKX2-5 linked to CHD and provide new insight into the molecular aetiology involved in the pathogenesis of CHD, which signifies potential implications for genetic diagnosis and gene-specific therapy for this common disease in the young.