

Organic cardiovascular disease (myocarditis, cardiomyopathy, congenital heart disease, rheumatic heart disease, valve)

[gw22-e0071] A NOVEL GATA4 MUTATION RESPONSIBLE FOR CONGENITAL VENTRICULAR SEPTAL DEFECTS

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Objective Ventricular septal defect (VSD) is the most common type of cardiovascular developmental anomaly and is an important risk factor for the substantially increased morbidity and mortality in newborns. Cumulative evidence implicates genetic defects in the pathogenesis of congenital VSD. However, VSD is genetically heterogeneous and the genetic determinants for VSD in most patients remain to be identified.

Methods In this study, the whole coding region of the GATA4 gene, which encodes a zinc-finger transcription factor pivotal to cardiogenesis, was initially sequenced in 210 unrelated patients with VSD. The relatives of the index patient carrying the identified mutation and 200 unrelated ethnically matched healthy individuals used as controls were subsequently genotyped. The functional effect of the mutant GATA4 was characterised in contrast to its wild-type counterpart using a luciferase reporter assay system.

Results A novel heterozygous GATA4 mutation, p.G296R, was identified in a family with VSD inherited as an autosomal dominant trait. Absent in 200 control individuals, the mutation co-segregated with VSD in the family with 100% penetrance and was completely conserved evolutionarily across

species. Functional analysis displayed that the p.G296R mutation of GATA4 was associated with a decreased transcriptional activity.

Conclusion The findings expand the spectrum of mutations in GATA4 linked to VSD and provide more insight into the molecular mechanism involved in VSD. The results of the present study imply the potential implications in the genetic diagnosis and gene-specific therapy of this common malformation in infancy.