HGM D and those at the National Center for Biotechnology Information, European Bioinformatics Institute and University of California Santa Cruz. We are pleased to say that a consortium of members of the Human Genome Variation Society (www.hgvs.org) has been responsible for hundreds of locus-specific mutation database systems being created, being publicly available and made use of by HGM D, and this effort will continue also under the banner of the Human Variome Project (www.humanvariomeproject.org).

In conclusion, we congratulate the curators of HGM D and OMIM for providing two such crucial resources for inherited disease diagnostics and research. Our study raised a number of explicable problems outlined by Stenson et al, many of which highlight the problems of the mutation database field: use of non-standard nomenclature, lack of coverage of all types of variation, lack of annotation of corrections, and the need for public and private versions of HGM D due to funding strictures.

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Competing interests: None.

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We need a detailed phenotype in the phenomenon of genetics and congenital heart disease

In their interesting manuscript, Tomita-Mitchell et al present four novel GATA4 sequence variations as pathogenic substrates for congenital heart disease (CHD) in humans. 1 CHD is the most common birth defect and affects almost 1% of all new borns. With the substantial improvement in surgical approaches that has occurred over the past decades, the number of adults living with CHD has increased. This fact demands better insights into the genetics and heredity of CHD.

The authors identified a variety of synonymous variants with a potential effect on the translational kinetics of GATA4. Interestingly, all 18 CHD-associated synonymous sequence variants were exclusively found in patients with septal or conotruncal defects (excluding dextro transposition of the great arteries; D-TGA), which led to the conclusion that the genetic aetiology of D-TGA may be different from other conotruncal defects. We agree that there is growing evidence of the functional consequences of “silent” sequence variations in cardiac diseases. Recently, mRNA analysis of plakophilin-2 in a patient with a congenital arhythmogenic cardiac disease revealed a cryptic splice site induced by a variant, which was predicted to be translationally silent. 2 We also reported the GATA4 C274C variant in two patients with isolated secundum atrial septal defect type II (ASDII), 3 supporting conclusion by Tomita-Mitchell et al of an association of prevalent synonymous variants with congenital septal defects. Nevertheless, functional studies are needed to further investigate this important issue.

Tomita-Mitchell et al presented four CHD associated GATA4 mutations. 1 The large population screened allowed the authors to draw conclusion about an overall prevalence of GATA4 mutations among patients with sporadic CHD. Combining results from previous sequencing approaches indicates that the prevalence of GATA4 mutations is around 0.4% (2 out of 482) in patients with sporadic CHD. 3,4 The overall rarity of CHD-associated GATA4 mutations is reinforced by Tomita-Mitchell et al, who reported four mutations among 628 subjects with sporadic CHD (0.6%). 5

The A411V variant is, to our knowledge, the first GATA4 mutation in a patient with isolated ventricular septal defect. We have also identified the A411V mutation in a female patient with cr ibiform ASDII and partial anomalous pulmonary venous return. 6 A secundum ASD of the cr ibiform type was previously described as a notable phenotype in a patient with a secundum ASD due to a mutation in N KX2.5. 6 Therefore, it seems likely that cr ibiform atrial septal defects have a greater association with transcription factor mutations than do other forms of ASDII, and patients with this specific phenotype may constitute interesting screening candidates. Thoroug h assessment of minor and more subtle clinical features may thus help to find common phenotypes in patients with a genetic CHD. Consequently, the lack of any medical features of the index patients and affected relatives in the paper of Tomita-Mitchell et al is regrettable. 1 Information about specific phenotypes of mutation carriers is indispensable for dealing with the future challenges of adults with CHD.

We believe that the vast heterogeneity of genetics in CHD demands systematic and detailed phenomic approaches, which may result in identification of common clinical features among patients with genetic CHD. Genotype-phenotype analyses may assist rapid clarification of the causative gene mutation and improve our tools for genetic counselling of patients with hereditary CHD.

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J Med Genet 2008;45:320. doi:10.1136/jmg.2007.057117

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