HGMD 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 HGMD, and this effort will continue also under the banner of the Human Variome Project (www.humanvariomeproject.org).

In conclusion, we congratulate the curators of HGMD 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 HGMD due to funding strictures.

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REFERENCES

1. **George RA,** Smith TD, Callaghan S, Hardman L, Pierides C, Horaitis O, Wouters MA, Cotton RG. General mutation databases: analysis and review. *J Med Genet* 2008;**45**:65–70.
2. **Stenson PD,** Ball E, Howells K, Phillips A, Mort M, Cooper DN. HGMD — towards a comprehensive central mutation database. *J Med Genet* 2007 2008;**45**:124–6.
3. **Sale MM,** Craig JE, Charlesworth JC, FitzGerald LM, Hanson IM, Dickinson JL, Matthews SJ, van Heyningen V, Fingert JH, Mackey DA. Broad phenotypic variability in a single pedigree with a novel 1410delC mutation in the PST domain of the PAX6 gene. *Hum Mut* 2004;**20**:322.
4. **Dworniczak B,** Aulehla-Scholz C, Horst J. Phenylketonuria: detection of a frequent haplotype 4 allele mutation. *Hum Genet* 1989;**84**:95–6.

We need a detailed phenome in the *phenome*non 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 newborns. 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 arrhythmogenic 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.[3–5] 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%).[1]

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 cribriform ASDII and partial anomalous pulmonary venous return.[3] A secundum ASD of the cribriform type was previously described as a notable phenotype in a patient with a secundum ASD due to a mutation in *NKX2.5*.[6] Therefore, it seems likely that cribriform 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. Thorough 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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REFERENCES

1. **Tomita-Mitchell A,** Maslen CL, Morris CD, Garg V, Goldmuntz E. GATA4 sequence variants in patients with congenital heart disease. *J Med Genet* 2007;**44**:779–83.
2. **Awad MM,** Dalal D, Tichnell C, James C, Tucker A, Abraham T, Spevak PJ, Calkins H, Judge DP. Recessive arrhythmogenic right ventricular dysplasia due to novel cryptic splice mutation in PKP2. *Hum Mutat* 2006;**27**:1157.
3. **Posch MG,** Perrot A, Schmitt K, Mittelhaus S, Esenwein EM, Stiller B, Geier C, Dietz R, Gessner R, Ozcelik C, Berger F. Mutations in GATA4, NKX2.5, CRELD1 and BMP4 are infrequently found in patients with congenital cardiac septal defects. *Am J Med Genet A* 2008;**146**:251–3.
4. **Nemer G,** Fadlalah F, Usta J, Nemer M, Dbaibo G, Obeid M, Bitar F. A novel mutation in the GATA4 gene in patients with tetralogy of Fallot. *Hum Mutat* 2006;**27**:293–4.
5. **Schluterman MK,** Krysiak AE, Kathiriya IS, Abate N, Chandalia M, Srivastava D, Garg V. Screening and biochemical analysis of GATA4 sequence variations identified in patients with congenital heart disease. *Am J Med Genet A* 2007;**143**:817–23.
6. **Hirayama-Yamada K,** Kamisago M, Akimoto K, Aotsuka H, Nakamura Y, Tomita H, Furutani M, Imamura S, Takao A, Nakazawa M, Matsuoka R. Phenotypes with GATA4 or NKX2.5 mutations in familial atrial septal defect. *Am J Med Genet A* 2005;**135**:47–52.