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New insights in genetics of congenital heart defects

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There is no doubt that in the last 20 years, genetic aspects of congenital heart defects (CHD) have not advanced in step with improvements in the diagnosis and treatment of cardiovascular malformations. The importance of genetics in the etiology of CHD is supported by the frequent association of CHD with genetic syndromes, the familial recurrence of certain defects and similarities between animal and human models.

The pathogenetic classification of CHD introduced by Clark¹ groups cardiac malformations according to possible morphogenetic pathways instead of anatomic or clinical criteria. The epidemiological results collected by the Baltimore-Washington Infant Study² have shown that one third of children with CHD are diagnosed as having a genetic syndrome or an extracardiac malformation.

Syndromes with a chromosomal anomaly identifiable by standard cytogenetic techniques were initially studied. The commonest were Down's syndrome, Turner's syndrome, trisomy 13, trisomy 18, and monosomy 8p. More recently developed cytogenetic techniques, including high resolution chromosomal analysis and fluorescent in situ hybridization (FISH), can detect subtle rearrangements in chromosomes which may be overlooked by standard methods. These techniques may be used in the diagnosis of syndromes due to a microdeletion, such as DiGeorge/velo-cardio-facial syndrome (caused by microdeletion 22q11.2) and William's syndrome (caused by microdeletion 7q11). Molecular instruments such as linkage analysis and positional cloning are being used to identify genes causing Mendelian monogenic syndromes with CHD. In general, the identification of genes is achieved by collecting pedigrees segregating the gene of interest. The genes responsible for Holt-Oram,³ Ellis-van Creveld,⁴ and Noonan⁵ syndromes have been mapped in this fashion. The ultimate proof of cloning the gene is provided by sequence analysis and demonstration of the mutation in the patient. The "candidate

gene” approach has been successfully utilised in cloning the gene involved in Marfan syndrome.⁶ The “lumping” of syndromes previously considered as separate disorders has been possible, following the identification of microdeletion 22q11.2 as the cause of DiGeorge, velo-cardio-facial and conotruncal anomaly face syndromes,⁷ and PTPN11 mutations in cases of Noonan and LEOPARD syndromes.⁸

A correlation between specific anatomic-cardiac patterns and the above mentioned genetic syndromes has been demonstrated,⁹ suggesting that specific morphogenetic mechanisms put in motion by genes can result in a specific cardiac phenotype. We can cite pulmonary stenosis with dysplastic valves in Noonan syndrome, the complete form of atrioventricular canal defect in Down syndrome and other chromosomal imbalances, the partial form of atrioventricular canal defect with left-sided obstructions in non-Down patients, the muscular ventricular septal defect in Holt-Oram syndrome, the subtype of tetralogy of Fallot with right or cervical aortic arch, absent infundibular septum or pulmonary valve in microdeletion 22. For clinicians, the delineation of the type and frequency of CHD in syndromes can be useful to guide diagnostic evaluation and management. As a practical aid, the presence of a specific subtype of CHD can guide the clinician to diagnose a specific genetic syndrome or to the search for commonly associated extracardiac defects. On the other hand, the diagnosis of a specific syndrome can guide the cardiologist to the search for specific cardiac defects.

Little information is yet available with regard to genes causing isolated CHD, in individuals who do not have a particular syndrome. In the earlier studies, the majority of non-syndromic CHDs were considered to have a “multifactorial” basis. Multifactorial means that CHD is due to the combined effect of one or more genes interacting with stochastic or environmental risk factors. Nevertheless, a higher occurrence risk for CHD has been noted in some families compared to that found in the general population.² A Mendelian transmission has been identified for some specific isolated defects, including atrial septal defect, atrioventricular canal defect, hypertrophic cardiomyopathy, supra-valvular aortic stenosis, and anomalous pulmonary venous return. Familial segregation of anatomically different CHD can shed light on pathogenetic mechanisms between different lesions, as occurring by the contemporary finding of complete transposition of the great arteries and congenitally corrected transposition in the same family, suggesting that both defects could be related to situs and looping abnormalities.¹⁰

A continuous and interactive interaction between clinicians, geneticists, embryologists and anatomists is needed for the further understanding of the pathogenetic mechanisms and possible genetic causes of CHD.

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