Catch me if you can: tracking down the genetic origins of congenital heart disease

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This editorial refers to 'Submicroscopic chromosomal imbalances detected by array-CGH are a frequent cause of congenital heart defects in selected patients’ by B. Thienpont et al., on page 2778.

Congenital heart disease (CHD) is the major cause of death in infants under 1 year of age. CHD kills more children than cancer and accounts for 25% of all birth defects, the single largest category of malformations. One newborn in 100 has CHD, and 1 newborn in 1000 will need surgery for CHD. Despite the impressive progress which has been made in deciphering the molecular events governing cardiogenesis, only a minority of heart defects are amenable to routine genetic diagnosis at the present time. Thus, the mechanism of disease remains elusive in the majority of patients, and classification and treatment of these malformations are based purely on morphological criteria.

Which leads can then be followed to track the genetic basis of CHD? One classic approach, linkage analysis, requires relatively large families segregating the disease trait in a Mendelian fashion. Apart from variable expressivity and reduced penetrance of mutations, which can obscure the Mendelian character of disease, the relative rarity of these families makes their recognition and ascertainment a challenging task (Table 1). Candidate gene approaches have been advocated based on the results of linkage studies, as well as based on the rapidly growing number of candidate genes which play important roles in embryonic heart formation. Clearly, some genotype–phenotype correlations have emerged from these studies—such as those linking mutations in NKX2.5 with atrial septal defects and atrioventricular conduction defects. Novel technologies are currently employed to speed up these efforts, and we can anticipate that cost-efficient whole-genome sequencing—the US$1000 genome—will contribute a large amount of data in this field. However, since most cases of CHD occur on a sporadic basis, it will become more important to gather information on family members, in order to address the questions of which sequence changes are actually disease causing and whether subclinical disease is segregating with such sequence changes. Lastly, the advent of large-scale genotyping of single nucleotide polymorphisms (SNPs) and repertories such as the HapMap project constitute another promising lead. Given the high heritability of at least some types of heart malformation, it is reasonable to expect that this approach will unravel novel loci conferring a risk for CHD.

Before the development of these techniques, several lines of evidence for genetic causes of CHD had already been established. To date, epidemiological studies such as those linking cardiac and extracardiac malformations or showing familial clustering of heart disease remain of prime importance to target further genetic investigations. As an example, the association of defects of the atrioventricular canal with Down syndrome was well recognized by the time trisomy 21 was discovered as the underlying genetic cause. Since this time, cytogenetics has come a long way: In addition to high-resolution karyotyping, numerous modern techniques now allow detection of aberrations which are below the resolution of light microscopy, such as of small deletions and duplications (copy number variations or CNVs). Whereas a routine karyotype will not detect rearrangements smaller than 5–10 megabases (Mb) in size, the more recent cytogenetic techniques have pushed this limit to 1 Mb and below. The approach employed in most cases can be interpreted as a two-step technique: first, array-based techniques will establish a molecular count of the patients’ genetic material at very dense intervals. Should the copy number vary from the expected two alleles at a certain locus, a precise characterization of the genomic anomaly is carried out in a second step.

Thienpont et al. have put these tools to use as an efficient short-cut in the hunt for genetic culprits. First, they established a cohort of 60 patients with CHD and a non-syndromic pattern of dysmorphic features or mental handicap. They then excluded known genetic disorders based on dysmorphology and high-resolution G-banding analysis. In fact, this selection procedure ensured that their cohort was enriched for patients who would be likely to present a chromosomal aberration, but were not affected by known syndromes. Using a BAC (bacterial artificial chromosome) array, which has a resolution of ~1 Mb, and applying stringent criteria for causality in every patient examined, the...
authors found a chromosomal aberration to be the aetiology of CHD in 17% of cases. This number is comparable with that found in patients with mental retardation and dysmorphism using similar technologies. Although CNVs are demonstrated to be an important cause of malformation and mental retardation, they also are the most frequent source of benign genomic variations involving 12% of the genome. Therefore, there have to be proceed with caution upon interpretation of CNVs as pathogenic, and precise cardiovascular phenotyping will have to be incorporated into CNV catalogues.

The importance of this study is 2-fold: first, the authors are able to put a name to hitherto unrecognized entities, thereby giving a diagnostic tool to clinicians. Furthermore, the burden of disease can be immense for patients and families such as those in the current study. The finding of a causative genetic abnormality often comes as a relief for the parents who are searching for answers. In parallel to efforts undertaken in human cancer, this approach merits further expansion into a more comprehensive catalogue of genetic variations observed in CHD patients. With increasing availability of techniques that allow detection of CNVs in the human genome, such a catalogue will establish genotype–phenotype correlations which are useful for patient management and genetic counselling. An example of a successful translation of this approach is the microdeletion 22q11: timeliness diagnosis of this disorder can help to guide further diagnostic steps and therapeutic interventions. Secondly, studies such as the one presented by Thiennon et al. present an important step towards identifying genetic factors underlying CHD. The discovery of karyotype anomalies was instrumental in the discovery of PROSIT240, a new member of the chromodomain gene family cause CHARGE syndrome.

Catch me if you can: The real character from Steven Spielberg’s film, a notorious character man, today helps banks and individuals to protect themselves against fraud. Much in parallel, we can anticipate that better knowledge of the genetic causes of CHD will lead to improved risk stratifications and preventive strategies. Platforms which integrate whole-genome SNP typing and detection of CNVs at the same time will move from the research arena to clinical application within the next few years at reasonable costs. Considering that CHD behaves like a complex trait in most cases, it will be crucial to determine to what extent phenotypes can be explained by SNPs, CNVs, and environmental factors. With all the necessary tools at hand, paediatric cardiologists and geneticists will have the task of developing genotype-phenotype catalogues which will benefit affected patients and families.

Conflict of interest: none declared.

References