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Bernard Keavney

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Congenital heart disease affects approximately seven in 1000 live births, and remains a significant worldwide cause of morbidity and mortality. Recurrence risk studies show that there is a substantial familial predisposition to congenital heart disease. It is currently estimated that approximately 20% of congenital heart disease cases can be attributed to chromosomal disorders (eg, Down’s syndrome), other known congenital malformation syndromes, teratogen exposure and maternal diabetes. The remaining 80% appears to behave as a ‘complex disease’, showing aggregation within families without Mendelian segregation, suggesting the importance of multiple genetic and environmental factors. Considering all congenital heart disease phenotypes together, there is approximately a threefold higher relative risk to future siblings of a case; however, this can be substantially higher in certain conditions, for example, atrioventricular septal defect and tetralogy of Fallot. Genetic studies have recently made significant progress in discovering some of the influences on other cardiovascular complex diseases such as hypertension and coronary artery disease 1 2; and a recent study of Tetralogy of Fallot suggested that as much as 10% of disease susceptibility could be caused by variations in the gene copy number in a variety of regions of the genome. In this issue of Heart, Alessandro de Luca and colleagues 3 (see page 673) investigate the impact of mutations in genes determining laterality on the risk of familial transposition of the great arteries (TGA).

The investigators sought to maximise the likelihood of detecting genetic factors by studying families in which there was a proband with TGA and at least one other member with some form of congenital heart disease. Seven families containing 14 affected members (one with and one without TGA per family) were included. They screened for

outcomes. Thus the only reasonable evidence was to suggest complete revascularisation in shocked patients on the basis of data from the SHOCK trial, but not in any others.

The caveat on the current study is that the reason for re-intervention in the first year might be driven by the knowledge of the coronary anatomy. If a patient gets chest discomfort and is known to have a ‘significant’ untreated lesion in the N-IRA, a readmission and re-intervention could be more likely. It is unclear if all readmissions were confirmed as ACS, and all revascularisation was ischaemia driven, with proved areas of ischaemia subtended by the N-IRA to be treated. In addition, lesion characteristics in all groups have not been given. The COR group had more diabetes, and might also have had more complex coronary lesions.

What is clear, however, is that treating the N-IRA appears to be safe, whether done at the same time (CR) or staged (SR). Leaving untreated vessels appears less safe. This would, if confirmed, lead to a change in practice on the part of many cardiologists, with complete revascularisation becoming the new goal in FPCI, as it is in stable coronary disease and non-ST elevation ACS. Although suggested to be a p


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mutations—genetic changes expected to make an impact on the structure or function of the protein—in 10 genes known from previous work to be important in the establishment of the left—right axis during development in humans. Patients with laterality defects typically have cardiac malformations; the hypothesis investigated by de Luca and colleagues was that some cases of TGA may in essence be laterality disturbances restricted to the heart in the absence of other features (eg, polysplenia or situs inversus), suggesting a more global problem with the left—right axis. They focused their efforts on the segments of the genes of interest that code for protein (exons), and on nearby regions (splice sites), which influence how those exons are assembled into a final RNA message. They tested whether any new mutations found were absent from 300 unaffected people. Any new mutations absent in the healthy control population were subjected to bioinformatic analyses using prediction algorithms to estimate the potential impact of the amino acid change on the protein. By contrast with recent large-scale studies of coronary disease and hypertension, which aimed to discover common variants with anticipated small effects on disease risk throughout the genome, the strategy of de Luca and colleagues was a focused search in specific genes for rare novel mutations likely to have a large effect on protein function.

De Luca and colleagues found three new sequence variants in their candidate genes that were absent from the control population, showed at least a degree of conservation throughout evolution, and were of predicted deleterious effect. Intriguingly, two individuals in the same family carried two of the three variants each, although they were not the same two variants. The investigators interpreted their results as indicating the mutations were causative of TGA, importantly suggesting that TGA is part of the same disease spectrum as laterality disturbances involving multiple organs.

A question left somewhat open by the study is the precise functional consequences of the variants discovered. In-silico evaluation of the likely impact of particular mutations is a critical step in deciding on whether in-vitro evaluation using molecular methods is warranted, but as the specificity of the programmes used is considerably less than 100%, it is not entirely secure to infer a deleterious functional effect from in-silico predictions alone. It has been thought for some time that as many as 20% of common human polymorphisms that affect amino acid coding damage the protein, yet for most of these genotype—phenotype correlations remain obscure. More recent data derived from whole-genome sequencing of particular individuals suggests that each one of us may carry approximately 1500 rare coding variants that are predicted by the usual algorithms employed to be deleterious. Given 20,000 genes in the human genome, it is clear that if any substantial number of genes were sequenced in disease cases, one or more such variants could be observed purely by chance. Of course, in the work of de Luca and colleagues, the earlier probability that the variants discovered were functional must have been substantially increased by the careful selection of candidate genes, but in-vitro investigation of the variants in future studies will be necessary to establish this beyond doubt.

The study also highlighted the potential complexity of inheritance patterns for congenital heart disease and the importance of considering interactions between genes in light of their positions in developmental genetic networks. One affected child in the study carrying two transcription factor mutations (one in ZIC3 and one in NKX2.5) inherited one from her unaffected father and one from her unaffected mother. It is entirely possible that the disruption to the genetic programmes involved in normal heart development could withstand one such ‘hit’, but not two. Unfortunately, even given the family-based design, DNA from the siblings of this case was not available to De Luca et al to test the robustness of this inference more thoroughly. To add further complexity, in this same family another case inherited two mutations (one in FOXH1 and one in ZIC3) both from her unaffected mother. If these mutations do play a causative role in TGA susceptibility, there are evidently other effects, genetic or environmental, which substantially modulate their effects.

This study has implications not only for the future investigation of congenital heart disease, but also for other complex cardiovascular phenotypes in which substantial effort is now being directed to investigating rare variants. Genome-wide association studies to date have identified common variants that even when taken together account for only very small fractions of the estimated heritability of the diseases studied. Most investigators believe that the ‘missing heritability’ resides in hitherto uncharacterised rare variants. To discover these, ultra-high throughput sequencing approaches are being undertaken, and the speed at which these approaches are developing technologically is astonishing. It is now possible to sequence all protein coding exons (some 250,000 in number encompassing 34 million bases or approximately 1.5% of the entire genome) in an individual as a routine matter. However, in order to overcome the problems of interpreting the multiple potentially deleterious mutations that will be found in large-scale sequencing of both cases and unaffected persons, much larger numbers of individuals than hitherto will need to be sequenced such that statistical comparisons of the frequency of potentially deleterious mutations by gene can be made. Similar approaches in well-defined candidate genes have already been successful in identifying rare alleles for a number of conditions including dyslipidaemia.

Thanks to the clinical advances of the past 50 years, most patients with congenital heart disease now survive to adulthood and hope to start families of their own. The work of de Luca and colleagues should add to our hope that within a short period of time our understanding of the molecular pathogenesis of the condition will similarly advance, potentially yielding individual-specific genetic counselling and therapeutic approaches to reduce recurrence risk in the children of these patients.

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Images in cardiology

Septic palmar emboli in a case of staphylococcal aortic endocarditis

A 47-year-old man with a history of diastolic murmur was admitted to the emergency ward for chest pain and fever. Physical examination, ECG findings and blood analyses were unremarkable. While the patient was thought to have viral pericarditis, two blood cultures were taken, and then the patient was treated with non-steroidal anti-inflammatory drugs. Two days later, thoracic pain and fever had resolved and the patient was discharged home. He was readmitted 24 h later because of the sudden onset of an excruciating pain in the right palm, followed in minutes by the appearance of a large ecchymotic palmar spot with multiple petechiae of the right hand and of the right toes (panel A). In front of such cutaneous lesions, highly suggestive of infective endocarditis, intravenous antibiotherapy with amoxicillin and gentamicin was rapidly undertaken. On the next day, blood cultures grew methicillin-sensitive Staphylococcus aureus. Amoxicillin was switched for oxacillin while gentamicin was continued. A transoesophageal echocardiography disclosed a large (9×16 mm) vegetation on a bicuspid aortic valve. Because the patient complained of a new left thoracic pain, a thoracoabdominal CT was realised that showed only mild left pleural effusion but revealed spleen and kidney infarctions. As the patient remained febrile while he was treated with antibiotics for several days, a new transoesophageal echocardiography showed no new cardiac lesions, especially neither new vegetation nor perivalvular abscess. The surgical exploration of the larger right palmar vegetation, carried out eighteen days after the initial admission, disclosed a subcutaneous abscess that grew no microorganisms.

H Weclawiak, S Vergne, M Alzieu
Correspondence marc.alzieu@ch-v-l-ariege.fr
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