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Editorial

Modifying Mendel
Approaches for Identification of Susceptibility Alleles for Human Cardiovascular Malformations

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Congenital cardiovascular malformations (CVMs) are the most common birth defect, affecting approximately 8 per 1000 live births. Roughly 25% of CVMs occur in the context of multiple congenital anomalies or as part of a genetic syndrome, while the other 75% of individuals present as an isolated, nonsyndromic CVM. Genomic disorders comprise the majority of syndromic CVMs, exemplified by aneuploidies such as trisomy 21 (Down syndrome) or monosomy X (Turner syndrome) and copy number variations (CNVs) such as deletion 22q11.2 (Velo-cardio-facial syndrome) and deletion 7q11.23 (Williams syndrome). There are also a few phenotypically well-characterized syndromes with CVMs that occur due to pathogenic variants in a single gene. These include the group of Noonan, Costello, and Cardiofaciocutaneous syndromes resulting from mutations in genes coding for proteins of the Ras pathway, and Holt-Oram syndrome which is caused by mutations in the gene TBX5.

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underlies the variable expressivity and reduced penetrance of most CVMs.

Although not as robust as the mouse data presented, the human T21 data also provide support to using a sensitized population as a method to identify modifiers that, in combination with the major genetic susceptibility, contribute to the final phenotype of CVM. Using 135 human subjects with T21 (39 reported previously), they identified nonsynonymous changes in CRELD1 among 4 T21 individuals, including predicted pathogenic changes among 3 individuals that were not identified in a control group ascertained from dbSNP (p.R329C and p.E414K) and an additional predicted benign change (p.V13 mol/L) also identified in one individual in the control population at low frequency (minor allele frequency of 0.006). Importantly, they identified the heterozygous p.R329C variant in a parent of both T21 individuals. In aggregate, the frequency of coding changes was not statistically significant between the cases and controls ($\chi^2$, 9/270 versus 2/1100, $P = 0.424$). Nevertheless, when taken together with the mouse data, this points the way to a shift from a simplistic view of aneuploidy and single-gene inheritance to a more complex pattern, and highlights a method to identify additional contributing factors in the cause of CVMs.

Genetic variation leading to susceptibility to CVMs, rather than causing disease, has generally only been recently accepted as a bona fide construct. An example in the CVM literature is the identification of mutations in NOTCH1 as both causing disease in families with aortic valve disease and causing susceptibility to disease in sporadic cases of aortic valve stenosis and related phenotypes of hypoplastic left heart syndrome and coarctation of the aorta. Likewise, heterotaxy spectrum CVMs are frequently characterized by rare variants in genes within well characterized developmental pathways for left-right patterning. In the majority of cases, the variant is inherited from an unaffected parent, but in vitro or in vivo functional testing, when available, demonstrates the deleterious nature of the variant. These findings illustrate the need to move beyond an expectation of Mendelian inheritance or complete segregation with disease when identifying alleles contributing to human CVMs.

Population genetic considerations, including the strong likelihood of reduced reproductive fitness, suggest that many CVMs are more likely to be caused by rare deleterious variants than common, very low-penetrance polymorphisms. The rare variant hypothesis suggests that inherited susceptibility to disease may be due to the cumulative effect of genetic variants, typically with a minor allele frequency ranging from 0.1% to 3%, which confer detectable increases in relative risk. Estimates of the effect of rare variants suggest that approximately 20% of missense variants are deleterious with an additional 53% being mildly deleterious and potentially acting as susceptibility alleles for complex traits.

Proof of principle for this idea has come from studies on colorectal adenomatous polyps as well as from plasma lipid studies. The overall frequency of rare variants in affected individuals was significantly higher than in controls, and functional studies of the variants confirmed their importance. The results are consistent with the supposition that the genetic architecture of these defects is characterized by locus heterogeneity and rare, incompletely penetrant variants or mutations.

The current availability of high throughput resequencing will allow the characterization of genetic variability in individuals with CVMs at a rapid rate. A predicted outcome is the identification of an excess of rare variants important in cardiac development among cases compared with controls. The comprehensive and simultaneous detection of multiple deleterious variants in genes and developmental pathways required in cardiac morphogenesis will provide insight into these more complex inheritance models in which the cumulative effect of multiple genetic risk factors leads to disease. As a result, there is an ongoing need for increasingly sophisticated bioinformatic prediction programs and statistical models to estimate pathogenicity and relative risk of novel or rare variants, as well as a need for refinement of genomic architecture (for example, enhancer and control regions). A major challenge for the study of congenital anomalies such as CVMs is the difficulty of functional analyses. Although many developmental pathways are amenable to in vitro studies to test the functional effect of a variant, extrapolation to cardiac morphogenesis should be done cautiously. Recent work has highlighted the utility of mouse to identify modifiers of CVMs in vivo, but these studies are time- and labor-intensive. Studies such as the current one highlight the importance of combining the strengths of animal models with human genetics to validate potential susceptibility alleles.

As studies move from Mendelian diseases to more complex patterns of inheritance, the traditional reductionist approaches that may have worked well for simple disease models require modification paired with innovative new approaches. The current study by Li et al using a sensitized population highlights one such innovative method, and thereby provides a new tool to understand the etiology of CVMs.

Disclosures

None.

References


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