Genetic Mechanisms Controlling Cardiovascular Development

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ABSTRACT: Congenital heart disease (CHD) is a major cause of morbidity and death in childhood in the West. The incidence is ~1/145 live births. Mendelian and Chromosomal syndromes account for ~20% of CHD. The genetic mechanisms underlying non-chromosomal/non-Mendelian "sporadic" CHD, which account for the remaining 80%, are poorly understood. The genetic architecture of sporadic CHD likely includes accumulation of rare non-synonymous variants in cardiac developmental genes leading to mutational loading of cardiac developmental networks, copy number variation in cardiac developmental genes, and common variants that may not be obviously linked to cardiac development but may alter genetic buffering pathways (e.g. folate metabolism). The rare mutations, typically associated with sporadic CHD, likely arise from the severe decrease in reproductive fitness selecting against any CHD-causing gene variant. The resulting allelic heterogeneity reduces the power of genome wide association studies for CHD. A complementary approach to the genetic analysis of CHD is to re-sequence candidate genes that have been shown to be necessary for mouse heart development. The number of such genes likely exceeds 1700. To identify these genes we have developed an enabling technology – high-throughput magnetic resonance imaging (MRI) of mouse embryos, which is used in combination with ENU/transposon mutagenesis and knockout techniques. Key future challenges now involve translating discoveries made in mouse models to human CHD genetics and understanding the mechanisms that create and disrupt genetic buffering. A long-term goal in congenital heart disease is to manipulate these pathways to enhance buffering and prevent disease, in a manner analogous to the use of folate in preventing neural tube defects.

KEYWORDS: Genetics, Congenital heart disease, MRI, Mutagenesis, Pleiotropy

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