Hypoplastic left heart syndrome (HLHS) is a severe, uniformly fatal congenital heart defect typically characterized by hypoplasia of the left ventricular chamber and aorta in association with stenosis and/or atresia of the mitral and aortic valves (1). Since the original description of HLHS over 150 years ago (2), there has been extraordinary progress in the management of this congenital heart lesion. Surgery usually involves the 3-staged Norwood procedure, which ultimately results in a 2-chamber heart in which the right ventricle functions as the systemic ventricle. In carefully selected patients, the current 5-year survival now approaches 90% (3). However, the long-term outcome for these patients is unknown, and the surgical strategy can still only be considered palliative.

Mechanistically, left-sided heart defects have been classified as so-called flow defects. Developmentally, chamber growth is intimately coupled to flow and/or other biophysical properties of heart function, and it is therefore likely that the final heart form is generated at least in part, by flow itself. It has been hypothesized that any lesion that compromises blood flow into or out of the developing left ventricle will cause, with graded severity, hypoplasia of the left-sided structures (4). Potentially, genetic mutations that impair normal prograde flow through the developing left ventricle could cause left-sided heart defects. As an example, clinically, there is a well-known association between the presence of ventricular septal defects and aortic arch hypoplasia (5). This has led to the hypothesis that aortic arch hypoplasia arises secondarily from decreased prograde blood flow to the ascending aorta, due to “steal” from the left side as a result of left-to-right shunting of blood across the ventricular septal defect. In mice, genetic and surgical interruption of blood flow through the outflow tract to the branchial arch arteries leads to abnormal branchial arch remodeling (6). Genetically engineered mice that have a large ventricular septal defect also demonstrate aortic arch hypoplasia (7), but only in some genetic backgrounds, suggesting differential genetic sensitivity to the flow effect. Therefore, identification of genes for HLHS will likely provide much needed insights into the primary mechanisms underlying the development of left-sided structures of the heart, including flow-responsive programs.

There has been a growing body of evidence supporting a genetic etiology for left-sided heart defects, including HLHS. Initially, case reports described familial recurrences of HLHS, with autosomal dominant, recessive, and X-linked modes of inheritance, and variable penetrance and phenotype (4). Subsequent studies employing a systematic analysis by echocardiography demonstrated that there was likely to be a strong genetic component for HLHS (8,9). Because there was a spectrum of severity of left-sided defects occurring in affected family members (ranging from HLHS to bicuspid aortic valve [BAV]), it has been hypothesized that left-sided heart defects can be due to a common genetic etiology. More recently, statistical analyses on families with HLHS and BAV provided evidence implicating a predominantly genetic etiology (10,11).

There is now strong evidence implicating multiple genetic loci for HLHS (4). Specifically, HLHS has been associated with trisomy 13, trisomy 18, chromosome X ( XO, Turner syndrome), and deletion of distal 11q (Jabob-sen syndrome) (12). Potential mutations in at least 4 genes—GLA1 (Connexin43, 6q22) (13), NXX2-5 (5q35) (14,15), NOTCH1 (9q34) (16), and HAND1 (5q33) (17) —have been associated with HLHS. Taken together, it is clear that HLHS and left-sided heart defects as a group are a genetically heterogeneous set of disorders.

In this issue of the Journal, Hinton et al. (18) provide further evidence for genetic heterogeneity for HLHS. Specifically, they performed a genomewide nonparametric linkage analysis on 33 families with at least 1 affected member with HLHS. They identified 2 chromosomal loci implicated in disease-causation for HLHS, with another 5 loci being suggestive. Four families contributed to the identification of both loci, which is consistent with complex inheritance of HLHS. One suggestive HLHS locus was also associated with BAV in a separate group of families. Although no obvious candidate genes were identified within these loci, the analysis will hopefully lead to the identification of additional disease-causing genes for HLHS and BAV and ultimately provide important new insights into the pathogenesis of these lesions.

At least 2 questions arise from the results of Hinton et al. (18). First, why were only 2 definitive loci identified, given
the previous evidence implicating numerous loci? Second, why did HLHS and BAV share linkage with only 1 common locus?

As described earlier, there is convincing evidence implicating as many as 8 other loci for HLHS and/or BAV, and none of these were identified by Hinton et al. (18). The most obvious explanation is that the number of families studied was insufficient to identify more loci, even though they likely exist. The careful and comprehensive phenotyping that was performed by echocardiography on over 1,000 patients demonstrates the anatomic variability of HLHS. Consequently, the anatomic subtypes could be due to the magnitude of genetic heterogeneity and could explain why more loci were not identified in this relatively small family grouping.

To answer the second question, there are at least 2 possible explanations. First, in some cases, a single gene mutation may be sufficient to cause BAV and HLHS in the same family, as for the 14q23 locus identified by Hinton et al. (18), with the specific phenotype being determined ultimately by genetic or epigenetic modifiers, and/or environmental influences. In that case, then 1 possibility is that not enough families were analyzed. Second, it is noteworthy that BAV is very common (1% of the general population), is a risk factor for aortic valve disease, and is known to have a complex and heterogeneous genetic etiology. Clearly, only a small subset of BAVs in utero, possibly those that are the most restrictive, progress to HLHS. Even so, the fact that there can be isolated aortic valve atresia with a normal left ventricle suggests that there are distinct genetic factors for aortic valve defects and susceptibility to HLHS. Given the heterogeneous origins of BAV unsolicited for functional severity in utero, distinct loci for HLHS and BAV might be predicted to be the predominant outcome.

Implications for therapies. One of the challenges in the management of some patients with left-sided heart defects is the decision to proceed with a 1- versus 2-ventricle repair for patients with mild left ventricular hypoplasia. Studies have demonstrated that in a subset of patients with left ventricle hypoplasia, the ventricle is capable of postnatal growth (19). Consequently, identification of the specific genetic cause in such patients may lead to a stratification scheme that could facilitate the selection of patients for a 1- versus 2-ventricle repair.

Currently, there are no medical cures for HLHS. Although the idea of treating HLHS with drug therapies in the future seems remote, the pioneering work by Brooke et al. (20) on Marfan syndrome is a case in point for how the identification of a genetic cause of a structural heart abnormality can lead to potential medical therapies that might replace current surgical approaches. Furthermore, some centers are exploring fetal intervention for HLHS. Based on the progressive nature of the defect in utero and the possibility of early diagnosis at fetal stages, correction of the obstructive lesion by ultrasound-guided balloon angioplasty may stimulate left ventricular growth (21,22). Understand-


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