Although congenital heart disease (CHD) is frequently associated with syndromes that affect multiple organs, the majority of cases present as isolated CHD, and typically defects are limited to a defined structure, suggesting a unique developmental mechanism. Despite the frequent occurrence of CHD, relatively few causative genes have been clearly identified (see review1). In this issue of Circulation Research, Christiansen et al2 describe the occurrence of isolated (nonsyndromic) CHD in association with the deletion of a 1.5- to 3-Mb region on chromosome 1q21.1. They suggest that the cardiac defects seen represent a contiguous gene deletion syndrome and cannot be explained by the deletion of any one gene located within the region. Notably, they present patients with isolated coarctation and interrupted aortic arch (IAA) type A.

But why does a contiguous gene hypothesis have to be invoked? In the three patients presented, a spectrum of left ventricular outflow tract obstruction, including subaortic stenosis and IAA, in addition to ventricular septal defect (VSD) and aortopulmonary window, is represented. All of these abnormalities have been experimentally linked to defects in neural crest ontogeny. Likewise, deletion of connexin40 (Cx40) in mice is associated with a high incidence of conotruncal abnormalities including Tetralogy of Fallot, double outlet right ventricle, and abnormal branching of the aortic arch.3,4 These similarly implicate abnormalities of neural crest migration.5

It would be tempting to try and unify the phenotypes observed by suggesting a single gene defect altering neural crest ontogeny. However, a closer look at the specific patient phenotypes observed makes primary neural crest defects, and exclusive Cx40 alterations, a bit difficult to conjecture. Although aortic arch vessel abnormalities have been described in the Cx40-null mice,6 none of the defects seen in the patients described by Christiansen et al were seen in the Cx40 KO mice. This suggests a potential modification of the phenotype by additional genes located within the deleted region of chromosome 1q21.1. Certainly IAA type B and occasionally IAA type C with VSD is associated with experimental neural crestopathies, as observed in several experimental models affecting cardiac neural crest including Semelin,6,7 Foxc1 and Foxc2,8,9 and components of the endothelin signaling cascade.10–12 But rarely, if ever, is IAA type A, as seen in this cohort of patients, detected in these animal models. This may coincide with the fact that cardiac neural crest is not thought to contribute to the smooth muscle investment of the aorta distal to the origin of the left subclavian artery, which demarcates the original 4th pharyngeal arch. Even more unique is the observation of discrete coarctation of the aorta. Although frequently seen in the human population, this phenotype has yet to be recapitulated in animal models. Original identification of the gridlock gene (also known as hey2, HRT2, CHF1, HERP1, and HESR2) in zebrafish13 raised speculation that this gene might explain isolated coarctation.14 However, mutations have not been identified in human patients. Subsequent deletion-mutations in the mouse suggested a more diffuse cardiovascular phenotype without coarctation,15–17 confirming a more wide spread role for the notch signaling pathway in cardiac development.

The phenotypes presented do, however, offer a potentially more intriguing explanation. If not a primary neural crest defect, what mechanistic process(es) might explain the defects seen? One attractive hypothesis is that coarctation of the aorta, and perhaps IAA type A, are lesions that merely reflect the most severe manifestations of a more diffuse arteriopathy related to altered endothelial-endothelial or endothelial-smooth muscle cell interactions, rather than to primary neural crest development.18 Although often thought to be an isolated lesion, 10% of patients with coarctation have intracranial lesions suggestive of more diffuse arterial defects. Recently, significant extrapulmonary vascular anomalies, including coarctation of the aorta, have been described in patients with Jagged-1 mutations or Alagille syndrome, highlighting this phenotype as consistent with a more diffuse alteration in the notch signaling pathway.19 Thus, coarctation and IAA type A would perhaps not be surprising given the observation that Cx40−/− mice have been shown to have a diffuse alteration in transmission of endothelium-dependent vasodilator responses.20 Although deletion of Cx40 alone may not be sufficient to cause arch obstruction, haploinsufficiency of Cx40 associated with attenuation of other genes (perhaps located in the 1q21.1 region) might be sufficient to result in a vasculopathy phenotype. Experimentally, the vasculature appears to be particularly vulnerable to alterations in gene dosage of multiple factors required for arterial and venous differentiation, as well as vascular remodeling.21–23 Likewise, defects in Cx40 null mice have been shown to be particularly sensitive to attenuation of other members of the connexin family.4 Although Cx50 is also deleted in the contiguous region, a specific interaction between Cx40 and Cx50 has yet to be identified.
Why does this matter? Most patients with coarctation or interrupted arch are repaired in early infancy and the etiology of the defects, either primary neural crest in origin or the result of a more diffuse vasculopathy (or a mixture of both) would appear to be of secondary concern after surgical repair. However, successful surgery does not alleviate all of the pathology. In fact, vascular dysfunction of large arteries is known to persist even after early repair in many children.24 Although early surgical intervention is known to decrease the prevalence of systemic hypertension, there remains an alarming subpopulation of children who are hypertensive at rest or during exercise despite the absence of residual obstruction.25,26 In this light, it is interesting to note the hypertensive phenotype described in Cx40-null mutant mice.27 Furthermore, there is a greater incidence of noncardiac abnormalities in patients with coarctation and VSD, as opposed to isolated coarctation28 and an increased incidence of cardiac lesions (particularly left sided obstructive lesions) in 1st degree relatives of patients with coarctation.29 However, it is currently impossible to determine which patients remain at risk for hypertensive complications, which patients will display extra cardiac abnormalities, and which patients’ siblings are more likely to have CHD. These are all issues that have direct implications for patient management, potentially affecting diagnosis, surgical repair, and postoperative care. While these are all concerns that might be explained by further mechanistic understanding of the specific etiology facilitated by animal studies, animal models are likely to provide only partial information on the pathology that involves multiple gene interactions. For these conditions, we must rely on our patients to point us in the right direction as only they know for sure which gene interactions are relevant to CHD. This information will only be accessible through precise phenotypic description and detailed genetic analysis. As evidenced by the work of Christiansen et al.,2 our patients may be giving us subtle hints that must be further investigated.

References

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Only Our Patients Know for Sure
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