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Editorial Comment

Developmental anomalies of the outflow tracts and aortic arch: towards an understanding of the role of deletions within the 22nd chromosome

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IN THIS ISSUE OF *Cardiology in the Young*, PAPERS BY Momma and colleagues[1] and Takahashi and colleagues[2] address the issue of deletions within chromosome 22q11 in patients with interruption of the aortic arch. These two articles can be added to the recent spate of descriptive and epidemiologic studies on the relationship between chromosomal deletions and congenital heart disease, which collectively serve to confirm that deletions of 22q11 are found in conjunction with a number of specific congenital cardiac anomalies, among which interrupted arch is notable for its frequency of association.[3–9]

Momma and colleagues diagnosed deletion of chromosome 22q11 in 7 of 13 patients with interruption of the arch between the left common carotid and subclavian arteries, and in none of 7 with interruption beyond the left subclavian artery.[1] The incidence of deletion in just over half the patients with the former type of interruption is similar to estimates reported in several previous studies, which have ranged from 50–90%.[6–9] The absence of a deletion in all of the patients with interruption beyond the left subclavian artery is also characteristic. In fact, prior to the case of deletion in a patient with interruption at the isthmus reported in this issue by Takahashi and colleagues.[2] only one such case had been described, and this was in a patient diagnosed with DiGeorge syndrome but not documented chromosomal deletion.[10] In addition to the focus on interruption of the arch, both of these reports touch directly on the issue of malformations of the subvalvar left ventricular outflow tract, with the former documenting an association between subarterial defects and interrupted arch in patients with chromosomal deletion, and the latter entertaining the relationship between subvalvar obstruction and the pathogenesis of interruption at the isthmus. Juxtaposed as they are in this issue, the reports by Momma and colleagues[1] and Takahashi and colleagues[2] lend themselves to a deeper inquiry into the pathogenesis of, and the causative role of deletions of chromosome 22q11 in, congenital anomalies of the aortic arch and ventricular outflow tracts.

Development and maldevelopment of the aortic arch and its branches

The aortic arch and its branches are derived from the embryonic pharyngeal arches, which develop initially as symmetric structures, but subsequently undergo patterned regression to yield the mature pattern of arterial branching. One of the notable features of the developing central arterial system is the inhabitance of certain branches, including the fourth arch but not the dorsal aorta, by cells from the cardiac neural crest.[11] In children born with interruption of the aortic arch, the processes of development and regression of the paired pharyngeal arches unfold with one or more aberrant steps. Exactly what goes awry is not known. In the form of interrupted arch with discontinuity between the left common carotid and subclavian arteries, the deficient segment of the aorta is that which is normally derived from the left fourth pharyngeal arch. When the interruption occurs distal to the left subclavian artery,

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in other words at the isthmus, the primordium of the absent or atretic segment is presumably a portion of the left dorsal aorta.[12]

In addition to deletions within the 22nd chromosome, interruption between the carotid and subclavian arteries is frequently associated with an aortic valve having two leaflets, posterior deviation and/or malalignment of the outlet septum and consequent subaortic stenosis, a ventricular septal defect, and anomalous origin of the subclavian artery supplying the arm on the opposite side to the aortic arch.[13,14] In contrast, in the less common form of interruption beyond the subclavian artery, the outlet septum usually is not deviated or malaligned, and accordingly subaortic stenosis is rarely present.[13–15] Ventricular septal defect and anomalous origin of the subclavian artery are unusual,[14,15] while there is a well-recognized association with aortopulmonary septal defect.[15]

As both Momma and colleagues[1] and Takahashi and colleagues[2] discuss, the extreme disparity between the two types of interruption regarding their association with deletions of chromosome 22q11 suggests a difference in etiology. The discrepancy in anomalies associated with the two types of interruption, as well as the disparate anlage of the deficient segments of the arch, reinforce this hypothesis. It is natural to attribute the difference in etiology, at least in part, to developmental aberrations that can be traced to the high frequency of deletions of chromosome 22q11 in patients with interruption between the left carotid and subclavian arteries, and the near lack of such an association in patients with interruption at the isthmus. Indeed, this difference in chromosomal deletion is almost certainly of import. It cannot serve, however, as the sole and complete explanation. For, as with most aspects of congenital heart disease, gray predominates over black and white, a pattern that applies as well to the association between chromosomal deletion and the pattern of interruption of the aortic arch. Not all patients with interruption between the carotid and subclavian arteries have the deletion, and some, albeit very few, with interruption at the isthmus do. Thus, we are compelled to recognize that the developmental processes leading to interruption of the aortic arch, wherever the interruption, are by no means simple.

Prior to the identification of deletions within the 22nd chromosome in patients with congenital heart disease, and to the philosophical hegemony of genetic determinism in developmental biology, one of the prevailing concepts in pediatric cardiology was that of cardiovascular development related to flow.[14,16–18] With respect to obstructive lesions of the aortic arch, an argument for the importance of flow-related factors was advanced by Rudolph and colleagues in 1972[16] and reiterated in chorus over the subsequent decade.[14,17,18] Essentially, what the theory of flow-related pathogenesis of arch obstruction proposes is that underdevelopment of the aortic isthmus, which is normally traversed by the least amount of blood flow in the fetal aorta, is a function of hemodynamic factors occurring during fetal life, which might be caused by a variety of associated defects or conditions. This argument is consistent with the discrepant association with deletions of chromosome 22q11 between the two types of interruption. Interruption between the carotid and subclavian arteries, frequently associated with chromosomal deletion, does not occur at a natural division of flow. In contrast, interruption beyond the left subclavian artery occurs at the isthmus, which is the location of most instances of coarctation, and which effectively constitutes the border zone between blood ejected from the left and right ventricles in the fetus.[16]

In light of the apparent etiologic distinction between the two forms of interrupted arch, one of the most compelling aspects of the case reported by Takahashi and colleagues[2] in this issue of *Cardiology in the Young* is that the presence of an interrupted arch beyond the left subclavian artery in a patient with 22q11 deletion obfuscates a dichotomy that is otherwise quite impressive. This perturbation reminds us of the need to acknowledge the complexity of cardiovascular morphogenesis and development, and that we must not succumb to an overwrought faith in the simplistic renderings of hypothesis. Although this reminder, this disruption of an otherwise startlingly clean etiologic boundary between the two primary types of arch interruption, may frustrate our ambition for complete understanding, such is the price of the quest for truth. Let us hope that this ubiquitous complexity, which may very well be indicative of an intrinsic developmental heterogeneity, provokes us to search more deeply for the satisfying comprehension that proves so elusive.

Development and maldevelopment of the outlet component of the ventricular septum

The formation of the outflow segment of the heart has been studied in detail in animal models.[11,19–24] Cells from the cardiac neural crest are known to migrate into the outflow region from the cranial pole. They remain concentrated in the prongs and central mass of the tissue complex which septates the arterial trunk, and are believed eventually to extend into the subvalvar septum. Initially, the

ventricular myocardium extends to the level of the sinutubular junction, and the origins of the coronary arteries are engulfed in myocardium. Only as the myocardium regresses do the arterial valvar sinuses distinctively become part of the arterial trunks. A subpopulation of the neural crest cells in the outflow tract region then undergo apoptosis.[23,24] This process has been proposed as a mechanism for resorption of the subaortic infundibulum, and for muscularization of the septum dividing the outflow tracts by cardiomyocytes, possibly by inducing elaboration of growth factors.[23,24] There is much that remains to be explained in the development of the outflow tracts, including the origin of the muscular outlet septum and its differentiation from the free-standing subpulmonary muscular infundibulum. For example, how it is possible for the pulmonary valvar leaflets to be supported on the muscular free-standing sleeve, and still for the facing commissure of the pulmonary valve to be at the same level as the facing commissure of the aortic valve, but with a right angle between the orientation of the subpulmonary and subaortic outflow tracts? (Fig. 1) As with interruption of the aortic arch, various defects of the ventricular outlets can be produced by disruption of the neural crest in the early embryo, including anomalies of ventriculo-arterial connections,[11] which are rarely seen in association with 22q11 deletion in humans.[6] Also, as with interrupted arch, little is known about the mechanisms of this dysmorphogenesis.

Perhaps the major contribution to the literature provided by the report of Momma and colleagues[1] is the recognition that interruption of the aortic arch in Japanese patients with deletions of chromosome 22q11 is frequently associated with a doubly-committed and juxta-arterial ventricular septal defect. In North America and Europe, the form of ventricular septal defect most commonly associated with arch interruption is perimembranous,[13,25] with only 14% of defects falling into the doubly committed variety in a multi-institutional study of 174 neonates who underwent repair at American and Canadian centers.[25] As Momma and colleagues indicate in their manuscript,[1] the doubly committed form of ventricular septal defect is relatively more common in Asian patients with isolated interventricular communications[26] and with tetralogy of Fallot[27] than in the United States and Europe. The extension of this pattern to patients with interrupted arch, however, has not previously been characterized.

While of interest for this finding, the study by Momma and colleagues unfortunately includes too few patients to determine accurate estimates of prevalence. Moreover, the fact that many of the patients were studied retrospectively may have

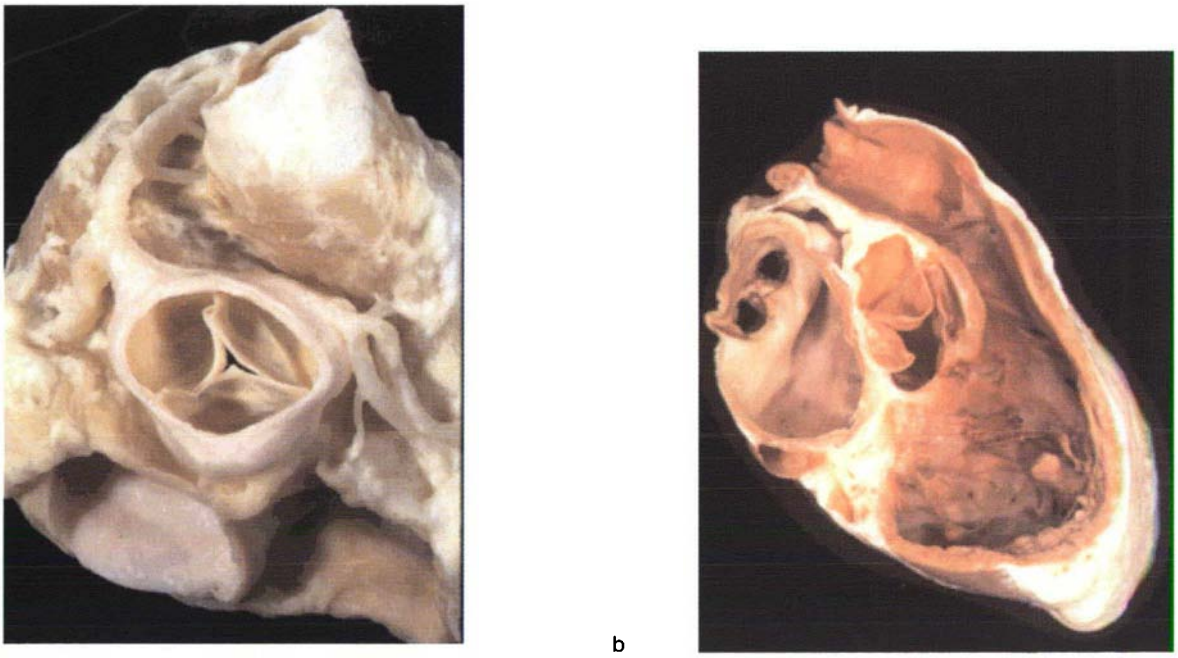

Figure 1.
Figure (a) shows a normal heart with the subpulmonary infundibulum dissected to demonstrate the free-standing muscular sleeve, and figure (b) is an oblique sagittal section through the right ventricle and pulmonary trunk. Together, these images demonstrate that the facing commissure of the pulmonary valve is at the same level as the facing commissure of the aortic valve, but with a right angle between the orientation of the subpulmonary and subaortic outflow tracts.

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introduced a substantial bias, given that survival of infants born with interrupted arch 15–20 years ago, when some of the patients in Momma's study were born, was fairly dismal, and mortality may not have been distributed independent of chromosomal deletion and/or the type of ventricular septal defect. Nevertheless, if the association found in their study of the doubly committed defects with interruption of the aortic arch and chromosomal deletion is representative of the broader pattern, it is interesting to note that the frequency of interruption in the setting of chromosome 22q11 deletions is so similar to that observed in the United States and Europe, independent of the type of ventricular septal defect. The association between interrupted arch and doubly committed ventricular septal defect found by Momma and colleagues[1] in Japanese patients with chromosomal deletion is one of the few such patterns to be recognized in the literature on congenital heart disease and chromosome 22q11.

Regarding their patient with interruption of the aortic arch at the isthmus, who also had a subarterial ventricular septal defect, Takahashi and colleagues[2] argue that the absence of subvalvar narrowing or discrete obstruction is inconsistent with the theory of flow-related pathogenesis.[16] Unfortunately, this teleological argument is not convincing. The anatomy of the subvalvar outflow tract in their patient does not appear to be distinctly different from that seen in other patients with this type of interruption.[13–15] Subaortic stenosis and malalignment or deviation of the outlet septum, characteristic features in patients with interruption between the carotid and subclavian arteries, are not commonly found in association with interruption beyond the left subclavian artery. Thus, the cardiovascular morphology described by Takahashi and colleagues[2] is not unique for this type of interruption, and their observations cannot stand as evidence in support of the argument that the pathogenesis of interruption in their patient was any different than other patients with interruption at the isthmus. Regardless of whether flow is a primary causative mechanism in the development of interruption at the isthmus in general, the most notable feature of their case is the association with a deletion of chromosome 22q11, not the subvalvar anatomy.

Towards an understanding of the role of deletions within the 22nd chromosome in anomalies of the arch and outflow tracts

Deletions of chromosome 22q11 are thought to affect migration or development of neural crest cells and, as a result, to interfere with embryogenesis of structures populated by the cardiac neural crest, such as the ventricular outlets and the embryonic pharyngeal arches, notably the fourth arch.[11,28] The collective literature has defined quite convincingly the frequency of association between deletions of chromosome 22q11 and interruption of the aortic arch, common arterial trunk, tetralogy of Fallot with pulmonary stenosis or atresia, as well as the lack of significant associations between chromosomal deletion and defects of the outflow tracts with discordant ventriculo-arterial connections. The proposed nexus of genotype (deletions of chromosome 22q11), embryogenetic mechanism (developmental abnormalities of the cardiac neural crest), and phenotype (congenital heart defects), nonetheless, is based on a syllogistic deduction. Namely, chromosomal deletions are associated in humans with interrupted aortic arch, common arterial trunk, tetralogy of Fallot, and some forms of ventricular septal defect and anomalies of the aortic arch,[3–9] while in animal models, many of these defects can be reproduced by ablation, pharmacologic disruption, or genetic manipulation of the cardiac neural crest,[29–32] which has been shown to populate the embryonic pharyngeal arches and portions of the developing outflow tract. The assumption is made that the mechanism by which deletions within chromosome 22q11 lead to cardiac defects is via the neural crest. While there are a number of shortcomings of this deduction, it is widely accepted, and will likely prove to be robust.

Thus, accepting the hypothesis that these associations are indicative of a causal relationship between deletions of chromosome 22q11 and congenital heart disease, a number compelling questions confront us: What is the mechanism of the causal nexus? What factors determine the phenotypic variation of the associated cardiovascular anomalies? What is the clinical significance of these associations?

Despite the extensive machinery that has been enlisted in the evaluation of deletions within the 22nd chromosome in patients with congenital heart disease, we have almost no knowledge of how this chromosomal defect translates into dysfunction of the cardiac neural crest. Several investigators have identified potential analogs of the human genes at the deleted 22q11.2 locus in animal models, but thus far these have translated into little insight into the human syndrome.[31–36] Recently, however, investigators identified an association between deletions of chromosome 22q11, congenital heart defects, and a protein coded by a specific gene in the 22q11.2 region.[35] The identified gene product is involved in the degradation of ubiquitinated proteins, and the

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investigators suggest that haploinsufficiency of this ubiquitin-specific protease may lead to accumulation of certain proteins and consequently defective survival of cardiac neural crest cells.

One of the interesting aspects of the aforementioned study is the recognition underlying the method by which the prospective ubiquitin-specific protease was identified. The investigators, aware that abnormal development of the cardiac neural crest can result from disruption of various genes and developmental pathways that do not map to chromosome 22q11 in humans, including dHAND, endothelin-1, and the endothelin receptor, undertook a suppressive-subtractive hybridization to screen the mouse genome for genes dependent on dHAND.[35] As these same investigators and others have demonstrated, a variety of genetic pathways can lead to maldevelopment of the cardiac neural crest, and to the characteristic heart defects seen in patients with deletions of chromosome 22q11.[31–34,36] Indeed, the variable mechanisms by which the cardiac neural crest can be perturbed may be one explanation for the variable deletion of chromosome 22q11 in patients with the associated heart defects. Thus, although deletion of 22q11 is the representative chromosomal abnormality that is studied in humans, there are likely to be other similarly important genetic defects identified over the ensuing years in humans with defects of the aortic arches and outflow tracts.

In addition to the variable association between deletions of chromosome 22q11 and the commonly associated cardiovascular defects, one of the confounding features of the syndrome of 22q11 haploinsufficiency (accepting, for now, the causal nexus) is the variable expressivity. In some respects, this falls along an apparent spectrum, from the simple doubly committed juxta-arterial ventricular septal defect to common arterial trunk (Fig. 2), and from ventricular septal defect with interruption of the aortic arch between the carotid and subclavian arteries to common arterial trunk with interruption of the arch at the same segment. There is a distinct category of anomalies, however, that is also highly associated with deletions of chromosome 22q11, which seem to fall along another spectrum, from perimembranous ventricular septal defect to tetralogy of Fallot to pulmonary atresia. In general, abnormalities of the aortic arch and its branches are more common in patients with these lesions who have the deletion than those who do not.[6] This tendency is not commensurate among the entire range of cardiovascular defects. For example, a right-sided aortic arch is common in patients with 22q11 deletion who have tetralogy of Fallot with pulmonary stenosis or atresia, and common arterial trunk, but is exceedingly rare in association with interruption of the aortic arch. How can we resolve this widely variable expressivity?

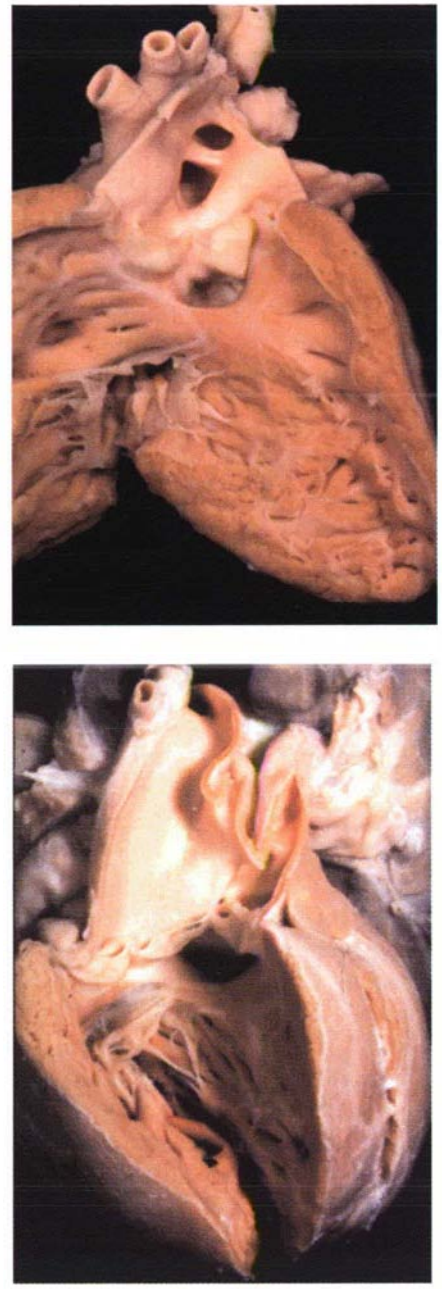

Figure 2.
Figure (a) shows a doubly-committed juxta-arterial ventricular septal defect in which the absence of a subpulmonary infundibular muscular sleeve is depicted. Figure (b) shows a heart with common arterial trunk, in which the interventricular communication is similar to that in the heart with the doubly-committed ventricular septal defect.

In a recent study that implicated for the first time cells from the cardiac neural crest in development of the myocardium, Waldo and colleagues proposed that the phenotypic heterogeneity of

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cardiovascular defects seen with disruption of the neural crest may be a function of the variable distribution of cardiac jelly in the affected embryo.[37] Another proposed explanation for the phenotypic variability seen with deletions of chromosome 22q11 is that other local genes, distant modifier genes, and/or environmental factors could contribute to such differences.[35] This brings us back to the issue of flow. It is difficult to study the effect of blood flow in the developing embryo and fetus. It is undeniable, however, that the better part of cardiac morphogenesis and growth occurs in the dynamic milieu of a functioning cardiovascular system. Using an avian model of unilateral ligation of a vitelline vein, Hogers and colleagues have demonstrated an interaction between altered embryonic hemodynamics and abnormal development of cells derived from the neural crest.[38] There is an extensive body of research on the effects of flow on endothelial cells *in vitro*,[39] and there is no reason not to suppose that flow in the developing fetus has potentially significant effects on gene expression and subsequent cardiovascular development. The interaction is likely to be inexorable, and the findings of Hogers and colleagues[38] suggest the complexity that inheres in the pathogenesis of the anomalies associated with deletions of chromosome 22q11.

The spectrum of anomalies of the aortic arches and ventricular outflow tracts is broad. In humans, most such lesions have been found in association with deletions of chromosome 22q11, although the frequencies of correlation vary as widely as the spectrum of anomalies itself. Given this variability, the clinical significance of chromosomal deletion within a cohort of patients with a given lesion assumes considerable importance. No study of which we are aware demonstrates any significant clinical difference between patients with a given defect who do and do not have deletions within the 22nd chromosome. The importance of this deficiency has been addressed in a recent editorial by Bristow and Bernstein.[40] Although such differences may very well exist, investigations to this effect simply have not been conducted. This question, that is, the clinical significance of chromosome 22q11 deletions in patients with congenital heart disease, deserves investigation, and such investigation must be prospective.

One suggestion of the present editorial comment has been that our understanding of the causal nexus between deletions of 22q11, abnormalities of the cardiac neural crest, and congenital heart disease, which is almost universally accepted, has been demonstrated by only circumstantial evidence. While we believe that this posture, strictly speaking, is accurate, its assumption here is primarily rhetorical. One of the arguments that it is designed to facilitate is that we must be careful about how we produce and proliferate knowledge, lest we devolve from a reliance on deductive reasoning to an indulgence in inductive logic. This caveat, we should point out, is not exaggerated. For instance, the literature on deletions of chromosome 22q11 associated with congenital heart disease has brought with it an expansion of the concept of the "conotruncal" heart defect. The notion of a "conotruncal" defect, apparently intended to signify defects in regions of the heart and great vessels derived from the embryonic conus and arterial trunk, has been expanded to encompass interruption of the aortic arch.[6] The concentration of chromosomal deletions in patients with lesions of the outflow tracts and aortic arch seems to have prompted an initiation of interrupted arch into the antiquated category of "conotruncal" defects– inductive reasoning at its finest. As we advance in our understanding of the genetic and molecular aspects of congenital heart defects, we should be equally prepared to invite change in how we select our terminology.

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