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Association of Chromosome 22q11 Deletion With Isolated Anomalies of Aortic Arch Laterality and Branching

Doff B. McElhinney, MD,*‡ Bernard J. Clark, III, MD,*‡ Paul M. Weinberg, MD,*‡ Maura L. Kenton, MS,† Donna McDonald-McGinn, MS,† Deborah A. Driscoll, MD,†§ Elaine H. Zackai, MD,†‡§ Elizabeth Goldmuntz, MD*‡

Philadelphia, Pennsylvania

OBJECTIVES The purpose of this study was to determine the frequency of chromosome 22q11 deletions in patients with isolated anomalies of the aortic arch and its branches.

BACKGROUND Chromosome 22q11 deletions are often present in patients with certain forms of congenital cardiovascular disease, including tetralogy of Fallot, truncus arteriosus and interruption of the aortic arch. Among patients with these anomalies, chromosome 22q11 deletion is more common in those with abnormal aortic arch laterality or branching.

METHODS We studied 66 patients with isolated anomalies of the aortic arch and no associated intracardiac defects for deletions within chromosome 22q11, using fluorescence in situ hybridization with the cosmid probe N25 (D22S75). Arch anomalies included: double aortic arch (n = 22); right aortic arch with aberrant left subclavian artery (n = 28); right aortic arch with mirror-image branching and a vascular ring formed by a left-sided ductus from the descending aorta (n = 5); right aortic arch with mirror-image branching and no vascular ring (n = 4); and left aortic arch with aberrant right subclavian artery (n = 7). In addition, four patients had a cervical aortic arch, four had aortic coarctation and six had hypoplasia/atresia of the proximal pulmonary arteries.

RESULTS Chromosome 22q11 deletions were found in 16 patients (24%) across the full spectrum of anomalies studied. Among the morphologic variables analyzed, only hypoplasia/atresia of the proximal pulmonary arteries correlated with the deletion ($p = 0.03$). Among patients with a double arch, the frequency of chromosome 22q11 deletion was higher in those with an atretic minor arch than it was in those with a patent minor arch ($p = 0.02$).

CONCLUSIONS Chromosome 22q11 deletion is associated with isolated anomalies of laterality or branching of the aortic arch in 24% of cases in our series. These findings should alert the clinician to consider deletion screening in patients with isolated anomalies of the aortic arch. (J Am Coll Cardiol 2001;37:2114–9) © 2001 by the American College of Cardiology

A deletion within chromosome 22q11 has been identified in the majority of patients with DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome and in some cases of Cayler cardiofacial syndrome and Opitz G/BBB syndrome (1,2). Phenotypic features associated with a chromosome 22q11 deletion are highly variable and include cardiovascular anomalies, palatal abnormalities, hypocalcemia, thymic hypoplasia/aplasia, immune dysfunction, renal abnormalities, characteristic facial features, motor developmental delay and speech and learning disabilities (1,2).

Over the past several years, numerous studies have shown that a deletion within chromosome 22q11 is associated with certain forms of congenital cardiovascular disease, including tetralogy of Fallot with and without pulmonary atresia, truncus arteriosus and interruption of the aortic arch (3–15). In a recent prospective investigation, we characterized the frequency of chromosome 22q11 deletions in an unselected series of 251 patients with a broad range of anomalies of the cardiac outflow tracts and aortic arch (3). We found that a 22q11 deletion was significantly more common in patients with abnormal branching or laterality of the aortic arch than it was in those with a left-sided arch and normal branching of the brachiocephalic vessels, regardless of the primary cardiovascular defect. Multiple logistic regression analysis showed that both right-sidedness (abnormal laterality) of the arch and aberrant branching of arteries derived from the pharyngeal arches (including the proximal PAs) were independently associated with an increased frequency of chromosomal deletion. Of note, approximately two-thirds of the 45 patients with a chromosome 22q11 deletion in that series had anomalies of the aortic arch or proximal PAs associated with their cardiac defect. The association between anomalies of the pharyngeal arch derivatives and chromosomal deletion has been noted by other investigators as well

From the *Division of Pediatric Cardiology and †Human Genetics and Molecular Biology, the ‡Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and the §Department of Pediatrics, Obstetrics and Gynecology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania. Supported by a grant from the NIH/NHLBI (HL 515331). Presented at the 73rd Scientific Sessions of the American Heart Association, New Orleans, Louisana, November 11–15, 2000.

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Abbreviations and Acronyms
PA = pulmonary artery
SCA = subclavian artery

(4,5,9,12). Based on these observations, we hypothesized that patients with aortic arch anomalies and normal intracardiac anatomy would have a high frequency of 22q11 deletion. To test this hypothesis, we studied 66 patients with an isolated anomaly of aortic arch laterality or branching for evidence of chromosome 22q11 deletion.

METHODS

Patients. We approached a total of 76 patients known to have abnormalities of branching or laterality of the aortic arch without associated intracardiac defects or interrupted aortic arch. Patients with an arch anomaly and associated abnormalities of arteries derived from the pharyngeal arches, such as hypoplasia or atresia of a proximal branch pulmonary artery (PA), or obstruction of a cervical aortic arch were included as long as no other cardiac anomalies were present. Approximately half of the 76 patients were approached prospectively at the time of admission for repair of vascular rings. The others were contacted retrospectively after referral for evaluation or repair of aortic arch anomalies.

Of the 76 patients contacted, 66 (87%) agreed to participate and underwent evaluation in accordance with our study protocol, which was approved by the Institutional Review Board for the Protection of Human Subjects at the Children's Hospital of Philadelphia. Written informed consent was obtained from all subjects before enrollment. Parents of 10 patients contacted retrospectively declined to participate and cited the desire not to subject their child to additional venipuncture as their primary reason for declining. The diagnoses of these patients did not differ notably from the cohort of participants. It is important to add that the retrospective arm of our enrollment process was not colored by survival bias. During the period from which surgical patients were enrolled, there were no deaths among patients undergoing repair of an isolated vascular ring.

Cardiovascular phenotype. There was a wide range of diagnoses among the 66 patients included in the study (Table 1). In all patients, the diagnosis was confirmed by echocardiography (n = 44), magnetic resonance imaging (n = 54), computed tomography (n = 2) and/or observation during surgery (n = 47). Twenty-two patients with double aortic arch were enrolled, 18 with a dominant right arch and 4 with a dominant left arch. Nine subjects with a right aortic arch and mirror-image branching of the brachiocephalic vessels were studied, including five with a vascular ring formed by a left-sided ductus arteriosus from the descending aorta to the left PA (four with a left descending aorta and one with a right-sided descending aorta) and four with a right-sided or bilateral ductus and no vascular ring. There were 28 subjects with a vascular ring formed by a right aortic arch with an aberrant left subclavian artery (SCA) arising from a retroesophageal diverticulum and a left-sided ductus. The remaining seven patients had a left aortic arch with an aberrant right SCA and no vascular ring. Altogether, 55

Table 1. Anomalies of Aortic Arch Laterality or Branching and Frequencies of Chromosome 22q11 Deletion in Our Study Cohort

Aortic Arch Abnormality	# of Patients	# (%) of Patients With 22q11 Deletion
Double aortic arch (ring)	22	3 (14%)
Right arch dominant	18	3 (17%)
Minor arch patent	11	0 (0%)
Minor arch atretic	7	3 (43%)
With obstructed right cervical arch	2	0 (0%)
With nonconfluent PAs, right PDA to RPA	1	1 (100%)
Left arch dominant	4	0 (0%)
Right aortic arch	37	11 (30%)
With mirror-image branching of brachiocephalic vessels	9	2 (22%)
With right/bilateral PDA and stenotic/atretic proximal LPA (No ring)§	3	2 (67%)
With bilateral PDA, atretic proximal LPA, distal LPA from left PDA (no ring)	1	0 (0%)
With PDA from DAo to LPA (ring)	5	0 (0%)
With aberrant LSCA from retroesophageal diverticulum and PDA to LPA (ring)	28	9 (32%)
With LPA hypoplasia	1	1 (100%)
With obstructed cervical arch	1	0 (0%)
Left aortic arch with aberrant RSCA (no ring)	7	2 (29%)
Total	66	16 (24%)

Indented abnormalities are subsets of the immediately preceding anomaly and may overlap, as in the case of double aortic arch with a dominant right arch, or represent only a fraction of the primary anomaly, as in the case of right aortic arch with aberrant LSCA from a retroesophageal diverticulum.

DAo = descending aorta; LPA = left pulmonary artery; LSCA = left subclavian artery; PAs = pulmonary arteries; PDA = ductus arteriosus/ligamentum arteriosum; RPA = right pulmonary artery; RSCA = right subclavian artery.

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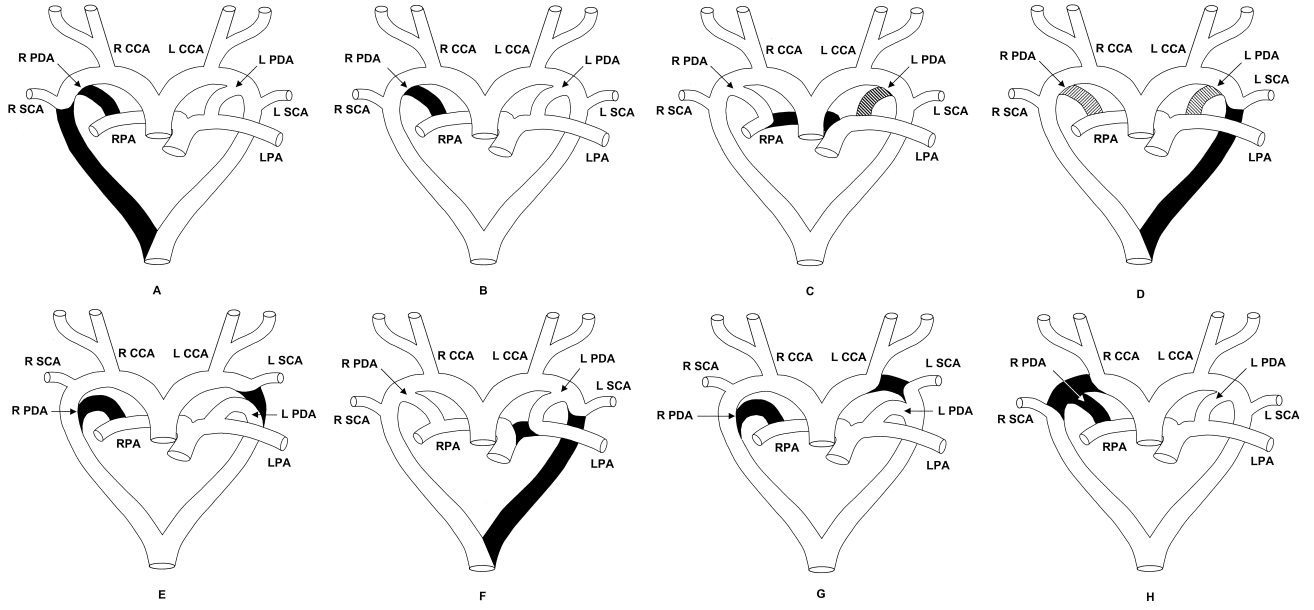

Figure 1. Schematic diagrams of a normal aortic arch and seven of the various forms of anomalous aortic arch laterality or branching included in this study, depicted as the segments of the pharyngeal arch system that regresses (shown in **black**) in order for the mature vascular anatomy to develop. Anomalies with a cervical aortic arch are not depicted. **(A)** Normal aortic arch. **(B)** Double aortic arch. The dominant and minor arches can vary in laterality and specific patterns of branching and segmental hypoplasia/atresia. These variables are not specified in the present diagram. All patients with a double aortic arch had a left-sided ductus arteriosus (L PDA). **(C)** Double aortic arch with nonconfluent pulmonary arteries and origin of the right pulmonary artery (RPA) from the right ductus (R PDA). **(D)** Right aortic arch with mirror-image branching of the brachiocephalic vessels and right/bilaterial ductus arteriosus **(hatched segments)**. **(E)** Right aortic arch with mirror-image branching of the brachiocephalic vessels and a left-sided ductus from the descending aorta to the left pulmonary artery (LPA). **(F)** Right aortic arch with mirror-image branching of the brachiocephalic vessels, bilateral ductus, absence of the proximal LPA and origin of the LPA from the left-sided innominate artery via the left ductus. **(G)** Right aortic arch with aberrant left subclavian artery (L SCA) arising from a retroesophageal diverticulum and an L PDA to the LPA. **(H)** Left aortic arch with aberrant right subclavian artery (R SCA). L CCA = left common carotid artery; R CCA = right common carotid artery.

patients had arch anomalies that constituted a vascular ring. In addition, four patients had a cervical aortic arch, four had coarctation of the dominant arch and six had nonconfluence or hypoplasia/atresia of the proximal PAs (Table 1). As depicted in Figure 1, the wide range of anomalies in our patient population represents abnormal persistence or regression of many different segments of the primitive pharyngeal arch system.

Evaluation of chromosome 22q11 deletion. Deletion analysis was performed by fluorescence in situ hybridization. Metaphase chromosomes from peripheral blood lymphocytes were cohybridized with the commercially available cosmid probe N25 (D22S75) and control probe pH17 (D22S39) that maps to the distal long arm of chromosome 22, as previously described (3).

Statistical analysis. Statistical analysis was performed to assess for differences in the frequency of chromosomal deletion between various diagnostic and demographic characteristics. For the purposes of analysis, arch anomalies were divided into the following four primary diagnostic categories: double aortic arch, right aortic arch with mirror-image branching of the brachiocephalic vessels, right aortic arch with aberrant branching of the brachiocephalic vessels and left aortic arch with aberrant branching of the brachiocephalic vessels. With respect to the categorization of vascular rings, we followed the standard approach (16). In addition to the primary diagnostic category, the following anatomic features were analyzed: presence of vascular ring, presence of a cervical aortic arch, coarctation of the dominant or sole aortic arch, abnormalities of the proximal branch PAs (nonconfluence, atresia or significant stenosis) and compression of the airway. Additional analysis of patients with double aortic arch was conducted according to laterality of the dominant arch and patency of the minor arch. Chi-square analysis was performed to assess for differences in the frequency of deletion according to primary diagnostic category, as well as differences related to secondary diagnostic features. Independent samples *t* test analysis was performed to assess for differences in age at the time of surgery or diagnosis between those with and without deletion. Odds ratios are given with 95% confidence intervals.

RESULTS

Deletions within chromosome 22q11 were identified in 16 of our 66 patients (24%). In particular, a 22q11 deletion was present in 14% of patients with a double aortic arch, 22% of patients with a right aortic arch and mirror-image branching of the brachiocephalic vessels, 32% of patients with a right aortic arch and aberrant left SCA and 29% of patients with a left aortic arch and aberrant right SCA. The frequencies of chromosomal deletion for each specific type of anomaly are summarized in Table 1.

In the analysis of the entire cohort of 66 patients, there

Table 2. Correlation Between Anatomic/Clinical Variables and Chromosome 22q11 Deletion

Variable	# of Patients	# (%) With 22q11 Deletion	Odds Ratio	p Value
Arch sidedness*				
Right	37	11 (30%)	1.1 (0.2–2.8)	0.46
Left	7	2 (29%)		
Double aortic arch				
Yes	22	3 (14%)	0.4 (0.1–1.6)	0.23
No	44	13 (29%)		
Dominance of double arch†				
Left dominant	4	0 (0%)	0.8 (0.6–1.0)	0.53
Right dominant	18	3 (17%)		
Minor arch patency†				
Patent	15	0 (0%)	0.2 (0.1–0.5)	0.02
Atretic	7	3 (43%)		
Vascular ring				
Yes	55	12 (22%)	0.5 (0.1–2.0)	0.44
No	11	4 (36%)		
Cervical aortic arch				
Yes	4	1 (25%)	1.1 (0.1–10.8)	0.68
No	62	15 (24%)		
Coarctation of the dominant arch				
Yes	4	1 (25%)	1.1 (0.1–10.8)	0.68
No	62	15 (24%)		
Proximal branch PAs				
Abnormal	6	4 (67%)	8.0 (1.3–49)	0.03
Normal	60	12 (19%)		
Airway compression‡				
Yes	55	9 (16%)	1.0 (0.1–10.2)	0.89
No	6	1 (16%)		

*Among patients without a double aortic arch (n = 44); †among patients with a double aortic arch (n = 22); ‡data only available for 61 patients.
PAs = pulmonary arteries.

were no significant differences in the frequency of chromosomal deletion among the primary diagnostic categories (Table 2). The only significant difference in frequency of chromosome 22q11 deletion was between patients with and without abnormalities of the proximal branch PAs, with a higher frequency of deletion in the former. Presence or absence of a double aortic arch, vascular ring, cervical aortic arch, coarctation of the aorta and airway compression did not correlate with chromosomal deletion. When patients with a double aortic arch were excluded from the analysis, arch laterality did not correlate with frequency of deletion. Among patients with a double aortic arch, those with an atretic minor arch had a significantly higher frequency of deletion than those with a patent minor arch, but there was no difference between patients with left and right dominance of the double arch (Table 2). There was no difference in age at diagnosis or surgery between patients with and without a 22q11 deletion in the entire study group ($p = 0.51$) or in the cohort of patients who required surgical intervention ($p = 0.84$).

In all 16 patients with a chromosome 22q11 deletion, comprehensive family histories and results of fluorescence in situ hybridization testing for 22q11 deletion in first-degree relatives were available. The only first-degree relative found to have a chromosome 22q11 deletion was the father of Patient 27. The patient had a right-dominant double aortic arch, while the father had a right aortic arch with mirror-image branching of the brachiocephalic arteries and no vascular ring.

DISCUSSION

Chromosome 22q11 deletion and anomalies of the aortic arch. We have demonstrated a significant association between deletions of chromosome 22q11 and isolated anomalies of aortic arch laterality or branching. The overall frequency of 22q11 deletion in this cohort is similar to other lesions commonly associated with chromosome 22q11 deletion (3). The frequency of deletion was similar across the spectrum of arch anomalies that we studied, with no significant differences between the four primary diagnostic categories. Among the associated anatomic features that were examined, the frequency of deletion was higher in patients with atresia or significant stenosis of the proximal branch PAs than it was in those without. However, there were only six patients with such abnormalities in our cohort. Among patients with a double aortic arch, those with an atretic minor arch were more likely to have a deletion within chromosome 22q11 than were those with a patent minor arch. Again, sample size was small and, therefore, this finding must be interpreted with caution.

Numerous anomalies of the aortic arch system have been described (16,17), including many rare defects that are not

represented in this study. Our study does not include several abnormalities of pharyngeal arch derivatives that have been reported in association with chromosome 22q11 deletion, such as isolation of a SCA and malposition of the branch PAs (otherwise known as crossed PAs) (5,9). Although malposition of the PAs is not an abnormality of the aortic arch and its branches, it most likely represents aberrant development of the proximal sixth pharyngeal arches, which are populated by cells from the cardiac neural crest in the same manner as the third and fourth pharyngeal arches (18). Similarly, nonconfluent or stenotic PAs have been linked to chromosome 22q11 deletion in previous reports of patients with tetralogy of Fallot or truncus arteriosus (4,12,13). Patients with the various arch anomalies not included in this study may also be at risk for a 22q11 deletion.

Genotype/phenotype considerations. Substantial clinical heterogeneity has been observed with respect to the cardiovascular lesions associated with deletion of chromosome 22q11 (3–15). The cardiac phenotype ranges from complex intracardiac and aortic arch anomalies to completely normal anatomy. Even among the isolated anomalies of the aortic arch that are included in this study, 10 distinct patterns were found in patients with a 22q11 deletion. Based on the primitive system of pharyngeal arches proposed by Edwards (19), each of the lesions in our series appears to result from a different process of aberrant vascular development (Fig. 1). Deletion size does not correlate with phenotype (20). Thus, the observed phenotypic variability associated with the 22q11 deletion remains to be explained. Both genetic background and in utero environmental exposures have been implicated. Animal models have been developed that may shed light on this issue (21).

Potential study limitations. This study was based largely on the ascertainment of patients with clinical signs or symptoms for which they underwent cardiopulmonary evaluation and, hence, may not reflect the true frequency of chromosome 22q11 deletion across the spectrum of isolated anomalies of aortic arch laterality or branching. For example, a right aortic arch with mirror-image branching and no associated cardiac anomalies is highly unusual (22), and may come to clinical attention only sporadically, either because of incidental detection of the right arch on imaging of the chest for other reasons, or as in the case of our four patients (who had stenosis or atresia of the proximal left PA), because of associated conditions that warranted cardiac evaluation. Similarly, individuals with a left aortic arch and aberrant right SCA may not come to clinical attention, as demonstrated in a recent autopsy report of nearly 5,000 patients (4 to 86 years of age) without known cardiovascular defects, in which the incidence of occult left arch with aberrant right SCA was 1.6 per 1,000 patients (23).

Clinical implications. These findings should alert the cardiologist that a chromosome 22q11 deletion occurs in a substantial number of patients with isolated aortic arch anomalies and normal intracardiac anatomy. Many patients with isolated arch anomalies present with symptoms as neonates or young infants. Screening for the deletion may be warranted in such patients, even in the absence of other overt features of the 22q11 deletion syndrome, since many of the typical features seen in the 22q11 deletion syndrome (1,2) may not be evident during infancy (24,25). In particular, facial features may not be apparent in infants, renal findings are not evident on routine examination, and the characteristic speech and learning difficulties typically do not become clear until beyond infancy. Features that help identify the infant at risk for chromosome 22q11 deletion include nasal regurgitation with feeding, thymic hypoplasia and hypocalcemia. Early diagnosis of a 22q11 deletion in infants with congenital cardiovascular disease allows for early detection of associated noncardiac features, as well as appropriate genetic counseling. In contrast, patients with isolated vascular anomalies who come to clinical attention at an older age are more likely to have evidence of other syndromic features if they have a chromosome 22q11 deletion, such that more selective chromosomal screening can be considered.

Reprint requests and correspondence: Dr. Elizabeth Goldmuntz, Division of Cardiology, Children's Hospital of Philadelphia, Abramson Research Center 702A, 3516 Civic Center Boulevard, Philadelphia, Pennsylvania 19104. E-mail: goldmuntz@email.chop.edu.

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