Chromosome 22q11 Deletion in Patients With Ventricular Septal Defect: Frequency and Associated Cardiovascular Anomalies

Doff B. McElhinney, MD*‡; Deborah A. Driscoll, MD§; Elissa R. Levin, MS*; Abbas F. Jawad, PhD†¶; Beverly S. Emanuel, PhD‡§; and Elizabeth Goldmuntz, MD*‡

ABSTRACT. Background. A ventricular septal defect (VSD) is the most common form of congenital heart disease and is one of the most common cardiovascular anomalies in individuals with chromosome 22q11 deletion syndrome. However, the frequency of a chromosome 22q11 deletion in patients with a VSD is not known. In addition, among patients with a VSD, it is not clear whether particular types of VSD or associated cardiovascular phenotypic features are associated with a chromosome 22q11 deletion.

Methods. We prospectively enrolled 125 patients with a conoventricular (n = 100), posterior malalignment (n = 14), or conoseptal hypoplasia (n = 11) VSD who were admitted to Children’s Hospital of Philadelphia between November 1991 and December 2001. Patients were studied for a chromosome 22q11 deletion by using fluorescence in situ hybridization.

Results. A chromosome 22q11 deletion was detected in 12 (10%) of the 125 patients. Anatomic features that were significantly associated with a chromosome 22q11 deletion included abnormal aortic arch sidedness, an abnormal aortic arch branching pattern, a cervical aortic arch, and discontinuous pulmonary arteries. There was no correlation between the type of VSD and chromosome 22q11 deletion. Of 20 patients with an abnormal aortic arch and/or discontinuous pulmonary arteries, 45% had a chromosome 22q11 deletion compared with only 3% of those with a left aortic arch, normal aortic arch branching pattern, and continuous branch pulmonary arteries.

Conclusions. A chromosome 22q11 deletion is common in individuals with a conoventricular, posterior malalignment, or conoseptal hypoplasia VSD and anomalies of the aortic arch or branch pulmonary arteries. On the basis of these findings, at a minimum, we recommend testing for a chromosome 22q11 deletion in patients with these types of VSD who have abnormalities of aortic arch sidedness or branching, a cervical aortic arch, and/or discontinuous pulmonary arteries. Testing of patients with these types of VSD but a normal aortic arch and pulmonary arteries may be performed routinely or guided by the presence of associated noncardiovascular features of chromosome 22q11 deletion syndrome. Pediatrics 2003;112:e472–e476. URL: http://www.pediatrics.org/cgi/content/full/112/6/e472; genetics, congenital heart disease, DiGeorge syndrome, velocardiofacial syndrome.

ABBREVIATIONS. VSD, ventricular septal defect; RR, relative risk; CI, confidence interval.

A ventricular septal defect (VSD) is the most common form of congenital heart disease,¹ and a VSD is found in 14% to 18% of individuals with a chromosome 22q11 deletion.²³ However, the frequency of a chromosome 22q11 deletion in individuals with a VSD is not well-defined. Moreover, it is not clear whether certain types of VSD are more commonly associated with a chromosome 22q11 deletion or whether particular cardiovascular anatomic features correlate with a chromosome 22q11 deletion in patients with a VSD. Accordingly, screening strategies for a chromosome 22q11 deletion are not as well-defined for the population of patients with a VSD as for other patients with cardiac anomalies associated with chromosome 22q11 deletion syndrome (eg, interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, and isolated anomalies of aortic arch sidedness and branching).⁴⁵ To improve our understanding of which patients with a conoventricular, posterior malalignment, and conoseptal hypoplasia VSD should undergo deletion testing, we studied 125 patients with a primary cardiac diagnosis of the aforementioned VSD types to determine the frequency of and additional cardiovascular features associated with a chromosome 22q11 deletion.

PATIENTS AND METHODS

Patients

Between November 1991 and December 2001, 125 patients with a primary cardiac diagnosis of VSD were enrolled prospectively in a study of the genetics of conotruncal cardiac malformations. For patients with a simple VSD, only those with conoventricular (perimembranous), conoseptal hypoplasia (outlet or subarterial), and posterior malalignment VSDs were included (Fig. 1).⁶ Because the broader focus of the study was the genetics of conotruncal cardiac malformations, patients with an isolated muscular or inlet (atrio-ventricular canal-type) VSD were excluded. Patients with complex cardiovascular anomalies of which a VSD is typically a component (eg, tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, transposition of the great arteries, double-outlet right ventricle, etc) were not included in the present study but are reported elsewhere.⁴ For logistic reasons, patients were enrolled primarily at the time of admission to Children’s Hospital of Philadelphia, for
surgery or cardiac catheterization, to allow for painless acquisition of a blood sample in accordance with a study protocol approved by the Institutional Review Board for the Protection of Human Subjects. Also for logistic reasons, particularly early in the study period, all eligible patients were not invited to participate. Written informed consent was obtained from all subjects. Ten patients in this study (6 with a posterior malalignment VSD and 4 with associated coarctation of the aorta) were reported previously.4

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 Oncor cosmid probe N25 (D22S75) and control probe pH17 (D22S39) that maps to the distal long arm of chromosome 22 as described previously.4

Morphologic Evaluation

Reports from echocardiograms, angiograms, and operative notes were reviewed to ascertain a defined set of cardiovascular morphologic features. In the event of missing data or diagnostic ambiguity, the original echocardiogram tapes or angiograms were reviewed to ascertain a defined set of cardiovascular features. The associations between chromosome 22q11 deletion and the various anatomic features enumerated above was assessed by using the 2-sided Fisher’s exact test. The relative risk (RR) and the 95% confidence intervals (CIs) were estimated. Significance testing was performed at α = 0.05, and determination of statistically significant association was made after adjustment for multiple comparisons.

RESULTS

Patients and Anatomic Details

Of the 125 patients studied, the type of VSD was conoventricular (perimembranous) in 100 (80%), posterior malalignment in 14 (11%), and conoseptal hypoplasia (outlet) in 11 (9%) (Table 1). In 3 patients, including 2 with a conoventricular VSD and 1 with a malalignment VSD, there was inlet extension of the VSD. Of the 14 patients with a posterior malalignment VSD, 3 had an element of conoseptal hypoplasia as well. Eight patients had multiple VSDs, with the secondary VSD located in the muscular septum in all 8. Associated anatomic features present with each type of VSD are summarized in Table 1. As expected, lesions causing left-sided obstruction (excluding interrupted aortic arch, as discussed above) including coarctation of the aorta (P < .001) and subvalvar aortic stenosis (P < .001) were more common in patients with a posterior malalignment VSD.

TABLE 1. Details of VSD Type and Associated Anatomic Features Among 125 Patients With a VSD Studied for a Chromosome 22q11 Deletion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (%)</th>
<th>Conoventricular* (%)</th>
<th>Conoseptal Hypoplasia (%)</th>
<th>Posterior Malignment*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>125</td>
<td>100 (80)</td>
<td>11 (9)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Associated anatomic feature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple VSDs</td>
<td>8 (6)</td>
<td>7 (7)</td>
<td>0 (0)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Aortic arch anomaly‡</td>
<td>18 (14)</td>
<td>14 (14)</td>
<td>1 (9)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>18 (14)</td>
<td>8 (7)</td>
<td>0 (0)</td>
<td>10 (71)§</td>
</tr>
<tr>
<td>Subvalvar aortic stenosis</td>
<td>12 (10)</td>
<td>5 (5)</td>
<td>1 (9)</td>
<td>6 (43)§</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>8 (6)</td>
<td>5 (5)</td>
<td>3 (27)‖</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chromosome 22q11 deletion</td>
<td>12 (10)</td>
<td>9 (9)</td>
<td>1 (9)</td>
<td>2 (14)</td>
</tr>
</tbody>
</table>

* There was inlet extension of the VSD in 3 patients, including 2 with a conoventricular VSD and 1 with a malalignment VSD. Primary VSDs of the inlet variety were not included.
† Three of these patients also had conoseptal hypoplasia.
‡ Arch anomalies include abnormal sidedness, an abnormal branching pattern, and/or a cervical aortic arch.
§ Significantly higher frequency than with other types of VSD (P < .001; after adjustment for 5 comparisons, the threshold for statistical significance was P = .005).
‖ Significantly higher frequency than with other types of VSD (P = .01; after adjustment for 5 comparisons, the threshold for statistical significance was P = .005).
and patients with a conoseptal hypoplasia VSD were more likely to have associated aortic regurgitation with prolapse of an aortic valve leaflet \( (P = .01) \).

**Frequency of a Chromosome 22q11 Deletion and Associated Anatomic Features**

A chromosome 22q11 deletion was found in 12 (10%) of the 125 patients. The frequency of a chromosome 22q11 deletion did not differ significantly between patients with different types of VSD (Table 1). Among the various cardiovascular features analyzed as independent variables, the only ones found to be significantly associated with a chromosome 22q11 deletion after adjustment for multiple comparisons were abnormal arch laterality (a right aortic arch or double aortic arch) (RR: 7.1; 95% CI: 3.2–16), abnormal aortic arch branching (RR: 13.3; 95% CI: 5.2–34.0), and the inclusive category of aortic arch and/or branch pulmonary artery anomalies (RR: 6.9; 95% CI: 3.6–13) (Table 2). Of 20 patients with an abnormal aortic arch and/or discontinuous pulmonary arteries, 9 (45%) had a chromosome 22q11 deletion compared with only 3 of the 92 patients (3%) with normal sidedness and branching of the aortic arch and continuous branch pulmonary arteries (arch data were incomplete for the remaining 13 patients).

**DISCUSSION**

**Chromosome 22q11 Deletion in Patients With a VSD**

Congenital heart disease is one of the most common phenotypic manifestations of chromosome 22q11 deletion syndrome.\(^2,3\) More than 75% of patients with a chromosome 22q11 deletion have some form of cardiovascular anomaly, with a VSD present in 14% to 18%.\(^2,3\) Although a VSD is known to be common in patients with a chromosome 22q11 deletion, little is known about the frequency of a chromosome 22q11 deletion in patients with a VSD or about anatomic details in patients with a VSD and a chromosome 22q11 deletion. Toscano et al\(^8\) identified various types of VSD in subjects with a chromosome 22q11 deletion. Four of 15 patients with a deletion had a conoseptal hypoplasia (subarterial) VSD, which is noteworthy given the relative rarity of this type of VSD in general.\(^6\) However, few studies have specifically defined the deletion frequency in patients with different types of VSD or other cardiovascular features associated with a deletion.\(^8\)–\(^14\) Fokstuen et al\(^11\) studied 110 patients with nonselected congenital heart defects and identified a chromosome 22q11 deletion in 2 of 32 patients (6%) with unspecified types of VSD. Yamagishi et al\(^13\) studied 22 consecutive Japanese patients with a conoseptal hypoplasia VSD for a chromosome 22q11 deletion, with 9 (45%) having a deletion compared with only 3 of the 92 patients (3%) with normal sidedness and branching of the aortic arch.

### Table 2. Anatomic Variables Associated With a Chromosome 22q11 Deletion Among 125 Patients With a VSD

<table>
<thead>
<tr>
<th>Morphologic Variable</th>
<th>No. of Patients ((n = 125) (%))</th>
<th>Chromosome 22q11 Deletion (Yes (n = 12) (%))</th>
<th>Chromosome 22q11 Deletion (No (n = 113) (%))</th>
<th>RR (95% CI)</th>
<th>(P) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic arch sidedness†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>16 (13)</td>
<td>7 (58)</td>
<td>9 (8)</td>
<td>7.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left</td>
<td>106 (87)</td>
<td>5 (42)</td>
<td>101 (92)</td>
<td>(3.2–16)</td>
<td></td>
</tr>
<tr>
<td>Aortic arch branching pattern†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abnormal</td>
<td>13 (12)</td>
<td>8 (67)</td>
<td>5 (5)</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>99 (88)</td>
<td>4 (33)</td>
<td>95 (95)</td>
<td>(5.2–34)</td>
<td></td>
</tr>
<tr>
<td>Branch pulmonary arteries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuous</td>
<td>4 (3)</td>
<td>2 (17)</td>
<td>2 (2)</td>
<td>9.4</td>
<td>.05</td>
</tr>
<tr>
<td>Continuous</td>
<td>121 (97)</td>
<td>10 (83)</td>
<td>111 (98)</td>
<td>(1.5–61)</td>
<td></td>
</tr>
<tr>
<td>Arch anomalies and/or discontinuous pulmonary arteries†‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>20 (18)</td>
<td>9 (75)</td>
<td>11 (10)</td>
<td>6.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Absent</td>
<td>92 (82)</td>
<td>3 (25)</td>
<td>89 (90)</td>
<td>(3.6–13)</td>
<td></td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>18 (14)</td>
<td>1 (8)</td>
<td>17 (15)</td>
<td>0.5</td>
<td>.69</td>
</tr>
<tr>
<td>Absent</td>
<td>107 (86)</td>
<td>11 (92)</td>
<td>96 (85)</td>
<td>(0.1–3.8)</td>
<td></td>
</tr>
<tr>
<td>Bileaflet aortic valve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>13 (10)</td>
<td>2 (17)</td>
<td>11 (10)</td>
<td>1.7</td>
<td>.61</td>
</tr>
<tr>
<td>Absent</td>
<td>112 (90)</td>
<td>10 (83)</td>
<td>102 (90)</td>
<td>(0.4–6.8)</td>
<td></td>
</tr>
<tr>
<td>Subvalvar aortic stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>12 (10)</td>
<td>1 (8)</td>
<td>11 (10)</td>
<td>0.9</td>
<td>.9</td>
</tr>
<tr>
<td>Absent</td>
<td>113 (90)</td>
<td>11 (92)</td>
<td>102 (90)</td>
<td>(0.1–6.1)</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>8 (6)</td>
<td>0 (0)</td>
<td>8 (8)</td>
<td>NA</td>
<td>.61</td>
</tr>
<tr>
<td>Absent</td>
<td>117 (94)</td>
<td>12 (100)</td>
<td>105 (92)</td>
<td>(0.1–4.0)</td>
<td></td>
</tr>
<tr>
<td>Anomalous right ventricular muscle bundles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>19 (15)</td>
<td>1 (8)</td>
<td>18 (16)</td>
<td>0.5</td>
<td>.69</td>
</tr>
<tr>
<td>Absent</td>
<td>106 (85)</td>
<td>11 (92)</td>
<td>95 (84)</td>
<td>(0.1–4.0)</td>
<td></td>
</tr>
</tbody>
</table>

NA indicates not able to calculate odds ratio.

* After adjustment for 9 comparisons, the threshold for statistical significance was \( P = .005 \).
† Data on aortic arch branching pattern were unavailable for 10 patients, and data on both arch sidedness and branching pattern were unavailable for 3.
‡ This category includes abnormal aortic arch sidedness, an abnormal aortic arch branching pattern, and/or discontinuous branch pulmonary arteries. Three patients, all of whom had either a right aortic arch or an aberrant aortic arch branching pattern, had a cervical aortic arch.
but no deletions were found. Iserin et al\textsuperscript{10} identified a chromosome 22q11 deletion in 6 of 9 patients (67\%) with a malalignment VSD, although it was not specified whether their study cohort included anterior malalignment (tetralogy of Fallot type) and/or posterior malalignment VSDs.

In this study, we conducted a large prospective analysis to estimate the frequency of a chromosome 22q11 deletion in patients with specific types of VSD and to assess cardiovascular anatomic features associated with a deletion. Our study focused on patients with a conoventricular (perimembranous), posterior malalignment, or conoseptal hypoplasia (outlet or subarterial) type VSD, because these defects have been reported in chromosome 22q11 deletion syndrome and might be related to other conotruncal defects etiologically and pathologically. We detected a chromosome 22q11 deletion in 12 (10\%) of 125 patients. Chromosome 22q11 deletions were found in patients with all of the types of VSD represented in our cohort, with no significant difference in the frequency of a chromosome 22q11 deletion according to the type of VSD.

** Associated Cardiovascular Abnormalities

In the recent case-control report by Toscano et al,\textsuperscript{8} 15 patients with chromosome 22q11 deletion syndrome and a VSD were compared with 50 control patients with a nonsyndromic VSD. They identified aortic arch anomalies in 6 of the 15 patients (40\%) with a VSD and chromosome 22q11 deletion syndrome, compared with 2 of 50 (4\%) that matched nonsyndromic controls (it is worth noting that 17 of the 50 control patients in their study had a muscular VSD compared with 1 of 15 study patients).\textsuperscript{8} Among other reports that included patients with a VSD who were evaluated for a chromosome 22q11 deletion, aortic arch anomalies also seemed to be associated with a deletion, although numbers were small in these series.\textsuperscript{9,10,12,13,15}

In the present series, patients with a right aortic arch and/or an abnormal aortic arch branching pattern were significantly more likely to have a chromosome 22q11 deletion than those with a normally branching left aortic arch. There was a trend toward significance in the association between a chromosome 22q11 deletion and discontinuous pulmonary arteries (2 of 4 patients with discontinuous branch pulmonary arteries had a chromosome 22q11 deletion), but the small number of patients with this anatomic feature limited the statistical power of this comparison. Almost half (45\%) of our 20 patients with abnormal aortic arch laterality, an abnormal aortic arch branching pattern, and/or discontinuous pulmonary arteries had a chromosome 22q11 deletion, whereas only 3\% of those with both a normal aortic arch and normal branch pulmonary arteries had a deletion. Moreover, 75\% of the 12 patients with a chromosome 22q11 deletion in this series had abnormal sidedness and/or branching of the aortic arch, including all 3 patients with a cervical aortic arch and 2 of 4 with discontinuous pulmonary arteries. There was no relationship between any of the other variables examined and the presence of a chromosome 22q11 deletion. However, there was limited follow-up, and certain features (such as anomalous right ventricular muscle bundles) might only develop with time. Studies designed to assess the development of these features over time may be warranted.

** Limitations of the Study

This study only included patients with particular types of VSD, most of whom underwent cardiac catheterization or surgery. Thus, our data predominantly reflect the population of patients with a conoventricular, posterior malalignment, or conoseptal hypoplasia VSD of potential hemodynamic significance or with important secondary anomalies (such as right- or left-sided obstruction or aortic regurgitation). A substantial number of individuals are born with a small muscular or conoventricular VSD that closes spontaneously.\textsuperscript{16,17} Such individuals were underrepresented in this study for practical purposes of recruitment. Therefore, our findings cannot necessarily be extended to the large population of individuals with smaller defects that do not require closure or invasive evaluation. Similarly, our findings do not apply to patients with isolated muscular or inlet VSDs. This study was also limited in that we were not able to ascertain noncardiac features of chromosome 22q11 deletion syndrome prospectively at a uniform age to assess the role of such features in predicting the presence of a deletion. Nonetheless, the findings of this study are important, because they demonstrate a frequency of chromosome 22q11 deletion in 10\% of patients with a clinically significant VSD as well as a clear association between a chromosome 22q11 deletion and anomalies of the aortic arch and/or branch pulmonary arteries in patients with a VSD.

** Clinical Implications

On the basis of these results, at a minimum we recommend screening for a chromosome 22q11 deletion in patients with a conoventricular, posterior malalignment, or conoseptal hypoplasia VSD who have abnormalities of aortic arch sidedness or branching, a cervical aortic arch, and/or discontinuous pulmonary arteries. As a corollary to this recommendation, it is essential that every effort be made to document the sidedness and branching pattern of the aortic arch in all patients with a VSD. Because only 3\% of patients with a normal left aortic arch and branching pattern had a chromosome 22q11 deletion, guidelines for testing this cohort are debatable. The high prevalence of a VSD with a normal aortic arch and branch pulmonary arteries may preclude universal testing for a chromosome 22q11 deletion in this subgroup, although universal screening would certainly allow for early diagnosis of the deletion and appropriate counseling. Thus, until cost-benefit and clinical outcome studies elucidate the utility of deletion testing in individuals with a VSD but normal aortic arch anatomy and pulmonary arteries, screening for a deletion may be routinely warranted but most likely will be guided by the presence of associated noncardiovascular features of chromosome
22q11 deletion syndrome, which include a characteristic facies, feeding abnormalities, absence/hypoplasia of the thymus, hypocalcemia, palatal anomalies, speech/learning disabilities, and various other findings.\textsuperscript{2,3,18}

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