Title
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Journal
Pediatric Cardiology, 34(7)

ISSN
0172-0643

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Publication Date
2013-10-01

DOI
10.1007/s00246-013-0694-4

Peer reviewed

Published in final edited form as:
Pediatr Cardiol. 2013 October ; 34(7): 1687–1694. doi:10.1007/s00246-013-0694-4.

22q11.2 Deletions in Patients with Conotruncal Defects: Data from 1610 Consecutive Cases

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Abstract

Background—The 22q11.2 deletion syndrome is characterized by multiple congenital anomalies including conotruncal cardiac defects. Identifying the patient with a 22q11.2 deletion (22q11del) can be challenging because many extracardiac features become apparent later in life. We sought to better define the cardiac phenotype associated with a 22q11del to help direct genetic testing.

Methods—1,610 patients with conotruncal defects were sequentially tested for a 22q11del. Counts and frequencies for primary lesions and cardiac features were tabulated for those with and without a 22q11del. Logistic regression models investigated cardiac features that predicted deletion status in tetralogy of Fallot (TOF).

Results—Deletion frequency varied by primary anatomic phenotype. Regardless of the cardiac diagnosis, a concurrent aortic arch anomaly (AAA) was strongly associated with deletion status (OR 5.07, 95% CI: 3.66–7.04). In the TOF subset, the strongest predictor of deletion status was an AAA (OR 3.14, 95% CI: 1.87–5.27, p <0.001), followed by pulmonary valve atresia (OR 2.03, 95% CI: 1.02–4.02, p= 0.04). Among those with double outlet right ventricle and transposition of the great arteries, only those with an AAA had a 22q11del. However, five percent of patients with an isolated conoventricular ventricular septal defect and normal aortic arch anatomy had a 22q11del, while no one with an IAA-A had a 22q11del.

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Disclosures: none

Conclusion—A subset of patients with conotruncal defects are at risk for a 22q11del. A concurrent AAA increases the risk regardless of the intracardiac anatomy. These findings help direct genetic screening for the 22q11.2 deletion syndrome in the cardiac patient.

Keywords

conotruncal cardiac defects; genes; genetic heart disease; congenital

Introduction

The 22q11.2 deletion syndrome is the most common deletion syndrome occurring in 1–4 per 6000 live births [1]. The associated phenotypic features are highly variable between individuals and include: cardiovascular anomalies, thymic hypoplasia or aplasia with immune dysfunction, palatal abnormalities, parathyroid hypoplasia or aplasia with hypocalcemia, characteristic dysmorphic features, renal abnormalities, developmental delay, behavioral disorders, learning disabilities and psychiatric disorders [2–6]. While some patients manifest a very mild phenotype (e.g. learning disabilities), and may not be recognized as carriers of a 22q11.2 deletion (22q11del) until their offspring are diagnosed, others manifest a severe phenotype with multi-organ system involvement and are diagnosed as neonates. Studies have identified a 22q11del in a subset of patients with conotruncal defects including: tetralogy of Fallot (TOF), truncus arteriosus (TA), interrupted aortic arch (IAA), and ventricular septal defects (VSD), and have identified a higher prevalence of a 22q11del among those with a concurrent aortic arch anomaly [7–14]. In contrast, a 22q11del is uncommonly reported in patients with other conotruncal defects such as double outlet right ventricle (DORV) and transposition of the great arteries (TGA) [8, 14, 15].

Given the limited size and description of cases reported in previous studies, it has been difficult to detail the cardiac anatomy associated with a 22q11del. For example, it is unclear whether an anatomic subset of TGA and DORV cases are more likely to have a 22q11del. Consequently, the selection of patients to test for the 22q11.2 deletion syndrome remains a challenge especially in the fetal or neonatal setting when syndromic features, such as delayed emergence of speech and learning disabilities are not apparent [16]. The purpose of this study was to determine which conotruncal defects are more likely to have a 22q11del in a large and phenotypically well-characterized cohort to better guide clinical screening.

Methods

Patients

Between January 1994 to February 2010, 1,993 patients with conotruncal defects (TOF, TA, IAA, VSD, DORV, TGA) were consecutively invited to participate in a protocol studying the genetic basis of congenital heart disease conducted in The Cardiac Center and the Division of Human Genetics at The Children’s Hospital of Philadelphia. A total of 1,610 patients consented to participate and were included in the study. This study was approved by the Institutional Review Board for the Protection of Human Subjects at the Children’s Hospital of Philadelphia.

Cardiovascular Phenotype

A detailed cardiac phenotype was ascertained from all available medical records including echocardiography, cardiac MRI, cardiac catheterization, and/or operative notes. If there was a discrepancy of the diagnosis in the medical records, the original images were inspected by one reviewer (E.G.).

For the purposes of this study, a normal aortic arch was defined as a left sided aortic arch with normal branching of a right innominate artery into a right subclavian and right carotid artery. An aortic arch anomaly (AAA) was defined as a right sided aortic arch with mirror image branching or aberrant left subclavian artery, a left sided aortic arch with an aberrant right subclavian artery, or a double aortic arch.

In addition, TOF was defined by anterior malalignment of the conal septum with mitral to aortic valve fibrous continuity. Patients with TOF were further classified by pulmonary valve anatomy (pulmonary stenosis, pulmonary atresia or absent pulmonary valve), and the presence or absence of an AAA, multiple aorto-pulmonary collateral arteries (MAPCA), and/or discontinuous branch pulmonary arteries (DPA).

VSDs were defined by the anatomical position of the VSD and included: conoventricular (also known as perimembranous) defect beneath the septal leaflet of the tricuspid valve in the membranous septum, malalignment (posterior malalignment of the conal septum), and conoseptal hypoplasia (also known as doubly-committed and sub-arterial) defect within the conal septum. Patients with only muscular or atrioventricular canal type VSDs were excluded from this study. VSDs were further classified by the presence or absence of an aortic coarctation and the presence or absence of an AAA.

DORV was defined by the lack of mitral to aortic valve fibrous continuity, and greater than 50% of the aorta over the right ventricle thereby assigning the aorta to the right ventricle. DORV subjects were further classified by atrioventricular valve anatomy, semilunar valve anatomy and single versus two-ventricle anatomy.

Finally for this study, TGA was defined as great vessel malposition with the aorta arising from the right ventricle and the pulmonary artery arising from the left ventricle (d-TGA), or the presence of ventricular inversion (l-TGA). Subjects with TGA were further classified by: 1) the presence or absence of a VSD, and 2) simple versus complex anatomy. Subjects were classified as “simple” or “complex” based on semilunar valve, atrioventricular valve, and single versus two ventricle anatomy. Those cases with atrioventricular valve abnormalities, aortic valve abnormalities and/or single ventricle anatomy were considered “complex”, while those with d-TGA, in the presence or absence of a VSD and/or pulmonary stenosis were considered “simple”.

22q11.2 Deletion Testing

Deletion status was determined by either fluorescence *in situ* hybridization or multiplex ligation-dependent probe amplification, as previously described [14, 17].

Statistical Analysis

Frequency distributions of demographic and clinical characteristics were tabulated for those with and without a 22q11del. Logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI) to determine the association between an aortic arch anomaly and 22q11.2 deletion status among the entire case group and by primary diagnosis (e.g., TOF, TA, IAA, VSD, DORV, and TGA). In order to better characterize the anatomic features of TOF, VSD, DORV and TGA, the following analyses were conducted: 1) counts of anatomic features of TOF stratified by valve anatomy; 2) counts and frequencies of anatomic subtypes of VSDs with and without a 22q11del stratified by aortic arch anatomy; 3) counts of anatomic subtypes of DORV stratified by semilunar valve anatomy; and 4) counts of anatomic subtypes of TGA stratified by the presence or absence of a VSD.

In addition, we evaluated factors that may predict a 22q11del in TOF. A chi-square analysis assessed differences between those with and without a 22q11del for the following factors: 1) TOF valve anatomy (pulmonary stenosis, pulmonary atresia, absent pulmonary valve); 2) presence of an aortic arch anomaly; 3) presence of multiple aorto-pulmonary collateral arteries; and 4) presence of discontinuous branch pulmonary arteries. These variables were then included in a multivariable logistic regression model assessing the association between selected characteristics and deletion status among TOF cases. For some phenotypes, where numbers permitted, positive predictive value was determined by dividing the number of individuals with a given phenotype and a 22q11del by the total number of individuals with the given phenotype (i.e., with and without a 22q11del). All analyses were conducted using Intercooled Stata, version 12.0 (StataCorp LP, College Station, TX).

Results

The total cohort included 1,610 cases in which there was a slight male predominance (57%). The majority of subjects were non-Hispanic white (68%). There was no difference in gender or race/ethnicity between cases with and without a 22q11del. A total of 187 subjects (13%) carried the 22q11.2 deletion. Deletion frequency varied by primary anatomic phenotype with the highest prevalence in IAA-B (56%) and the lowest in DORV (< 1%) and TGA (< 1%) (Table 1). Regardless of the primary cardiac diagnosis, aortic arch anatomy was strongly associated with 22q11del status (OR 5.07, 95% CI: 3.66–7.04). In particular, a 22q11del was more likely with a concurrent aortic arch anomaly as compared to a normal aortic arch in TA (OR 10.4, 95% CI: 3.50–30.92), VSD (OR 3.51, 95% CI: 1.43–8.64), IAA-B (OR 3.02, 95% CI: 1.30–7.03), and TOF (OR 2.92, 95% CI: 1.81–4.71). Because there was only one case with a 22q1ldel in patients with DORV and TGA, odds ratios were not calculated for these lesions (Table 2).

Tetralogy of Fallot

The cardiac phenotype of all TOF patients is presented in detail in supplemental table 1. A chi-square analysis suggests that these anatomical features vary between deleted and non-deleted patients. In particular, pulmonary atresia, AAA, and MAPCAs are more commonly seen among deleted as compared to non-deleted patients (Table 3). In the multivariable logistic regression model, AAA was the feature that most strongly predicted 22q11del status

among all TOF cases. Specifically, those with an AAA were 3.14 times more likely to have a 22q11del (95% CI: 1.87–5.27, p <0.001) compared to those with a normal aortic arch anatomy, after adjusting for valve anatomy, the presence of MAPCAs, and the presence of DPAs. Those with pulmonary atresia were also more likely to have a 22q11del (OR 2.03, 95% CI: 1.02–4.02) compared to those with pulmonary stenosis. Although the presence of MAPCAs was modestly associated with deletion status (OR 1.50, 95% CI: 0.73–3.06), the association was not significant (p = 0.27). Finally, the presence of DPAs was not associated with deletion status (Table 4).

Ventricular Septal Defects

Seven of the 136 (5%) patients with a VSD, normal aortic arch anatomy (normal sidedness and branching pattern) and no aortic coarctation had a 22q11del, all of whom had a conoventricular VSD (Table 5). Of interest, those with normal aortic arch anatomy and a posterior malalignment type VSD did not have a 22q11del whether or not a coarctation of the aorta was present. However, a 22q11del was seen in patients with all subtypes of VSDs if an AAA was present, consistent with the overall association of an AAA and a 22q11del (Table 5).

A 22q11del was identified in seven patients with a conoventricular VSD and normal aortic arch anatomy by the research protocol rather than clinical testing; five were identified at less than one year, one at six years and one at 12 years of age reflecting their age of recruitment. Subsequent screening for additional syndromic features noted characteristic dysmorphic facies in two patients less than one year of age, one of which had an absent thymus at the time of deletion screening, and one who had hypocalcemia at the time of deletion screening and was later found to have an absent thymus. However, two of the younger patients did not have any extracardiac features at the time of deletion screening and were only later found to have extra-cardiac abnormalities including velopharyngeal insufficiency and a mild learning disability. The two patients recruited into the protocol and found to have a 22q11del later in childhood had very mild features including mild facial dysmorphic features in one and minor learning disabilities in the other.

DORV/TGA

All anatomic subtypes of DORV were represented in this study cohort including those with two-ventricle anatomy (n= 74) and single ventricle anatomy (n= 64). In particular, 41 patients were diagnosed with DORV in conjunction with pulmonary valve stenosis/atresia and two normally sized ventricles, physiologically similar to but anatomically distinct from TOF (Supplemental table 2). Only one patient with DORV had a 22q11del, namely a patient with DORV, pulmonary valve stenosis, and a right aortic arch with an isolated left subclavian artery.

All anatomical subtypes of TGA, (d-TGA and l-TGA) including cases with single and two-ventricle anatomy were included (Supplemental table 3). Of this subset, only one patient with d-TGA {S,D,D}, VSD, and a right aortic arch with an aberrant left subclavian artery had a 22q11del.

Interrupted aortic arch

Though 22q11.2 deletions were commonly identified in cases with IAA-B (56%), no deletions were seen in cases with IAA-A (Table 1), either in the context of a VSD (n= 11), or in conjunction with more complex conotruncal malformations such as DORV or TGA (n= 9).

Discussion

As reported previously, we found that patients with a subset of conotruncal defects (TOF, TA, VSD and IAA-B) commonly carry a 22q11del and are more likely to have a 22q11del in the presence of an arch anomaly [6, 8, 12–14, 18–23]. However, the large size of our cohort ascertained from a single center with detailed cardiac phenotypes enabled us to identify cardiac features that may predict 22q11.2 deletion status and thus help guide screening practices.

In particular, previous studies have suggested that TOF with pulmonary atresia and MAPCA's is more commonly associated with a 22q11del as compared to other subtypes of TOF [8, 22, 24]. In our analysis, pulmonary atresia and MAPCA's were more commonly seen among deleted patients. However, only pulmonary atresia significantly predicted 22q11del status, whereas the presence of MAPCAs did not. The positive predictive value (PPV) of TOF with pulmonary atresia for a 22q11del was 21%, whereas the PPV of TOF without pulmonary atresia for a 22q11del was 11% (Table 1). Furthermore, the strongest predictor of 22q11del status among anatomic features in TOF was a concurrent AAA. In this case, the PPV of TOF with AAA for a 22q11del was 21%, while the PPV of TOF with a normal aortic arch was 8% (Supplemental table 1).

Studies have shown that patients with a VSD can also have a 22q11del [18, 21]. Given the frequency of a 22q11del in congenital heart disease characterized by malalignment VSDs (TOF, IAA-B), we expected patients with posterior malalignment type VSDs (particularly with an aortic coarctation) to be at similar risk for a 22q11del. However, at least in our cohort, the small subset of patients with a malalignment VSD and coarctation of the aorta only had a 22q11del in the presence of a concurrent AAA. In contrast, subjects with an isolated conoventricular VSD had a 22q11del with and without a concurrent AAA. Screening practices in patients with a conoventricular VSD may be debatable given the general prevalence of these defects. However, the absence of characteristic extracardiac syndromic features in many cases challenges our ability to identify the at-risk patient by clinical features alone. In our cohort of seven patients with a conoventricular VSD and a 22q11del, four did not have extra-cardiac clinical features early in life to suggest a 22q11del. Thus, early screening of patients with conoventricular VSD's would identify those with a 22q11del before many extracardiac features become apparent, allowing for early intervention and counseling.

Our study demonstrates that patients with DORV and TGA are very unlikely to have a 22q11del unless an AAA is present. Many patients with DORV were physiologically similar to but anatomically distinct from TOF. However, in spite of this physiologic similarity, only one DORV patient with a concurrent AAA carried a 22q11del.

Finally, our cohort had the largest number of patients with an IAA-A reported to date and demonstrated no risk for a 22q11del regardless of the intracardiac anatomy.

Biological Implications

In addition to outflow tract abnormalities, the association of AAAs with deletion status highlights the role of fourth pharyngeal arch development in the 22q11.2 deletion syndrome. This developmental pattern mirrors those observed in mouse models of this deletion syndrome [19, 25–27]. While DORV and TGA represent abnormalities of the outflow tracts and are thus classified as conotruncal lesions, an increasing body of evidence suggests that a subset of cases with DORV and TGA share a genetic basis with laterality disorders [28–31]. Consequently, from a genetic perspective, DORV and TGA may at times be more closely related to heterotaxy syndrome rather than conotruncal defects.

Genetic Screening for a 22q11.2 Deletion

Screening strategies for a 22q11del continue to evolve [32–37]. Often fetuses, neonates and infants with a conotruncal defect may not immediately demonstrate clinical features typically associated with a 22q11del, thus limiting our ability to identify those carrying the deletion. Adults may have escaped diagnosis given the subtlety of some associated features, the timing with which testing for a 22q11del has become available, and their often sporadic engagement with cardiology services. To determine whether clinical assessment alone can predict deletion status in patients with cardiac malformations, Agergaard and colleagues performed a meta-analysis of 14 studies that used clinical exam to predict deletion status [16]. They found that approximately 25% of the patients with a 22q11del would be missed if testing were dependent on examination only. They concluded that testing should be performed on all patients with conotruncal cardiac defects.

Our study provides additional data to guide genetic testing for a 22q11del in the patient with congenital heart disease. Our data suggest that a prenatal or postnatal diagnosis of TOF, TA, IAA-B or conoventricular VSD should prompt testing for a 22q11del based on the prevalence of a 22q11del and the subtlety of presentation. An aortic arch anomaly markedly increases the risk for a 22q11del, regardless of the intracardiac anatomy. A diagnosis of DORV and TGA should not prompt testing unless a concurrent AAA is present. Similarly, it appears that a diagnosis of IAA-A does not require testing for a 22q11del. The adult with at-risk cardiac diagnoses should be carefully evaluated for additional features, including speech and learning disabilities, and reproductive interests should be considered in the decision to test for a 22q11del.

Early identification of a 22q11del in the cardiac patient allows for timely intervention on many of the associated extracardiac features, such as hypocalcemia, feeding issues, learning disabilities, and speech and psychological impairments. In addition, early diagnosis permits timely and appropriate counseling on clinical outcomes for a patient with a 22q11del and a cardiac defect. Increasing evidence suggests that cardiac patients with a 22q11del requiring surgical intervention have longer hospital length of stay, higher post-operative complications, and in some anatomic subsets, higher mortality as compared to those without the deletion syndrome [38–40]. Finally, diagnosing a 22q11del early in the fetal or neonatal

period allows for accurate recurrence risk counseling and parental screening for a 22q11del, given that approximately 6% of childhood cases are inherited in an autosomal dominant fashion, and an affected parent has a 50% chance of transmitting the 22q11del to his or her offspring [11]. Screening for a 22q11del in a previously undiagnosed adult patient with congenital heart disease can also assist in accurate recurrence risk counseling given the increasing numbers of adults with congenital heart disease who are planning on reproducing.

In conclusion, early identification of the 22q11.2 deletion syndrome can allow for family planning, timely counseling on clinical outcomes and early intervention for many of the clinical features that become apparent later in childhood and adult life. These findings should assist the clinician to perform targeted genetic screening for the 22q11.2 deletion syndrome in patients with conotruncal defects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: The work in the manuscript was supported by the National Institute of Health (Grant #'s: HL062177 & HL074731) as well as support by Grant Number UL1RR024134 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Center for Research Resources or the National Institutes of Health.

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Table 1

Characteristics of cases with a conotruncal cardiac defect with and without a 22q11.2 deletion

Characteristic	Without 22q11 deletion (*N* = 1,423) No. (%)	With 22q11 deletion (*N* = 187) No. (%)
Race/ethnicity		
Non-Hispanic White	964 (67.7)	126 (67.4)
Non-Hispanic Black	189 (13.3)	25 (13.4)
Hispanic	129 (9.1)	16 (8.5)
Other	141 (9.9)	20 (10.7)
Sex		
Female	611 (42.9)	90 (48.1)
Male	812 (57.1)	97 (51.8)
Aortic Arch Anomaly		
No	1,004 (70.6)	60 (32.1)
Yes	419 (29.4)	127 (67.9)
Primary Diagnosis*		
Tetralogy of Fallot† (n= 619)	537 (86.7)	82 (13.2)
Pulmonary stenosis	392 (89.2)	47 (10.7)
Pulmonary atresia	107 (78.7)	29 (21.3)
Absent pulmonary valve	25 (86.2)	4 (13.8)
NOS	13 (86.7)	2 (13.3)
Truncus arteriosus† (n= 93)	60 (64.5)	33 (35.5)
Truncus arteriosus – A1	28 (58.3)	20 (41.7)
Truncus arteriosus – A2	19 (82.6)	4 (17.4)
Truncus arteriosus – A3	3 (37.5)	5 (62.5)
Truncus arteriosus – A4	9 (75.0)	3 (25.0)
Truncus arteriosus – NOS	1 (50.0)	1 (50.0)
Interrupted aortic arch – A	11 (100)	0
Interrupted aortic arch – B	35 (43.8)	45 (56.2)
Interrupted aortic arch – NOS	2 (100)	0
Ventricular septal defect‡ (n= 361)	336 (93.1)	25 (6.9)
Double outlet right ventricle	137 (99.3)	1 (0.7)
D-Transposition of the great arteries	228 (99.6)	1 (0.4)
L-Transposition of the great arteries	56 (100)	0
Transposition of the great arteries, NOS	21 (100)	0

NOS= not otherwise specified

*For primary diagnosis, percentages are presented by row

†All types

‡Subtypes of ventricular septal defects: conoventricular, posterior malalignment and conoseptal hypoplasia

Table 2

The association between aortic arch anatomy and a 22q11.2 deletion in cases with a conotruncal cardiac defect

Primary diagnosis	Aortic Arch anomaly	No Deletion (%)	Deletion (%)	OR (95% CI)
Overall	No	1,004 (70.6)	60 (32.1)	
	Yes	419 (29.4)	127 (67.9)	5.07 (3.66–7.04)
TOF	No	350 (65.2)	32 (39.0)	
	Yes	187 (34.8)	50 (61.0)	2.92 (1.81–4.71)
TA	No	39 (65.0)	5 (15.2)	
	Yes	21 (35.0)	28 (84.8)	10.40 (3.50–30.92)
IAA	No	30 (62.5)	16 (35.6)	
	Yes	18 (37.5)	29 (64.4)	3.02 (1.30–7.03)
VSD	No	194 (57.7)	7 (28.0)	
	Yes	142 (42.3)	18 (72.0)	3.51 (1.43–8.64)
DORV	No	106 (77.4)	0	
	Yes	31 (22.6)	1 (100.0)	N/A
TGA	No	285 (93.4)	0	
	Yes	20 (6.6)	1 (100.0)	N/A

TOF= Tetralogy of Fallot; TA= Truncus Arteriosus; IAA= Interrupted aortic arch;

VSD= Ventricular septal defect; DORV= Double outlet right ventricle; TGA= Transposition of the great arteries; N/A= not applicable

Table 3

Distribution of anatomic features in cases with tetralogy of Fallot by 22q11.2 deletion status

Characteristic	Without 22q11 deletion No. (%)	With 22q11 deletion No. (%)	*P* value*
TOF valve anatomy			
Pulmonary stenosis	392 (74.8)	47 (58.7)	0.01
Pulmonary atresia	107 (20.4)	29 (36.2)	
Absent pulmonary valve	25 (4.7)	4 (5.0)	
Aortic arch anomaly			
No	350 (65.2)	32 (39.0)	<0.001
Yes	187 (34.8)	50 (61.0)	
Multiple aortopulmonary collateral arteries			
No	425 (84.7)	53 (69.7)	0.001
Yes	77 (15.3)	23 (30.3)	
Discontinuous branch pulmonary arteries			
No	485 (95.5)	72 (91.1)	0.10
Yes	23 (4.5)	7 (8.9)	

*Chi-square analysis

Table 4

The association between selected characteristics* and 22q11.2 deletion status among tetralogy of Fallot cases

Characteristic	OR (95% CI)	*P* value†
TOF valve anatomy		
Pulmonary stenosis	1.00 (Ref.)	
Pulmonary atresia	2.03 (1.02–4.02)	0.04
Absent pulmonary valve	1.29 (0.41–4.08)	0.66
Aortic arch anomaly	3.14 (1.87–5.27)	<0.001
Multiple aortopulmonary collateral arteries	1.50 (0.73–3.06)	0.27
Discontinuous branch pulmonary arteries	1.05 (0.38–2.90)	0.93

*All variables assessed simultaneously

†Multivariable Logistic Regression

Table 5

Venticular septal defect cases by aortic arch anatomy and deletion status

VSD anatomy	Total No.	Normal anatomy*		Aortic arch anomaly	
		Without 22q11 deletion No. (%)	With 22q11 deletion No. (%)	Without 22q11 deletion No. (%)	With 22q11 deletion No. (%)
Malalignment					
No coarctation	16	11 (100)	0	3 (60.0)	2 (40.0)
Coarctation	12	10 (100)	0	1 (50.0)	1 (50.0)
NOS	9	0	0	9 (100)	0
Conoventricular					
No coarctation	171	129 (94.8)	7 (5.1)	25 (71.4)	10 (28.6)
Coarctation	23	23 (100)	0	0	0
NOS	95	0	0	92 (96.8)	3 (3.2)
Conoseptal hypoplasia					
No coarctation	20	19 (100)	0	0	1 (100)
Coarctation	3	2 (100)	0	0	1 (100)
NOS	12	0	0	12 (85.7)	0
Total No.		**194**	**7**	**142**	**18**

NOS= not otherwise specified

*Normal anatomy: Normal aortic arch sidedness and branching pattern