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ORIGINAL ARTICLE

22q11.2 Deletions in Patients with Conotruncal Defects: Data from 1,610 Consecutive Cases

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Abstract 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. 1,610 patients with conotruncal defects were sequentially tested for a 22q11del. The counts and frequencies of primary lesions and cardiac features were tabulated for those with and those without a 22q11del. Logistic regression models investigated cardiac features that predicted deletion status in tetralogy of Fallot (TOF). Deletion frequency varied by primary anatomic phenotype. Regardless of the cardiac diagnosis, a concurrent aortic arch anomaly (AAA) was strongly associated with deletion status [odds ratio (OR), 5.07; 95 % confidence interval (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, 5 % of the patients with an isolated conoventricular ventricular septal defect and normal aortic arch anatomy had a 22q11del, whereas no one with an interrupted aortic arch type A had a 22q11del. 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 to direct genetic screening for the 22q11.2 deletion syndrome in the cardiac patient.

Keywords Congenital · Conotruncal cardiac defects · Genes · Genetic heart disease

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The 22q11.2 deletion syndrome is the most common deletion syndrome, occurring in 1–4 per 6,000 live births [5]. 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 [7, 9, 30, 33, 35]. Whereas 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 it is diagnosed in their offspring, others manifest a severe phenotype with multi-organ system involvement, diagnosed when they are 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 defect (VSD), as well as a higher prevalence of a 22q11del among those with a concurrent aortic arch anomaly [12, 20, 21, 23, 27, 32, 38, 40]. 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) [12, 26, 27].

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 is more likely to have a 22q11del. Consequently, the selection of patients to be tested 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 [1].

This study aimed 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 and 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 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 magnetic resonance imaging (MRI), cardiac catheterization, and operative notes. If the diagnosis in the medical records showed a discrepancy, 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 artery and a right carotid artery. An aortic arch anomaly (AAA) was defined as a right-sided aortic arch with mirror image branching or an 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 aortopulmonary collateral arteries (MAPCAs), and/or discontinuous branch pulmonary arteries (DPAs).

A VSD was defined by its anatomic position and included a 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 a conoseptal hypoplasia (also known as doubly committed and subarterial) defect within the conal septum. Patients with only muscular or atrioventricular canal-type VSDs were excluded from this study. Ventricular septal defects 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 more 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.

TGA was defined as great vessel malpositioning, 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 the presence or absence of a VSD and 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, or single-ventricle anatomy were considered "complex," whereas those with d-TGA in the presence or absence of a VSD, pulmonary stenosis, or both were considered "simple."

Finally for this study, subjects with IAA were further classified by the type of defect. Subjects either had IAA type A (IAA-A), which is defined by an interruption in the aortic arch distal to the left subclavian artery or IAA type B (IAA-B), which is defined by an interruption in the aortic arch between the left carotid artery and left subclavian artery.

22q11.2 Deletion Testing

Deletion status was determined by either fluorescence in situ hybridization or multiplex ligation-dependent probe amplification, as previously described [12, 39].

Statistical Analysis

Frequency distributions of demographic and clinical characteristics were tabulated for those with and those without a 22q11del. Logistic regression models were used to calculate odds ratios (ORs) and 95 % confidence intervals (CIs) to determine the association between an AAA and 22q11.2 deletion status among the entire case group and by primary diagnosis (e.g. TOF, TA, IAA, VSD, DORV, and TGA).

For better characterization of the anatomic features that accompany TOF, VSD, DORV, and TGA, the following analyses were conducted: (1) counts of anatomic features that accompany 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 those without a 22q11del for the following factors: TOF valve anatomy (pulmonary stenosis, pulmonary atresia, absent pulmonary valve), presence of an AAA, presence of multiple aortopulmonary collateral arteries, and presence of discontinuous branch pulmonary arteries. These variables then were included in a multivariable logistic regression model assessing the association between selected characteristics and deletion status among TOF cases. For some phenotypes, when 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. those with and those without a 22q11del). All analyses were conducted using Intercooled Stata, version 12.0 (StataCorp LP, College Station, TX, USA).

Results

The total cohort included 1,610 cases, with a slight male predominance (57 %). The majority of subjects were non-Hispanic white (68 %). The cases with and those without a 22q11del did not differ in terms of gender or race/ethnicity.

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 AAA 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 only one case of 22q11del was found among the patients with DORV or TGA, the ORs were not calculated for these lesions (Table 2).

Tetralogy of Fallot

Supplemental Table 1 presents the cardiac phenotype of all the TOF patients in detail. A chi-square analysis suggests that these anatomic features vary between deleted and non-deleted patients. In particular, pulmonary atresia, AAA, and MAPCAs are more commonly seen among deleted than among 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; $p < 0.001$) than those with a normal aortic arch anatomy after adjustment for valve anatomy, the presence of MAPCAs, and the presence of DPAs. Those with pulmonary atresia also were 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

Among the 136 patients with a VSD, normal aortic arch anatomy (normal sidedness and branching pattern), and no aortic coarctation, 7 patients (5 %) had a 22q11del, all of whom had a conoventricular VSD (Table 5). Interestingly, those with normal aortic arch anatomy and a posterior malalignment type VSD did not have a 22q11del whether a coarctation of the aorta was present or not. 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 a normal aortic arch anatomy by the research protocol rather than by clinical testing. Five patients were identified at less than one year of age, one patient at 6 years of age, and one patient at 12 years of age, reflecting their age at recruitment.

Table 1 Characteristics of cases with a conotruncal cardiac defect with and without a 22q11.2 deletion

Characteristic	Without 22q11.2 deletion ($n = 1,423$) *n* (%)	With 22q11.2 deletion ($n = 187$) *n* (%)
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[a]		
Tetralogy of Fallot[b] ($n = 619$)	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[b] ($n = 93$)	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[c] ($n = 361$)	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

[a] For primary diagnosis, percentages are presented by row

[b] All types

[c] Subtypes of ventricular septal defects (VSDs): conoventricular VSD, posterior malalignment, and conoseptal hypoplasia

Subsequent screening for additional syndromic features noted characteristic dysmorphic facies in two patients less than one year of age. One of the two had an absent thymus at the time of deletion screening, and the other one 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 extracardiac 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 the one patient 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 those with 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 anatomic subtypes of TGA (d-TGA and l-TGA), including cases with single- and two-ventricle anatomy, were included (Supplemental Table 3). In this subset, only one patient with d-TGA, VSD, and a right aortic arch with an aberrant left subclavian artery had a 22q11del.

IAA

Although 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 [2, 4, 12, 21–24, 27, 29, 34, 35]. However, the large size of our cohort enrolled 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 MAPCAs is more commonly

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

Primary diagnosis	Aortic arch anomaly	No deletion *n* (%)	Deletion *n* (%)	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

OR odds ratio, *CI* confidence interval, *TOF* tetralogy of Fallot, *TA* truncus arteriosus, *IAA* interrupted aortic arch, *VSD* ventricular septal defect, *DORV* double-outlet right ventricle, *N/A* not applicable, *TGA* transposition of the great arteries

Table 3 Distribution of anatomic features in cases with tetralogy of Fallot (TOF) by 22q11.2 deletion status

Characteristic	Without 22q11.2 deletion *n* (%)	With 22q11.2 deletion *n* (%)	*p* value[a]
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)	

[a] Chi-square analysis

Table 4 Association between selected characteristics and 22q11.2 deletion status among tetralogy of Fallot (TOF) cases

Characteristic	OR (95 % CI)	*p* value[a]
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 were assessed simultaneously

OR odds ratio, *CI* confidence interval

[a] Multivariable logistic regression

associated with a 22q11del than other subtypes of TOF [27–29]. In our analysis, pulmonary atresia and MAPCAs 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 %. 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 %, whereas the PPV of TOF with a normal aortic arch for a 22q11del was 8 % (Supplemental Table 1).

Studies have shown that patients with a VSD can also have a 22q11del [2, 24]. 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 those 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 had a 22q11del only in the presence of a concurrent AAA. In contrast, subjects with an isolated conoventricular VSD had a 22q11del with and without a concurrent AAA.

Table 5 Ventricular septal defect cases by aortic arch anatomy and deletion status

VSD anatomy	Total no.	Normal anatomy[a]		Aortic arch anomaly	
		Without 22q11.2 deletion *n* (%)	With 22q11.2 deletion *n* (%)	Without 22q11.2 deletion *n* (%)	With 22q11.2 deletion *n* (%)
Posterior 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

[a] Normal aortic arch sidedness and branching pattern

Screening practices for patients with a conoventricular VSD may be debatable given the general prevalence of this defect. However, the absence of characteristic extracardiac syndromic features in many cases challenges our ability to identify the at-risk infant by clinical features alone. In our cohort of seven patients with a conoventricular VSD and a 22q11del, four did not have extracardiac clinical features early in life to suggest a 22q11del. Thus, early screening of patients with conoventricular VSDs would identify those with a 22q11del before many extracardiac features become apparent, allowing for early intervention and counseling.

Our study demonstrated 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 patients with 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.

Biologic 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 that observed in mouse models of this deletion syndrome [14, 17, 25, 34]. Although DORV and TGA represent abnormalities of the outflow tracts and thus are classified as conotruncal lesions, an increasing body of evidence suggests that a subset patients with DORV and TGA share a genetic basis with laterality disorders [6, 8, 13, 31]. Consequently, from a genetic perspective, DORV and TGA may at times be more closely related to heterotaxy syndrome than to conotruncal defects.

Genetic Screening for a 22q11.2 Deletion

Screening strategies for a 22q11del continue to evolve [3, 10, 11, 16, 19, 36]. 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 during which testing for a 22q11del has become available, and their often sporadic engagement with cardiology services.

To determine whether clinical assessment alone can predict the deletion status in patients with cardiac malformations, Agergaard et al. [1] performed a meta-analysis of 14 studies that used clinical examination to predict deletion status. They found that $\sim$25 % of the patients with a 22q11del would be missed if testing were dependent on examination alone. They concluded that testing should be performed for 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 pre- 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 AAA 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 a longer hospital stay, more postoperative complications, and in some anatomic subsets, higher mortality as compared to those without the deletion syndrome [15, 18, 37].

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 $\sim$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 [20]. Screening for a 22q11del in a previously undiagnosed adult patient with congenital heart disease can assist in accurate recurrence risk counseling given the increasing numbers of adults with congenital heart disease who reach reproductive age.

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 in performing targeted genetic screening for the 22q11.2 deletion syndrome in patients with conotruncal defects.

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