

22q11.2 Deletion Status and Disease Burden in Children and Adolescents With Tetralogy of Fallot

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Background—Patients with repaired tetralogy of Fallot experience variable outcomes for reasons that are incompletely understood. We hypothesize that genetic variants contribute to this variability. We sought to investigate the association of 22q11.2 deletion status with clinical outcome in patients with repaired tetralogy of Fallot.

Methods and Results—We performed a cross-sectional study of tetralogy of Fallot subjects who were tested for 22q11.2 deletion, and underwent cardiac magnetic resonance, exercise stress test, and review of medical history. We studied 165 subjects (12.3±3.1 years), of which 30 (18%) had 22q11.2 deletion syndrome (22q11.2DS). Overall, by cardiac magnetic resonance the right ventricular ejection fraction was 60±8%, pulmonary regurgitant fraction was 34±17%, and right ventricular end-diastolic volume was 114±39 cc/m². On exercise stress test, maximum oxygen consumption was 76±16% predicted. Despite comparable right ventricular function and pulmonary regurgitant fraction, on exercise stress test the 22q11.2DS had significantly lower percent predicted: forced vital capacity (61.5±16 versus 80.5±14; $P<0.0001$), maximum oxygen consumption (61±17 versus 80±12; $P<0.0001$), and work (64±18 versus 86±22, $P=0.0002$). Similarly, the 22q11.2DS experienced more hospitalizations (6.5 [5–10] versus 3 [2–5]; $P<0.0001$), saw more specialists (3.5 [2–9] versus 0 [0–12]; $P<0.0001$), and used ≥1 medications (67% versus 34%; $P<0.001$).

Conclusions—22q11.2DS is associated with restrictive lung disease, worse aerobic capacity, and increased morbidity, and may explain some of the clinical variability seen in tetralogy of Fallot. These findings may provide avenues for intervention to improve outcomes, and should be re-evaluated longitudinally because these associations may become more pronounced with time. (*Circ Cardiovasc Genet.* 2015;8:74-81. DOI: 10.1161/CIRCGENETICS.114.000819.)

Key Words: echocardiography ■ exercise test ■ genetics ■ magnetic resonance imaging ■ tetralogy of Fallot

Despite notable surgical success, many patients with tetralogy of Fallot (TOF) experience significant morbidity and early mortality. Postsurgical pulmonary insufficiency (PI) with consequential right ventricular (RV) remodeling and dysfunction is thought to contribute significantly to long-term outcomes, such as decreased exercise performance, increased incidence of arrhythmias, and risk of sudden death.^{1–3} Outcomes in adults have been extensively described, although little is known about the intermediate cardiovascular status preceding symptoms and the apparent need for pulmonary valve replacement.^{1,2,4–7} Moreover, clinical variability is not explained on the basis of PI alone.

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TOF is a disease of considerable genetic heterogeneity. The 22q11.2 deletion syndrome (22q11.2DS) and trisomy 21 account for ≈15% and 7% of all TOF cases, respectively. TOF is also a characteristic finding in many syndromes (eg, Alagille,

CHARGE, and VACTERL [Vertebral defects, Anal atresia, Cardiac defects, Tracheo-esophageal fistula, Renal anomalies and Limb deformities] syndromes), and is associated with a growing list of copy number variants (eg, 1p21.1) and single gene disorders (eg, NKX2.5 and FOG2/ZFPM2).^{8–12} As noted, 22q11.2DS is the most common finding, present in 15% to 20% of TOF with pulmonary stenosis and nearly 50% of those with pulmonary atresia and major aorto-pulmonary collaterals.^{13–16} 22q11.2DS is a multisystem disorder characterized by congenital heart disease, palate anomalies, hypocalcemia, immunodeficiency, speech and learning disabilities, behavioral and psychiatric disorders, and characteristic facial features.¹⁷ We postulate that genotype could explain at least, in part, the clinical variability seen in TOF. We, therefore, hypothesized that 22q11.2DS is independently associated with clinical outcomes in TOF and sought to investigate the contribution of 22q11.2DS to RV function, exercise performance and disease burden in school age and adolescent children with repaired TOF.

Received July 29, 2014; accepted November 24, 2014.

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Circ Cardiovasc Genet is available at <http://circgenetics.ahajournals.org>

DOI: 10.1161/CIRCGENETICS.114.000819

Methods

Study Population and Data Collection

We performed a cross-sectional study of subjects operated for TOF who underwent genetic testing, cardiac magnetic resonance (CMR), and cardiopulmonary exercise testing (EST) within at most 3 months of one another at The Children's Hospital of Philadelphia as part of a study protocol. Subjects were identified from existing studies and clinical databases at our institution. Inclusion required the confirmed diagnosis of TOF by review of medical records, a history of complete surgical TOF repair, and age 8 to 18 years on study enrollment.¹⁸ TOF was defined as the presence of anterior malalignment of the conal septum, override of the aorta and mitral to aortic valve fibrous continuity. Preoperative echocardiographic reports, cardiac catheterization studies, and operative notes were reviewed to confirm the diagnosis. Genetic testing was performed using fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, or both to classify subjects as del22q11.2 positive (22q11.2DS) or del22q11.2 negative (nondeleted [ND]).^{17,18} Both tests were performed in 47% of the subjects, multiplex ligation-dependent probe amplification only in 28% (most of the ND had multiplex ligation-dependent probe amplification testing), and fluorescence in situ hybridization only in 26%.^{19,20} Cases with other recognized genetic syndromes were excluded, including those with Noonan syndrome, CHARGE association, VACTERL, Williams syndrome, and Goldenhar syndrome. Cases who were unrepaired, had only palliative procedures, or underwent a heart transplant were likewise excluded. Patients with trisomy 21 and Alagille syndrome were enrolled in the study but excluded from this analysis because of small numbers that would not allow for meaningful comparisons. Detailed review of medical history was undertaken to assess resource use and disease burden reflected by the number of significant medical encounters. Detailed review of medical records and interviews with families provided data on cardiac and noncardiac medical and surgical history, subspecialty visits, and prescribed medications at the time of enrollment.

Surgical repair for TOF was defined as (1) complete (relief of outflow tract obstruction and closure of the ventricular septal defect in the same operative procedure), (2) complete after palliation (complete repair preceded by palliation with a Blalock Taussig shunt), or (3) staged (separate operations performed to achieve complete repair). Primary surgery was defined as the initial operation(s) performed to achieve relief of outflow tract obstruction and closure of the ventricular septal defect. Procedures performed, thereafter, were classified as subsequent operations.

Cardiac Magnetic Resonance

CMR studies were performed on a 1.5-T Avanto Whole Body Magnetic Resonance System (Siemens Medical Solutions, Erlangen, Germany) using a standard imaging protocol, as described previously.²¹

Exercise Stress Test

Subjects exercised to maximal ability using a ramp cycle protocol on an electronically braked cycle ergometer (SensorMedics, Yorba Linda, CA), as described previously.²² Eighteen subjects who were <130 cm tall exercised on a treadmill (Marquette Series 2000, Milwaukee, WI). Resting spirometry included forced vital capacity, which was considered normal if >80% of predicted. Breathing reserve was obtained as a measure of pulmonary function at peak exercise (normal >15%).²³ At peak exercise, data included oxygen consumption (VO_2), maximum physical working capacity, oxygen pulse (a surrogate of ventricular stroke volume), and the maximal respiratory exchange ratio to identify subjects who achieved maximum effort. The percent predicted of maximum VO_2 (mVO_2), the VO_2 at the anaerobic threshold and maximum work were calculated for each patient according to normative values and considered normal if >80% of predicted.^{24,25} Exercise performance (aerobic capacity) was defined by percent predicted mVO_2 and VO_2 at the anaerobic threshold. An EST was considered maximal if the respiratory exchange ratio was

>1.1. The anaerobic threshold was used as an effort-independent surrogate of the ability of the cardiovascular system to support the metabolic demands during exercise.²⁶ Impaired chronotropic response was defined as peak heart rate <180 bpm.

Electrocardiogram

Electrocardiogram (ECG) was performed on MAC 5000 machine (General Electric) using a standard clinical protocol, and interpreted by a single experienced reader (R.T.).

Statistical Analysis

Continuous variables are presented as mean and SD or as median with the first and third quartile range. Categorical variables are described using count and percentage. The differences between 22q11.2DS and ND groups were tested with the Wilcoxon Rank Sum test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Covariates were compared with Pearson correlation coefficient. Poisson regression adjusting for age and years of follow-up with the Generalized Estimating Equations method for repeated measurements was used to assess the independent associations between deletion status and number of hospitalizations, procedures, medications, and operations. Subgroup analyses were performed for subjects with maximal EST. Statistical significance was reached for $P < 0.05$ (2-sided tests). All analyses were performed using SAS statistical software version 9.2 (Cary, NC).

Results

There were 754 age-appropriate potential subjects identified in our clinical and research databases. Forty-nine subjects were excluded given the presence of other genetic syndromes (Noonan syndrome, CHARGE association, VATER and VACTERL, Williams syndrome, and Goldenhar syndrome) or surgical issues that included unrepaired TOF, palliation only, single ventricle-type operations, or heart transplant. Fifty-three percent of the potential 754 subjects could not be contacted or were deceased ($n=90$). Therefore, of the 309 potential subjects who met inclusion criteria, 57% consented to the study ($n=177$). After exclusion of subjects with trisomy 21 or Alagille syndrome, this analysis included 165 subjects, of which 30 had 22q11.2DS (18%; Figure 1). In those subjects where both fluorescence in situ hybridization and multiplex ligation-dependent probe amplification was performed to identify a 22q11.2 deletion, there was 100% agreement between the 2 techniques. Age at cardiac testing was 12.3 ± 3.1 years, with a predominance of males and whites. The groups were comparable in terms of demographic, anatomic, and surgical characteristics, as detailed in Table 1.

Cardiovascular Status

We examined the cardiovascular status of the study population by CMR, EST, and ECG. The full study cohort demonstrated normal ventricular function on CMR, with considerable PI (pulmonary regurgitant fraction=37% [26–45]) and dilated RVs (Tables 2).

On EST, most subjects achieved a maximal EST. Resting forced vital capacity was diminished in 59% of subjects, suggesting restrictive lung disease. At peak exercise, mVO_2 was decreased, physical working capacity was low normal and breathing reserve was preserved (Table 3). There was no association between aerobic capacity and measures of resting RV ejection fraction ($P=0.97$) and PI ($P=0.49$) by CMR. Impaired chronotropic response was present in 42% of the

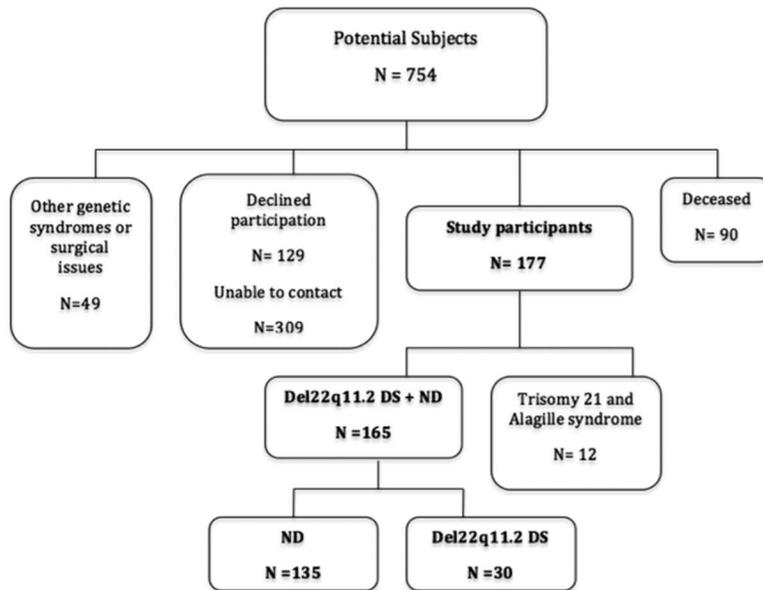


Figure. Description of the study population. The flow chart represents the number of subjects with tetralogy of Fallot who were available for recruitment from our institution's databases and the final composition of the study cohort. ND indicates nondeleted.

subjects. There was no association between peak heart rate and mVO_2 ($P=0.10$) for subjects achieving a maximal test.

On ECG, most subjects had right bundle-branch block. (Table 4) QRS duration and RV end-diastolic volume were modestly associated ($R=0.39$; $P<0.0001$).

22q11.2 Deletion Status and Clinical Outcome

Cardiovascular Status

The 22q11.2DS and ND groups had comparable RV function and RV hypertrophy, measured as RVEF and RV mass/ m^2 on CMR, respectively. The RV end-diastolic volume was comparable when the analysis was adjusted for reoperations that would diminish PI (RV-pulmonary artery conduit and pulmonary valve replacements; Table 2).

On EST, however, the 22q11.2DS group performed worse as compared with the ND. On resting spirometry, the forced vital capacity was significantly lower in the 22q11.2DS, suggesting worse restrictive lung disease in the 22q11.2DS group. This association was not affected by the presence of scoliosis, which was more prevalent in the 22q11.2DS group, present in 8 subjects (27%) as compared with 10 in the ND group (7%; $P=0.002$). However, scoliosis was neither an independent predictor of forced vital capacity nor was it a confounder of the association between deletion status and forced vital capacity (data not shown). Although percent predicted VO_2 was similar at anaerobic threshold, at peak exercise, the 22q11.2DS subjects had significantly impaired aerobic capacity with diminished mVO_2 , accomplished less work and had lower oxygen pulse, in keeping with lower measured indexed stroke volume on CMR (Table 3). 22q11.2DS was independently negatively associated with physical working capacity and oxygen pulse ($P=0.005$ and $P<0.0001$, respectively). A subanalysis limited to the subjects that achieved a maximal EST (respiratory exchange ratio ≥ 1.1) demonstrated similar results.

Intermediate Medical and Surgical History

The 22q11.2DS group reported more overall hospitalizations and significantly greater medication use. Specifically,

the 22q11.2DS group had significantly more cardiac hospitalizations and used ≥ 1 cardiac medications. Similarly, the 22q11.2DS group reported significantly more noncardiac hospitalizations as compared with the ND and significantly greater noncardiac medication use (Table 5). Cardiac medications used included aldactone (n=1 22q11.2DS), aspirin (n=6 ND and n=3 22q11.2DS), atenolol (n=1 ND), chlorothiazide (n=1 ND), digoxin (n=9 ND and n=4 22q11.2DS), enalapril (n=2 ND and n=1 22q11.2DS), lasix (3 in each group), and mexiletine (n=1 ND). One subject with 22q11.2DS used 5 medications, including aldactone, aspirin, digoxin, enalapril, and lasix.

On multivariable analysis, there was a difference in the incidence of cardiac surgeries (primary and/or subsequent); however, this difference did not reach statistical significance ($P=0.007$). There was no significant difference in cardiac catheterizations according to 22q11.2 deletion status. However, absent pulmonary valve leaflets was an independent predictor of primary and subsequent cardiac surgeries when compared with pulmonary valve stenosis (Table 6). Finally, the 22q11.2 DS group saw significantly more specialists as compared with the ND (3.5 [2–9] versus [0–1]; $P<0.0001$, respectively; Table 6).

Discussion

In this study, we found that children and adolescents with repaired TOF demonstrate relatively preserved ventricular performance, despite significant PI, and yet demonstrate diminished exercise performance. Furthermore, we found that the 22q11.2DS subset display worse exercise performance and markedly increased resource use as compared with their ND counterparts. Given that in general exercise performance peaks in adolescence and decreases with age, our cohort and the 22q11.2DS subset, in particular, would seem to be at a distinct disadvantage starting adolescence with decreased exercise performance.²⁷

Previous studies report conflicting results with respect to exercise performance in the operated TOF population, some observing decreased mVO_2 and others reporting normal

Table 1. Patient Characteristics

	Total, n=165	ND, n=135	22q11.2DS, n=30	P Value
Age at consent, y	12.3±3.1	12.5±3.1	11.6±3.2	1.0
Sex				
Female	57 (35)	47 (35)	10 (33)	1.0
Male	108 (65)	88 (65)	20 (67)	
Race				
White	139 (84)	116 (86)	23 (77)	0.49
Black	15 (9)	11 (8)	4 (13)	
Other	11 (7)	8 (6)	3 (10)	
BMI	19.2±4.1	19.1±4	18.7±4.6	0.30
Pulmonary valve anatomy at initial presentation				
Stenosis	127 (77)	107 (79)	20 (67)	0.35
Atresia	29 (18)	22 (16)	7 (23)	
Absent	9 (5)	6 (4)	3 (10)	
Surgical approach				
Complete repair	138 (84)	116 (86)	22 (73)	0.27
Complete after palliation	22 (13)	15 (11)	7 (23)	
Staged	5 (3)	4 (3)	1 (3)	
Age at complete repair, y	0.42±0.63	0.43±0.66	0.36±0.49	0.11
Age at Blalock-Taussig shunt	0.21±0.45	0.23±0.48	0.17±0.41	0.37
Age at complete repair if preceded by Blalock-Taussig shunt	1.5±1.72	1.59±1.95	1.32±1.22	0.44
Surgical repair				
Transannular patch	120 (73)	102 (76)	18 (60)	0.28
Nontransannular patch*	11 (7)	10 (7)	1 (3)	
VSD closure only	12 (7)	8 (6)	4 (13)	
RV-PA conduit	20 (12)	14 (10)	6 (20)	

Data are expressed as mean (±SD) or as number (percentage). VSD closure only indicates that a transannular patch or extensive right ventricular outflow tract reconstruction was not required. Resection of muscles bundles was performed as needed. 22q11.2DS indicates 22q11.2 deletion syndrome; BMI, body mass index; ND, nondeleted; RV-PA, right ventricle to pulmonary artery; and VSD, ventricular septal defect.

* Nontransannular patch refers to relief of RV outflow tract obstruction without crossing the pulmonary valve annulus.

exercise performance.^{28–30} The precise mechanisms leading to decreased exercise performance in TOF have not been fully elucidated. Proposed etiologies include chronotropic impairment, cardiovascular limitations, restrictive pulmonary function and more recently, deficient habitual exercise.^{22,31–34} In our cohort, maximal heart rate was not associated with $m\dot{V}O_2$, measures of cardiac performance on CMR were relatively well preserved, and the high respiratory exchange ratio achieved by the majority of subjects (62%) suggests that in many cases the cardiovascular function did not limit exercise performance, despite abnormal resting pulmonary function. Thus, the mechanisms underlying poor exercise performance in this cohort are likewise poorly defined and probably represent a combination of factors, including perhaps genotype and/or a lack of habitual physical exercise. Our group recently demonstrated that habitual exercise correlates with $m\dot{V}O_2$ better than CMR measures of function, such that subjects in this age

group and range of ventricular function that exercise regularly perform better on EST.²² This is not surprising given that both cardiopulmonary, as well as peripheral muscular conditioning contribute significantly to the overall variance in aerobic capacity for any population.^{29,30,35}

Our study further demonstrates that 22q11.2 deletion status is associated with outcome as measured by exercise performance, noncardiac interventions, and resource use. Subjects with 22q11.2DS performed significantly worse on exercise testing, a finding that persisted in a subset analysis of those achieving a maximal effort. Several factors, including decreased effort or executive function may explain why fewer 22q11.2DS subjects completed a maximal exercise study as compared with their ND counterparts.^{36,37} Given that resting lung mechanics are highly effort dependent, limited ability to properly perform the maneuver may underestimate pulmonary capacity in the 22q11.2DS. However, given that the

Table 2. Cardiovascular Status: Cardiac Magnetic Resonance

Cardiac Magnetic Resonance	Total, n=148	ND, n=108	22q11.2DS, n=26	P Value
RV ejection fraction, %	60±8	60±8	60±10	0.98
Pulmonary regurgitant fraction, %	34±17	35±16	28±19	0.11
RV end-diastolic volume, mL/m ²	114±39	117±40	104±35	0.04*
RV end-diastolic volume, mL/m ² , adjusted	113(87–144)	115 (90–149)	106 (82–138)	0.40*
RV end-diastolic volume Z score	3.1±2.9	3.4±2.8	1.8±2.8	0.0093
RV end-systolic volume, mL/m ²	48±20	49±19	43±23	0.062
RV cardiac index, L/min per m ²	5.5±1.5	5.7±1.4	5.1±1.5	0.043
RV stroke volume, mL/m ²	69.7±19	72±18.5	61±18	0.01
Indexed RV mass, g/m ²	76±23	77±24	68±21	0.10
LV ejection fraction, %	69±7	70±7	66±8	0.05
LV cardiac output, L/min per m ²	3.7±0.7	3.7±0.7	3.6±0.8	0.61

Data are expressed as mean (±SD), or number (percentage). 22q11.2DS indicates 22q11.2 deletion syndrome; LV, left ventricle; ND, nondeleted; and RV, right ventricle.

* RV end-diastolic volume adjusted for reoperations to limit pulmonary insufficiency (RV to pulmonary artery conduit or pulmonary valve replacement).

22q11.2DS subset achieving a maximal performance demonstrated diminished exercise capacity by several EST measures, the presence of a 22q11.2 deletion probably confers as of yet unexplained deficiencies that could become more apparent with time. These findings could also reflect decreased participation of 22q11.2DS subjects in habitual exercise.²²

Measures of RV volume were slightly lower in the 22q11.2DS subgroup as compared with the ND. This finding could either represent less RV dilation for a given amount of PI in the 22q11.2DS subgroup or reflect more interventions aimed at limiting the degree of PI resulting in less RV dilation. The difference in RV volume disappeared after controlling for

Table 3. Cardiovascular Status: Exercise Stress Test

Exercise Stress Test	Total, n=156	ND, n=129	22q11.2DS, n=27	P Value
Maximal effort (RER≥1.1)	94 (63)	84 (68)	10 (40)	0.012
Forced vital capacity, L	2.3±0.9	2.41±0.9	1.5±0.6	<0.0001
% Predicted forced vital capacity	77±16	81±14	62±16	<0.0001
Cardiovascular response at peak exercise				
mVO ₂ , mL/kg per min	32±8	33±8	24±7	<0.0001
Predicted mVO ₂ , %	76±18	80±17	61±17	<0.0001
Maximum work, W	112±48	117±49	83±28	0.0041
% Predicted maximum work	83±23	86±22	64±18	0.0002
Oxygen pulse, mL oxygen/beat	7.4±2.9	7.8±2.9	5.4±2.2	<0.0001
Oxygen pulse/m ² , mL oxygen/beat per m ²	5.5±1.4	5.8±1.3	4.4±1.2	<0.0001
Breathing reserve, %	16±13	15±13	19±10	0.12
Maximum heart rate, bpm	180±15	182±14	175±17	0.08
Anaerobic threshold measurements				
VO ₂ at anaerobic threshold, mL/kg per min**	21±5	21±5	19±6	0.036
Predicted VO ₂ at anaerobic threshold, %	86±18	87±17	80±21	0.085

22q11.2DS indicates 22q11.2 deletion syndrome; mVO₂, maximum oxygen consumption; ND, nondeleted; RER, respiratory exchange ratio; and VO₂, oxygen consumption.

Table 4. Cardiovascular Status: ECG

ECG	Total, n=155	ND, n=129	22q11.2DS, n=26	P Value
PR interval	137±25	135±24	147±25	0.04
QRS duration	126±25	125±25	130±24	0.44
QTc interval	446±26	446±27	450±25	0.47
Right bundle branch block	106 (84)	88 (85)	18 (75)	0.037

ND indicates nondeleted; and QTc, QT interval corrected for heart rate.

reinterventions addressing the RV outflow tract (ie, conduit and valve replacements), and yet we did not find a statistically different rate of subsequent intervention in the 22q11.2DS cohort in this age group. Our inability to detect a difference between cardiac surgical rates of reintervention may be because of the age of study subjects and the relatively small number of subsequent surgeries to date, leaving open the possibility that such differences exist and become more apparent with age.

It is evident that subjects with a 22q11.2 DS experience a heavier disease burden than the ND. As noted, there was no statistically significant difference in the number of cardiac procedures, although some data, including the number of cardiac-related hospitalizations, the smaller RV volumes on CMR, and the number of prescribed cardiac medications, suggest otherwise. In all likelihood, this study was underpowered to detect a difference in this younger cohort and could have been affected by selection bias; therefore, larger and/or longitudinal studies might reveal otherwise. A study by Kyburz^{37a} in 2008 examining long-term outcomes in patients with 22q11.2DS and various heart defects found a significant number of cardiac reinterventions in subjects with 22q11.2DS.¹⁷

Our study found a remarkable difference in noncardiac health-related issues in the subset of TOF subjects with 22q11.2DS as compared with the ND, represented by significantly more hospital admissions, noncardiac surgical interventions, subspecialty care, and prescribed medications. Such findings could significantly affect quality of life for the 22q11.2DS subgroup. Although not well defined in the literature, 1 study similarly reported that subjects with 22q11.2DS had 6 nonpsychiatric admissions in a lifetime, mostly in childhood and adolescence, in keeping with our findings.³⁸ Of note, although the 22q11.2DS cohort reported a wide and predictable range of medical issues, including speech and educational problems, they did not report more frequent psychiatric

Table 5. Comparison of ND and 22q11.2DS Groups for Number of Hospitalizations and Use of Medications

	ND	22q11.2DS	P Value
Overall hospitalizations (n, IQR)	3 (2–5)	6.5 (5–10)	<0.0001
Used ≥1 medication, %	34	67	<0.0001
Cardiac hospitalizations (n, IQR)	2 (1–3)	3 (1–4)	0.032
Used ≥1 cardiac medication, %	13	23	0.044
Noncardiac hospitalizations (n, IQR)	1 (0–3)	4 (2–7)	<0.0001
Used ≥1 noncardiac medication, %	25	60	<0.0001

22q11.2DS indicates 22q11.2 deletion syndrome; IQR, interquartile range; and ND, nondeleted.

diagnoses or neuropsychiatric medication use as compared with the ND subgroup at this age. These findings suggest that either psychiatric disorders present in older 22q11.2DS subjects, or possibly, that psychiatric conditions were underdiagnosed in this age group.^{39,40}

There are several acknowledged limitations to this study. The cross-sectional design identifies associations without necessarily identifying causation. We acknowledge potential recall bias when interviewing parents for medical history. In addition, our study incurred the risk of selection bias by subjects not enrolled (death and contact issues) and because we were limited by those willing to participate in a full day of testing. However, all subjects were equally invited to participate in the study. As such, our results may not be generalizable to all subjects operated for TOF. However, this study represents one of few performed in this age group. Future longitudinal studies in this population will allow us to identify presymptomatic changes that predict outcomes and allow for better informed pre-emptive interventions. In addition, this study included research driven assessments (CMR and EST) scheduled in close proximity to one another, which were performed and interpreted by research technicians and single physicians, respectively to minimize variability in data acquisition and provide temporally related hemodynamic data.

In conclusion, this study provides unique insight into the clinical status of TOF cases at an interim age between infancy and adulthood, and the contribution of 22q11.2 deletion status to clinical outcomes. Although 22q11.2 DS and ND cases demonstrate similar cardiac function as measured by cardiac MRI, those with a 22q11.2 deletion demonstrate even worse exercise performance and increased morbidity relative to their ND counterparts. Whether subtle cardiovascular differences and the consequences of poor exercise performance become more pronounced over time remain to be explored in a longitudinal study. Regardless, future studies should incorporate genotype, and in particular, 22q11.2 deletion status, into the analyses of TOF outcomes. Our study also serves to highlight the multisystem nature of 22q11.2DS and brings attention to noncardiac factors that contribute to the variability seen in TOF outcomes. As such, this study serves as a paradigm for the relationship to be explored between specific genotypes and clinical outcomes in the congenital heart disease population. Moreover, our results provide avenues for early intervention and contribute to our ability to counsel subjects and families about potential outcomes. Early diagnosis might lead to better management in the newborn period for hypocalcemia, immunodeficiency, and feeding difficulties; it may also allow for identifying exercises that are skill appropriate and that will ultimately lead to improved exercise capacity and quality of life. In addition, early diagnosis and understanding of the causes for additional hospital admissions may allow for identification of elements of the noncardiac care that can affect overall status. Finally, early diagnosis allows for anticipation of problems, thus avoiding the so-called medical odyssey, decreasing the burden to patients and families. The burden to this patient population might be alleviated by a multidisciplinary approach to 22q11.2DS.

Table 6. Multivariable Analysis Comparing the ND and 22q11.2DS Groups for Incidence Rate of Cardiac and Noncardiac Surgeries, Hospitalizations, and Cardiac Catheterizations

Dependent Variables	β	SE	OR*	95% CI	P Value	
Cardiac catheterizations	0.32	0.19	1.38	0.95–2.01	0.09	
Noncardiac surgeries	1.26	0.24	3.54	2.23–5.62	<0.0001	
Hospitalizations	0.60	0.14	1.82	1.39–2.38	<0.0001	
Total cardiac surgeries†	0.18	0.10	1.20	0.99–1.45	0.07	
Primary cardiac surgeries adjusting for time from birth to last primary surgery and PV anatomy						
Genotype	22q11.2DS vs ND	0.19	0.18	1.21	0.85–1.72	0.29
PV anatomy†	PA vs PS	–0.28	0.17	0.76	0.55–1.06	0.10
	Abs PV vs PS	2.06	0.35	7.83	3.98–15.39	<0.0001
Subsequent surgeries adjusting for time from last primary surgery to last follow-up and PV anatomy						
Genotype	22q11.2DS vs ND	0.49	0.35	1.63	0.83–3.22	0.16
PV anatomy	PA vs PS	0.33	0.39	1.40	0.65–2.9	0.39
	Abs PV vs PS	1.14	0.43	3.13	1.34–7.30	0.008

22q11.2DS indicates 22q11.2 deletion syndrome; Abs PV, absent pulmonary valve leaflets; CI, confidence interval; ND, nondeleted; OR, Odds ratio; PA, pulmonary atresia; PS, pulmonary stenosis; and PV, pulmonary valve.

*Odds ratios correspond to the independent association of genotype 22q11.2DS with outcome after adjusting for age and years of follow-up.

†Adjusting for presenting pulmonary valve anatomy.

Acknowledgment

We thank S. Edman, MS, who acted as a database manager for this project.

Sources of Funding

This work was supported by the National Institutes of Health (NIH; P50-HL74731 [Dr Goldmuntz], 5T32HL007915 [Dr L. Mercer-Rosa]), as well as Grant UL1TR000003 from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health. 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 NIH.

Disclosures

None.

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CLINICAL PERSPECTIVE

Patients with repaired tetralogy of Fallot experience variable clinical outcomes for reasons that are incompletely understood. We hypothesize that genetic variants contribute to this variability and, therefore, sought to investigate the association of 22q11.2 deletion status with outcome in this population. We performed a cross-sectional study of 165 tetralogy of Fallot subjects (12.3±3.1 years) who were tested for 22q11.2 deletion, and underwent cardiac magnetic resonance, exercise stress test, and review of medical history. A 22q11.2 deletion was present in 30 (18%) of cases. Despite comparable right ventricular function (60±8%) and pulmonary regurgitation (regurgitant fraction 34±17%), subjects with 22q11.2 deletion syndrome (22q11.2DS) had significantly lower exercise parameters (percent predicted forced vital capacity (61.5±16% versus 80.5±14%; $P<0.0001$), and maximum oxygen consumption (61±17% versus 80±12%; $P<0.0001$)). Similarly, patients with the 22q11.2DS experienced more hospitalizations (6.5 [5–10] versus 3 [2–5]; $P<0.0001$), saw more specialists (3.5 [2–9] versus 0 [0–12]; $P<0.0001$) and used ≥1 medications (67% versus 34%; $P<0.001$). This large study provides unique insight into the clinical status of patients operated for tetralogy of Fallot at an interim age between infancy and adulthood, and the contribution of 22q11.2 deletion status to clinical outcomes, in particular, with respect to exercise performance and increased morbidity relative to their counterparts, even in the setting of similar cardiac function.

22q11.2 Deletion Status and Disease Burden in Children and Adolescents With Tetralogy of Fallot

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Circ Cardiovasc Genet. 2015;8:74-81; originally published online January 5, 2015;
doi: 10.1161/CIRCGENETICS.114.000819

Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1942-325X. Online ISSN: 1942-3268

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