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Authors

Mercer-Rosa, Laura
Paridon, Stephen M
Fogel, Mark A
et al.

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

Laura Mercer-Rosa, MD[1], **Stephen M. Paridon, MD**[1], **Mark A. Fogel, MD**[1], **Jack Rychik, MD**[1], **Ronn E. Tanel, MD**[2], **Huaqing Zhao, PhD**[3], **Xuemei Zhang, MS**[4], **Wei Yang, PhD**[5], **Justine Shults, PhD**[4], and **Elizabeth Goldmuntz, MD**[1]

[1]Division of Cardiology, Department of Pediatrics, The Children's Hospital of Philadelphia & University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

[2]Division of Pediatric Cardiology, Department of Pediatrics, UCSF Benioff Children's Hospital, UCSF School of Medicine, San Francisco, CA

[3]Temple Clinical Research Center, Temple University School of Medicine

[4]Department of Biostatistics & Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[5]Center for Clinical Epidemiology & Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Abstract

Background—Patients with repaired tetralogy of Fallot (TOF) 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 TOF.

Methods and Results—We performed a cross sectional study of TOF subjects who were tested for 22q11.2 deletion, and underwent cardiac magnetic resonance (CMR), exercise stress test (EST) 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 CMR the right ventricular (RV) ejection fraction was 60±8%, pulmonary regurgitant fraction 34±17%, and RV end-diastolic volume 114±39 cc/m^2. On EST, maximum oxygen consumption (mVO2) was 76±16% predicted. Despite comparable RV function and pulmonary regurgitant fraction, on EST the 22q11.2DS had significantly lower percent predicted: forced vital capacity (61.5 ± 16 vs. 80.5 ± 14, p< 0.0001); mVO2 (61±17 vs. 80±12, p<0.0001); and work (64±18 vs. 86±22, p=0.0002). Similarly, the 22q11.2DS experienced more hospitalizations (6.5 [5; 10] vs. 3 [2; 5], p<0.0001), saw more specialists (3.5 [2; 9] vs. 0 [0; 12], p<0.0001) and used one or more medications (67 vs. 34%, p <0.001).

Correspondence: Elizabeth Goldmuntz, MD, The Children's Hospital of Philadelphia, Abramson Research Center 702A, 3615 Civic Center Boulevard, Philadelphia, PA 19104-4318, Tel: 215-590-5820, Fax: 267-426-9800, goldmuntz@email.chop.edu.

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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 TOF. These findings may provide avenues for intervention to improve outcomes, and should be re-evaluated longitudinally as these associations may become more pronounced with time.

Keywords

echocardiography; exercise test; genetics; magnetic resonance imaging; tetralogy of Fallot

Introduction

Despite notable surgical success, many patients with tetralogy of Fallot (TOF) experience significant morbidity and early mortality. Post-surgical 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, though 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.

TOF is a disease of considerable genetic heterogeneity. The 22q11.2 deletion syndrome (22q11.2DS) and trisomy 21 account for approximately 15% and 7% of all TOF cases respectively. TOF is also a characteristic finding in many syndromes (e.g. Alagille, CHARGE and VATER syndromes), and is associated with a growing list of copy number variants (e.g. 1p21.1) and single gene disorders (e.g. NKX2.5, 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 multi-system 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.

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 three 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 upon 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. Pre-operative echocardiographic reports, cardiac catheterization studies and operative notes were reviewed to confirm the diagnosis. Genetic testing was performed using fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), or both to classify subjects as del22q11.2 positive (22q11.2DS) or del22q11.2 negative (non-deleted or ND).(17, 18) Both tests were performed in 47% of the subjects, MLPA only in 28% (most of the ND had MLPA testing), and FISH 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 due to small numbers that would not allow for meaningful comparisons. Detailed review of medical history was undertaken to assess resource utilization 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 non-cardiac medical and surgical history, sub-specialty 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, Erlanghen, Germany) using a standard imaging protocol, 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 (VO2), maximum physical working capacity, oxygen pulse (a surrogate of ventricular stroke volume), and the maximal respiratory exchange ratio (RER) to identify subjects who achieved maximum effort. The percent predicted of maximum VO2 (mVO2), the VO2 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 mVO2 and VO2 at the anaerobic threshold. An EST was considered maximal if the RER 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 less than 180 bpm.

Electrocardiogram (ECG)

ECG was performed on MAC 5000's machine (General Electric, USA) using a standard clinical protocol, and interpreted by a single experienced reader (RT).

Statistical Analysis

Continuous variables are presented as mean and standard deviation 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 Chi-square test or Fisher's exact test for categorical variables. Covariates were compared with Pearson's 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-values < 0.05 (2-sided tests). All analyses were performed using SAS statistical software version 9.2 (Cary, NC, USA).

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, 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 that 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 FISH and MLPA was performed to identify a 22q11.2 deletion, there was 100% agreement between the two 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 pulmonary insufficiency (PI) [pulmonary regurgitant fraction = 37% (26; 45)] and dilated RVs (Table 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, mVO2

was decreased, physical working capacity was low normal and breathing reserve was preserved (Table 2). 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 subjects. There was no association between peak heart rate and mVO2 (p=0.10) for subjects achieving a maximal test.

On ECG, most subjects had right bundle branch block. (Table 2) QRS duration and RVEDV 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 to 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 to 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 VO2 was similar at anaerobic threshold, at peak exercise, the 22q11.2DS subjects had significantly impaired aerobic capacity with diminished mVO2, accomplished less work and had lower oxygen pulse, in keeping with lower measured indexed stroke volume on CMR (Table 2). 22q11.2DS was independently negatively associated with physical working capacity and oxygen pulse (p-values of 0.005 and <0.0001, respectively). A sub-analysis limited to the subjects that achieved a maximal EST (RER≥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 one or more cardiac medications. Similarly, the 22q11.2DS group reported significantly more non-cardiac hospitalizations as compared to the ND and significantly greater non-cardiac medication use (Table 3). Cardiac medications used included aldactone (n= 1 22q11.2DS), aspirin (n=6 ND, n= 3 22q11.2DS), atenolol (n=1 ND), chlorothiazide (n= 1 ND), digoxin (n= 9 ND, n= 4 22q11.2DS), enalapril (n= 2 ND, 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 to pulmonary valve stenosis (Table 4). Finally, the 22q11.2 DS group saw significantly more specialists as compared to the ND [3.5 (2; 9) vs. (0; 1), p<0.0001, respectively) (Table 4).

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. Further, we found that the 22q11.2DS subset display worse exercise performance and markedly increased resource utilization as compared to 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 appear 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 mVO2 and others reporting normal 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 mVO2, measures of cardiac performance on CMR were relatively well preserved, and the high RER 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 likely 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 mVO2 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, non-cardiac interventions and resource utilization. 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 to 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 22q11.2DS subset achieving a maximal performance demonstrated diminished exercise capacity by a number of EST measures, the presence of a 22q11.2 deletion likely 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 to 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 re-interventions addressing the right ventricular outflow tract (i.e.: 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 re-intervention may be due to 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, though 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 in 2008 examining long-term outcomes in patients with 22q11.2DS and various heart defects found a significant number of cardiac re-interventions in subjects with 22q11.2DS.[17]

Our study found a remarkable difference in non-cardiac health-related issues in the subset of TOF subjects with 22q11.2DS as compared to the ND, represented by significantly more hospital admissions, non-cardiac surgical interventions, subspecialty care and prescribed medications. Such findings could significantly impact upon quality of life for the 22q11.2DS subgroup. Though not well defined in the literature, one study similarly reported that subjects with 22q11.2DS had six non-psychiatric admissions in a lifetime, mostly in childhood and adolescence, in keeping with our findings.[38] Of note, while 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 diagnoses or neuropsychiatric medication use as compared to the ND subgroup at this age. These findings suggest that either psychiatric disorders present in older 22q11.2DS subjects, or quite possibly, that psychiatric conditions were under-diagnosed 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, 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 very few performed in this age group. Future longitudinal studies in this population will allow us to identify pre-symptomatic 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 their analyses of TOF outcomes. Our study also serves to highlight the multisystem nature of 22q11.2DS and brings attention to non-cardiac 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 also 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 regarding hypocalcemia, immunodeficiency and feeding difficulties; it also may 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 non-cardiac care that can impact 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.

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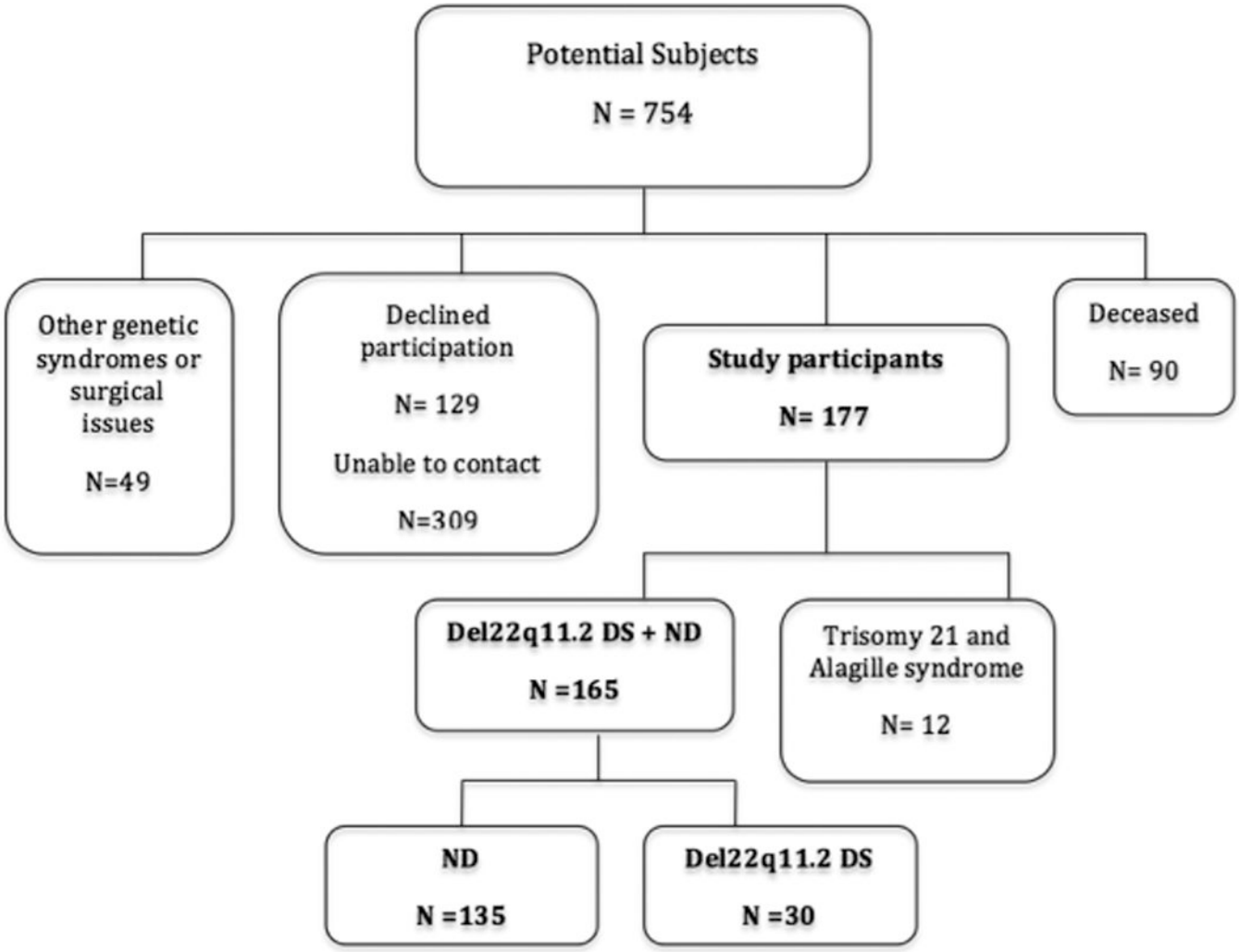

Figure 1.

Description of the study population. The flow chart represents the number of subjects with TOF that were available for recruitment from our institution's databases and the final composition of the study cohort.

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Table 1

Patient Characteristics

		Total N=165	ND* N=135	22q11.2DS† N=30	P-value
Age at consent (years)		12.3±3.1	12.5±3.1	11.6±3.2	1.0
Gender	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
	African American	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 (years)		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					0.28
Transannular patch		120(73)	102(76)	18(60)	
Non-transannular 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 (± standard deviation) or as number (percentage).

[*] ND = non-deleted

[†] 22q11.2DS = 22q11.2 deletion syndrome

[‡] BMI = Body mass index

[§] Non-transannular patch refers to relief of right ventricular outflow tract obstruction without crossing the pulmonary valve annulus.

[//] VSD = ventricular septal defect. 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.

[#] RV-PA = right ventricle to pulmonary artery.

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Table 2

Cardiovascular Status: Cardiac Magnetic Resonance, Exercise Stress Test and Electrocardiogram

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/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 (grams/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/m^2)	3.7±0.7	3.7±0.7	3.6±0.8	0.61
EXERCISE STRESS TEST	**N=156**	**N=129**	**N=27**	
Maximal effort (RER≥1.1)#	94 (63)	84 (68)	10 (40)	0.012
Forced vital capacity (Liters)	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				
mVO2 (mL/kg/min)**	32±8	33±8	24±7	<0.0001
Predicted mVO2 (%)	76±18	80±17	61±17	<0.0001
Maximum work (watts)	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/m2 (ml oxygen/beat/m2)	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 (beats per minute)	180 ± 15	182 ± 14	175 ± 17	0.08
Anaerobic Threshold Measurements				
VO2 at anaerobic threshold (mL/kg/min)**	21 ± 5	21 ± 5	19 ± 6	0.036
Predicted VO2 at anaerobic threshold (%)	86 ± 18	87 ± 17	80 ± 21	0.085
ELECTROCARDIOGRAM	**N=155**	**N=129**	**N=26**	
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

Data are expressed as mean (± standard deviation), or number (percentage).

*ND = non-deleted

† 22q11.2DS = 22q11.2 deletion syndrome

‡ RV = right ventricle

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

// LV = left ventricle

RER = respiratory exchange ratio

** mVO2 = maximum oxygen consumption. VO2 indicates oxygen consumption

†† QTc = QT interval corrected for heart rate

Table 3

Comparison of ND and 22q11.2DS groups for number of hospitalizations and use of medications

	ND	22q11.DS	P value
Overall hospitalizations [n, interquartile range (IQR)]	3 [2; 5]	6.5 [5; 10]	<0.0001
Used one or more medication (%)	34	67	<0.0001
Cardiac hospitalizations (n, IQR)	2 [1; 3]	3 [1; 4]	0.032
Used one or more cardiac medication (%)	13	23	0044
Non-cardiac hospitalizations (n, IQR)	1[0; 3]	4 [2; 7]	<0.0001
Used one or more non-cardiac medication (%)	25	60	<0.0001

Table 4

Multivariable analysis comparing the ND* and 22q11.2DS† groups for incidence rate of cardiac and non-cardiac surgeries, hospitalizations, and cardiac catheterizations

Dependent variables		Beta	SE	OR‡	95% CI	P value
Cardiac Catheterizations		0.32	0.19	1.38	0.95; 2.01	0.09
Non-Cardiac 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

*ND = non-deleted

†22q11.2DS = 22q11.2 deletion syndrome

‡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

//PV = pulmonary valve

#¶PA = pulmonary atresia

**#PS = pulmonary stenosis

††**Abs PV= absent pulmonary valve leaflets