The Link Between 22q11.2 Deletions and Tetralogy of Fallot

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Background

- Tetralogy of Fallot has no known cause.
- TOF can be lethal (20).
- TOF is made up of four heart defects:
  - Over-riding aorta.
  - ventricle septal defect.
  - right ventricular outflow obstruction.
  - right ventricular hypertrophy (1 & 20).

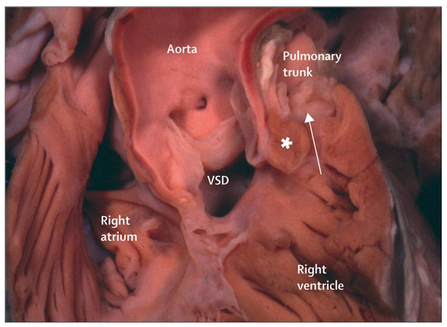

Figure 1: Shows an image of a heart that has Tetralogy of Fallot, indicating the locations of the structural defects (1).

- 22q11 Deletions/22q11.2 microdeletion syndrome; can lead to a wide range of structural and developmental defects (4, 8, 12, 13. & 19).
  - Located on chromosome 22.
  - Associated with cardiac malformations (4, 8, 13, & 19).

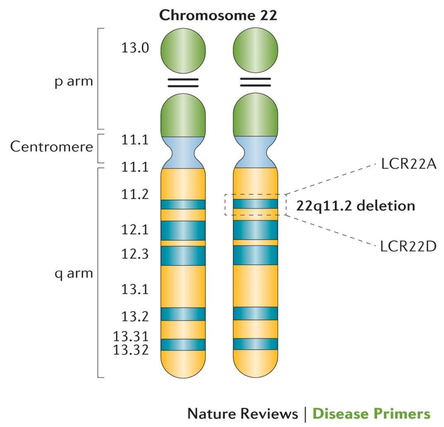

Figure 2: Depicts Chromosome 22 and the location where 22q11.2 microdeletions occur (12).

Methods

Papers used for this literature were chosen based on these criteria:

1. Primary or Secondary Source
   - Four secondary sources
   - Sixteen primary sources
2. Discussed patients that presented with both TOF and 22q11/22q11.2 deletions
3. Discussed one or more of the following:
   - The care of these patients
   - The medical outlook for these patients
   - The prevalence of other conditions in these patients
   - The potential hereditary nature of the 22q11/22q11.2 deletions

Hereditary Results

Multiple studies have stated a high occurrence rate of patients having both TOF and 22q11/22q11.2 deletions being present. These rates range from 6.5%-16% within various studies (2, 4, 5, 9, 10, 13, 18, & 21).

TABLE II. Prevalence of 22q11.2 Deletion in Tetralogy of Fallot (TOF) Patients*

Cardiac diagnosis[A]	Number of patients	Number of cases of deletion (%)
TOF-PS	173	15 (8.6)
TOF-PA-PDA	22	4 (18.2)
TOF-PA-MAPCA	17	9 (5.3)
Total	212	28 (13.2)

*TOF-PS = Tetralogy of fallot with pulmonary stenosis; PA = pulmonary atresia; PDA = patent ductus arteriosus; MAPCA = major aortico-pulmonary collateral arteries.

Figure 3: Depicts the number and percentage of patients with TOF that either have or do not have 22q11.2 microdeletions in one of the studies reviewed (10).

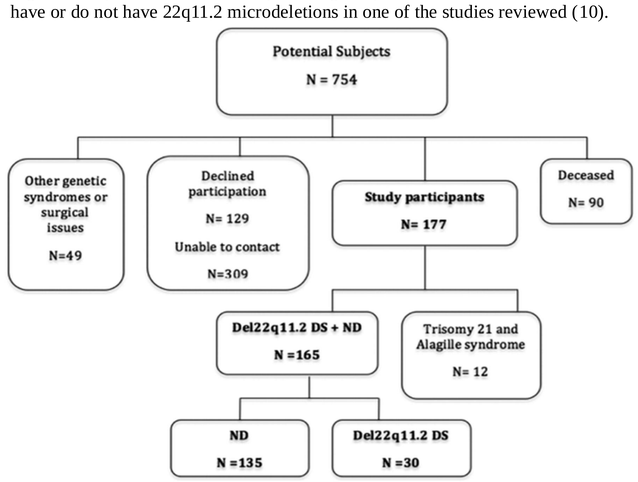

Figure 4: Depicts how one study reviewed determined their population for their study. This figure includes how many of those participants had 22q11.2 deletions (13).

Multiple studies have found that 22q11.2 deletions in TOF patients do not appear to have a hereditary association, but the deletion rather occurs de novo (2, 3, 6, 9, 17, & 21).

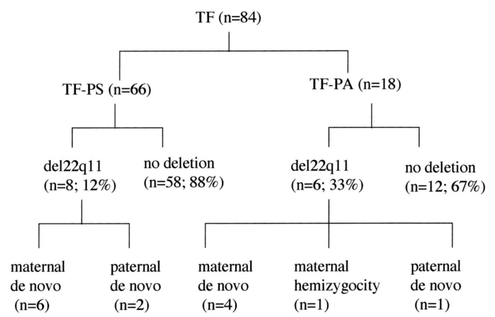

Figure 5: Depicts how many TOF patients within a study reviewed had either pulmonary stenosis (PS) or pulmonary atresia (PA) and from these populations how many had 22q11 deletions and the hereditary nature of these deletions (9).

Co-occurring Condition Results

Multiple conditions have been found to be in co-occurrence with TOF and 22q11.2 deletions. These conditions include the following:

- DiGeorge Syndrome/Facial Anomalies (3, 9, 16, & 21).
- Down Syndrome (3).
- Mild to severe intellectual disabilities (9 & 18).
- Pulmonary Atresia (9, 10, 13, & 18).

Table 2 Summary of genetic findings in 42 out of 230 patients with tetralogy of Fallot

n	%	Gene/locus	Mutation/aberration	Phenotype
17	7.4	22q11.2	Common 3 Mb microdeletion (16x) Proximally nested 1.5 Mb deletion (1)	DiGeorge/VCFS spectrum

Figure 6: Depicts some of the overall phenotype and genotype results from patients with TOF in one study reviewed. For this review, results microdeletions in 22q11.2 were of most interest. These patients were noted to have facial anomalies/DiGeorge Syndrome (18).

Treatment Outcome Results

Treatment was more extensive for TOF patients with 22q11/22q11.2 deletions than for those without (11 & 14). Mortality rates tend to be higher in those with both TOF and 22q11/22q11.2 deletions, however, some studies have found evidence to contradict this (7, 13, & 15).

Variable	ND (N=164)	22q11.2DS (N =44)	P-Value
Length of stay, days †	6 (4; 13)	9 (6; 16)	0.053
Length of stay if discharged home, days	6.0 (4; 11)	9.0 (5; 15)	0.02
Hospital stay > 4 weeks	9 (5)	2 (5)	1.00
Intensive Care, days	4 (3; 7)	6 (4; 12)	0.007
Cardiopulmonary bypass, minutes	74 (±30)	84 (±31)	0.02
Resource Utilization			
Number of consultations			
0	125 (76)	22 (50)	0.001
1	20 (12)	7 (16)	
≥2	19 (12)	15 (34)	
Discharge Characteristics	N=161	N=43	
Number of Medications ‡	2 (1; 3)	3 (2; 5)	0.0001

Data are expressed as mean (±sd), median (interquartile range) or as number (percentage). † Length of stay for the whole cohort, ‡ Includes survivors only.

Figure 7: Highlights some of the outcomes of TOF patients with deletions in 22q11.2 in one study reviewed. This table shows the average hospital length stays, medications at discharge, cardiac bypass time, etc. (14).

Treatment Outcomes Included:

- Longer hospital/ICU stays (11 & 14).
- More unplanned non-cardiac repairs (11).
- Higher occurrence of fungal and wound infections (11).
- Higher need for pulmonary shunts (14).
- Extra medications (14).
- Extra consultations (11).
- Longer cardiac bypass times (14).
- Higher need for multistage repairs (11).

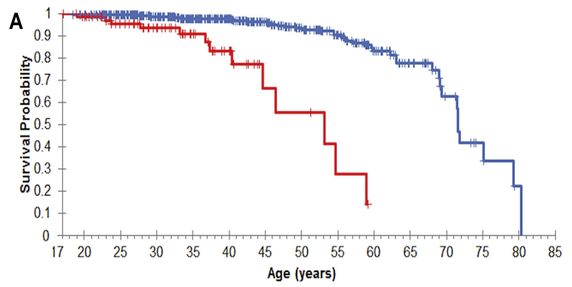

Figure 8: Shows mortality results from one study reviewed. These results show that the patients with TOF and 22q11.2 deletions typically had much lower survivability (shown in red) than those who did not have deletions (shown in blue). The dashed line is those that also had pulmonary atresia (15).

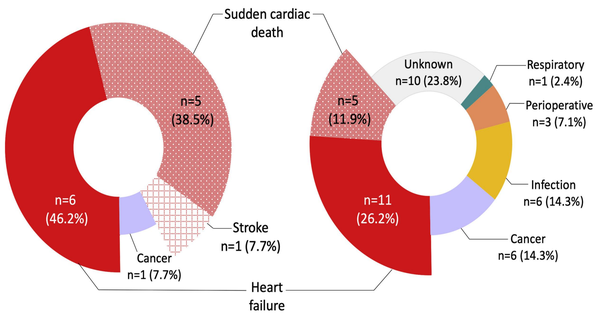

Figure 9: Shows the causes of death for the patients in one study reviewed. This graph depicts the causes of death for those who had TOF and 22q11.2 microdeletions vs those with TOF who did not have the deletions (15).

Conclusions

- 22q11/22q11.2 deletions are found in high occurrence with TOF but are de novo.
- Those who have both 22q11/22q11.2 deletions and TOF are likely to have other developmental conditions.
- Those who have both 22q11/22q11.2 deletions and TOF may have higher mortality rates and need more extensive care.
- TOF patients who have 22q11/22q11.2 deletions may need more treatment in part due to their higher likelihood of having other conditions and this should be considered during treatment.

Bibliography QR Code