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A single misstep in cardiac development explains the co-occurrence of tetralogy of Fallot and complete atrioventricular septal defect in Down syndrome

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Abstract

Tetralogy of Fallot and a complete atrioventricular septal defect are thought to arise by distinct mechanisms, yet their co-occurrence is a recognized association. Analysis of the prevalence of co-occurrence in Down syndrome suggests a common developmental basis. Trisomy 21 may perturb cardiac progenitor cells before they enter the heart tube.

Keywords

Trisomy 21; Down syndrome; second heart field; tetralogy of Fallot; atrioventricular septal defect

During embryonic development, cells from the cardiac crescent form the heart tube. Subsequently, cells from the second heart field are added to the arterial and venous poles (alternatively referred to as anterior or cranial and posterior or caudal, respectively). Defects of second heart field development are classified accordingly, and their investigation largely focuses upon events at either pole. For example, DiGeorge syndrome is associated with malformations such as tetralogy of Fallot (TOF) and truncus arteriosus. *TBX1*, the gene that underlies the DiGeorge cardiac phenotypes, regulates development at the anterior second heart field. Mutations of genes that perturb posterior development, such as *Wnt2*, cause an atrioventricular septal defect (AVSD) (1).

The co-occurrence of TOF and AVSD is associated with Down syndrome (2). The mechanism of co-occurrence is unknown but must involve either one or two developmental missteps. If each defect arises from two, independent events at the arterial and venous poles,

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then the prevalence of co-occurrence should equal the product of the prevalences of each defect in Down syndrome. If just one misstep causes both defects, then the prevalence should exceed that predicted by a two-misstep model. Statistical analyses of patients at our institution and in two population-based studies suggest a common developmental basis for the co-occurrence.

Methods

We calculated the prevalences among patients seen at St. Louis Children's Hospital by querying the Clinical Investigation Data Exploration Repository (CIDER) at Washington University School of Medicine. CIDER contains the electronic medical records of >5 million adult and pediatric patients. The search was approved by the Institutional Review Board. Patients born on or after January 1, 1997 and seen by August 30, 2013 were searched by ICD9 codes and key words. We confirmed each instance of Down syndrome, AVSD, TOF and every combination of diagnoses by reading every cardiology and genetics clinic note (N > 5000), echocardiogram report (N = 4917) and operative summary (N = 1710). Fisher exact tests were performed to compare prevalences in our institution with published data. Chi-square tests were performed to test the two-misstep model. The expected number of co-occurrences in Down cases is given by: Expected number = (Down TOF cases/Down cases) × (Down AVSD cases/Down cases) × Down cases.

To obtain an independent estimate of the proportion of TOF-AVSD patients who have Down syndrome, we performed a meta-analysis of surgical case series that reported Down syndrome status. The reports were identified through PubMed and cited references.

Results

Among >630,000 patients evaluated at St. Louis Children's Hospital, 1146 had Down syndrome. The prevalence of TOF was 4.4% (50/1146), which is greater than the 2.6% reported by the National Down Syndrome Project, a population-based study from the United States (P = 0.02) (3). The prevalence of AVSD was 17.4% (199/1146), which is greater than the reported 12.8% (P = 0.001). Consequently, the expected number of co-occurrences for a two-misstep model may be overestimated and biased against a one-misstep model.

TOF and AVSD co-occurred in 1.8% of Down syndrome patients (20/1146). The prevalence exceeds the 0.68 and 1.2% reported by population-based studies in the National Down Syndrome Project and Singapore probably because children who have heart disease are more likely to be seen at a major center (3,4). Conversely, 74% of TOF-AVSD patients had Down syndrome (20/27). The percentage is similar to the 67% (43/64) reported in a multi-centered, Italian series (P = 0.6) (2). The percentage is also similar to the 71% (183/258) calculated from a meta-analysis of 16 surgical case series published from 1974 to 2009 (P = 0.8) (5-20). The similar proportions in our institution, Italy and surgical series suggest that the numerator, 20, is accurately estimated for testing the two-misstep model (Figure 1, A).

The prevalence of co-occurrence of TOF and AVSD in Down syndrome consistently exceeds that expected by a two-misstep model (Figure 1, B). More than twice as many patients are observed than expected ($P = 2 \times 10^{-5}$). Similarly in the National Down

Syndrome Project and Singapore the observed number of cases is twice the expected (P = 0.02 for both) (3,4).

Discussion

TOF and AVSD are thought to arise by distinct mechanisms, but the present results suggest that their co-occurrence in Down syndrome shares a common developmental basis. Recently, cellular subdomains of the second heart field, as delineated by their overlap with broad domains of *Hoxb1*, *Hoxa1* and *Hoxa3* expression, have been described in the early embryo (21). *Hox* transcription factors, which are encoded in four clusters on human chromosomes 2, 7, 12, and 17, pattern the embryonic anterior-posterior (cranial-caudal) axis. *Hoxb1*$^{+}$/*Hoxa1*$^{+}$/*Hoxa3*$^{-}$ and *Hoxb1*$^{+}$/*Hoxa1*$^{+}$/*Hoxa3*$^{+}$ subdomains contribute primarily to the distal right ventricular outflow tract, whereas a *Hoxb1*-only subdomain gives rise to structures in both the right ventricular outflow tract and the atrioventricular junction (21). The abnormal development of these structures cause TOF and AVSD (22,23). We postulate that trisomy 21 perturbs the *Hoxb1*-only subdomain and so disrupts the future development of the two daughter cell populations that contribute to either pole of the heart (Figure 2). The model leaves unexplained the predilection for AVSD over TOF in Down syndrome, but it parsimoniously explains the association of each defect and their co-occurrence. Other genetic, epigenetic or environmental factors likely influence the specific cardiac presentation (24-28).

Alternatively, one unknown modifier gene could predispose to both TOF and AVSD in Down syndrome. Modifier genes do not cause but rather influence the presentation of a mutant phenotype. In a mouse model, alleles of modifier genes alter the risk of specific defects caused by mutations of the cardiac transcription factor *NKX2-5*. Some modifier genes may influence more than one type of defect (26,27). Rare human polymorphisms of *CRELD1*, *HEY2* and genes in the VEGF pathway have been associated with AVSD in Down syndrome (24,25), but none is known for TOF. The one-gene and one-misstep hypotheses are not mutually exclusive. A hypothetical genetic polymorphism could exert its effect at the *Hoxb1*-only subdomain or simultaneously at the arterial and venous poles.

The analysis is limited mainly by the accuracy of the observed number of TOF-AVSD patients who have Down syndrome. Referral bias to a single, major pediatric center may cause an overestimate. Even if the observed number were overestimated by 50%, the two-misstep hypothesis would still be rejected. This high an overestimate is unlikely because the proportion of TOF-AVSD patients who have Down syndrome would fall to ~50%, which is much less than reported by other groups (2,5-20). Validation of the statistical result in two population-based studies suggests that any overestimate is not so large as to alter the main conclusion.

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Abbreviations

TOF	Tetralogy of Fallot
CIDER	Clinical Investigation Data Exploration Repository
AVSD	Atrioventricular septal defect

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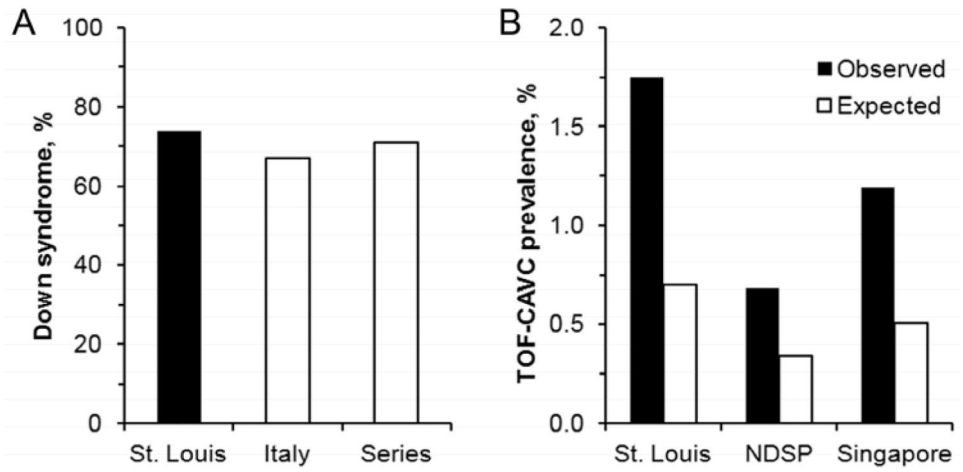

Figure 1.

(A) Approximately 70% of TOF-AVSD patients have Down syndrome in St. Louis, Italy (2), and a meta-analysis of 16 surgical case series (5-20). (B) The observed prevalences of TOF-AVSD in Down syndrome are twice that expected by a two-misstep model in St. Louis (20 vs. 8/1146, $P = 2.1 \times 10^{-5}$), the National Down Syndrome Project (10 vs. 5/1469, P = 0.02) and Singapore (7 vs. 3/588, P = 0.02). Percentages are shown for comparison; absolute numbers were used in Chi-squared tests.

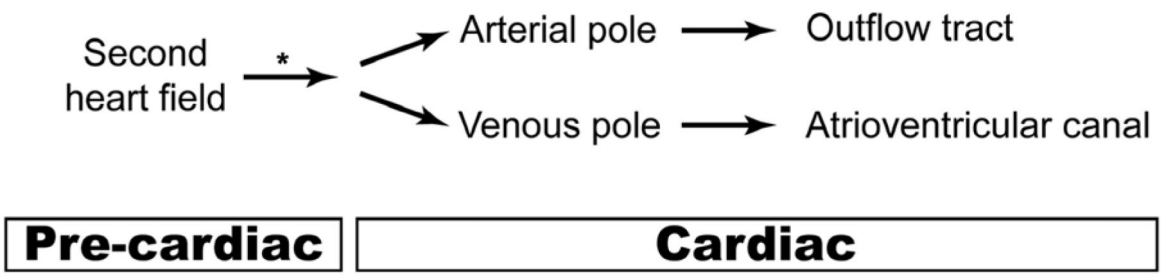

Figure 2.

One developmental misstep explains the co-occurrence of TOF and AVSD in Down syndrome. Trisomy 21 may perturb progenitor cells in the second heart field before they enter the heart tube (*). The defective cells then localize to the arterial or venous poles to make the structures malformed in TOF and AVSD. Alternatively, a modifier gene that increases the risk of both TOF and AVSD could act before or after cells from the second heart field have localized to either pole of the heart.