The Combination of Tetralogy of Fallot and Common Atrioventricular Canal in Down syndrome is explained by a Single Misstep in Second Heart Field Development

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Introduction: The co-occurrence of tetralogy of Fallot (TOF) and a common atrioventricular septal defect (AVSD) is rare. Affected patients commonly have Down syndrome. The developmental basis of the combination is unknown, but the combination must arise either from one or two separate missteps during cardiac development. If each defect arises independently, then the incidence of co-occurrence should be equal to the product of the incidences of each defect in Down syndrome patients.

Methods: To calculate the relevant incidences, we queried the Clinical Investigation Data Exploration Repository (CIDER) at Washington University School of Medicine. CIDER permits anonymized data mining of inpatient and outpatient information collected at Barnes-Jewish-Christian Hospital practice sites, including St. Louis Children's Hospital (SLCH). We counted the patients seen between January 1, 1995 and June 28, 2013 who had Down syndrome, TOF, AVSD, and every combination of the diagnoses. We identified patients by ICD9 codes and a keyword search of echocardiography reports and operative summaries. Comparisons were analyzed by chi-square tests.

Results: Consistent with multiple population-based surveys, 6 and 22% of Down syndrome patients (N = 1236) have TOF or AVSD, respectively. Of TOF/AVSD patients, 64% (27/42) have Down syndrome; the same proportion was reported by a large, multi-center Italian series. The incidence of TOF/AVSD in Down syndrome significantly exceeds that predicted by a model in which TOF and AVSD develop independently (2.1 versus 1.3%, $p = 0.006$).

Conclusion: TOF and AVSD in Down syndrome appear to share a common developmental basis. Recently, several groups have described a subdomain of the second heart field that gives rise to the subpulmonary myocardium and atrioventricular septal structures. We suggest that the gene that underlies the heart defects in trisomy 21, although still unknown, affects the embryonic development of this subdomain.