Oral Presentation Finalist

SHROOM3 is a Novel Component of the Planar Cell Polarity Pathway Whose Disruption Causes Congenital Heart Disease

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Background: Congenital heart disease (CHD) is a significant contributor to neonatal mortality, yet the molecular mechanisms underlying most disease remain unknown. In a patient with CHD we previously utilized whole exome sequencing to identify a novel CHD candidate gene, SHROOM3. SHROOM3 is implicated in human neural tube and kidney defects but mostly unexplored in CHD. SHROOM3 encodes a protein which localizes to the apical portion of cells and induces cytoskeletal changes, including ACTOMYOSIN constriction. In addition, SHROOM3 binds DISHEVELED2 and ROCK1, both key components of the noncanonical Wnt/planar cell polarity signaling pathway (PCP). PCP signaling influences numerous developmental processes, in part through regulating ACTOMYOSIN constriction. In previous studies, the Ware Lab identified that Shroom3gt/gt mice have incompletely penetrant heart defects, including ventricular septal defects (VSD), double outlet right ventricle (DORV) and left ventricular noncompaction, and Shroom3gt/gt mice have diminished cardiac neural crest cell staining in the outflow tract; this CHD spectrum phenocopies PCP disruption. We hypothesize that SHROOM3 is a novel component of the PCP pathway and disruption of this gene results in CHD.
Methods: Heterozygous SHROOM3gt/+ and DVL2-/+ mice are phenotypically normal and fertile. To demonstrate that SHROOM3 interacts with DVL2 and the PCP pathway during cardiac development, we analyzed compound SHROOM3gt/+;DVL2-/+ embryos for CHD phenotypes. We also employed immunohistochemistry (IHC) to assess for evidence of PCP disruption in homozygous SHROOM3gt/gt embryos.
Results: There is a decreased frequency of compound SHROOM3gt/+;DVL2-/+ embryos as compared to anticipated Mendelian ratios (observed: 18.4%; expected: 25%; n=76), suggesting potential embryonic lethality. One compound SHROOM3gt/+;DVL2-/+ embryo has DORV and VSD, characteristic of PCP disruption. IHC also demonstrates disrupted actomyosin in the SHROOM3gt/gt mice, characteristic of PCP disruption.
Conclusion: These data help strengthen SHROOM3 as a novel CHD candidate gene and a component of the PCP Signaling pathway. Further characterization of this gene is important for CHD diagnosis and therapeutic development.

Alison Schmidt is a third year medical student currently undecided on a specialty; however, she's especially enjoyed her experiences with neonatology and maternal fetal medicine. For Schmidt, "it is evident that genetics will play a major role in shaping the way we care for patients in the future." She explains that her research experience "illustrated the complexity behind translating a piece of genetic information into an understanding of the molecular implications on embryogenesis and ultimately hopefully into improved diagnosis and therapies."