
海外招請講演

海外招請講演1 (IL-01)

小児循環器領域の遺伝子医学の革新

座長:

小垣 滋豊 (大阪大学大学院医学系研究科 情報統合医学小児科学)

2016年7月6日(水) 09:35 ~ 10:05 第E会場 (シンシア ノース)

I-IL-01

09:35 ~ 10:05

[I-IL-01]Notch1 Signaling and Aortic Valve Disease: From Human Genetics to Mouse Models

○Vidu Garg (Director of the Center for Cardiovascular Research at Nationwide Children's hospital (OH, USA))

Congenital heart disease (CHD) is the most common type of birth defect. Malformations involving the cardiac outflow tract and semilunar valves account for more than 50% of these cases predominantly due to bicuspid aortic valve (BAV), which has a prevalence of ~1% in the population. Mutations in NOTCH1 are a cause of BAV in humans. We have published a highly penetrant mouse model of aortic valve disease, consisting of dysplastic stenotic and regurgitant aortic valves with associated aortopathy, in Notch1 haploinsufficient adult mice backcrossed into a Nos3-null background. Analysis of Notch1+/-;Nos3-/- compound mutant embryos has demonstrated a spectrum of congenital anomalies involving the cardiac outflow tract, which are the result of loss of Notch1 in endothelial and endothelial-derived cells. Additional investigation using compound mutant mice heterozygous for both Notch1 and a Marfan syndrome disease-causing mutation in Fbn1 demonstrate that haploinsufficiency of Notch1 exacerbates the aortopathy phenotype of the Marfan syndrome mouse (Fbn1C1039G/+). Interestingly, heterozygous loss of Notch1 in the second heart field (SHF) lineage, not endothelial cells, recapitulates the exacerbated aortopathy in this murine model. Our findings support cell lineage specific roles for Notch1 in BAV and associated aortopathy.