THE ROLE OF INVERSIN AND VANGL2 GENES IN THE DEVELOPMENT OF THE HEART

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Introduction

- Inversin has a key role of determining left-right axis during embryonic development.
- Vangl2, a member of the multi-planar cell polarity pathway, regulates directional cell movements and polarization of cells within the developing outflow tract.
- Inversin mutant mice show situs inversus while any disturbance in Vangl2 shows double outlet right ventricle, ventricular septal defects and common arterial trunk, but not atrial septal defects.

Aim

- To study the interaction between Inversin and Vangl2 gene in the embryonic development of the heart.

Hypothesis

- Inversin and Vangl2 interact in the myocardium and endocardium of the heart. Knocking out both if these genes in the Nkx2.5-Cre expression domain will result in cardiac defects not seen when either gene is knocked out in isolation.

Method

- Crosses were set up as shown in Figure 1.
- Inversin gene is knocked out in all cells while Vangl2 gene is only knocked out in Nkx2-5 cardiac progenitor cells using cre-recombinase mechanism.
- Nkx2.5-Cre is expressed in the myocardium and endocardium throughout the heart.

$Inv^{+/-}$:$Vangl2^{F/+}$:Nkx2-5-cre+

$Inv^{-/-}$:$Vangl2^{F/+}$:Nkx2-5-cre+

$Inv^{+/-}$:$Vangl2^{F/F}$:Nkx2-5-cre+

Figure 2: Genotypes focused in this study

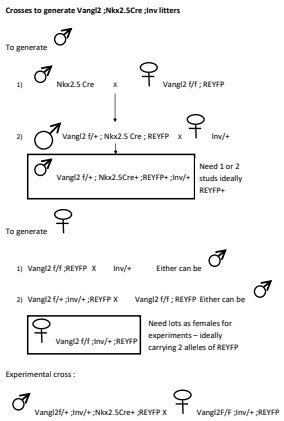

Figure 1: Crossing between Inversin and Vangl2 flox and Nkx2-5 Cre mice

Results

$Inv^{+/-}$:$Vangl2^{F/+}$:Nkx2-5-cre+

- All 12 embryos of this genotype showed normal results.

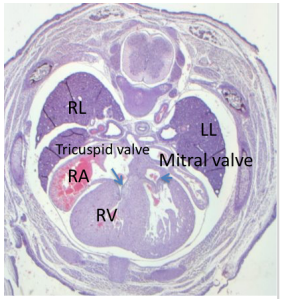

Figure 3: A E15.5 $Inv^{+/-}$:$Vangl2^{F/+}$:Nkx2-5-cre+ mouse shows a normal heart. Right lung (RL), left lung (LL), right atrium (RA) and right ventricle (RV).

$Inv^{-/-}$:$Vangl2^{F/+}$:Nkx2-5-cre+

- 4 out of 5 embryos of this genotype showed abnormalities. One of the abnormal phenotypes seen is shown in Figure 4.

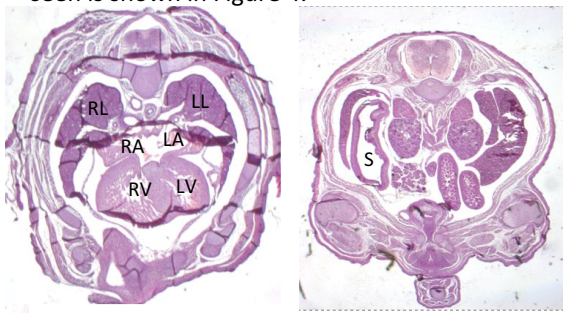

Figure 4: A E15.5 $Inv^{-/-}$:$Vangl2^{F/+}$:Nkx2-5-cre+ mouse shows right isomerism of the lung, atrial septal defect and stomach on the right. Right lung (RL), left lung (LL), right atrium (RA) and right ventricle (RV), left atrium (LA), left ventricle (LV), stomach (S).

$Inv^{+/-}$:$Vangl2^{F/F}$:Nkx2-5-cre+

- All 8 embryos of this genotype showed normal results.

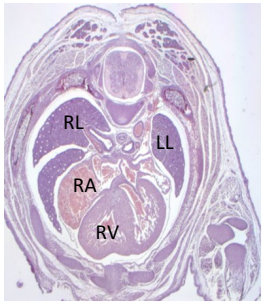

Figure 5: E15.5 $Inv^{+/-}$:$Vangl2^{F/F}$:Nkx2-5-cre+ mouse shows a normal heart. Right lung (RL), left lung (LL), right atrium (RA) and right ventricle (RV).

Conclusion

- Most embryos with $Inv^{-/-}$:$Vangl2^{F/+}$:Nkx2-5-cre+ genotype showed the expected phenotype (situs inversus) whereas embryos with $Inv^{+/-}$:$Vangl2^{F/F}$:Nkx2-5-cre+ genotype did not at all show any abnormal phenotype which suggests that there is no interaction with Inversin.

Future Work

- Determine if there is an interaction between Inversin and Vangl2 gene in the embryonic development of the heart by observing more embryos with these 3 genotypes.

References

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