"Proof of genetic heterogeneity in cardiac septal defects and in heterotaxy"

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Abstract
The prevalence of congenital heart defects is approximately 1% of all births, yet the causative factors remain largely uncharacterized. For the majority, the physiopathogenesis is believed to be multifactorial, hindering the identification of causative factors. However, several genes have been identified for septation defects that are part of a syndrome. Yet, in non-syndromic septal defects it has been difficult to identify predisposing genetic factors. When I started this thesis project, only one gene had been identified to be responsible for non-syndromic septal defects. We collected families in which two or more individuals were affected with non-syndromic cardiac septal defects. In five families, arrhythmia was associated with ASD/VSD. We screened the CSX/NKX2-5 gene, previously identified to be responsible for ASD and PR prolongation, and identified 3 novel missense mutations. In parallel, we screened the CSX/NKX2-5 gene in sporadic and familial cases of other cardiopathies, but...

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**Fig. 1a Specification of cardiac precursor cells** (adapted from Zaffran et al., Circ Res. 2002)

BMP, FGF8 and Wnt inhibitors induce cardiogenesis. On the contrary Wnt secreted from the neural plate inhibits cardiac differentiation. Cardiac precursor cells are specified in regions where BMP, FGF and Wnt antagonists coincide.

**Fig. 1b Inductive signals for cardiac specification**

The repressive effect of Wnt 3a/-8 is counteracted by Wnt inhibitors such as Cerberus, DKK and Crescent. Wnt inhibitors, FGF8 and BMP2/4 induce cardiac specification.