The role of Tbx2 in the development of the atrioventricular canal and conduction system of the heart. ‘Making the beat go on and on’
Aanhaanen, W.T.J.

Citation for published version (APA):
Aanhaanen, W. T. J. (2011). The role of Tbx2 in the development of the atrioventricular canal and conduction system of the heart. ‘Making the beat go on and on’
Scope of the thesis

The heart is the first organ to develop and already starts beating three weeks after conception in human. The formation of the four-chambered heart is an intricate process, complicated by the constant requirement of its pump function to supply the developing embryo of sufficient nutrients. The complexity of this process is reflected in the high incidence of congenital heart diseases with a prevalence of up to 1% at birth, and which are a major cause of intrauterine and early postnatal death. To understand how these malformations arise, it is essential to gain insight into the normal development of the heart.

Subsequent to the formation of the tubular heart, the dorsal and ventral side of this structure locally differentiate and balloon to form the working myocardium of the atria and ventricles. In between the atria and ventricles lies the atrioventricular canal. The myocardium surrounding this canal does not differentiate into chamber myocardium, due to the local expression of transcription factors that repress differentiation into working myocardium. Important transcriptional repressors in this region are Tbx2 and Tbx3. During development the myocardium of the atrioventricular canal remodels and partakes in septation and alignment of the atria and ventricles, provides signals to initiate valve formation and is involved in the formation of the atrioventricular conduction axis. Therefore, many cardiac defects, including partial or complete atrioventricular septal defects, atrioventricular valve defects and arrhythmias, e.g. atrioventricular re-entry tachycardia, atrioventricular nodal block and ventricular pre-excitation, can take origin from incorrect formation of the atrioventricular canal myocardium. Insight into the developmental and molecular mechanisms, including the cellular origin and fate, that underlie the formation of the atrioventricular canal myocardium, will aid in the understanding of atrioventricular canal related defects.

This thesis will explore the developmental and molecular mechanisms that underlie formation of the myocardium of the atrioventricular canal, with a special interest for the relation of this embryonic structure with the development of the atrioventricular conduction system. In Chapter 1, the findings concerning the origin, fate and development of the myocardium of the atrioventricular canal are reviewed and the implications for the development of the atrioventricular conduction system addressed. In Chapter 2, the origin and fate of the atrioventricular canal myocardium is described using the Tbx2Cre allele in a genetic lineage study. Secondly, the role of Tbx2 in early atrioventricular canal development is explored. In Chapter 3, the 3-dimensional architecture and development of the atrioventricular conduction axis are described, using various genetic lineage tracers and providing a 3-dimensional model based on key functional markers. In Chapter 4, the generation of a Tbx2-conditional-null allele is described. This allele can be used to inactivate Tbx2 in specific lineages. In Chapter 5, evidence is provided that accessory atrioventricular pathways, that bypass the atrioventricular conduction system and can lead to preexcitation of the ventricles, can arise from an early developmental defect of the atrioventricular canal myocardium. In Chapter 6, the thesis is summarized in English and Nederlands.