VARIATIONS IN PITX2C EXPRESSION: ALTERING SUSCEPTIBILITY TO ATRIAL FIBRILLATION?

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Introduction: Intergenic variations on chromosome 4q25, close to the PITX2 gene, are associated with atrial fibrillation (AF) in several population-wide GWAS studies. We therefore tested whether adult hearts express PITX2 and whether variations in expression affect cardiac function.

Methods and Results: In left atria (LA) of man and mouse, PITX2 isoform c was robustly expressed at levels comparable to other transcription factors (MEF2c, NKX2-5 e.g.). Pitx2c expression in the other cardiac chambers was about 100-fold lower. In mice heterozygous for Pitx2c (Pitx2c+/-) LA Pitx2c expression was 60% of wild-type (WT). Upon echocardiography, cardiac morphology, chamber size and contractile function were not altered in Pitx2c+/- mice (Pitx2c+/- (n=18) vs. WT (n=11): RVDdiast: 1.83 ± 0.05 mm vs. 1.92 ± 0.06 mm; LADdiast: 2.38 ± 0.10 mm vs. 2.22 ± 0.07 mm; LADsyst: 1.93 ± 0.08 mm vs 1.82 ± 0.07 mm), except for elevated pulmonary flow velocity (0.67 ± 0.04 m/s vs. 0.54 ± 0.03 m/s; p<0.05). Histology did not find interstitial fibrosis in Pitx2c+/- hearts, nor differences in atrial cell size and sinuatrial node morphology when compared with WT (n=4 per genotype). Isolated Pitx2c+/- hearts were susceptible to AF during programmed stimulation in Langendorff experiments (12/27 vs. 4/17; p<0.05). At short paced cycle lengths, atrial action potential durations (APD) were shorter in Pitx2c+/- than in WT (APD70 - 7ms, APD50 - 5 ms vs. APD70 - 12 ms, APD50 - 9 ms; p<0.05). Perfusion with the β-receptor agonist orciprenaline abolished inducibility of AF, and reduced the effect on APD. Spontaneous heart rates, atrial conduction velocities and activation patterns were not affected in Pitx2c+/- hearts (n=5 per genotype), suggesting that APD shortening caused wave length reduction and inducibility of AF. Expression array analyses comparing Pitx2c+/- to WT, identified genes related to calcium ion binding, gap and tight junctions as being affected by the reduced expression of Pitx2c (n=5 per genotype).

Conclusions: Together, our findings suggest a physiological role for PITX2 in the adult left atrium of man and mouse and support the hypothesis that dysregulation of PITX2 expression can be responsible for susceptibility to AF.