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PRDM16 is a possible therapeutic target for heart failure

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Introduction: Individuals with del1p36 syndrome commonly have cardiomyopathy and/or structural heart defects. We have recently described the role of the transcription factor PRDM16 (PR domain containing 16) in cardiomyopathy associated with monosomy 1p36, and confirmed its relevance in non-syndromic left ventricular noncompaction cardiomyopathy (LVNC) and dilated cardiomyopathy (DCM). PRDM16 has not previously been associated with cardiac disease.

Results: We identified a minimal deletion for cardiomyopathy associated with del1p36 that included only PRDM16. Resequencing of PRDM16 in non-syndromic patients with LVNC detected de novo mutations. In addition, in a series of cardiac biopsies from individuals with DCM, we found previously unreported non-synonymous variants in the coding region of PRDM16. Modeling of PRDM16 haploinsufficiency and a human truncation mutant in zebrafish resulted in both contractile dysfunction and partial uncoupling of cardiomyocytes, and also revealed evidence of impaired cardiomyocyte proliferative capacity. The cardiac phenotype in the zebrafish mutants can be completely rescued by the application of 5 structurally related compounds. Wildtype zebrafish demonstrate a significant increase in cardiomyocyte numbers after treatment with the compounds suggesting a pro-proliferative effect of the compounds. With the zebrafish model system we are currently identifying the role of PRDM16 in the heart. We will also present our approach on the underlying PRDM16 signaling pathway using in vitro culture systems.

Conclusion: The zebrafish model will serve to identify new interaction partners for PRDM16 in the heart. The rescue of the cardiac phenotype in the zebrafish might lead to novel therapeutic targets for heart failure.