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Early disease onset and high penetrance of severe cardiomyopathy in RBM20 p.P638L mutation carriers in toddler's age

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Introduction: Mutations in RBM20 are associated with dilated cardiomyopathy (DCM) and aberrant myocardial splicing. A German family with high prevalence of DCM was screened by next generation sequencing resulting in identification of the heterozygous mutation RBM20 p.P638L known for high penetrance and severe cardiomyopathy and/or sudden cardiac death in adults. However, little is known on its molecular pathomechanisms and disease course.

Methods: Aberrant myocardial splicing of TTN and RYR2 was analysed by Real-Time-PCR in 3 patients. To compare the localization of RBM20 wildtype and mutants RBM20-EYFP chimera was analyzed in different cell lines. The heterozygous genotype was modeled in vitro by coexpression of wildtype and mutant. Before genetic testing of 4 pediatric family members (< 1, 1.5, 10, 14 ys.) clinical investigation was done by echo.

Results: Real-time-PCR revealed in mutation carriers aberrant myocardial splicing of RBM20 target genes - a hallmark of pathogenic RBM20 mutations. In vitro lack of nuclear localization for RBM20 p.P638L suggests a relevant molecular pathomechanism. Interestingly, coexpression of wildtype and mutant RBM20 had no influence on the subcellular localization of the wildtype protein. In both young children aged 2-3 ys. first evidence of subclinical mild DCM was identified by echo. In both adolescents stress echocardiography revealed pathological hemodynamics. The younger of both was later mechanically bridged to heart transplantation (HTx) aged 24. The older received ICD-implantation and is in supervision for HTx.

Conclusions: Detection of myocardial splice defects have impact for the identification of pathogenic RMB20 mutations. RBM20 p.P638L leads to subcellular mislocalisation presumably causing aberrant myocardial splicing, is associated with early onset cardiomyopathy and high penetrance. Echocardiographic evidence was found in early childhood, deterioration under stress in adolescence and terminal heart failure in early adulthood. For RBM20 mutations early onset of cardiac phenotypes and genetic predictive testing for RBM20 in early childhood should be considered. Identification of the molecular pathomechanisms in the affected patients allows insights into the disease mechanisms and may reveal drug targets for preventive or even curative treatment.