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COMMENTARY

Screening for mutations in human cardiomyopathy- is *RBM24* a new but rare disease gene?

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With great interest we have read the study of Liu et al. (2018) revealing the role of RNA binding protein 24 (RBM24) on global alternative splicing and dilated cardiomyopathy (DCM) in mice. As suggested previously, deficiency of *Rbm24* causes embryonic lethality limiting the functional analyses (Yang et al., 2014). To circumvent this limitation the authors generated cardiac specific *Rbm24* deficient mice and showed that homozygous deletion of *Rbm24* at postnatal stage leads to rapidly progressive DCM and heart failure (Liu et al., 2018).

DCM is considered as the most common type of cardiomyopathy (Fu and Eisen, 2018). It is estimated that about 60% of DCM cases have a genetic etiology (Klauke et al., 2017). However, the associated genotypes are highly diverse and mutations in at least 50 genes have been described with DCM (Stenson et al., 2003). These genes are encoding proteins of the sarcomere, the cytoskeleton, the nuclear envelope, components of the Ca^{2+} transient, ion channels and transcription (co)-factors. In addition, several regulators of alternative splicing like muscleblind like splicing regulator 1 (MBNL1) (LeMasters et al., 2012), RNA binding fox-1 homolog 1 (RBFOX1) (Gao et al., 2016), RNA binding fox-1 homolog 2 (RBFOX2) (Wei et al., 2015), RBM24 (Liu et al., 2018) might have impact on cardiac development and/or the cardiac function in animal models. However, the role of these proteins in human cardiomyopathy is still unknown. At present, only mutations in the gene *RBM20* encoding a cardiac splice factor have been shown to be associated with cardiomyopathy (Brauch et al., 2009; Wells et al., 2013; Beqqali et al., 2016).

Conditional deletion of *Rbm24* is associated with 590 altered splicing events in mice. The affected proteins are involved in cytoskeleton organization, striated muscle cell differentiation, heart contraction and cardiovascular development (Liu et al., 2018). Interestingly, the study of Liu et al. demonstrated convincingly that one of the direct splicing targets of murine Rbm24 is *Ttn,* coding for the giant sarcomeric protein titin. RNA binding protein 20 (RBM20) was the only known splicing factor of *TTN* (Guo et al., 2012). Remarkably, mutations in *RBM20* are not so rare among DCM-patients and cause frequently a severe clinical phenotype (Brauch et al., 2009; Ma et al., 2016).

We think that the study of Liu et al. might has also relevance for human cardiovascular genetics because it can be suggested that *RBM24* mutations might be involved in human cardiomyopathies, especially because no disease associated *RBM24*-mutations have been described until now.

Even if familial cardiomyopathy is suspected, the identification of the causative pathogenic gene mutation is not always possible. In consequence, the identification of novel cardiomyopathy associated genes remains a major issue of human cardiovascular genetics having clinical impact for genetic counselling of affected families.

As RBM24 was already established as a major regulator of muscle-specific alternative splicing (Yang et al., 2014) we analyzed the coding sequence of three *RBM24*-splice variants (NM_001143942, NM_153020, NM_001143941) in 190 cardiomyopathy index patients by Sanger sequencing. To our surprise, we did not find any pathogenic *RBM24* mutation. Although we cannot exclude that in further specific cases pathogenic *RBM24* mutations might be found, our data suggest that *RBM24* mutations are rare in human cardiomyopathy patients. Thus, the data of our cohort suggests an allele frequency in non-ischemic cardiomyopathy patients below <0.5%. These findings are supported by the fact that only the homozygous *Rbm24* deficient mice developed DCM in the study by Liu and colleagues (2018).

In summary, it remains an open question if *RBM24* can be established as a rare cardiomyopathy associated gene.

However, with relevance for clinical cardiovascular genetics this gene deserves further attention in genetic screenings.

COMPLIANCE WITH ETHICS GUIDELINES

Anna Gaertner, Andreas Brodehl and Hendrik Milting declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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