EDITORIAL

WILEY

RBM20 mutations in left ventricular non-compaction cardiomyopathy

Cardiomyopathies are among the most prevalent causes of premature death in the Western world. A significant amount of cardiomyopathies has a genetic etiology. Currently, mutations in more than 170 genes associated with different cardiomyopathies, channelopathies, or syndromes with cardiac involvement are described.[1]

Left ventricular non-compaction (LVNC) is a rare cardiomyopathy and characterized by the presence of excessive left ventricular trabeculation, deep intra-trabecular recesses, and a thin compacted myocardial layer[2] with a >2-fold thickening of the noncompacted endocardium compared with the compacted epicardium (NC/C>2).[3-5] Currently, the pathogenesis of LVNC is incompletely understood. Especially, it is unclear if LVNC is just an anatomical phenotype or a pathological entity as 1.3%–2.3% of the asymptomatic population fulfill all four current cardiac magnetic resonance (CMR) imaging criteria for diagnosis of LVNC.[6] Interestingly, while the American Heart Association (AHA) classifies LVNC as an independent genetic cardiomyopathy, the European Society of Cardiology (ESC) defines it as an unclassified entity.[4] Nevertheless LVNC has gained attention because of improvements in cardiac imaging that allow more detailed visualization and clinical awareness of this disease.[7,8] Genetics play an important role in LVNC because 17%–50% of patients have a family member with cardiomyopathy.[9,10] It is supposed that the inherited phenotype can arise due to a gene mutation, which disrupts the physiological compaction of the developing embryonic myocardium.[11] Mutations are identified in 17%–41% of LVNC cases, indeed.[12,13] Most of the LVNC-associated genetic defects have also been reported in patients with dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (ACM) sometimes in combination with LVNC and even within the same family.[12,14,15] These findings might indicate a genetic overlap of different cardiomyopathies. Additionally, LVNC shares several symptoms and clinical findings with other cardiomyopathies. Characterization of the phenotypic expression of LVNC identified distinct subtypes including benign LVNC with preserved systolic and diastolic function, dilated, hypertrophic, restrictive, and arrhythmogenic LVNC.[16] The reasons for the clinical variability are widely unknown and might be influenced by the genetic background. Otherwise it may be that patients currently diagnosed with LVNC are those with an anatomical LVNC phenotype, who subsequently develop DCM or HCM.[6]

In more than 80% of genetic LVNC the specific mutation can be identified in sarcomeric genes (*MYH7*, *MYBPC3* or *TTN*).[15] However, also rare pathogenic mutations in other genes, like *RBM20* are associated with LVNC.[11,15,17] Nevertheless, the majority of the known pathogenic *RBM20*-mutations is associated with DCM.[18-21] *RBM20* encodes the vertebrate specific RNA Binding Motif Protein 20 (RBM20), which is involved in post-transcriptional splicing of many sarcomeric and calcium-handling genes in the cardiomyocyte.[22-24] Loss of RBM20 function leads to mis-splicing of target genes in humans and rodent models.[22-25] RBM20 is composed of two zink finger domains, one RNA-recognition motif (RRM)-type RNA binding domain and an arginine-/serine-(RS)-rich region. In 2019, two mutational hot spot regions in exons 9 and 11 of *RBM20* have been recognized.[26] The majority of pathogenic *RBM20* mutations is localized in the RS domain.[11,18,19,23] Nevertheless, a global understanding of variant pathogenicity across the *RBM20*-coding transcript remains elusive. An *RBM20* patient registry has been assembled and reveals a high prevalence of sudden cardiac deaths and early onset cardiomyopathies.[26]

In this clinical context, Sun et al[27] describe in the current issue of *Pediatric Investigation* two independent young LVNC patients carrying *RBM20* missense mutations. Both mutations have been identified before in DCM patients.[18,19,28] Furthermore, the mutation *RBM20*-p.R636H was described in one case with LVNC[29] but in contrast to the present manuscript by Sun et al[27] without detailed clinical description.

Interestingly, the authors used trio whole exome

DOI: 10.1002/ped4.12184

sequencing and discovered that both mutations occurred *de novo* in the pediatric index patients. No further cardiomyopathy associated mutations were discovered. In conclusion, the manuscript by Sun et al emphasizes the clinical need for genetic testing even in cases without a known family history and *RBM20* should be considered as a LVNC associated gene as previously suggested.[11,15] Especially in children with genetic forms of LVNC the risk for major adverse cardiac events might be increased.[15] Hence, the genetic diagnosis of LVNC might have relevance for risk prediction and clinical management of patients and their relatives.[15]

Anna Gaertner, Bärbel Klauke, Andreas Brodehl, Hendrik Milting
Heart and Diabetes Center NRW, University Hospital of the Ruhr-University Bochum, Clinic of Thoracic and Cardiovascular Surgery, Erich and Hanna Klessmann Institute for Cardiovascular Research and Development, Georgstrasse 11, D-32545 Bad Oeynhausen, Germany

Correspondence
Anna Gaertner, Heart and Diabetes Center NRW, Ruhr-University Bochum, Erich and Hanna Klessmann Institute, Georgstrasse 11, D-32545 Bad Oeynhausen, Germany
Email: agaertner@hdz-nrw.de

CONFLICT OF INTEREST

None.

REFERENCES

1. Brodehl A, Gaertner-Rommel A, Milting H. FLNC (Filamin-C): A new(er) player in the field of genetic cardiomyopathies. Circ Cardiovasc Genet. 2017;10:pii:e001959.
2. Arbustini E, Weidemann F, Hall JL. Left ventricular noncompaction: a distinct cardiomyopathy or a trait shared by different cardiac diseases? J Am Coll Cardiol. 2014;64:1840-1850.
3. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113:1807-1816.
4. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29:270-276.
5. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart. 2001;86:666-671.
6. Weir-McCall JR, Yeap PM, Papagiorcopulo C, Fitzgerald K, Gandy SJ, Lambert M, et al. Left ventricular noncompaction: Anatomical phenotype or distinct cardiomyopathy? J Am Coll Cardiol. 2016;68:2157-2165.
7. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation. 2003;108:2672-2678.
8. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol. 2005;46:101-105.
9. Weiford BC, Subbarao VD, Mulhern KM. Noncompaction of the ventricular myocardium. Circulation. 2004;109:2965-2971.
10. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol. 2000;36:493-500.
11. Sedaghat-Hamedani F, Haas J, Zhu F, Geier C, Kayvanpour E, Liss M, et al. Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. Eur Heart J. 2017;38:3449-3460.
12. Hoedemaekers YM, Caliskan K, Michels M, Frohn-Mulder I, van der Smagt JJ, Phefferkorn JE, et al. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. Circ Cardiovasc Genet. 2010;3:232-239.
13. Klaassen S, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. Circulation. 2008;117:2893-2901.
14. Gati S, Rajani R, Carr-White GS, Chambers JB. Adult left ventricular noncompaction: reappraisal of current diagnostic imaging modalities. JACC Cardiovasc Imaging. 2014;7:1266-1275.
15. van Waning JI, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM, et al. Genetics, clinical features, and long-term outcome of noncompaction cardiomyopathy. J Am Coll Cardiol. 2018;71:711-722.
16. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. Lancet. 2015;386:813-825.
17. Miszalski-Jamka K, Jefferies JL, Mazur W, Głowacki J, Hu J, Lazar M, et al. Novel genetic triggers and genotype-phenotype correlations in patients with left ventricular noncompaction. Circ Cardiovasc Genet. 2017;10:pii:e001763.
18. Brauch KM, Karst ML, Herron KJ, de Andrade M, Pellikka PA, Rodeheffer RJ, et al. Mutations in ribonucleic acid binding protein gene cause familial dilated cardiomyopathy. J Am Coll Cardiol. 2009;54:930-941.
19. Li D, Morales A, Gonzalez-Quintana J, Norton N, Siegfried JD, Hofmeyer M, et al. Identification of novel mutations in *RBM20* in patients with dilated cardiomyopathy. Clin Transl Sci. 2010;3:90-97.
20. Beqqali A, Bollen IA, Rasmussen TB, van den Hoogenhof MM, van Deutekom HW, Schafer S, et al. A mutation in the glutamate-rich region of RNA-binding motif protein 20 causes dilated cardiomyopathy through missplicing of titin

and impaired Frank-Starling mechanism. Cardiovasc Res. 2016;112:452-463.
21. Klauke B, Gaertner-Rommel A, Schulz U, Kassner A, Zu Knyphausen E, Laser T, et al. High proportion of genetic cases in patients with advanced cardiomyopathy including a novel homozygous *Plakophilin 2*-gene mutation. PLoS One. 2017;12:e0189489.
22. Li S, Guo W, Dewey CN, Greaser ML. Rbm20 regulates titin alternative splicing as a splicing repressor. Nucleic Acids Res. 2013;41:2659-2672.
23. Guo W, Schafer S, Greaser ML, Radke MH, Liss M, Govindarajan T, et al. *RBM20*, a gene for hereditary cardiomyopathy, regulates titin splicing. Nat Med. 2012;18:766-773.
24. Maatz H, Jens M, Liss M, Schafer S, Heinig M, Kirchner M, et al. RNA-binding protein RBM20 represses splicing to orchestrate cardiac pre-mRNA processing. J Clin Invest. 2014;124:3419-3430.
25. Murayama R, Kimura-Asami M, Togo-Ohno M, Yamasaki-Kato Y, Naruse TK, Yamamoto T, et al. Phosphorylation of the RSRSP stretch is critical for splicing regulation by RNA-Binding Motif Protein 20 (RBM20) through nuclear localization. Sci Rep. 2018;8:8970.
26. Parikh VN, Caleshu C, Reuter C, Lazzeroni LC, Ingles J, Garcia J, et al. Regional variation in *RBM20* causes a highly penetrant arrhythmogenic cardiomyopathy. Circ Heart Fail. 2019;12:e005371.
27. Sun Q, Guo J, Hao C, Guo R, Hu X, Chen Y, et al. Whole-exome sequencing reveals two *de novo* variants in the *RBM20* gene in two Chinese patients with left ventricular non-compaction cardiomyopathy. Pediatr Invest. 2020;4:11-16.
28. Wells QS, Becker JR, Su YR, Mosley JD, Weeke P, D'Aoust L, et al. Whole exome sequencing identifies a causal *RBM20* mutation in a large pedigree with familial dilated cardiomyopathy. Circ Cardiovasc Genet. 2013;6:317-326.
29. Richard P, Ader F, Roux M, Donal E, Eicher JC, Aoutil N, et al. Targeted panel sequencing in adult patients with left ventricular non-compaction reveals a large genetic heterogeneity. Clin Genet. 2019;95:356-367.

How to cite this article: Gaertner A, Klauke B, Brodehl A, Milting H. *RBM20* mutations in left ventricular non-compaction cardiomyopathy. Pediatr Invest. 2020;4:61-63. https://doi.org/10.1002/ped4.12184