

# Lessons on the non-linear path of medical progress and biological complexity from mouse models of the Brugada syndrome

Mathis Korseberg Stokke <sup>1\*</sup> and Markéta Bébarová <sup>2</sup>

<sup>1</sup>Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, PB 4956 Nydalen, NO-0424 Oslo, Norway; and <sup>2</sup>Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Online publish-ahead-of-print 14 June 2024

**This editorial refers to ‘Genetic background determines the severity of age-dependent cardiac structural abnormalities and arrhythmia susceptibility in Scn5a-1798insD mice’, by G.A. Marchal et al., <https://doi.org/10.1093/europace/euae153>.**

Despite decades of research and early categorization as a monogenic disease, Brugada syndrome keeps on challenging clinicians and scientists alike. Key questions related to risk prediction, therapy, and individual differences in phenotype expression remain hot topics for debate.<sup>1</sup> Improvements will undoubtedly depend on multicentre studies to accumulate knowledge from a sufficient number of patients suffering from this relatively rare disease with a worldwide prevalence of 0.5 per 1000,<sup>2</sup> but also on improved mechanistic insight from translational studies.<sup>3,4</sup> In this edition of *Europace*, Gerard A. Marchal and colleagues from the Amsterdam University Medical Center illustrate the role of translational research in this process, as well as the non-linear path of medical progress and the complexity of biology.<sup>5</sup>

From original descriptions of a monogenic channelopathy with electrophysiological abnormalities, current descriptions of the Brugada syndrome comprise genetic and external modifiers resulting in an arrhythmogenic syndrome with both electrophysiological and structural features. Possible modifying genetic as well as non-genetic factors in SCN5A-related arrhythmias has been reviewed by Verkerk et al.<sup>6</sup> For the Brugada syndrome and other conditions with convincingly identified pathogenic genetic variants, transgenic mouse lines play a non-replaceable role as tools in mechanistic studies due to the opportunity to change single factors within the complex setting of the intact organism. However, the potential influence of variations in the genetic background is a well-known property even in these models.<sup>7,8</sup> In a creative approach, Marchal and colleagues turned this limitation into a tool to explore the effect of genetic background on a well-described pathogenic genetic variant found in patients with Brugada syndrome. The authors employed two different mouse strains with the murine equivalent of the human SCN5A-1795insD mutation. In previous studies, the same group has shown that mice carrying this mutation recapitulate key electrophysiological characteristics of Brugada syndrome.<sup>9</sup> In the current publication,

differences observed between the experimental groups in terms of electrophysiological and structural abnormalities illustrate that genetic background has a modulatory effect on the phenotype resulting from the Scn5a-1798inD mutation. Furthermore, young and old mice were compared, with one strain showing clear age-dependent development of structural changes.

Besides paving the way for further work to understand the mechanisms underlying the observed effects of age and genotype, this publication provides valuable reminders for both clinicians and basic scientists. The results add important information to the debate on the genotype–phenotype ‘mismatch’ and genetic modifiers in the Brugada syndrome that have been observed even in patient-specific cardiomyocytes derived from human-induced pluripotent stem cells.<sup>10</sup> Although still categorized as a monogenic channelopathy, it has become increasingly clear that other genes and SNPs crucially influence the phenotype expression.<sup>11,12</sup> This is perhaps most clearly illustrated by the development of polygenic risk scores, which currently seems to move the field in a promising direction after years of disputing candidate genes associated with the disease.<sup>13</sup> Studies like the current one could move the field towards a deeper understanding of the underlying genetic basis for differences in phenotype.

Explorations of differences in phenotype despite the same underlying mutation are especially interesting for Scn5a-1798inD mutation, as the authors of the current article have previously shown that non-genetic factors, such as co-morbidities, might also have a modulatory effect.<sup>14</sup> The authors should again be complimented for using a translational approach to pursue their earlier findings to gain a deeper understanding of this aspect of the disease. The previous results become even more interesting as the current study shows an age-dependent phenotype expression that was different between the two mice strains. As co-morbidities of course increase with age, progression in some patients with the underlying genotype might be expected. It is further worth noting that the authors even show differences between male and female mice, with less fibrosis in the females. Together, the results from the current article point to a complex interaction between age, genotype, and external factors to explain the phenotypic expression of this mutation. Whether the same applies to other genetic variants

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

\* Corresponding author. Tel: +47 2301 6800. E-mail address: m.k.stokke@medisin.uio.no

© The Author(s) 2024. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

associated with the Brugada syndrome could be explored in a similar approach.

The use of animal *in vivo* models is essential for the transfer of new knowledge to clinical practice.<sup>15</sup> However, the translation of insight from mouse to human should indeed be made with great caution. Nevertheless, an interesting finding in the current article is that structural and electrophysiological aspects of the pathology associated with the Brugada syndrome are not necessarily depending on the same factors. It is tempting to speculate that this might reconcile seemingly opposing views about the Brugada syndrome and explanations for its variations in phenotypic expression. As is well known to the readers of *Europace*, one theory explained the typical Brugada ECG pattern by transmural repolarization differences,<sup>16</sup> whereas others focused on depolarization and conduction deficits,<sup>17</sup> or even on discontinuous conduction throughout the myocardium.<sup>18</sup> Importantly, the individual hypotheses are not mutually exclusive, as different factors can contribute to the phenotype in various patients. The current paper indicates that differences in genotype and exposure to external factors might promote different aspects of the pathophysiology, and thereby induce different abnormalities with a final common electrophysiological expression. This discussion has centred around the physiology of the right ventricle and especially the right ventricular outflow tract,<sup>19</sup> which also illustrates an obvious limitation of mouse models where detailed studies of regional anatomy and physiology is difficult. Such studies will need to be pursued in larger mammals and humans for further mechanistic insight.

The current study also provides an important reminder to scientists employing mouse models for translational research. The background strain and measures to avoid genotypic drift in these inbred models can no longer be overlooked when reporting results. As a minimum, the specific background should be described sufficiently for other researchers to compare with their model, and descriptions of routines in the reporting lab to avoid untoward genetic drift should become a requirement. To our knowledge, clear rules in the form of guidelines are not available even though previous papers have emphasized the role of genetic background in the final phenotype and, thus, in the suitability of the selected model for concrete purposes.<sup>20</sup>

The current study should also be an inspiration for research not to simply resign when models unexpectedly 'loose' their phenotype over time, but instead use it as an opportunity to identify new factors with importance for the phenotype expression. Rightly heralded as a key tool for the reductionist approach in mechanistic studies employing animal models, transgenic mouse models also illustrate the complexity of biology and the difficulties in truly manipulating only one factor without affecting others at the same time. This lesson should stand as a humbling reminder to the clinician facing patients with varying phenotypes, as well as the translational scientist employing mouse models to elucidate biology.

**Conflict of interest:** None declared.

## References

- Krahn AD, Behr ER, Hamilton R, Probst V, Laksman Z, Han HC. Brugada syndrome. *JACC Clin Electrophysiol* 2022;**8**:386–405.
- Vutthikraivit W, Rattanawong P, Putthapiban P, Sukhumthamarat W, Vathesatogkit P, Ngarmukos T et al. Worldwide prevalence of Brugada syndrome: a systematic review and meta-analysis. *Acta Cardiol Sin* 2018;**34**:267–77.
- Sipido KR, Tedgui A, Kristensen SD, Pasterkamp G, Schunkert H, Wehling M et al. Identifying needs and opportunities for advancing translational research in cardiovascular disease. *Cardiovasc Res* 2009;**83**:425–35.
- Crotti L, Brugada P, Calkins H, Chevalier P, Conte G, Finocchiaro G et al. From gene-discovery to gene-tailored clinical management: 25 years of research in channelopathies and cardiomyopathies. *Europace* 2023;**25**:euaad180.
- Marchal GA, Rivaud MR, Wolswinkel R, Basso C, van Veen TAB, Bezzina CR et al. Genetic background determines the severity of age-dependent cardiac structural abnormalities and arrhythmia susceptibility in *Scn5a*-1798insD mice. *Europace* 2024. doi: 10.1093/eurpace/eaue153.
- Verkerk AO, Amin AS, Remme CA. Disease modifiers of inherited SCN5A channelopathy. *Front Cardiovasc Med* 2018;**5**:137.
- Garcia-Menendez L, Karamanlidis G, Kolwicz S, Tian R. Substrain specific response to cardiac pressure overload in C57BL/6 mice. *Am J Physiol Heart Circ Physiol* 2013;**305**:H397–402.
- Rowlands CT, Owen T, Lawal S, Cao S, Pandey SS, Yang HY et al. Age- and strain-related aberrant Ca<sup>2+</sup> release is associated with sudden cardiac death in the ACTC E99K mouse model of hypertrophic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2017;**313**:H1213–26.
- Remme CA, Verkerk AO, Nuyens D, van Ginneken AC, van Brunschot S, Belterman CN et al. Overlap syndrome of cardiac sodium channel disease in mice carrying the equivalent mutation of human SCN5A-1795insD. *Circulation* 2006;**114**:2584–94.
- Sun Y, Su J, Wang X, Wang J, Guo F, Qiu H et al. Patient-specific iPSC-derived cardiomyocytes reveal variable phenotypic severity of Brugada syndrome. *EBioMedicine* 2023;**95**:104741.
- Probst V, Wilde AA, Barc J, Sacher F, Babuty D, Mabo P et al. SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. *Circ Cardiovasc Genet* 2009;**2**:552–7.
- Bersell KR, Yang T, Mosley JD, Glazer AM, Hale AT, Kryshtal DO et al. Transcriptional dysregulation underlies both monogenic arrhythmia syndrome and common modifiers of cardiac repolarization. *Circulation* 2023;**147**:824–40.
- Honarbaksh S, Providencia R, Garcia-Hernandez J, Martin CA, Hunter RJ, Lim WY et al. A primary prevention clinical risk score model for patients with Brugada syndrome (BRUGADA-RISK). *JACC Clin Electrophysiol* 2021;**7**:210–22.
- Rivaud MR, Jansen JA, Postema PG, Nannenber EA, Mizusawa Y, van der Nagel R et al. A common co-morbidity modulates disease expression and treatment efficacy in inherited cardiac sodium channelopathy. *Eur Heart J* 2018;**39**:2898–907.
- Odening KE, Gomez AM, Dobrev D, Fabritz L, Heinzel FR, Mangoni ME et al. ESC working group on cardiac cellular electrophysiology position paper: relevance, opportunities, and limitations of experimental models for cardiac electrophysiology research. *Europace* 2021;**23**:1795–814.
- Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. *J Cardiovasc Electrophysiol* 2001;**12**:268–72.
- Meregalli PG, Wilde AA, Tan HL. Pathophysiological mechanisms of Brugada syndrome: depolarization disorder, repolarization disorder, or more? *Cardiovasc Res* 2005;**67**:367–78.
- Bebarova M. Arrhythmogenesis in Brugada syndrome: impact and constraints of current concepts. *Int J Cardiol* 2013;**167**:1760–71.
- Behr ER, Ben-Haim Y, Ackerman MJ, Krahn AD, Wilde AAM. Brugada syndrome and reduced right ventricular outflow tract conduction reserve: a final common pathway? *Eur Heart J* 2021;**42**:1073–81.
- Taft RA, Davissou M, Wiles MV. Know thy mouse. *Trends Genet* 2006;**22**:649–53.