Effect of genetic background on the cardiac phenotype in a mouse model of Emery-Dreifuss muscular dystrophy

Nicolas Vigniera, Nathalie Mougenotb, Gisèle Bonnea, Antoine Muchirab,*

a Sorbonne Université, INSERM UMR574 Centre de Recherche en Myologie, Institut de Myologie, G.H. Pitié Salpêtrière, F-75651, Paris Cedex 13, France
b Sorbonne Université, INSERM UMS28 Phénotypage du petit animal, Faculté de Médecine Pierre et Marie Curie, F-75013, Paris, France

ARTICLE INFO

Keywords:
LMNA
A-type lamins
Cardiomyopathy
Mouse models
Genetic background

ABSTRACT

A-type lamins gene (LMNA) mutations cause an autosomal dominant inherited form of Emery-Dreifuss muscular dystrophy (EDMD). EDMD is characterized by slowly progressive muscle weakness and wasting and dilated cardiomyopathy, often leading to heart failure-related disability. EDMD is highly penetrant with poor prognosis and there is currently no specific therapy available. Clinical variability ranges from early onset with severe presentation in childhood to late onset with slow progression in adulthood. Genetic background is a well-known factor that significantly affects phenotype in several mouse models of human diseases. This phenotypic variability is attributed, at least in part, to genetic modifiers that regulate the disease process. To characterize the phenotype of A-type lamins mutation on different genetic background, we created and phenotyped C57BL/6JRj-LmnaH222P/H222P mice (C57BL/6JRj-LmnaH222P/H222P) and compared them with the 129S2/SvPasCrl-LmnaH222P/H222P mice (129S2/SvPasCrl-LmnaH222P). These mouse strains were compared with their respective control strains at multiple time points between 3 and 10 months of age. Both contractile and electrical cardiac muscle functions, as well as survival were characterized. We found that 129S2/SvPasCrl-LmnaH222P mice showed significantly reduced body weight and reduced cardiac function earlier than in the C57BL/6JRj-LmnaH222P mice. We also revealed that only 129S2/SvPasCrl-LmnaH222P mice developed heart arrhythmias. The 129S2/SvPasCrl-LmnaH222P model with an earlier onset and more pronounced cardiac phenotype may be more useful for evaluating therapies that target cardiac muscle function, and heart arrhythmias.

1. Introduction

Emery-Dreifuss muscular dystrophy (EDMD) is characterized by the clinical triad of i/slowly progressive muscle weakness and wasting in a scapulo-humeroperoneal distribution; ii/early contractures of the elbows, ankles, and posterior neck; and iii/cardiac conduction defects associated with dilated cardiomyopathy [1]. LMNA mutations encoding nuclear A-type lamins are responsible for the autosomal forms of EDMD [2]. Genetically engineered mouse models of EDMD have brought valuable insights in our understanding of the molecular mechanisms of the disease [3]. They have been instrumental in the identification of signaling pathways responsible for the cardiac dysfunction and have provided invaluable tools for proposing novel treatment for this disease [4–10]. The knock-in LmnaH222P/H222P mouse model carrying the LMNA p.H222P mutation previously described in patient with classical form of EDMD [11], recapitulates all the features of EDMD [12]. In particular, LmnaH222P/H222P mice developed a dilated cardiomyopathy associated with cardiac conduction defects [11,13].

LmnaH222P/H222P mice were generated using a C57BL/6 background, an inbred strain and useful reductionist tool to study effects of single gene mutations. However in the clinic, LMNA mutations show a strong degree of pleiotropy and therefore understanding how genetic background influences this is likely to prove important. It is known that phenotypic variation that arises due to the influence of genetic background can be of importance to genetically engineered mouse models [14,15]. More recently, it has been showed that the genetic background was a determining factor for the severity of muscular dystrophy in a mouse model of Duchenne muscular dystrophy [16,17]. To investigate the effect of genetic background on the cardiac involvement of EDMD, we have backcrossed LmnaH222P/H222P mice to different pure genetic background, C57BL/6JRj (C57BL/6JRj-LmnaH222P/H222P) and 129S2/SvPasCrl (129S2/SvPasCrl-LmnaH222P). We found that cardiac involvement was more pronounced in the 129S2/SvPasCrl-LmnaH222P mouse strain compared with the C57BL/6JRj-LmnaH222P mouse strain, suggesting that genetic background significantly modifies the severity of dilated cardiomyopathy linked to LMNA mutations.

* Corresponding author.
E-mail address: a.muchir@institut-myologie.org (A. Muchir).

https://doi.org/10.1016/j.bbrep.2019.100664
Received 6 May 2019; Received in revised form 6 June 2019; Accepted 2 July 2019
2405-5808/ © 2019 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
2. Results

2.1. Genetic characterization of mouse strains

To assess the genetic background of the C57L<sup>Lmna</sup><sup>p.H222P</sup> and 129L<sup>Lmna</sup><sup>p.H222P</sup> mouse strains, we used a marker-assisted selection protocol (MASP) based on genome-wide analysis of genetic polymorphisms, which allows the discrimination between different strains of mice [18].

We used simple sequence length polymorphism (SSLP) that correspond to short cytosine, adenine nucleotide tandem repeats (CA). The number n of (CA) repeats is specific for C57BL/6JRj or 129S2/SvPasCrl strains [19]. We screened for 50 SSLPs, covering the entire mouse genome, on all four mouse strains (Table S1). We observed that all the 50 SSLPs were homozygous and matched in length for both C57BL/6JRj and C57L<sup>Lmna</sup><sup>p.H222P</sup> mice (Fig. 1A). Besides, we found that 48 of the 50 SSLPs were homozygous and matched in size in 129L<sup>Lmna</sup><sup>p.H222P</sup> mice compared with 129S2/SvPasCrl mice (Fig. 1A). Furthermore, one SSLP (D16-Mit-57a), located on chromosome 16, was heterozygous with one allele from C57BL/6JRj strain and the second from 129S2/SvPasCrl (D16-Mit-57a), located on chromosome 16, was heterozygous with one allele from C57BL/6JRj strain and the second from 129S2/SvPasCrl strain. Hence, the C57<sup>Lmna</sup><sup>p.H222P</sup> mouse strain was entirely derived on C57BL/6JRj background of 129S2/SvPasCrl [1], C57BL/6JRj [3] and C57L<sup>Lmna</sup><sup>p.H222P</sup> [4] mouse strains.

2.2. Body weight

The loss of body weight characterizes the progression of the disease in L<sup>mna</sup><sup>p.H222P</sup> mice [12]. To follow the time course of the disease of the 129L<sup>lmm</sup><sup>p.H222P</sup> and C57L<sup>lmm</sup><sup>p.H222P</sup> mice, we weighed mice every month from 3 to 10 months of age. The 129L<sup>lmm</sup><sup>p.H222P</sup> mice started to lose weight from 6 months of age compared with 129S2/SvPasCrl mice (Fig. 2A). The C57L<sup>lmm</sup><sup>p.H222P</sup> mice started to lose weight at 7 months of age compared with C57BL/6JRj mice (Fig. 2A). The median survival of the 129L<sup>lmm</sup><sup>p.H222P</sup> mice was 7 months of age, while the median survival of C57L<sup>lmm</sup><sup>p.H222P</sup> mice was 10 months. (Fig. 2B). The weight loss was correlated with decreased lifespan for both 129L<sup>lmm</sup><sup>p.H222P</sup> and C57L<sup>lmm</sup><sup>p.H222P</sup> mice. The coefficient determination R<sup>2</sup> between weight and percentage of survival was 0.89 for 129L<sup>lmm</sup><sup>p.H222P</sup> mice and 0.98 for C57L<sup>lmm</sup><sup>p.H222P</sup> mice (Table S3). The RR interval was significantly increased in 129L<sup>lmm</sup><sup>p.H222P</sup> mice compared with the C57L<sup>lmm</sup><sup>p.H222P</sup> mouse strain.

2.3. Cardiac structure and function

Cardiac structure and function were determined by echocardiography in the four different groups of mice. Compared with 129S2/SvPasCrl mice, 129L<sup>lmm</sup><sup>p.H222P</sup> mice had significantly increased left-ventricular end systolic diameter, starting at 4 months of age (Fig. 3A and C, Table S2). The left-ventricular end diastolic diameters started to be significantly increased in 129L<sup>lmm</sup><sup>p.H222P</sup> mice at 8 months of age (Fig. 3A and B, Table S2). Compared with C57BL/6JRj mice, C57L<sup>lmm</sup><sup>p.H222P</sup> mice had significantly increased left-ventricular end systolic and left-ventricular end diastolic diameters at 6 months of age (Fig. 3A and C, Table S2). We observed a statistically significant decreased fractional shortening (FS) for 129L<sup>lmm</sup><sup>p.H222P</sup> mice compared with wild type 129S2/SvPasCrl animals at 4 months of age (Fig. 3D, Table S2), while it was noticeable at 5 months of age for C57L<sup>lmm</sup><sup>p.H222P</sup> mice. Taken together, these results showed a more severe cardiac phenotype in the 129L<sup>lmm</sup><sup>p.H222P</sup> mice compared with the C57L<sup>lmm</sup><sup>p.H222P</sup> animals.

2.4. Conduction defects and arrhythmias

Given that conduction defects and arrhythmias have been previously described in L<sup>mna</sup><sup>p.H222P</sup>/H<sup>222P</sup> mice [12,13], we set out to assess of the cardiac electrical conduction disturbances (Fig. 4A) in the four different groups of mice. The PR interval and the QRS complex duration were extended, without reaching significance (Table S4), in 129L<sup>lmm</sup><sup>p.H222P</sup> mice and C57L<sup>lmm</sup><sup>p.H222P</sup> mice compared with 129S2/SvPasCrl mice and C57BL/6JRj mice, respectively (Fig. 4B and C). Both PR interval and QRS complex increases were more pronounced in the 129L<sup>lmm</sup><sup>p.H222P</sup> mice than in the C57L<sup>lmm</sup><sup>p.H222P</sup> mice, with an earlier onset in 129L<sup>lmm</sup><sup>p.H222P</sup> mice (Table S3). The RR interval was
more, ECG analyses revealed that neither C57BL/6J mice nor C57
129S2/svPasCrl mice. #75
months compared with C57BL/6J mice (Fig. 4D, Table S3). Further-

( ) Regression analysis of weight and survival percentage for 129S2/svPasCrl (n = 12), 129
– Lmna p.H222P and C57BL/6J mice. Values are presented as mean ± SD. Multiple group comparison was performed with Kruskal Wallis test with Dunn’s test post-test. *p ≤ 0.01 between 129Lmna p.H222P mice and 129S2/svPasCrl mice. *p ≤ 0.01 between C57Lmna p.H222P and C57BL/6JRj mice. (B) Kaplan–Meier survival curves for 129S2/svPasCrl (n = 12), 129Lmna p.H222P (n = 9), C57BL/6JRj (n = 8), and C57Lmna p.H222P (n = 6) mice. Survival curves comparison was performed with the logrank test (mantel-cox test). **p ≤ 0.01 between C57Lmna p.H222P and 129Lmna p.H222P mice. ####p ≤ 0.0001 between 129Lmna p.H222P and 129S2/svPasCrl mice. (C) Regression analysis of weight and survival percentage for 129Lmna p.H222P and C57Lmna p.H222P mice. Values are presented as mean ± SD.

3. Discussion

The phenotype of a given single-gene mutation in genetically en-
gineered mouse models is modulated by the genetic background. This

effect is attributable to modifier genes, which function in combination
with the causative gene. Developing congenic mouse strains not only
helps us to investigate the effect of LMNA mutations on phenotype but
would also facilitate the development of mouse models that more ac-
curately mimic certain features of EDMD. Using validation of single
sequence length polymorphism, a method that can be routinely per-
formed, we demonstrated that this approach could be successfully used
to certify inbred strains of mouse models of muscular dystrophies. We showed here significant strain-dependent differences in cardiac func-
tion between inbred strains of Lmna p.H222P mouse. Particularly, the

cardiac phenotype was more pronounced in the 129S2/svPasCrl genetic
background. These findings demonstrate the complex effects of genetic
divergence between inbred strains on cardiac functions in mouse models of EDMD.

Unlike the C57Lmna p.H222P mice, we found that 129Lmna p.H222P mice
showed exacerbated arrhythmia susceptibility. This is in agreement
with previously reported findings that C57BL/6J mice are resistant to
arrhythmia [20,21]. It is known that genetic background dominates the
susceptibility to ventricular arrhythmias [22]. In this context, this
should be considered when studying cardiac electrical activity in mice.

Further exploration of the genetic differences between the two congenic
mouse strains, which account for the difference in the cardiac pheno-
types of the same Lmna p.H222P mutation, is warranted. Indeed, geno-
omic analysis of the 129Lmna p.H222P mice and C57Lmna p.H222P mice
will be of interest to identify specific locus associated to arrhythmia.
Such a study may provide new mechanistic and clinically relevant in-
sight into the alteration of cardiac function between these strains.
Moreover, the relatively sensitive 129S2/svPasCrl mouse would be of
great value to investigate the genetic basis underlying ventricular ar-

rhythmic. In conclusion the 129Lmna p.H222P mouse cardiac phenotype
was more deleterious than in C57Lmna p.H222P mouse, at least in part
because genetic background of 129S2/svPasCrl present a predisposition
for arrhythmia. In human EDMD, arrhythmia-related symptoms fre-
cently preceded heart dilation and heart failure symptoms ([23]).

In summary, our data suggest that 129Lmna p.H222P mice have a se-
vere progressive cardiac muscle disease with early-onset deficits. Thus,
this mouse model may be a particularly suitable model for evaluating
therapeutic strategy for EDMD.

4. Material and methods

4.1. Mouse strains

Lmna p.H222P/H222P mice [12] were backcrossed eight times with the
congenic strains C57BL/6JRj and 129S2/svPasCrl (Janvier Labs). The
animals were fed chow and housed in a disease-free barrier facility at
12 h/12 h light/dark cycles. The French Ministry of Health has ap-
proved all animal experiments (approval number #00982.03). Accre-
dited personnel dedicated to the Care and Use of Experimental Animals
has conducted all animal experiments (accreditation number #75–679).

The animal experiments were performed according to the guidelines
from Directive 2010/63/EU of the European Parliament on
the protection of animals used for scientific purposes.

Fig. 2. Effect of genetic background on the weight and the lifespan of 129Lmna p.H222P and C57Lmna p.H222P mice.

Fig. 3. Cardiac phenotype was more pronounced in the 129S2/svPasCrl genetic background. These findings
demonstrate the complex effects of genetic divergence between inbred strains on cardiac functions in mouse models of EDMD.

(significantly prolonged in the 129Lmna p.H222P mice at 3, 5 and 6 months
of age compared with 129S2/svPasCrl mice (Fig. 4D, Table S3). Simi-
larly, RR interval was also lengthened in the C57Lmna p.H222P mice at 6
months compared with C57BL/6JRj mice (Fig. 4D, Table S3). Further-
more, ECG analyses revealed that neither C57BL/6JRj mice nor C57Lmna
p.H222P mice develop heart arrhythmias at 3 or 5 months of age (Fig. 4E,
F, 4G, 4H). However, 129Lmna p.H222P mice developed heart arrhythmia
(supraventricular premature contractions and sinoventricular blocks) at
3 (Figure 4I) and 5 months of age (Fig. 4J). We noted that 129S2/svPasCrl mice did not have heart arrhythmia at 3 months of age (Fig. 4K) but developed some by 5 months of age (Figure 4L). Taken

together these results showed a higher susceptibility to conduction defects in 129Lmna p.H222P mice.

A

B

C

4.2. NMR H2 O
4.2. Simple Sequence Length Polymorphisms screening

Genomic DNA was extracted from mouse tail samples digested in 0.4 mg/ml proteinase K digestion buffer (Tris pH 8.5 100 mM, EDTA 5 mM, SDS 0.2%, NaCl 200 mM), precipitated by 100% isopropanol and suspended in water at 500 ng/μl final concentration. Polymerase chain reaction (PCR) was performed using AmpliTaq Gold™ 360 Master Mix according to the provider recommendations. PCR cycle were 95 °C for 10 mn, 10 cycles (95 °C for 10 s, 60 °C for 10 s, 72 °C for 10 s), 72 °C for 5 mn. PCR products were analyzed in 5% Nuseive CTG agarose gel.

4.3. Echocardiography

Mice were anesthetized with 0.75% isoflurane in O2 and placed on a heating pad (25 °C). Echocardiography was performed using an Vivid7 ultrasound with an 11 MHz transducer applied to the chest wall. Cardiac ventricular dimensions and fractional shortening were measured in 2D mode and M-mode, 3 times per animal. A blinded experimenter, unaware of the genotype performed the examinations.

4.4. Electrocardiography

Electrocardiograms were recorded from living mice using the non-invasive ecgTUNNEL™ (Emka Technologies). Waveforms were recorded using Iox Software v1.8.9.18 and intervals were measured with ecgAUTO v1.5.12.50, using the average of three representative consecutive beats. A blinded experimenter, unaware of the genotype performed the examinations.

4.5. Statistics

Statistical analyses were performed using GraphPad Prism software.

Fig. 3. Effect of genetic background on the 129\textsuperscript{Lmna} p.H222P and C57\textsuperscript{Lmna} p.H222P mice cardiac function.

(A) Representative echocardiographic M-mode images at 5 months of age from 129S2/svPasCrl, 129\textsuperscript{Lmna} p.H222P, C57BL/6JRj and C57\textsuperscript{Lmna} p.H222P mice.

(B) Graph representing the left-ventricular end systolic diameters (LVDs) from 129S2/svPasCrl, 129\textsuperscript{Lmna} p.H222P, C57BL/6JRj and C57\textsuperscript{Lmna} p.H222P mice from 2 to 12 months of age. Values are presented as mean ± SD. Multiple group comparison was performed with Kruskal Wallis test with Dunn’s test post-test.

(C) Graph representing the left-ventricular end systolic diastolic (LVDd) from 129S2/svPasCrl, 129\textsuperscript{Lmna} p.H222P, C57BL/6JRj and C57\textsuperscript{Lmna} p.H222P mice from 2 to 12 months of age. Values are presented as mean ± SD. Multiple group comparison was performed with Kruskal Wallis test with Dunn’s test post-test.

(D) Graph representing the fractional shortening (FS) from 129S2/svPasCrl, 129\textsuperscript{Lmna} p.H222P, C57BL/6JRj and C57\textsuperscript{Lmna} p.H222P mice from 2 to 12 months of age. Values are presented as mean ± SD. Multiple group comparison was performed with Kruskal Wallis test with Dunn’s test post-test. *\(p \leq 0.01\), **\(p \leq 0.001\) and ***\(p \leq 0.0001\) between 129\textsuperscript{Lmna} p.H222P and 129S2/svPasCrl mice. *\(p \leq 0.01\), **\(p \leq 0.001\) and ***\(p \leq 0.0001\) between C57\textsuperscript{Lmna} p.H222P and 129\textsuperscript{Lmna} p.H222P mice. **\(p \leq 0.01\) between C57\textsuperscript{Lmna} p.H222P and 129\textsuperscript{Lmna} p.H222P mice.
Fig. 4. Effect of genetic background on the cardiac conduction and arrhythmias
(A) Representation of electrocardiogram (ECG) trace with the P wave, the QRS complex, the PR interval and the RR interval.
(B) Graphs showing PR interval, for the 129Lmna p.H222P mice, 129S2/svPasCrl mice, C57Lmna p.H222P and C57BL/6JRj mice. Values are presented as mean ± SD. Multiple group comparison was performed with Kruskal Wallis test with Dunn's test post-test.
(C) Graphs showing QRS interval, for the 129Lmna p.H222P mice, 129S2/svPasCrl mice, C57Lmna p.H222P and C57BL/6JRj mice. Values are presented as mean ± SD. Multiple group comparison was performed with Kruskal Wallis test with Dunn's test post-test.
(D) Graphs showing RR interval, for the 129Lmna p.H222P mice, 129S2/svPasCrl mice, C57Lmna p.H222P and C57BL/6JRj mice. Values are presented as mean ± SD. Multiple group comparison was performed with Kruskal Wallis test with Dunn's test post-test.
(E-L) Variation of the RR interval from the four mouse strains at 3 and 5 months.
* \( p \leq 0.05 \) and ** \( p \leq 0.005 \) between 129Lmna p.H222P mice and 129S2/svPasCrl mice. * \( p \leq 0.05 \) and ** \( p \leq 0.005 \) between C57Lmna p.H222P and C57BL/6JRj mice.
Statistical significance between groups of mice was analyzed with a corrected parametric test, Welch's t-test when compared two sets of data, or Kruskal Wallis test with Dunn's test post-test when compared multiple sets data, with a value of P ≤ 0.05 being considered significant. To validate results of echocardiographic analyses, we performed a non-parametric test (Wilcoxon-Mann-Whitney test). Survival curves were generated using the method of Kaplan and Meier, and survival curves comparison was performed with the log rank test (mantel-cox test). Regression analysis was performed for a confidence interval of 95%.

Competing interests

All other authors have declared no conflicts of interest.

Conflict of interest

None for all the authors.

Author contribution

Conceptualization, A.M. and N.V.; Investigation, N.V. and N.M.; Writing – Original Draft, A.M; Writing – Review & Editing, N.V., G.B., and A.M.; Funding Acquisition, A.M.; Supervision, A.M.

Acknowledgements

This study was supported by funds from the Association Francaise contre les Myopathies, from the Institut National de la Santé et de la Recherche Médicale and Sorbonne University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2019.100664.

References

[1] A.E. Emery, X-linked muscular dystrophy with early contractures and cardiomyopathy (Emery-Dreifuss type), Clin. Genet. 32 (1987) 360–367.
[2] G. Bonne, M.R. Di Barletta, S. Varnous, et al., Mutations in the gene encoding lamin A/C cause autosomal dominant Emery- Dreifuss muscular dystrophy, Nat. Genet. 21 (1999) 285–288.
[3] F. Aziziani, A. Muchir, N. Vignier, G. Bonne, A.T. Bertrand, Striated muscle lamino- pathies, Semin. Cell Dev. Biol. 29 (2014) 107–115.
[4] A. Muchir, P. Pavlidis, V. Decostre, A.J. Herros, T. Arinuma, et al., Activation of MAPK pathways links LMNA mutations to cardiomyopathy in Emery-Dreifuss muscular dystrophy, J. Clin. Investig. 117 (2007) 1282–1293.
[5] A. Muchir, W. Wu, J.C. Choi, S. Iwata, J. Morrow, et al., Abnormal p38 mitogen-activated protein kinase signaling in dilated cardiomyopathy caused by lamin A/C gene mutation, Hum. Mol. Genet. 21 (2012) 4325–4333.
[6] J.C. Choi, A. Muchir, W. Wu, S. Iwata, S. Homma, et al., Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation, Sci. Transl. Med. 4 (2012) 144ra102.
[7] M. Chatzifrangkeskou, C. Le Dour, W. Wu, J.P. Morrow, L.C. Joseph, et al., ERK1/2 directly acts on CTGF/CCN2 expression to mediate myocardial fibrosis in cardio- myopathy caused by mutations in the lamin A/C gene, Hum. Mol. Genet. 25 (2016) 2220–2233.
[8] N. Vignier, M. Chatzifrangkeskou, B. Morales Rodriguez, M. Mericskay, N. Mougenot, et al., Rescue of biosynthesis of nicotinamide adenine dinucleotide (NAD+) protects the heart in cardiomyopathy caused by lamin A/C gene mutation, Hum. Mol. Genet. 27 (2018) 3060–3076.
[9] M. Chatzifrangkeskou, D. Yadin, T. Marais, S. Chardonne, M. Cohen-Tannoudji, et al., Coffin-Lowry syndrome: genotype-phenotype correlation in patients with LMNA mutations, Hum. Mol. Genet. 14 (2005) 115–126.
[10] C. Le Dour, C. Macquart, F. Sera, S. Homma, G. Bonne, et al., Decreased WNT/b- catenin signalling contributes to the pathogenesis of dilated cardiomyopathy caused by mutations in the lamin A/C gene, Hum. Mol. Genet. 26 (2017) 333–343.
[11] N. Vignier, M. Chatzifrangkeskou, B. Morales Rodriguez, G. Sinagra, M. Lusby, et al., Mice model carrying H222P-Lmna mutation develops muscular dystrophy and dilated cardio- myopathy similar to human striated muscle laminopathies, Hum. Mol. Genet. 14 (2005) 155–169.
[12] T. Arinuma, A. Helbling-Leclerc, C. Massart, S. Varnous, F. Niel, et al., Mouse model carrying H222P-Lmna mutation develops muscular dystrophy and dilated cardio- myopathy caused by mutation in A-type lamin gene, Hum. Mol. Genet. accepted (2018).
[13] J. Rivera, L. Tessarollo, Genetic background and the dilemma of translating mouse data to humans, Immunity 28 (2008) 1–4.
[14] J. Estill, J.A. Garcia, A marker assisted selection protocol (MASP) to generate C57BL/6J or 129S6/SvEvTac speed conhgenic or consomic strains, Genesis 28 (2000) 164–166.
[15] W.D. Coley, L. Bogdanik, M.C. Vila, Q. Yu, J.H. Van Der Meulen, et al., Emtosis in dilated cardiomyopathy caused by lamin A/C gene mutation, Hum. Mol. Genet. 27 (2018) 3060–3076.
[16] M.R. Taylor, P.R. Fain, G. Sinagra, M.L. Robinson, A.D. Robertson, et al., Natural killer cells reduce the susceptibility to ventricular arrhythmias in a murine model of b-adrenergic stimula- tion, Sci. Transl. Med. 4 (2012) 144ra102.
[17] A. Muchir, W. Wu, J.C. Choi, S. Iwata, J. Morrow, et al., Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation, Sci. Transl. Med. 4 (2012) 144ra102.