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1 **Cardiometabolic assessment of lamin A/C gene mutation carriers:**
2 **a phenotype–genotype correlation**

3

4 Kwapich M^{1*}, Lacroix D^{2*}, Espiard S³, Ninni S⁴, Brigadeau F⁴, Kouakam C⁴, Degroote P⁴, Laurent
5 JM⁴, Tiffreau V⁵, Jannin A⁶, Humbert L⁶, Ben Hamou A⁶, Tard C⁷, Ben Yaou R⁸, Lamblin N², Klug
6 D², Richard P⁹, Vigouroux C¹⁰, Bonne G¹¹, Vantyghem MC¹²

7 and the Diamenord–AEDNL Working Group

8 Averous V, Balavoine AS, Bourdelle MF, Boury S, Bouzaib S, Caiazzo R, Cortet C, Cuisset JM,
9 Defrance F, Derveaux A, Devemy F, Douillard C, Ernst O, Evrard A, Gheerbrand D, Girardot C,
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12 Merlen E, Mouton F, Mycinski B, Parent E, Pattou F, Pigny P, Prudhomme M, Ryndak A, Trinel C,
13 Topolinski H, Vatier C, Verkindt H (all MDs)

14 * These authors contributed equally to this work.

15

16 ¹ MD, CHU Lille, Endocrinology, Diabetology and Metabolism, F-59000, Lille, France

17 ² MD-PhD, Professor CHU Lille, Cardiology Department, Lung-Heart Institute, F-59000 Lille, France

18 ³ MD-PhD, Assistant professor, CHU Lille, Endocrinology, Diabetology and Metabolism, F-59000
19 Lille, France

20 ⁴ MD, CHU Lille, Cardiology Department, Lung-Heart Institute, F-59000 Lille, France

21 ⁵ MD, assistant professor, CHU Lille, Rehabilitation Department, Reference Center for Neuromuscular
22 Disorders, F-59000 Lille, France

23 ⁶ MD CHU Lille, Endocrinology, Diabetology and Metabolism, F-59000 Lille, France

24 ⁷ MD, CHU Lille, INSERM U1171, Neurology Department, Reference Center for Neuromuscular
25 Disorders, F-59000 Lille, France

26 ⁸ MD, Université Pierre et Marie Curie-Paris, UMR-S974, CNRS, UMR-7215, Institut de Myologie,
27 IFR14, Groupe Hospitalier Pitié-Salpêtrière, F-75013 Paris, France

28 ⁹ MD, Université Pierre et Marie Curie-Paris, Molecular and cellular cardiogenetic and myogenetic
29 department, Groupe Hospitalier Pitié-Salpêtrière, F-75013 Paris, France

30 ¹⁰ MD-PhD, Professor, Department of Molecular Biology and Genetics, Department of Endocrinology,
31 Diabetes and Reproductive Endocrinology, National Reference Centre for Rare Diseases of Insulin
32 Secretion and Insulin Sensitivity, INSERM UMR S938, Saint-Antoine Research Center, Institute of
33 Cardiometabolism and Nutrition, Sorbonne Universities, UPMC Univ Paris 6, F-75012 Paris, France

34 ¹¹ MD-PhD, Professor, Université Pierre et Marie Curie-Paris, UMR-S974, CNRS, UMR-7215,
35 Institut de Myologie, IFR14, Groupe Hospitalier Pitié-Salpêtrière, Paris, F-75013 France

36 ¹² MD-PhD Professor, CHU Lille, Endocrinology, Diabetology and Metabolism, Univ Lille, INSERM,
37 UMR 1190, Translational research in diabetes; EGID European Genomic Institute for Diabetes, F-
38 59000 Lille, France

39

40 **Corresponding author:**

41 Prof. M.C. Vantyghem

42 Service d'Endocrinologie et Métabolisme, Hôpital C Huriez Centre Hospitalo-universitaire de Lille, 1
43 rue Polonovski, 59 037 Lille Cedex, France

44 Email: mc-vantyghem@chru-lille.fr

45 Tel: +333 20 44 45 35; Fax: +333 20 44 69 85

46

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49 **ABSTRACT**

50 *Aims.* – Mutations of the *LMNA* gene encoding lamin A/C induce heterogeneous phenotypes ranging
51 from cardiopathies and myopathies to lipodystrophies. The aim of this study was to compare
52 cardiometabolic complications in patients with heterozygous *LMNA* mutations at the 482nd codon, the
53 ‘hotspot’ for partial lipodystrophy, with carriers of other, non-R482 *LMNA* mutations.

54 *Methods and results.* – This study included 29 patients with R482 *LMNA* mutations, 29 carriers of
55 non-R482 *LMNA* mutation and 19 control subjects. Cardiac and metabolic phenotypes were compared
56 between groups. A family history of either cardiac implantable electronic devices (CIEDs; $P < 0.001$)
57 or sudden death ($P < 0.01$) was more frequent in non-R482 than R482 carriers. The non-R482 carriers
58 also had more abnormalities on electrocardiography and received CIEDs more often than R482
59 carriers ($P < 0.001$). On cardiac ultrasound, non-R482 patients had greater frequencies of left atrial
60 enlargement ($P < 0.05$) and lower left ventricular ejection fractions ($P < 0.01$) than R482 carriers. In
61 contrast, R482 carriers had lower BMI ($P < 0.05$), leptin ($P < 0.01$) and fat mass ($P < 0.001$), but
62 higher intra-/total abdominal fat-mass ratios ($P < 0.001$) and prevalences of diabetes ($P < 0.01$) and
63 hypertriglyceridaemia ($P < 0.05$) than non-R482 carriers, with a trend towards more coronary artery
64 disease. However, non-R482 carriers had higher intra-/total abdominal fat-mass ratios ($P < 0.02$) and
65 prevalences of diabetes ($P < 0.001$) and hypertriglyceridaemia ($P < 0.05$) than the controls.

66 *Conclusion.* – Non-R482 carriers present more frequently with arrhythmias than R482 carriers, who
67 twice as often have diabetes, suggesting that follow-up for laminopathies could be adjusted for
68 genotype. Non-R482 mutations require ultra-specialized cardiac follow-up, and coronary artery
69 disease should not be overlooked. Although overlapping phenotypes are found, *LMNA* mutations
70 essentially lead to tissue-specific diseases, favouring genotype-specific pathophysiological
71 mechanisms.

72

73 **Key words:** Coronary artery disease; Laminopathy; Lipodystrophy; *LMNA* gene; Rhythm disorders

74 INTRODUCTION

75 Lamin A/C gene mutations are associated with heterogeneous phenotypes ranging from
76 cardiomyopathies with or without muscular dystrophies to lipodystrophies—collectively referred to as
77 ‘laminopathies’ [1, 2]. The *LMNA* gene encodes A-type lamins (lamins A/C), members of the
78 intermediate filament protein family that are required for nuclear lamina formation. Recent studies
79 have suggested that *LMNA* mutations affect epigenetic regulation of developmental pathways [3–5].
80 Lamin A/C gene mutations have been described over the entire gene. Nevertheless, the rarity of the
81 disease makes phenotype–genotype correlation difficult. Familial partial lipodystrophy type 2
82 (FPLD2) is characterized by progressive fat loss in the extremities at puberty, associated with severe
83 insulin resistance, diabetes and hypertriglyceridaemia with muscle hypertrophy [6, 7]. FPLD2 is
84 related to heterozygous *LMNA* gene mutations, especially those at the ‘hotspot’ codon Arg482 (R482)
85 in exon 8.

86 The severity of *LMNA*-related cardiomyopathies has been demonstrated in several studies showing
87 frequent atrioventricular blocks and ventricular arrhythmias often requiring cardiac implantable
88 electronic devices (CIEDs), as well as severe heart failure, especially in the context of dilated
89 cardiomyopathy [8–23]. Recommendations have already been given concerning the need for
90 implanting defibrillators rather than pacemakers in laminopathies with cardiac involvement [24, 25].
91 However, some of these reports could have been biased by exclusive cardiac recruitment [23]. Indeed,
92 patients with the R482 genotype, whose metabolic phenotype is well described, have rarely been
93 reported to have primary cardiomyopathies, although ischaemic heart disease might be more prevalent
94 [26, 27]. Nevertheless, unlike the cardiovascular phenotype, the metabolic phenotype of cardiac
95 laminopathies remains largely unknown.

96 Thus, the aim of the present study was to compare cardiometabolic complications in patients with
97 *LMNA* mutations at R482, the hotspot for FPLD2, with those in carriers of other *LMNA* mutations.

98

99 PATIENTS and METHODS

100 **Study design**

101 This retrospective longitudinal study was conducted at one university hospital over a 15-year period
102 (from 2000 to 2015). All patients referred to the institution's endocrinology and metabolism
103 department with a diagnosis of laminopathy were included. Patients were classified into two groups
104 according to genotype: (i) those with the heterozygous *LMNA* R482 mutation; or (ii) those with other
105 lamin A/C mutations. The cardiometabolic phenotypes in these two groups were then compared, while
106 the metabolic phenotypes in these two groups were further compared with a control group.

107

108 **Patients**

109 A total of 157 patients were referred because of suspected laminopathy by either endocrinologists who
110 suspected lipodystrophic syndromes, or by cardiologists or geneticists because of unexplained cardiac
111 abnormalities or familial screening. After subjecting these patients to careful clinical and biological
112 examinations, and obtaining their written informed consent, their *LMNA* genes were studied by direct
113 sequencing. Clinical and biological data were collected from patients' medical files. In addition to
114 gender, their age at the time of their first and last cardiometabolic evaluations were recorded for
115 calculation of the average follow-up duration. In addition, 19 healthy subjects matched for age and
116 gender, and recruited from the PHRC-Clin.gov2009-AO-1169-48 trial, served as the control group for
117 metabolic assessment.

118

119 **Cardiac outcomes**

120 The following cardiac parameters were collected from the patients' medical files: (i) family history of
121 CIED or sudden death, considered positive for any patient with at least one first-degree relative with
122 an implanted device or who had died suddenly; (ii) abnormal electrocardiography (ECG), defined as
123 the presence of at least one of the following during follow-up: atrial fibrillation, atrial flutter, high-
124 grade atrioventricular (AV) block, ventricular ectopy, or complete left bundle branch block; (iii)

125 abnormal ECG on Holter monitoring, defined as the presence of non-sustained (NSVT) or sustained
126 ventricular tachycardia (VT), high-grade AV block, or atrial flutter or atrial fibrillation; (iv) use of a
127 CIED, defined as a pacemaker or automatic implantable cardiac defibrillator (ICD) acquired during
128 follow-up (before or after diagnosis of the *LMNA* mutation); (v) CIED interrogation, when ventricular
129 rhythm disorders correspond to the presence of at least one NSVT or VT episode retrieved from stored
130 electrograms during scheduled follow-up visits; (vi) abnormalities on echocardiography, defined by
131 the presence of at least one of the following as per international guidelines for echocardiography
132 measurements: left ventricular ejection fraction (LVEF) < 50%; left atrial enlargement; and/or LV
133 hypertrophy or LV enlargement [28]; patients with non-ischaemic heart disease (cardiomyopathies),
134 defined by LV dilatation and/or altered LVEF, were also noted, and LV diastolic function was
135 assessed by E/A ratio if available; (vii) smoking status, recorded as either currently active or over the
136 past 3 years; (viii) screening for ischaemic heart disease, which included myocardial ischaemia
137 screening with an exercise stress test in five patients with R482 and six patients with non-R482
138 mutations, radionuclide angiography (six R482, one non-R482) or dobutamine stress
139 echocardiography (two R482); and coronary angiography in four patients because of positive non-
140 invasive screening or acute coronary syndrome (two patients); and (ix) screening for atheromatosis by
141 Doppler ultrasound of the carotid and lower-limb arteries.

142

143 **Metabolic outcomes**

144 The following metabolic parameters were also collected from patients' medical records of the last
145 endocrinological evaluation or, for the control group, from the PHRC-Clin.gov2009-AO-1169-48
146 database: (i) body mass index (BMI), assessment of fasting blood glucose (FBG) and triglycerides, as
147 measured by routine techniques, and fasting C-peptide and leptin using radioimmunoassay [RIA-coat
148 C-peptide (Mallinckrodt France SARL, Paris, France), detection limit: 0.2 ng/mL] and Human Leptin
149 RIA kits (EMD Millipore Corporation, Burlington, MA, USA; normal range in normal-weight
150 subjects: women 7.4 ± 3.7 ng/mL, men 3.8 ± 1.8 ng/mL), respectively; (ii) diabetes and glucose

151 intolerance by subjecting participants not already being treated for diabetes at inclusion to a 75-g oral
152 glucose tolerance test (OGTT), which was interpreted according to American Diabetes Association
153 criteria; (iii) hypertension, defined as blood pressure > 140/90 mmHg or use of an antihypertensive
154 drug; (iv) use of lipid-lowering agents (such as statins, fibrates, ezetimib); (v) use of antidiabetic
155 treatments (such as metformin or any other antidiabetic drugs, including glucagon-like peptide-1
156 receptor agonists and insulin); (vi) body fat-mass percentage, as measured by dual-energy X-ray
157 absorptiometry (DXA; Lunar DPX-IQ, GE Healthcare, Chicago, IL, USA); and (vii) ratio of intra-
158 abdominal/total abdominal fat mass, as calculated by measurement of subcutaneous and visceral fat
159 surface areas from 1-cm reconstructed slices of abdominal L4 magnetic resonance imaging (MRI),
160 which is contraindicated in cases of CIED and was therefore only performed in 22 R482 and 12 non-
161 R482 patients.

162

163 **Statistical analysis**

164 Qualitative variables, expressed in absolute numbers and percentages, were compared by chi-squared
165 or Fisher's exact test for values < 5. For quantitative variables, the Shapiro–Wilk test for normality
166 was performed, with results expressed as medians with interquartile ranges (Q25–Q75), and compared
167 using the Mann–Whitney test. Analyses were carried out with GraphPad Prism 6 software (GraphPad
168 Software Inc., La Jolla, CA, USA). Any differences with *P* values < 0.05 were considered significant.

169

170 **RESULTS**

171 **Description of the two groups**

172 In all, 60 patients carried *LMNA* mutations; however, as two were excluded because their
173 medical files were incomplete, 58 patients were ultimately included in this study: 29 patients from
174 eight families carried the heterozygous R482W mutation, and 29 patients from 16 families carried
175 another heterozygous *LMNA* mutation.

176 The gender ratio between the *LMNA* R482 and non-R482 groups did not differ, although the
177 number of women tended to be higher in the R482 group (22 vs 16; $P = 0.09$). There were also no
178 differences between the two groups in terms of age at first evaluation [R482: 43 (24–50.5) years vs
179 non-R482: 39 (28.2–47.5) years; $P = 0.9$] and duration of follow-up [R482: 5 (2–11) years vs non-
180 R482: 4 (1–9) years; $P = 0.42$]. These patients' genotypes and their main phenotypic features are
181 presented in [Table I](#), and their diagnostic circumstances are depicted in [Fig. 1](#). The proportion of
182 diabetes patients in the R482 group increased during the follow-up period from 11 to 24 out of 29
183 patients (from 37.9% to 82.7%), and from 6 to 12 out of 29 patients (from 20.7% to 41.4%) in the non-
184 R482 group, as determined at the last evaluation.

185

186 **Cardiovascular phenotype ([Table II](#), [Fig. 2 A](#))**

187 The frequency of a family history of sudden death ($P < 0.01$) or CIED use ($P < 0.001$) was
188 significantly lower in the R482 vs non-R482 mutation groups, as was the frequency of abnormal ECG
189 ($P < 0.001$). The frequency of abnormal Holter monitoring also differed significantly between the two
190 groups, with a greater frequency of abnormalities, especially NSVT, in the non-R482 mutation group
191 compared with the R482 group ($P < 0.01$).

192 In addition, the frequency of implantable CIEDs was significantly lower in R482 vs non-R482
193 mutation patients ($P < 0.001$). More specifically, the only patient in the R482 group (R482Q mutation)
194 with a CIED, a pacemaker implanted at age 46, died at age 60 after several years of dialysis. In the
195 non-R482 group, there were 16 CIEDs, including eight pacemakers, seven of which were later
196 upgraded to defibrillators when their indication for cardiac laminopathies was standardized [23], and
197 eight defibrillators as first-line devices. The only remaining non-R482 patient with a pacemaker,
198 implanted at age 33, developed end-stage renal disease (ESRD) and died suddenly during dialysis at
199 age 50, just before genetic results were obtained. Seven VT episodes were recorded by CIEDs in seven
200 different non-R482 patients.

201 There was no difference in frequency of cardiac ultrasound abnormalities between the two patient
202 groups ($P = 0.18$). Nevertheless, the frequency of left atrial enlargement was significantly lower in
203 patients with R482 vs non-R482 mutations ($P < 0.05$), and median LVEF was significantly higher in
204 patients with R482 vs non-R482 mutations ($P < 0.01$), but with no difference in LV hypertrophy ($P =$
205 1.00) or LV diastolic diameter ($P = 0.76$). Five patients, all in the non-R482 group, had a cardiac
206 phenotype of non-ischaemic heart disease (Table I). Of the remaining population, 16 (seven R482 and
207 nine non-R482 carriers) had normal systolic function and E/A measurements. In the R482 group, 4/7
208 had impaired relaxation ($E/A < 1$) vs none in the non-R482 group whereas, in the non-R482 group, 3/9
209 had restrictive filling patterns ($E/A > 2$) vs none in the R482 group (Table II). The rate of deaths
210 during the follow-up period was similar in both groups ($P = 1.00$), but was more often related to
211 cardiac causes in the non-R482 group. ESRD related to long-term severely insulin-resistant diabetes
212 worsened the prognosis in two cases.

213 There was no difference in the number of smokers ($P = 0.33$) between the two groups. Also, no patient
214 in the non-R482 group tested positive for cardiac ischaemia or significant coronary stenosis, which
215 contrasted with positive diagnoses in 38% and 14% of patients, respectively, with R482 mutations.
216 However, screening tests for cardiac ischaemia tended to be performed more often ($P = 0.09$) in
217 patients with R482 mutations, who more often had diabetes ($P < 0.01$) than the non-R482 patients.
218 Comparison of peripheral atherosclerotic features showed no differences between the two groups
219 (lower limb: $P = 0.78$; carotid atheromatosis: $P = 0.42$).

220

221 **Metabolic phenotype (Table III, Fig. 2 B, C)**

222 BMI ($P < 0.05$), blood leptin ($P < 0.01$) and high-density lipoprotein (HDL) cholesterol levels ($P <$
223 0.05) and fat-mass percentages ($P < 0.001$) were all significantly lower in patients with R482 vs non-
224 R482 mutations. In contrast, median fasting C-peptide ($P < 0.05$) and glucose (< 0.001) levels, intra-
225 abdominal/total abdominal fat-mass ratio ($P < 0.001$), and frequencies of diabetes or glucose
226 intolerance ($P < 0.01$), metformin treatment ($P < 0.01$) and hypertriglyceridaemia ($P < 0.05$) were all

227 significantly higher in patients with R482 *vs* non-R482 mutations. There were no differences between
228 the two groups in rates of hypertension ($P = 0.11$) or in median triglyceride ($P = 0.15$), total
229 cholesterol ($P = 0.73$) and low-density lipoprotein (LDL) cholesterol ($P = 0.82$) levels, or use of lipid-
230 lowering ($P = 0.10$) or antidiabetic treatments other than metformin ($P = 0.24$), including insulin ($P =$
231 0.14).

232 Comparison of the two *LMNA* mutation groups to an age- and gender-matched healthy control group
233 (Table III) revealed that BMI ($P < 0.02$), intra-/total abdominal fat-mass ratio ($P < 0.05$; [Fig. S1](#); see
234 [supplementary materials associated with this article online](#)), leptin levels ($P < 0.01$), frequency of
235 hypertriglyceridaemia ($P < 0.05$) and diabetes or glucose intolerance ($P < 0.001$) were significantly
236 higher, whereas HDL levels ($P < 0.02$) were significantly lower, in the non-R482 group compared
237 with the controls. Similarly, intra-/total abdominal fat-mass ratio ($P < 0.001$; [Fig. S1](#)) and frequency of
238 hypertriglyceridemia ($P < 0.05$) and diabetes or glucose intolerance ($P < 0.001$) were significantly
239 higher, but HDL level ($P < 0.02$) and fat-mass percentage significantly lower, in the R482 *vs* the
240 control group.

241

242 **DISCUSSION**

243 This large-scale, single-centre, *LMNA* mutation cohort comparing cardiometabolic
244 complications in patients with R482 mutations with carriers of other *LMNA* mutations showed more
245 arrhythmias in the non-R482 than R482 group, which tended to have a greater frequency of coronary
246 artery disease. On the other hand, the rate of diabetes in the non-R482 group was 40%, but twofold
247 higher than that in the R482 group. Each group also showed higher intra-/total abdominal fat-mass
248 ratios, a hallmark of lipodystrophy, than the control group.

249 Recognized only since 1999, laminopathies are rare diseases with multiple phenotypes, some of which
250 overlap [1]. Yet, despite their rarity, nearly 60 patients from 24 families were identified at our centre
251 alone, with a greater number of families with non-R482 than R482 mutations (16 *vs* 8 patients,
252 respectively). As the northern region of France, where our patients were from, has four million
253 inhabitants, the prevalence of patients with *LMNA* mutations and *LMNA*-related FPLD2 in this area is

254 estimated to be 14.5 and 7.25 cases/million people, respectively, which is twice the prevalence
255 reported in a recent study [29]. Moreover, our results do not reflect any founder-effect bias, as 16
256 different mutations were identified in the non-R482 group, two of the eight R482 families were of
257 Portuguese descent, and two of the remaining six families had two different types of mutations
258 (R482W and R482Q). Indeed, laminopathies are most likely underrecognized, given their variable
259 phenotype [1, 2, 7], although the phenotype may perhaps be better recognized in this region, known
260 for its high levels of obesity and diabetes, due to an anticipation phenomenon [30].

261 One limitation of our study is that it was retrospective. All investigations were not performed in every
262 patient, but were adjusted according to clinical situation and guidelines for follow-up of type 2
263 diabetes. For this reason, the number of patients who underwent each investigation has been
264 systematically mentioned. On the other hand, the size of our cohort was relatively large for such a rare
265 disease, and all evaluations were performed at the same centre using the same methods, thereby
266 strengthening all data comparisons.

267 Concerning the cardiac phenotype, there was a marked difference between the R482 and non-R482
268 groups in familial history of CIED use or sudden cardiac death, arguing in favour of a better cardiac
269 prognosis for R482 than for other *LMNA* mutations. This point, which has never been emphasized
270 before, was easy to explore during clinical assessment of the patients' medical histories and was
271 confirmed by cardiac investigations. Indeed, the frequencies of abnormal ECG and left atrial dilatation
272 were significantly lower, and LVEF significantly higher, in patients with R482 *vs* non-R482
273 mutations. The latter patients were also more likely to have CIEDs, and five cases of non-ischaemic
274 heart disease were found in this group. In contrast, patients with R482 mutations tended to have more
275 frequent positive non-invasive tests for ischaemia or documented severe coronary artery disease.
276 However, diastolic function was altered in some patients in both groups, but with different patterns:
277 there was restrictive filling in non-R482 carriers, but impaired relaxation in R482 carriers, a possible
278 consequence of the high incidence of diabetes in the latter. Also, the large number of carriers in the
279 R482 families suggests that the prognosis for the R482W group in terms of mortality may be better.
280 Finally, although gender did not significantly differ, there tended to be more men in the non-R482

281 group, which might reflect a bias, as male gender has been reported to be a risk factor for sudden
282 cardiac death in laminopathies [31]. However, this link was possibly related to the fact that male
283 gender is more often associated with non-R482 mutations, including non-missense mutations, which
284 are also known to be associated with higher risk of severe cardiac disorders [31]. Nevertheless, no
285 definitive conclusions concerning coronary artery disease can be drawn, as there was also a trend for
286 more frequent screening in the R482 group, most likely because those patients more often also had
287 diabetes.

288 From a metabolic perspective, the prevalence of diabetes and hypertriglyceridaemia was higher in
289 R482 than in non-R482 carriers. The R482 carriers also had lower BMIs, and lower levels of leptin
290 and fat mass, but higher MRI-assessed visceral fat levels, than non-R482 carriers, which is in
291 accordance with the lipodystrophic phenotype of R482 carriers. Interestingly, the intra-/total
292 abdominal fat-mass ratio, a hallmark of lipodystrophy [32], was significantly higher in the non-R482
293 vs control group, thereby arguing for a specific lipodystrophy fat distribution even in patients with
294 non-R482 mutations. It is also noteworthy that the frequency of diabetes reached 40% in the non-R482
295 group, but often required OGTT to make the diagnosis. Diabetes is known to promote atherosclerosis
296 and findings *in vitro* favour a direct proatherogenic effect of the *LMNA* R482W mutation in
297 endothelial cells, which is consistent with the trend towards a greater frequency of coronary heart
298 disease in the R482 group [26, 27]. However, the diagnosis of lipodystrophy is easier to make, as the
299 metabolic syndrome (MetS) is more severe in women than in men [33–35]. This gender difference in
300 disease phenotype might be modulating the expression of coronary artery disease, thereby worsening
301 the cardiovascular prognosis for women which, before menopause, is usually considered better than
302 that for men. Also, our results support more systematic screening for MetS, especially by OGTT, in
303 the non-R482 group, and for silent myocardial ischaemia in both groups of mutations, especially in
304 cases with diabetes.

305 Finally, comparisons between R482 and non-R482 carriers have revealed different cardiometabolic
306 phenotypes with different types of risk, a point that has never been emphasized before. Patients with
307 R482 mutations have an FPLD2 phenotype, which may sometimes be associated with other features,

308 such as myopathy [7]. In this group, diabetes is present in 80% of cases, yet the cardiac phenotype
309 seems less severe than in non-R482 cases, and is mostly the result of insulin resistance and
310 atherosclerosis. These findings are concordant with the low frequency of arrhythmia events reported in
311 patients with R482 mutations in the literature in contrast to the non-negligible frequency of coronary
312 artery disease [26, 27]. Indeed, patients with non-R482 mutations often have a severe cardiac
313 phenotype, such as an initial conduction or rhythm disorder with a risk of sudden cardiac death, and
314 diabetes is present in 40% of these patients. Thus, such patients should be screened for ventricular
315 arrhythmias and dilated cardiomyopathy by Holter monitoring and echocardiography, with
316 consideration of electrophysiological studies, CIED use or cardiac transplantation where appropriate.
317 In any case, the presence of ventricular arrhythmias, especially when associated with diabetes or a
318 familial history of CIED use, should prompt *LMNA* genetic testing and subsequent ICD implantation.

319 The reason for the different expressions of the disease in our two patient groups remains unexplained.
320 Limited peripheral adipose tissue storage capacity has recently been emphasized in the pathogenesis of
321 human insulin resistance [36]. Frequent and/or early atherosclerotic complications could be mediated
322 through oxidative stress and mitochondrial dysfunction. Recent studies suggest that *LMNA* mutations
323 affect epigenetic regulation of developmental pathways, and might alter myogenesis and adipogenesis
324 processes in a genotype-specific manner [3–5]. These mechanisms, however, have yet to be explored.

325

326 In conclusion, these results suggest that cardiac follow-up of laminopathies might be adjusted
327 according to genotype, with more aggressive screening for arrhythmias in non-R482 patients. Also, it
328 is important to consider laminopathies as a differential diagnosis when faced with an unexplained
329 rhythm disorder, especially if there is a familial history of CIED use, sudden cardiac death and/or a
330 personal history of diabetes. In addition, coronary artery disease should not be overlooked, especially
331 when diabetes is present.

332

333

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344

345 **Appendix supplementary material**

346 Supplementary material (Fig. S1) associated with this article can be found at
347 <http://www.sciencedirect.com> at doi . . .

348

349

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- 457

458 **FIGURE LEGENDS**

459 Fig. 1. Flow chart of patient recruitment for the study.

460

461 Fig. 2. Main differences between R482 and non-R482 groups in cardiac and metabolic outcomes.

462 CIED: cardiac implantable electronic device; LVEF: left ventricular ejection fraction; BMI: body mass

463 index; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

464

465

466 Fig. S1. Comparison of intra-abdominal/total abdominal fat-mass ratios as measured by magnetic

467 resonance imaging in R482 (dark grey) and non-R482 (light grey) mutation groups, and age- and

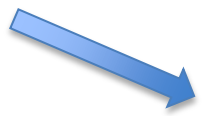
468 gender-matched healthy controls (striped). * $P < 0.02$; *** $P < 0.001$.

Figure 1

Flowchart of patients recruitment

Fig 1

60 *LMNA*-mutated patients



2 patients : lack of data

58 *LMNA*-mutated patients included



29 R482
8 families
7 male / 22 female
Diagnosis circumstances
11/29 diabetes
18/29 genetic inquiry (0/18 diabetes)

29 non-R482
16 families
13 male / 16 female
Diagnosis circumstances
9/29 cardiac disease (3/9 diabetes)
17/29 genetic inquiry (3/17 diabetes)
2/29 myopathy
1/29 lipodystrophy

Figure 2

**Main differences in cardiac and metabolic outcomes
between R482 (dark) and non-R482 (light) groups**

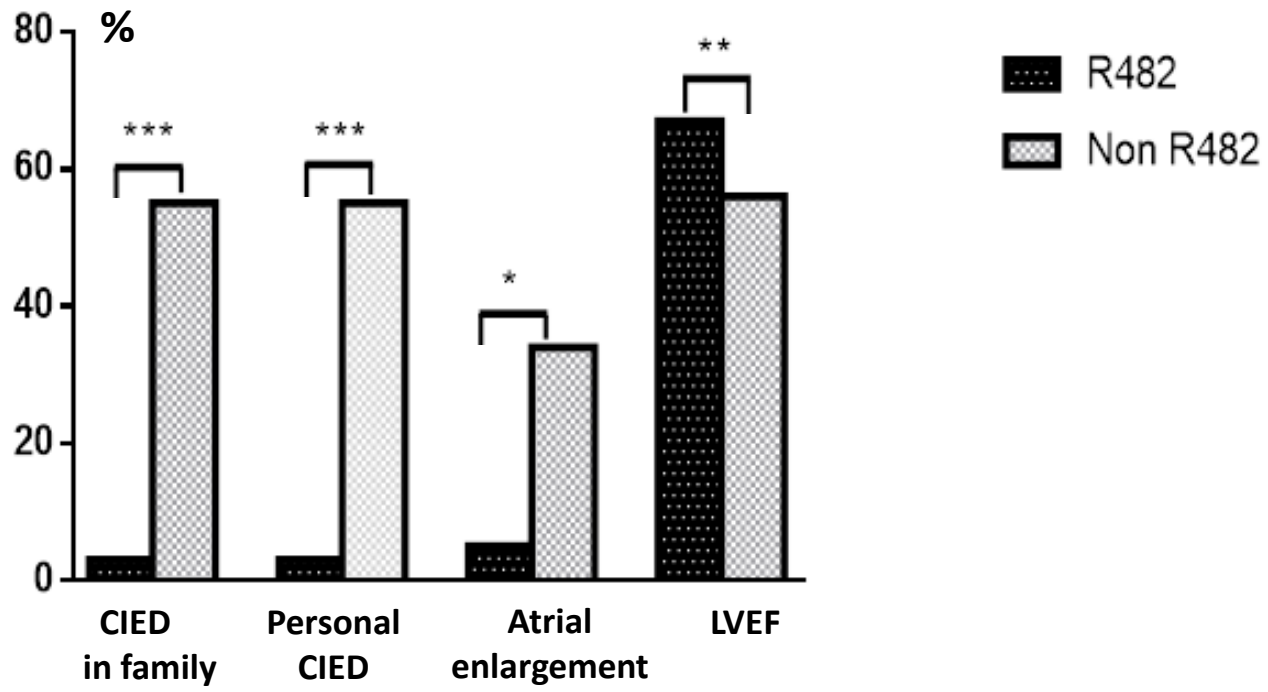
CIED: Cardiac implantable electronic device

LVEF : Left ventricular ejection fraction

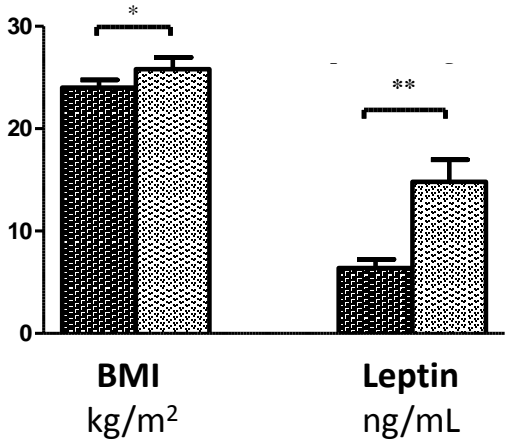
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Fig 2

A



B



C

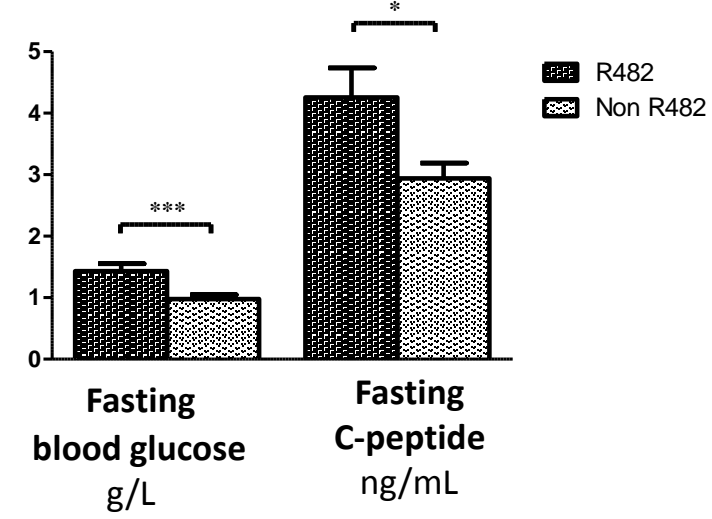


Table I

Main characteristics of the R482 and non-R482 mutation groups

	Families (n)	Patients (n)	ITG or diabetes (n)	Personal CIED use (n)	Specific features (n)	Variant dbSNP ID or reference
R482 group	8	29	24	1	29 FPLD	
c.1444C>T p.(Arg482Trp)	6	23	19	0	1 severe myopathy	rs57920071
c.1445G>A p.(Arg482Gln)	2	6	5	1		rs11575937
Non-R482 group	16	29	12	16		
c.139G>T p.(Asp47Tyr)		1	1	1	1 CGL + progeria	[1, 2]
c.310C>G p.(Leu104Val)		1	0	1	1 FPLD	NPR
c.398G>T p.(Arg133Leu)		2	1	1	2 CGL + progeria	rs60864230
c.448A>G p.(Thr150Ala)		4	2	2	1 NIHD	rs58917027
c.467G>A p.(Arg156His)		1	0	0	1 FPLD	rs764475194
c.481G>A p.(Glu161Lys)		4	0	1	1 NIHD	rs28933093
c.694G>C p.(Gly232Arg)		1	1	0	1 CGL + myopathy	rs267607609

c.751C>T p.(Gln251*)	1	0	1	1 NIHD	NPR
c.860del p.(Ala287Valfs*193)	1	1	1	1 FPLD	NPR
c.949G>A (p.Glu317Lys)	3	1	2	1 NIHD	rs56816490
c.1157G>C p.(Arg386Thr)	2	1	1	1 FPLD	rs267607545
c.1173dup p.(Ser392Glnfs*34)	3	1	3	1 NIHD	NPR
c.1238del p.(Gly413Alafs*67)	1	1	1	1 FPLD + myopathy	NPR
c.1315C>T p.(Arg439Cys)	1	0	0	FPLD	rs62636506
c.1357C>T p.(Arg453Trp)	1	1	1	Severe myopathy	rs58932704
c.1930C>T p.(Arg644Cys)	2	1	0	1 FPLD	rs142000963

[1] Caron et al., Cell Death Differ, 2007; 14 (10): 1759–67; [2] Todorovic et al., Horm Res 2012; 78 (Suppl 1), p. 164.

ITG: glucose intolerance; CIED: cardiac implantable electronic device; dbSNP ID: Single Nucleotide Polymorphism Database identification number; CGL: congenital generalized lipodystrophy; FPLD: familial partial lipodystrophy; NPR: never previously reported; NIHD: non-ischaemic heart disease

Table II

Cardiac phenotype: comparison of R482 and non-R482 mutation groups

	R482 (N = 29)	Non-R482 (N = 29)	P
ARRHYTHMIA DISORDERS			
Familial history of sudden cardiac death, n/N (%)	3/29 (10.3%)	13/29 (44.8%)	< 0.01
Familial history of CIED, n/N (%)	1/29 (3.4%)	16/29 (55.2%)	< 0.001
Abnormal ECG n ¹ /N (%)	2/29 (6.9%)	15/29 (51.7%)	< 0.001
Abnormal Holter ECG, n/n ¹ (%)	0/16 (0%)	9/26 (35.6%)	< 0.01
CIED, n/N (%)	1/29 (3.4%)	16/29 (55.2%)	< 0.001
Type of CIED	1 PM	1 PM, 15 Defib	
VT episodes	0 recorded	7/16	
Abnormal/performed echocardiography, n/n ² (%)	3/19 (15.8%)	10/26 (38.5%)	0.18
Atrial enlargement, n/n ² (%)	1/19 (5.3%)	9/26 (34.6%)	< 0.05
LV ejection fraction, median (%) [IQR]	67.5 [61.2–70]	56.5 [45–62.7]	< 0.01
LV hypertrophy, n/n ² (%)	2/19 (10.5%)	2/26 (7.7%)	1
LV diastolic diameter, median (mm) [IQR]	50 [43–54]	51 [44–54]	0.76
Number of E/A < 1/N E/A measured	4/7 (57%)	0/9 (0%)	–
Number of E/A > 2/N E/A measured	0/7 (0%)	3/9 (33%)	–
CARDIAC ISCHAEMIC DISORDERS			
Smokers, n/N (%)	4/29 (13.8%)	8/29 (27.6%)	0.33
Screening test for myocardial ischaemia, n ³ /N (%)	13/29 (45%)	7/29 (24%)	0.09
Abnormal test, n/n ³ (%)	5/13 (38%)	0/7 (0%)	0.11
Coronarography, n ⁴ /N (%)	4/29 (14%)	2/29 (7%)	0.67
Significant coronary stenosis, n/n ⁴	4/4 (2 ACS)	0/2	0.06
Angioplasty/stenting, n/N (%)	2/29 (7%)	0/29 (0%)	0.46
Death during follow-up, n/N (%)	3/29 (10.3%)	3/29 (10.3%)	1
	1 Parkinson's disease	2 cardiac failure	
	1 myopathy	1 dialysis + PM	
	1 dialysis + PM		
PERIPHERAL ATHEROMATOSIS			
Lower-limb vascular Doppler US, n ⁵ /N (%)	15/29 (52%)	11/29 (38%)	0.29

Atheromatosis, n/n ⁵ (%)	6/15 (40%)	5/11 (45%)	0.78
Carotid Doppler US, n ⁶ /N (%)	15/29 (52%)	11/ 29 (38%)	0.29
Atheromatosis, n/n ⁶ (%)	4/15 (26.6%)	5/11 (45%)	0.42

n: number of cases; N: number of investigated patients; ^{1,2,3,4,5,6} refer to the number of cases performed in each category

CIED: cardiac implantable electronic device; ECG: electrocardiography; PM: pacemaker; Defib: defibrillator; VT: ventricular tachycardia; LV: left ventricular; IQR: interquartile range (Q25–Q75); ACS: acute coronary syndrome; US: ultrasound

1 **Table III**

2 Metabolic phenotype: R482 and non-R482 mutation groups compared with age- and gender-matched healthy controls

	R482 (N = 29)	Non-R482 (N = 29)	P (R482 vs non-R482)	Controls (N = 19)	P (controls vs R482 and/or non-R482)
Body mass index, kg/m ²	24 [22–27]	27 [22–29]	< 0.05	22 [21–24]	< 0.02 vs non-R482
Diabetes or glucose intolerance, n/N (%)	24/29 (82.7%)	12/29 (41.4%)	< 0.01	0/19 (0%)	0.001 vs R482 and non-R482
Hypertension, n/N (%)	17/29 (58.6%)	11/29 (37.9%)	0.11	0/19 (0%)	–
HDL cholesterol, mg/dL	0.4 [0.3–0.4]	0.48 [0.4–0.5]	< 0.05	0.63 [0.45–0.74]	< 0.02 vs R482 and non-R482
Triglyceride > 150 mg/dL, n/N (%)	16/29 (55.2%)	8/29 (27.6%)	< 0.05	0/19	< 0.05 vs R482 and non-R482
Metformin, n/N (%)	17/29 (58.6%)	7/29 (24%)	< 0.01	0/19 (0%)	–
Lipid-lowering treatment, n/N (%)	14/29 (48.3%)	8/29 (27.6%)	0.10	0/19 (0%)	–
Fat mass, %	20 [17.7–22.8]	29.7 [18.7–38.1]	< 0.001	22 [20–30]	< 0.01 vs R482, 0.07 vs non-R482
Intra-/total abdominal fat-mass ratio	0.59 [0.47–0.67]	0.36 [0.22–0.45]	< 0.001	0.20 [0.11–0.30]	< 0.001 vs R482, < 0.02 vs non-R482
Leptin, ng/mL	5.2 [2.8–8.0]	15.9 [5.2–22.3]	< 0.01	4.6 [4.1–10.7]	< 0.01 vs non-R482

3 Data are expressed as medians [Q25–Q75] unless otherwise indicated

4 HDL: high-density lipoprotein