Metabolic and cardiac phenotype characterization in 37 atypical Dunnigan patients with nonfarnesylated mutated prelamin A

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Background Laminopathies are associated with a broad spectrum of clinical manifestations, from lipodystrophy to cardiac diseases. The purpose of this study was to assess genotype-phenotype correlations in a lipodystrophic laminopathy caused by the *Lamin A (LMNA)* mutation T655fsX49. This mutation leads to synthesis of nonfarnesylated-mutated prelamin A that does not undergo the physiologic lamin A maturation process.

Methods and results We studied 35 patients originating from Reunion Island who carried the *LMNA* T655fsX49 mutation. Comparisons of cardiac and endocrinologic features were made between homozygous and heterozygous patients. Homozygous patients presented more overlapping syndromes with severe cardiac phenotypes, defined by cardiolaminopathy, early atheroma with coronary heart disease (CHD) and high-degree conduction disorder compared with heterozygous (40% vs 4%; $P = .016$). Moreover, homozygous patients had earlier onset (49.6 vs 66 years old; $P = .0002$). Left ventricle lowered ejection fraction associated with heart failure was more frequent in homozygous than in heterozygous patients (40% vs 0%, respectively). Lipodystrophic traits were more marked in the homozygous group but only reached statistical significance for L4 subcutaneous fat measurement (2.8 ± 2.16 vs 18.7 ± 8.9 mm; $P = .008$) and leptin levels (2.45 ± 1.6 vs 11.26 ± 7.2 ng/mL; $P = .0001$).

Conclusions Our results suggest that there is a relationship between mutated prelamin-A accumulation and the severity of the phenotypes in homozygous familial partial lipodystrophy type 2 patients who harbor the *LMNA* T655fsX49 mutation. A dose-dependent effect seems likely. (Am Heart J 2015;169:587-93.)

Background

Dunnigan syndrome, also known as familial partial lipodystrophy type 2 (FPLD2), is a rare disease with an estimated prevalence of 1 in 200,000 people.[1] Patients usually have a normal phenotype in childhood and may secondarily and inconstantly develop fat loss in the extremities and trunk associated with an excess of subcutaneous fat in the chin, supraclavicular area and face; as well as muscular hypertrophy.[2] The mutations responsible for this autosomal dominant syndrome are located in the gene coding for lamin A/C (*LMNA*) on chromosome 1q21-22 and are part of the family of laminopathies (Online Mendelian Inheritance in Man 151660). Endocrinologic manifestations include metabolic syndrome[3] with insulin resistance, diabetes mellitus, liver steatosis, acanthosis nigricans, ovarian hyperandrogenism, and dyslipidemia. The ubiquitous expression of *LMNA* also underlies the broad spectrum of lamin-related diseases, such as skeletal myopathies;[4] cardiomyopathy; and the premature aging syndrome, Hutchinson-Gilford progeria. Charcot-Marie-Tooth disease type 2B1, restrictive dermopathy, and mandibuloacral dysplasia are also caused by lamin A/C mutations.[5] Multiple overlapping syndromes caused by the presence of different phenotypes in the same individual were described in a previously published meta-analysis.[6]

Cardiac involvement in laminopathy may be caused by premature atherosclerosis in the setting of metabolic syndrome or independent of cardiovascular risk factors. Cardiolaminopathy may combine cardiac conduction disorders, atrial fibrillation,[7] and dilated cardiomyopathy.[8,9]

Mortality is often due to sudden cardiac death[10] with ventricular arrhythmias or terminal heart failure.[11] Incomplete penetrance, especially in younger individuals,

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often makes diagnosis challenging in the absence of familial screening. Cardiovascular complications develop progressively with age.[8]The phenotype may be related to the position of the *LMNA* mutation relative to the nuclear localization signal sequence. It has been suggested that cardiac phenotypes correspond to mutations close to the N terminus, thus explaining their association with skeletal myopathy.[12]

Mutations associated with FPLD2 are mostly in exon 8 near the C-terminal end, and they are rarely present in cardiac manifestations. Dunnigan syndrome is not rare on Reunion Island (≥41 cases in 850,000 inhabitants), and it is mostly caused by the same *LMNA* mutation, T655fsX49 (37 cases), present as either a heterozygous or homozygous mutation. In the 3 other patients, Dunnigan syndrome was caused by a heterozygous mutation, R482W.[13,14] This syndrome may be under diagnosed because it is difficult to recognize, and the disease is generally not well known.

Homozygous mutations in patients with Dunnigan syndrome are rare and have mostly been described once in populations like ours with strong endogamy.[15] The phenotype is usually more severe than that observed in patients with Dunnigan syndrome associated with a heterozygous mutation.

In a previous study, we demonstrated that, in homozygous fibroblasts, there is increased oxidative stress, a more senescent aspect, and more prelamin-A accumulation than in heterozygous fibroblasts.[16] However, the cardiac and endocrinologic phenotypic heterogeneity among homozygous and heterozygous subjects for the same mutation of FPLD2 has not been studied in its entirety. To assess the role of genotype in patients with FPLD2 and its phenotypic correlations, such as endocrinologic and cardiac manifestations, we compared homozygous versus heterozygous subjects.

Methods

Patient population

We retrospectively analyzed a database of 37 patients who carry the Reunion Island (Indian Ocean, France) mutation of lamin A/C (*LMNA*) (*LMNA* p. T655fsX49) in exon 11 as previously described by Le Dour et al.[16] Data were collected between January and December 2009 by the Groupe Hospitalier Sud Reunion (Reunion Island, France). The patients were either probands or relatives detected by familial screening as being either homozygous or heterozygous. All of them harbored the same mutation, confirmed by 2 different genetic analyses. All patients provided their written informed consent for genotyping. Since the previous publication of Wiltshire et al,[15] we have collected many new cases (4 homozygous and 17 heterozygous) diagnosed by their clinical presentation or because they were from families known to carry the mutation.

Endocrinologic evaluation

Clinical examination of probands and relatives was carried out by a senior endocrinologist, who evaluated specific signs of FPLD2 (muscular dystrophy) as shown in Figure 1.

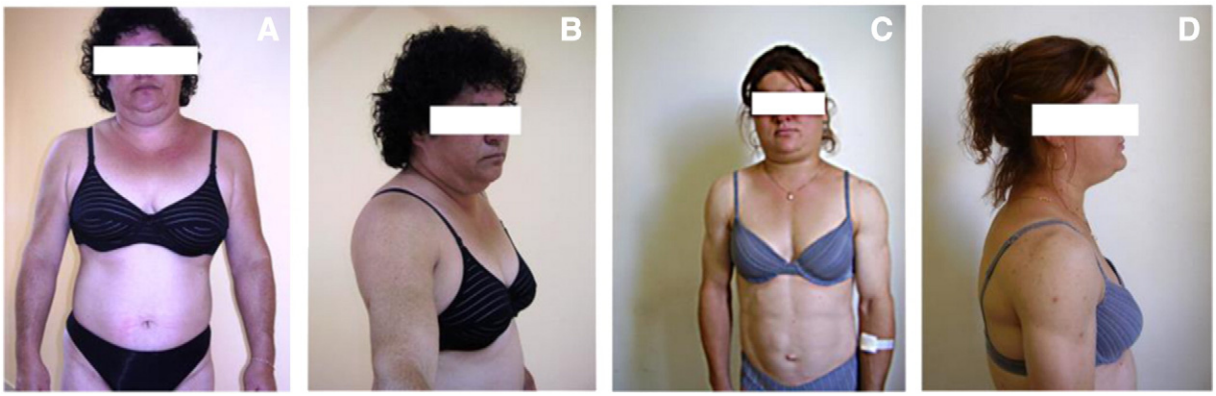
Anthropometric measurements such as skinfolds were measured with a Harpenden calliper and the mean of arm, forearm, and calf skinfolds. The presence of thyroid goiter due to a reported high prevalence in patients with *LMNA* mutations was also investigated.[17]In cases of diabetes mellitus, microangiopathy (retinopathy, nephropathy, and neuropathy) was assessed. Acanthosis nigricans, the homeostasis model assessment, and total insulin dosages were used to evaluate insulin resistance. Metabolic investigations were performed after a 12-hour fasting period; glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, C peptide, and insulinemia were measured with a Cobas Roche analyzer, and glycated hemoglobin level was measured with a Tosoh G8 automated glycol-hemoglobin level analyzer. Adiponectin and leptin levels were determined by enzyme-linked immunosorbent assay (Quantikine; R&D Systems, Oxford, United Kingdom). Liver steatosis was identified with abdominal ultrasound. Measurements of subcutaneous adipose tissue were done via an abdominal computed tomographic scan (L4 level).

Cardiovascular evaluation

A cardiologist performed systematic clinical examinations of the patients. Investigations included 12-lead electrocardiography (ECG) and, except for 1 patient, transthoracic echocardiography. Fifteen patients also underwent 24-hour Holter monitoring. Significant cardiac manifestations in the subset of cardiolaminopathy included ≥1 of the following findings: (*a*) cardiomyopathy defined by hypokinetic cardiopathy or ischemic cardiomyopathy (ICM), (*b*) conduction disorder atrioventricular block (AVB) and any bundle branch block, and (*c*) supraventricular or ventricular arrhythmias. Two-dimensional transthoracic echocardiography was performed to measure left ventricular ejection fraction (LVEF), which was considered altered if values were <45%. *Atrioventricular block* was defined as first (PR interval >0.20 seconds), second, or third degree. *Coronary heart disease* (*CHD*) was defined by angina, previous myocardial infarct, coronary stenting, or angioplasty.

Dyslipidemia was defined in untreated patients as plasma triglyceride >1.72 mmol/L and/or HDL cholesterol <1.30 mmol/L or the use of hypolipidemic drugs. The following definitions were used for atheromatous lesion classification: CHD with coronary stenosis >50% and carotid stenosis >40% according to NASCET classification. Lower extremity peripheral artery disease was present if there were symptoms of stage 2 Fontaine classification or higher. History of transient ischemic attack or ischemic stroke was recorded. Other cardiologic data were retrieved from medical records, such as active smoking,

Figure 1



Typical clinical aspects of Dunnigan syndrome: Loss of subcutaneous fat from the 4 limbs in contrast with accumulation of cervico facial adipose tissue with a pseudo-cushingoid aspect. Heterozygous subjects (face and profile views [**A** and **B**]) harbor less marked lipodystrophic and muscular hypertrophic features than homozygotes (**C** and **D**).

implantable devices, results of exercise testing or stress echography, 24-hour Holter ECGs when performed, and the presence or absence of supraventricular or ventricular arrhythmias. Nonsustained ventricular tachycardia (NSVT), recorded by24-hour Holter monitoring or implantable cardioverter-defibrillator (ICD) memory, was defined as ≥3 consecutive ventricular beats with a rate of 120 beat/min and a duration of <30 seconds.

Mutation screening

Genomic DNA was obtained from peripheral white blood cells. *LMNA* exons 1 to 12 and the surrounding intronic sequences were amplified by polymerase chain reaction with primers and conditions as previously described by Vigouroux et al.[18]After purification on Qiagen columns, the polymerase chain reaction products were directly sequenced using the ABI Dye terminator mix.

Statistical analysis

Student *t* test was carried out for all quantitative variables because of the small number of subjects. Results are expressed as adjusted means ± SD. Fisher exact test was performed to compare the 2 groups with regard to all qualitative traits (eg, gender and cardiac disease). Because of multiple analyses, a lower *P* value of <.02 was considered statistically significant. Analyses were performed with Stata software, version 11.

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Results

Population characteristics

There were 9 families, which included 25 patients and 12 other patients with no pedigrees available. Among the 37 patients, 12 harbored a homozygous *LMNA* mutation, and 25 were heterozygous. All of the homozygous individuals except for 1 (a 19-year-old man detected by familial screening) had typical lipodystrophic traits. Of 25 patients, 7 patients with heterozygous mutations had no clinical features of FPLD2. None of our patients exhibited progeroid or neuromuscular manifestations, except for muscular hypertrophy. Serum creatine phosphokinase levels were normal in all patients. Because of missing data, 2 patients among those with homozygous mutations could not be included.

In a previous article that investigated 7 homozygous patients who were included in the present report, genealogical investigations revealed that all probands were issued from consanguineous families that shared a common ancestor who arrived at Reunion Island in the 17th century.[16]The mean age was 45 ± 15 years for the heterozygous group versus 43 ± 12 years in the homozygous group (*P* = .7).Only 3 men were included in the study (8%).

Homozygous subjects had more severe cardiologic disease

There were no significant differences between homozygous and heterozygous patients with regard to cardiovascular risk factors such as atheromatous sites, the presence of atrial fibrillation, and QTc interval length. Of 35 patients (29%), 10 had cardiac involvement. The homozygous group had a greater proportion of cardiac manifestations (70% vs 12% in the heterozygous group; *P* = .0015), which occurred at a mean younger age (49.6 vs 66 years for homozygous and heterozygous participants, respectively; *P* = .0002). The proportion of conduction disorders was similar between the homozygous and heterozygous groups for first-degree AVB (1/10 vs 2/25 homozygous vs heterozygous patients,

respectively). However, second-degree or greater AVB was more frequent and severe in the homozygous versus heterozygous group (3/10 vs 1/25 patients, respectively). Left bundle branch block (complete or incomplete) was also more frequent in the homozygous group (50% homozygous vs 4% heterozygous). Of 10 patients, 4 had an ICD in the homozygous group compared with none in the heterozygous group ($P = .004$). In the homozygous group, 2 patients had ventricular arrhythmias; one of them had NSVT and the other had sustained VT.

One homozygous patient with Dilated Cardiomyopathy (DCM) and 25% LVEF died of heart failure due to ventricular arrhythmia at the age of 39 years while waiting for ICD implantation. Another woman died at the age of 42 years from acute respiratory distress secondary to acute pulmonary edema, probably caused by ventricular arrhythmia. There was 1 ICM in the heterozygous group, which developed when the patient was 66 years old, versus 2 in the homozygous group (3 if DCM with significant atheromatous lesions was included) and 2 DCM with premature death in the homozygous group. None of our patients underwent cardiac transplantation. Detailed cardiologic descriptions of each patient are presented in Table I.

Homozygous patients had more marked lipodystrophic features

Lipodystrophy and muscular hypertrophy were present in the 2 groups. The mean skinfold measurements did not differ significantly between the groups (3.7 ± 0.28 vs 6.4 ± 3.5 mm for homozygous and heterozygous groups, respectively). There was almost complete phenotypic penetrance in the homozygous group (90%; including a 19-year-old man, vs 80% in the heterozygous group). Subclinical lipodystrophy was more common in the homozygous group (L4 subcutaneous anterior fat tomodensitometry measurement: 2.8 ± 2.16 vs 18.07 ± 8.9 mm in homozygous and heterozygous groups, respectively; $P = .008$).

Serum leptin was significantly lower in the homozygous group (3.97 ± 0.64 vs11.52 ± 6.92 mg/L for homozygous and heterozygous groups, respectively; $P = .0009$). Global fat loss was confirmed by body mass index (BMI) measurements, which were 19.8 in the homozygous group versus 25.1 in the heterozygous group ($P < .0001$). Total fat was 16.1% versus 31.2%in homozygous and heterozygous groups, respectively ($P = .0016$).

In the 25 patients who were analyzed, serum adiponectin was equally lowered in homozygous (3.66 μg/mL) and heterozygous (3.65 μg/mL) patients. Hypertriglyceridemia was more frequent in homozygous subjects (75% vs 52%; $P = .06$) with higher levels (5.23 ± 6.77 vs 1.76 ± 0.9 mmol/L for homozygous and heterozygous groups, respectively; $P < .04$), which was associated with a higher presence of hepatic steatosis (40% vs 12%; $P = .15$), although these results did not reach the level of statistical significance. Low levels of HDL occurred frequently in both groups, but there was no statistically significant difference between the 2 groups in this regard (64% vs 66% for homozygous and heterozygous groups, respectively). The prevalence of diabetes was not significantly different between the 2 groups (70% for homozygous vs 44% for heterozygous patients; $P = .26$) with an increased insulin resistance measured by homeostasis model assessment index (6.13 ± 3.76 in homozygous vs 5.7 ± 4.46 in heterozygous; not significant). The presence of microangiopathy, independent of its site, also did not differ between the 2 groups (40% for homozygous vs 16% for heterozygous patients; $P = .18$). Thyroid goiter was increased in both groups with no significant differences (33% in the homozygous group vs 8% in the heterozygous; $P = .12$).

Detailed endocrinologic data are available, as supplementary material Table II contains comparisons of the cardiologic and endocrinologic features of the homozygous and heterozygous individuals in the study (Figure 2).

Discussion

This study demonstrated that patients who are homozygous for lamin mutations have more severe cardiologic disease and more pronounced lipodystrophy compared with heterozygous patients. We also found that leptin levels, BMI, and L4 adipose measurements were the only endocrinologic variables that differed significantly between heterozygous and homozygous individuals. This suggests a more severe but still subclinical lipoatrophy within the homozygous population.

To our knowledge, this is the largest described cohort of patients with FPLD2 who harbors the same mutation, with several homozygous subjects, and it is the first clinical comparison between homozygous and heterozygous patients with FPLD2. Because they reside on an island, the population has low admixture rates, and because of its genetic homogeneity, the population is likely to be free from population stratification, which is usually a critical source of confusion in such studies.

Cardiac manifestations were more severe in the homozygous group. These manifestations were also more frequent and had an earlier onset compared with the heterozygous group. Complete or incomplete left bundle branch block appeared to be a reliable marker of underlying cardiomyopathy. There also were 2 sudden cardiac deaths. Compared with other laminopathies, the rate of AVB (20%) and atrial fibrillation (5%) was lower than described in previously published series of patients with cardiolaminopathies[8] or Emery-Dreifuss muscular dystrophy,[19] which reported 25% and 43% of patients, respectively, with atrial fibrillation and 85% and 72% of patients, respectively, with AVB. Taken together, these findings suggest that the less frequent cardiac involvement observed in our study could be explained by the

Table I. Detailed cardiologic characteristics

Patients	Sex	Age	Cardiovascular risk factor	Atherom	Cardiac conduction abnormalities	Arrhythmias	LVEF, <45%	Main clinical end points
Heterozygous LMNA p.T655fsX49 subjects								
IX 2	F	50	HBP, DL, AS	IS	–	–	–	IS hemiplegia
I2	F	27	–	–	–	–	–	No cardiac symptoms
I3	M	32	AS	–	–	–	–	No cardiac symptoms
II 3	F	38	DL, DM	–	–	–	–	No cardiac symptoms
I4	F	20	–	–	–	–	–	No cardiac symptoms
I5	F	49	DL	–	–	–	–	No cardiac symptoms
III 2	M	66	DL, DM	–	AVB2	AF	–	AVB2, AF normal coronarography and EPS Cordarone-induced hyperthyroidia
VIII 2	F	27	–	–	–	–	–	No cardiac symptoms
–	F	66	HBP, DL, DM	CHD, CA, LL	AVB1, LBBBc	–	–	ICM, LAD stent
IV 5	F	43	–	–	–	–	–	No cardiac symptoms
VI 2	F	42	DL, DM, AS	–	–	–	–	No cardiac symptoms
IV 2	F	39	DL	–	–	–	–	No cardiac symptoms
V 3	F	44	HBP, DL	–	–	AVNRT	–	AVNRT
III 1	F	22	–	–	–	–	–	No cardiac symptoms
II 2	F	43	HBP, DM	–	–	–	–	No cardiac symptoms
–	F	64	HBP, DL, DM	–	–	–	md	No cardiac symptoms
V 1	F	63	HBP, DL, DM	CA	–	–	–	TIA, no other cardiac symptoms
V 2	F	68	HBP, DM	CA	AVB1	–	–	AVB1
–	F	30	–	–	–	–	–	No cardiac symptoms
II 1	F	70	HBP, DL, DM	CA, LL	–	–	–	No cardiac symptoms normal stress echocardiography and scintigraphy
–	F	37	DL	–	–	–	–	No cardiac symptoms
–	F	52	HBP, DL, DM	–	–	–	–	No cardiac symptoms negative EPS
–	F	52	HBP, DL, DM	–	–	–	–	No cardiac symptoms
VI 1	F	47	–	–	–	–	–	No cardiac symptoms
IV 6	F	26	HBP	–	–	–	–	No cardiac symptoms
Homozygous *LMNA* p.T655fsX49 subjects								
VII 2	F	47	HBP, DL	–	AVB1, LBBBc	–	–	AVB1
VII 1	F	42	HBP, DL, DM	CA	LBBBi	VT	+	LMNAC LVEF 30% nonatheromatous coronary arteries, death by acute pulmonary edema or ventricular arrhythmia
IV 1	F	39	DL, DM	–	LBBBi	VT	+	LMNAC LVEF 25% no coronarian atherom death by ventricular arrhythmia before ICD implantation
IV 4	F	25	–	–	–	–	–	No cardiac symptoms
IX 1	F	54	HBP, DL, DM	–	AVB2	NSVT	–	AVB2, NSVT, ICD
–	F	56	HBP, DL, DM	CA, CHD, LL	AVB3, LBBBi	–	+	AVB3, LMNAC + anterior ICM 3 vessel lesions, 2 stents LVEF 30%, ICD
I 1	F	52	HBP, DL, DM	CHD, LL	AVB2, LBBBi	AF, SVT	–	AVB2, permanent AF, ICM circumflex stent sustained VT LVEF 50%, ICD
–	F	34	DL, DM	–	–	–	–	No cardiac symptoms
VIII 1	F	55	HBP, DL, DM	CA, CHD, LL, IS	AVB3	–	+	Multiple ischemic stroke, inferior ICM left leg amputation, ICD
IV 3	M	19	AS	–	–	–	–	No cardiac symptoms

Abbreviations: *F*, female; *HBP*, high blood pressure; *DL*, dyslipidemia; *AS*, active smoking; *IS*, ischemic stroke; *M*, male; *DM*, diabetes mellitus; *AVB2*, second-degree AVB; *AF*, atrial fibrillation; *EPS*, electrophysiologic study; *AVNRT*, Atrioventricular Nodal Reentrant Tachycardia; SVT, Supraventricular Tachycardia; *CA*, carotidian; *LL*, lower limbs; *AVB1*, first-degree AVB; *LBBBc*, complete left bundle branch block; *LAD*, left anterior descending coronary artery; *md*, missing data; *TIA*, transient ischemic attack; *LBBBi*, incomplete left bundle branch block; *VT*, ventricular tachycardia; *+*, presence; *LMNAC*, LMNA cardiolaminopathy; *AVB3*, third-degree AVB; *–*, absence; cardiovascular risk factors: atherom localization: cardiac conduction abnormality: arrhythmias.

type of lamin mutation and its position in relation to the nuclear localization signal sequence.[12]

In our study, only homozygous patients had an overlapping syndrome with cardiac involvement. This finding suggests a dose-dependence mechanism, with prelamin-A accumulation. This mutation, which was described and documented by Le Dour et al,[16] causes a frame shift in *LMNA* that yields an aberrant sequence of 48

Table II. Comparison of cardiologic and endocrinologic characteristics between homozygous and heterozygous subjects

Charateristics	Homozygous, n = 10	Heterozygous, n = 25	*P*
Mean age (y)	45 ± 15	43 ± 12	0.7
Age of cardiac manifestations onset (y)	49.3	66.7	0.002
Cardiolaminopathy manifestations (%)	70	12	0.0015
AVB or bundle branch block (%)	70 (7/10)	12 (3/25)	0.0016
ICD implantation	4/10	0/25	0.004
Impaired LVEF, <45%	4/10	0/25	0.004
Supraventricular and ventricular arrythmias	4/10	1/25	0.016
Endocrinologic charateristics			
BMI	19.8	25.1	<0.0001
Total fat (%)	16.1	31.2	0.0016
Serum leptin (ng/mL)	2.45 ± 1.6	11.26 ± 7.2	0.0001
L4 Tomodensitometry fat measurement (mm)	2.8 ± 2.16	18.77 ± 8.9	0.008
High blood pressure	6/10	11/25	0.47
Dyslipidemia	8/10	14/25	0.26
Presence of diabetes	70% (7/10)	44% (11/25)	0.26
Microangiopathy (unifocal or plurifocal)	40% (4/10)	16% (4/25)	0.18
Atherom location (monofocal or plurifocal)	4/10	5/25	0.39
Hepatic steatosis	40% (4/10)	12% (3/25)	0.15
Thyroid goiter	3/10	2/25	0.12

amino acids in the prelamin-A C terminus, thus abolishing the farnesylation site that is required for protein maturation. As a result, there is accumulation of a nonfarnesylated form of unprocessed prelamin A, which causes toxicity by affecting the nuclear pore complexes, in either the presence or absence of mature lamin A. These findings were documented by Le Dour et al[16] in fibroblast culture, by mass spectrometry, analysis of the morphology of fibroblast nuclei, and immunofluorescence microscopy. In patients who are homozygous for the p.T665fsX49 *LMNA* mutation, there was exclusive expression of nonfarnesylated prelamin A and an absence of mature lamin A. Heterozygous p.T655fsX49 LMNA-mutated fibroblasts expressed both mature lamin A and mutated prelamin A. There was no lamin B deficiency in either group.

Premature atherosclerosis[20] with an endothelial dysfunction mechanism[21] is known to be associated with FPLD2. In a study that investigated the fibroblasts of our patients,[16] oxidative stress was increased by a mean of 1.7-fold in the homozygous group compared with controls without the mutation. This may explain the higher prevalence of ICM in the homozygous group that would have been caused by the laminopathy itself and not only by first-world diet and lifestyle, but the hypothesis remains to be proved.

To assess the prevalence of laminopathies in metabolic syndrome, nuclear shape abnormalities were investigated in a previous study of patients with metabolic syndrome.[22] Of 100 patients, 2 patients with a heterozygous *LMNA* mutation and nuclear shape abnormality were found to have reduced lamin A/C expression, no prelamin-A accumulation, and no clinical manifestations of laminopathy. The same features were present in many of our heterozygous patients. In the same study,[22] 1 patient harbored a ZMPSTE24 heterozygous missense mutation that caused an accumulation of prelamin A in fibroblast cells, similar to our homozygous subjects, with a phenotype of DCM without clinical lipodystrophy. Thus, prelamin-A accumulation does not appear to be the sole determinant of the phenotype. Other mechanisms are likely to be involved that will explain organ selectivity.

Clinical implications

Because lipodystrophic features are not always present, particularly in heterozygous patients due to age-related penetrance, genetic testing is crucial for the detection of the disease, and familial screening is essential. Testing could be performed in patients with lipodystrophic features (either associated with metabolic syndrome or not) and cardiac manifestations because prevalence in general population might be underestimated.

Echocardiography ECGs, Holter monitoring, exercise testing, and coronarography if necessary, should be conducted on a regular basis to detect early onset of cardiolaminopathy particularly in homozygous patients. Treatment of other cardiovascular risk factors associated with metabolic syndrome, especially diabetes, dyslipidemia, and high blood pressure, is also critical for all FPLD2 patients. Cardiologists and endocrinologists should be aware of cardiac involvement other than atherosclerosis and metabolic syndrome in FPLD2 patients. This is particularly true in the setting of cardiac conduction abnormalities and DCM associated with lipodystrophic features. A multidisciplinary approach is worthwhile. Because of the high rate of sudden cardiac death, implanting an ICD as soon as a pacemaker is needed for AVB is recommended.

Conclusions

The results of this study strengthen the hypothesis that accumulation of prelamin A, with a direct quantitative effect, rather than the absence of mature lamin A, is a cause of the various symptoms described in laminopathies associated with the LMNA p.T655fsX49 mutation. Our study emphasizes the need for a multidisciplinary approach to the diagnosis and monitoring of patients with FPLD2.

Figure 2

Endocrinological characteristics.		
Clinic: More marked and earlier lipodystrophic traits and pseudo athletic features. *Biologic:* lower levels of serum leptin		
Cardiological characteristics.		
Conduction disorders	*Cardiomyopathy*	*Arrhythmias*
Incomplete/ left bundle block branch Second or greater AV block	Ischemic cardiomyopathy Hypokinetic cardiomyopathy	Ventricular tachycardia

Frequent features of homozygous subjects.

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