

ELECTRONIC LETTER

A new mutation of the lamin A/C gene leading to autosomal dominant axonal neuropathy, muscular dystrophy, cardiac disease, and leuconychia

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The *LMNA* gene encodes two nuclear envelope proteins, lamins A and C, derived from alternative splicing. First identified in autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD),¹ mutations in this gene are implicated in up to seven diseases including autosomal recessive EDMD (AR-EDMD),² limb-girdle muscular dystrophy type 1B (LGMD1B),³ dilated cardiomyopathy with conduction defects (DCM-CD),^{4,5} autosomal dominant partial lipodystrophy of Dunnigan type,⁶ autosomal recessive axonal Charcot-Marie-Tooth disease (AR-CMT2),⁷ mandibuloacral dysplasia,⁸ and Hutchinson-Gilford progeria syndrome.^{9,10} In addition, some patients appear to have a combination of these different phenotypes^{11,12} or a clinical variant including skin abnormalities.¹³ To extend the clinical spectrum of laminopathies, we report a previously undescribed dominant missense mutation, E33D, identified in *LMNA* and clinically characterised by the combination of axonal neuropathy with myopathic features, cardiac disease including dilated cardiomyopathy, conduction disturbances and arrhythmia, and leuconychia. The *LMNA* gene is therefore the first gene implicated in both autosomal dominant and recessive forms of CMT2.

CASE REPORT

The pedigree of a white family originating from the south west of France is shown in fig 1. The index case (II-5) and his affected daughter (III-13) were neurologically and cardiologically assessed by one of our team; only partial information was available for other affected members through questioning of patient III-13. The clinical features of all the affected members are shown in table 1. The results of nerve electrophysiological examination of patients II-5 and III-13 are shown in table 2. A muscle CT scan performed for patient II-5 showed wasting and marked fatty infiltration predominating in paraspinal, vasti, hamstring, and gastrocnemius muscles (fig 2). Fig 3 shows the fingernails of patients II-5 and III-13, exhibiting leuconychia.

Clinical and electrical data are consistent with the diagnosis of autosomal dominant axonal neuropathy (AD-CMT2) associated with muscular dystrophy, cardiac disease, and leuconychia in patients II-5 and III-13. Owing to the lack of data this association was not always fully documented for other family members, but a CMT2 phenotype could not be formally excluded in these patients. The variable association of axonal neuropathy, muscular dystrophy, cardiac abnormalities, and leuconychia observed in this family was intriguing. Cardiac disease and/or muscular dystrophy and/or leuconychia are not considered as classical features associated with CMT2. As *LMNA* gene mutations can result in up to seven diseases affecting specifically nerve, muscle, and/or heart, we subsequently performed DHPLC analysis of the coding region of this gene.¹⁴ DNA samples for genetic analysis

Key points

- Mutations of the lamin A/C gene (*LMNA*) are responsible for up to seven diseases involving muscle, heart, nerve, fat, bone, and skin tissues.
- Until now, only one mutation had been reported, in an autosomal recessive form of axonal Charcot-Marie-Tooth disease.
- We describe two members of a large family who share clinical features including axonal neuropathy, muscular dystrophy, cardiac disease, and leuconychia. Some of these features were reported in other family members.
- A new *LMNA* heterozygous missense mutation, E33D, was identified in the two patients.
- To our knowledge, this is the first *LMNA* mutation to be found in an autosomal dominant form of CMT2, and implies that *LMNA* is responsible for both autosomal dominant and recessive forms of axonal Charcot-Marie-Tooth disease.

were obtained from peripheral blood lymphocytes from two patients (II-5 and III-13) and from one healthy family member (II-14), after their informed consent. DHPLC screening identified a variant of the *LMNA* exon 1 in the DNA samples of patients II-5 and III-13. Further sequencing of the *LMNA* exon1 identified a heterozygous 99G→T transition that corresponds to a missense mutation of codon 33, E33D, at the protein level in the DNA of the two patients. This mutation, affecting E33, an amino acid highly conserved through various species and types of lamins (fig 4), was not found in the healthy family member, III-14, nor in 200 healthy unrelated control subjects.

DISCUSSION

Successive identification of *LMNA* mutations in seven different entities has dramatically extended the phenotypic spectrum of laminopathies.¹⁻¹⁰ Cases displaying a combined phenotype of these entities have also been described.¹¹⁻¹³ The

Abbreviations: AD-CMT2, autosomal dominant Charcot-Marie-Tooth disease; AR-CMT2, autosomal recessive Charcot-Marie-Tooth disease; AD-EDMD, autosomal dominant Emery-Dreifuss muscular dystrophy; AR-EDMD, autosomal recessive Emery-Dreifuss muscular dystrophy; DCM-CD, dilated cardiomyopathy with conduction defects; LGMD1B, limb girdle muscular dystrophy type 1B

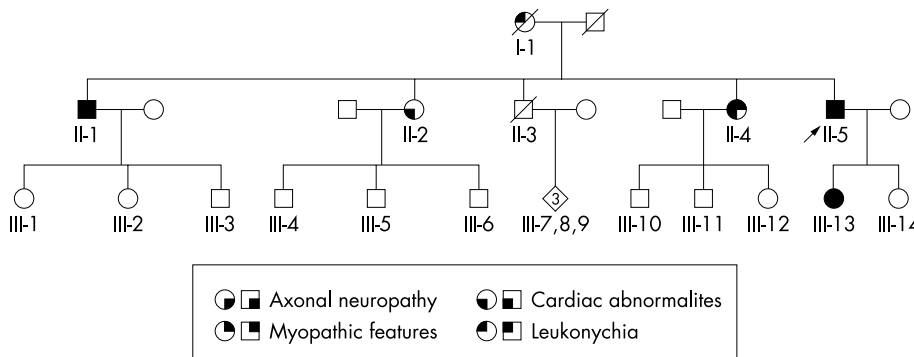


Figure 1 Pedigree of the family. Arrow indicates the index case. Black infill in the lower right quarter of a symbol in solid indicates the presence of axonal neuropathy, in the lower left quarter the presence of cardiac abnormalities, in the upper left quarter the presence of myopathic features, and in the upper right quarter the presence of leukonychia.

Table 1 Clinical features of the affected family members

No.	Sex	Onset	Age at last exam	Muscle weakness and wasting				Sensory abnormalities		Electrophysiological examination					
				LL	UL	LL	UL	Areflexia	CPK	Nerve conduction study	Needle electromyography	Muscle biopsy	Heart	Leu	
I-1	F	-	-	-	-	-	-	-	-	-	-	-	-	-	Y
II-1	M	Teens	58	Pelvic, quadriceps	N	N	N	Y (generalised)	x 2	-	Mixed pattern (LL)	-	-	AF/Normal echocardiography	Y
II-2	F	-	-	-	-	-	-	-	-	-	-	-	-	Arrhythmia/ Cardiomyopathy	-
II-4	F	Juvenile	50	Pelvic, quadriceps	N	-	-	-	x 3	-	Myopathic pattern (LL)	Dystrophic	-	Cardiomyopathy	Y
II-5	M	Teens	55	Pelvic and distal, pes cavus	N	Y (distal)	N	Y (generalised)	x 1.8	Sensorimotor neuropathy	Neuropathic pattern	Dystrophic	-	AF/bradycardia/ Pacemaker/Normal echocardiography	Y
III-5	M	-	-	-	-	-	-	-	-	-	-	-	-	Arrhythmia/ Cardiomyopathy	-
III-13	F	Teens	26	N	N	Y (distal)	Y (distal)	Y (achillean)	x 6.7	Sensorimotor neuropathy	Neuropathic pattern	ND	-	1st degree AVB/ Normal echocardiography	Y

ND, not done; CPK, Creatine phosphokinase expressed in number time of upper normal value; -: no data available; UL, upper limbs; LL, lower limbs; Y, presence of abnormality; N, absence of abnormality; AF, atrial fibrillation; AVB, atrioventricular block; Leu, leukonychia

new E33D *LMNA* mutation reported here leads to an original dominantly inherited clinical variant combining axonal neuropathy, muscular dystrophy, cardiac disease, and leukonychia.

So far, only one homozygous *LMNA* missense mutation, R298C, was reported to be associated with an autosomal form of axonal neuropathy (AR-CMT2) in four families.⁷⁻¹⁵ Histological features, highly similar to the CMT2 phenotype

observed in humans, has also been reported in transgenic *LMNA* null mice.⁷ Our index case and his affected daughter suffered from a clinically and electrically evident axonal neuropathy, with a less severe course than previously observed,¹⁵ suggesting that the axonal neuropathy related to *LMNA* mutation could also be dominantly inherited.

In addition to the CMT2 features, our two patients displayed proximal muscle involvement in the lower limbs.

Table 2 Electrophysiological study of patients II-5 and III-13

	Motor nerves				Sensory nerves									
	MNCV (m/s)		DL (ms)		CMAP (mV)		F-wave latency (ms)		SNCV (m/s)		DL (ms)		SNAP (µV)	
	II-5	III-13	II-5	III-13	II-5	III-13	II-5	III-13	II-5	III-13	II-5	III-13	II-5	III-13
Peroneal (R/L)	UR/35.1	49/54	UR/6	4.2/4.1	UR/2*	7.4/6.5	UR/UR	UR/UR	ND	29	ND	3.8	ND	2.2†
Ulnar (L)	45	ND	3.8	ND	5.7	ND	35.7	ND	43.1	50.3	2.9	1.7	1.5†	8.3†
Posterior tibial (R/L)	32.7/32.8	ND/57.7	6.1/5.4	ND/4.9	0.2/0.3*	ND/8.6	UR/UR	ND/46						
Median (L)	42.6	54.3	4.6	2.8	4.8	8.9	35	28						
Sural (R/L)									37.1/37.8	31/30	3.5/3.7	3.5/3	3.7/3.3†	1.8/2.2†
Radial (R/L)									51.9/44.2	ND/42.9	1.8/2.4	ND/2.1	3.6/3.1†	ND/8†

MNCV, motor nerve conduction velocities; SNCV, sensory nerve conduction velocities; CMAP, compound action motor potential; SNAP, sensory nerve action potential; DL, distal latency; L, left; R, right; ND, not done; UR, unrecordable.

Note the reduced or abolished CMAP* and reduced SNAP† with normal or slightly reduced MNCV proportional to the reduction of CMAP.

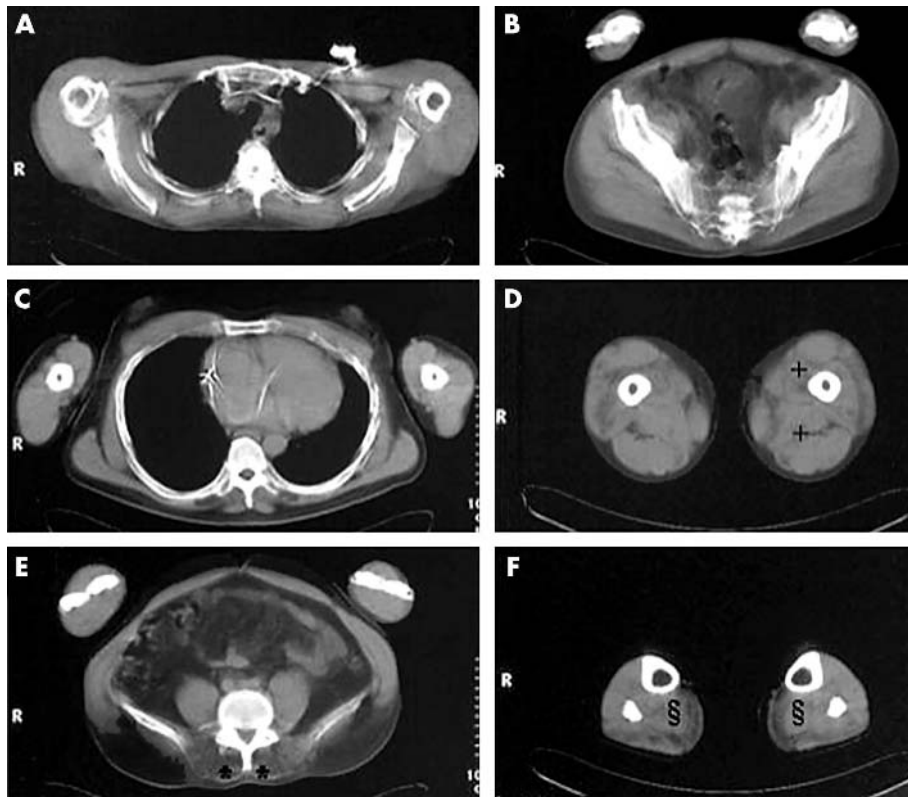


Figure 2 Muscle CT scan of patient II-5. Cross section of the scapular girdle (A), pelvic girdle (B), arms (C), thighs (D), forearms and paraspinal muscles (E), and legs (F). Note the selective atrophy and marked fatty infiltration predominating in paraspinal (*) and gastrocnemius (§) muscles.

This latter observation can be explained by a probable primary involvement of muscular tissues associated to the nerve degeneration. It is supported in our family by the increased level of serum CPK present in the index case (II-5)

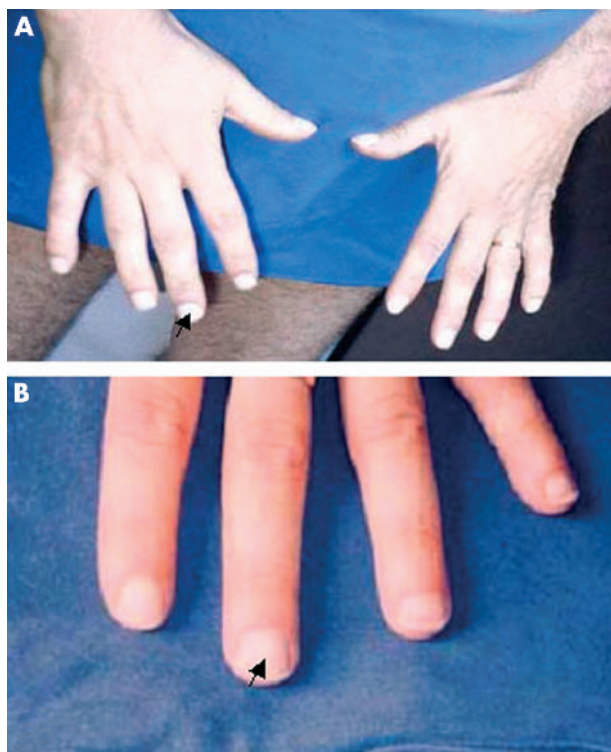


Figure 3 Leuconychia features. Fingernails of index case (A) with complete leuconychia and of his daughter (B) with partial leuconychia starting at the periphery of the fingernails (arrows).

and his daughter (III-13), brother, and sister (II-1 and II-4), the dystrophic pattern observed on muscle biopsy of the index case and his sister (II-4), and the muscle CT scan aspect of index case, which shows a predominant fatty infiltration of paraspinal, vasti, hamstring, and gastrocnemius muscles while other muscles in lower limbs were mildly affected. This specific pattern of infiltration is similar to those observed in AD-EDMD,¹⁶ and in two cases of laminopathies with a combined phenotype.¹¹ This family confirms that muscular and nerve degeneration may occur concomitantly in laminopathies.

Cardiac abnormalities were obvious in our family whereas cardiac investigations remained normal in the families reported by De Sandre *et al.*⁷ Several authors have described such CMT families with cardiac abnormalities including cardiomyopathy, conduction abnormalities, and rhythm disturbances.¹⁷⁻²² Some groups consider this association to be the coincidental occurrence of a relatively common disorder, heart disease, and a less common entity, CMT.²⁰⁻²² In contrast, others suggest that involvements of heart and nerve have a common primary origin.¹⁷⁻¹⁹⁻²¹ In a recent review,²³⁻²⁴ the authors do not consider cardiac disease to be a feature found in CMT2. The cardiac abnormalities reported in the present family are similar to the typical features observed in patients with laminopathies affecting the striated muscle—that is, EDMD, LGMD1B, and DCM-CD, characterised by dilated cardiomyopathy with conduction system disease and rhythm disturbances.²⁻⁵⁻¹¹⁻¹²⁻¹⁴ Therefore, our family is the first report of a family carrying a *LMNA* mutation, in which cardiac disease co-segregates with CMT2 features.

Finally, the co-segregation of leuconychia in several affected members of this family is also unexpected, as it has never been reported in patients carrying the *LMNA* mutation or CMT2 phenotype. Our observation argues for including this feature in the clinical spectrum of laminopathies. It could be included in the group of skin and phaners premature ageing features observed in mandibuloacral dysplasia and Hutchinson-Gilford progeria syndrome.

↓

Patient	lamin A/C	17	SSTPLSPTRITRLQEKEDDLQELNDRLAVYIDRVRSLS	52
human	lamin A/C	17	SSTPLSPTRITRLQEKEDDLQELNDRLAVYIDRVRSLS	52
mouse	lamin A/C	17	SSTPLSPTRITRLQEKEDDLQELNDRLAVYIDRVRSLS	52
rat	lamin A	17	SSTPLSPTRITRLQEKEDDLQELNDRLAVYIDRVRSLS	52
chicken	lamin A	16	SGTPLSPTRITRLQEKEDDLQELNDRLAVYIDKVRSL	51
xenopus	lamin A	12	THTPLSPTRITRLQEKEDDLQELNDRLAVYIDKVRSL	48
xenopus	Lamin IIIA	16	AQSPGSPTRISRMQEKEDLRHLNDRLAAYIERVRSLS	51
D. mel	lamin Dmo	39	ASSPLSPTRHSRVAEKVELQNLNDRLATYIDRVRNLS	75
D. mel	lamin C	30	ATSPTSPTRTSRQEKEDDLQELNDRLACVYIDRMNLS	67
human	lamin B1	18	PTTPLSPTRLSRLQEKEDLRELNDRALAVYIDKVRSL	53
mouse	lamin B1	19	PATPLSPTRLSRLQEKEDLRELNDRALAVYIDKVRSL	54
chicken	lamin B1	17	ASAALSPTRISRRLQEKEDLRELNDRALAVYIDKVRSL	52
xenopus	Lamin IIIB	16	AQSPGSPTRISRMQEKEDLRHLNDRLAAYIERVRSLS	51
xenopus	Lamin I1	18	MSTPLSPTRITRLQEKEDDLQELNDRLALAVYIDTVRSLS	53
mouse	lamin B2	1	--TPLSPTRLSRLQEKEDLRELNDRALAVYIDRVRSLS	45
chicken	lamin B2	2	-GTPLSPTRISRRLQEKEDLRELNDRALAVYIDRVRSLS	46
xenopus	Lamin II	21	TSTPLSPTRISRRLQEKEDLRELNDRALAVYIDRVRSLS	56

Figure 4 Amino acid sequences alignment of lamins A, B and C from various species. Divergent amino acids are shaded. The conservation of E33 is presented in bold. Xenopus: *Xenopus laevis*; D. mel: *Drosophila melanogaster*.

From the pathophysiological point of view, lamins A and C are intermediate filaments that localise at the nucleoplasmic surface of the inner nuclear membrane as a meshwork structure, and have multiple interactions with proteins and chromatin.²⁵ It has been speculated that the primary defect may have downstream effects on chromatin structure or gene expression, explaining in part the tissue specificity observed in laminopathies.²⁵ Despite the growing number of mutations identified in *LMNA*, no clear phenotype–genotype relation has been established. Several mutations affecting amino acids close to E33 have been reported. S22L, R25P, R28W, ΔK32, A43T, Y45C, R50P, and R50S lead to EDMD of variable severity, DCM-CD or combination of partial lipodystrophy with cardiomyopathy, but no CMT2 features have been observed.^{12 14 26–28} Interestingly, a mutation (98A→G) affecting the same codon and leading to E33G was identified in two patients who had typical EDMD phenotype without any CMT2 features (unpublished data). This illustrates the difficulties in establishing any phenotype–genotype relation. However, the involvement of peripheral nervous system observed in our family probably suggests that E33, like R298, is functionally important for the nerve tissue. These observations highlight the crucial role of *LMNA* in the maintenance of peripheral nervous system integrity.

In conclusion, the present cases are the first report of AD-CMT2 due to *LMNA* mutation. We propose that *LMNA* should be included in the spectrum of genes responsible for AD-CMT2 particularly when associated with proximal muscle involvement, cardiac abnormalities, or leuconychia. Thus, *LMNA* represents the first gene implicated in both recessive and dominant forms of CMT2.

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