ELECTRONIC LETTER

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

C Goizet, R Ben Yaou, L Demay, P Richard, S Bouillot, M Rouanet, E Hermosilla, G Le Masson, A Lagueny, G Bonne, X Ferrer

J Med Genet 2004;**41**:e29 (http://www.jmedgenet.com/cgi/content/full/41/3/e29). doi: 10.1136/jmg.2003.013383

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.

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.

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 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

J Med Genet: first published as 10.1136/jmg.2003.013383 on 1 March 2004. Downloaded from http://jmg.bmj.com/ on January 27, 2021 by guest. Protected by copyright.

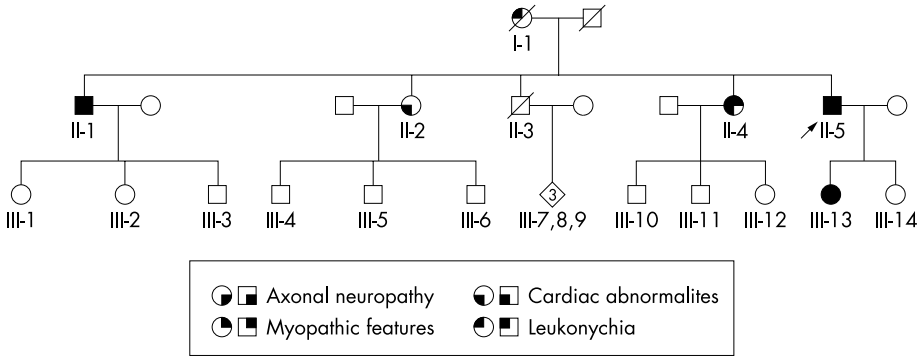

Figure 1 Pedigree of the family. Arrow indicates the index case. Black infill in the lower right quarter of a symbol in solid indicates the presence of axonal neuropathy, in the lower left quarter the presence of cardiac abnormalities, in the upper left quarter the presence of myopathic features, and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

Table 1 Clinical features of the affected family members

				Muscle weakness and wasting		Sensory abnormalities				Electrophysiological examination				
No.	Sex	Onset	Age at last exam	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	Arrhythmia/ 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, leuconychia

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

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.

J Med Genet: first published as 10.1136/jmg.2003.013383 on 1 March 2004. Downloaded from http://jmg.bmj.com/ on January 27, 2021 by guest. Protected by copyright.

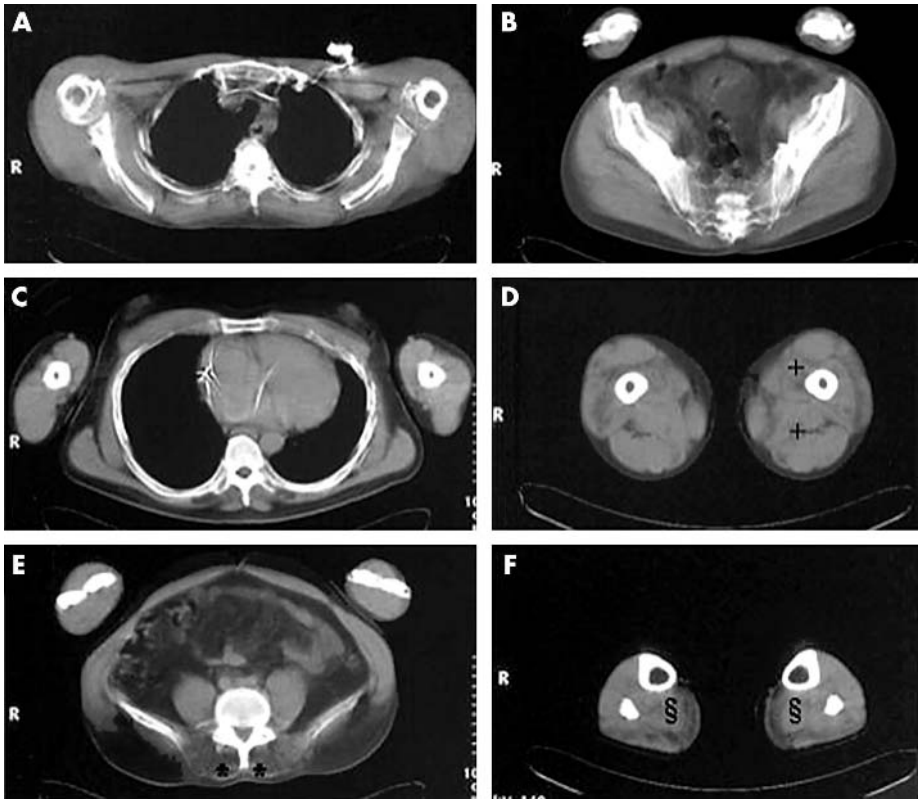

Figure 2 Muscle CT scan of patient II-5. Cross section of the scapular girdle (A), pelvic girdle (B), arms (C), thighs (D), forearms and paraspinal muscles (E), and legs (F). Note the selective atrophy and marked fatty infiltration predominating in paraspinal (*), vasti, harmstring (+) and gastrocnemius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

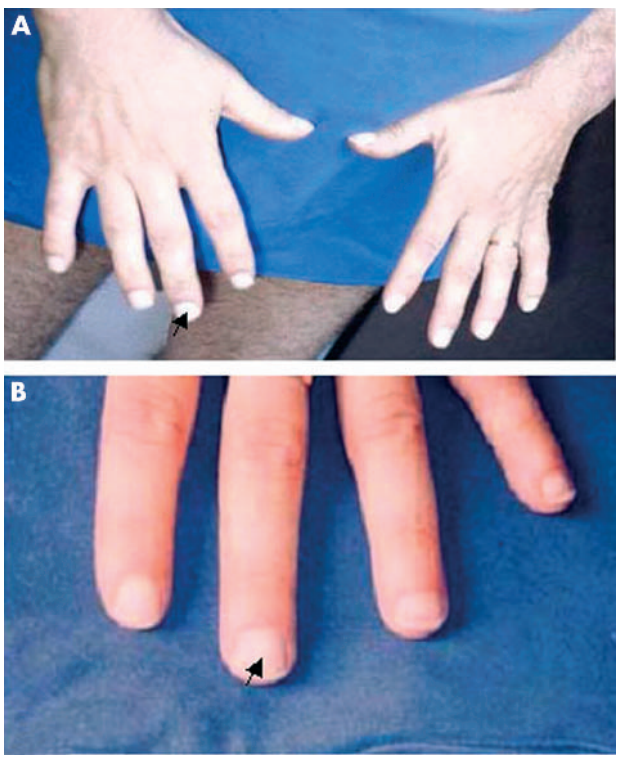

Figure 3 Leuconychia features. Fingernails of index case (A) with complete leuconychia and of his daughter (B) with partial leuconychia starting at the periphery of the fingernails (arrows).

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.

J Med Genet: first published as 10.1136/jmg.2003.013383 on 1 March 2004. Downloaded from http://jmg.bmj.com/ on January 27, 2021 by guest. Protected by copyright.

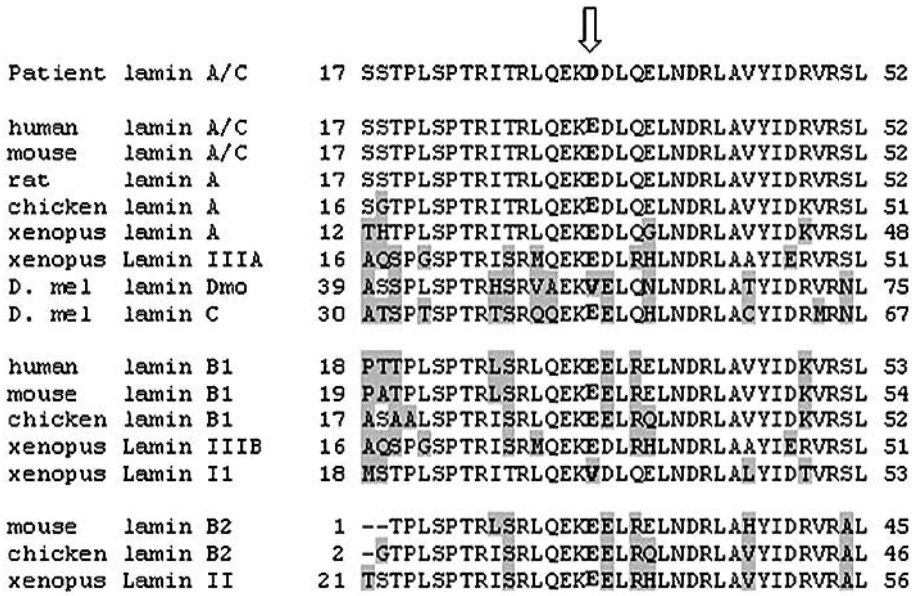

Figure 4 Amino acid sequences alignment of lamins A, B and C from various species. Divergent amino acids are shaded. The conservation of E33 is presented in bold. Xenopus: *Xenopus laevis*; D. mel: *Drosophila melanogaster*.

From the pathophysiological point of view, lamins A amd 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.

ACKNOWLEDGEMENTS

We are grateful to the family members for their participation and cooperation in this study. This study was supported by grants from the European Union Fifth Framework (Myo-Cluster Euromen, contract #QLG1-1999-00870) and from INSERM/AFM (French rare disease network ''EDMD and other nucleopathies'', contract #4MR06F).

Authors' affiliations

C Goizet, G Le Masson, Service de Neurologie, CHU Pellegrin, Bordeaux, France
R Ben Yaou, G Bonne, Inserm U582, Institut de Myologie, GH Pitié-Salpêtrière, Paris, France
L Demay, P Richard, UF Cardiogénétique et Myogénétique, Service de Biochimie B, GH Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, France
S Bouillot, Laboratoire d'Anatomie Pathologique, CHU Pellegrin, Bordeaux, France
M Rouanet, Service d'Exploration Fonctionnelle du Système Nerveux, CHU Pellegrin, Bordeaux, France
E Hermosilla, A Lagueny, X Ferrer, Service de Neurologie, Hôpital Haut-Lévêque, Pessac, France

Correspondence to: Dr C Goizet, Service de Neurologie, CHU Pellegrin, Place Amélie Raba-Léon, F-33076 Bordeaux Cedex, France; cyril.goizet@chu-bordeaux.fr

Received 7 October 2003
Accepted 14 October 2003

REFERENCES

1 **Bonne G**, Di Barletta MR, Varnous S, Becane H, Hammouda EH, Merlini L, Muntoni F, Greenberg CR, Gary F, Urtizberea JA, Duboc D, Fardeau M, Toniolo D, Schwartz K. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nature Genet* 1999;**21**:285–8.
2 **di Barletta MR**, Ricci E, Galluzzi G, Tonali P, Mora M, Morandi L, Romorini A, Voit T, Orstavik KH, Merlini L, Trevisan C, Biancalana V, Housmanowa-Petrusewicz I, Bione S, Ricotti R, Schwartz K, Bonne G, Toniolo D. Different mutations in the LMNA gene cause autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy. *Am J Hum Genet* 2000;**66**:1407–12.
3 **Muchir A**, Bonne G, van der Kooi AJ, van Meegen M, Baas F, Bolhuis PA, de Visser M, Schwartz K. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). *Hum Mol Genet* 2000;**9**:1453–9.
4 **Fatkin D**, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ, Spudich S, De Girolami U, Seidman JG, Seidman CE, Muntoni F, Muehle G, Johnson W, McDonough B. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–24.
5 **Bécane H-M**, Bonne G, Varnous S, Muchir A, Ortega V, Hammouda EH, Urtizberea J-A, Lavergne T, Fardeau M, Eymard B, Weber S, Schwartz K, Duboc D. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. *Pacing Clin Electrophysiol* 2000;**23**:1661–6.
6 **Shackleton S**, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, Gregory S, O'Rahilly S, Trembath RC. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nature Genet* 2000;**24**:153–6.
7 **De Sandre-Giovannoli A**, Chaouch M, Kozlov S, Vallat JM, Tazir M, Kassouri N, Szepetowski P, Hammadouche T, Vandenberghe A, Stewart CL, Grid D, Levy N. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot- Marie-Tooth Disorder Type 2) and mouse. *Am J Hum Genet* 2002;**70**:726–36.

J Med Genet: first published as 10.1136/jmg.2003.013383 on 1 March 2004. Downloaded from http://jmg.bmj.com/ on January 27, 2021 by guest. Protected by copyright.

8 **Novelli G**, Muchir A, Sangiuolo F, Helbling-Leclerc A, Rosaria d'Apice M, Massart C, Capon F, Sbraccia P, Federici M, Lauro R, Tudisco C, Pallota R, Scarano G, Dallapiccola B, Merlini L, Bonne G. Mandibuloacral dysplasia is caused by a mutation in LMNA encoding lamins A/C. *Am J Hum Genet* 2002;**71**:426–31.
9 **De Sandre-Giovannoli A**, Bernard R, Cau P, Navarro C, Amiel J, Boccacio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Levy N. Lamin A truncation in Hutchinson-Gilford progeria. *Science* 2003;**300**:2055.
10 **Eriksson M**, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* 2003; **25**:25.
11 **van der Kooi AJ**, Bonne G, Eymard B, Duboc D, Talim B, Van der Valk M, Reiss P, Richard P, Demay L, Merlini L, Schwartz K, Busch HF, de Visser M. Lamin A/C mutations with lipodystrophy, cardiac abnormalities, and muscular dystrophy. *Neurology* 2002;**59**:620–3.
12 **Garg A**, Speckman RA, Bowcock AM. Multisystem dystrophy syndrome due to novel missense mutations in the amino-terminal head and alpha-helical rod domains of the lamin A/C gene. *Am J Med* 2002;**112**:549–55.
13 **Caux F**, Dubosclard E, Lascols O, Buendia B, Chazouilleres O, Cohen A, Courvalin JC, Laroche L, Capeau J, Vigouroux C, Christin-Maitre S. A new clinical condition linked to a novel mutation in lamins A and C with generalized lipoatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy. *J Clin Endocrinol Metab* 2003;**88**:1006–13.
14 **Bonne G**, Mercuri E, Muchir A, Urtiziberea A, Becane HM, Reca D, Merlini L, Wehnert M, Boor R, Reuner U, Vorgerd M, Wicklein EM, Eymard B, Duboc D, Penisson-Besnier I, Cuisset JM, Ferrer X, Desguerre I, Lacombe D, Bushby K, Pollitt C, Toniolo D, Fardeau M, Schwartz K, Muntoni F. Clinical and molecular genetic spectrum of autosomal dominant Emery Dreifuss muscular dystrophy due to mutations of the lamin A/C gene. *Ann Neurol* 2000;**48**:170–80.
15 **Chaouch M**, Allal Y, De Sandre-Giovannoli A, Vallat JM, Amer-el-Khedoud A, Kassouri N, Chaouch A, Sindou P, Hammadouche T, Tazir M, Levy N, Grid D. The phenotypic manifestations of autosomal recessive axonal Charcot- Marie-Tooth due to a mutation in lamin A/C gene. *Neuromuscul Disord* 2003;**13**:60–7.
16 **Mercuri E**, Counsell S, Allsop J, Jungbluth H, Kinali M, Bonne G, Schwartz K, Bydder G, Dubowitz V, Muntoni F. Selective muscle involvement on magnetic resonance imaging in autosomal dominant Emery-Dreifuss muscular dystrophy. *Neuropediatrics* 2002;**33**:10–14.
17 **Leak D**. Paroxysmal atrial fibrillation in peroneal muscular atrophy. *Br Heart J* 1961;**23**:326–8.
18 **Littler W**. Heart block and peroneal muscular atrophy. A family study. *Q J Med* 1970;**39**:431–40.
19 **Bowers D**. Charcot-Marie-Tooth disease, Wolff-Parkinson-White syndrome, and abnormal intracardiac conduction. *Am Heart J* 1973;**86**:535–8.
20 **Isner JM**, Hawley RJ, Weintraub AM, Engel WK. Cardiac findings in Charcot-Marie-Tooth disease. A prospective study of 68 patients. *Arch Intern Med* 1979;**139**:1161–5.
21 **Lowry PJ**, Littler WA. Peroneal muscular atrophy associated with cardiac conducting tissue disease: further observations. *Postgrad Med J* 1983;**59**:530–52.
22 **Dyck PJ**, Swanson CJ, Nishimura RA, Kazmier FJ, Lie JT. Cardiomyopathy in patients with hereditary motor and sensory neuropathy. *Mayo Clin Proc* 1987;**62**:672–5.
23 **Workshop report**. 2nd Workshop of the European CMT Consortium: 53rd ENMC International Workshop on Classification and Diagnostic Guidelines for Charcot-Marie-Tooth Type 2 (CMT2-HMSN II) and Distal Hereditary Motor Neuropathy (distal HMN-Spinal CMT) 26–28 September 1997, Naarden, The Netherlands. *Neuromuscul Disord* 1998;**8**:426–31.
24 **Gemignani F**, Marbini A. Charcot-Marie-Tooth disease (CMT): distinctive phenotypic and genotypic features in CMT type 2. *J Neurol Sci* 2001;**184**:1–9.
25 **Hutchison CJ**. Lamins: building blocks or regulators of gene expression? *Nat Rev Mol Cell Biol* 2002;**3**:848–58.
26 **Pethig K**, Peters T. LMNA mutations in cardiac transplant recipients with familial dilated cardiomyopathy. *Circulation* 2001;**104**(Suppl II):17.
27 **Brown CA**, Lanning RW, McKinney KQ, Salvino AR, Cherniske E, Crowe CA, Darras BT, Gominak S, Greenberg CR, Grosmann C, Heydemann P, Mendell JR, Pober BR, Sasaki T, Shapiro F, Simpson DA, Suchowersky O, Edward Spence J. Novel and recurrent mutations in lamin A/C in patients with Emery-Dreifuss muscular dystrophy. *Am J Med Genet* 2001;**102**:359–67.
28 **Vytopil M**, Ricci E, Dello Russo A, Hanisch F, Neudecker S, Zierz S, Ricotti R, Demay L, Richard P, Wehnert M, Bonne G, Merlini L, Toniolo D. Frequent low penetrance mutations in the lamin A/C gene, causing Emery Dreifuss muscular dystrophy. *Neuromuscul Disord* 2002;**12**:958–63.

J Med Genet: first published as 10.1136/jmg.2003.013383 on 1 March 2004. Downloaded from http://jmg.bmj.com/ on January 27, 2021 by guest. Protected by copyright.