

Review

The laminopathies: a clinical review

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The laminopathies are a diverse group of conditions caused by mutations in the *LMNA* gene (MIM*150330). *LMNA* encodes the nuclear envelope proteins lamin A and lamin C by utilization of an alternative splice site in exon 10. The human *LMNA* gene was identified in 1986 but it was another 13 years before it was found to be the causative gene for a disease, namely Emery Dreifuss muscular dystrophy. Since then, a further eight clearly defined phenotypes have been associated with *LMNA* mutations. The diversity of these phenotypes is striking with features such as premature ageing, axonal neuropathy, lipodystrophy and myopathy being seen. These phenotypes and the emerging genotype/phenotype correlations are the subject of this review.

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Lamins and the *LMNA* gene

Lamins are intermediate filament proteins whose structure allows them to polymerize to form a two-dimensional lattice. A central alpha helical domain, responsible for dimer formation, is flanked by a short amino terminal head and larger carboxy terminal tail (1) (Fig. 1). The nuclear lamina is a meshwork of polymerized lamins, which lies between the inner nuclear membrane and the chromatin, maintaining the size and shape of the nucleus. Lamins interact directly with the chromatin and also with the integral proteins of the inner nuclear membrane, including emerin (2) (reviewed by Goldman et al. in 3). They therefore appear to have both a structural and a regulatory role. A-type lamins (lamin A and lamin C) are encoded by the *LMNA* gene and are expressed in terminally differentiated cells but are largely absent from embryonic and adult stem cells. The different isoforms are generated by use of an alternative 5' splice site in exon 10 (4) (Fig. 1). B-type lamins are encoded by two genes, *LMNB1* and *LMNB2*, and are expressed in all cells (3). To date, no human disease has been linked to mutations in the B-type lamins.

Laminopathy phenotypes (see Table 1)

Autosomal dominant Emery Dreifuss muscular dystrophy (EDMD-AD)

Emery Dreifuss muscular dystrophy (EDMD) is characterized by the triad of contractures, muscle weakness and cardiac involvement. This phenotype exhibits locus heterogeneity and can be caused by mutations in the *STA* gene located at Xq28 (see subsequently), as well as by mutations in *LMNA* (5, 6). In a male, the clinical presentation of the X-linked form (also designated EDMD1) may be indistinguishable from that of the autosomal dominant form (designated EDMD2 or EDMD-AD). Females who carry a mutation in the *STA* gene rarely have weakness but may manifest heart block (6). The description below summarizes the features of EDMD-AD but highlights some of the differences between this and the X-linked form.

EDMD-AD typically presents during childhood (3–8 years) with difficulty walking or running, although symptoms may start at almost any age (5, 8, 9 and reviewed in 6, 7). Slowly progressive weakness and wasting, initially of the humeroperoneal muscles and then limb girdle muscles, occur with characteristic contractures of

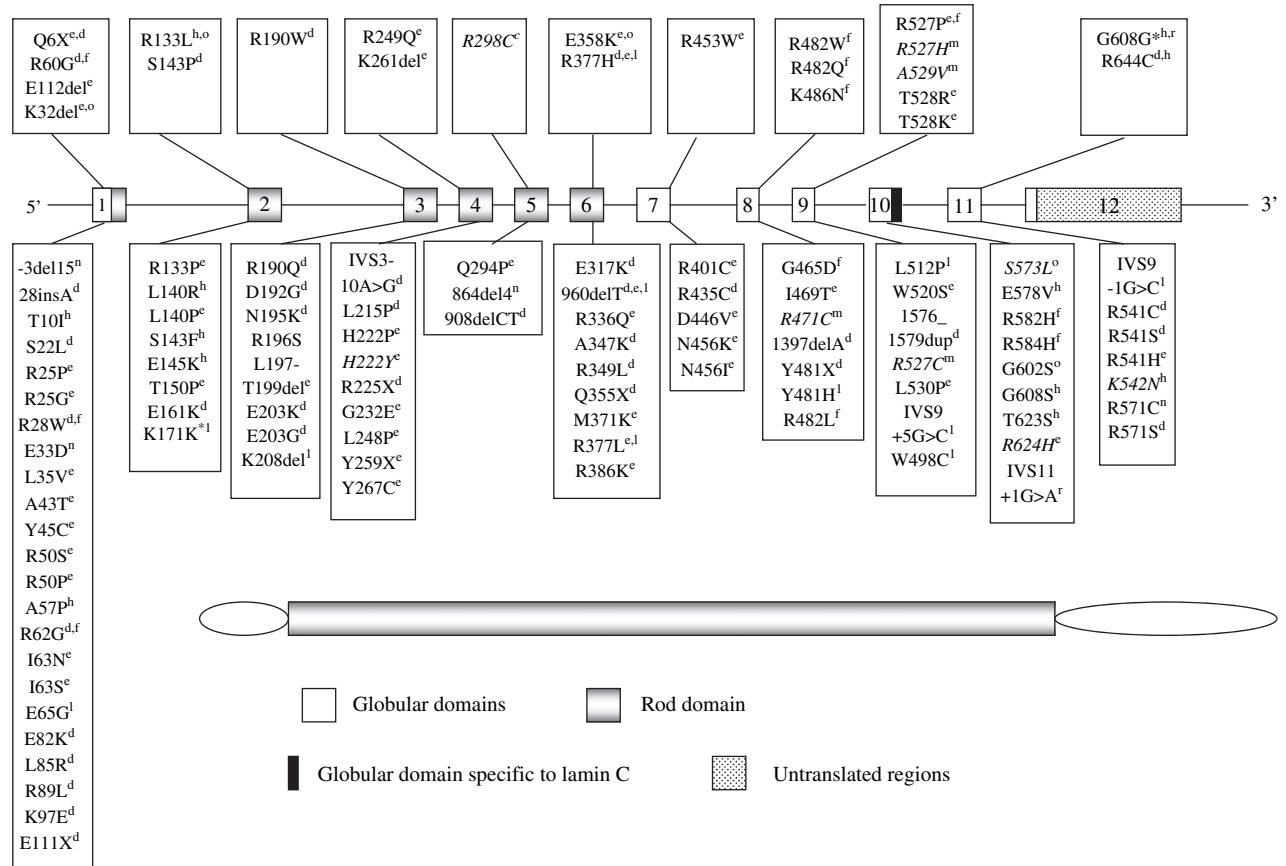


Fig. 1. Summary of reported *LMNA* mutations and schematic diagram of A type lamin protein. Phenotypes e = Emery Dreifuss muscular dystrophy (EDMD), n = neuropathic variant of EDMD, l = Limb girdle muscular dystrophy 1B, d = dilated cardiomyopathy with conduction system disease (DCM-CSD; may be just DCM, just CSD or both), f = familial partial lipodystrophy; Dunnigan type (includes atypical cases), h = Hutchinson–Gilford progeria syndrome (HGPS; atypical HGPS or atypical Werner syndrome), m = mandibuloacral dysplasia, r = restrictive dermopathy, c = Charcot Marie Tooth disease, o = other or unclassified. Recurrent/founder mutations are described by codon, splice site mutations and deletions by nucleotide (cDNA) number according to accession number NM_005572.1. Mutations marked with an asterisk are synonymous substitutions that have been shown to alter mRNA splicing.

the Achilles, elbows and post-cervical muscles (Fig. 2a). Contractures are usually seen after muscle weakness is apparent but may occur before and have been congenital in some cases (5, 6, 9). Scoliosis may occur and can require surgical treatment (9) and significant respiratory impairment has recently been reported in some patients (8). Most patients follow a mild disease course but some, 17% in one series, have more severe disease with onset before 2 years and loss of ambulation in some (5, 9, 10). Creatine kinase (CK) is typically moderately elevated but can be normal (5, 6, 9). Muscle biopsy findings are non-specific with mild myopathic changes including fibre-type disproportion, variation in fibre size and occasional muscle fibre degeneration or necrosis (11). Lamin A/C and emerin immunostaining is normal in muscle from EDMD-AD patients, whereas emerin expression is usually

absent in the X-linked form of EDMD (6, 9, 10, 11).

Cardiac involvement, usually after the onset of muscle disease, is very common with conduction system disease, arrhythmias and later a dilated cardiomyopathy (DCM). For example, detailed assessment of nine EDMD-AD cases with *LMNA* mutations revealed cardiac involvement in eight, with no evidence of cardiac disease in one 15-year-old patient (14). In this series, the age at first evidence of cardiac disease ranged from 9 to 41 years (median 15.5 years), which was 7 to 35 years (median 13 years) after the onset of skeletal myopathy. In a meta-analysis of published details of 190 *LMNA* mutation carriers with either EDMD or limb girdle muscular dystrophy (LGMD) (see subsequently), evidence of cardiac dysrhythmia (including atrioventricular block or atrial or ventricular dysrhythmia)

was reported in 57% overall and in 92% of those aged over 30 years (15). There is a high risk of sudden cardiac death [see section on dilated cardiomyopathy with conduction system disease (DCM-CSD)].

The EDMD-AD phenotype is very similar to the X-linked form of EDMD caused by mutations in the *STA* gene, which encodes emerin, a protein of the inner nuclear membrane with which the lamins interact (3, 6). However, one striking difference is the marked intra- and interfamilial phenotypic variability of the autosomal dominant form. Non-penetrance of the skeletal muscle phenotype has been observed in some family members who may still be at risk of cardiac involvement (9, 16, 17). Bonne et al. (5) first identified *LMNA* as the causative gene for EDMD-AD in 1999, and *LMNA* mutations have since been detected in a large proportion of patients with a clinical diagnosis of EDMD (see Table 2). Interestingly, many cases are isolated, and there appears to be a high new mutation rate (9, 18). The majority of mutations in EDMD-AD are missense, although nonsense mutations, small deletions and splice site mutations have been reported (see Fig. 1). Mutations are found throughout the gene and for this phenotype there is, as yet, no apparent correlation with genotype.

Autosomal recessive EDMD

This appears to be far less common than the autosomal dominant form and few cases have been reported. A child with a severe skeletal myopathy presenting at the age of 3 years was found to be a compound heterozygote for E358K and R624H (19). Another severely affected individual with difficulty walking from 14 months and inability to stand by 5 years was found to be homozygous for the missense mutation H222Y (18). This patient had no evidence of cardiac involvement by 42 years (14), and clinical assessment of the carrier parents, including detailed cardiac assessment, showed them to be unaffected (18).

Limb girdle muscular dystrophy type 1B (LGMD1B)

The limb girdle muscular dystrophies are clinically and genetically heterogeneous (reviewed in 7, 20). LGMD1B is a dominantly inherited disorder characterized by progressive limb girdle weakness, usually affecting the pelvic girdle before the humeral muscles. Contractures are absent and peroneal and tibial muscles are spared but cardiac involvement, with conduction system disease and DCM, is common (see section on

DCM-CSD). Calf hypertrophy may be present (10). LGMD1B and EDMD-AD were found to be allelic in 2000 (21), and it is now apparent that both phenotypes can be caused by the same mutation and can occur within the same family (22).

Dilated cardiomyopathy with conduction system disease

The cardiac phenotype of EDMD-AD cases with *LMNA* mutations, along with linkage data prompted Fatkin et al. (23) to look for *LMNA* mutations in families with autosomal dominant DCM. Five out of 11 families had *LMNA* mutations, most of which were missense changes affecting the rod domain of lamins A and C. *LMNA* mutations, affecting the globular as well as the rod domains, have since been identified in many other cases of DCM, both familial and isolated (see Fig. 1) (14, 22, 24, 25).

Evidence of skeletal muscle disease is found in some individuals from some families (12, 22, 24), but in many only cardiac involvement is present (23, 26). Typically, the earliest sign of cardiac involvement is atrioventricular block sometimes with supraventricular arrhythmias, with DCM developing later. However, some patients may have only DCM or only conduction system disease (17). Pathological examination of hearts after cardiac transplant shows four-chamber dilatation, myocyte hypertrophy and fibrosis without inflammation (23). Both supraventricular and ventricular arrhythmias occur, and sudden death is common. In a meta-analysis of the published literature on 299 *LMNA* mutation carriers (of which 190 had a diagnosis of EDMD or LGMD1B and 109 a diagnosis of DCM), 92% of those aged over 30 years had evidence of a cardiac arrhythmia and 46% of reported deaths were due to sudden death (15). Of all patients, 28% had a pacemaker, but this did not appear to alter the rate of sudden death. The authors highlighted characteristic electrocardiogram changes common to many cases, including low amplitude p wave, prolonged PR interval and narrow QRS complex.

Evidence of cardiac involvement can sometimes be present in the first decade (14). A 2-year-old with the E358K mutation developed a paroxysmal ventricular tachycardia following general anaesthesia and then transient cardiac failure following pneumonia at the age of 4 years (11). A patient with EDMD due to the R541H mutation developed severe DCM requiring heart transplant at the age of 12 years (unpublished case known to the authors). However, presentation is usually in the second to sixth decade (23, 24).

Table 1. A summary of the main laminopathy phenotypes and their causative mutations (see text for details)

Phenotype	Typical features	Common mutations	Overlapping phenotypes/associated features	References
EDMD-AD	Childhood onset, slowly progressive weakness of humeroperoneal muscles, contractures of Achilles, elbows, post-contractures. Cardiac involvement with conduction system disease and cardiomyopathy common	Mostly missense mutations throughout gene Recurrent mutations include E112del, R249Q, K261del, R453W, T528R	DCM-CSD (cardiac involvement common, EDMD-AD, LGMD1B and isolated DCM-CSD reported in same family) CMT (axonal neuropathy in some individuals and families) FPLD (lipodystrophy reported in some individuals and families)	5, 6–10, 14, 15, 18, 22, 62–65, 73, 78
EDMD-AR	Severe myopathy Much rarer than EDMD-AD	E358K/R624H H222Y/H222Y		18, 19
LGMD1B	Slowly progressive weakness of pelvic girdle then humeral muscles. No contractures. Cardiac involvement with conduction system disease and cardiomyopathy common	Mostly missense mutations throughout gene	DCM-CSD common LGMD1B, EDMD-AD and DCM-CSD reported in same family FPLD (lipodystrophy reported in some individuals and families)	10, 20–22, 30, 70
DCM-CSD	Usually presents second to sixth decade. Atrioventricular block, atrial and ventricular arrhythmias. Dilated cardiomyopathy follows. Sudden death common	Mostly missense mutations throughout gene	EDMD-AD, LGMD1B in some families. Many families have no evidence of skeletal muscle involvement	14, 22–25
FPLD	Accumulation of fat in neck and face, loss of fat from limbs and trunk after puberty. Tendency to insulin resistance, dyslipidaemia, hirsutism in females	Heterozygous codon 482 mutations in majority	LGMD1B, DCM-CSD. Evidence of skeletal and cardiac muscle involvement present in some families but absent from others. No apparent correlation with genotype	27–31, 33
HGPS	Severe failure to thrive from early childhood, premature ageing, early death from coronary artery disease or stroke	<i>De novo</i> heterozygous c.1824C>T (G608G) in majority Homozygous K542N	MAD; skeletal features may be present in HGPS cases RD; two cases (G608G heterozygotes) with phenotype intermediate between HGPS and RD. Myopathy; axial weakness with features of HGPS reported in one case (<i>de novo</i> , heterozygous S143F mutation)	36, 37, 42, 71
MAD	Post-natal growth retardation, skeletal abnormalities (hypoplasia of mandible and clavicles, delayed closure of cranial suture, acroosteolysis), lipodystrophy	Homozygous R527H or A529V Also, rarer recessive <i>ZMPSTE24</i> mutations (see text)	FPLD; lipodystrophy recognized part of MAD phenotype	51–55
RD	Tight skin with hyperkeratosis, intrauterine growth retardation, skeletal abnormalities (dysplastic clavicles, mineralization defects of skull), multiple joint contractures, early neonatal death	c.1824C>T (G608G) Recessive <i>ZMPSTE24</i> mutations more common (see text)	HGPS; two c.1824C>T (G608G) heterozygotes with intermediate RD/HGPS phenotype	44, 57, 58
CMT2	Sensorimotor axonal neuropathy, onset first to third decades, rapidly progressive with pelvic girdle weakness in some, scoliosis and <i>pes cavus</i> in some	Homozygous R298C in 10 Algerian families	Axonal neuropathy reported in <i>LMNA</i> heterozygotes with myopathy	59–65
Unclassified	Novel syndrome of arthropathy, tendinous calcinosis and progeroid features	Homozygous S573L in one case		69

Table 1. Continued

Phenotype	Typical features	Common mutations	Overlapping phenotypes/associated features	References
Unclassified	Insulin resistance, acanthosis nigricans and dyslipidaemia	Heterozygous G620S in one family		66
Unclassified	Neonatal death, respiratory insufficiency, multiple joint contractures and fractures, generalized severe muscular dystrophy	Single case report Homozygous Y259X Heterozygous parents had features of mild EDMD-AD and FPLD		68

EDMD-AD, autosomal dominant Emery Dreifuss muscular dystrophy; EDMD-AR, autosomal recessive Emery Dreifuss muscular dystrophy; LGMD1B, limb girdle muscular dystrophy type 1B; DCM-CSD, dilated cardiomyopathy with conduction system disease; CMT2, Charcot Marie Tooth disease type 2; FPLD, familial partial lipodystrophy; Dunnigan type; HGPS, Hutchinson–Gilford progeria syndrome; MAD, mandibuloacral dysplasia; RD, restrictive dermopathy.



Fig. 2. (a) Severe wasting of humeral muscles with elbow contracture in a patient with Emery Dreifuss muscular dystrophy who is heterozygous for the *LMNA* mutation R527P. Reproduced with consent from the patient. (b) Accumulation of fat in the face and neck with reduction of fat in the limbs of a patient with familial partial lipodystrophy. Reproduced with consent from the patient and reprinted from *Emery's Elements of Medical Genetics* (12th edition) by P. D. Turnpenny and S. Ellard, copyright (2005) with permission from Elsevier.

As well as typical DCM, there have been reports of restrictive cardiomyopathy, right ventricular dilatation, left ventricular non-compaction and other non-DCMs in *LMNA* mutation carriers (14, 25, 26). Sebillon et al. (24) reported an unusual family in which five individuals with an E161K mutation presented with atrial fibrillation without significant heart block.

The prevalence of *LMNA* mutations in unselected, non-familial DCM cases is low (24, 25), but the yield increases if only those with additional evidence of conduction system disease are included and further still for familial cases and those with evidence of skeletal muscle weakness (see Table 2) (26). Some families appear to have a particularly severe cardiac phenotype with a rapidly progressive cardiomyopathy and a high risk of sudden death (23). Some *LMNA* mutations, for example S143P, may be particularly associated with a malignant phenotype (26).

Familial partial lipodystrophy; Dunnigan type (FPLD)

After puberty, there is progressive loss of fat from the limbs and trunk with accumulation of fat in the face and neck (see Fig. 2b). Magnetic

Table 2. The prevalence of LMNA mutations in selected patient groups with proposed guidelines for mutation searching

Phenotype	Patient group	Detected LMNA mutations	References	Should LMNA mutation searching be offered to this patient group?
Cardiac	Dilated cardiomyopathy (unselected for family history)	1/30	17	No, yield too low
Cardiac	Cardiac conduction defect (unselected for family history)	4/92	78	No, yield too low
Cardiac	Sporadic dilated cardiomyopathy	1/25	17	No, yield too low
Cardiac	Sporadic dilated cardiomyopathy with conduction system disease	1/72 Finnish patients	26	No, yield too low
Cardiac	Familial dilated cardiomyopathy unselected for presence or absence of conduction system disease	0/19 0/32 0/8	24 25 91	No, yield too low
Cardiac	Familial dilated cardiomyopathy with conduction system disease	5/18 Finnish families (all families had conduction system disease, see below; founder mutation)	26	Yes, however, yield will be higher in the presence of conduction system disease
Cardiac	Familial dilated cardiomyopathy with conduction system disease	5/11 (all families had conduction system disease)	23	
Cardiac	Familial dilated cardiomyopathy with conduction system disease	3/47 (conduction system disease was mostly lacking in one family but present in two families)	24	
Cardiac	Familial dilated cardiomyopathy with conduction system disease	2/35 (one family had conduction system disease and one did not)	25	
Cardiac	Familial dilated cardiomyopathy with conduction system disease	5/15 Italian families	91	Yes
Muscle	EDMD patients who have not had muscle biopsy	5/10 Finnish families (founder mutation) No data	26	In an isolated male case, consider immunostaining of muscle or other tissue (fibroblasts, buccal cells, leucocytes) for emerin first. In an isolated female case or in a family with male-to-male transmission offer LMNA mutation analysis first Yes
Muscle	Unrelated EDMD patients with normal emerin staining on muscle biopsy (unselected for family history)	15/38	17	Yes
Muscle	As above plus evidence of cardiac involvement	10/15	17	Yes
Muscle	Unclassified muscular dystrophies (EDMD excluded)	1/32	17	No, yield too low
Muscle	LGMD (unselected)	Heterozygous mutation found in familial LGMD No data		No, this group is genetically heterogeneous and genetic testing should be guided by muscle biopsy findings and/or by expert advice Yes
FPLD	FPLD families	14/15	31	

Table 2. Continued

Phenotype	Patient group	Detected <i>LMNA</i> mutations	References	Should <i>LMNA</i> mutation searching be offered to this patient group?
HGPS	HGPS	5/5 Canadian 4/4 13/13 20/23 of which 18 were the same <i>de novo</i> mutation (c.1824C>T)	33 92 28 37	Yes
CMT	CMT2 recessive	4/23 consanguineous Algerian families with axonal neuropathy	59, 60	Insufficient data for guidelines
MAD RD	MAD RD	4/6 MAD families 2/12 cases	53, 54 44, 57	Yes, also consider <i>ZMPSTE24</i> Consider <i>ZMPSTE24</i> first

EDMD, Emery Dreifuss muscular dystrophy; LGMD, limb girdle muscular dystrophy; CMT2, Charcot Marie Tooth disease type 2; FPLD, familial partial lipodystrophy; Dunnigan type; HGPS, Hutchinson–Gilford progeria syndrome; MAD, mandibuloacral dysplasia; RD, restrictive dermopathy.

resonance imaging reveals reduction of subcutaneous adipose tissue in the trunk and limbs but with retention of intra-abdominal and intrathoracic fat (27, 28). The phenotype is less pronounced in males (29, 30). Thick hands with spindle-shaped fingers as well as hirsutism, polycystic ovary syndrome and irregular menstruation have been reported in affected women (30). Insulin resistance can occur with up to 50% of affected females having diabetes mellitus. Hypertriglyceridaemia is common and can sometimes be severe enough to cause recurrent acute pancreatitis (30, 31). There may be associated cutaneous stigmata such as eruptive xanthomata and acanthosis nigricans (31), and hepatic steatosis is common (32). Families with and without evidence of skeletal or cardiac muscle involvement have been reported (29, 30). Shackleton et al. (28) identified *LMNA* as the causative gene in 2000. The majority of FPLD mutations occur in exon 8 which encodes the globular carboxy terminal portion of lamins A and C. Nearly all mutations are at codon 482 (see Fig. 1 and Table 1) (28, 31, 33), and these appear to be recurrent mutations as there is no evidence for common ancestry in reported families (28, 31). Recurrence of R482W may be due to deamination of C to T at a CpG site (28). FPLD families with other mutations have been reported (see Table 1). For example, a family with R582H had an atypical phenotype with less-pronounced loss of subcutaneous fat (31, 34), whereas in a family with R584H the phenotype was typical (29).

Hutchinson–Gilford progeria syndrome (HGPS)

Affected individuals appear normal at birth, but severe failure to thrive usually develops in the first year or two of life followed by features of premature ageing (35). Typically, there is alopecia of scalp hair, eyebrows and eyelashes; loss of subcutaneous fat with prominence of superficial veins; midface hypoplasia; micrognathia and skeletal involvement with osteolysis and pathological fractures. Premature atherosclerosis may develop and has been reported as early as 5 years of age. The median age of death is 13.4 years, usually from coronary artery disease or stroke (<http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=176670>). In 2003, two groups identified *de novo* heterozygous *LMNA* mutations in HGPS patients (36, 37). The splice site mutation, c.1824C>T (G608G) was present in all cases except for two, one of whom harboured a G608S missense change with a similar effect on splicing and the other an E145K missense change (37).

The c.1824C>T mutation results in production of lamin A protein lacking 50 amino acids from the carboxy terminal tail, and the term progerin has been used for the deleted protein. The mutation does not alter lamin C protein. Intriguingly, Eriksson et al. (37) also reported two HGPS cases in which they found evidence of uniparental disomy of chromosome 1q (the chromosomal location of *LMNA*) in the absence of a *LMNA* sequence change. They postulate that such cases originally harboured a typical *LMNA* mutation but that a somatic rescue event, either *in vivo* or *in vitro*, resulted in loss of the mutation and a subsequent survival advantage for the cells tested (37). Further HGPS cases have since been found to carry the c.1824C>T mutation and a small number of additional cases, some with atypical features, have been found to carry other mutations (37, 38). D'Apice et al. (39) studied three HGPS cases with a *de novo* c.1824C>T mutation and demonstrated paternal origin of the mutation in all. Transmission of c.1824C>T by an unaffected mother who showed somatic and germline mosaicism has been reported (40). A different splice site mutation, T623S, is predicted to encode lamin A with a 35 amino acid deletion which overlaps with the 50 amino acid deletion associated with the c.1824C>T (G608G) mutation and has been reported in a male with mild HGPS who survived to 45 years (41). A homozygous missense mutation (K542N) was detected in four cases from a consanguineous family in which affected individuals had in addition some skeletal features of mandibuloacral dysplasia (MAD, see subsequently) (42). The heterozygous parents were unaffected. Milder HGPS phenotypes were reported in three cases harbouring heterozygous missense mutations (43). The c.1824C>T (G608G) mutation has also been detected in a patient with a phenotype intermediate between HGPS and restrictive dermopathy (RD, see subsequently) (44). An HGPS patient found to be a compound heterozygote for R527C and R471C has since been suggested to have MAD rather than HGPS (38, W. T. Brown, personal communication, <http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=150330>). *LMNA* missense mutations have been detected in four cases reported to have atypical Werner syndrome (WS), a condition characterized by premature ageing with later onset and milder course than in HGPS (45). Some have argued that these cases lacked typical features of WS as, for example, three of the cases had no cataracts and that, in addition, features of laminopathy such as DCM and phalangeal osteosclerosis were present

(46–48). It has been suggested that such cases should be considered as atypical HGPS rather than atypical WS (48). Recessive *ZMPSTE24* mutations (see subsequently) were identified in a patient with a severe HGPS phenotype with features in common with RD and MAD (90).

Mandibuloacral dysplasia

This condition presents with post-natal growth retardation along with typical skeletal abnormalities such as hypoplasia of the mandible and clavicles, acroosteolysis, delayed closure of the cranial sutures, joint contractures, mottled skin pigmentation and loss of subcutaneous fat from extremities with accumulation of fat in the neck and trunk in some (49, 50). There may be subtotal alopecia in males, premature loss of teeth, acanthosis nigricans and insulin resistance with hypertriglyceridaemia, and so MAD shows considerable overlap with HGPS and FPLD.

In five consanguineous families from central Italy, the same R527H homozygous missense mutation was found in nine affected individuals, all of whom shared a common haplotype, suggesting a founder mutation (51). The same mutation has since been described in Mexican and further Italian families (52, 53), and a different homozygous mutation, A529V, has been found in two patients from two Turkish pedigrees (54). All the reported cases were similar with typical features of MAD noted at around the age of 4–6 years. The heterozygous parents were clinically normal apart from mild fasting hyperinsulinaemia and mild hypertriglyceridaemia being found in most R527H heterozygotes (53).

Interestingly, Agarwal et al. (55) have identified recessive *ZMPSTE24* (see subsequently) mutations in an individual with a clinical diagnosis of MAD. However, the phenotype of this patient was more severe than that of the MAD cases with *LMNA* mutations in that she had earlier onset of skin and skeletal involvement (aged 2 years) and some progeroid features with loss of subcutaneous fat being generalized rather than limited to extremities. She developed renal failure and died at the age of 24 years.

Restrictive dermopathy

Hyperkeratosis of the epidermis, thinning of the dermis and severe reduction of elastic fibres result in tight and rigid skin with foetal akinesia (56). Polyhydramnios, pulmonary hypoplasia and intrauterine growth retardation occur, and there is premature delivery, usually at around 31 weeks gestation. Death frequently occurs within

the first hours or days, although survival to 4 months has been reported (56). Other characteristic clinical features include skin erosions, prominent superficial veins, small mouth with pinched appearance of the nose and, in common with HGPS, sparse or absent eyebrows and eyelashes. There are skeletal abnormalities with mineralization defects of the skull, dysplastic clavicles and joint contractures.

Heterozygous *LMNA* mutations were reported in two of 12 cases of RD (44, 57), the remainder having recessive *ZMPSTE24* mutations (see subsequently). One of the *LMNA* mutations was c.1824C>T (G608G), the HGPS mutation, and this patient was described as being of intermediate severity between HGPS and RD. A further similar patient harbouring the same mutation has since been reported (58). The second *LMNA* mutation reported by Navarro et al. (44) was a novel splice site mutation leading to in-frame skipping of exon 11 and predicted to result in a 90 amino acid deletion from the carboxy terminal end of the protein precursor.

Charcot Marie Tooth disease type 2 (CMT2)

Twenty-nine patients from 10 Algerian families with CMT2 have been found to be homozygous for the R298C mutation, and a common haplotype suggests a founder mutation (59–61). Typically, there is distal weakness and muscle wasting in the lower, and in many the upper, limbs with onset from 4 to 27 years. Later in the course of the disease a glove-and-stocking sensory disturbance occurs. In some the disease is rapidly progressive, and in addition, several cases have had severe, proximal lower limb weakness. In one case a deltoid muscle biopsy and CK were normal, but this patient had no proximal muscle involvement (60). There may also be *pes cavus* and scoliosis.

Several families have now been described with heterozygous *LMNA* mutations segregating with an axonal neuropathy (62–64). However, in all families reported to date, the affected individuals have had in addition evidence of skeletal muscle disease (albeit only a moderately raised CK in one patient; 62) and in some there has been cardiomyopathy or conduction system disease as well. In one family leukonychia was present (62). Neuropathy was first recognized in some when sensory symptoms were reported (62) and in others when both neuropathic and myopathic features were noted on muscle biopsy or electromyography (63, 64). Interestingly, the existence

of a neurogenic variant of EDMD was noted by Alan Emery in 1989 (65).

Other phenotypes

A number of reports of cases and families with diverse, but unclassified, phenotypes due to *LMNA* mutations have been published. All have included some features of the recognized laminopathy syndromes listed above. A family with insulin resistance, acanthosis nigricans and, in the female proband, hyperandrogenaemia was found to have a novel heterozygous missense change, G602S (66). The phenotype included features seen in FPLD but without the typical lipodystrophy. A further unusual case with insulin resistance, hypertriglyceridaemia, hepatic steatosis, leukomelanodermic papules, hypertrophic cardiomyopathy and generalized lipodystrophy was found to carry the mutation R133L, since reported in two cases with features of premature ageing (45, 67).

In an LGMD1B family with a nonsense mutation, Y259X, a severely affected child homozygous for the familial mutation, was born to consanguineous parents (68). There were contractures and generalized severe muscular dystrophy with almost complete absence of fibres in the intercostal muscles. The baby died at birth from respiratory insufficiency. Immunohistochemical studies of fibroblasts revealed absence of lamins A and C.

Van Esch et al. (69) described a patient with a unique phenotype comprising arthropathy, tendinous calcinosis and features of progeria. He was homozygous for the novel mutation S573L.

A patient with prominent neck extension weakness and only mild axial and limb girdle weakness ('Dropped head syndrome') was found to carry a *de novo* heterozygous deletion, c.94–96delAAG, previously detected in patients with typical EDMD-AD (13). The EDMD-AD mutation E358K had previously been reported by Mercuri et al. (8) in a patient with a very similar phenotype.

Overlapping phenotypes

While the laminopathy phenotypes reviewed above have been considered as separate entities, it is becoming apparent that there is not always such a clear distinction. For example, the co-existence of EDMD-AD, LGMD1B and DCM-CSD within a family is well recognized (22). In addition, some individual cases may have features of more than one laminopathy phenotype.

Rankin and Ellard

FPLD together with limb girdle weakness (which can be severe) and cardiac involvement have been reported in patients carrying codon 482 mutations (30) as well as in patients with other mutations (70). The severity of the myopathy does not correlate with the severity of the lipodystrophy. Three unrelated patients heterozygous for R133L had a combination of premature ageing and lipodystrophy (45, 67). A girl with features of progeria as well as myopathy with progressive spinal rigidity was found to harbour a heterozygous missense mutation S143F (71). Interestingly, a different substitution of the same amino acid, S143P, is a common mutation in Finnish families with DCM-CSD but no muscle involvement (26).

Different phenotypes caused by the same mutation

Some mutations are associated with diverse phenotypes in unrelated individuals. Heterozygous E358K has been reported in typical and in early onset EDMD-AD cases as well as in a case with additional features reminiscent of FPLD (9). R644C can cause DCM-CSD, FPLD, skeletal myopathy and atypical HGPS (72, 73 and cases known to authors).

Genotype/phenotype correlations and laminopathies

For many of the reported phenotypes there is no clear genotype–phenotype correlation. Overlapping phenotypes and pleiotropy of phenotypes associated with single mutations led Bonne and Levy (48) to conclude that the laminopathies are ‘a functional continuum of related disorders rather than separate diseases’. Mutations causing EDMD, LGMD and DCM-CSD are found throughout the gene. Some earlier publications reported a correlation between an isolated DCM-CSD phenotype and missense mutations in the rod domain (23), but this has not been supported by subsequent reports (see Fig. 1) (14).

However, for other phenotypes there is a clear correlation. Most patients with FPLD harbour heterozygous mutations of codon 482, and conversely, all reported codon 482 mutation carriers have had features of FPLD, albeit with additional cardiac or skeletal muscle features in some (30).

The majority of HGPS cases harbour the same splicing mutation, c.1824C>T (G608G), and all reported patients with this mutation have HGPS or a phenotype intermediate between HGPS and RD (36–38, 44, 58). Two other mutations in exon 11 (G608S and T623S) cause HGPS through

aberrant splicing (37, 41), and a cluster of missense mutations in exon 2 (R133L, S143F, E145K) has been reported in atypical cases with features of HGPS (37, 45, 71).

Recessive mutations causing MAD are restricted to three amino acid residues in exons 8 and 9 (R471, R527 and A529; 51–54) (see Fig. 1). Codon 527 mutations are relatively common and show a genotype–phenotype relationship with heterozygous R527H mutations having no phenotype, the more severe R527P heterozygous substitution causing EDMD and homozygous R527H mutations resulting in MAD (2, 51–53). Heterozygous mutations at the adjacent residue, T528K and T528R, also cause EDMD (9, 18).

Truncating mutations (nonsense and frame-shifts due to small insertions, deletions or aberrant splicing) have been reported only in patients with EDMD, LGMD and DCM-CSD. These mutations are located in exons 1–10, affect both lamins A and C and may cause disease by haploinsufficiency. In contrast, the exon 11 splicing mutations reported in patients with HGPS or RD may be classified as gain-of-function mutations since they specifically affect processing of lamin A (see subsequently).

Disease pathogenesis

It is interesting to consider how mutations in the *LMNA* gene can cause such diverse phenotypes, and several models have been proposed (74–76). A detailed discussion of these is outside the scope of this review. However, some current hypotheses are of particular note.

One hypothesis proposes that nuclear fragility with disruption of nuclear architecture underlies disease pathogenesis. Nuclear abnormalities have been reported in skeletal muscle fibres, fibroblasts and lymphoblastoid cells from patients with EDMD-AD (77); in cardiomyocytes from patients with DCM (78); in fibroblasts from patients with FPLD (79) and in fibroblasts and lymphocytes from HGPS patients (36, 37, 80), as well as in cells from homozygous null mice (81–83). The abnormalities include irregular shape, herniation of the nuclear envelope and fragmentation but are only present in a proportion of cells studied.

Secondly, it has been proposed that *LMNA* mutations may affect cellular signalling pathways or alter gene expression, possibly by altering interaction between lamins and chromatin or other nuclear proteins (75). Disruption of normal lamin A organization inhibits the synthesis of both DNA and mRNA (84, and reviewed in 4),

and some *LMNA* mutations affect its interaction with the nuclear envelope protein emerin (85). Overexpression of mutant lamin A harbouring the EDMD-AD mutation R453W (but not the FPLD mutation R482W) resulted in failure of *in vitro* differentiation of myoblasts, and the authors propose that this is due to impairment of expression of muscle-specific genes (86). In addition, it has been proposed that another myopathy, facioscapulohumeral muscular dystrophy, results from altered interaction between the long arm of chromosome 4 and components of the nuclear envelope including lamins (87).

Finally, the discovery of nuclear accumulation of pre-lamin A in fibroblasts harbouring the HGPS mutation c.1824C>T (G608G) has led to the suggestion that mutant lamin A protein may interfere with the processing of pre-lamin A to mature lamin A by a dominant negative effect (44, 57, 80, 88, 89). Mature lamin A protein is normally produced from a precursor protein, pre-lamin A, by a series of post-translational modifications including farnesylation and subsequent cleavage of the C terminal 18 residues. The mutation c.1824C>T (G608G) is predicted to cause a 50 amino acid deletion which removes a cleavage site meaning that the mutant protein remains farnesylated. It is proposed that this leads to abnormal processing and accumulation of pre-lamin A which interferes with normal lamin function and results in nuclear abnormalities. Recently, inhibition of farnesylation has been shown to ameliorate the nuclear shape abnormalities seen in fibroblasts harbouring the c.1824C>T mutation, possibly by reduced targeting of pre-lamin A to the nuclear lamina (88, 89). However, not all *LMNA* mutant cell lines with abnormal nuclear morphology show accumulation of pre-lamin A and so additional hypotheses must be sought. Intriguingly, homozygous mutations have been found in the *ZMPSTE24* gene (also called *FACE1*) in patients with HGPS (90) and with RD (57). *ZMPSTE24* encodes a metalloproteinase which is involved in the post-translational processing of pre-lamin A. Such patients show similar nuclear accumulation of pre-lamin A and could be considered to have an indirect or secondary laminopathy (57, 90).

The above hypotheses are not necessarily mutually exclusive, and the mechanisms of pathogenesis for this diverse group of conditions are likely to be complex.

Conclusions

Since the identification of the first human *LMNA* mutation in 1999, the emerging evidence shows

that the laminopathies are a complex group of multisystem disorders. It is clear that many of the phenotypes cannot be considered as discrete entities but rather show considerable overlap, some individuals and families having features of several different laminopathies and some mutations causing diverse manifestations in different individuals. This raises important questions, firstly about medical management and counselling of patients harbouring *LMNA* mutations. For example, should all *LMNA* mutation carriers have cardiac screening regardless of presenting phenotype and should all patients be counselled that there is a high risk of sudden death? We recently identified the R644C mutation, previously described in DCM-CSD, in a patient with FPLD and so cardiac investigations will be appropriate in this individual but should all FPLD families undergo such screening and to what age? Secondly, the issue of appropriate selection of patients for *LMNA* mutation analysis needs attention. Some indications are clear. The *LMNA* mutation yield in typical HGPS and FPLD patients is high and testing is indicated (Table 2). Conversely, the detection rate in apparently isolated DCM cases is low, and without further selection, testing is probably not indicated. However, familial DCM with conduction system disease is an example of an intermediate situation where pickup is modest but where testing may still be appropriate. Further data are needed before robust clinical criteria for *LMNA* testing and for management of patients with laminopathies can be drafted but in the meantime we tentatively propose guidelines for testing as set out in Table 2.

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Rankin and Ellard

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