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Minireview

Laminopathies: Multisystem dystrophy syndromes

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Abstract

Laminopathies are a heterogeneous group of genetic disorders due to abnormalities in type A lamins and can manifest varied clinical features affecting many organs including the skeletal and cardiac muscle, adipose tissue, nervous system, cutaneous tissue, and bone. Mutations in the gene encoding lamins A and C (*LMNA*) cause primary laminopathies, including various types of lipodystrophies, muscular dystrophies and progeroid syndromes, mandibuloacral dysplasia, dilated cardiomyopathies, and restrictive dermopathy. The secondary laminopathies are due to mutations in *ZMPSTE24* gene which encodes for a zinc metalloproteinase involved in processing of prelamin A into mature lamin A and cause mandibuloacral dysplasia and restrictive dermopathy. Skin fibroblast cells from many patients with laminopathies show a range of abnormal nuclear morphology including bleb formation, honeycombing, and presence of multi-lobulated nuclei. The mechanisms by which mutations in *LMNA* gene cause multisystem dystrophy are an active area of current investigation. Further studies are needed to understand the underlying mechanisms of marked pleiotropy in laminopathies.

Keywords: Laminopathy; Lipodystrophy; Progeria; Muscular dystrophy; Lamin A/C; *LMNA*

Introduction

Laminopathies are a heterogeneous group of inherited disorders resulting from abnormalities of type A lamins (lamins A and C) which are due to mutations in the lamin A/C (*LMNA*) gene (primary laminopathies) or mutations in zinc metalloproteinase (*ZMPSTE24*) gene involved in post-translational processing of prelamin A (secondary laminopathies) [1]. To date, seven distinct autosomal-dominant and four autosomal-recessive primary laminopathies have been reported [1]. The autosomal-dominant disorders include familial partial lipodystrophy of Dunnigan variety (FPLD), puberty-onset generalized lipodystrophy, Hutchinson–Gilford progeria syndrome (HGPS), Emery–Dreifuss muscular dystrophy (EDMD), limb-girdle muscular dystrophy (LGMD), type 1B, dilated cardiomyopathy (DCM) type 1A, and restrictive dermopathy [1,2]. The autosomal-recessive syndromes include autosomal-recessive EDMD, mandibuloacral dysplasia (MAD), type A, Charcot–Marie–Tooth (CMT) disorder, type 2B1, and progeria-associated arthropathy [1,3]. Secondary laminopathies include two autosomal-recessive disorders, mandibuloacral dysplasia, type B, and restrictive dermopathy. These syndromes affect different organ systems and have some overlapping features. For example, the predominant feature of EDMD and LGMD is wasting of striated muscles, whereas the loss of adipose tissue is a classical characteristic of FPLD patients.

Structure and expression of lamins

Lamins are nuclear proteins which dimerize to form the nuclear lamina, a filamentous network located just underneath the inner nuclear membrane. The nuclear lamina, which was once thought to be a silent structural element of

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the nucleus, is now found to have an important role in keeping membrane integrity and in controlling gene expression. There are two types of nuclear lamins, type A lamins and type B lamins. Type A lamins are the product of *LMNA* gene, whereas type B lamins are encoded by two separate genes, type B1 by *LMNB1* and type B2 by *LMNB2* [4].

The nuclear lamins belong to type V intermediate filament family of proteins. They have an amino-terminal end, a central α-helical coiled-coil "rod" domain, and a globular C-terminal "tail" domain [4]. The expression of different nuclear lamins varies during development and differentiation of mammalian cells [5]. Lamin A is expressed during or after differentiation, whereas lamin B2 is expressed at a constant level throughout development and lamin B1 is expressed during development and proliferation [4]. Thus, lamins have a crucial role in cell differentiation.

Type A lamins

The *LMNA* gene is located on chromosome 1q21-22 region; it is 24 kb in size and contains 12 exons. Through alternative splicing, the *LMNA* gene encodes for lamins A and C, which are the major products and lamins AΔ10 and C2, which are the minor products [1,6]. Lamin A is produced by post-translational modifications of its precursor prelamin A. Prelamin A is encoded by all 12 exons of *LMNA* and contains a CAAX motif at the C-terminal. Post-translational modification of prelamin A involves a step-wise process which includes farnesylation, proteolytic cleavage of the terminal three amino acids, carboxymethylation, and a second proteolytic cleavage of another 15 carboxy-terminal amino acids resulting in mature form of lamin A. The enzyme, zinc metalloproteinase (ZMPSTE24), is responsible for the first and second steps of the proteolysis. Mature lamin A shares 566 amino-terminal amino acids with lamin C but has 98 unique carboxy-terminal amino acids [1,7]. Lamin C is produced by alternative splicing of exon 10 and contains 6 unique amino acids at its carboxy-terminus. Lamin AΔ10, which lacks exon 10, is expressed at low levels in cell lines established from lung and breast carcinomas and normal colon tissues [6]. Lamin C2 is a 52-kDa protein with a short N-terminus composed of 6 amino acids, compared to the 86 amino acids present in the rod domain of the lamin C structure, and it is specifically expressed during spermatogenesis [8].

Clinical syndromes due to abnormal type A lamins

Many different mutations cause laminopathies which result in distinct syndromes as well as syndromes with overlapping features. In this paper, we report mutations both at the nucleotide and amino acid level. The nucleotide numbering starts with the adenine of the first ATG codon and the amino acid numbering starts with the first residue, methionine, at the amino-terminal end [9].

Autosomal-dominant primary laminopathies

Familial partial lipodystrophy, Dunnigan variety

Clinical features. This is a rare autosomal-dominant disorder characterized by gradual atrophy of sc adipose tissue from the extremities and the trunk beginning at the time of puberty, and followed by excess fat accumulation on the face and neck (Fig. 1A) [10]. These patients often develop insulin-resistant diabetes, hypertriglyceridemia, and reduced concentration of high-density lipoprotein (HDL) cholesterol.

Magnetic resonance imaging studies in affected patients have revealed paucity of adipose tissue in all four extremities and accumulation of sc fat in the face and neck. The intermuscular fat appears to be more prominent in these subjects whereas the visceral adipose tissue is slightly increased [11].

The phenotype is easily recognized in women but is hard to diagnose men affected with FPLD. Also prepubertal children do not manifest the phenotype. Women are also more severely affected by the metabolic complications such as diabetes mellitus, hypertriglyceridemia, low HDL-cholesterol, and atherosclerotic vascular disease than men [12].

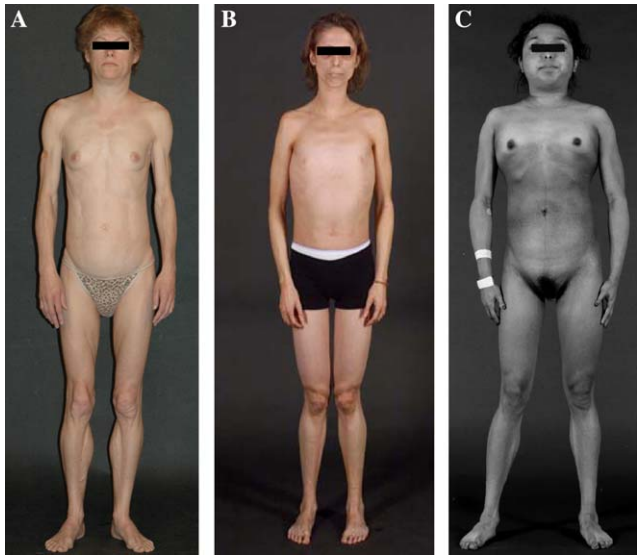

Fig. 1. Patients with primary laminopathies. (A) A 47-year-old Caucasian female with familial partial lipodystrophy of Dunnigan type and K515E heterozygous *LMNA* mutation. She has loss of subcutaneous fat from the arms, legs, and trunk which began at puberty. Note the excess accumulation of fat in the face and neck. (B) A 24-year-old Portuguese female with atypical progeroid syndrome and R133L heterozygous *LMNA* mutation [25]. She has generalized lipodystrophy with atrophic skin over the extremities and prominent veins. Note thinning of hair, sparse eyebrows and thin lips. (C) A 20-year-old Hispanic female with mandibuloacral dysplasia and R527H homozygous *LMNA* mutation. She had mandibular hypoplasia requiring surgical correction, clavicular hypoplasia and acro-osteolysis of the finger and toes. She also had loss of sc fat over the extremities leading to a muscular appearance with prominent veins. Note increased fat accumulation over the neck and face [63]. Panels (B) and (C) were reproduced with permission from the authors (Copyright 2005 and 2002, respectively, The Endocrine Society) [25,63].