Laminopathies and Atherosclerosis

Khalid Z. Al-Shali, Robert A. Hegele

Abstract—Laminopathies are genetic diseases that encompass a wide spectrum of phenotypes with diverse tissue pathologies and result mainly from mutations in the LMNA gene encoding nuclear lamin A/C. Some laminopathies affect the cardiovascular system, and a few (namely, Dunnigan-type familial partial lipodystrophy [FPLD2] and Hutchinson–Gilford progeria syndrome [HGPS]) feature atherosclerosis as a key component. The premature atherosclerosis of FPLD2 is probably related to characteristic proatherogenic metabolic disturbances such as dyslipidemia, hyperinsulinemia, hypertension, and diabetes. In contrast, the premature atherosclerosis of HGPS occurs with less exposure to metabolic proatherogenic traits and probably reflects the generalized process of accelerated aging in HGPS. Although some common polymorphisms of LMNA have been associated with traits related to atherosclerosis, the monogenic diseases FPLD2 and HGPS are more likely to provide clues about new pathways for the general process of atherosclerosis. (Arterioscler Thromb Vasc Biol. 2004;24:1-5.)

Key Words: nuclear envelope ■ insulin resistance ■ aging ■ vascular disease ■ progeria

The nuclear lamina is a 20-nm filamentous meshwork that underlies the inner nuclear membrane and plays a central role in defining interphase nuclear architecture, DNA replication, and chromatin organization. Nuclear lamins are type V intermediate filaments that are the major components of the nuclear lamina. Mutations in the genes encoding lamins have been discovered in a staggering variety of inherited diseases called “laminopathies,” which at least superficially seem to share little with one another. Causative genes for some diseases encode lamina-associated proteins, such as EMD encoding emerin (MIM 300384), which causes X-linked Emery–Dreifuss muscular dystrophy (MIM 301300), and LBR encoding the lamin B receptor (MIM 600024), which causes both Pelger–Huet anomaly (MIM 169400) and Greenberg skeletal dysplasia (MIM 215140). However, the “pure” laminopathies are so far associated only with mutations in LMNA (MIM 150330) on chromosome 1q21 encoding lamin A/C.

To date, at least 10 different human diseases result from LMNA mutations (see Table). The position of the mutation within LMNA appears to be a key determinant of affected cell type and anatomic distribution. For instance, >90% of subjects affected the mutations causing Dunnigan-type familial partial lipodystrophy (FPLD2; MIM 151660) affect LMNA codon 482, and all involve the sequence encoding the lamin A isoform specifically. Genetically modified mice have provided insights into the possible pathogenic mechanisms of LMNA mutations. For instance, monocytes from Lmna-deficient mice showed displaced fragmented heterochromatin and disorganized, detached desmin filaments. Also, mechanical strain applied to fibroblasts from Lmna-deficient mice was associated with increased nuclear fragility and altered gene transcription. A 2-step disease model for LMNA mutations is favored presently: (1) mutations cause mechanical abnormalities of the nucleus, followed by (2) perturbed interactions with transcription factors and abnormal regulation of gene expression. However, our understanding of how LMNA mutations cause such a wide spectrum of diseases is still very rudimentary.

Some laminopathies involve the cardiovascular system. For instance, cardiac conduction is abnormal in inherited early onset atrial fibrillation, dilated cardiomyopathy, and Emery–Dreifuss muscular dystrophy (Table). Other laminopathies, particularly FPLD2 and Hutchinson–Gilford progeria syndrome (HGPS; MIM 176670), are associated with premature atherosclerosis. As with other monogenic diseases, such as familial hypercholesterolemia (FH), FPLD2 and HGPS might help illuminate key atherogenic mechanisms. Atherosclerosis in FPLD2 is probably related to insulin resistance, whereas in HGPS, atherosclerosis occurs at a chronologically young age but seems to be commensurate with the generalized accelerated aging that affects all tissues and organs.

FPLD2: A Monogenic Form of Metabolic Syndrome With Early Atherosclerosis

The National Cholesterol Education Program Adult Treatment Panel has defined the common metabolic syndrome (MetS) according to deviation from threshold values for any 3 or more of 5 clinical quantitative traits, namely blood pressure, waist circumference, and plasma concentrations of glucose, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG). The common MetS phenotype results from interaction between environment and genes and has
been associated prospectively with development of type 2 diabetes mellitus (T2DM) and all-cause and cardiovascular mortality. Because FPLD2 patients have insulin resistance that progresses to T2DM, they are considered to represent a human monogenic model system for the common MetS. Heterozygosity for germline LMNA mutations causes FPLD2, but a very similar phenotype (FPLD3) can result from mutation in PPARG (MIM 601487), which encodes peroxisomal proliferator activated receptor-γ. Prevalence of FPLD2 may be as high as 1:200,000 in some populations. FPLD2 subjects begin life with normal fat distribution, but around puberty, they begin to lose adipocytes in specific depots, such as subcutaneous fat on limbs and in the gluteal region, with sparing of facial, truncal, visceral, and bone marrow fat stores. Insulin resistance is the biochemical hallmark of FPLD2, and other features include acanthosis nigricans, hirsutism, menstrual abnormalities, and polycystic ovaries. As in the common MetS, FPLD2 subjects have an increased ratio of central to peripheral fat, almost an infinite ratio in some cases. Insulin resistance is the biochemical hallmark of FPLD2, and other features include acanthosis nigricans, hirsutism, menstrual abnormalities, and polycystic ovaries. Careful phenotypic or “phenomic” studies performed in extended FPLD2 kindreds have shown metabolic changes that were similar to those seen in the common MetS. In young adulthood, the characteristic biochemical profile seen in FPLD2 carriers of mutant LMNA included elevated plasma concentrations of free fatty acids, insulin and C-peptide, TG, and C-reactive protein (CRP), with depressed plasma concentrations of HDL cholesterol, leptin, and adiponectin. Depressed adiponectin in particular could be a potent atherosclerosis risk factor in lipodystrophy syndromes. Hypertension usually presents next, followed by T2DM that causes profound changes in the metabolic intermediate traits. However, the extended biochemical profile in FPLD2 was distinct from that seen in MetS because plasma fibrinolytic variables were unchanged, whereas both serum leptin and adiponectin were depressed. Early coronary heart disease (CHD) has been observed in FPLD2, especially in women. Compared with normal family controls, FPLD2 subjects with heterozygous LMNA mutations in codon 482 had an odds ratio of ~6 for having a CHD end point <age 55. Furthermore, female LMNA codon 482 mutation carriers <55 years old were >100-fold more likely to be hospitalized for coronary artery bypass surgery than women in the general Canadian population. Subjects with mutant LMNA with CHD also had T2DM, suggesting that extensive metabolic progression is necessary for expression of vascular disease. It has been proposed that further careful evaluation of subphenotypes in LMNA mutation carriers at younger ages might identify other biomarkers associated with atherosclerosis susceptibility.

**Atherosclerosis in Laminopathies With a Lipodystrophy Component**

Some LMNA mutations produce complex conditions that feature lipodystrophy as but 1 component. For instance, mandibuloacral dysplasia (MAD; MIM 248370) is a rare recessive disorder characterized by postnatal growth retardation, mandibular and clavicular hypoplasia, acro-osteolysis,...

<table>
<thead>
<tr>
<th>Laminopathies Listed According to Mode of Inheritance</th>
<th>MIM No.</th>
<th>Illustrative Mutations*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal dominant (AD) disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emery–Dreifuss muscular dystrophy (AD-EMD2)</td>
<td>181350</td>
<td>Q6X; R453W; R527P; L530P</td>
</tr>
<tr>
<td>Dilated cardiomyopathy with CCA (CMD1A)</td>
<td>115200</td>
<td>R60G; L85R; N195K; E203G;</td>
</tr>
<tr>
<td>R571S; exon 1 28insA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset atrial fibrillation</td>
<td>607554</td>
<td>G161K</td>
</tr>
<tr>
<td>FPLD2</td>
<td>151660</td>
<td>R492Q; R492W; R492L; R582H</td>
</tr>
<tr>
<td>HGPS</td>
<td>176670</td>
<td>G608G; G608S</td>
</tr>
<tr>
<td><strong>Atypical progeria syndromes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical HGPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Werner Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overlapping syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIRLLC</td>
<td>608056</td>
<td>R133L</td>
</tr>
<tr>
<td>CMD1A+QM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD-EMD2+LD+CCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Autosomal recessive (AR) disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emery–Dreifuss muscular dystrophy (AR-EMD2)</td>
<td>604929</td>
<td>H222Y</td>
</tr>
<tr>
<td>Charcot Marie Tooth disease (AR-CMT2B1)</td>
<td>605588</td>
<td>R298C</td>
</tr>
<tr>
<td>Limb-girdle muscular dystrophy (LGM1B)</td>
<td>159001</td>
<td>R377H; delK208; IVS9 +5G&gt;C</td>
</tr>
<tr>
<td>Mandibuloacral dysplasia (MAD)</td>
<td>248370</td>
<td>R527H; C07H471C/R527C</td>
</tr>
</tbody>
</table>

LD indicates lipodystrophy; CCA, cardiac conduction abnormality; QM, quadriceps myopathy; del, deletion; IVS, intervening sequence (intron); C07H, compound heterozygote; LIRLLC, lipatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy.

*Mutations for AD disorders are present in the heterozygous state, whereas mutations for the AR disorders are present either in the homozygous or in the C07H state where indicated.
Atherosclerosis in HGPS
Subjects with HGPS may appear normal at birth but display severe growth retardation by the first year of life. Additional features include growth failure of the facial bones and mandible, prominent eyes, alopecia, prominent scalp veins, loss of subcutaneous fat, stiff, enlarged joints, thin limbs, thin, wrinkled and dry skin, dystrophic nails, delayed dentition, a high-pitched voice, and absent sexual maturation. Recently, de novo point mutations in LMNA have been found in most subjects with HGPS, with the most common mutation at codon 608. This mutation creates a cryptic splice site within exon 11, which results in deletion of a proteolytic cleavage site within the expressed mutant lamin A.27

HGPS subjects have a median life span of <14 years, and death is most frequently from cardiovascular causes, with atherosclerosis being the predominant pathology. The coronary arteries are frequently stenosed or occluded by atherosclerotic plaques. Most reported necropsies of HGPS subjects have documented aortic atherosclerosis, ranging from small fatty plaques to complicated, calcified lesions. Most reported necropsies of HGPS subjects have also documented significant myocardial changes, which included healed and recent myocardial infarction (MI), diffuse interstitial fibrosis, and ventricular hypertrophy and dilation. MI in HGPS is associated strongly with severe coronary atherosclerosis but occasionally also with narrowing of the small intramural arteries. A few HGPS subjects have diffuse myocardial fibrosis without significant coronary atherosclerosis.

Atherosclerosis may also affect the cerebrovasculature in HGPS. Angiographic evidence of atherosclerosis affecting both the carotid and vertebral systems and MRI evidence of cerebral infarction has been documented in HGPS children with localizing neurological findings. Mandera et al. reported epidural hematomas in a 10-year-old HGPS boy after mild head injury and suggested that these resulted in part from advanced atherosclerosis of the intracranial vessels.

The mechanisms underlying the atherosclerosis in HGPS remain unclear. Although the general aging process extracts a toll on the vasculature, it is possible that vascular deterioration might in turn contribute to tissue changes associated with aging, in effect setting up a vicious cycle. Importantly, the vascular changes in HGPS are similar to those seen in the general aging process and differ from other forms of precocious atherosclerosis in children. For instance, Stehbens et al suggested that the xanthomatous vascular lesions that are typical for homozygous FH are not seen in the atherosclerosis of HGPS. Furthermore, serum lipoproteins in HGPS are relatively normal, except for occasional reports of depressed HDL cholesterol. Exposure to risk factors such as poor diet, smoking, or hypertension is an unlikely proatherogenic mechanism in HGPS. Similarly, the variable association with insulin resistance does not fully explain atherosclerosis in HGPS. Marked reduction in insulin receptor gene expression was observed in lymphoblasts from a 15-year-old girl with severe insulin resistance; however, insulin resistance alone would not be expected to cause expression of CHD end points within the first 2 decades of life.

It is more likely that the same mechanism(s) by which mutant LMNA produces accelerated aging in tissues, such as replicative senescence, telomere shortening, decreased capacity to propagate in subculture, decreased repair capacity, may also affect vascular wall components. For instance, endothelial cells with mutant LMNA might not regenerate fully to restore intact integrity after injury. Also, vascular smooth muscle cells in HGPS were susceptible to hemodynamic and ischemic stress injury and were depleted from arterial media. An alternative proposed mechanism for atherosclerosis in HGPS is hyperhyaluronic acidemia and aciduria, which are suggested to cause vascular calcification despite the fact that these biochemical abnormalities are not specific for either HGPS or atherosclerosis. Other cardiovascular changes in HGPS, such as calcification of cardiac valves, are similar to those seen in the general aging process.

Association Studies of LMNA SNPs With Metabolic Traits
A few studies report association of common LMNA single nucleotide polymorphisms (SNPs) with metabolic and cardiovascular traits. The results of these studies are subject to the usual limitations of association studies. The most commonly evaluated LMNA SNP is the synonymous 1908C/T polymorphism in exon 10, wobbling the third base of codon 566, which is the last codon shared in common between lamin A and C before alternative splicing gives rise to the 2 distinct proteins. In nondiabetic Canadian aboriginal subjects, those with the 1908T/1908T genotype had significantly higher plasma leptin than the subjects with either the 1908C/1908T or 1908C/1908C genotypes, after adjustment for age and sex. Physical indices of obesity, such as body mass index, percent body fat, and ratio of waist-to-hip circumference, were also higher among subjects with the LMNA 1908T/1908T genotype compared with those with either the 1908C/1908T or 1908C/1908C homozygotes. This was later replicated in an independent, genetically distinct Canadian aboriginal sample. In a Japanese study, there was a nonsignificant trend to an association of diabetes with the 1908T allele, and both diabetic and nondiabetic carriers of the 1908T allele showed significantly higher fasting insulin, TG, total cholesterol, and lower HDL cholesterol levels than 1908C/C subjects. An analysis in Pima Indians indicated that the 1908T allele was associated with reduced age-,
and body fat–adjusted mean abdominal adipocyte size. Finally, a report in the current issue provides evidence that the 1908T allele was associated with elevated TG, lower HDL cholesterol, and a higher frequency of the MetS in the Old Order Amish. Thus, although the phenotypes varied, the association studies have generally tended to agree that the 1908T allele was associated with more deleterious metabolic traits.

Conclusions

The recent characterization of numerous rare inherited disorders that result from mutations in the LMNA gene has been an interesting chapter in human molecular genetics. The laminopathies encompass a wide range of phenotypes with diverse tissue pathologies. Thus, it is not surprising that some laminopathies affect the cardiovascular system and that a few feature atherosclerosis as a key component. The atherosclerosis of FPLD2 is premature, with end points occurring in midadulthood, and is very likely to be related to the wide range of proatherogenic metabolic disturbances (such as dyslipidemia, elevated CRP, hyperinsulinemia, hypertension, and diabetes) that are characteristic of that condition. In contrast, the very premature atherosclerosis of HGPS occurs with less exposure to metabolic proatherogenic traits. The generalized process of accelerated aging in HGPS appears to affect the vascular system with the same intensity as other tissues. These monogenic diseases that result from defective structure and function of a nuclear membrane component may provide clues to new pathways for the general process of atherosclerosis.

Acknowledgments

R.A.H. is supported by a Canada research chair (tier I) in human genetics and a career investigator award from the Heart and Stroke Foundation of Ontario. Support has come from the Canadian Institutes for Health Research, the Canadian Genetic Diseases Network, the Canadian Diabetes Association, and the Blackburn Group.

References

27. Hutchinson J. Congenital absence of hair and mammary glands with atrophic condition of the skin and its appendages in a boy whose mother had been almost totally bald from alopecia areata from the age of six. Medicochirurgical Transactions. 1866;69:473–477.
32. Atkins L. Progeria: report of a case with post-mortem findings.
Laminopathies and Atherosclerosis
Khalid Z. Al-Shali and Robert A. Hegele

Arterioscler Thromb Vasc Biol. published online June 17, 2004;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2004/06/17/01.ATV.0000136392.59656.8b.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/