

Brief Report

Common Variation in *LMNA* Increases Susceptibility to Type 2 Diabetes and Associates With Elevated Fasting Glycemia and Estimates of Body Fat and Height in the General Population

Studies of 7,495 Danish Whites

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Mutations in *LMNA* encoding lamin A and C proteins cause monogenic syndromes characterized by muscular dystrophy and familial partial lipodystrophy. Eight tag single nucleotide polymorphisms in the *LMNA* locus were genotyped in 7,495 Danish whites and related to metabolic and anthropometric traits. The minor T-allele of rs4641 was nominally associated with type 2 diabetes (odds ratio 1.14 [95% CI 1.03–1.26], $P = 0.01$) in a study of 1,324 type 2 diabetic patients and 4,386 glucose-tolerant subjects and with elevated fasting plasma glucose levels in a population-based study of 5,395 middle-aged individuals ($P = 0.008$). The minor T-allele of rs955383 showed nominal association with obesity in a study of 5,693 treatment-naïve subjects (1.25 [1.07–1.64], $P = 0.01$), and after dichotomization of waist circumference, the minor alleles of rs955383 and rs11578696 were nominally associated with increased waist circumference (1.14 [1.04–1.23], $P = 0.003$; 1.12 [1.00–1.25], $P = 0.04$). The minor G-allele of rs577492 was associated with elevated fasting serum cholesterol and short stature ($P = 3.0 \cdot 10^{-5}$ and $P = 7.0 \cdot 10^{-4}$). The findings are not corrected for multiple comparisons and are by nature exploratory. However, if replicated, these findings suggest that less severe variation in a gene locus known to harbor severe mutations causing monogenic syndromes may modestly increase susceptibility to common metabolic and anthropometrical phenotypes of polygenic origin. *Diabetes* 56:694–698, 2007

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IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; SNP, single nucleotide polymorphism.

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L*MNA* encodes lamin A and C proteins, which are components of the nuclear lamina. This protein network is involved in DNA replication, chromatin organization, nuclear growth, spatial arrangement of nuclear pores, and anchorage of nuclear membranes (1,2). Lamin A and C proteins are co-expressed and widely distributed, e.g., in adipocytes and myocytes (3). Alternative RNA splicing of exon 10 in *LMNA* produces either lamin A or C, both of which play important roles in physiology as demonstrated in studies of animal models. Lamin A knockout mice develop normally to term, whereas at 2–3 weeks their growth is impaired and characterized by muscular dystrophy and cardiac and skeletal myopathy (4). Lamins A and C, but not lamin B1, regulate nuclear mechanisms (4,5), and fibroblasts from *Lnma*^{-/-} mice show increased nuclear deformation and an impaired mechanically activated expression of mechanosensitive genes, as well as all attenuated nuclear factor κ B-regulated luciferase activity (6).

Human *LMNA* has been mapped to chromosome 1q21.2-q21.3 (7), a locus previously linked to type 2 diabetes (8–11). Several mutations have been identified in *LMNA*, of which most have shown association with monogenic syndromes, e.g., muscular dystrophy, cardiomyopathy, progeroid syndromes, and familial partial lipodystrophy; the latter being characterized by altered fat distribution, type 2 diabetes, and severe insulin resistance (12–17). Interestingly, in a study of 306 nondiabetic Canadian Oji-Cree subjects, the 1908C>T (rs4641, His566His) polymorphism located at the site of alternative splicing in exon 10, homozygous carriers of the T-allele had higher levels of fasting plasma leptin, BMI, percentage body fat, and waist-to-hip ratio than C/T and C/C carriers (18). Most of these findings were replicated in studies of 186 nondiabetic Canadian Inuits, indicating that lamin A/C may influence obesity-related traits (19). In a study of the metabolic syndrome involving 971 first- and second-degree relatives of Amish type 2 diabetic probands, the *LMNA* rs4641 polymorphism was associated with the metabolic syndrome, higher fasting serum levels of triglyceride, and lower HDL cholesterol (20). Thus, the chromosomal localization of *LMNA* and previous findings of relationships

TABLE 1

Genotype distribution and minor allele frequencies of the rs4641 polymorphism of *LMNA* among 1,324 (1,416 subjects available for genotyping) type 2 diabetic patients and 4,386 control subjects (4,883 subjects available for genotyping) who were both glucose tolerant and had normal fasting glucose

rs4641	Control subjects	Type 2 diabetic patients	P_{GD}	P_{AF}
<i>n</i> (male/female)	4,386 (2,039/2,347)	1,324 (801/523)		
CC	2,517 (57)	709 (54)	0.04	
CT	1,589 (36)	516 (39)		
TT	280 (6)	99 (8)		
MAF (95% CI)	24.5 (23.6–25.4)	27.0 (25.3–28.7)		0.01

Data are number of subjects with each genotype (percent of each group) and minor allele frequency (MAF). P values compare genotype distribution (P_{GD}) and allele frequency (P_{AF}) between type 2 diabetic patients and control subjects and are calculated using Fisher's exact test. All genotype groups obeyed Hardy-Weinberg equilibrium.

between variation in this gene locus and metabolic phenotypes make *LMNA* a positional and biological candidate gene in the pathogenesis of type 2 diabetes, obesity, and quantitative traits of growth and metabolism.

The objective of the present study was to tag the *LMNA* locus (44 kb) and to evaluate whether these tag single nucleotide polymorphisms (SNPs) associate with type 2 diabetes, obesity, or quantitative metabolic or anthropometric traits in the Danish middle-aged population.

To cover the *LMNA* region, the following polymorphisms were chosen from previous published data and by browsing the HapMap project (www.hapmap.org/index.html): rs4641, rs622834, rs12063564, rs577492, rs6661281, rs955383, rs11578696, and rs12035615. The minor T-allele of rs4641 was more prevalent among 1,324 type 2 diabetic patients than among 4,386 glucose-tolerant subjects (odds ratio [OR] 1.14 [95% CI 1.03–1.26], $P = 0.01$) (Table 1). Studies of quantitative traits among 5,395 middle-aged individuals without known diabetes showed that those carrying the rs4641 T-allele had elevated fasting plasma glucose levels ($P = 0.008$) and lower fasting serum LDL cholesterol levels ($P = 0.04$). In a study of 5,693 treatment-naïve subjects, the minor C-allele of rs955383 was a risk allele for obesity (BMI <30 vs. ≥ 30 kg/m²: 1.25 [1.07–1.64], $P = 0.01$; BMI <25 vs. ≥ 30 kg/m²: 1.16 [1.03–1.3], $P = 0.02$) (online appendix Table A [available at <http://dx.doi.org/10.2337/db06-0927>]). The treatment-naïve subjects were dichotomized according to their waist circumference (waist <94 cm for men and <80 cm for women vs. waist ≥ 94 cm for men and ≥ 80 cm for women) and rs955383 or rs11578696 genotype, respectively (online appendix Table A). The minor C-allele of rs955383 and the minor G-allele of rs11578696 were associated with larger waist circumference (1.14 [1.04–1.23], $P = 0.003$ and 1.12 [1.00–1.25], $P = 0.04$, respectively). Interestingly, homozygous carriers of the minor G-allele of rs577492 had shorter stature when assuming a recessive model ($P = 3.0 \cdot 10^{-5}$) and had higher fasting serum levels of total cholesterol and triglyceride ($P = 0.0007$ and $P = 0.003$) (Table 2).

Haplotype blocks were constructed using linkage disequilibrium patterns ($R^2 > 0.8$) (www.hapmap.org/index.html). Two blocks were identified: block 1 comprising rs4641, rs622834, and rs577492 and block 2 comprising rs12063564, rs12035615, and rs6661281. We selected common haplotypes (frequency >0.05) from each block; however, there was no significant association between common haplotypes and type 2 diabetes, obesity, or quantitative metabolic or anthropometric traits (data not shown).

In the present study, we tagged the region of *LMNA* including the promoter using eight SNPs and showed that

variation in this gene locus may associate with several traits related to metabolism and body stature. Assuming an additive model, we found nominal association of the minor T-allele of the *LMNA* rs4641 with type 2 diabetes and at the population level of unrelated, middle-aged individuals to elevated fasting glycemia. These effects of the *LMNA* variant were independent of body weight. The present findings of genotype-phenotype associations are consistent with previous reports on the impact of variation of *LMNA* (17,18). Thus, the association with type 2 diabetes is in accordance with the type 2 diabetes-like phenotype caused by severe *LMNA* mutations in the same gene of patients with familial partial lipodystrophy (21). The relationship between rs4641 and diabetes susceptibility has also been examined in 2,490 U.K. type 2 diabetic case and 2,556 control subjects with unknown glucose tolerance status. Although the British study failed to confirm our finding, the minor allele at rs4641 tended to be more frequent in case subjects (allelic OR 1.07 [95% CI 0.98–1.17], $P = 0.15$), and the CIs showed substantial overlap. Moreover, in a combined analysis with other available data (including the present study), the evidence that rs4641 has a modest effect on diabetes susceptibility was more convincing (1.10 [1.04–1.16], $P = 0.001$) (22).

We have also provided evidence of an association of the minor C-allele of *LMNA* rs955383 with obesity and larger waist circumference, whereas the minor G-allele of rs577492 was associated with increased fasting serum levels of total cholesterol and triglycerides. Similarly, Hegele et al. (19) demonstrated that variation in *LMNA* was associated with obesity-related traits. Also, the present observations of *LMNA* genotypes and altered fasting serum lipid profiles are consistent with findings in patients with familial partial lipodystrophy (21). A possible mechanistic explanation for the association of *LMNA* variation and altered glucose metabolism might be related to interference of the minor T-allele of the *LMNA* rs4641 with alternative splicing of exon 10. Such splicing variation may change the lamin A-to-C ratio and thereby prevent the lamin A and C proteins from forming functional polymers. Eventually, this may affect signaling cascades in adipose and muscle cells (3). In murine studies of lamin A-deficient mice, lamin C has been shown to be sufficient for health (5). This might, however, not be the case in humans; in mice, only homozygous carriers of *Lmna* mutations are affected, whereas human laminopathies are caused by dominant heterozygous mutations (23).

The finding that variation in *LMNA* associates with a pleiotropic impact on lipid metabolism, as well as on body composition/stature, might in part be related to the

TABLE 2

Anthropometric and metabolic characteristics of treatment-naïve subjects stratified according to *LMNA* rs4641 or rs577492 genotype (6,071 treatment-naïve subjects were available for genotyping)

	C/C	C/T	T/T	<i>P</i>
rs4641				
<i>n</i> (male/female)	3,051 (1,522/1,529)	1,981 (995/986)	363 (163/200)	
Age (years)	46 ± 8	46 ± 8	46 ± 8	
Height (cm)	172 ± 9	172 ± 9	172 ± 9	1.0
BMI (kg/m ²)	26.2 ± 4.5	26.2 ± 4.5	26.5 ± 5.0	0.3
Waist circumference (cm)	86 ± 13	86 ± 13	86 ± 14	0.3
Fasting serum lipids (mmol/l)				
Cholesterol	5.5 ± 1.1	5.5 ± 1.1	5.5 ± 1.0	0.8
HDL cholesterol	1.4 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	0.1
LDL cholesterol	3.6 ± 1	3.5 ± 0.9	3.5 ± 0.9	0.04
VLDL cholesterol	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	0.3
Triglyceride	1.3 ± 1.2	1.3 ± 1	1.3 ± 0.9	0.2
Plasma glucose (mmol/l)				
Fasting	5.5 ± 0.8	5.6 ± 0.9	5.6 ± 1.0	0.008
30-min post-OGTT	8.7 ± 1.9	8.7 ± 1.9	8.7 ± 1.8	0.8
120-min post-OGTT	6.2 ± 2.1	6.2 ± 2.2	6.3 ± 2.1	0.5
rs577492	A/A	A/G	G/G	
<i>n</i> (men/women)	5,140 (2,548/2,592)	628 (330/298)	21 (10/11)	
Age (years)	46 ± 8	46 ± 8	44 ± 10	
Height (cm)	172 ± 9	173 ± 9	166 ± 9	3 · 10 ⁻⁵
BMI (kg/m ²)	26.2 ± 4.6	26.3 ± 4.5	26.4 ± 3.4	0.7
Waist circumference (cm)	86 ± 13	87 ± 13	86 ± 9	0.4
Fasting serum lipids (mmol/l)				
Cholesterol	5.5 ± 1.1	5.5 ± 1.0	6.2 ± 1.0	0.0007
HDL cholesterol	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	0.7
LDL cholesterol	3.5 ± 1	3.5 ± 1	4.4 ± 0.6	0.01
VLDL cholesterol	0.6 ± 0.3	0.6 ± 0.3	1.0 ± 0.5	0.002
Triglyceride	1.3 ± 1.4	1.3 ± 1.0	2.5 ± 3.4	0.003
Plasma glucose (mmol/l)				
Fasting	5.5 ± 0.8	5.5 ± 0.7	5.6 ± 0.7	0.5
30-min post-OGTT	8.7 ± 1.9	8.7 ± 1.8	8.7 ± 1.9	0.6
120-min post-OGTT	6.2 ± 2.1	6.2 ± 2.0	6.5 ± 2.4	0.4

Data are means ± SD. Values of serum triglyceride were logarithmically transformed before statistical analysis. Calculated *P* values were adjusted for age, sex, and BMI (where appropriate) and were for rs4641, calculated assuming an additive model, and for rs577492, calculated assuming a recessive model.

implication of lamin proteins in organizing DNA transcription, replication, and repair (1,2), and, thereby, these proteins might in pre- and postnatal life have the potential to interfere with the expression of multiple genes involved in maintenance of cellular growth and differentiation, as well as energy metabolism.

The observed difference in height among 21 homozygous carriers of the rs577492 G-allele is of particular interest, since *Lmna*^{-/-} mice are growth retarded (4). The finding of association of variation in *LMNA* with shortened stature is a phenotype also observed in Werner's syndrome and Hutchinson-Gilford progeria syndrome, which are caused by mutations in *LMNA* (17).

In contrast to the single-variant analyses, the analyses of the haplotypes in *LMNA* did not demonstrate any significant association with the examined traits.

Taken together, the phenotypic diversity of both the lamin A knockout mouse (which is growth retarded and has several metabolic abnormalities) and the phenotypes of laminopathies do clinically appear in much less severe forms to be mirrored by the diversity of phenotypes of human carriers of minor variation in *LMNA*. Obviously, given the explorative nature of the present study and since no corrections for multiple comparisons were applied, these preliminary findings call for further studies in statistically powered and carefully phenotyped study samples.

RESEARCH DESIGN AND METHODS

The rs4641 (C>T), rs622834 (T>C), rs12063564 (C>T), rs577492 (A>G), rs6661281 (T>C), rs955383 (T>C), rs11578696 (A>G), and rs12035615 (C>T) polymorphisms were genotyped in 7,495 unrelated white subjects comprising three study groups. An LD plot of the tag SNPs is shown in Fig. 1. The first is a population-based sample (Inter99) of middle-aged Danes sampled at the Research Centre for Prevention and Health (24). The mean ± SD age of the Inter99 participants was 46 ± 8 years (BMI 26 ± 4 kg/m²), and 4,523 subjects were both normoglycemic in the fasting state and had normal glucose tolerance following an oral glucose tolerance test (OGTT); 1,196 had either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), 100 had known diabetes, and 252 had screen-detected type 2 diabetes. The second group comprised 360 subjects with both fasting normoglycemia and normal glucose tolerance, with a mean age of 62 ± 5 years and a mean BMI of 26 ± 4 kg/m², recruited from the Research Centre for Prevention and Health (25). The third group comprised 1,064 type 2 diabetic patients (aged 59 ± 11 years, age of clinical diagnosis 52 ± 11 years, BMI 29 ± 5 kg/m², and A1C 8.1 ± 1.6%) sampled through the out-patient clinic at Steno Diabetes Center. Normal subjects (from study groups 1 and 2 [4,883 subjects]) and type 2 diabetic patients (from study groups 1 and 3 [1,416 subjects]) were included in the case-control study of type 2 diabetes. Diabetes and pre-diabetes categories were diagnosed according to the 1999 World Health Organization criteria (26). Patients with diabetes due to known chronic pancreatitis, hemochromatosis, severe insulin resistance, maturity-onset diabetes of the young, maternally inherited diabetes and deafness, a family history of first-degree relatives with type 1 diabetes, insulin requirement within the first year after diabetes diagnosis, or a fasting serum C-peptide level ≤150 pmol/l at time of recruitment were excluded from the category of clinically defined type 2 diabetes. There was no evidence of population stratification bias (27). All subjects of study groups 1 and 2 underwent a standard 75-g OGTT in the fasting state in the morning. The treatment-naïve subjects were also examined in a study of

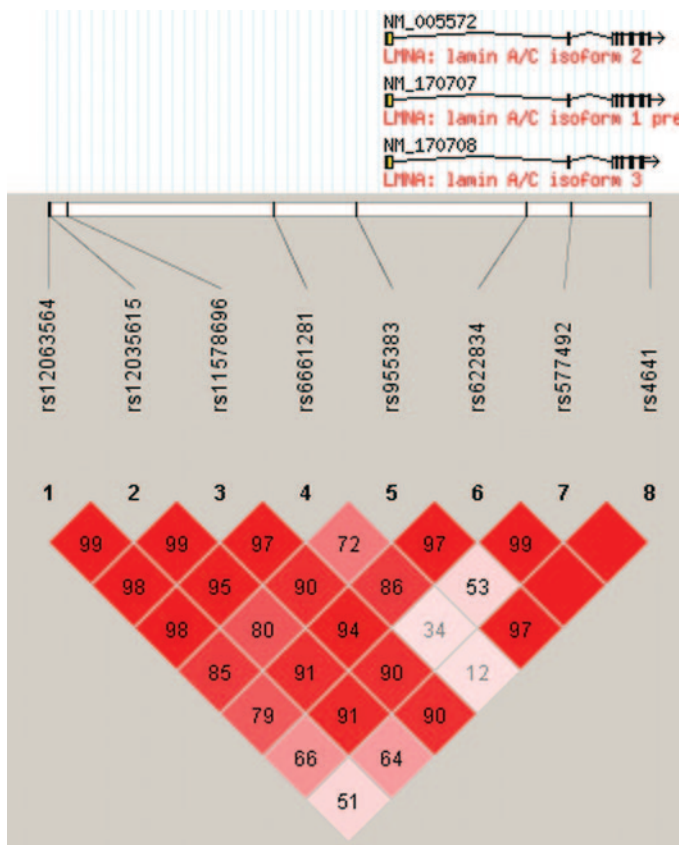


FIG. 1. Structure of the *LMNA* gene and linkage disequilibrium structure of the *LMNA* locus. Haplotype plot of pairwise D' calculated from our data. Bright red indicates $D' = 1.0$; shades of pink/red indicates $D' < 1$.

quantitative traits (6,071 subjects), including normal subjects (i.e., those fulfilling the criteria of both fasting normoglycemia and normal glucose tolerance during an OGTT), subjects with IFG or IGT, and screen-detected type 2 diabetic subjects of study group 1.

The case-control study of obesity and waist circumference involved 6,071 treatment-naïve subjects (having both normal fasting glycemia and glucose tolerance, IGT, IFG, or screen-detected type 2 diabetes) from study group 1. The cut off values for BMI and waist circumference (online appendix Table A) were taken as recommended (28,29). The number of subjects included in Tables 1 and 2 and in the online appendix Table A differs from the above numbers for various SNPs due to variation in genotyping success rates (see below). Informed written consent was obtained from all subjects before participation. The study was approved by the Ethical Committee of Copenhagen County and was in accordance with the principles of the Declaration of Helsinki.

Anthropometrical and biochemical measurements. Height and body weight were measured in light indoor clothes and without shoes, and BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured in the standing position midway between the iliac crest and the lower costal margin and hip circumference at its maximum. Blood samples were drawn after a 12-h overnight fast. Plasma glucose was analyzed by a glucose oxidase method (Granustest; Merck, Darmstadt, Germany). A1C was measured by ion-exchange high-performance liquid chromatography (normal reference range 4.1–6.4%), and serum insulin [excluding des(31,32) and intact proinsulin] was measured using the AutoDELFIA insulin kit (Perkin-Elmer, Turku, Finland). Serum triglyceride and total and HDL cholesterol were analyzed using enzymatic colorimetric methods (GPO-PAP and CHOD-PAP; Roche Molecular Biochemicals, Mannheim, Germany).

Genotyping. SNPs were selected from the HapMap project and previously published data capturing >90% of common variation in the selected region at an r^2 of 0.8. Genotyping of *LMNA* rs4641 was performed using chip-based matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry analysis of PCR-generated primer extension products as described (30) (Sequenom, San Diego, CA). The remaining polymorphisms were genotyped using TaqMan allelic discrimination (KBioscience, Herts, U.K.).

The genotyping success rate was >90% for rs4641 and >95% for the remaining SNPs, and among 451 replicate samples, there were <0.05% mismatches. Genotype distributions obeyed Hardy-Weinberg equilibrium in all study groups.

Statistical analysis. Fisher's exact test was applied to examine for differences in allele frequencies and genotype distributions between type 2 diabetic patients and control subjects, as well as for the case-control studies of obesity and waist circumference. Quantitative trait studies were performed using a general linear model including sex and genotype as fixed factors and age and BMI as covariates. Quantitative traits were checked for normality of the residuals and, if appropriate, logarithmically transformed. $P < 0.05$ was considered significant. Haplotype analyses were performed as a case-control study of type 2 diabetes, obesity, and for association with selected quantitative traits, with adjustment for sex, age, and BMI. Analyses were performed using RGui version 2.2.0.

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REFERENCES

- Aebi U, Cohn J, Buhle L, Gerace L: The nuclear lamina is a meshwork of intermediate-type filaments. *Nature* 323:560–564, 1986
- Zhang C, Jenkins H, Goldberg MW, Allen TD, Hutchison CJ: Nuclear lamina and nuclear matrix organization in sperm pronuclei assembled in *Xenopus* egg extract. *J Cell Sci* 109:2275–2286, 1996
- Lin F, Worman HJ: Structural organization of the human gene encoding nuclear lamin-a and nuclear lamin-c. *J Biol Chem* 268:16321–16326, 1993
- Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, Nagashima K, Stewart CL, Burke B: Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. *J Cell Biol* 147:913–920, 1999
- Fong LG, Ng JK, Lammerding J, Vickers TA, Meta M, Cote N, Gavino B, Qiao X, Chang SY, Young SR, Yang SH, Stewart CL, Lee RT, Bennett CF, Bergo MO, Young SG: Prelamin A and lamin A appear to be dispensable in the nuclear lamina. *J Clin Invest* 116:743–752, 2006
- Lammerding J, Schulze PC, Takahashi T, Kozlov S, Sullivan T, Kamm RD, Stewart CL, Lee RT: Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J Clin Invest* 113:370–378, 2004
- Wydner KL, McNeil JA, Lin F, Worman HJ, Lawrence JB: Chromosomal assignment of human nuclear envelope protein genes LMNA, LMNB1, and LBR by fluorescence in situ hybridization. *Genomics* 32:474–478, 1996
- Elbein SC, Hoffman MD, Teng K, Leppert MF, Hasstedt SJ: A genome-wide search for type 2 diabetes susceptibility genes in Utah Caucasians. *Diabetes* 48:1175–1182, 1999
- Vionnet N, Hani EH, Dupont S, Gallina S, Francke S, Dotte S, De Matos F, Durand E, Leprêtre F, Lecoeur C, Gallina P, Zekiri L, Dina C, Froguel P: Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2 diabetes locus on chromosome 1q21–q24. *Am J Hum Genet* 67:1470–1480, 2000
- Wiltshire S, Bottazzo GF, Gesu PB, Foxon R: A genomewide scan for loci predisposing to type 2 diabetes in a U.K. population (The Diabetes UK Warren 2 Repository): analysis of 573 pedigrees provides independent replication of a susceptibility locus on chromosome 1q. *Am J Hum Genet* 69:553–569, 2001
- Langefeld CD, Wagenknecht LE, Rotter JI, Williams AH, Hokanson JE, Saad MF, Bowden DW, Haffner S, Norris JM, Rich SS, Mitchell BD: Linkage of the metabolic syndrome to 1q23–q31 in hispanic families: the Insulin Resistance Atherosclerosis Study Family Study. *Diabetes* 53:1170–1174, 2004
- 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: 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* 341:1715–1724, 1999
13. Bonne G: Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet* 21:285–288, 1999
 14. Hegele RA, Cao H, Huff MW, Anderson CM: LMNA R482Q mutation in partial lipodystrophy associated with reduced plasma leptin concentration. *J Clin Endocrinol Metab* 85:3089–3093, 2000
 15. Raffaele-Di B, 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* 66:1407–1412, 2000
 16. Bonne G, Mercuri E, Muchir A, Urtizberea A, Bécane HM, Recan 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* 48:170–180, 2000
 17. 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* 423:293–298, 2003
 18. Hegele RA, Cao H, Harris SB, Zinman B, Hanley AJ, Anderson CM: Genetic variation in LMNA modulates plasma leptin and indices of obesity in aboriginal Canadians. *Physiol Genomics* 3:39–44, 2000
 19. Hegele RA, Huff MW, Young TK: Common genomic variation in LMNA modulates indexes of obesity in Inuit. *J Clin Endocrinol Metab* 86:2747–2751, 2001
 20. Steinle NI, Kazlauskaitė R, Imumorin IG, Hsueh WC, Pollin TI, O'Connell JR, Mitchell BD, Shuldiner AR: Variation in the lamin A/C gene: associations with metabolic syndrome. *Arterioscler Thromb Vasc Biol* 24:1708–1713, 2004
 21. Cao H, Hegele RA: Nuclear lamin A/C R482Q mutation in canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* 9:109–112, 2000
 22. Owen KR, Groves CJ, Hanson RL, Knowler WC, Shuldiner AR, Elbein SC, Mitchell BD, Froguel P, Ng MCY, Chan JC, Jia W, Deloukas P, Hitman GA, Walker M, Frayling TM, Hattersley AT, Zeggini E, McCarthy MI: Common variation in the LMNA gene (encoding lamin A/C) and type 2 diabetes: association analyses in 9,518 subjects. *Diabetes* 56:879–883, 2007
 23. Pendas AM, Zhou Z, Cadinanos J, Freije JMP, Wang J, Hultenby K, Astudillo A, Wernerson A, Rodriguez F, Tryggvason K, Lopez-Otin C: Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice. *Nat Genet* 31:94–97, 2002
 24. Jørgensen T, Borch-Johnsen K, Thomsen TF, Ibsen H, Glümer C, Pisinger C: A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovasc Prev Rehabil* 10:377–386, 2003
 25. Drivsholm T, Ibsen H, Schroll M, Davidsen M, Borch-Johnsen K: Increasing prevalence of diabetes mellitus and impaired glucose tolerance among 60-year-old Danes. *Diabet Med* 18:126–132, 2001
 26. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1. Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
 27. Andersen G, Overgaard J, Albrechtsen A, Glumer C, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O: Studies of the association of the GNB3 825C > T polymorphism with components of the metabolic syndrome in white Danes. *Diabetologia* 49:75–82, 2006
 28. Campfield LA, Smith FJ: The pathogenesis of obesity. *Best Pract Res Clin Endoc Metab* 13:13–30, 1999
 29. Lean ME, Han TS, Seidell JC: Impairment of health and quality of life in people with large waist circumference. *Lancet* 351:853–856, 1998
 30. Buetow KH, Edmonson M, MacDonald R, Clifford R, Yip P, Kelley J, Little DP, Strausberg R, Koester H, Cantor CR, Braun A: High-throughput development and characterization of a genomewide collection of gene-based single nucleotide polymorphism markers by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Proc Natl Acad Sci U S A* 98:581–584, 2001