Risk Factors for Diabetes in Familial Partial Lipodystrophy, Dunnigan Variety

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OBJECTIVES — Familial partial lipodystrophy, Dunnigan variety (FPLD), is an autosomal dominant disorder due to missense mutations in the lamin A/C (*LMNA*) gene encoding nuclear lamina proteins. It is characterized by loss of subcutaneous fat from the extremities and trunk and accumulation of fat in the head and neck region beginning at puberty. Patients with FPLD are predisposed to metabolic complications of insulin resistance such as diabetes. We sought to identify risk factors for diabetes in patients with FPLD.

RESEARCH DESIGN AND METHODS — A cross-sectional study comparing clinical, biochemical, and anthropometric variables and *LMNA* genotypes in FPLD patients with and without diabetes.

RESULTS — We studied 52 women and 24 men with FPLD from 18 different families. Twenty-eight women (54%) but only four men (17%) had diabetes ($P < 0.001$); therefore further comparisons were mostly limited to women. Compared with women without diabetes, those with diabetes had higher BMI (median values 23 vs. 24 kg/m^2, respectively; $P = 0.03$), increased chin skinfold thickness (10 vs. 20 mm; $P = 0.001$), lower rates of nulliparity (60% vs. 28%; $P = 0.04$), and higher levels of fasting serum triglycerides (2.4 vs. 3.5 mmol/l; $P < 0.001$) but similar serum leptin levels (3.4 vs. 3.6 ng/ml; $P = 0.9$). The prevalence of diabetes was not related to age, menopausal status, family history of type 2 diabetes in unaffected relatives, or *LMNA* genotype.

CONCLUSIONS — We conclude that increased adiposity as reflected by excess subcutaneous fat accumulation in the chin region and parity may predispose women with FPLD to develop diabetes.

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Familial partial lipodystrophy, Dunnigan variety (FPLD) (Mendelian Inheritance in Man #151660), is a rare monogenic adipose tissue disorder with increased predisposition of affected subjects to insulin resistance and its metabolic complications, such as glucose intolerance, diabetes, dyslipidemia, and hepatic steatosis (1–4). Patients with FPLD develop gradual loss of subcutaneous fat from the extremities and trunk starting at puberty. Subsequently, some accumulate excess fat in the head, neck, and intra-abdominal regions (5). The disorder is inherited in an autosomal dominant fashion and recently has been shown to be due to missense mutations in the gene encoding lamins A and C (*LMNA*) on chromosome 1q21–22 (6–9). Lamins A and C belong to the intermediate filament family of proteins and are structural components of nuclear lamina. Previously, we have shown that compared with affected men, women with FPLD are particularly predisposed to develop diabetes (10). However, the risk factors that predispose patients with FPLD to develop diabetes remain unclear. For example, it is not clear whether a particular *LMNA* mutation, the degree of fat loss from the extremities and trunk, or the excess fat deposition predisposes patients to develop diabetes. In the present study, therefore, we sought to determine the risk factors for the development of diabetes in a cross-sectional comparison of a large number of well-characterized patients with FPLD with and without diabetes.

RESEARCH DESIGN AND METHODS

Subjects

All subjects gave written informed consent. Appropriate institutional review boards approved the protocol. Only adults (>18 years of age) were included in this analysis. FPLD was diagnosed on the basis of characteristic phenotype and the presence of missense mutations in the *LMNA* gene. All unaffected relatives were genotyped for the presence of the missense mutation identified in their family and had only wild-type alleles. We studied 24 men and 52 women with FPLD belonging to 18 different families. All families were of European origin, except family F2600, which was of Asian Indian origin. Most of these pedigrees have been previously reported (7,9,11,12). All the families were evaluated at the University of Texas Southwestern Medical Center at Dallas, except F1000 and F2500 families (24 subjects), who were evaluated at the National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland. Nineteen of these subjects (six women and three men with diabetes and five women and five men without diabetes)

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Abbreviations: FPLD, familial partial lipodystrophy, Dunnigan variety.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical characteristics of FPLD patients with and without diabetes*

	Women			Men		
	Diabetic	Nondiabetic	*P*	Diabetic	Nondiabetic	*P*
n	28	24		4	20	
Age (years)	41.5 (23–67)	40.5 (19–71)	0.7	39 (21–59)	35 (19–83)	0.9
BMI (kg/m^2)	24.0 (19.8–30.2)	23.1 (20.8–37)	0.03	28.0 (23.9–37.4)	26.3 (20.6–34.9)	0.3
Type 2 diabetes in unaffected relatives	52	41	0.6	50	45	1.0
Lipid-lowering drugs	69	23	0.002	50	0	0.02
Hypertension	53.6	27.3	0.08	50	21	0.3
Acanthosis nigricans	29	27	0.1	0	5	1.0
Acute pancreatitis	25	7	0.3	0	0	NA
PCOS	63	47	0.5	—	—	
Nulliparous	28	60	0.04	—	—	
Premenopausal	54	61	0.9	—	—	

*Data are medians (ranges) or %. PCOS, polycystic ovarian syndrome.

visited the General Clinical Research Center of the University of Texas Southwestern Medical Center at Dallas for evaluation; information and blood samples on the other 33 patients were obtained by mail as described previously (10).

Questionnaire

All subjects reported demographic data, date of birth, height, and weight, as well as health history, particularly related to the presence or absence of diabetes, dyslipidemia, hypertension, acanthosis nigricans, parity, menopausal status, menstrual irregularity, hirsutism, and polycystic ovaries and use of medications. Diabetes was diagnosed on the basis of previous history, use of hypoglycemic medications, or if fasting serum glucose concentration exceeded 7.0 mmol/l. Hypertension was diagnosed on self-report or use of antihypertensive medications or if either systolic or diastolic blood pressure exceeded 140 or 90 mmHg, respectively.

Anthropometry

In the 19 subjects evaluated at Dallas, skinfold thickness was measured with a Lange caliper (Cambridge Scientific Industries, Cambridge, MD) at the chin and five truncal (chest, mid-axillary, abdomen, subscapular, and suprailiac) and six peripheral (biceps, triceps, forearm, hip, thigh, and calf) sites on the right side of the body. The mean of three repeat measurements at each site was calculated.

Biochemical studies

Blood was collected after a 12-h overnight fast for analysis of HbA_{1c} and for serum chemistry profile, lipoproteins, insulin, and leptin concentrations. Fasting serum samples were analyzed for cholesterol, triglycerides, and HDL cholesterol as described previously (10). Blood HbA_{1c} was measured using ion exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA). Serum insulin and leptin levels were determined by radioimmunoassay using commercial kits (Linco Research, St. Charles, MO).

Mutational analysis

Mutational analysis of *LMNA* was performed on all the patients by direct sequencing of the coding region and the splice-site junctions, as described previously (7).

Statistical analyses

Categorical data were compared by Fisher's exact test. The biochemical parameters and anthropometric data were compared using Wilcoxon's rank-sum test. Data are expressed as median (range), and *P* value <0.05 was considered statistically significant.

RESULTS — All patients, except one man, were previously diagnosed to have diabetes. Forty-three percent of them were treated with insulin, 23% with oral hypoglycemic agents, and 34% with nonpharmacological measures, including diet and physical activity. The prevalence of diabetes among women was approximately three times higher than in men with FPLD (56% vs. 17%, respectively; $P < 0.001$). Although comparative data on genotypes, clinical characteristics, and biochemical parameters in both men and women with and without diabetes are presented, main conclusions are limited to the data on women because of small sample size of men with diabetes. Median age of onset of diabetes was 30 years (range, 17–51 years) in women and 34 years (25–39 years) in men. Whereas the prevalence of hypertension was similar in women and men (42% vs. 26%; $P = 0.3$), more women reported taking lipid-lowering medications (92% vs. 55%; $P = 0.001$).

Comparison of women with and without diabetes revealed similar age and prevalences of type 2 diabetes in unaffected relatives, acanthosis nigricans, polycystic ovarian syndrome, and premenopausal status (Table 1). Versus women without diabetes, however, those with diabetes had significantly higher BMI ($P = 0.03$), increased use of lipid-lowering medications ($P = 0.002$), and lower rates of nulliparity ($P = 0.04$) (Table 1). The prevalence of hypertension tended to be slightly higher among women with diabetes, although it did not reach statistical significance ($P = 0.08$).

Comparison of men with and without diabetes revealed similar age, BMI, history of type 2 diabetes in unaffected relatives, hypertension, and acanthosis nigricans. Two of the four men with diabetes were receiving lipid-lowering medications,

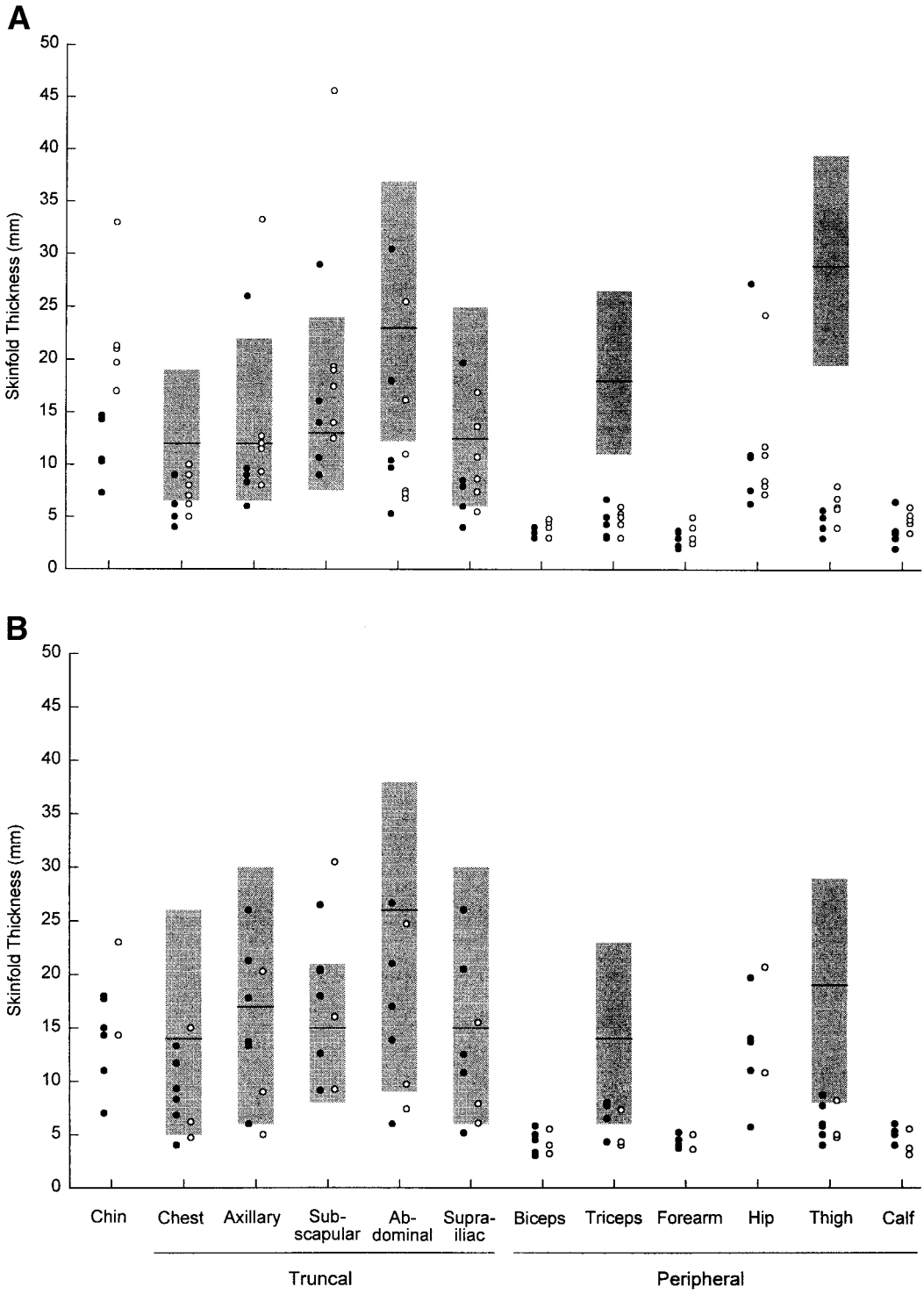

Figure 1—*Skinfold thickness at various anatomic sites in women* (A) *and men* (B) *with FPLD.* ○, *patients with diabetes;* ●, *patients without diabetes. The shaded bars represent the median and 10th and 90th percentile values of skinfold thickness for normal women aged 18–55 years in* A *(13) and for normal men aged 18 to 61 years in* B *(14). Women with diabetes had more fat accumulation at the chin and biceps than those without diabetes* ($P < 0.05$).

versus none among men without diabetes ($P = 0.02$).

Skinfold measurements were available in six women with diabetes and five women without diabetes, and in three men with diabetes and six men without diabetes. Versus women without diabetes, those with diabetes had significantly increased skinfold thickness at the chin (10.4 mm [7.3–14.7 mm] vs. 20.3 mm [17–33 mm], respectively; $P = 0.01$) and at the biceps (4.5 mm [3–5.7 mm] vs. 6 mm [4–8 mm]; $P = 0.03$) (Fig. 1*A*). There were no significant differences in the skinfold thickness of the other peripheral and truncal sites between women with and without diabetes (Fig. 1*A*). In comparison with normal values (13), all women with FPLD had markedly reduced peripheral skinfold thickness at the triceps and thigh regions; however, truncal skinfolds at the chest, axillary, subscapular, abdominal and suprailiac regions ranged from <10th percentile to >90th

Table 2—*Biochemical parameters in FPLD patients with and without diabetes*

	Women			Men		
	Diabetic	Nondiabetic	*P*	Diabetic	Nondiatetic	*P*
n	28	24		4	20	
Glucose (mmol/l)	9.1 (3.9–15.2)	5.1 (2.1–6.9)	<0.0001	12.7 (6.2–18.1)	5 (4.1–5.8)	<0.01
Insulin (pmol/l)*	123 (62–660)	87 (27.6–384)	0.2	138	114 (38.4–264)	0.8
HbA_{1c} (%)	7.5 (4.5–12.3)	5.15 (4.6–6.4)	<0.0001	9.6 (6–11.6)	5.1 (3.2–5.7)	<0.01
Triglycerides (mmol/l)	3.5 (1.4–33.5)	2.4 (0.8–12.2)	<0.001	2.2 (1.7–19.3)	1.7 (0.5–7.2)	0.2
Cholesterol (mmol/l)	6.2 (3.6–12.1)	5.6 (3.8–7.5)	0.07	5.2 (4.8–7.8)	5.1 (3.3–6.5)	0.4
HDL cholesterol (mmol/l)	0.85 (0.3–1.9)	1.0 (0.5–2.4)	0.08	1.1 (0.8–1.2)	1.1 (0.4–1.9)	0.7
Uric acid (μmol/l)	345 (220–595)	262 (160–428)	0.05	309 (220–494)	363 (208–553)	0.6
Leptin (ng/ml)	3.4 (0.9–56)	3.6 (1.4–14.6)	0.9	0.9 (0.4–1.8)	2.9 (0.23–13.5)	0.03

Data are medians (ranges). *Insulin levels from patients receiving hypoglycemic agents were excluded; insulin levels were available for 9 women with diabetes and 21 women without diabetes and 1 man with diabetes and 18 men without diabetes.

percentile. No statistically significant differences were seen in the skinfold measurements between the FPLD men with and without diabetes (Fig. 1*B*). All men tended to have reduced peripheral skinfold thickness compared with normal values (14).

Plasma glucose and blood HbA_{1c} concentrations were higher in subjects with diabetes; however, plasma insulin levels were not significantly different (Table 2). Fasting plasma triglycerides and uric acid levels were higher in women with diabetes versus those without diabetes (P = 0.002 and 0.04, respectively), but plasma total cholesterol and HDL cholesterol levels were similar. Serum leptin levels were similar in women with and without diabetes (3.4 and 3.6 ng/ml; P = 0.9). There were no differences in plasma triglycerides, cholesterol, and HDL cholesterol concentrations between the two groups of men. The four male subjects with diabetes had lower serum leptin levels than the men without diabetes (median values, 0.9 vs. 2.9 ng/ml; P = 0.03).

We found eight different missense mutations in the *LMNA* gene in these patients (Table 3). Some of these mutations have been previously described by us (7,11,12); R419C and L515E are novel mutations, involving exons 7 and 9. All previous mutations in FPLD have been reported in exons 1, 8, and 11. Overall results revealed that the genotype did not predict increased prevalence of diabetes, although women carrying R482Q tended to have somewhat higher prevalence of diabetes than those with R482W (58 vs. 38%; P = 0.3).

CONCLUSIONS — Our data suggest that women with FPLD may be predisposed to develop diabetes owing to excess fat deposition in areas not affected by lipodystrophy. This was supported by the finding of higher BMI in women with diabetes versus those without diabetes. Since the loss of fat from most of the peripheral and truncal subcutaneous sites (except biceps) was similar between women with and without diabetes, this difference in BMI may relate to excess fat deposition in the head, neck, and intraabdominal regions. Certainly, women with diabetes had excess chin (submental) fat versus those without diabetes. Increased chin fat may represent deposition of fat in the areas unaffected by lipodystrophy such as intra-abdominal depots, and as such may be accompanied by fat deposition in other important organs such as the liver and skeletal muscles. Interestingly, patients with type 2 diabetes have been reported to have increased subscapular, chest, and abdominal skinfold thickness and decreased thigh and calf skinfold thickness (15,16).

Another predisposing factor for diabetes in women was parity, as less nulliparous women had diabetes. Kritz-Silverstein et al. (17) reported that parity was an independent risk factor for future development of type 2 diabetes, but other studies have found that the magnitude of this effect is reduced after adjusting for age, socioeconomic status, and BMI (18). Pregnancy is a well-known diabetogenic state and is a time of efficient fat storage. Because pregnant women with FPLD may not be able to accumulate fat in most of the subcutaneous regions, which are affected by lipodystrophy, they may accumulate excess fat in the face, neck, and intraabdominal region, predisposing them to diabetes.

Previous studies have identified dyslipidemia, particularly hypertriglyceridemia, as a predisposing risk factor for type 2 diabetes (19,20). Consistent with those studies, hypertriglyceridemia was also associated with predisposition to diabetes among women with FPLD. However, this association may be due to poor glycemic

Table 3—*Prevalence of* LMNA *mutations in FPLD patients with and without diabetes*

Amino acid change	Pedigrees with mutation	Women		Men	
		Diabetic	Nondiabetic	Diabetic	Nondiabetic
R28W	F100	1	0	0	1
R62G	F600	2	1	0	3
R419C	F4100	1	0	1	1
G465D	F1100	1	0	1	1
R482Q	F200, F500, F100, F2500, F2800	15	11	0	7
R482W	F300, F700, F1400, F2600, F2900	6	10	2	6
L515E	F3900	1	0	0	0
R582H	F2700	1	2	0	1

No statistically significant difference between diabetic and nondiabetic subjects in prevalence of mutations.

control in FPLD women with diabetes. Of note, a previous study reported higher serum triglyceride concentrations in FPLD patients with diabetes even when glycemic control was excellent (21). The onset of hypertriglyceridemia has reportedly antedated the onset of hyperglycemia in FPLD patients (21,22). Women with diabetes also had higher serum uric acid levels than those without diabetes. Interestingly, fasting serum insulin levels were not significantly different among FPLD women with and without diabetes. However, only nine women with diabetes had fasting serum insulin concentrations available because those on hypoglycemic therapy were excluded from this analysis.

Our anthropometric data, although limited, indicate that severity of lipodystrophy does not differ among FPLD women with and without diabetes, as most of the peripheral and truncal skinfold thicknesses were similarly reduced in the two groups. Serum leptin levels also were similarly reduced in the women with and without diabetes, compared with normal women matched for BMI (21). We have recently reported that serum adiponectin levels are reduced in FPLD subjects with diabetes versus those without diabetes (4.3 [1.9–12.7] vs. 7.6 [2.7–23.2] μg/ml, respectively; $P < 0.05$) (22). Reduced plasma adiponectin levels have been reported in other insulin-resistant states as well (23,24). These data suggest that FPLD patients with diabetes may be more insulin resistant than those without diabetes.

Another important aim of the study was to identify if any particular *LMNA* variant carried a high risk of diabetes among FPLD subjects. On the basis of study of a small pedigree, we have previously reported that R582H mutation may cause mild lipodystrophy as well as less severe metabolic complications, possibly because this particular mutation in exon 11 of *LMNA* affects transcription of lamin A only, whereas other previously reported mutations in FPLD patients in exon 1 and 8 affect transcription of both lamins A and C (11). However, our study did not have enough patients with some of the rare *LMNA* mutations to perform meaningful comparisons. When the two most prevalent mutations among FPLD subjects (R482Q and R482W) were compared, women carrying R482Q had somewhat higher prevalence of diabetes than those carrying R482W; however, this difference did not achieve statistical significance. Therefore, overall, prevalence of diabetes was not related to specific *LMNA* mutations. However, it is likely that insulin resistance in some of the FPLD patients may be due to modifier alleles of other genes implicated in causing insulin resistance.

Interestingly, some of the well-recognized risk factors for development of type 2 diabetes, such as, age, family history of type 2 diabetes, hypertension, and acanthosis nigricans (25,26), were not predictive of diabetes in women with FPLD. It is likely that the *LMNA* mutation may impart such a high risk of developing diabetes that it overshadows potential influence of these established risk factors for type 2 diabetes. FPLD being a rare disease, we consider data on 76 individuals as a large collection of subjects. Nonetheless, compared with previous population-based studies in type 2 diabetes (26,27), the number of subjects in our study is certainly limited and thus, the study may have lacked power to identify some of these risk factors. The lack of power certainly affected comparison of FPLD men with and without diabetes, since only four men had diabetes. Our study did not assess dietary intake and physical activity, which may be important confounding variables. Further, our data were cross-sectional and thus confirmation of our findings will require prospective longitudinal studies.

We conclude that women with FPLD are more predisposed to diabetes than men. This tendency among women may be due to increased adiposity in regions not affected by lipodystrophy, as reflected by increased submental deposition of subcutaneous fat. Furthermore, parity may predispose women with FPLD to diabetes. Age, menopausal status, family history of type 2 diabetes, and *LMNA* variants do not predict predisposition to diabetes.

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References

1. Dunnigan MG, Cochrane MA, Kelly A, Scott JW: Familial lipoatrophic diabetes with dominant transmission: a new syndrome. *Q J Med* 43:33–48, 1974
2. Jackson SN, Howlett TA, McNally PG, O'Rahilly S, Trembath RC: Dunnigan-Kobberling syndrome: an autosomal dominant form of partial lipodystrophy. *Q J Med* 90:27–36, 1997
3. Robbins DC, Horton ES, Tulp O, Sims EA: Familial partial lipodystrophy: complications of obesity in the non-obese? *Metab Clin Exp* 31:445–452, 1982
4. Haque WA, Vuitch F, Garg A: Postmortem findings in patients with familial partial lipodystrophy, Dunnigan variety. *Diabet Med* 19:1022–1025, 2002
5. Garg A, Peshock RM, Fleckenstein JL: Adipose tissue distribution pattern in patients with familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab* 84:170–174, 1999
6. 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
7. Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, Taylor SI, Lovett M, Bowcock AM: Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. *Am J Hum Genet* 66:1192–1198, 2000
8. Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, Gregory S, O'Rahilly S, Trembath RC: LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet* 24:153–156, 2000
9. Peters JM, Barnes R, Bennett L, Gitomer WM, Bowcock AM, Garg A: Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21–22. *Nat Genet* 18:292–295, 1998
10. Garg A: Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab* 85:1776–1782, 2000
11. Garg A, Vinaitheerthan M, Weatherall PT, Bowcock AM: Phenotypic heterogeneity in patients with familial partial lipodystrophy (Dunnigan variety) related to the site of missense mutations in lamin A/C gene. *J Clin Endocrinol Metab* 86:59–65, 2001

12. Garg A, Speckman RA, Bowcock AM: Multisystem dystrophy syndrome due to novel missense mutations in the amino-terminal head and alpha-helical rod domains of the lamin A/C gene. *Am J Med* 112:549–555, 2002
13. Jackson AS, Pollock ML, Ward A: Generalized equations for predicting body density of women. *Med Sci Sports Exercise* 12: 175–181, 1980
14. Jackson AS, Pollock ML: Generalized equations for predicting body density of men. *Br J Nutr* 40:497–504, 1978
15. Feldman R, Sender AJ, Siegelaub AB: Difference in diabetic and nondiabetic fat distribution patterns by skinfold measurements. *Diabetes* 18:478–486, 1969
16. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM: Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes* 45:1684–1693, 1996
17. Kritz-Silverstein D, Barrett-Connor E, Wingard DL: The effect of parity on the later development of non-insulin-dependent diabetes mellitus or impaired glucose tolerance. *N Engl J Med* 321:1214–1219, 1989
18. Boyko EJ, Alderman BW, Keane EM, Baron AE: Effects of childbearing on glucose tolerance and NIDDM prevalence. (erratum appears in *Diabetes Care* 13: 1138, 1990). *Diabetes Care* 13:848–854, 1990
19. Haffner SM: Diabetes, hyperlipidemia, and coronary artery disease. *Am J Cardiol* 83:17F–21F, 1999
20. Haffner SM, Mykkanen L, Festa A, Burke JP, Stern MP: Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation* 101:975–980, 2000
21. Ruhl CE, Everhart JE: Leptin concentrations in the United States: relations with demographic and anthropometric measures. *Am J Clin Nutr* 74:295–301, 2001
22. Haque WA, Shimomura I, Matsuzawa Y, Garg A: Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab* 87:2395, 2002
23. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA: Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86:1930–1935, 2001
24. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 20:1595–1599, 2000
25. Shaten BJ, Smith GD, Kuller LH, Neaton JD: Risk factors for the development of type II diabetes among men enrolled in the usual care group of the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:1331–1339, 1993
26. Ramachandran A, Snehalatha C, Viswanathan V, Viswanathan M, Haffner SM: Risk of noninsulin dependent diabetes mellitus conferred by obesity and central adiposity in different ethnic groups: a comparative analysis between Asian Indians, Mexican Americans and Whites. *Diabetes Res Clin Pract Suppl* 36:121–125, 1997
27. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 41: 715–722, 1992