

Köbberling Type of Familial Partial Lipodystrophy

An underrecognized syndrome

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OBJECTIVE — The phenotypic expression of partial lipodystrophy is present in two familial syndromes: familial partial lipodystrophy type 1 (FPLD1), with fat loss from the extremities, and central obesity and FPLD type 2, with fat loss from the extremities, abdomen, and thorax. The latter disorder is associated with mutations in the *LMNA* gene. FPLD1 is thought to be rare. Here, we report 13 subjects with FPLD1, suggesting that this syndrome is more common than previously thought.

RESEARCH DESIGN AND METHODS — Fasting glucose, plasma lipids, leptin, HbA_{1c}, and anthropomorphic measurements were evaluated in 13 subjects with clinical features of FPLD1 and are compared with two age-matched control groups, with and without diabetes.

RESULTS — Only women with clinical features of FPLD1 have been identified. Although they lack extremity and gluteal subcutaneous fat, they do have truncal obesity. Skinfold thickness on the arm and leg was significantly less than that in control subjects. The ratio of skinfold thickness from abdomen to thigh was significantly higher in subjects, suggesting an easy method for identifying affected patients. FPLD1 subjects also had components of the metabolic syndrome, including hypertension, insulin resistance, and severe hypertriglyceridemia resulting in pancreatitis. Premature coronary artery disease was present in 31% of subjects. None of the subjects had coding mutations in the *LMNA* gene or in the gene coding for peroxisome proliferator-activated receptor (PPAR)- γ .

CONCLUSIONS — FPLD1 is more common than previously described, but the diagnosis is often missed. Early recognition and intensive treatment of hyperlipidemia and diabetes in FPLD1 is important for prevention of pancreatitis and early cardiovascular disease.

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Familial partial lipodystrophies (FPLDs) are syndromes with partial loss of subcutaneous fat. FPLD type 1 (FPLD1), or Köbberling-type lipodystrophy, was first reported by Köbberling et al. (1,2) in 1971 and again in 1975 in a family with three affected subjects, as well as in two unrelated individuals. FPLD1 is

characterized by fat loss confined to the extremities, with normal or increased distribution of fat on the face, neck, and trunk. FPLD type 2 (FPLD2), also known as Dunnigan-type lipodystrophy, is a rare syndrome with loss of subcutaneous fat from the limbs and trunk and excess fat accumulation around the neck and labia

and has been well characterized in the literature (3–7). Mutations for some individuals with FPLD2 have been identified in the *LMNA* gene, which encodes lamins A and C. These nuclear lamins are members of the intermediate filament family and make up most of the lamina associated with the inner nuclear membrane (7,8); however, the mechanism whereby *LMNA* gene mutation leads to relative fat loss and severe insulin resistance remains elusive (9), and other possible mutations remain to be identified. Much less is known about FPLD1. Since the initial description (1), there have been only a few case reports (10–13) and descriptions of two families (14,15); therefore, this syndrome is considered rare (5). In this report, we describe 13 unrelated subjects, seen in our clinics, who have phenotypes consistent with FPLD1. Our experience suggests that this syndrome is more common than previously thought and that physicians, because of unfamiliarity with the clinical features of FPLD1, may miss the diagnosis.

RESEARCH DESIGN AND METHODS

Thirteen Caucasian women, who presented to University of Washington clinics (diabetes, endocrine, or lipid clinics) for evaluation of diabetes, obesity, and/or marked hypertriglyceridemia, were identified as having FPLD1 using criteria from previous reports of this syndrome (childhood absence of palpable subcutaneous fat from the arms and legs, normal subcutaneous fat on the face and trunk, moderate truncal obesity, and normal genitalia [1,2,15]). Comparisons of phenotype and metabolic characteristics were made to age-matched normolipidemic, nondiabetic subjects (nondiabetic control subjects) and subjects with type 2 diabetes (diabetic control subjects). Nondiabetic control subjects were recruited from hospital staff. Diabetic control subjects were recruited by advertisement at the Diabetes Care Center at the University of Washington. All subjects gave informed consent before participation in

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Abbreviations: CAD, coronary artery disease; FPLD, familial partial lipodystrophy; PPAR, peroxisome proliferator-activated receptor.

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

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this study, which was approved by the Human Subjects Committee at the University of Washington.

Diabetes was identified as fasting glucose >126 mg/dl (16) or by use of hypoglycemic medications. Hypertension was documented by history and by the use of antihypertensive medications. Hospital records were used to confirm diagnoses, including history of pancreatitis and/or vascular disease.

Skinfold measurement

All measurements of skinfolds were done by one individual (K.L.H.) in triplicate at all sites and on the dominant extremity using a Lange skinfold caliper. One subject was not included because she had significant redistribution of fat after treatment with a thiazolidinedione before caliper measurements.

DNA sequencing

Exons 8–11 of *LMNA*, the gene coding for two splice products, lamins A and C, and exons 1–6 and 8 of the gene coding for *PPAR-γ* (*PPARG*) were sequenced as previously described (17) using published primers (18,19).

Laboratory tests

Measurements of fasting total plasma cholesterol, triglycerides, HDL, LDL, glucose, and HbA_{1c} were performed at the Department of Laboratory Medicine of the University of Washington. Fasting leptin was analyzed by radioimmunoassay in the Immunoassay Core at the Diabetes and Endocrinology Research Center.

Statistics

All data are presented as means ± SE. Data were initially analyzed by ANOVA. Data with significance, set at *P* < 0.05, were further analyzed by Student's *t* test or Spearman's test (for triglycerides).

RESULTS

Body composition

All of the subjects in this report are women. To date, no men with FPLD1 have been identified. The average age of the FPLD1 subjects was 53.4 ± 2.2 years (range 43–65), not significantly different from the diabetic (53.1 ± 3.9 years) and nondiabetic (49.1 ± 2.6 years) control groups. The anatomic and metabolic criteria used for the diagnosis of FPLD1, as well as the number of subjects with each

Table 1—Anatomic, metabolic, and clinical features of subjects with FPLD1

Anatomic criteria	
Lack of extremity subcutaneous fat	13 (100)
Lack of gluteal fat	13 (100)
Ledge of fat superior to the gluteal	13 (100)
Ledge of fat below the deltoid/triceps	12 (92)
Truncal obesity	13 (100)
Metabolic criteria	
Diabetes	12 (92)
Hypertriglyceridemia	12 (92)
Clinical manifestations	
Acanthosis nigricans	1 (7.7)
CAD	4 (31)
Hypertension	10 (77)
Pancreatitis	7 (54)
Polycystic ovarian syndrome	0 (0)

Data are n (%).

feature, are described in Table 1. Using the criteria of paucity of fat on the extremities and buttocks, we noted a prominent ledge of fat in all subjects above the gluteal area (Fig. 1A). With further examination, we also detected a ledge at the upper arm over the deltoid region and upper triceps (Fig. 1B) and in the upper medial thigh. Thin wrinkles of skin under the buttocks confirm the absence of subcutaneous fat. Extremities often appear muscular with visible veins (Fig. 1C) or thin without obvious veins. The fat on the face, chin, and neck can be either normal or excessive (Fig. 1D).

Anthropomorphic measurements are shown in Table 2. BMI was significantly higher in the FPLD1 subjects (34.7 ± 2.3 kg/m², *P* < 0.01) and in the diabetic control group (40.1 ± 2.9, *P* < 0.03) than in the nondiabetic control group (25.2 ± 0.8). Waist-to-hip ratio was significantly higher in the FPLD1 subjects (1.1 ± 0.03, *P* < 0.01) and in the diabetic control group (0.93 ± 0.03, *P* < 0.03) than in the nondiabetic control group (0.81 ± 0.04). The FPLD1 subjects had a significantly higher waist-to-hip ratio than the diabetic control subjects (*P* < 0.01), reflecting the significant lack of buttock fat in the hip measurement of the FPLD1 subjects. The diabetic control subjects had the largest skinfold measurements in the upper triceps (39.7 ± 2.9 mm), and the FPLD1 subjects had the smallest skinfold measurements of the upper forearm (11.0 ± 2.5). The skinfold ratio of triceps to forearm (3.7 ± 0.7) was significantly higher in the FPLD1 subjects than in either the diabetic (2.0 ± 1.4, *P* < 0.02) or nondiabetic (2.0 ± 0.21, *P* < 0.03) control

groups, reflecting the lack of subcutaneous fat below the shoulder ledge (Fig. 2A). Skinfold measurements of the abdomen were not significantly different in FPLD1 subjects compared with either control group; however, the skinfold measurements of the abdomen were significantly higher in the diabetic control subjects (47.7 ± 4.1 mm, *P* < 0.04) than in the nondiabetic control subjects (34.5 ± 4.2). Since the average skinfold thickness of the thigh (11.3 ± 2.9 mm) and calf (7.3 ± 1.9) in FPLD1 subjects was markedly lower than in either the diabetic (42.8 ± 3.3 and 28.8 ± 3.6, respectively) or nondiabetic control groups (34.4 ± 3.3 and 25.2 ± 2.3, respectively), the ratio of abdomen to thigh was highest in FPLD1 subjects (6.8 ± 1.5), with minimal overlap (Fig. 2B) with the diabetic (1.2 ± 0.13, *P* < 0.002) and nondiabetic (0.98 ± 0.12, *P* < 0.0009) control groups.

All of the subjects documented to have FPLD1 by the criteria outlined in Table 1 describe their current body habitus as the same since childhood, except for one individual (61 years of age) who developed her current body composition after menopause. All subjects denied significant changes in body composition through puberty, except for development of secondary sexual characteristics. Any change in body composition with age was limited by history to an increase in fat in the abdomen or thorax (breast). The genitalia were normal. Five of the 12 subjects were able to identify female, but not male, relatives with similar phenotypes.

Clinical characteristics of the FPLD1 subjects are included in Table 1. All but one of the subjects had diabetes. Three of

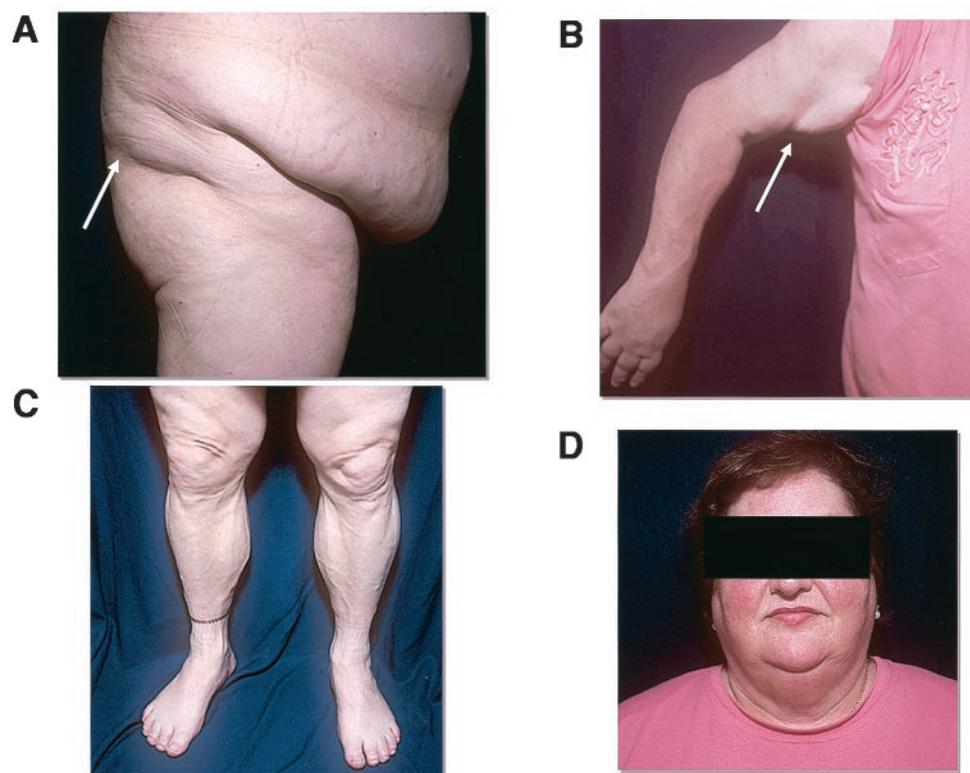


Figure 1—Anatomic features of FPLD1. A: Gluteal view demonstrating central adiposity and the ledge of fat above the gluteal area (arrow). B: Upper and lower arm demonstrating ledge of fat over triceps area (arrow). C: Lower extremities demonstrating prominent musculature and veins. D: Face and neck demonstrating “Cushingoid” appearance of face, with moon facies and fat under chin.

the subjects with diabetes were on very high doses of insulin (>100 units/day), and six were being treated with thiazolidinediones. Five of the subjects were being treated with metformin. Interestingly, of the subjects with diabetes, only one subject (with a BMI >51 kg/m²) had acanthosis nigricans. All but one of the subjects had hypertriglyceridemia, defined as triglyceride levels >2.3 mmol/l (200 mg/dl); many ($n = 9$) had markedly elevated levels (defined as >11.3 mmol/l [1,000 mg/dl]). Of the subjects with marked hypertriglyceridemia, 64% had a history of pancreatitis. A majority of the subjects had hypertension (77%), and 31% had documented coronary artery disease (CAD). None of the subjects had clinical features of the polycystic ovarian syndrome (no hirsutism, normal menses, and normal levels of testosterone).

In Table 2, the average biochemical and metabolic characteristics of the FPLD1 subjects are compared with the diabetic and nondiabetic control subjects. Values were the maximal values while medically treated within the year before enrolling in the current study. Levels of total cholesterol were significantly higher in the FPLD1 subjects (488.9 ± 102.1 mg/dl) than in the diabetic (247.6 ± 43.3 ,

$P < 0.05$) and nondiabetic (202.9 ± 13.3 , $P < 0.02$) control groups. Triglycerides were significantly higher in the FPLD1 subjects ($3,811 \pm 1,077$ mg/dl) than in either the diabetic ($1,062 \pm 1,365.5$, $P < 0.03$) or nondiabetic (98.7 ± 12.9 , $P < 0.01$) control groups. Triglycerides were also significantly higher in the diabetic than in the nondiabetic control group ($P < 0.004$). HDL was significantly lower in both FPLD1 subjects (45.4 ± 5.6 mg/dl, $P < 0.02$) and in the diabetic control group (47.2 ± 4.1 , $P < 0.01$) when compared with the nondiabetic control group (62.9 ± 3.5). There was no significant difference in LDL between groups. Glucose values were significantly higher in the FPLD1 subjects (271.7 ± 43.8 mg/dl, $P < 0.0005$) and the diabetic control subjects (213.4 ± 25.4 , $P < 0.00008$) than in the nondiabetic control subjects (90.3 ± 1.8). HbA_{1c} values also were significantly higher in the FPLD1 subjects ($9.7 \pm 0.8\%$, $P < 0.01$) and the diabetic control subjects ($8.4 \pm 0.5\%$, $P < 0.01$) than in the nondiabetic control subjects ($5.3 \pm 0.1\%$) during medical treatment of diabetes.

Leptin levels were measured in 9 of the 13 FPLD1 subjects. The correlation

between BMI and leptin levels was significant ($r = 0.825$, $P < 0.05$).

Intra-abdominal fat, measured in one of the subjects (BMI 33 kg/m²) by a computed tomography scan of the abdomen at the level of the umbilicus, was 101.6 cm², less than that reported for obese insulin-resistant women with an average BMI of 31.5 ± 3.9 kg/m² (136 ± 59 cm²) but greater than that for lean insulin-resistant women (75 ± 42) with an average BMI of 23.8 ± 1.8 (20).

None of the FPLD1 subjects had mutations in exon 8, 9, or 11 of the *LMNA* gene, where reported mutations for FPLD2 are located (17,21,22). Three of nine subjects screened were heterozygous for a silent substitution in codon 566 (CAC to CAT), both of which encode histidine. None of the FPLD1 subjects had mutations in exons 1–6 or 8 of *PPARG*.

CONCLUSIONS—This report presents a description of the anthropomorphic, clinical, and metabolic characteristics of FPLD1. Without formal advertisement, we were able to identify 13 subjects with FPLD1 within tertiary care outpatient clinics at the University of Washington over the course of a few months. This suggests that this syndrome may be more

Table 2—Body composition and anthropomorphic and metabolic measures in FPLD1 and control subjects

Parameter	FPLD1 subjects	Diabetic control subjects	Nondiabetic control subjects
n	12§	12	12
BMI (kg/m ²)	34.7 ± 2.3*	40.1 ± 2.9*	25.2 ± 0.8
Waist-to-hip ratio	1.1 ± 0.03*†	0.93 ± 0.03*	0.81 ± 0.04
Caliper measurements			
Upper tricep (mm)	28.6 ± 3.4	39.7 ± 2.9*	27.6 ± 2.2
Upper forearm (mm)	11.0 ± 2.5†	21.6 ± 2.3*	15.0 ± 1.7
Tricep/forearm	3.7 ± 0.7*†	2.0 ± 0.14	2.0 ± 0.21
Abdomen (mm)	45.6 ± 3.7	47.7 ± 4.1*	34.5 ± 4.2
Thigh (mm)	11.3 ± 2.9*†	42.8 ± 3.3*	34.4 ± 3.3
Abdomen/thigh	6.8 ± 1.5*†	1.2 ± 0.13	0.98 ± 0.12
Calf (mm)	7.3 ± 1.9*†	28.8 ± 3.6	25.2 ± 2.3
Metabolic characteristics			
Glucose (mg/dl)	271.7 ± 43.8*	213.4 ± 25.4*	90.3 ± 1.8
HbA _{1c} (%)	9.7 ± 0.8*	8.4 ± 0.5*	5.3 ± 0.1
Total cholesterol (mg/dl)	488.9 ± 102.1*†	247.6 ± 43.3	202.9 ± 13.3
Triglycerides (mg/dl)‡	3,811 ± 1,077*†	1,062 ± 1,365*	98.7 ± 12.9
LDL (mg/dl)	150.4 ± 35.6	95.3 ± 9.4	120.3 ± 12.6
HDL (mg/dl)	45.4 ± 5.6*	47.2 ± 4.1*	62.9 ± 3.5

Data are means ± SE. *P < 0.05 vs. diabetic control group; †P < 0.05 vs. nondiabetic control group. ‡Lipid values are those when triglycerides are at maximal values during 1 year prior to enrollment in the current study. §n = 13 for metabolic characteristics.

common than previously thought. In a recent review, FPLD1 was considered a rare condition because “only a few affected women from two small pedigrees, and four sporadic cases, have been reported” (5). However, Köbberling and Dunnigan (15) stated, “Familial partial lipodystrophy is almost certainly commoner (sic) than indicated by the few published reports of the syndrome.” It is unlikely that we are dealing with a founder effect or that the syndrome is more common in the Pacific Northwest, as the subjects with FPLD1 described in this study were born in cities scattered across the U.S.

Only women have been diagnosed with FPLD1 to date. This was the same situation encountered with FPLD2 until mutations were identified in *LMNA*. Men with FPLD2 have a more subtle phenotype and metabolic abnormalities (3). Although not studied here, FPLD1 appears to be familial for some subjects, but may also occur spontaneously. If the gene for FPLD1 can be determined, men with FPLD1 may be identified. Alternatively, the gene for FPLD1 may be lethal in the XY state (15).

The hallmark anthropomorphic features of FPLD1 absolutely required for diagnosis include extremities that lack subcutaneous fat, forming a ledge where

the subcutaneous fat ends. This ledge is easily palpable by examination on the upper extremity and around the gluteal area. Formal measurements of skinfolds with calipers should demonstrate high triceps-to-forearm and abdomen-to-thigh ratios. The absence of subcutaneous fat in the forearm and thigh, ascertained by simply pinching the skin between the thumb and forefinger, can also be useful.

The FPLD1 subjects reported here had significant central adiposity. Intra-abdominal fat, measured in one of the subjects by a computed tomography scan at the level of the umbilicus, was less than that reported for obese insulin-resistant women but greater than that for lean insulin-resistant women (20). Measurement of body composition radiologically in this population will be important to further define fat distribution.

The faces and chins of the FPLD1 subjects had normal to excess fat resembling moon facies, resulting in some of these subjects being referred or evaluated for Cushing’s syndrome (Fig. 1D). The FPLD1 subjects, however, did not have skin atrophy, violaceous striae, muscle weakness, or elevated 24-h urinary free cortisol levels as in Cushing’s syndrome (data not shown). None of the FPLD1 subjects had characteristics of polycystic

ovarian syndrome. They did have components of the metabolic syndrome, including central obesity, diabetes, hypertension, and hypertriglyceridemia (Tables 1 and 2). In fact, the hypertriglyceridemia was so severe that 64% of FPLD1 subjects with hypertriglyceridemia had a history of pancreatitis due to chylomicronemia syndrome (23). In addition, 31% of the subjects with FPLD1 had premature CAD (age range 46–52 years). The prevalence of pancreatitis and early CAD in FPLD1 make early diagnosis crucial in order to implement dietary and drug control of lipids and hyperglycemia and to eliminate or change medications that can lead to hypertriglyceridemia (e.g., oral estrogen, diuretics, β-blockers, and steroids). Fibrin acid derivatives should be used to prevent pancreatitis (23). Fibrin acids should not be stopped abruptly in FPLD1 individuals because of the risk of inducing rebound hypertriglyceridemia and triglyceride-induced acute pancreatitis.

Not all metabolic features of FPLD1 were found in each subject; therefore, their presence is not absolutely necessary for the diagnosis of FPLD1. Köbberling and Dunnigan (15) also make the point that clinical and metabolic abnormalities are not consistently associated with all cases of FPLD1. FPLD2 families demonstrate an increase in metabolic complications with age (24), which might also occur for patients with FPLD1. This suggests that FPLD1 may be identified at a younger age before metabolic features have manifest.

Leptin concentrations correlate with BMI in subjects with FPLD1, in agreement with data from an ethnically mixed group (25). This suggests that the levels of leptin were appropriate for the fat content. Leptin levels are low in subjects with FPLD2 consistent with their lack of subcutaneous adipose tissue (7).

The childhood onset of the clinical features noted here for the diagnosis of FPLD1, including thin legs and arms, as well as central adiposity, differs from FPLD2 subjects who are described to undergo a redistribution of fat around the time of puberty (5). None of the women with FPLD1 had fat in their labia majora or mutations of the *LMNA* gene that are associated with FPLD2 (22). The genetic defect associated with FPLD1 is currently unknown.

Only one of the subjects with FPLD1 had acanthosis nigricans, a marker of se-

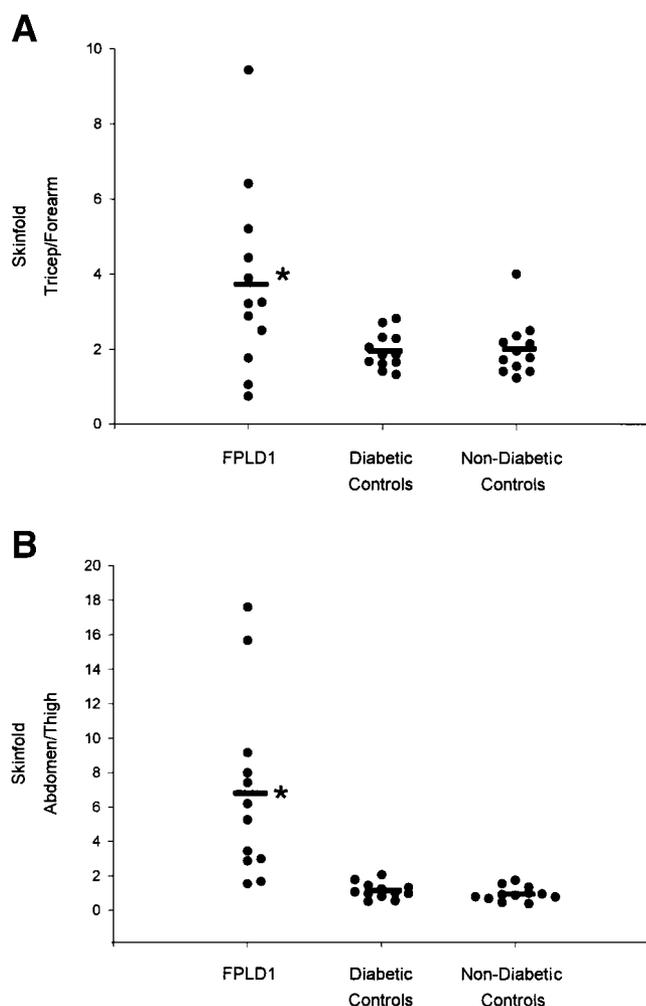


Figure 2—Ratio of skinfold thickness in individual FPLD1 subjects compared with diabetic and nondiabetic control subjects. A: Ratio of upper triceps area to upper forearm. B: Ratio of abdomen to thigh. Horizontal lines represent average values in each group. * $P < 0.05$ vs. control subjects.

were insulin resistance. The FPLD1 subjects, however, likely had insulin resistance as supported by the high insulin doses or the use of insulin sensitizers (thiazolidinediones) required to maintain glycemic control. None of the subjects with FPLD1 had mutations in *PPARG*. Mutations in *PPARG* have been found in individuals with reported similarities to our cohort but with less central adiposity (26,27) and in individuals with severe insulin resistance with paucity of subcutaneous limb fat and atrophy of buttock fat (28,29).

In summary, FPLD1 is likely a more common FPLD than previously thought. Until the genetic marker for its diagnosis becomes available, the diagnosis should be made clinically, particularly by the presence of the palpable ledge between the normal and lipodystrophic areas, and

by appropriate skinfold ratios. Because of their very high incidence of pancreatitis and premature CAD, triglyceride-lowering agents and approaches to prevent cardiovascular disease should be aggressively undertaken early after recognition of the syndrome.

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