Familial Partial Lipodystrophy linked to a novel peroxisome proliferator activator receptor -γ (PPARG) mutation, H449L

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AIMS

Familial partial lipodystrophy (FPL) is a rare genetic disorder characterized by a selective lack of subcutaneous fat that is associated with insulin resistance and diabetes. This study aimed i) to describe the phenotype associated with a novel heterozygous missense *PPARG* mutation discovered in a Turkish family; and ii) to compare the fat distribution and metabolic characteristics of subjects with the *PPARG* mutation to that of a cluster of FPL patients with various *LMNA* mutations.

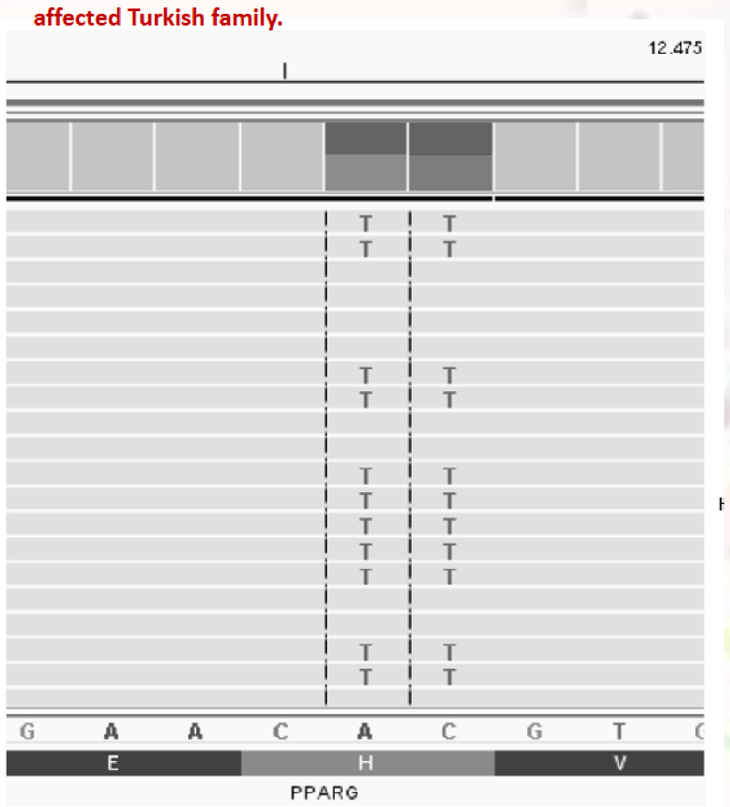
METHODS

The study involved 4 FPL patients with a novel *PPARG* mutation (H449L) and 5 patients with various *LMNA* mutations including a novel *LMNA* mutation (L306V, R482W, R582H and T528M).

RESULTS

Compared to patients with *LMNA* mutations, fat loss was generally less prominent in subjects with *PPARG* H449L mutation. Partial fat loss was limited to the extremities whilst truncal fat mass was preserved. The *PPARG* H449L mutation was associated with insulin resistance, hypertriglyceridemia and non-alcoholic fatty liver disease in all affected subjects but the severity was variable. Three of four mutation carriers were overtly diabetic or had impaired glucose tolerance. Pioglitazone therapy in these three individuals resulted in a modest improvement in their metabolic control, and regular menstrual cycles in both females.

Figure 1: PPARG, H449L (c.1346 A>T) mutation detected in the affected Turkish family.



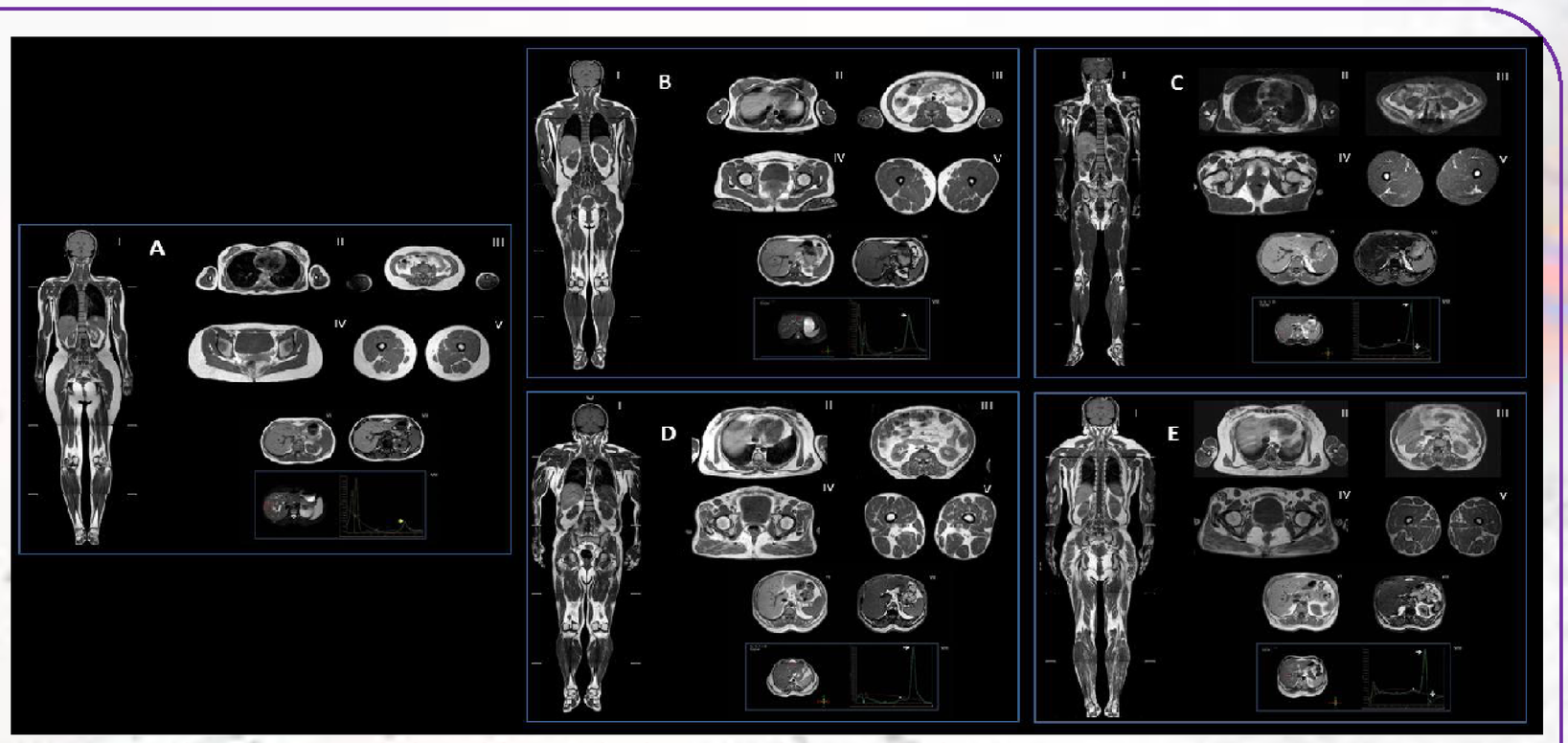


Figure 2: MR images and MR spectroscopy findings of the control and patients with FPL in each subgroup.
A: Female control, age: 28 years, height: 167 cm, weight: 58 kg, BMI: 20.8 kg/m2, waist: 70 cm, hip: 94 cm, waist to hip ratio: 0.75. B: Patient 3, PPARG, H449L; C: Patient 5, LMNA R482W; D: Patient 8, LMNA T528M; and E: Patient 7, LMNA R582H. Whole body T1 WI (I), axial T1 WIs at the level of breast (II), abdomen (III), gluteal region (IV) and thigh (V) reveal fat distribution of the body and extremities. Dual phase T1 WIs (VI and VII) show signal loss on out of phase images (VII) in affected patients which is in consistent with variable degree of hepatosteatosis. MRS spectra of affected patients indicate the variable degree of hepatosteatosis (VIII, arrows).

Table-1: The clinical characteristics of patients with FPL caused by *PPARG* and *LMNA* mutations.

	PPARG				LMNA				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Current age	26	30	28	56	30	32	41	47	18
Gender	Female	Female	Female	Male	Female	Female	Female	Female	Female
Mutation	PPARG, H449L	PPARG, H449L	PPARG, H449L	PPARG, H449L	LMNA, R482W	LMNA, R482W	LMNA, R582H	LMNA, T528M	LMNA, L306W
The age when fat loss was first noticed (years)	16	13	13	?	13	17	20	16	15
The age when FPL was first diagnosed (years)	23	28	26	55	19	27	33	43	17
Follow-up (months)	36	24	24	12	132		96	48	12
Diabetes duration (years)	4	Not diabetic	IFG + IGT	3	10	9	6	18	IGT
BMI (kg/m²)	23.6	19.9	23.7	22.1	20.8	31	27.3	30.6	20.4
Hypertriglyceridemia	+	+	+	+	+	+	+	+	-
Low HDL	+	-	-	+	-	+	+	+	+
HT	-	-	-	+	+	+	-	+	-
PCO	+	-	+	NA	+	-	+	+	-
Acanthosis nigricans	+	-	+	+	+	+	+	+	-
Hepatosteatosis	+	+	+	+	+	+	+	+	+
Macrovascular complications	-	-	-	CAD	-	-	-	CAD	-
Microvascular complications	-	-	-	+	-	Proteinuria	-	Retinopathy, microalbuminuria	-
Current treatment	Metformin, pioglitazone, insulin	NA	Metformin, pioglitazone	Metformin, pioglitazone, sitagliptin, ramipril	Metformin, pioglitazone, gliclazide, gemfibrozil, irbesartan	Metformin, insulin, fenofibrat, fish oil, ramipril	Metformin, pioglitazone, fenofibrat	Metformin, pioglitazone, insulin, fenofibrat, irbesartan	Metformin
Insulin dose (per day)	22 units	NA	NA	NA	NA	102 units	NA	110 units	NA

FPL: Familial partial lipodystrophy, *PPARG*: Peroxisome proliferator-activated receptor -gamma, *LMNA*: Lamin A/C, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, BMI: Body mass index, HDL: High density lipoprotein, HT: Hypertension, PCO: Polycystic ovaries, CAD: Coronary artery disease, NA: Not available.

Table-2: Laboratory levels of patients with FPL caused by PPARG and LMNA mutations.

	PPARG				LMNA				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Fasting glucose (mmol/L)	4.11	5.05	6.27	8.6	6.44	13.1	6.49	9.6	4.44
HbA1c (%)	5.7	NA	6	8.3	7.6	10.2	6.2	8.7	5.7
HbA1c (mmol/mol)	39	NA	42	67	60	88	44	72	39
Total cholesterol (mmol/L)	5.04	5.53	4.24	4.39	5.04	4.52	4.73	7.57	3.82
Triglyceride (mmol/L)	2.02	2.35	2.38	2.02	6.5*	9.03*	1.91*	3.54*	1.05
HDL cholesterol (mmol/L)	1.16	1.31	1.29	0.95	0.85	0.54	0.98	1.08	0.74
LDL cholesterol (mmol/L)	2.94	3.23	1.86	2.51	3.25	1.57	2.87	4.86	2.58
Creatinin (mg/dL)	0.63	0.64	0.56	0.84	0.59	0.6	0.71	0.68	0.5
ALT (U/L)	29	21	102	118	35	21	32	71	12
GGT (U/L)	18	13	47	129	39	22	14	76	27
Protein excretion (mg/L)	6.7	9.1	9.6	172	4.5	313	5	30.25	4
C3 (mg/dL)	129	121	153	158	114	154	129	144	NA
C4 (mg/dL)	25	16.4	27	25	28.8	20	20.5	46.2	NA
Fasting insulin (µIU/mL)	NA**	6.69	96.88	27.76	20.77	NA**	26.5	NA**	33
HOMA	NA**	1.35	26.79	10.33	5.73	NA**	7.51	NA**	6.52
Fasting C-peptid (ng/mL)	5.2	2.38	10.2	5.88	5.24	1.9	4.93	1.88	4.34
Fasting leptin (ng/ml)	7.83	16.52	6.7	14.88	3.72	3.66	11.86	9.77	NA***
Fasting adiponectin (µg/ml)	3.93	33.62	8.57	8.03	8.57	4.04	9.9	10.27	NA***

FPL: Familial partial lipodystrophy, *PPARG*: Peroxisome proliferator-activated receptor -gamma, *LMNA*: Lamin A/C, HDL: High density lipoprotein, LDL: Low density lipoprotein, ALT: Alanine transaminase, GGT: Gamma-glutamyl transferase, HOMA: Homeostasis model assessment, C3: Complement component 3, C4: Complement component 4. * Lipid levels were taken under lipid lowering treatment. **Insulin and HOMA scores were not available for selected patients as they were being treated with insulin injections. ***Leptin and adiponectin levels were not available for patient 9 as she was discovered to be pregnant when she was scheduled for the test.

CONCLUSIONS

We suggest that relatively modest fat loss in patients with *PPARG* mutations may render the recognition of the syndrome more difficult in routine clinical practice. The *PPARG* H449L mutation is associated with insulin resistance and metabolic complications; however the severity is variable among the affected subjects.

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