Diabetologia (2004) 47:753–763

Diabetologia

Letters

Observations

Familial partial lipodystrophy associated with compound heterozygosity for novel mutations in the *LMNA* gene

Keywords Compound heterozygosity · Insulin resistance · Lamin · Partial lipodystrophy

To the Editor: Dunnigan-Köbberling syndrome or familial partial lipodystrophy (FPL) is an inherited form of partial lipodystrophy characterised by selective loss of subcutaneous limb and gluteal fat, and excess facial fat deposition [1]. Some authors have suggested that FPL be subclassified into Dunnigan and Köbberling subtypes [2], the key difference being the loss of subcutaneous truncal fat in the Dunnigan subtype; this depot is preserved or increased in Köbberling FPL. Although the molecular mechanisms responsible for the unusual fat distribution seen in FPL remain unknown, the majority of cases are the result of heterozygous mutations in the *LMNA* gene (dominant-negative mutations in *PPARG* account for some of the remainder). Lamin A/C is principally a structural nuclear envelope protein which, like other intermediate filament proteins, consists of a central α-helical coiled-coil rod domain flanked by two globular domains. To date, the majority of mutations associated with FPL have been confined to exons 8 and 11 of *LMNA*, both of which contribute to the carboxy-terminal immunoglobulin-like globular domain. Structural modelling of this region suggests that the exon 8 FPL mutations occupy a discrete superficial patch on this globular domain [3] and are likely to alter protein–protein interactions either between lamin proteins themselves or between lamin proteins and other nuclear elements. As *LMNA* mutations are currently the most common explanation for inherited forms of partial lipodystrophy, we routinely sequence exons 8 to 12 in all probands with partial lipodystrophy.

Three unrelated Caucasian pedigrees harbouring a novel heterozygous *LMNA* serine-583-leucine (S583L; nt-1748 [C→T]) mutation in exon 11 were identified (Table 1). The S583L variant was associated with a stereotyped pattern of partial lipodystrophy in which subcutaneous limb and gluteal fat was lost but subcutaneous abdominal, facial and neck fat was preserved (Fig. 1). This Köbberling-type FPL phenotype was apparent in kindreds A, B and C, and is consistent with that previously described in carriers of a mutation in the preceding residue (R582H) [4]. It was suggested that the fact that the R582H mutation is lamin A specific (exon 11 is not transcribed in lamin C), as opposed to exon 8 mutations which affect the structure of lamins A and C, might account for the subtle Köbberling-type FPL phenotype seen in carriers of this mutation [4]. However, this explanation is not supported by two reports describing carriers of an R584H mutation with typical Dunnigan-type FPL [5, 6]. Three patients in kindred C (subjects CI, CIV and CVI) were notable for a lack of subcutaneous truncal as well as subcutaneous limb fat (Fig. 1). They were subsequently found to be compound heterozygotes for S583L and a threonine-528-methionine (T528M; nt-1547 [C→T]) *LMNA* mutation in exon 9. Carriers of the T528M mutation alone (subjects CII and CV) were not clinically lipodystrophic, although both had slightly increased fasting triglycerides and subject CII was noted to be diabetic and hypertensive at the time of screening. Interestingly, a more substantial amino acid change involving a charge change at this residue (threonine-528-lysine) is known to produce a form of Emery-Dreifuss muscular dystrophy [7]. None of the T528M carriers reported muscular weakness or palpitations. Results of clinical evaluation, creatine kinase measurement and electrocardiography were also unremarkable in these subjects. Acanthosis nigricans and features of the metabolic syndrome were variably present in both single heterozygotes and compound heterozygotes (Table 1).

Neither the S583L nor the T528M *LMNA* variant was present in 100 unrelated control subjects (200 alleles). Serine 583 and threonine 528 are highly conserved residues (identical in human, rat, mouse, chick and *Xenopus*). The S583L mutation is bracketed by two known mutations in exon 11, R582H [4] and R584H [5, 6], which are only expressed in lamin A. Although the T528M mutation is not expected to alter the structure of the globular C-terminal domain substantially, it may modify the phenotypic impact of the S583L mutation. The notion that a mutation without a clinically discernable phenotype might, in combination with a second mutation, produce a pathological phenotype is supported by the observations made in kindreds with an arginine-527-histidine (R527H) mutation. R527H heterozygotes were said to be phenotypically "normal", whilst R527H homozygotes develop mandibulo-acral dysplasia [8], a complex phenotype including partial lipodystrophy and insulin resistance. Compound heterozygosity has been reported in one other subject with FPL [5]. In that particular case, the subject was a compound heterozygote for a R482Q and V440M mutation and was reported to have the typical Dunnigan pattern of lipodystrophy accompanied by very severe insulin resistance, diabetes and aggressive cardiovascular disease. The single mutation carriers in this family had a similar pattern of lipodystrophy but less severe metabolic consequences.

In summary, we have identified two novel *LMNA* mutations. The S583L variant was associated with a stereotyped pattern of "atypical" partial lipodystrophy, in which subcutaneous abdominal fat was preserved, in three unrelated kindreds (Köbberling-type FPL). One of these kindreds also harboured the T528M variant, and compound heterozygotes manifest typical Dunnigan-type FPL. These observations add to the remarkably complex genotype–phenotype relationships associat-

DOI 10.1007/s00125-004-1360-4
Received: 4 December 2003 / Accepted: 16 January 2004
Published online: 10 March 2004

Table 1. Subject characteristics

Subject	Clinical phenotype							Biochemical phenotype				
	LMNA genotype	Age/ Sex	BMI (kg/m^2)	Hyp	AN	L/G L	ASF	Ins (<60 pmol/l)	Glu (3.5–6.3 mmol/l)	Trig (<2 mmol/l)	HDL (>1 mmol/l)	Therapy/ Comments
Kindred A												
AI (Proband)	S583L	38 Female	32.4	No	Yes	Yes	Yes	366	9.9[a]	2.2	2.2	Metformin
AII (Mother)	S583L Female	64	30.0	Yes	No	Yes	Yes	81	8.8[a]	2.2	1.53	
Kindred B												
BI[b] (Proband)	S583L	40 Female	28.0	Yes	Yes	Yes	Yes	67	24[a]	>30	0.7	Insulin Thyroxine Simvastatin
BII (Mother)	WT	70 Female	43.7	Yes	No	No	Yes	228	12.9[a]	2.7	1.3	Sulfonylurea
BIII (Sister)	S583L	42 Female	25.9	No	No	Yes	Yes	49	5.1	1.9	0.9	–
BIV (Brother)	S583L	49 Male	34.9	No	No	Yes	Yes	113	5.5	2.0	1.4	–
Kindred C												
CI (Proband)	S583L T528M	32 Female	21.5	Yes	No	Yes	CU	141	4.6	2.3	0.9	Ramipril
CII (Mother)	T528M	63 Female	29.9	Yes	No	No	Yes	117	8.2[a]	4.2	ND	–
CIII (Father)	S583L	58 Male	ND	No	No	ND	Yes	ND	ND	ND	ND	($HbA_{01}C$ 5.8%)
CIV (Sister)	S583L T528M	39 Female	25.0	Yes	No	Yes	CU	239	7.6[a]	6.6	0.9	Metformin Atenolol Fibrate
CV (Brother)	T528M	36 Male	28.0	No	No	No	Yes	117	4.7	2.4	ND	–
CVI (Brother)	S583L T528M	35 Male	24.6	No	No	Yes	CU	44	4.2	2.9	1.0	–

All blood samples were drawn after an overnight fast; [a] diabetic; [b] subject BI's father died (aged 50 years) from ischaemic heart disease; AN, acanthosis nigricans; ASF, abdominal subcutaneous fat; CU, clinically undetectable; Glu, glucose; Hyp, hypertension; Ins, insulin; L/G L, limb/gluteal lipodystrophy; ND, no data; Trig, triglycerides; WT, wild type

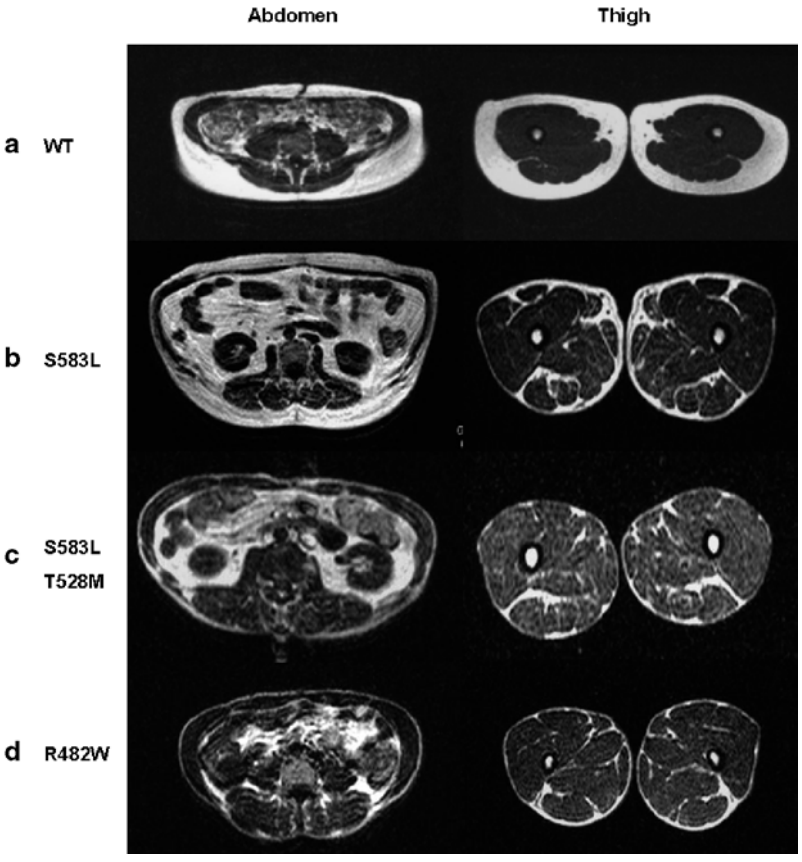

Fig. 1. Characterisation of fat distribution. Transverse T1-weighted magnetic resonance images of the abdomen and thighs from women with *LMNA* mutations: (**a**) Lean, healthy control female (WT, wild type for *LMNA* gene); (**b**) S583L alone (subject AI); (**c**) S583L and T528M (subject CI); (**d**) R482W (30-year-old woman). Note that while subcutaneous abdominal fat is strikingly reduced in typical Dunnigan-type FPL (R482W) and the compound heterozygote, it is preserved in the subject harbouring the S583L mutation alone

ed with human "laminopathies". They also highlight the notion that mutations which in themselves produce very subtle manifestations can in combination with additional genetic variants and/or additional environmental stressors result in extreme disease phenotypes. By this we mean that whilst lean carriers of the S583L mutation alone appear to have relatively minor metabolic abnormalities, compound heterozygotes harbouring a second *LMNA* mutation, and obese carriers (subjects AI and AII) manifest a more severe phenotype with a predisposition to insulin resistance and other features of the metabolic syndrome.

Acknowledgements. We are indebted to the subjects of this study for their participation. This work was supported by The Wellcome Trust (D. B. Savage and S. O'Rahilly).

D. B. Savage · M. A. Soos · A. Powlson · S. O'Rahilly
Department of Medicine and Clinical Biochemistry,
University of Cambridge, UK Box 232,
Addenbrooke's Hospital, Cambridge, UK

I. McFarlane · D. J. Halsall
Department of Clinical Biochemistry,
Addenbrooke's NHS Trust, Addenbrooke's Hospital,
Cambridge, UK

I. Barroso
The Wellcome Trust Sanger Institute,
The Wellcome Trust Genome Campus, Hinxton,
Cambridge, UK

E. L. Thomas · J. D. Bell
Medical Research Centre Clinical Sciences Centre,
Imperial College School of Medicine,
Hammersmith Hospital, London, UK

I. Scobie
Peter Simons Diabetes Centre, Medway Maritime Hospital,
Gillingham, UK

P. E. Belchetz
Department of Endocrinology, The General Infirmary at Leeds,
Leeds, UK

W. F. Kelly
James Cook University Hospital, Middlesbrough, UK

A. J. Schafer
Incyte, Palo Alto, California, USA

References

1. Jackson SN, Howlett TA, McNally PG, O'Rahilly S, Trembath RC (1997) Dunnigan-Kobberling syndrome: an autosomal dominant form of partial lipodystrophy. QJM 90:27–36
2. Garg A (2000) Lipodystrophies. Am J Med 108:143–152

3. Burke B, Stewart CL (2002) Life at the edge: the nuclear envelope and human disease. Nat Rev Mol Cell Biol 3:575–585
4. Garg A, Vinaitheerthan M, Weatherall PT, Bowcock AM (2001) 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
5. Hegele RA, Cao H, Anderson CM, Hramiak IM (2000) Heterogeneity of nuclear lamin A mutations in Dunnigan-type familial partial lipodystrophy. J Clin Endocrinol Metab 85:3431–3435
6. Vigouroux C, Magre J, Vantyghem MC et al. (2000) Lamin A/C gene: sex-determined expression of mutations in Dunnigan-type familial partial lipodystrophy and absence of coding mutations in congenital and acquired generalized lipoatrophy. Diabetes 49:1958–1962
7. Bonne G, Mercuri E, Muchir A et al. (2000) 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
8. Novelli G, Muchir A, Sangiuolo F et al. (2002) Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. Am J Hum Genet 71:426–431

S. O'Rahilly (✉)
Department of Medicine and Clinical Biochemistry,
University of Cambridge, UK Box 232,
Addenbrooke's Hospital, Hills Road, Cambridge,
CB2 2QQ UK
E-mail: sorahill@hgmp.mrc.ac.uk
Tel.: +44-1223-336855, Fax: +44-1223-330160/330598

Abbreviations: FPL, familial partial lipodystrophy

D.B. Savage and I. McFarlane contributed equally to this work