Familial partial lipodystrophy: two types of an X linked dominant syndrome, lethal in the hemizygous state

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SUMMARY Familial lipodystrophy (referred to in publications as the Köbberling-Dunnigan syndrome) comprises at least two clinical phenotypes which are consistent within each pedigree. In type 1 familial lipodystrophy, loss of subcutaneous fat is confined to the limbs, sparing the face and trunk. In type 2 familial lipodystrophy, the trunk is also affected with the exception of the vulva, giving an appearance of labial hypertrophy. Diabetes mellitus, hyperlipoproteinaemia, and acanthosis nigricans are present to a variable degree in some but not all patients with familial lipodystrophy, and the abnormal distribution of subcutaneous fat is the essential hallmark of the syndrome.

In addition to a survey of published reports, new cases with the syndrome are described. Both types of partial lipodystrophy, occurring either as familial disease or as sporadic cases, have only been observed in female patients. Study of the pedigrees of five families with familial lipodystrophy (two Scottish and three German) suggests an X linked dominant mode of transmission, lethal in the hemizygous (XY) state. The two clinical phenotypes with their variably expressive metabolic abnormalities are consistent either with different mutants of the same allele or with two genes on adjacent loci. Other clinical phenotypes of familial lipodystrophy may exist due to further mutations of the same allele or of genes on adjacent loci.

The nature of the disorder in patients with familial lipodystrophy usually escapes recognition for many years and the syndrome is almost certainly much commoner than the few families described to date suggest.

Before the description of the syndrome which forms the subject of the present communication, three clinical syndromes were recognised which share as their common distinguishing feature the partial or total absence of subcutaneous fat (lipoatrophy or lipodystrophy). In progressive partial lipodystrophy (Barraquer-Simon syndrome^{1,2}) fat is lost from the face and, in most cases, from the trunk with normal or excessive fat deposition on the pelvic girdle and lower limbs. Most affected subjects are female and show no other abnormality; a minority develop glomerulonephritis, diabetes, or hyperlipidaemia. The condition is usually sporadic. Seip³ and Berardinelli⁴ described congenital lipodystrophy in which total loss of subcutaneous fat was noted

within the first two years of life. This condition is commonly associated with parental consanguinity and is recessively inherited. The sexes are equally affected. Hepatosplenomegaly, hypertrichosis, acanthosis nigricans, and genital hypertrophy are usual, and neurological, cardiac, and renal abnormalities are frequent. Hyperlipidaemia and abnormal glucose tolerance are commonly associated metabolic abnormalities. Lawrence⁵ described acquired lipoatrophic diabetes which usually begins in adolescence or early adult life, predominantly in females, and is sporadic. This syndrome shares certain features with congenital lipodystrophy, such as hepatosplenomegaly, leading to frank cirrhosis in some cases, and acanthosis nigricans. Hyperlipidaemia and insulin resistant diabetes mellitus are invariable but neurological, cardiac, and renal abnormalities are absent.

In 1974 Dunnigan *et al*⁶ described a syndrome of 'familial lipoatrophic diabetes'. Three female members of one Scottish family and one female member of another family showed the complete absence of subcutaneous fat from the limbs and trunk with normal or excessive adipose tissue on the face and neck. All four patients had hyperlipoproteinaemia of varying severity, three had diabetes mellitus, and one showed impaired glucose tolerance. Other dead female members of both families were reported to have been affected and the disorder involved four generations in one family and three generations in the other, suggesting a dominant mode of inheritance.

In 1975 Köbberling *et al*⁷ described three female members of a German family who showed complete absence of subcutaneous fat from the limbs with normal fat on the face and trunk. In this family, the disorder also appeared to be inherited in a dominant fashion over two generations. Only the proband also showed diabetes mellitus and severe hyperlipoproteinaemia. A second family was later described by the same authors.⁸ A mother and two of her three daughters showed limb lipodystrophy but only the former exhibited hyperlipidaemia and diabetes.

Since the description of the cases cited above, the syndrome of familial partial lipodystrophy has been referred to as the Köbberling-Dunnigan syndrome.¹⁻⁹⁻¹¹ There is some doubt, however, about the similarities and differences between the families described by Köbberling *et al*⁷ in Germany and by Dunnigan *et al*⁶ in Scotland. The present communication clarifies these and reports a further German family with the 'Scottish' variety of the syndrome. A new interpretation of the genetics of familial lipodystrophy is proposed, together with a review of other case reports of familial lipodystrophy.

The clinical phenotype of familial lipodystrophy

The terms lipoatrophy and lipodystrophy are often used synonymously. In the syndromes in which lipoatrophy is present in one part of the body, subcutaneous fat may be present in excess in other sites. The more comprehensive term lipodystrophy is used in the present report to describe the abnormal distribution of subcutaneous fat, whether absent or present in excess.

The only condition common to all affected patients with familial lipodystrophy is the abnormal distribution of subcutaneous fat. Metabolic abnormalities show varying degrees of expressivity, being absent in some patients and present in severe degree in others. The essential clinical phenotype of the

syndrome is thus the abnormality of subcutaneous fat distribution itself. The phenotype is variable but consistent within each pedigree. More detailed descriptions of the two clinical phenotypes seen in our German and Scottish families are given below. These may be designated as limb lipodystrophy (familial lipodystrophy type 1) and limb and trunk lipodystrophy (familial lipodystrophy type 2) respectively.

LIMB LIPODYSTROPHY (TYPE 1)

Patients with this form of familial lipodystrophy show the complete absence of visible or palpable subcutaneous fat from the arms and legs. The subcutaneous veins appear prominent and the muscles hypertrophied. In contrast, subcutaneous fat is normal on the face and trunk and some patients show moderate truncal obesity (fig 1). The face does not show the broad, acromegaloid, or rounded features frequently found in the type 2 variety of the syndrome (see below) and the hands and feet are of normal size and shape. The genitalia are normal and there is no apparent hypertrophy of the labia majora, minora, or clitoris. No other clinical or metabolic abnormalities are consistently associated

FIG 1 Proband of the second German family with familial lipodystrophy type 1 (fig 2, family 4, No 1). Lack of subcutaneous fat on the legs with prominent veins and musculature but well developed fat on the trunk.

with all cases of the syndrome. Acanthosis nigricans occurs only in patients with diabetes and hyperlipoproteinaemia. All affected patients were aware that they had an unusual appearance and that their loss of subcutaneous fat had been present since early childhood. There was no history of parental consanguinity in any of the affected patients.

Insulin dependent diabetes mellitus developed in the proband of the first family (fig 2, family 3, No 2) at 11 years of age.⁷ At 16 years of age the patient developed tuberous xanthomata on the buttocks, hands, and extensor aspects of the limbs associated with gross hyperlipoproteinaemia. The patient's diabetes remained poorly controlled despite large doses of insulin. An intravenous insulin tolerance

test showed a degree of insulin resistance, but insulin receptors on the patient's monocytes were normal (H W Rüdiger, 1980, personal communication). The hyperlipoproteinaemia varied over a number of years, conforming to Fredrickson types III, IV, and V on different occasions. Lipid lowering drugs were ineffective and the hyperlipoproteinaemia responded partially to a carbohydrate restricted diet; low fat diets were ineffectual. From the age of 27 years the patient eventually developed severe complications associated with poor control of both her diabetes and hyperlipoproteinaemia. She became blind from advanced proliferative retinopathy, had a limb amputation because of severe peripheral vascular disease, and was eventually dialysed because of

FIG 2 Five pedigrees of familial lipodystrophy. For families 1 and 2 see Dunnigan et al.,⁶ for family 3 see Köbberling et al.,⁷ for family 4 see Köbberling et al.⁶ Family 5 is newly described.

advanced diabetic nephropathy. She died at the age of 35 years from complications of chronic renal failure. The patient's mother and sister, who show a similar total absence of subcutaneous fat from the limbs, remain alive and well. The mother has slight hyperlipoproteinaemia (type IIb) and the sister is metabolically normal.

The proband of the second family described with the type 1 variety of the syndrome (fig 2, family 4, No 1) developed mild maturity onset diabetes at the age of 58 years and was found to have moderate hyperlipoproteinaemia in addition to her limb lipodystrophy.⁸ The hyperlipoproteinaemia is difficult to classify, showing an abnormal serum lipoprotein of pre- β mobility (triglyceride/cholesterol ratio of 4/1; density D 0.95). The patient's affected daughter was metabolically normal.

Two sporadic cases with the same phenotype have been described by Köbberling *et al.*⁷ A further, apparently sporadic, case of limb lipodystrophy has recently been seen in a German woman aged 62 years with insulin dependent diabetes without insulin resistance and normal serum lipids (unpublished).

Post-heparin lipolytic activity (PHLA) has been found to be reduced in all four patients with the syndrome tested to date.⁸ This defect is not confined to patients with hyperlipoproteinaemia and diabetes and has been found in patients who were both non-diabetic and normolipoproteinaemic. The significance of this abnormality, which appears fully compensated in some persons, is unknown.

LIMB AND TRUNK LIPODYSTROPHY (TYPE 2)
All three members of the first family seen with this variety of familial lipodystrophy (fig 2, family 2) showed the absence of subcutaneous fat from the trunk and limbs, broad faces, with short, thick set necks, and slight prognathism.⁶ Despite these rather acromegaloid features, the hands and feet were normal in size and shape. The proband of the second family (fig 2, family 1, No 13) also showed absent subcutaneous fat from the trunk and limbs but the facies appeared Cushingoid with excess fat on the face, neck, and supraclavicular fossae. The hands and feet were normal in size and shape. Enquiry of the patients and their unaffected relatives, supported by family photographs, indicated that other female members of the preceding three generations of the first family and two generations of the second family had been similarly affected. The nature of the disorder, in so far as it affected the patient's appearance, was well known to the members of both families. There was no history of parental consanguinity in either family.

Metabolic abnormalities associated with the syn-

drome were variable, ranging from severe hyperlipoproteinaemia and insulin resistant diabetes in the proband of the first family to asymptomatic impaired glucose tolerance and mild type IV hyperlipoproteinaemia in the proband of the second family. No other endocrine or metabolic abnormality was associated with the disorder and in a number of affected subjects the clinical phenotype appeared consistent with a normal life span.

Following the original description of the syndrome in 1974, the proband of the first family (fig 2, family 2, No 12) continued to show poor diabetic control and gross type V hyperlipoproteinaemia with crops of tuberous xanthomata. The hyperlipoproteinaemia and diabetes continued to respond at intervals to a low fat and carbohydrate-restricted diet supplemented with medium chain triglycerides, but compliance with this dietary regimen was poor. Three years later, at 28 years of age, the gross type V hyperlipoproteinaemia spontaneously moderated to mild type IV with the disappearance of tuberous xanthomata. Diabetic control deteriorated and insulin was required in 1975. Poor control led to the development of diabetic microangiopathy with proliferative retinopathy, diabetic nephropathy, and peripheral and autonomic neuropathy. In 1982 deteriorating renal function led to the starting of chronic ambulatory peritoneal dialysis (CAPD). The patient became blind as a result of severe diabetic retinopathy with retinal haemorrhages but has in other respects remained stable with relatively good control of her diabetes. Her hyperlipoproteinaemia was exacerbated by the starting of CAPD and now shows a type IV pattern with a gross excess of very low density lipoprotein (VLDL) of normal pre- β mobility and reduced concentrations of low density lipoprotein (LDL) and high density lipoprotein (HDL).

The affected mother of the proband (fig 2, family 2, No 10) died in 1969 of a hypernephroma. The affected aunt of the proband (fig 2, family 2, No 9), who had developed insulin dependent diabetes in 1965, showed moderate to severe type V hyperlipoproteinaemia with recurrent crops of tuberous xanthomata. She showed continuing poor diabetic control after the recognition of the syndrome in 1974 and developed severe diabetic nephropathy and ischaemic heart disease in 1975, dying in 1976 of congestive cardiac and renal failure.

The proband of the second family (fig 2, family 1, No 13), first seen in 1971 aged 49 years, remains well in 1984 aged 63 years. She continues to show mild type IV hyperlipidaemia and impaired glucose tolerance.

No evidence of hepatic impairment or of progression to hepatic cirrhosis has been evident in the

affected members of either Scottish family, as is common in acquired lipoatrophic diabetes.⁵ No evidence of abnormalities of the renal tract or central nervous system has been seen as in congenital lipodystrophy,³ and there has been no evidence of abnormalities of the complement system or of glomerulonephritis as in many patients with acquired progressive partial lipodystrophy.^{1,2} Levels of serum complement fractions in the probands of both Scottish families were normal.

Following the discovery of reduced levels of post-heparin lipolytic activity in German patients with familial lipodystrophy, the proband of the first family (fig 2, family 2, No 12) was found to have reduced levels of this enzyme in 1982 while normal levels were found in the proband of the second family (Walli and Köbberling, unpublished observations).

ADDITIONAL CASE REPORT

Type 2 familial lipodystrophy, so far documented in two Scottish families, has now been seen in two female members of a German family (fig 2, family 5, No 1 and 2). In 1981 a woman of 25 years, under investigation for secondary amenorrhoea, was referred because of the discovery of grossly hyperlipaemic serum.

Clinical examination showed the patient to have a full round face with a full neck and the complete absence of subcutaneous fat on the trunk and limbs (fig 3 and 4). The genitalia appeared prominent with a considerable amount of fat on the mons pubis but were otherwise normal (fig 4). In general, the patient resembled the patients described by Dunnigan *et al.*⁶ Acanthosis nigricans was present in the

FIG 3 Newly described patient with familial lipodystrophy type 2 (fig 2, family 5, No 1). Note the lack of subcutaneous fat on the arm and the acanthosis nigricans at the axilla.

FIG 4 Same patient as in fig 3. Lack of subcutaneous fat on the trunk but well developed fat on the face and the vulva, giving an appearance of labial hypertrophy.

axillae (fig 3) and antecubital areas, and tuberous xanthomata were present over the buttocks, knees, and elbows. The patient also showed moderate hirsutism of the face and trunk (fig 4).

Endocrine investigations showed raised levels of plasma testosterone but tests of ovarian and anterior pituitary function were within normal limits and the ovaries were not enlarged. Regular menstruation was not induced by clomiphene, bromocriptine, or cyclic LRH infusions. The reasons for both the raised plasma testosterone levels and persistent secondary amenorrhoea remain unclear. Adrenal function was normal.

The patient showed gross type V hyperlipoproteinaemia which has so far proved resistant to all therapeutic measures. Cholesterol levels ranged between 9 and 22 mmol/l and triglycerides between 18 and 72 mmol/l. The nature of the lipoprotein disorder has not yet been fully clarified. Post-heparin lipolytic activity was normal.

When the patient was first seen in 1981, she had impaired glucose tolerance with high levels of endogenous plasma insulin. In 1983 she developed overt diabetes which is controlled at present by diet and oral hypoglycaemic agents.

The patient's mother died suddenly at the age of 40; the cause of death was uncertain. She had suffered from irregular menstruation but no investigations into the cause of the menstrual irregularity had been carried out. The patient commented that her mother had had the same physical appearance as herself with thin, muscular extremities and a full, round face. Family photographs confirmed this description. Neither the patient nor her mother had any sibs and nothing is known about other members of the family. There was no history of parental consanguinity.

The genetics of familial lipodystrophy

In all pedigrees seen to date, the syndrome of familial lipodystrophy has been transmitted over two to four generations. In a few further cases the disorder appeared sporadic but there is a lack of reliable information about other family members in these cases. Both original descriptions suggested a dominant mode of inheritance with variable expressivity, in contrast to congenital lipodystrophy which is inherited recessively³ or the non-genetic acquired lipodystrophies.⁵ To date, only female patients have been described in affected families and as sporadic cases. It may be argued that female predominance is a matter of selection since the syndrome is more obvious in females than in males with less subcutaneous fat. This argument, however, can only apply to the proband of each family and in view of the considerable number of cases now observed it seems highly unlikely that the exclusive occurrence of the syndrome in females is due to chance. Moreover, the syndrome has never been transmitted by an unaffected male.

The only dominant mode of inheritance confined to females is transmission by the X chromosome where the disorder is lethal in the hemizygous (XY) state. If this is true of familial lipodystrophy, all male children receiving the mutant X chromosome might be expected to die during fetal life and the total number of sons born to affected mothers should be, on average, half the number of daughters. Further, all male children born to affected mothers should be normal while half the daughters should, on average, be affected. When the known pedigrees of both types of familial lipodystrophy are considered together, there have been 11 normal daughters, 10 affected daughters (excluding the probands), seven normal sons, and no affected sons born to affected mothers (table). This is close to the ratio of 1:1:1:0 to be expected if the hypothesis of an X linked dominant transmission, lethal in the hemizygous state, is correct.

TABLE Children of affected mothers (numbers according to fig 2). The probands are given in brackets and are not included in the calculation.

Affected mother	Affected daughters	Normal daughters	Normal sons
Family 1 No 1	3	1	
No 2	1	1	
No 8 (1)	(1)		3
Family 2 No 1	2	2	2
No 4	1	1	
No 5	2	1	
No 10 (1)	(1)		1
Family 3 No 1	1+(1)	1	
Family 4 No 1	1	2	
No 2		2	
Family 5 No 1	(1)		
Total	10	11	7

Other reports of familial and sporadic lipodystrophy

In recent years a number of other reports of familial lipodystrophy have appeared and there have also been a number of reports of sporadic lipodystrophy resembling either the type 1 or type 2 variants described in the present communication.

In 1975, Davidson and Young¹² reported several female members of an American family with familial lipodystrophy in whom subcutaneous fat was absent from the limbs and lower trunk but present on the face and upper trunk. Eight members of the family were observed over three generations. Lipodystrophy was not seen in males although five male members of the family were diabetic. According to the reported pedigree the ratio of normal daughters, affected daughters, normal sons, and affected sons born to affected mothers was 7:8:10:0 respectively. Thus, an X linked dominant mode of inheritance, lethal in the hemizygous state, may also be assumed in this family.

A family with familial lipodystrophy and dominant inheritance was described by Ozer *et al.*¹³ A 52 year old woman, five of her six sibs, and three of her four children were found to have a syndrome characterised by excessive accumulation of fat on the face, neck, shoulder girdle, axillae, back, and genitalia. In contrast, the limbs showed no subcutaneous fat with prominent musculature and dilated superficial veins. All affected members of the family had type IV hyperlipidaemia and frank diabetes was observed in two. Unfortunately, the sex of the affected sibs and children was not given.

Lillystone and West¹⁴ described a girl of 11 years with lipodystrophy of the limbs, labial hypertrophy, acanthosis nigricans, hypertriglyceridaemia, and insulin resistant diabetes. No other family members were affected. Chait *et al.*¹⁵ described a female

patient with secondary amenorrhoea who lacked subcutaneous fat on the hands, forearms, and legs but had normal fat distribution over the trunk and face. The patient had severe hypertriglyceridaemia and hyperinsulinaemia. This case also appears to have been sporadic.

Wachslicht-Rodbard *et al*¹⁰ described four cases of partial lipodystrophy of the 'face sparing' type in a study of 'heterogeneity of the insulin receptor interaction in lipoatrophic diabetes'. Insulin receptors were found to be normal in these cases, in contrast to other varieties of lipoatrophic diabetes. No further details of the family history, of whether the four cases were related, or of the distribution of the lipodystrophy were provided.

In summary, despite some deficiencies of information, all published reports are consistent with a proposed inheritance of familial lipodystrophy as an X chromosomal dominant trait, lethal in the hemizygous state.

Discussion

Familial lipodystrophy can be divided into at least two types on the basis of the clinical phenotype of either limb lipodystrophy (type 1) or trunk and limb lipodystrophy (type 2). Both varieties of lipodystrophy can also occur sporadically. As the published case reports indicate, there may be other clinical phenotypes which are genetically closely related to the two described in the present communication but which differ slightly in the distribution of the lipodystrophy. The clinical phenotype is consistent within each pedigree and there was never any doubt about which family members were affected. There is thus no doubt that it represents a monogenic segregating syndrome.

Familial lipodystrophy is almost certainly commoner than indicated by the few published reports of the syndrome. Most of our index patients had been seen by several physicians before the disorder was recognised. The proband of the first Scottish family had been investigated over four years by several physicians for her skin xanthomata and hyperlipoproteinaemia until her mother's admission to hospital with an unrelated illness prompted recognition of the lipodystrophy and its familial nature. The aunt of this proband had attended a diabetic clinic in another hospital for many years without her lipodystrophy being recognised. The proband of the second Scottish family had attended a cardiologist with mild mitral stenosis and had been referred to an endocrinologist as a possible case of Cushing's syndrome without her lipodystrophy being recognised. The condition was recognised by a physician who had seen all three members of the

first family and referred the patient to one of the authors (MGD).

The proband of the second German family⁸ was treated in hospital by one of the co-authors of the description of the first Germany family⁷ without being recognised as a further case. The recently recognised German patient with type 2 lipodystrophy had been investigated for several years by a number of physicians for secondary amenorrhoea. She had been seen by a clinical geneticist who described her hirsutism, vulvar hypertrophy, and acanthosis nigricans but not her truncal and limb lipodystrophy. After lecturing on the lipodystrophies in another University Hospital, one of the authors (JK) was immediately shown a ward patient with typical type 1 lipodystrophy. The patient was diabetic but not hyperlipidaemic. Photographs of a second patient presented on the same occasion suggested that she belonged to the type 2 variety with absent subcutaneous fat from the limbs and trunk and pseudohypertrophy of the vulva. The families of these two patients living in south Germany have not yet been investigated.

Diabetes and hyperlipidaemia are frequently present in patients with familial lipodystrophy but do not occur in all cases. Only a few patients exhibit the typical characteristics of acquired lipoatrophic diabetes. Severe insulin resistant diabetes associated with gross hyperlipoproteinaemia and lipodystrophy was first described by Lawrence⁵ and is likely to attract the attention of physicians. It is not surprising that several of the probands of both the Scottish and German families showed this severe metabolic disturbance. Some patients with familial lipodystrophy have mild hyperlipoproteinaemia or mild diabetes only and have only abnormal glucose tolerance with hyperinsulinaemia. Other affected patients show no metabolic abnormality. Acanthosis nigricans is only seen in patients with insulin resistant diabetes.

The relationship between the metabolic abnormalities found only in some patients with familial lipodystrophy and the lipodystrophy itself remains unclear.¹ Post-heparin lipoprotein lipase activity has been reduced in all four cases of type 1 lipodystrophy investigated to date⁸ and the enzyme was reduced in the grossly hyperlipidaemic proband of one Scottish family with type 2 lipodystrophy. It was normal in the second proband with mild type IV hyperlipidaemia and the newly described type 2 patient from Germany. The frequency and the significance of reduced levels of this enzyme in familial lipodystrophy are thus at present unclear.

Both types of familial lipodystrophy appear to be transmitted as an X linked dominant trait which is lethal in the hemizygous (XY) state. In females, the

normal second X chromosome partially compensates for the defective X chromosome, and a varying degree of X chromosome inactivation as in the Lyon hypothesis may explain the variability in expressivity of the metabolic abnormalities. Whether the two types of familial lipodystrophy seen to date represent different mutants of the same allele or two genes on adjacent loci is uncertain. Linkage analysis using other X chromosomal inherited traits may clarify this question in future as more cases are described.

The genetic disorders comprising the syndrome of familial lipodystrophy may be more formally designated as 'X linked dominant familial lipodystrophy type 1' and 'X linked dominant familial lipodystrophy type 2'. The cases described by Davidson and Young¹² and Lillystone and West¹⁴ most closely resemble the type 2 variety of the syndrome. The case described by Chait *et al*¹⁵ appears to belong to the type 1 variety. The cases described by Ozer *et al*¹³ and Wachslight-Rodbard *et al*¹⁰ cannot be assigned to either type without further information and the possibility remains that further types of familial lipodystrophy may exist due to mutations of the same allele or genes on adjacent loci.

The clinical phenotypes of patients with both varieties of familial lipodystrophy and of the recessively inherited congenital total lipodystrophy (Seip-Berardinelli syndrome^{3,4}) are of interest with respect to the genetics of subcutaneous fat development. Lipodystrophy also occurs as sporadic phenocopies in acquired lipoatrophic diabetes⁵ and in progressive partial lipodystrophy.^{1,2} Whether the occasional sporadic cases of limb and trunk lipodystrophy are also phenocopies, or represent insufficient knowledge of the family history, or are new mutations is uncertain. Further cases of familial lipodystrophy will undoubtedly be described and the study of a larger number of patients should elucidate both the genetics and metabolic abnormalities associated with this fascinating syndrome.

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