January 2023

Lipodystrophy – How to Recognise it and What to Do

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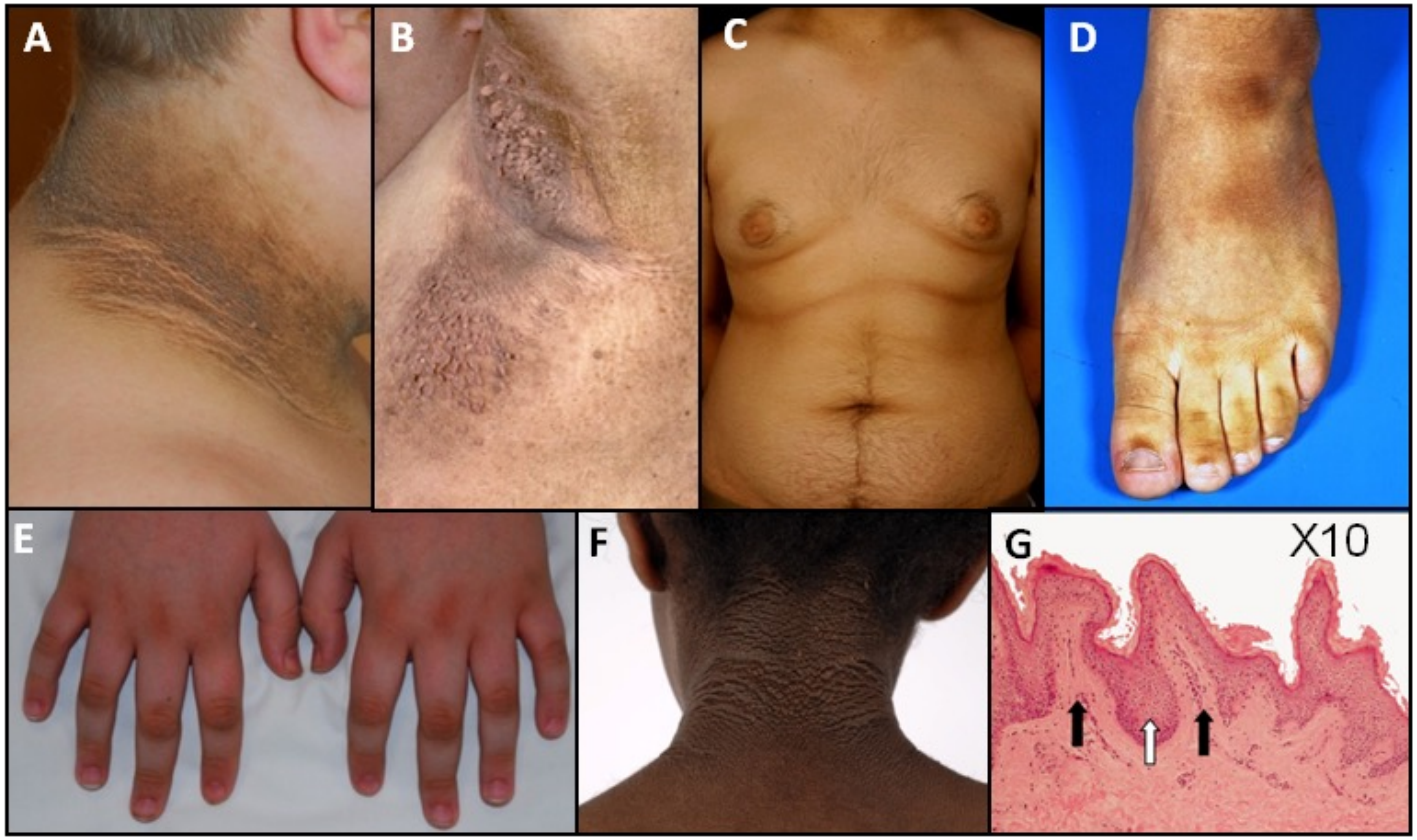
Disclosures

- I have received honoraria from Novo Nordisk, Eli Lilly and Amryt for delivering CPD talks on lipodystrophy and severe insulin resistance at sponsored meetings
- I have acted as Consultant and am UK PI for a Clinical Trial in Segmental Overgrowth (not endocrine) for Novartis

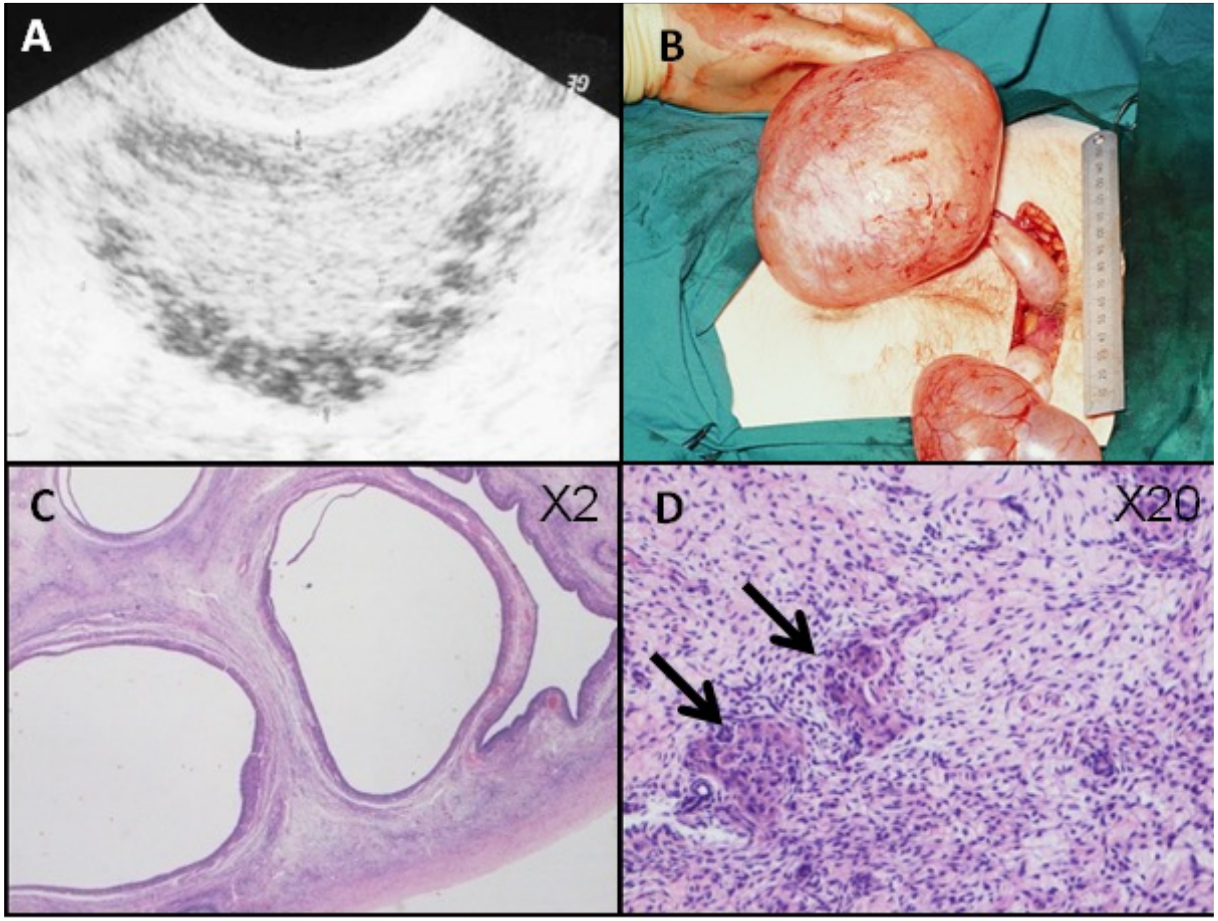
Clinical Features of Severe IR

Acanthosis Nigricans



Semple R *et al Endocr Rev.* 2011 Aug;32(4):498-514

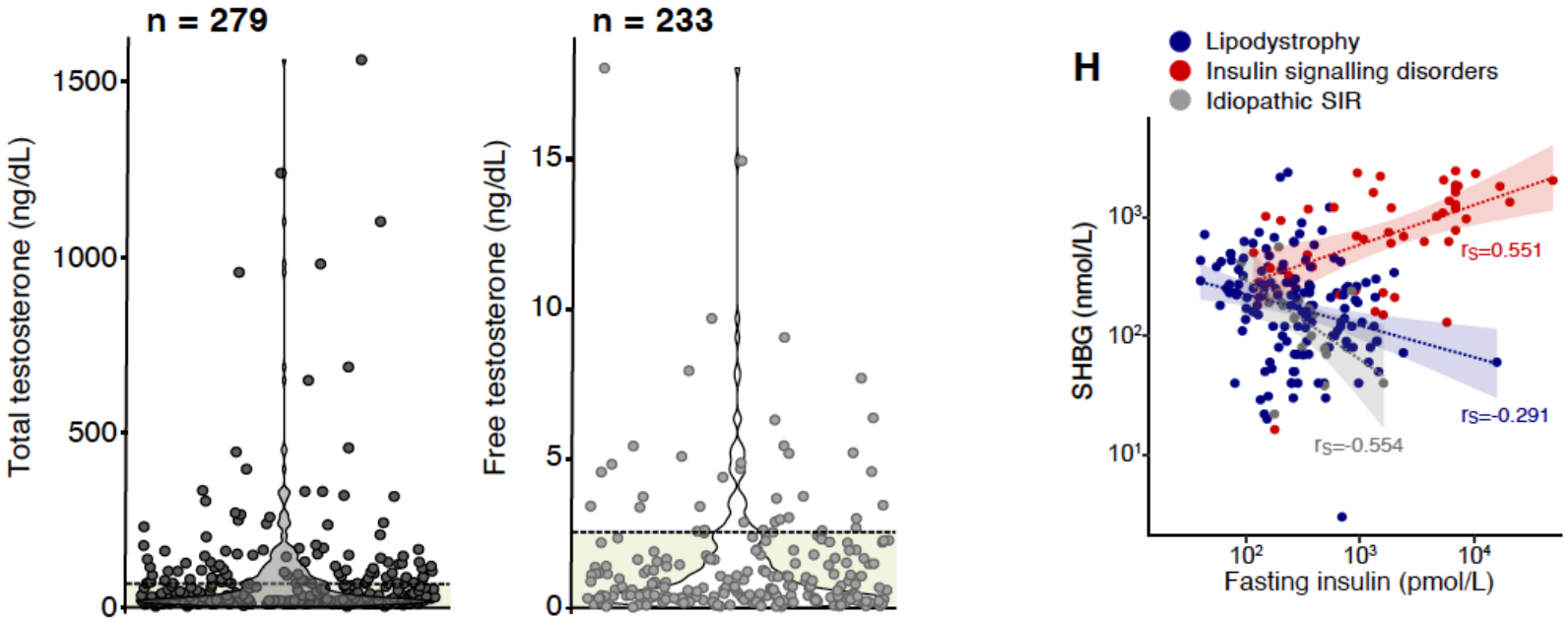
Ovaries and Severe Insulin Resistance



Semple *et al Endocr Rev.* 2011 Aug;32(4):498-514

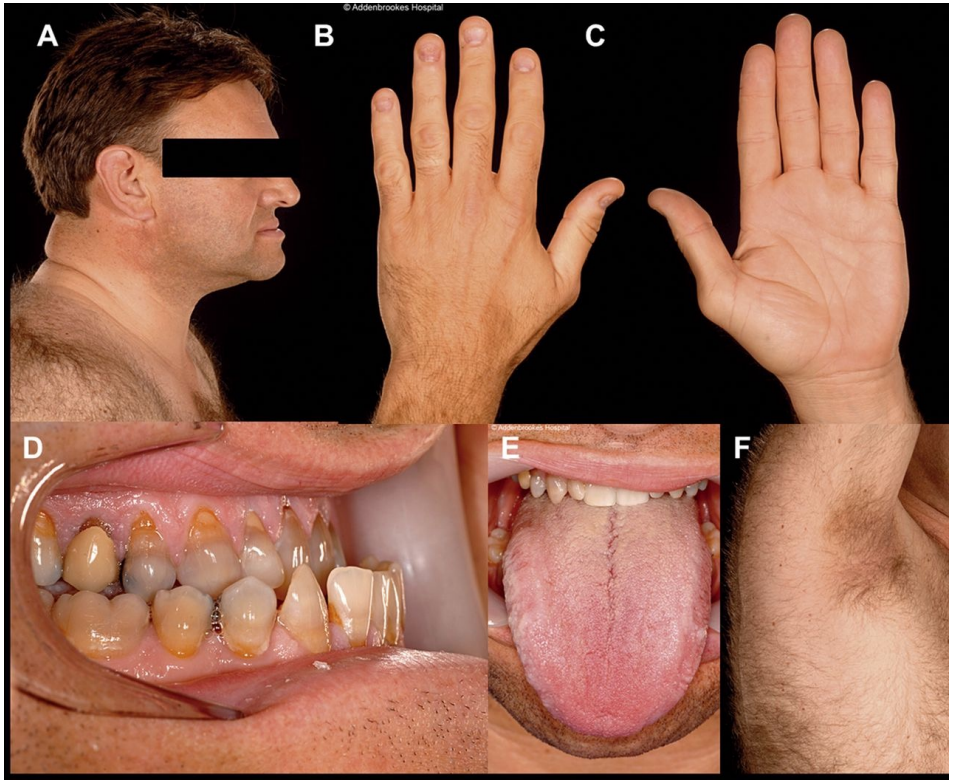
Ovarian Hyperandrogenism and Response to Gonadotropin-releasing Hormone Analogues in Primary Severe Insulin Resistance

Isabel Huang-Doran,[1,2] Alexandra B. Kinzer,[3] Mercedes Jimenez-Linan,[4] Kerrie Thackray,[1,2] Julie Harris,[1,2] Claire L. Adams,[1,2] Marc de Kerdanet,[5] Anna Stears,[6] Stephen O'Rahilly,[1,2] David B. Savage,[1,2] Phillip Gorden,[3] Rebecca J. Brown,[3,*] and Robert K. Semple[7,1,*]

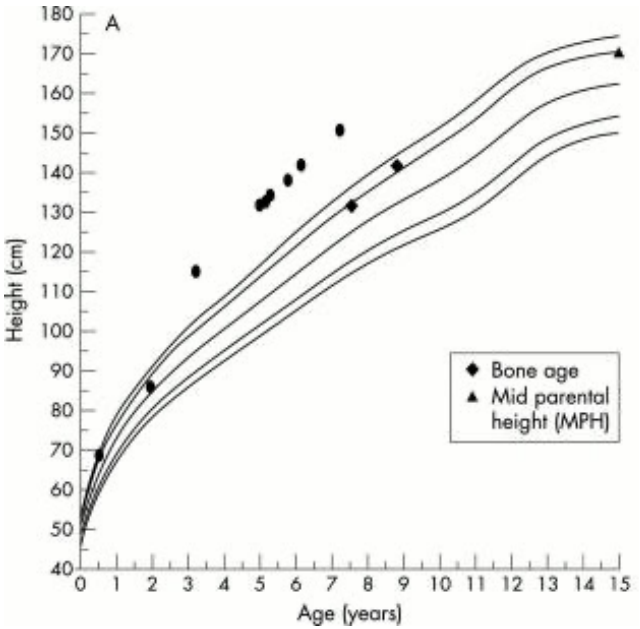


The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 8, 2367–2383

Pseudoacromegaly or Prepubertal overgrowth



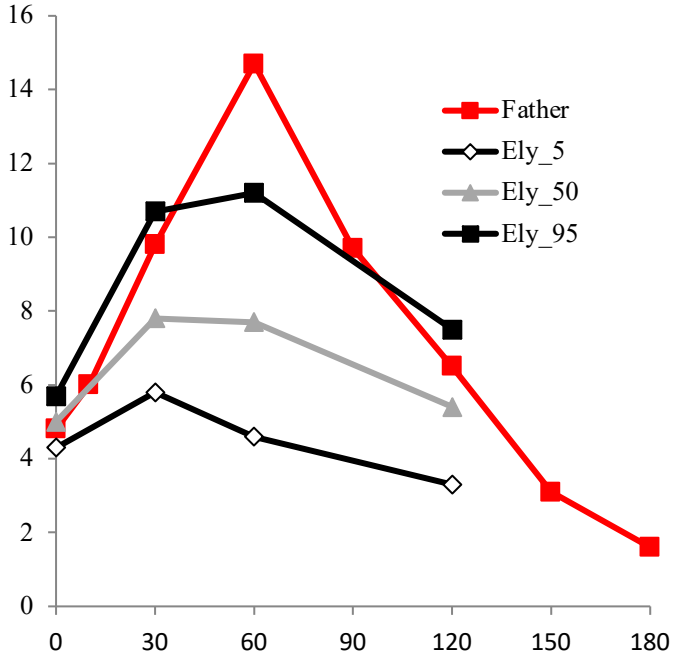
Parker, Semple *Eur J Endocrinol*. 2013;169(4):R71-80.



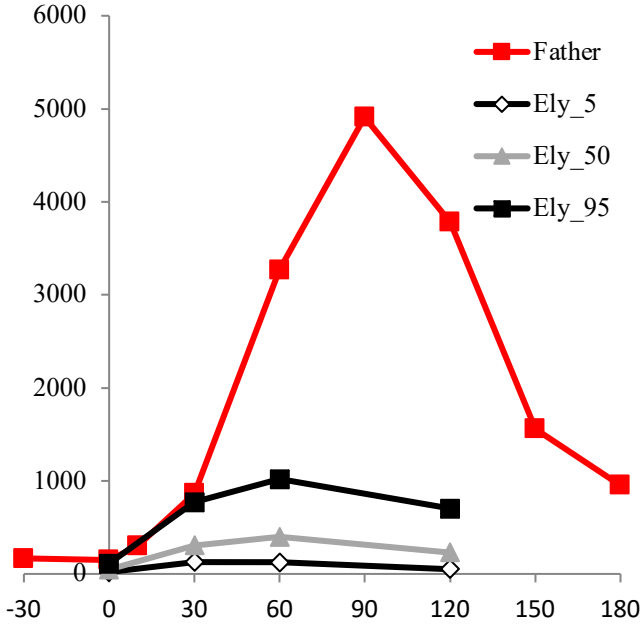
Srinivasan S *et al Arch Dis Child*. 2003 Apr;88(4):332-4

Hypoglycaemia

Glucose

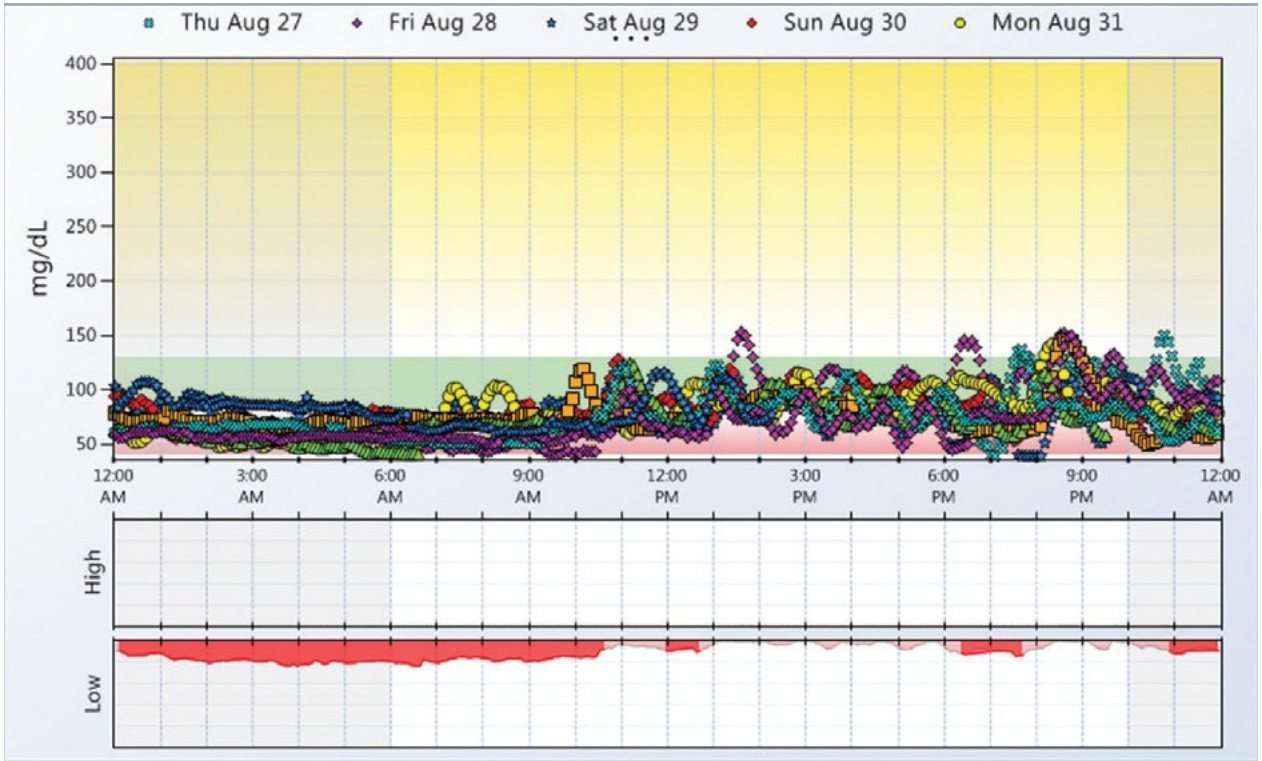


Insulin



CASE REPORT

Severe insulin resistance in disguise: A familial case of reactive hypoglycemia associated with a novel heterozygous *INSR* mutation



Innaurato *et al, Pediatric Diabetes*. 2018;19:670–674

Severe Insulin Resistance in Paediatrics

	Presenting prepubertally	Presenting postpubertally
Lipodystrophic	• **Congenital generalised LD** • **Acquired LD** • (Familial partial LD)	• **Familial partial LD** • **Acquired LD** • (Congenital generalised LD)
Non lipodystrophic	• **Donohue syndrome** • **Rabson Mendenhall syndrome** • **SHORT syndrome** • Dyslipidaemic IR (mostly idiopathic) • (Acquired)	• **Generalised or "Type A" IR** • Acquired or "Type B" IR • **Dyslipidaemic IR** (mostly idiopathic)
Complex/ syndromic	• Alström Syn • Werner Syn • Bloom Syn • MOPDII • MDP Syn. • Mandibuloacral dysplasia • Other	• *Formes frustes*?

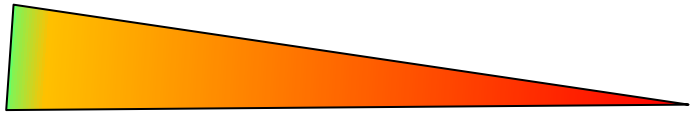
Lipodystrophy

Definition of Lipodystrophy

- Diagnosis remains largely clinical/subjective, although collateral support from MRI, DXA, clinical anthropometry may be garnered
- Conventionally denotes regional or global lack of adipose tissue despite adequate nutrition
- Conceptually linked to obesity with metabolic complications by the ideas of adipose tissue expandability and “adipose failure”

Obesity

“Relative” Adipose Failure



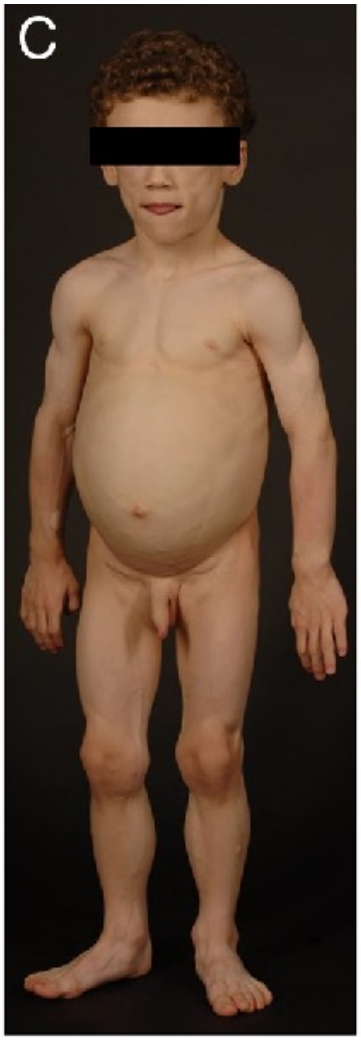
Lipodystrophy

“Absolute” Adipose Failure

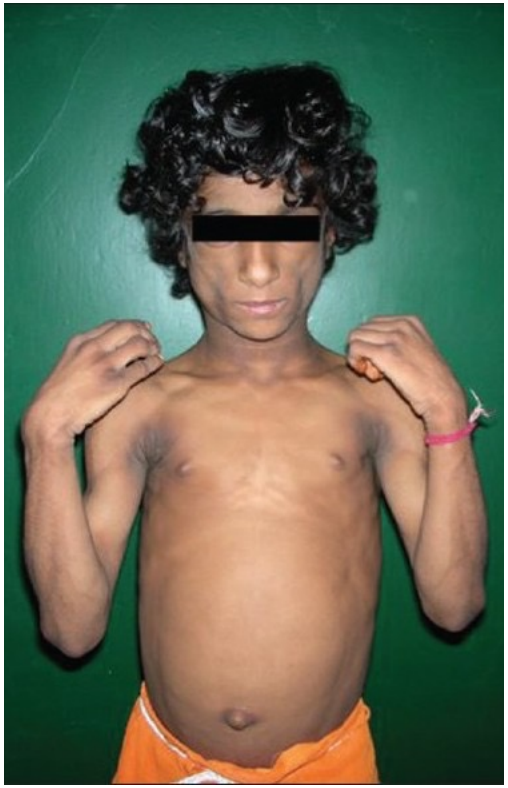
Clinical Presentation of Lipodystrophy

- Regional or global lack of adipose tissue, especially femorogluteal
- Muscular appearance
- Severe hypertriglyceridaemia
- Previous episodes of pancreatitis
- Severe fatty liver with or without inflammation/fibrosis
- Features of severe insulin resistance (acanthosis nigricans, DM, severe PCOS)

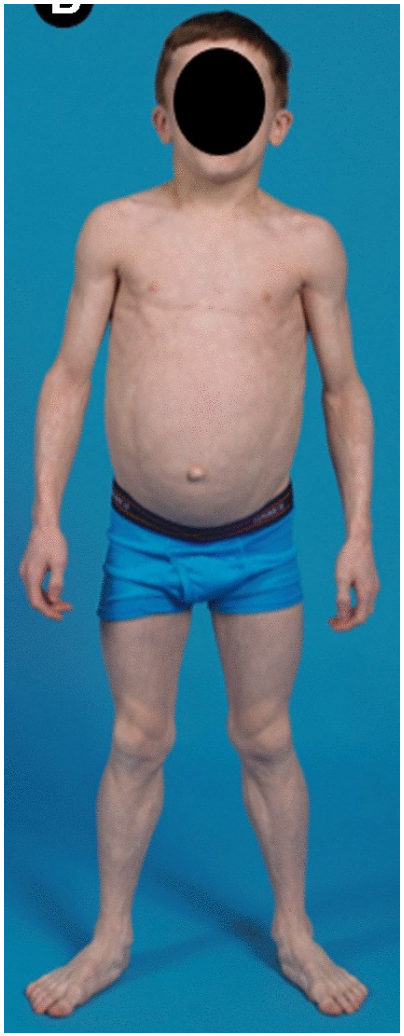
Generalised Lipodystrophy



Brown et al JCEM
2016 Dec;101(12):4500-4511



Khandpur et al
Net Case 2011:77:3;402-402



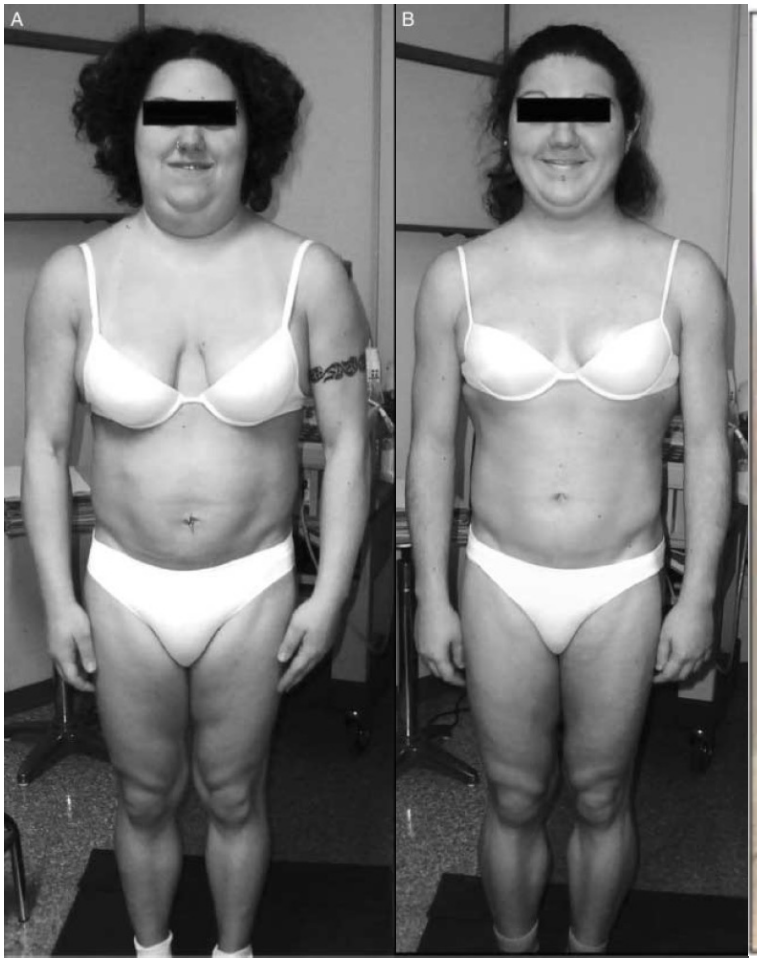
Patni & Garg
Curr Diabetes Reports 22,
461–470 (2022)

Araújo-Vilar & Santini
J. Endo. Inv. 42, 61–73 (2019)

Dunnigan Köbberling Lipodystrophy

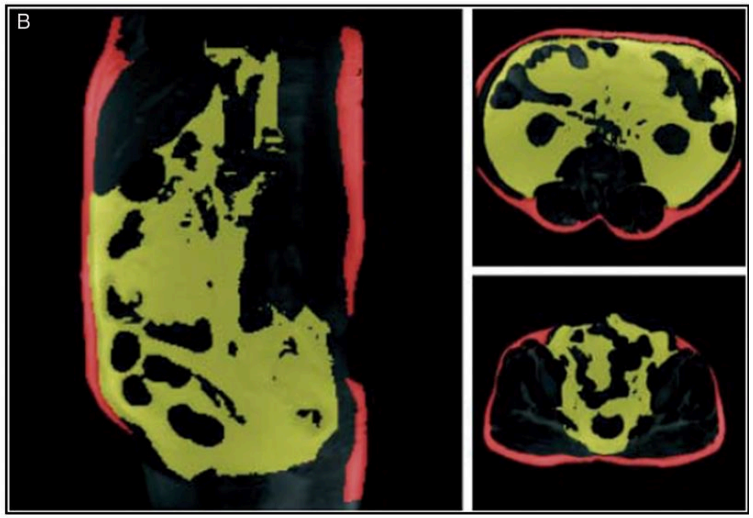
(Familial Partial Lipodystrophy Type 2; FPLD2)

Autosomal dominant; *LMNA*



Gambineri *et al*,
Eur J Endocrinol. 2008;59:347-3553.

Araújo-Vilar & Santini
J. Endo. Inv.
42, 61–73 (2019)

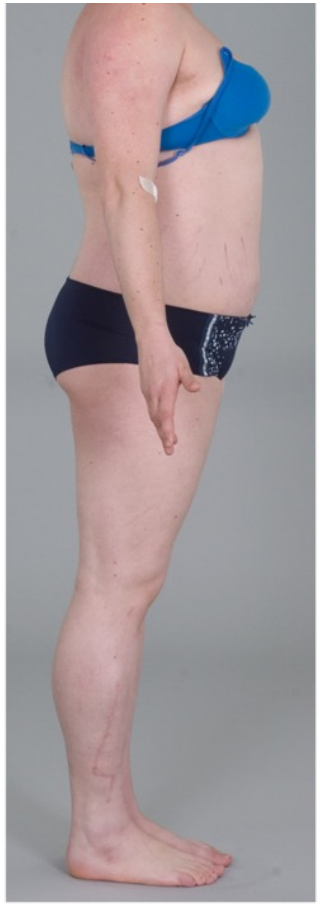


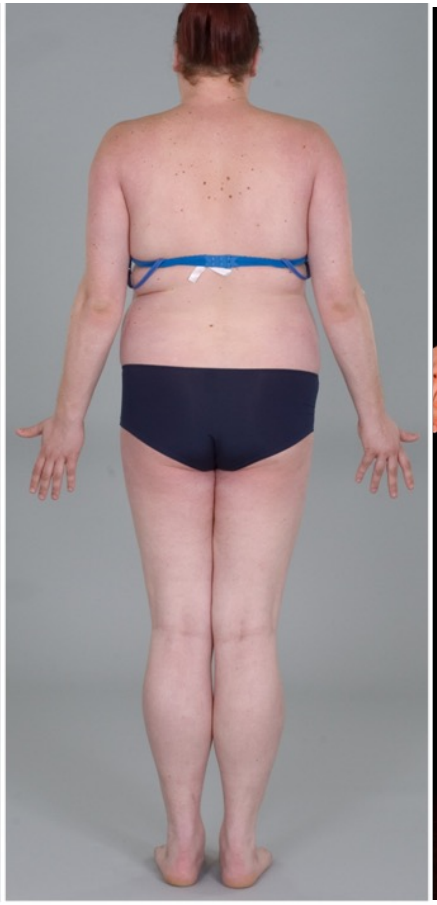
Parker & Semple
Eur J Endocrinol. 2013;169(4):R71-80.

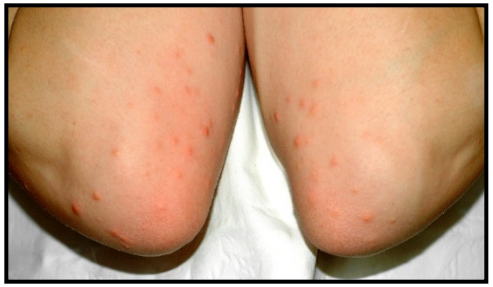
PPARgamma Ligand Resistance Syndrome

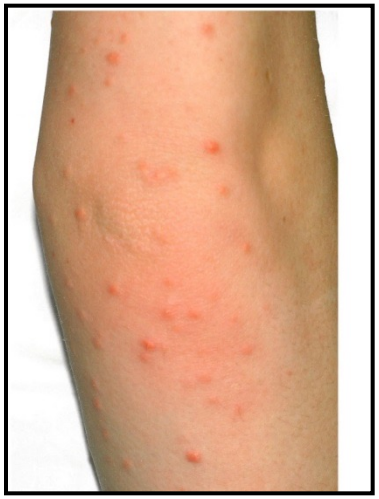
(*PPARG* mutations; FPLD3)

Autosomal Dominant

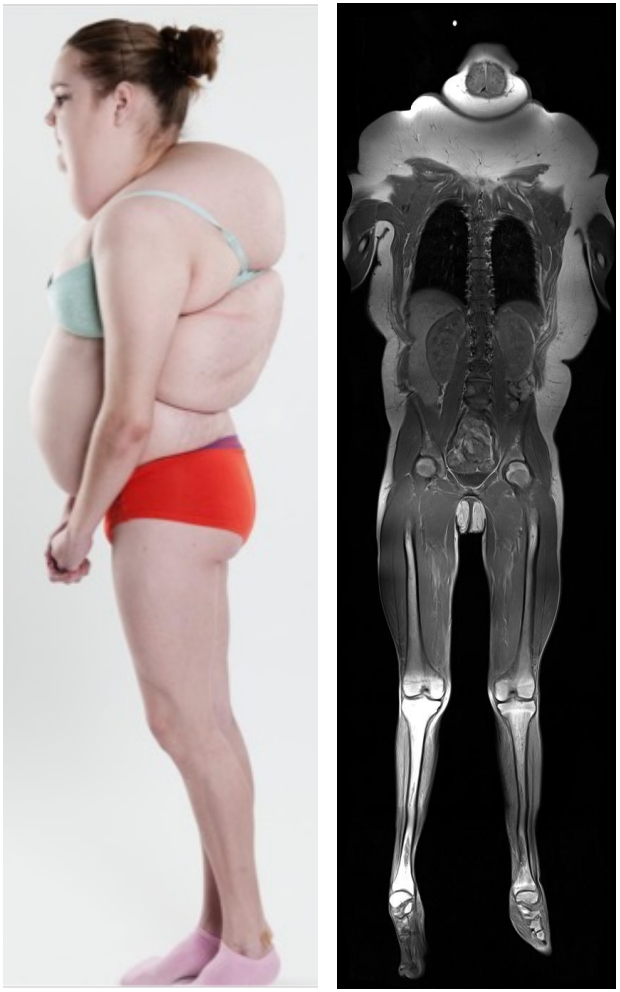




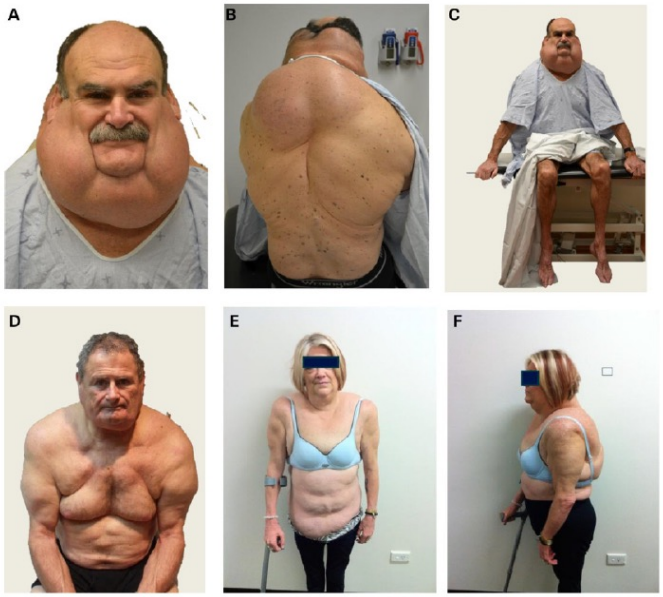




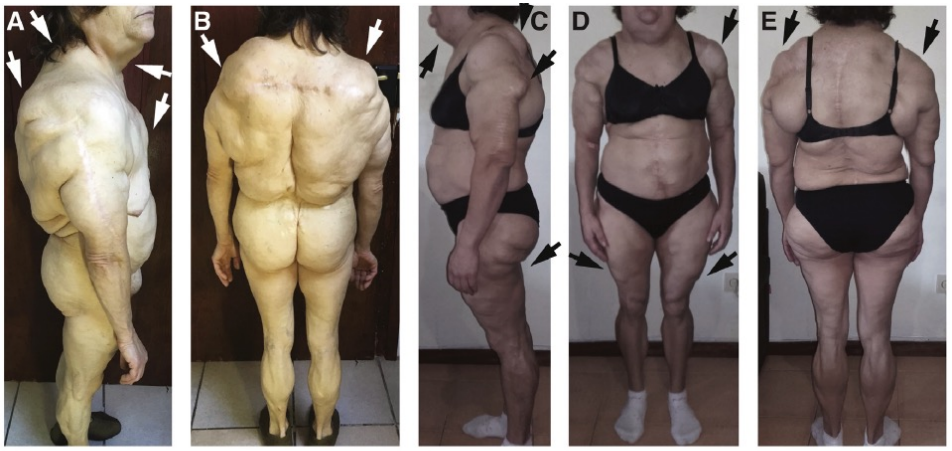
Mitofusin 2-related Lipodystrophy



Rocha *et al*, eLife, 2017

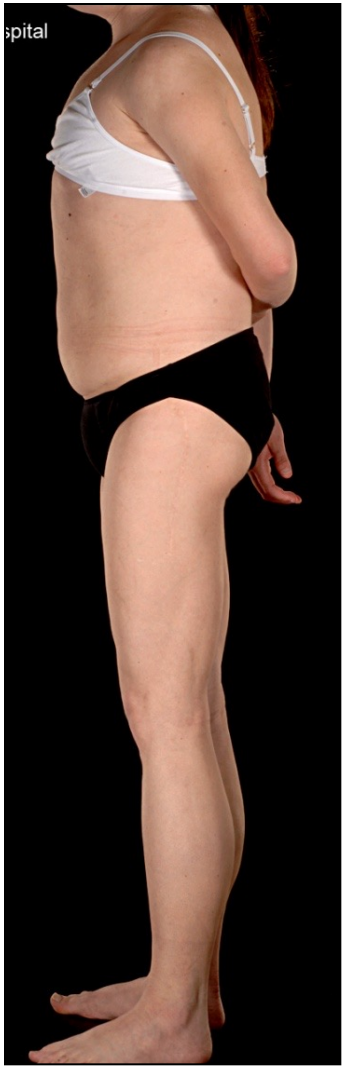


Hum Mol Genet. 2015;24:5109-14.



Capel *et al*, J Clin Lipidol. 2018

Lipodystrophy after childhood cancer treatment



- "Metabolic syndrome" increased in cancer survivors
- In some cases IR and dyslipidaemia extreme; metabolic phenocopy of lipodystrophy
- Centripetal adiposity common; frank lipodystrophy rare
- Risk greatest with whole body irradiation

Modelled in mice (*Poglio et al, Am J Path 2009*):

- Female *ob/ob* mice exposed to 8 Gy TBI plus BMT
- No appetite change but reduced adipose accumulation
- More severe IR and hepatic steatosis
- Fewer small adipocytes in irradiated animals

Mayson et al, Endoc. Prac. 2013

Example of Chemotherapy-induced Lipodystrophy

- 18-year-old female survivor of **neuroblastoma**, treated by partial resection, focal irradiation, chemotherapy, TBI, and autologous BMT at 3-4 years old.
- Slipped femoral epiphyses, bilateral cataracts, short stature, and secondary oligomenorrhea.
- T2DM at age 12; poor control (HbA1c > 11%) despite increasing insulin. Triglyceride levels severely elevated with hepatic steatosis.
- Acute pancreatitis developed when serum triglycerides 52 mmol/l.
- Height 147 cm, BMI 20.5 kg/m^2. Adipose deposition pronounced centripetally. Flexural acanthosis nigricans, multiple acrochordons. Eruptive xanthomata on dorsal surface of forearms, upper arms, liver palpably enlarged at 18 cm in the mid-axillary line.
- Despite low fat diet, fenofibrate and insulin hyperglycaemia and hypertriglyceridaemia persisted, requiring U500 insulin.
- At 24-months after pancreatitis pioglitazone was begun, with good effect

Published Cases

Lorini R, Cortona L, Scaramuzza A, et al. Hyperinsulinemia in children and adolescents after bone marrow transplantation. *Bone Marrow Transplant* 1995; 15: 873–77.

Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood

Mervi Taskinen, Ulla M Saarinen-Pihkala, Liisa Hovi, Marita Lipsanen-Nyman

Lancet 2000; **356:** 993–97

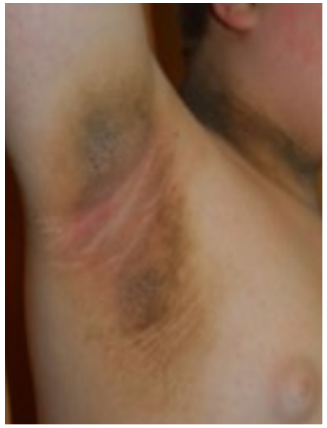
Adverse metabolic and cardiovascular risk following treatment of acute lymphoblastic leukaemia in childhood; two case reports and a literature review

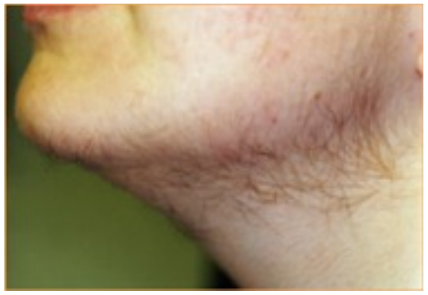
P. Amin, S. Shah, D. Walker* and S. R. Page

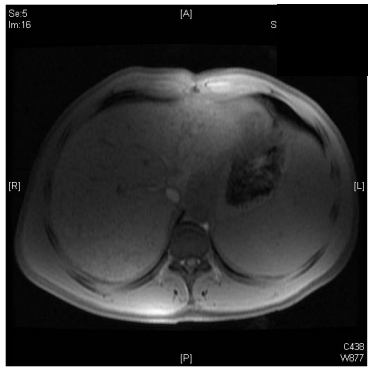
 Diabetic Medicine, **18**, 849–853

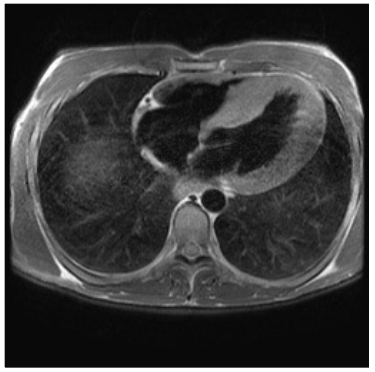
Consequences of Lipodystrophy

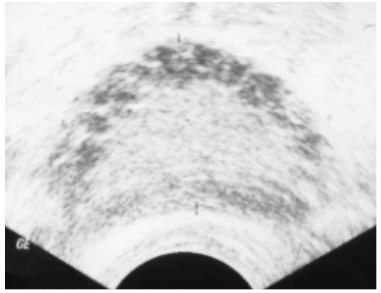
- Generic SIR complications
  - Acanthosis nigricans
  - Hyperandrogenism
  - Female subfertility
  - Precocious puberty
  - Diabetes mellitus
  - Soft tissue overgrowth
- Lipotoxic complications
  - Severe dyslipidaemia
  - NAFLD, cirrhosis, HCC
  - Premature atherosclerosis
- Specific to LD
  - **Cosmetic distress**
  - “Mechanical” problems

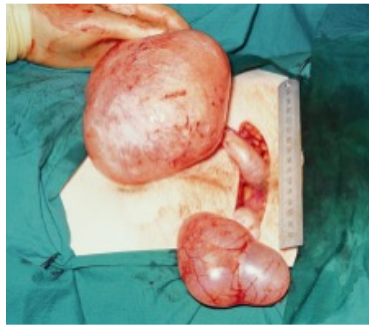












Principles of Management of Lipodystrophy

Lipodystrophy = "Adipose Failure"

1. Offload adipose tissue
   - "obesity therapies", guided by rationale and clinical experience
   - Low fat, hypocaloric diet, orlistat, GLP1 agonists, SGLT2 inhibitors are all used **off licence**
   - Bariatric surgery described
   - Leptin licensed in a subset of patients
2. Maximise insulin sensitivity
   - Exercise
   - Metformin, (pioglitazone) **off licence**
4. Treat dyslipidaemia, hypertension, hyperandrogenism
5. Address QoL, cosmetic issues, genetic counselling

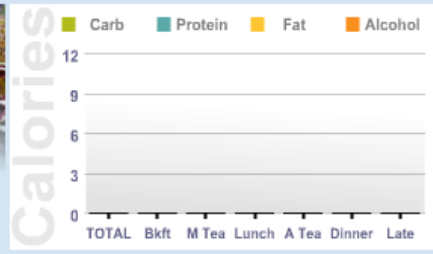
Gaining information - food diary

< Wednesday, 14 March 12 >

Search foods

Go

unbranded only



favourite foods

enter foods

create meals

Food Desc	Qty	g	Cals	Fat	Carb	Pro
Breakfast						
Meal/Recipe Porridge	1	127	256	5	46	8
TEA Made With Water With Semi-Skimmed Milk	1	300	21	1	2	2
Total Breakfast			**277**	**6**	**48**	**10**
Morning Tea						
Graze Fruit squash	1	41	183	10	19	5
Twinings TEA Fruit Or Herbal, Made With Water	1	200	8	0	2	0
Marks & Spencer Chocolate cornflake bites	1	0	40	2	6	1
Total Morning Tea			**231**	**12**	**27**	**6**
Lunch						
Graze Americas nut mix	1	41	266	26	3	7
PEAS Sugar Snap, Average	1	50	17	0	2	2
TOMATOES Cherry, Average	1	100	19	0	3	1
Total Lunch			**302**	**26**	**8**	**10**
Afternoon Tea						
Oranges raw, navels	1	140	69	0	18	1
FLAPJACK Average	1	14	68	4	8	1
Strawberries raw	11	132	42	0	10	1
Total Afternoon Tea			**179**	**4**	**36**	**3**
Dinner						
LAMB Grill Steak, Prime, Average	1	110	343	28	2	20
BROCCOLI Purple Sprouting, Boiled, Average	1	90	17	1	1	2
Asparagus cooked, boiled, drained	1	90	20	0	4	2
Tetley TEA Decaf	1	100	1	0	0	0
Total Dinner			**381**	**29**	**7**	**24**
Late						
SATSUMAS Fresh, Raw	1	100	36	0	9	1
Tetley TEA Decaf	1	100	1	0	0	0
Total Late			**37**	**0**	**9**	**1**
Grand Total			**1407**	**77**	**135**	**54**

Food calorie target (after exercise) 841

Calories remaining -566

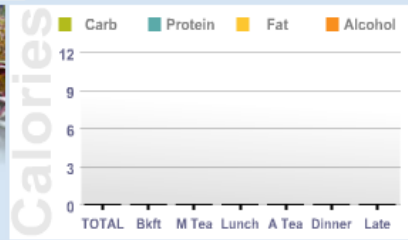
home | food log | exercise log | body log | dashboard | resources | profile

< Monday, 23 April 12 >

Search foods

Go

unbranded only



favourite foods

enter foods

create meals

Food Desc	Qty	g	Cals	Fat	Carb	Pro
Breakfast						
Danone YOGHURT Peach, Bio Activia 0%	1	125	64	0	11	5
TEA Made With Water With Semi-Skimmed Milk	1.5	300	21	1	2	2
Boots FLAPJACK Fruit With Raisins	1	75	329	16	43	4
Total Breakfast			**414**	**17**	**56**	**11**
Morning Tea						
Oranges raw, navels	1	140	69	0	18	1
Harvest Morn Yoghurt and fruit bars	2	36	152	5	25	2
Total Morning Tea			**221**	**5**	**43**	**3**
Lunch						
Look what we found Chicken and sage soup	1	300	189	11	13	10
Ryvita CRISPBREAD Pumpkin Seeds & Oats	0.5	25	91	2	14	3
TEA Made With Water With Semi-Skimmed Milk	1.5	300	21	1	2	2
Total Lunch			**301**	**14**	**29**	**15**
Afternoon Tea						
Apples raw, with skin	2	212	110	0	29	1
Dinner						
BREAKFAST CEREAL All Bran, Original, Kellogg's	1	40	112	1	19	6
MILK Semi Skimmed, Average	1	100	49	2	5	3
Blueberries raw	0.5	50	29	0	7	0
Bananas raw	1	118	105	0	27	1
Total Dinner			**295**	**3**	**58**	**10**
Late						
Tetley TEA Decaf	6	600	6	0	2	0
McVitie's BISCUITS Rich Tea	2	16	76	2	12	1
Danone YOGHURT Peach, Bio Activia 0%	1	125	64	0	11	5
Total Late			**146**	**2**	**25**	**6**
Grand Total			**1487**	**41**	**240**	**46**

Food calorie target (after exercise) 841

Calories remaining -646

delete item *add to your favourite foods*

Patient feedback

- What have they learnt from the food diary / changes made?

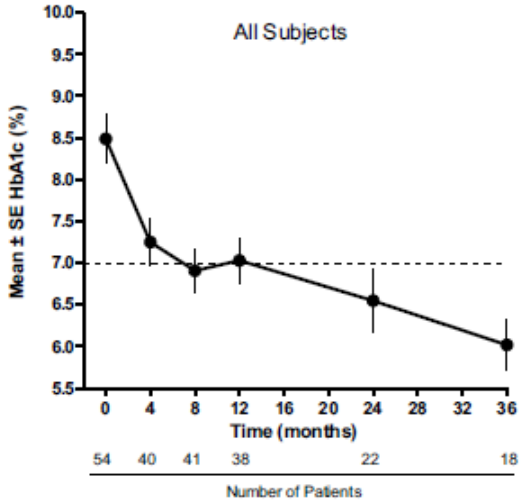
Nutrient	**Your intake** (average over 7 days)	**Recommended intake**
Energy	2,100kcal	Aiming for 5% weight loss 1,600kcal
Protein	15.5%	20%
Fat	38.2%	20-30%
Carbohydrate	46.3%	55-60%

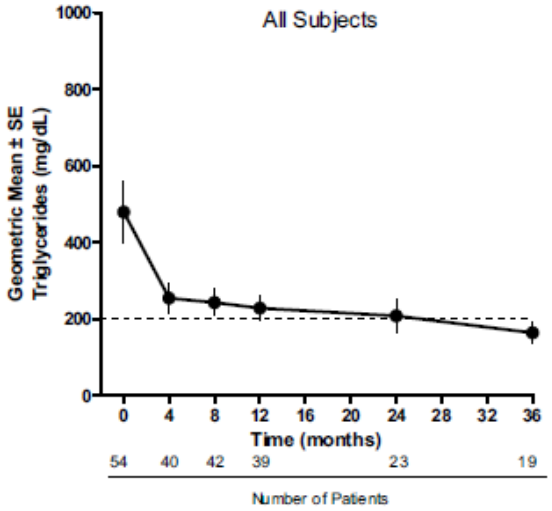
- Individualised plans based on this

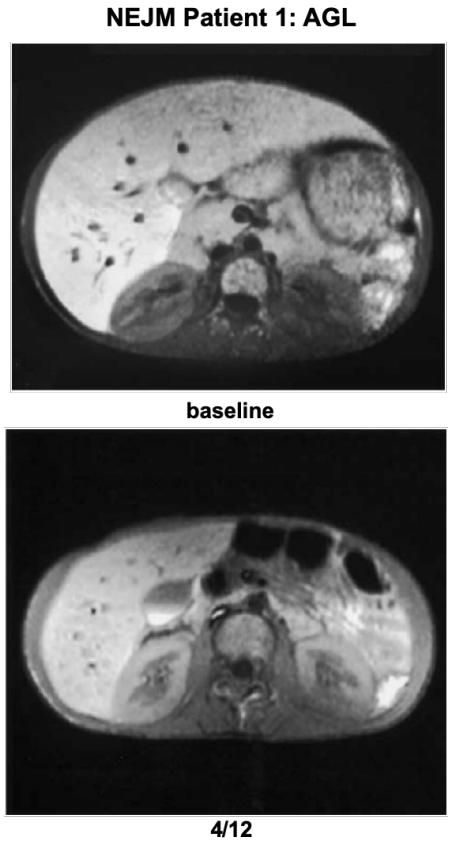
Leptin therapy

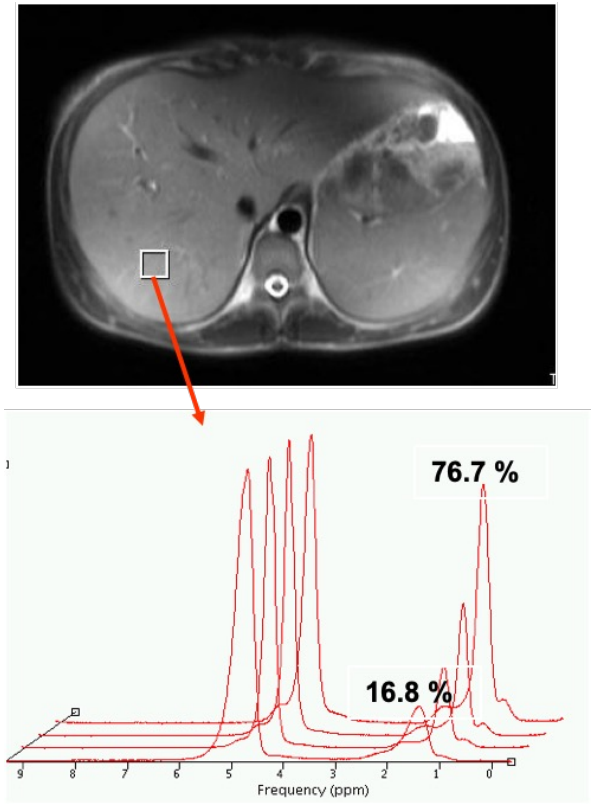
- Leptin is produced by adipocytes
- A low leptin concentration signals starvation and increases hunger
- Patients with lipodystrophy may have a low leptin concentration and increased appetite
- In well chosen patients s/c leptin therapy (metreleptin, od or bd) has marked benefits in terms of metabolic control and QoL
- Metreleptin is now licensed and approved by NICE for treating the complications of leptin deficiency in generalised lipodystrophy for people 2 years and over, and as an option in partial lipodystrophy for people 12 years and over, with poor metabolic control (HbA1c > 58 mmol/mol fasting Tg > 5.0 mM; SMC is currently considering
- Metreleptin is a high cost treatment which should only be started in liaison with the National Severe IR service or equivalent

Leptin treatment in Generalised LD







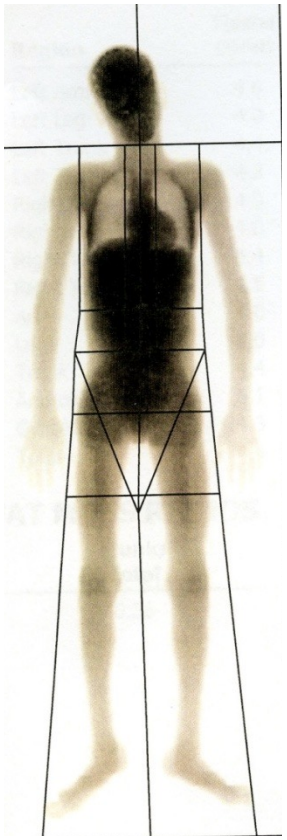


Prof David Savage

Oral *et al* N Engl J Med. 2002 Feb 21;346(8):570-8.

Case History

- 8 year old female
- Born at 37 weeks, birthweight 2.5kg
- Poor feeding, jaundice, admitted to PICU
- Diagnosis of generalised lipodystrophy at 12 months, mutation in *BSCL2* gene
- Developed diabetes aged 5 years
- Poor control despite metformin 500mg bd
- Developmental delay, acanthosis nigricans, hepatomegaly, precocious puberty, HOCM
- 'Always hungry'



BODY COMPOSITION

Region	Tissue (%Fat)
Left Arm	4.0
Left Leg	4.0
Left Trunk	4.4
Left Total	4.3
Right Arm	4.0
Right Leg	4.0
Right Trunk	4.4
Right Total	4.5
Arms	4.0
Legs	4.0
Trunk	4.4
Android	6.1
Gynoid	4.3
Total	4.4

FAT MASS RATIOS

Trunk/ Total
0.55

Case History ctd

	15/03/2012	14/06/2012
HbA1c (%)	8.7	6.4
HbA1c (mmol/mol)	72	46
Glucose (mmol/l)	5.8	4.4
Insulin (0-60 pmol/l)	571	270
C Peptide (pmol/l)	3343	1916
Adiponectin (ug/ml)	2.9	3.2
Leptin (ug/L)	<0.1	48.4
Triglyceride (mmol/l)	3.2	1.9
Cholesterol (mmol/l)	4.4	3.6
Alk Phos (30- 135 U/L)	362	383
ALT (0-50 U/L)	64	64
Height (cm)	145.2	147.2
Weight (kg)	32.4	32.2
BMI (kg/m2)	15.4	14.9

Other management issues

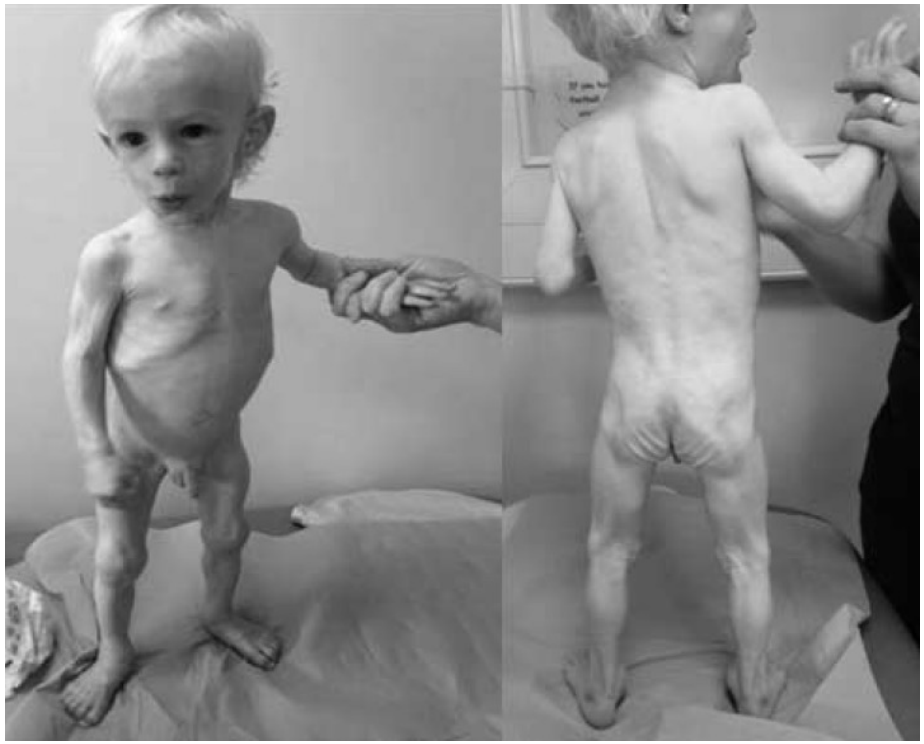
- Screening for complications (liver, cardiac)
- Treatment of hyperandrogenism
- Treatment of hypertension (*PPARG* patients)
- Genetic counselling
- Cosmetic appearance
- Mechanical symptoms

A case of diencephalic syndrome presenting with isolated lipodystrophy

John H. McDermott[a,c], Julie Harris[e], Joanne Fédée[h], Mars Skae[b,d], Robert Semple[f,g] and Sofia Douzgou[a,c]

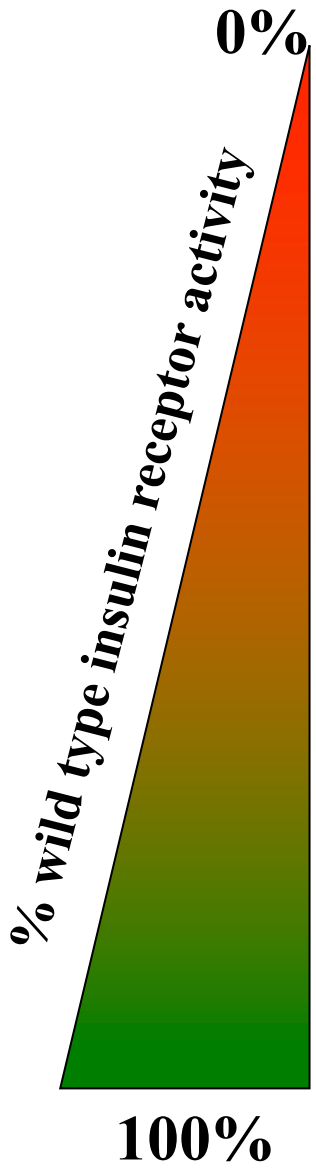
Clinical Dysmorphology 2018, 27:122–125

- Beware "Lipodystrophy" without biochemical "adipose failure"
- Consider CNS tumours



Primary Insulin Signalling Defects

Genetic Insulin Receptoropathies



- Donohue Syndrome
- Rabson-Mendenhall Syndrome
- Type A Insulin Resistance
- HAIR-AN
- Risk of Milder Insulin Resistance

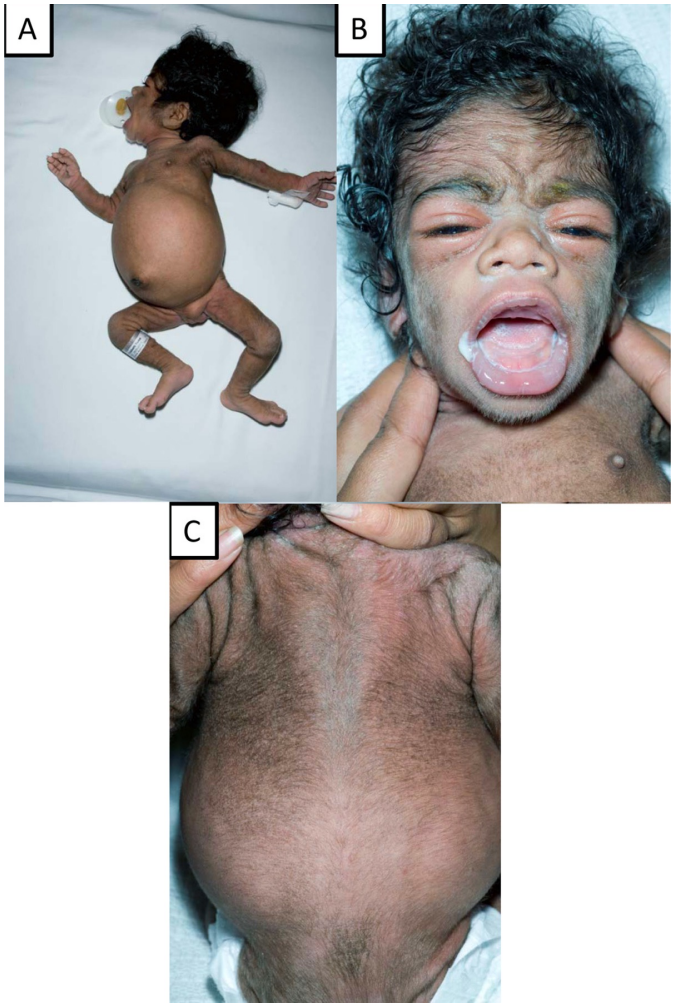
Donohue Syndrome

(formerly Leprechaunism; AR; Little/no INSR function)

- IUGR, severe failure to thrive
- ↓adipose tissue, muscle, Frequent infections

- Large, low-set ears, Wide nostrils, Thick lips, Gingival hyperplasia
- Breast hyperplasia, Prominent nipples, Enlarged external genitalia, Cystic ovaries
- Abdominal distention, Cholestasis, Hepatic fibrosis, rectal prolapse
- Large hands/feet, Acanthosis, Hypertrichosis
- Nephromegaly, nephrocalcinosis
- LVH

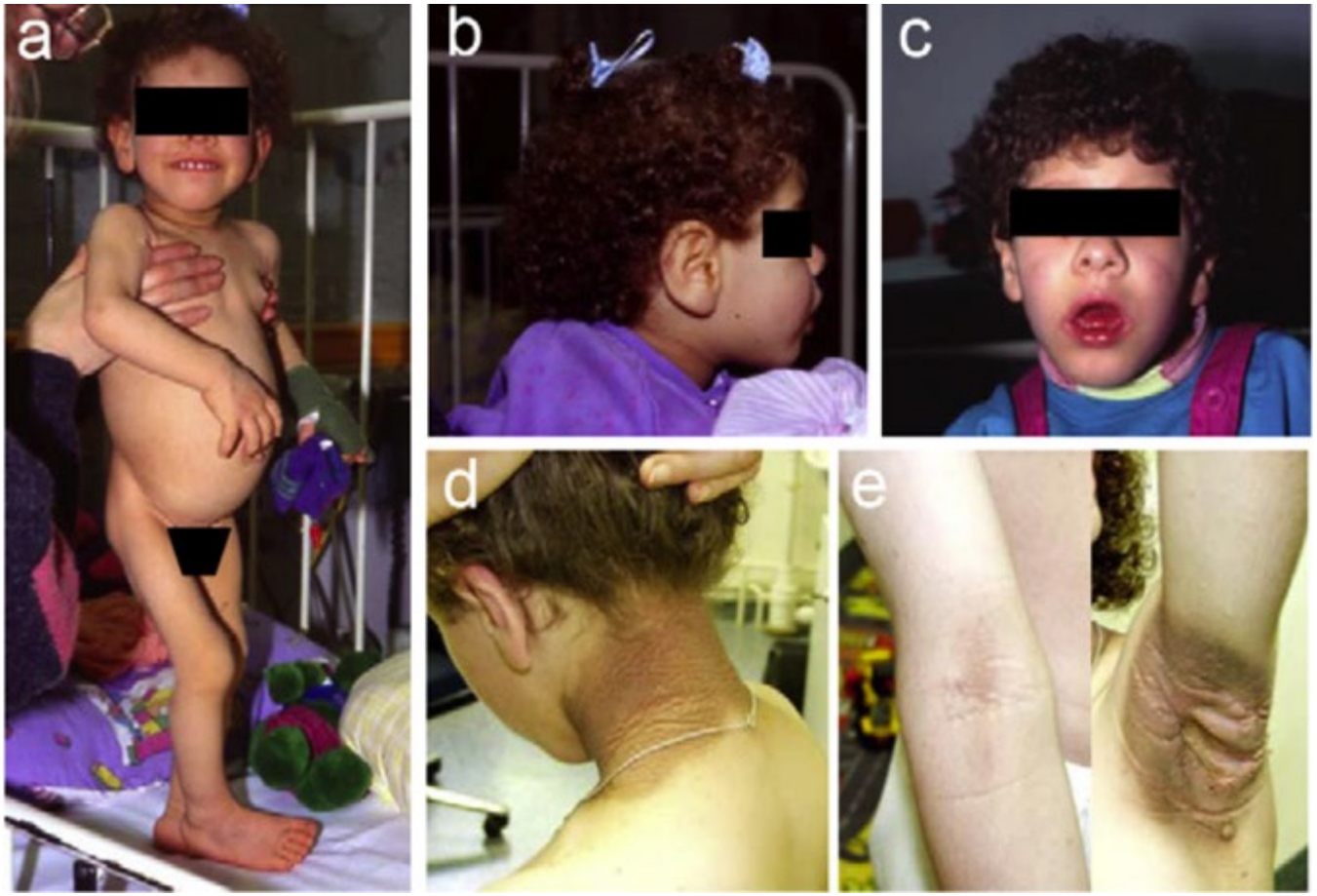
- Extreme hyperinsulinaemia, Islet hyperplasia, Postprandial hyperglycemia, Fasting hypoglycemia



De Bock *et al, J Clin Endocrinol Metab*, 2012, 97(5):1416–1417

Rabson Mendenhall Syndrome

(AR; 5-10% INSR function?)



C.T. Thiel *et al. Molecular Genetics and Metabolism* 94 (2008) 356–362

Type A Insulin Resistance

- Presentation usually peri-puberty
- Precocious puberty
- Oligomenorrhoea/amenorrhoea
- Hyperandrogenism
- Cystic ovaries
- Acanthosis nigricans
- Severe hyperinsulinaemia
- Hypoglycaemia
- Insulin-resistant diabetes

Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J. *N Engl J Med*. 1976, 294(14):739-45

SHORT syndrome and Severe IR: *PIK3R1*

Insulin

↓

Insulin Receptor

↓

IRS

↓

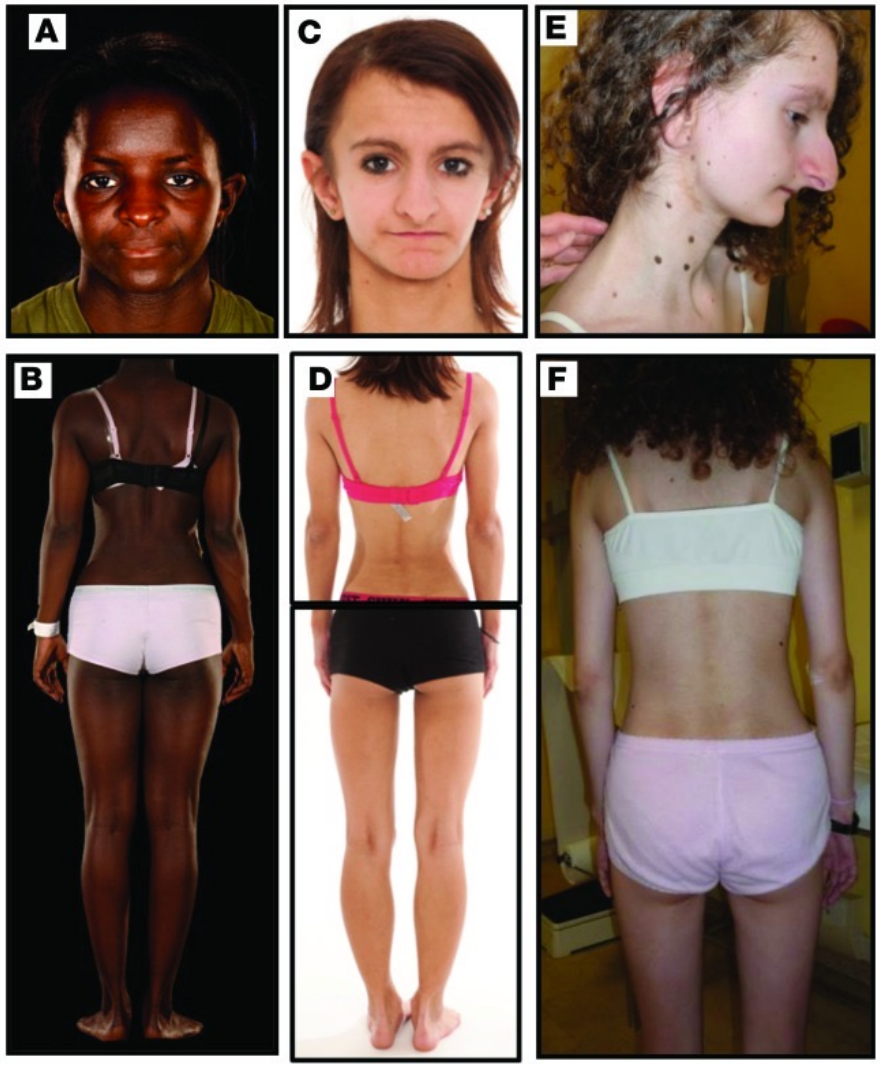
PI3K

↓

AKT2

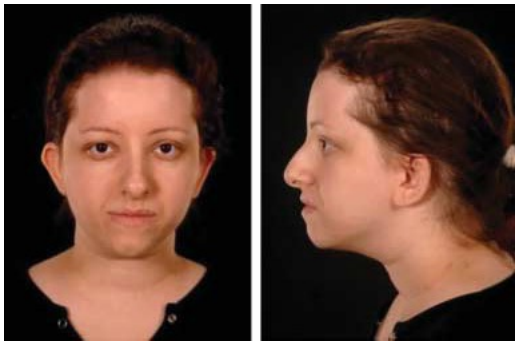
↓

AS160



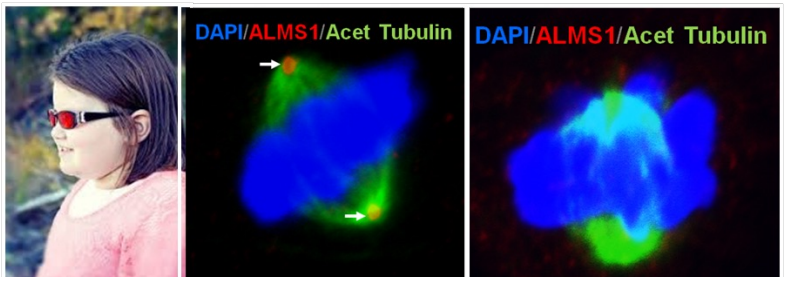
Huang-Doran *et al, JCI Insight*, JCI Insight;1(17):e88766.

IR in Complex Syndromes



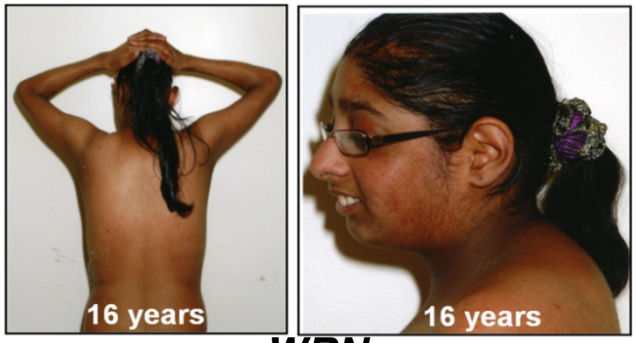
POC1A (SOFT syndrome)

Chen *et al, J. Mol Endo 55(2):147-58.*



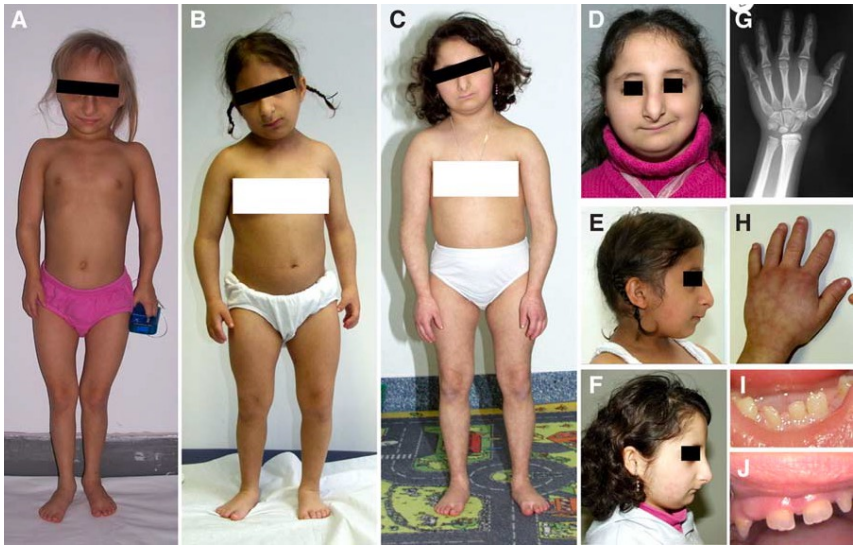
ALMS1 (Alstrom syndrome)

Hearn J Mol Med (Berl). 2019 97(1):1-17



WRN

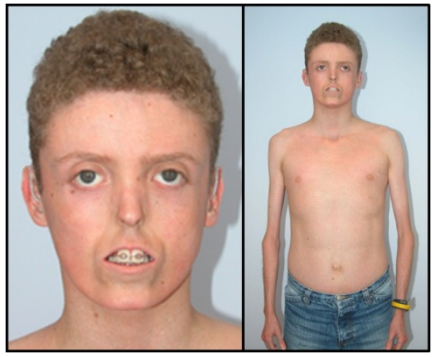
Raffan *et al, Front Endo* 2011 29;2:8



PCNT (MOPDII)

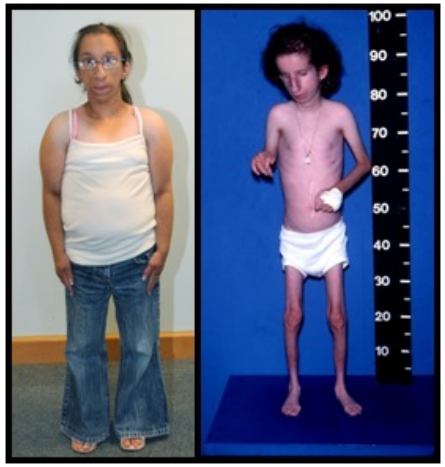
Rauch *et al, Science* 2008 319, 816-819

Huang Doran *et al, Diabetes* 60:925–935, 2011



POLD1

Weedon *et al, Nat Gen* 2013 45(8):947-50.

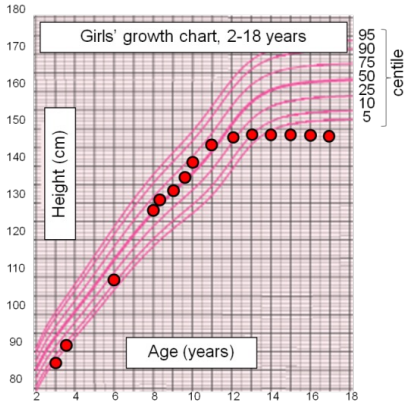


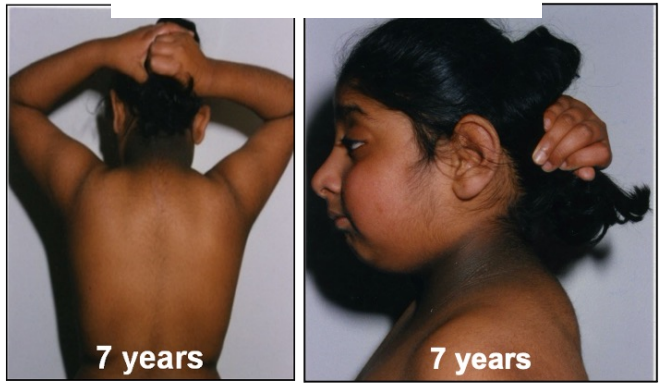
NSMCE2

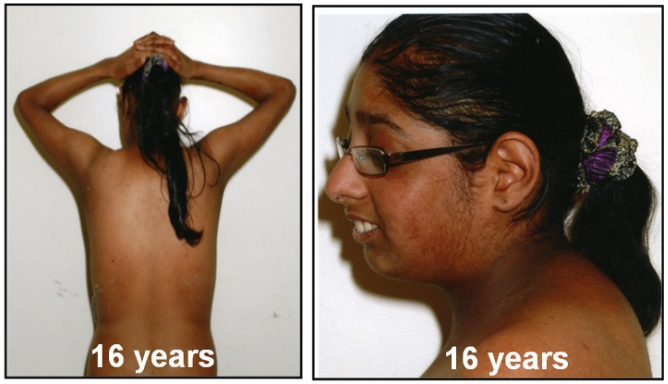
Payne et al, J Clin Invest. 2014124(9):4028-38.

Werner Syndrome, 1904

- Mutations in the *WRN* gene, encoding a DNA helicase
- Features include
  - Premature ageing (hair, skin)
  - Short stature, Subfertility
  - Sclerodermatous skin changes
  - Loss of subcutaneous fat
  - Insulin resistance, diabetes, dyslipidaemia
  - Malleolar ulceration
  - Cataracts
  - Premature arteriosclerosis
  - Cancer
  - Osteoporosis
  - Sarcopenia





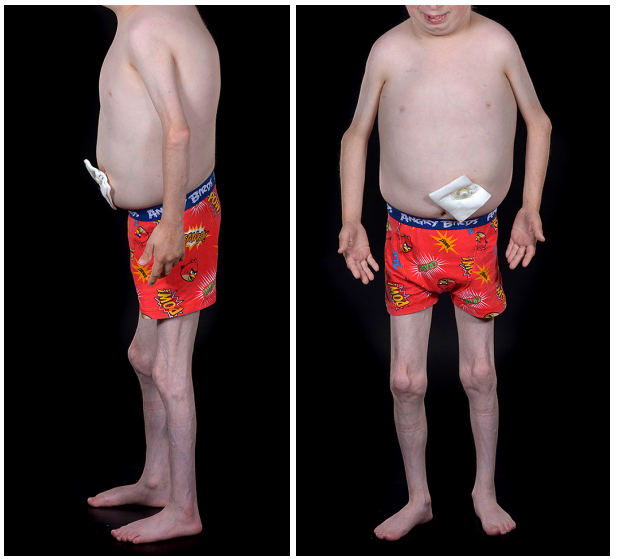


Raffan *et al*, Frontiers in Endocrinology 2011

Atallah *et al*, J Clin Lipidol 2022

The dangers of “feeding up” in lipodystrophy

- Children with lipodystrophy may never be able to gain adipose tissue
- Supplementing caloric intake to try to achieve this may cause harm
- Atypical body composition and energy expenditure may complicate calculations of requirements



Logan *et al*, Am J Hum Genet 2018 Dec 6;103(6):1038-1044.

Practical Summary: Lipodystrophy in Scotland

- Generalised lipodystrophy may be acquired or congenital – easy to identify in girls, less so in boys
- Clues are fatty liver, high Tg, low HDL-chol, episodes of pancreatitis, often with acanthosis, and PCOS from end of the first decade
- Partial lipodystrophy may be much more subtle. Important to assess in underwear. The above metabolic abnormalities should trigger consideration even if LD not clinically obvious
- When “fat failure” is recognized, OFFLOAD fat with “obesity therapies. Beware attempt to correct FTT nutritionally
- If LD generalized or extensive, then check serum leptin and refer – subcutaneous metreleptin has striking benefit and should hopefully be available soon in Scotland.