Genetic Syndromes of Severe Insulin Resistance

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Short title:

Severe insulin resistance syndromes

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Abstract

Insulin resistance underpins the link between obesity and most of its associated metabolic disorders including type 2 diabetes, fatty liver disease, dyslipidaemia and cardiovascular disease. Despite its importance and extensive scientific endeavour, its precise molecular pathogenesis remains unclear. Monogenic syndromes of extreme insulin resistance, whilst rare in themselves, can provide unique insights into the pathogenesis of human insulin resistance. Severe insulin resistance syndromes are broadly classified into three categories: lipodystrophies, primary insulin signalling defects or complex syndromes including severe insulin resistance. Genetically confirmed classification has facilitated the identification of robust diagnostic biochemical features accelerating accurate clinical diagnosis. Interestingly the biochemical features of lipodystrophies are far more closely aligned to what is seen in prevalent forms of insulin resistance than those of primary insulin signalling defects, suggesting that lipodystrophy could be a relevant model for common disease. This assertion is supported by genome-wide association data indicating that SNPs associated with fasting hyperinsulinemia and metabolic dyslipidaemia, are strongly associated with a subtle reduction in hip fat, suggesting that subtle forms of lipodystrophy are likely to be a significant contributor to prevalent insulin resistance.

Introduction

Severe insulin resistance syndromes(SIRS) are a complex group of disorders with impaired cellular responsiveness to insulin manifesting as reduced biological activity to a given concentration of the hormone(1). The normal pancreatic response to insulin resistance(IR) is to increase beta cell insulin secretion(2). Insulin is measurable in plasma and a fasting or glucose stimulated level is often sufficient to make the diagnosis of IR(3). However, insulin is infrequently measured in clinical practice, and often only considered after an individual has presented with one of the hallmarks of chronic hyperinsulinemia. The first of these are cutaneous manifestations of IR including acanthosis nigricans, a velvety hyperpigmented thickening of the skin and acrochordan's (skin tags) which are fibrous dermal benign tumours often localised to skin creases(4, 5). The purported pathogenesis relates to the cross reactivity of insulin with the IGF-1 receptor(6). Polycystic ovaries, menstrual irregularities and hyperandrogenism are prevalent in syndromes of severe IR and often constitute the primary clinical manifestation in women. Hyperinsulinemia has been implicated in the pathogenesis of PCOS (polycystic ovary syndrome); a notion supported by improvements in PCOS features in states of reversible hyperinsulinemia such as type B IR due to insulin receptor autoantibodies(7, 8). Another trait commonly observed in states of severe IR is altered glucose homeostasis. Impaired glucose tolerance and diabetes mellitus develop when the beta cell compensatory response to IR is insufficient to regulate glucose metabolism(9). This may reduce the diagnostic utility of insulin measurements.

SIRS are grouped into three categories 1. Disorders characterised by a primary impairment of adipocyte energy storage with adverse secondary impact on glucose handling by muscle and liver (Lipodystrophies) 2. Primary insulin signalling defects; and 3. Complex syndromes associated with IR. In this review we will briefly discuss recent progress in genetically classifying these syndromes, how they can be distinguished phenotypically and how they inform mechanistic understanding of more prevalent IR.

Severe Insulin Resistance Syndromes

- **The Lipodystrophies**

White adipose tissue is critical for the efficient storage of excess energy as triglyceride (TG) in lipid droplets. Lipodystrophies are a heterogeneous group of rare disorders characterised by a loss of adipose tissue and a depletion of lipid storage capacity(10, 11). The failure of this system places a demand on non-adipose sites, typically liver and muscle, to buffer excess circulating TG. The principle of adipose tissue expandability refers to the hypothesis that humans have a 'limited capacity' to increase the size and number of adipocytes(12, 13). In states of sustained positive energy balance, adipose tissue stores TG up to this threshold but once exceeded ectopic TG deposition occurs, and in turn results in impaired insulin action in target tissues like the liver and skeletal muscle(14).

Lipodystrophies are classified according to the extent of adipose loss (generalised or partial) and the primary cause of the disorder (genetic or acquired). Congenital generalised lipodystrophies(CGL) represent the severe end of the spectrum with a near complete loss of subcutaneous adipose tissue presenting from birth(15). *AGPAT2* and *BSCL2* were the earliest loci identified in Berardenelli-Seip syndromes with significant overlap between the phenotypes(16). Owing to the degree of adipose failure seen in CGL secondary complications manifest in childhood where in addition to developing the hallmarks of IR those effected have dyslipidaemia and non-alcoholic fatty liver disease(NAFLD) with the potential for developing steatohepatitis, cirrhosis and hepatic failure. In contrast to CGL, familial partial lipodystrophies (FPLD) are heritable disorders with varying degrees of subcutaneous fat loss, usually manifesting around puberty in girls and somewhat later in men. The best characterised subtypes include: 1) FPLD1 or Köbberling syndrome presenting with adipose tissue loss in the extremities but preserved or excess abdominal adiposity(17); 2) FPLD2, a monogenic disorder caused by *LMNA* mutations which in contrast to Köbberling syndrome classically presents with reduced subcutaneous adipose tissues in the limbs, abdomen and torso with adipose tissue accumulation in the face, neck and labia majora in females(18); 3) FPLD3 due to mutations in *PPARG* has a pattern of fat loss similar to FPLD1 although severe labile hypertriglyceridemia and hypertension are more frequent in affected individuals(19, 20). Metabolic complications vary depending on the extent of the lipodystrophic phenotype but NAFLD, IR, dyslipidaemia and secondary diabetes are common in all three. Recently a number of other genetic loci have been identified for both generalised and partial

lipodystrophy **(table 1)**. In two very rare subtypes due to mutations in CIDEC and PLIN1, the mutant proteins are almost exclusively expressed in adipocytes where they are directly involved in TG storage within lipid droplets, providing proof-in-principle that primary defects in adipose lipid storage are sufficient to cause the metabolic syndrome(11).

Acquired lipodystrophies have also been reported; not infrequently associated with other autoimmune disorders. Barraquer-Simons is well described as cephalocaudal fat loss, a deficiency in complement (C3), part of the innate immune response and mesangioproliferative glomerulonephritis(21). A metabolic phenotype is rarely seen in this condition, likely due to the sparing of gluteofemoral subcutaneous tissue (GSAT) depots which sequester excess TG. This finding is in contrast to the severity of metabolic disease observed in lipodystrophies where GSAT is depleted. Acquired generalised lipodystrophies(AGL) are very rare and may be idiopathic, associated with radiotherapy and/or drug exposure, or very rarely a cluster of conditions including haemolysis, hepatitis and low C4 complement levels(22). The precise pathophysiology of AGL has not been delineated though it is assumed to be autoimmune and the metabolic sequelae can be very severe(22, 23).

- **Insulin Receptor Signalling Defects**

Mutations in the *INSR* gene or a gene encoding a protein mediating its downstream signalling can cause severe IR. The most severe syndromes are associated with biallelic *INSR* mutations, namely Donohoe and Rabson-Mendenhall syndromes(24, 25). Both present after birth with failure to thrive, reduced muscle and adipose mass, and developmental delay. The ensuing hyperinsulinemia in the face of defective *INSR* function lead to the clinical manifestations of IR. Less deleterious, often heterozygous, mutations affecting the *INSR* may present with a milder, though still severe, phenotype manifesting post-pubertally; this presentation is often referred to as Type A IR(26). Type B IR differs physiologically from *INSR* mutations presenting acutely with features of severe IR due to the development of anti-insulin receptor antibodies. This condition is most often described in females of African ethnicity (27). Beyond the insulin receptor there is a complex cascade of intracellular proteins and kinases that if disrupted may

also manifest with an insulin resistant phenotype **(table 1);** collectively these disorders can be classified under the term 'insulin receptoropathy'.

The study of patients with lipodystrophies and insulin receptoropathies has led to the identification of distinct clinically useful differences between the phenotypes enabling stratification prior to genetic testing – these include:

1. Dyslipidaemia and NAFLD are common complications of lipodystrophic syndromes and will almost certainly be present in patients who are insulin resistant at the time, whereas conditions of impaired proximal insulin receptor signalling are free of such metabolic derangement. The proposed mechanism relates to an increase in de novo lipogenesis (DNL) and the TG rich very low density lipoprotein cholesterol (VLDLc) release from the liver in response to hyperinsulinemia. In lipodytrophic conditions the partially functioning insulin signalling pathway fails to fully suppress glucose production but does appear to induce DNL(28). DNL is probably only part of the pathogenesis of NAFLD in this setting with increased non-esterified fatty acid delivery to the liver another likely contributor(29). In contrast, insulin receptoropathies do not manifest increased DNL (Figure 1)(28) .

2. Adiponectin is an adipokine produced exclusively by adipocytes. Although its function is not entirely clear circulating concentrations correlate with insulin sensitivity in most settings. When measured in lipodystrophic patients circulating adiponectin is low, whereas individuals with insulin receptoropathies have surprisingly normal or even elevated adiponectin concentrations(30). The implication being that adiponectin production by adipocytes is suppressed by the hyperinsulinemia of lipodystrophy and that a functioning insulin receptor is important to this activity. The observation that post insulin receptor signalling defects in AKT2 are associated with lower adiponectin levels similar to those in lipodystrophy suggests that a post-receptor process is involved(28). Adipose specific INSR knockout mice also manifest elevated adiponectin levels(31).

- **Complex syndromes of insulin resistance**

A number of complex syndromes have been described in which severe IR is a characteristic feature. The mechanism of IR in these disorders has often not been well characterised but there some intriguing mechanistic 'threads' eg. ciliary body function(32) and DNA repair mechanisms(33, 34). Although lipodystrophy and IR have been reported in a number of syndromes, adipose tissue loss is not a universal feature.

Recent highlights

- **Common genetic variation is associated with adipose expandability**

Genome-wide association studies have identified common variants implicated in many diseases. Beyond monogenic disorders of severe IR the most common presentation of IR is in individuals with increasing BMI and this is a major factor in the pathogenesis of type 2 diabetes mellitus(T2DM), yet the vast majority of genetic loci implicated in the pathogenesis of T2DM influence insulin secretion(35, 36).

Untangling the genetic loci associated with IR at a population level was greatly enhanced by using fasting insulin as the primary phenotype and then adjusting for BMI. Strikingly, several genomic regions associated with IR based on fasting insulin and adjusted for BMI correlated with lower HDL and increased TG levels(37, 38). Further, Scott *et al* noted that these alleles were associated with a lower BMI, total body fat, hip circumference and gynoid and leg fat based on DEXA fat mass quantification(39). More recently Lotta *et al* reported that SNPs in 53 distinct genomic regions were associated with increased fasting insulin(adjusted for BMI), higher TG and lower HDLc levels. A SNP score generated using the lead SNP in each of the 53 genomic regions was used to evaluate the strength of association between these loci and IR. Enrichment for the SNP score was associated significantly with lower insulin sensitivity as measured by hyperinsulinemic euglycemic clamps and frequently sampled oral glucose tolerance test, considered gold standard measurements of insulin sensitivity. The 53-SNP genetic score was also significantly associated with lower levels of leg and gynoid fat, and consequently with increased type 2 diabetes mellitus and coronary heart disease risk.

Amongst a cohort of individuals who gained weight, those enriched for the SNP score were less likely to deposit fat in the gluteofemoral region(40). These observations suggest that enrichment for SNPs in IR loci is linked to reduced peripheral or hip adipose expandability, not dissimilar to the observations made in partial lipodystrophies. Individuals with FPLD1, a more prevalent partial lipodystrophy subtype are significantly enriched for the SNP score, suggesting a polygenic inheritance(40). The pattern of association observed in these studies strongly suggests that subtle differences in adipose tissue expandability contribute to IR in the general population, providing compelling human genetic support for the lipid overflow or expandability hypothesis.

- **Multiple Symmetric Lipomatosis**

Phenotype-genotype correlation in rare disease continues to offer a rewarding approach in the study of human biology. Multiple Symmetric Lipomatosis (MSL) is a condition of abnormal adipose tissue distribution first described in the 1800's(41). Although the phenotype is heterogeneous it frequently presents with symmetrical fat accumulation in the upper back, neck and face. Metabolic complications (including insulin resistance, type 2 diabetes, dyslipidemia and NAFLD), peripheral and autonomic neuropathies are variably present (42). Early suggestions that defective mitochondrial function may be implicated in the pathogenesis of the condition emerged following observations of the association of MSL with myoclonus epilepsy and red ragged fibres (MERRF) a condition known to be caused by a mitochondrial DNA mutation(43). Recently, whole exome sequencing identified Mitofusin 2 (*MFN2)* as a candidate gene in three individuals with severe upper body symmetric lipomatosis, lower limb lipodystrophy and charcot marie tooth (CMT) axonal neuropathy(44). Another study describing three more affected patients affirmed these findings and the presence of a very specific missense mutation in at least one affected allele, namely the MFN2 p.R707W mutation(45). All cases described to date have either been homozygous for this variant or carried it alongside a second null allele. Mutations in other regions of the gene are strongly linked to CMT2a without lipodystrophy(45). Mitofusin 2 is a GTPase localised to the mitochondrial membrane and plays a critical role in the process of mitochondrial fusion through the formation of homotypic and heterotypic dimers with a similar GTPase Mitofusin 1(46). Individuals with MFN2 mutations have low leptin levels despite relatively normal

adipocyte morphology(44, 47). The expanded adipose depots are due to unilocular adipocyte hyperplasia and negative for brown adipose tissue markers such as UCP1. Electron microscopy revealed abnormal mitochondria in adipose samples from affected patients and mRNA analysis highlighted a mitochondrial stress response in keeping with elevated circulating lactate levels(47). Interestingly the lowest levels of leptin expression were observed among patients with the most severe adipose phenotype(47). Leptin is widely acknowledged as a signal of adipose energy stores which increases and decreases with changes in fat mass, though exactly how each adipocyte regulates leptin synthesis and secretion remains unclear. Total leptin deficiency is rare but has a striking phenotype of extreme hyperphagia and hypothalamic dysfunction and it has been observed in patients (and mice) with mutations of the leptin gene and in generalised lipodystrophies where a paucity of functional adipose tissue accounts for the lack of leptin. In MFN2 associated MSL, we have a condition associated with mitochondrial dysfunction in hyperplastic adipose tissue associated with very low leptin levels suggesting that mitochondrial function is an important determinant of leptin gene expression.

- **Insights into insulin receptor signalling**

A consistent feature of the *INSR* mutation phenotype is normal or elevated adiponectin and an absence of dyslipidaemia and NAFLD. PI3 kinases are intracellular enzymes regulating membrane phosphoinositide phosphorylation immediately downstream of the *INSR* and insulin receptor substrate (IRS) proteins, and have long been considered as prime candidates for monogenic IR. They are composed of distinct regulatory and catalytic subunits encoded for by different genes forming heterodimers and mediating intracellular signalling. There have been a number of PI3Kinase subclasses identified sharing homology in the catalytic subunit but differing in their regulatory elements. Class 1A regulatory subunits are encoded by 3 different genes *PI3KR1, PI3KR2 and PI3KR3(48).* SHORT syndrome is a rare condition characterised by the presence of short stature, hyper flexibility, ocular depression, a developmental defect of the iris and an abnormality in teething, it is accompanied by partial lipodystrophy and IR. It was recently shown to arise from loss-of-function mutations in the *PIK3R1* gene encoding the p85alpha regulatory subunit(49-51). The detailed study of individuals with SHORT syndrome arising due to heterozygous nonsense or missense

mutations in *PIK3R1* confirmed severe IR in affected cases without dyslipidaemia or fatty liver, and in all but one with significantly elevated adiponectin levels(52). These observations suggest that proximal insulin signalling defects are associated with preserved adiponectin expression rather than defects exclusive to the insulin receptor.

- **Tissue-specific IR**

It is noteworthy that not all defects in insulin signalling have an equal impact on liver and muscle. Dash et al described a family with a primary defect in a RAB-GAP protein that regulates the trafficking of GLUT4 to the cell surface, this resulted in severe post-prandial IR in the face of normal fasting glucose and insulin levels (largely determined by hepatic responses to insulin; which do not involve GLUT4)(53). Moltke *et al* have shown that a mutation in a muscle-specific isoform of the same gene is highly prevalent in Greenland Inuit populations where it results in selective post-prandial hyperinsulinemia and hyperglycemia(54).

- **Conclusions**

We have reviewed rare disorders of adipose tissue and primary insulin signalling defects causing severe IR emphasizing instances where the identification and study of affected individuals has yielded significant insights into the consequences of adipose dysfunction, as well as the relevance of this paradigm to prevalent forms of IR, and/or the complexities of insulin signalling. As is the case with *MFN2* mutations, monogenic disorders continue to pose challenging scientific questions and efforts continue to untangle the molecular biology of such conditions.

Table 1: Syndromes of Severe Insulin Resistance

Gene	Gene product and function	Phenotype	Ref
Generalised Lipodystrophies			
Congenital			
AGPAT2	1-acylglycerol-3phosphate O-acyltransferase 2; ER protein regulating triglyceride biosynthesis	Generalised Lipoatrophy from birth, severe IR, dyslipidaemia, NAFLD, low leptin and adiponectin.	(15, 16, 55, 56)
BSCL2	Seipin; ER protein involved in lipid droplet biogenesis		
CAV1	Caveolin-1; involved in formation of membrane caveolae	As above plus short stature	(57)
PTRF	Polymerase 1 and transcript release factor; localises to caveolae regulating formation and stability	Generalised lipoatrophy and muscular dystrophy with milder metabolic phenotype.	(58)
Acquired			
Idiopathic/Radiotherapy/Drug-related/ autoimmune	NA	Generalised lipoatrophy, IR	(22)
Partial Lipodystrophies			
Familial			
FPLD1	NA; likely polygenic in many cases	Peripheral lipoatrophy, prominent abdominal adiposity, IR. Low adiponectin	(59)
LMNA	Lamin A/C; Nuclear envelope protein	Limb, gluteofemoral and truncal subcutaneous fat loss, IR. Sparing adipose tissue at the neck and face, low adiponectin.	(59, 60)
PPARG	Peroxisome proliferator activated receptor gamma; Nuclear transcription factor regulating adipocyte differentiation and function	Peripheral lipoatrophy prominent, variable abdominal adiposity, hypertension, hypertriglyceridemia, low adiponectin	(19, 20)
PLIN1	Perilipin 1; Lipid droplet coat protein involved in the regulation of lipolysis	Limb and gluteofemoral fat loss, IR.	(61)
CIDEC	Cell death inducing DFFA like effector C; required for unilocular lipid droplet formation in adipocytes	Peripheral lipoatrophy with some multilocular adipocytes	(62)
AKT2	Akt serine/threonine kinase 2; key proximal insulin signalling intermediate	IR, Dyslipidaemia and fatty liver, low adiponectin, lipodystrophy	(63)
PCYT1A	Phosphate cytidylyltransferase 1, choline, alpha; involved in phosphatidylcholine synthesis	Lipoatrophy, IR, low adiponectin, short stature.	(64)
Acquired			
Autoimmune	NA	Cephalocaudal lipoatrophy, minimal metabolic phenotype, Low C3, MPGN +/- other autoimmune disease	(21, 22)
HIV/ARV associated	NA	Progressive thinning of subcutaneous adipose tissue in the face, arms and legs. Increased truncal and abdominal adiposity may also be present	
Insulin Receptoropathies			
Complete/Proximal			
INSR	Insulin receptor; Tyrosine Kinase receptor for insulin	Severe IR without dyslipidaemia or NAFLD, normal or high adiponectin, SHBG, IGF1	(65)
Anti-insulin receptor Antibodies	NA	IR, normal or high Adiponectin +/-Autoimmune disease.	(27, 66)
Partial/Distal			
AKT2	See above	See above	
TBC1D4	TBC domain family member 4; Rab-GTPase activating protein, regulates insulin dependent trafficking of GLUT4	Post prandial IR	(53)
Complex Syndromes			

POLD1	DNA Polymerase delta 1	Mandibulo hypoplasia, deafness, progeria, lipodystrophy (MDLP syndrome)	(33, 67)
PIK3R1	Phosphoinositide-3-kinase 85alpha regulatory subunit; key insulin signalling intermediate	Short stature, hyper extensibility, ocular depression, rieger anomaly, teething delay (SHORT syndrome)	(49, 50)
WRN	Werner syndrome RecQ like helicase; DNA helicase	Lipodystrophy, premature aging (Werner syndrome)	(34, 68)
ALMS1	Alms1, centrosome and basal body associated protein involved in microtubule/ciliary function	Rod-cone dystrophy, hepatic and renal dysfunction, deafness, IR (Alstrom's syndrome)	(32, 69)
BLM	Bloom syndrome RecQ like helicase; DNA helicase	Lipodystrophy, Short stature, telangiectasia, IR (Bloom's syndrome)	(70)
ZMPSTE24 (AND *LMNA*)	Zinc metallopeptidase STE24; regulates posttranslational cleavage of prelamin	Mandibuloacral dysplasia, Lipodystrophy, IR	(71)

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Figure 1: Monogenic disorders of insulin receptor signalling as a model for the uncoupling of insulin's metabolic actions.

Insulin binds to its transmembrane receptor activating a downstream signalling cascade regulating the hormone's metabolic functions to increase glucose transport into the cell and consequently glycogen and lipid synthesis while suppressing hepatic glucose production. Defects (red shading) affecting the insulin receptor (INSR; Type A insulin resistance, Donohue and Rabson-Mendenhall syndromes), PI3Kinase p85alpha catalytic subunit (SHORT syndrome) and AKT2 lead to an uncoupling of insulin's glucose lowering effects from SREPB1c regulated de novo lipogenesis. IRS, insulin receptor substrate; PIP2/3, phosphatidylinositol-(4,5)-bisphosphate 2/3; mTOR1, mammalian target of rapamycin complex 1; SREBP1c, sterol regulatory element binding protein 1; FOXO1, forkhead box protein O1 and GSK3, glycogen synthase kinase 3.