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## CALL FOR PAPERS | *Metabolic Syndrome*

# Genetic and physiological insights into the metabolic syndrome

Robert A. Hegele and Rebecca L. Pollex

Blackburn Cardiovascular Genetics Laboratory, Robarts Research  
Institute and University of Western Ontario, London, Ontario, Canada

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**Hegele, Robert A., and Rebecca L. Pollex.** Genetic and physiological insights into the metabolic syndrome. *Am J Physiol Regul Integr Comp Physiol* 289: R663–R669, 2005. First published May 12, 2005; doi:10.1152/ajpregu.00275.2005.—The metabolic syndrome (MetS) is a common phenotype that is clinically defined by threshold values applied to measures of central obesity, dysglycemia, dyslipidemia, and/or elevated blood pressure, which must be present concurrently in any one of a variety of combinations. Insulin resistance, although not a defining component of the MetS, is nonetheless considered to be a core feature. MetS is important because it is rapidly growing in prevalence and is strongly related to the development of cardiovascular disease. To define etiology, pathogenesis and expression of MetS, we have studied patients, specifically Canadian families and communities. One example is familial partial lipodystrophy (FPLD), a rare monogenic form of insulin resistance caused by mutations in either *LMNA*, encoding nuclear lamin A/C (subtype FPLD2), or in *PPARG*, encoding peroxisomal proliferator-activated receptor- $\gamma$  (subtype FPLD3). Because it evolves slowly and recapitulates key clinical and biochemical attributes, FPLD seems to be a useful monogenic model of MetS. A second example is the disparate MetS prevalence between two Canadian aboriginal groups that is mirrored by disparate prevalence of diabetes and cardiovascular disease. Careful phenotypic evaluation of such special cases of human MetS by using a wide range of diagnostic methods, an approach called “phenomics,” may help uncover early presymptomatic disease biomarkers, which in turn might reveal new pathways and targets for interventions for MetS, diabetes, and atherosclerosis.

dyslipidemia; insulin resistance; cardiovascular disease; Canadian aboriginals; genetics

THE METABOLIC SYNDROME (MetS) is a commonly occurring cluster of phenotypes that are strongly related to cardiovascular disease. MetS is characterized by disturbed carbohydrate and insulin metabolism and is clinically defined by threshold values applied to indexes of central obesity, dysglycemia, dyslipidemia, and/or elevated blood pressure, which must be present concurrently in any one of a variety of combinations (11). Definitions for the MetS have been proposed by the World Health Organization (WHO) (3) and the National Cholesterol Education Program (NCEP) Expert Panel (11). The presence of the MetS according to the NCEP definition is prospectively associated with the development of type 2 diabetes (35) and both all-cause and cardiovascular mortality (36). Atherosclerosis susceptibility in the MetS is likely related to multiple biochemical and metabolic disturbances (30, 33, 35–37, 56, 57).

MetS is considered to result from the interaction of environmental factors, such as caloric excess and physical inactivity,

with genetic susceptibility factors (22, 37, 47). The resistance of such tissues as skeletal muscle, fat, and liver to insulin, while not a defining component of the MetS, is nonetheless considered to be a core feature. Indeed, the terms “MetS” and “insulin resistance syndrome” are often used interchangeably. Study of monogenic insulin resistance syndromes might help to understand the common MetS, just as the study of patients with familial hypercholesterolemia (FH) (9) helped improve understanding of cholesterol metabolism, leading ultimately to development of statin drugs, which have profoundly affected clinical cardiology. In this article, we present two examples of how the study of specific presentations of the MetS in Canadian kindreds and communities has revealed certain features that may be relevant to common MetS. These patients provide an opportunity to systematically search for early presymptomatic phenotypes or biomarkers of cardiovascular risk in mutation carriers by using an approach that has been called “phenomics” (13, 16, 23, 49).

### EXAMPLE 1: PARTIAL LIPODYSTROPHY SYNDROMES (FPLD2 AND FPLD3)

**History and definition of FPLD.** Lipodystrophy is characterized by loss of fat stores in some anatomical sites, with excess accumulation of fat in nondystrophic adipose tissue and such sites as liver and muscle (14). Lipodystrophies can be genetic or acquired. The most rapidly growing type of lipodystrophy seen clinically is the one associated with the use of highly active antiretroviral treatment (HAART) (5). Among inherited lipodystrophies, some have been characterized at the molecular genetic level, including the Berardinelli-Seip form of generalized lipodystrophy and the Dunnigan-type familial partial lipodystrophy (FPLD) (20). Of these, FPLD, which may affect ~1:100,000 individuals of Northern European descent, evolves more slowly and may provide a better model reflecting the metabolic evolution of MetS.

Kobberling and Dunnigan (32) described patients who were normal at birth but who during puberty lost subcutaneous fat from extremities and the gluteal region, resulting in prominent, well-defined musculature, together with excess fat deposition within the face and neck, axillae, back, and intra-abdominally. Imaging studies showed absence of subcutaneous fat but preservation of inter- and intramuscular, intra-abdominal, intrathoracic, and bone marrow fat (15). The hallmark of FPLD is insulin resistance. Type 2 diabetes presents later in adulthood.

Address for reprint requests and other correspondence: R. A. Hegele, 406-100 Perth Drive, London, Ontario, Canada N6A 5K8 (e-mail: hegele@robarts.ca).

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Dyslipidemia and hypertension are common, but acanthosis nigricans, hirsutism, and polycystic ovaries are variable. The FPLD locus was mapped to chromosome 1q21 (42), and candidate gene sequencing of Canadian FPLD subjects identified a mutation in *LMNA* encoding the nuclear envelope protein lamin A/C (10), a finding confirmed by others (50, 51). At present, the mechanisms by which *LMNA* mutations cause disease are incompletely defined, and speculation exceeds the scope of this review [see Mounkes et al. (39)].

**FPLD2 phenomics: evaluation of intermediate quantitative traits.** Identification of carriers of mutant *LMNA* in FPLD2 before the onset of type 2 diabetes and the concomitant gross distortion of metabolic variables allowed us to evaluate whether at-risk carriers had any early biochemical changes (28). We studied 35 nondiabetic adult FPLD2 subjects with either the *LMNA* R482Q or R482W missense mutations and 51 matched normal first-degree relatives, who were also matched for glucose and glycated hemoglobin. We found that, compared with normal controls, *LMNA* mutation carriers had significantly higher plasma concentrations of insulin, triglycerides (TG), nonesterified free fatty acids (FFA), and C-reactive protein (CRP), together with significantly lower plasma high-density lipoprotein (HDL) cholesterol, leptin, and adiponectin (28). Furthermore, these differences were more pronounced in women. Resistin, fibrinogen, and plasminogen activator inhibitor-1 were not different between the groups. The characteristic biochemical abnormalities were present long before diabetes developed, because diabetic *LMNA* mutation carriers in these families were ~10 yr older than nondiabetic carriers (25, 28). This indicates that a characteristic cluster of biochemical abnormalities in carriers antedates the decompensation of glycemia.

To confirm the clinical impression of increased atherosclerosis risk in FPLD2, subjects >35 yr were stratified by genotype for a *LMNA* codon 482 missense mutation (24). *LMNA* mutation carriers had significantly more type 2 diabetes, hypertension, and dyslipidemia than did normal family control subjects (24). Eight *LMNA* mutation carriers had suffered from coronary heart disease (CHD) end points compared with one normal control [odds ratio 5.9, 95% confidence interval (CI) 1.2 to 30.2]. Among female *LMNA* mutation carriers, 28.6% (4 of 14) had been hospitalized between ages 35 and 54 yr for coronary arterial bypass graft surgery (CABG) (24). In contrast, data from the general Canadian population indicated that only 0.014% of women had been hospitalized between ages 35 and 54 yr for CABG (24). Thus female *LMNA* mutation carriers of ages 35 to 54 yr had a hospitalization rate for CABG that was several orders of magnitude higher than that of the general Canadian population. Importantly, all *LMNA* mutation carriers with CHD also had type 2 diabetes, suggesting that development of clinical end points required the presence of diabetes.

**FPLD3: a subtype of partial lipodystrophy due to mutation in *PPARG*.** Whereas mutations in *LMNA* have been found in ~50% of families with FPLD, a substantial number of individuals referred with this phenotype had no mutation in the *LMNA* coding region, intron-exon boundaries, promoter, or 5'- and 3'-untranslated regions, implying genetic heterogeneity. *PPARG* encodes peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), a nuclear receptor that induces transcription of genes involved in insulin sensitivity, adipocyte differentiation,

and inflammation (52). PPAR- $\gamma$  mediates the pharmacological enhancement of insulin signaling by thiazolidinedione (TZD) drugs (52), which have earned an established place in the management of insulin resistance and type 2 diabetes. Because PPAR- $\gamma$  has an important role in adipocyte biology, *PPARG* was a good candidate gene to analyze in lipodystrophic subjects with normal *LMNA* sequence.

In a three-generation Canadian kindred with partial lipodystrophy and a normal *LMNA* sequence, we found heterozygotes for the *PPARG* F388L mutation (26), which was absent from normal alleles and cosegregated with the disease. The in vitro transcriptional activity of the mutant receptor was three times lower than that of wild-type receptor, but transcriptional activities were similar with a saturating amount of the TZD rosiglitazone (26). Dose-response curves showed that F388L had reduced affinity for ligands. The F388L mutation altered a highly conserved residue but had neither reduced protein expression nor dominant negative activity against the wild-type receptor (26). Because the PPAR- $\gamma$  agonist TZD drugs are widely used to treat insulin-resistant patients, the demonstration that PPAR- $\gamma$  deficiency causes insulin resistance underscores the importance of the gene product in the MetS.

Earlier studies indicated that germline *PPARG* mutations did not cause lipodystrophy (6, 40). Later reevaluation of some subjects with *PPARG* mutations confirmed the findings from the F388L kindred that *PPARG* mutations also caused lipodystrophy (48). Furthermore, heterozygosity for *PPARG* R425C was found in a single patient who was ascertained on the basis of a clinical diagnosis of partial lipodystrophy (1). We also reported a Dutch FPLD3 kindred with a -14A→G mutation within the promoter of the  $\gamma$ 4 isoform that was associated with decreased expression and no qualitative protein abnormalities (2). These findings together indicated that mutations resulting in PPAR- $\gamma$  deficiency cause partial lipodystrophy. An unresolved issue is whether the metabolic abnormalities follow primarily from the adipose loss or whether the *PPARG* mutations themselves have other independent effects in various target tissues (29). One clue may come from careful evaluation of phenotypic distinctions between partial lipodystrophy due to mutant *PPARG* and that due to mutant *LMNA*.

**Phenomics: comparison of FPLD2 and FPLD3 subtypes.** Our data are consistent with genuine clinical and biochemical differences between FPLD2 and FPLD3 subtypes (2, 21). Specifically, there were no limb or gluteal fat stores in FPLD2 subjects, whereas FPLD3 subjects had some upper arm and gluteal fat. The age of diabetes onset was ~10 yr sooner in FPLD3 compared with FPLD2. Hypertension was particularly severe in FPLD3. Systemic signs of insulin resistance, such as acanthosis nigricans, hepatic steatosis, and polycystic ovarian disease, were more severe in FPLD3. FPLD2 was associated with early CHD, whereas among the *PPARG* mutations, only F388L was clearly associated with CHD (26). Dyslipidemia was common among subjects with both FPLD2 and FPLD3. However, mean insulin concentrations were increased to a greater degree in FPLD3 than in FPLD2, consistent with more severe insulin resistance in FPLD3. Concentrations of FFA and CRP, where measured, were similarly increased with both partial lipodystrophy types. Concentrations of leptin and adiponectin were depressed in both partial lipodystrophy types, with quite marked depression in subjects with the *PPARG*

P467L mutation. There was less responsiveness to TZDs in FPLD3 subjects (21).

Thus, compared with FPLD2, FPLD3 is associated with 1) less extensive adipose tissue loss, 2) more severe biochemical and clinical signs of insulin resistance, 3) more severe hypertension, and 4) earlier onset of type 2 diabetes. Early atherosclerosis was clearly seen in women with FPLD2 compared with those with FPLD3, although numbers of reported patients are small for the latter partial lipodystrophy type. The clinical and biochemical abnormalities in subjects with FPLD3 appear to be out of proportion to the extent of lipodystrophy when compared with subjects with FPLD2, implying that *PPARG* mutations may have additional and independent effects on metabolism (29).

**Reconstructing metabolic progression in FPLD.** Using the accumulated clinical experience and genetic insights from the FPLD kindreds, we have been able to define a pattern of disease evolution with parallel treatment strategies for each disease stage. Figure 1 schematically shows the temporal progression of the clinical and biochemical features seen among patients with FPLD2, but the pattern is similar for FPLD3. The germline mutation is present at birth. Clinically, the first manifestation in early adolescence is fat redistribution. Although no treatment is accepted for this early stage, future treatments might be directed toward impeding adipose tissue loss, stimulating regrowth, or replacing lost tissue.

Midstage disease has a characteristic biochemical profile, including elevated plasma concentrations of FFA, insulin and C-peptide, TG, and CRP, with depressed plasma concentrations of HDL cholesterol, leptin, and adiponectin. Physical signs of insulin resistance, such as acanthosis nigricans, fatty liver, and polycystic ovaries, appear. Hypertension emerges as a problem. Treatment now focuses on vascular disease prevention, with control of hypertension and dyslipidemia. Future

treatments may include preemptive use of insulin sensitizers and/or leptin with or without adiponectin.

Late-stage disease is characterized by development of diabetes, which causes profound metabolic changes. Treatment at this stage is focused on intensive control of glycemia, dyslipidemia, and hypertension to prevent complications. Future treatments may include leptin with or without adiponectin.

Final stage disease is characterized by the development of diabetic macro- and microvascular complications. Premature atherosclerosis is a feature of patients with FPLD2 (26), although most subjects with CHD were diabetic, suggesting that diabetes is necessary for expression of vascular disease. Therapies include stabilization of metabolic variables, palliation, and secondary prevention of vascular disease.

Based on this construction of disease evolution, there are some theoretical therapeutic options in treatment of partial lipodystrophy. Treatments might come from among new agents under development, including new selective agonists for PPAR- $\gamma$ , - $\alpha$ , and - $\delta$ , dual ligands for PPAR- $\alpha$  and - $\gamma$ , and target gene-selective PPAR receptor modulators (SPPARMs) that might selectively affect adipose differentiation and viability (38) in subjects with FPLD2 and possibly even FPLD3. Newer drugs for dyslipidemia (7) also might be appropriate for managing hypertriglyceridemia, prophylaxis of pancreatitis, and secondary prevention of vascular disease in partial lipodystrophy. Finally, leptin administration over a relatively short period has been shown to improve the metabolic disturbances in FPLD (41).

**FPLD: a helpful model for MetS.** There are several reasons why partial lipodystrophy resulting from mutations in either *LMNA* (FPLD2) or *PPARG* (FPLD3), among all lipodystrophies, may be a superior model of the common MetS in addition to the lipodystrophy syndrome associated with HAART. These include the following: 1) FPLD is characterized by gradual fat redistribution to central depots rather than outright global fat loss; 2) FPLD is progressive, evolving relatively slowly by defined stages over years; and 3) FPLD recapitulates many clinical and biochemical attributes of the common MetS. Future treatments for maintaining balanced distribution of adipose stores, improving insulin sensitivity, improving glycemic control, improving metabolic control, and reducing micro- and macrovascular complications in partial lipodystrophy also may find application in management of MetS, type 2 diabetes, and/or acquired lipodystrophy syndromes.

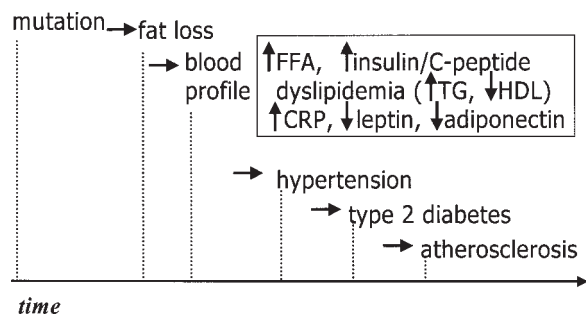


Fig. 1. An example of phenomic evaluation in familial partial lipodystrophy (FPLD) is shown. The schematic shows the temporal progression of clinical and biochemical features in FPLD2, but a similar pattern applies for FPLD3. The abscissa refers to passage of time moving from left to right. The germline *LMNA* mutation is present at birth. Clinically, the first manifestation is redistribution of fat in early adolescence, which most investigators agree is the triggering event. In young adulthood, the biochemical profile seen in FPLD2 includes elevated plasma concentrations of free fatty acids (FFA), insulin and C-peptide, triglycerides (TG), and C-reactive protein (CRP), with depressed plasma concentrations of high-density lipoprotein (HDL) cholesterol, leptin, and adiponectin. Hypertension usually presents next, later in adulthood, followed by diabetes that causes profound changes in the quantitative traits. Premature atherosclerosis is a feature of FPLD2, although almost all subjects with cardiovascular end points had developed type 2 diabetes, suggesting that this is necessary for expression of vascular disease. Examination of plasma of prediabetic carriers may reveal additional biochemical abnormalities associated with the insulin-resistant atherosclerosis susceptible state.

#### EXAMPLE 2: METABOLIC SYNDROME IN ABORIGINAL CANADIANS

Canadian aboriginal populations have been called “populations in transition,” as the introduction of sedentary activities and the Western diet impacts their traditional lifestyle. Over the past few decades, new health issues, such as diabetes (62), obesity (59), childhood obesity (60), and cardiovascular disease (4), have emerged in epidemic proportions in many communities. For instance, based on survey data of Northern Ontario Oji-Cree from the early 1990s, the combined prevalence of type 2 diabetes and impaired glucose tolerance was ~40%, one of the highest in the world (18). Alongside this rise in diabetes has been a tripling in hospitalizations for coronary heart disease despite declining trends in the general Canadian

population (19). The Inuit, on the other hand, have been considered to be healthier, in terms of diabetes and cardiovascular disease, than the general population (61, 63). Arctic peoples have a much shorter and less intense history of Western contact and acculturation, which may explain the lower rates of associated chronic diseases; however, the situation may easily change. Given the recent identification of MetS as a new risk factor for type 2 diabetes and cardiovascular disease, we have taken this opportunity to estimate the prevalence of MetS and its individual components in the Keewatin Inuit and the Oji-Cree of Northern Ontario, two distinctive populations in terms of cardiovascular disease and diabetes risk, in hopes of drawing some insight into the characterization of this phenotype.

**Inuit of the Keewatin region.** The Inuit in our study were from a 1989–1991 survey of eight communities in the Keewatin region of Nunavut. According to the standard NCEP ATP III criteria for MetS diagnosis, the Inuit were found to have a lower prevalence of MetS (13.1%) compared with both resident Caucasian controls from the Keewatin region (20.8%) and with Caucasian subjects from a larger contemporaneous American survey (23.8%) (45). Similarly, the prevalence of diabetes was also markedly lower in the Keewatin Inuit, with only ~2% diagnosed diabetes cases (Table 1). Not only was the Inuit prevalence of MetS low, but also a significant portion of the Inuit was free from meeting the cutoff criteria for any of the metabolic abnormalities. The low prevalence of MetS was largely due to the low prevalence of MetS in the male Inuit population; female Inuit had a significant approximately sevenfold increase in MetS prevalence (Table 1). Such a disparity in MetS prevalence between genders also has been observed in African Americans and Hispanics (12), although not in Caucasian populations, highlighting the importance of both gender and ethnicity in MetS expression.

We next examined the prevalence of each of the MetS components and discovered that Inuit had a favorable lipid profile, specifically lower TGs and higher HDL cholesterol, despite a trend to an increased prevalence of higher waist circumference (Table 1) (45). Although genetic factors may have played a role in the distribution of the MetS components for the Inuit (55), certainly environmental factors, such as a diet high in marine-based fats (61), may play an equally strong role.

Although the lower prevalence of MetS in the Inuit was consistent with the previous impression of lower cardiovascular disease and diabetes prevalence, there is no guarantee that

this population will remain free from the rising tide of MetS. There is already a high degree of elevated fasting glucose, with >50% of the population at the 6.1 mmol/l NCEP ATP III cutoff, hinting at a strong prediabetic susceptibility. If even one-third of this population develops diabetes, the incidence rise would be alarming. However, with early identification of high-risk individuals and culturally appropriate intervention, we believe that the expected increase in the onset of diabetes and cardiovascular disease in the Inuit can be reduced.

**Oji-Cree of Northern Ontario.** Hundreds of kilometers to the south, the Oji-Cree are nestled in the subarctic boreal forest of Northern Ontario, still isolated, yet closer to the influence of the greater Canadian population. Lifestyle changes over just the past few decades (new high-fat, high-sugar food choices and modern conveniences requiring less physical exertion) have ushered in a wave of diabetes into what was once an almost “diabetes-free” zone (34, 58). As would be expected, in contrast to the Keewatin Inuit, the prevalence of MetS for the Oji-Cree was high, with almost 1 of 3 individuals meeting the NCEP ATP III criteria and only one-fifth of the population completely free of any MetS component (Table 1) (43). Similar to the Inuit, the majority of subjects with MetS were females. The high prevalence of MetS in the female Oji-Cree population also mirrored the larger numbers of female Oji-Cree with type 2 diabetes. These MetS rates observed for the Oji-Cree, reaching up to ~45% when adults  $\geq 35$  yr of age were considered, are some of the highest rates in any subpopulation (43).

Increased abdominal obesity and depressed HDL cholesterol were the most dominant features of MetS for the Oji-Cree, among females especially, whereas increased blood pressure was the least prevalent feature (Table 1). Abdominal obesity is indeed one of the most frequently found MetS components observed in a number of population studies, irrespective of ethnicity (8, 12, 31). Questions have been raised regarding the use of uniform cutoff points for abdominal obesity, drawing to attention the necessity of ethnic-specific guidelines (46). Some investigators have already employed modified MetS criteria to better identify Asian individuals with MetS (53), yet clearly more investigation is required in this respect. Interestingly, other components, such as blood pressure, show distinctive variability between ethnic groups, being dominant features in African American populations (12) and Korean males (31), yet quite infrequent in both the Inuit and Oji-Cree populations. Do these cutoff points, and those for the other MetS components, have the necessary sensitivity and specificity required to appropriately identify those with MetS, given the ethnic variability?

Table 1. Demographics, MetS prevalence, and components of MetS for Inuit and Oji-Cree ( $\geq 18$  yr old)

	Inuit	Inuit Males	Inuit Females	Oji-Cree	Oji-Cree Males	Oji-Cree Females
Number	168	87	81	515	220	295
Gender, %female	48.2			57.3		
Age, yr	38.3 (15.5)	37.1 (16.9)	39.7 (14.0)	35.8 (14.5)	35.8 (14.5)	35.7 (14.6)
Diabetes, %	2.04	1.32	2.82	22.0	20.0	23.6
MetS, %	13.1	3.5	23.5†	29.9	24.6	33.9*
Abdominal obesity, %	28.6	10.3	48.2†	57.7	37.3	72.9†
High fasting glucose, %	53.6	44.8	63.0*	31.1	30.9	31.2
Hypertriglyceridemia, %	7.1	4.6	9.9	32.8	36.8	29.8
Low HDL-C, %	20.8	12.6	29.6*	48.0	35.9	57.0†
High BP, %	11.9	14.9	8.6	10.1	11.4	9.2

Values are means (SD) unless otherwise indicated. MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure. \* $P < 0.05$ ; † $P < 0.0005$  (between genders).

Although lifestyle changes, namely, increased caloric intake and decreased physical activity levels (34, 58), certainly have had a major impact on the higher prevalence of MetS observed for the Oji-Cree, underlying genetic factors are also likely important. In our study of genetic determinants for MetS, we found that functional polymorphisms in three candidate genes for plasma lipoproteins and blood pressure (*AGT* T174M, *GNB3* 825C→T, and *APOC3* -455T→C) were all significantly associated with MetS for female adults (43). A recent study found similar associations for *APOC3* with MetS in a southern Indian population (17). However, genetic associations appear to be minor, and susceptibility to MetS appears to be greater than the sum of susceptibility to the individual parts, because no association with other genes involved in obesity and fasting glucose levels was observed.

Part of the elevated risk of type 2 diabetes in the Oji-Cree population stems from the presence of a genetic susceptibility allele: a private nonsynonymous mutation (G319S) in *HNF1A* encoding hepatic nuclear factor-1 $\alpha$  (27, 54). In vitro studies have shown a decreased transactivation ability for the mutant transcription factor (54). In a cross-sectional analysis, *HNF1A* G319S was present in ~40% of diabetic subjects and had a strong statistical association with type 2 diabetes, and each dose of the S319 allele accelerated the age of diabetes onset by ~7 yr (27, 54). Interestingly, in our analysis of type 2 diabetes risk, we observed that Oji-Cree with MetS (modified to exclude the fasting glucose component) had a diabetes risk similar to that of *HNF1A* G319S carriers (odds ratio ~5) (44), confirming the important role of the MetS phenotype on diabetes expression. Furthermore, subjects with the inopportune combination of both the *HNF1A* S319 allele and modified MetS had an ~20-fold increased risk for type 2 diabetes (44).

*The MetS message from studies in aboriginal Canadians.* Through our studies in two unique aboriginal Canadian groups, we have observed that MetS prevalence mirrors the prevalence of diabetes and cardiovascular disease. For the Inuit, the low prevalence of MetS corresponds to the low prevalence of diabetes, and likewise the high MetS prevalence for the Oji-Cree is accompanied by high rates of both diabetes and cardiovascular disease. Variability was observed in the distribution of MetS components between these groups, with abdominal obesity being the predominant feature of Oji-Cree subjects, whereas high fasting glucose predominates among the Inuit. Ethnic-specific criteria for MetS probably will be required for optimal identification of at-risk individuals, considering the inherent variability that exists between groups, such as defining appropriate waist circumference ranges. Finally, it is clear that both genetic and environmental components, whose relations may differ between genders, are involved with MetS. Although modest associations with MetS were found with a few genes involved in blood pressure and lipid metabolism for the Oji-Cree, it is likely that environmental influences, such as dietary habits, probably play an equal or bigger role in MetS expression.

In conclusion, these examples of MetS provide some evidence for the potential benefits of careful phenomic assessment to better understand the components of a complex phenotype such as MetS, in addition to clarifying temporal relationships and novel pathways that could be targets for interventions. For instance, FPLD2 implicates structural abnormalities of the nuclear envelope as causing insulin resistance, diabetes, and,

ultimately, atherosclerosis (22–25). FPLD3 proves that inherited partial lipodystrophy is clinically and genetically heterogeneous, clarifying the metabolic phenotype of PPAR- $\gamma$ -deficiency due to mutant *PPARG* and confirming the key role of PPAR- $\gamma$  in adipogenesis and metabolism. FPLD3 shows less severe lipodystrophy and more severe insulin resistance, suggesting that additional mechanisms underlie insulin resistance and metabolic changes beyond those that can be attributed solely to adipose tissue loss. This further suggests that intervening on the *PPARG* pathway could have multiple beneficial effects on metabolic phenotypes and downstream complications such as atherosclerosis. The metabolic progression for both FPLD subtypes indicates that disturbances in fat and lipid metabolism precede the development of carbohydrate disturbances, particularly diabetes as a result of the relative breakdown of glycemic control mechanisms.

The examples of Oji-Cree and Inuit highlight population-specific differences in expression of MetS. Also, the findings indicate that different thresholds, applied to critical defining values for key quantitative phenotypes in different populations, may be required. In both communities, the importance of environmental factors is underscored. In Oji-Cree, we are working with the community to stem the tide of MetS and diabetes by increasing levels of activity and modifying diet to one that more closely reflects a “traditional diet.” In Inuit, the full wrath of MetS has not yet struck, and it remains possible that the complications can be avoided at an early stage with preventive measures.

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#### REFERENCES

1. Agarwal AK and Garg A. A novel heterozygous mutation in peroxisome proliferator-activated receptor- $\gamma$  gene in a patient with familial partial lipodystrophy. *J Clin Endocrinol Metab* 87: 408–411, 2002.
2. Al-Shali K, Cao H, Knoers N, Hermus AR, Tack CJ, and Hegele RA. A single-base mutation in the peroxisome proliferator-activated receptor  $\gamma$ 4 promoter associated with altered in vitro expression and partial lipodystrophy. *J Clin Endocrinol Metab* 89: 5655–5660, 2004.
3. Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15: 539–553, 1998.
4. Anand SS, Yusuf S, Jacobs R, Davis AD, Yi Q, Gerstein H, Montague PA, and Lonn E. Risk factors, atherosclerosis, and cardiovascular disease among Aboriginal people in Canada: the Study of Health Assessment and Risk Evaluation in Aboriginal Peoples (SHARE-AP). *Lancet* 358: 1147–1153, 2001.
5. Barbaro G. HIV-associated lipodystrophy: pathogenesis and clinical features. *Adv Cardiol* 40: 97–104, 2003.
6. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, Chatterjee VK, and O’Rahilly S. Dominant negative mutations in human PPAR $\gamma$  associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* 402: 880–883, 1999.
7. Bays H and Stein EA. Pharmacotherapy for dyslipidaemia—current therapies and future agents. *Expert Opin Pharmacother* 4: 1901–1938, 2003.

8. **Bonora E, Kiechl S, Willeit J, Oberholzenzer F, Egger G, Bonadonna RC, and Muggeo M.** Metabolic syndrome: epidemiology and more extensive phenotypic description. Cross-sectional data from the Bruneck Study. *Int J Obes Relat Metab Disord* 27: 1283–1289, 2003.
9. **Brown MS and Goldstein JL.** A receptor-mediated pathway for cholesterol homeostasis. *Science* 232: 34–47, 1986.
10. **Cao H and Hegele RA.** Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* 9: 109–112, 2000.
11. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001.
12. **Ford ES, Giles WH, and Dietz WH.** Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287: 356–359, 2002.
13. **Freimer N and Sabatti C.** The human genome project. *Nat Genet* 34: 15–21, 2003.
14. **Garg A.** Lipodystrophies. *Am J Med* 108: 143–152, 2000.
15. **Garg A, Peshock RM, and Fleckenstein JL.** Adipose tissue distribution pattern in patients with familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab* 84: 170–174, 1999.
16. **Gerlai R.** Phenomics: fiction or the future? *Trends Neurosci* 25: 506–509, 2002.
17. **Guettier JM, Georgopoulos A, Tsai MY, Radha V, Shanthirani S, Deepa R, Gross M, Rao G, and Mohan V.** Polymorphisms in the fatty acid-binding protein 2 and apolipoprotein C-III genes are associated with the metabolic syndrome and dyslipidemia in a South Indian population. *J Clin Endocrinol Metab* 90: 1705–1711, 2005.
18. **Harris SB, Gittelsohn J, Hanley A, Barnie A, Wolever TM, Gao J, Logan A, and Zinman B.** The prevalence of NIDDM and associated risk factors in native Canadians. *Diabetes Care* 20: 185–187, 1997.
19. **Harris SB, Zinman B, Hanley A, Gittelsohn J, Hegele R, Connelly PW, Shah B, and Hux JE.** The impact of diabetes on cardiovascular risk factors and outcomes in a native Canadian population. *Diabetes Res Clin Pract* 55: 165–173, 2002.
20. **Hegele RA.** Lamin mutations come of age. *Nat Med* 9: 644–645, 2003.
21. **Hegele RA.** Lessons from human mutations in PPAR $\gamma$ . *Int J Obes Relat Metab Disord*, 29 Suppl 1: S31–S35, 2005.
22. **Hegele RA.** Monogenic forms of insulin resistance: apertures that expose the common metabolic syndrome. *Trends Endocrinol Metab* 14: 371–377, 2003.
23. **Hegele RA.** Phenomics, lipodystrophy, and the metabolic syndrome. *Trends Cardiovasc Med* 14: 133–137, 2004.
24. **Hegele RA.** Premature atherosclerosis associated with monogenic insulin resistance. *Circulation* 103: 2225–2229, 2001.
25. **Hegele RA, Anderson CM, Wang J, Jones DC, and Cao H.** Association between nuclear lamin A/C R482Q mutation and partial lipodystrophy with hyperinsulinemia, dyslipidemia, hypertension, and diabetes. *Genome Res* 10: 652–658, 2000.
26. **Hegele RA, Cao H, Frankowski C, Mathews ST, and Leff T.** PPAR $\gamma$  F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. *Diabetes* 51: 3586–3590, 2002.
27. **Hegele RA, Cao H, Harris SB, Hanley AJ, and Zinman B.** The hepatic nuclear factor-1 $\alpha$  G319S variant is associated with early-onset type 2 diabetes in Canadian Oji-Cree. *J Clin Endocrinol Metab* 84: 1077–1082, 1999.
28. **Hegele RA, Kraw ME, Ban MR, Miskie BA, Huff MW, and Cao H.** Elevated serum C-reactive protein and free fatty acids among nondiabetic carriers of missense mutations in the gene encoding lamin A/C (LMNA) with partial lipodystrophy. *Arterioscler Thromb Vasc Biol* 23: 111–116, 2003.
29. **Hegele RA and Leff T.** Unbuckling lipodystrophy from insulin resistance and hypertension. *J Clin Invest* 114: 163–165, 2004.
30. **Juhan-Vague I, Alessi MC, and Morange PE.** Hypofibrinolysis and increased PAI-1 are linked to atherothrombosis via insulin resistance and obesity. *Ann Med* 32, Suppl 1: 78–84, 2000.
31. **Kim MH, Kim MK, Choi BY, and Shin YJ.** Prevalence of the metabolic syndrome and its association with cardiovascular diseases in Korea. *J Korean Med Sci* 19: 195–201, 2004.
32. **Kobberling J and Dunnigan MG.** Familial partial lipodystrophy: two types of an X linked dominant syndrome, lethal in the hemizygous state. *J Med Genet* 23: 120–127, 1986.
33. **Koenig W.** Insulin resistance, heart disease and inflammation. Identifying the “at-risk” patient: the earlier the better? The role of inflammatory markers. *Int J Clin Pract Suppl*: 23–30, 2002.
34. **Kriska AM, Hanley AJ, Harris SB, and Zinman B.** Physical activity, physical fitness, and insulin and glucose concentrations in an isolated Native Canadian population experiencing rapid lifestyle change. *Diabetes Care* 24: 1787–1792, 2001.
35. **Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, and Lakka TA.** Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol* 156: 1070–1077, 2002.
36. **Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, and Salonen JT.** The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288: 2709–2716, 2002.
37. **Liese AD, Mayer-Davis EJ, and Haffner SM.** Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* 20: 157–172, 1998.
38. **Miller AR and Etgen GJ.** Novel peroxisome proliferator-activated receptor ligands for type 2 diabetes and the metabolic syndrome. *Expert Opin Investig Drugs* 12: 1489–1500, 2003.
39. **Mounkes L, Kozlov S, Burke B, and Stewart CL.** The laminopathies: nuclear structure meets disease. *Curr Opin Genet Dev* 13: 223–230, 2003.
40. **Okazawa H, Mori H, Tamori Y, Araki S, Niki T, Masugi J, Kawanishi M, Kubota T, Shinoda H, and Kasuga M.** No coding mutations are detected in the peroxisome proliferator-activated receptor- $\gamma$  gene in Japanese patients with lipotrophic diabetes. *Diabetes* 46: 1904–1906, 1997.
41. **Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, and Garg A.** Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 346: 570–578, 2002.
42. **Peters JM, Barnes R, Bennett L, Gitomer WM, Bowcock AM, and Garg A.** Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21–22. *Nat Genet* 18: 292–295, 1998.
43. **Pollex RL, Hanley AJG, Zinman B, Harris SB, Khan HM, and Hegele RA.** Metabolic syndrome in aboriginal Canadians: prevalence and genetic associations. *Atherosclerosis*. April 30, 2005 [Epub ahead of print].
44. **Pollex RL, Hanley AJG, Zinman B, Harris SB, Khan HM, and Hegele RA.** Synergism between mutant *HNF1A* and the metabolic syndrome in Oji-Cree type 2 diabetes. *Diabet Med*. In press.
45. **Pollex RL, Khan HM, Connelly PW, Young TK, and Hegele RA.** The metabolic syndrome in Inuit. *Diabetes Care* 27: 1517–1518, 2004.
46. **Razak F, Anand S, Vuksan V, Davis B, Jacobs R, Teo KK, and Yusuf S.** Ethnic differences in the relationships between obesity and glucose-metabolic abnormalities: a cross-sectional population-based study. *Int J Obes Relat Metab Disord* 29: 656–667, 2005.
47. **Reaven GM.** Pathophysiology of insulin resistance in human disease. *Physiol Rev* 75: 473–486, 1995.
48. **Savage DB, Tan GD, Acerini CL, Jebb SA, Agostini M, Gurnell M, Williams RL, Umpleby AM, Thomas EL, Bell JD, Dixon AK, Dunne F, Boiani R, Cinti S, Vidal-Puig A, Karpe F, Chatterjee VK, and O’Rahilly S.** Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor- $\gamma$ . *Diabetes* 52: 910–917, 2003.
49. **Schork NJ.** Genetics of complex disease: approaches, problems, and solutions. *Am J Respir Crit Care Med* 156: S103–S109, 1997.
50. **Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, Gregory S, O’Rahilly S, and Trembath RC.** LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet* 24: 153–156, 2000.
51. **Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, Taylor SI, Lovett M, and Bowcock AM.** Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. *Am J Hum Genet* 66: 1192–1198, 2000.
52. **Spiegelman BM.** PPAR- $\gamma$ : adipogenic regulator and thiazolidinedione receptor. *Diabetes* 47: 507–514, 1998.
53. **Tan CE, Ma S, Wai D, Chew SK, and Tai ES.** Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 27: 1182–1186, 2004.
54. **Triggs-Raine BL, Kirkpatrick RD, Kelly SL, Norquay LD, Cattini PA, Yamagata K, Hanley AJ, Zinman B, Harris SB, Barrett PH, and**

- Hegele RA.** HNF-1 $\alpha$  G319S, a transactivation-deficient mutant, is associated with altered dynamics of diabetes onset in an Oji-Cree community. *Proc Natl Acad Sci USA* 99: 4614–4619, 2002.
55. **Wang J, Burnett JR, Near S, Young K, Zinman B, Hanley AJ, Connelly PW, Harris SB, and Hegele RA.** Common and rare ABCA1 variants affecting plasma HDL cholesterol. *Arterioscler Thromb Vasc Biol* 20: 1983–1989, 2000.
56. **Wilson PW and Grundy SM.** The metabolic syndrome: practical guide to origins and treatment: part I. *Circulation* 108: 1422–1424, 2003.
57. **Wilson PW and Grundy SM.** The metabolic syndrome: a practical guide to origins and treatment: part II. *Circulation* 108: 1537–1540, 2003.
58. **Wolever TM, Hamad S, Gittelsohn J, Gao J, Hanley AJ, Harris SB, and Zinman B.** Low dietary fiber and high protein intakes associated with newly diagnosed diabetes in a remote aboriginal community. *Am J Clin Nutr* 66: 1470–1474, 1997.
59. **Young TK.** Obesity among aboriginal peoples in North America: epidemiological patterns, risk factors and metabolic consequences. In: *Progress in Obesity Research* 7, edited by Angel A, Anderson H, Bouchard C, Lau D, Leiter L, and Mendelson R. London: John Libby, 1996, p. 337–342.
60. **Young TK, Dean HJ, Flett B, and Wood-Steiman P.** Childhood obesity in a population at high risk for type 2 diabetes. *J Pediatr* 136: 365–369, 2000.
61. **Young TK, Moffatt ME, and O’Neil JD.** Cardiovascular diseases in a Canadian Arctic population. *Am J Public Health* 83: 881–887, 1993.
62. **Young TK, Reading J, Elias B, and O’Neil JD.** Type 2 diabetes mellitus in Canada’s first nations: status of an epidemic in progress. *Can Med Assoc J* 163: 561–566, 2000.
63. **Young TK, Schraer CD, Shubnikoff EV, Szathmary EJ, and Nikitin YP.** Prevalence of diagnosed diabetes in circumpolar indigenous populations. *Int J Epidemiol* 21: 730–736, 1992.

