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The Genetics of Insulin Resistance: Where's Waldo?

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Abstract

The physiologic hallmarks of type 2 diabetes are insulin resistance in hepatic and peripheral tissues and pancreatic β-cell dysfunction. Thus, genetic loci underlying susceptibility to type 2 diabetes are likely to map to one of these endophenotypes. Genome-wide association studies have now identified up to 38 susceptibility loci for type 2 diabetes and a number of other loci underlying variation in type 2 diabetes–related quantitative traits. The majority are of unknown biology or map to pancreatic β-cell dysfunction. A seemingly disproportionate minority map to insulin resistance. We briefly discuss the known insulin resistance loci identified from genome-wide association, and then discuss reasons why additional insulin resistance loci have not been identified. We present alternative views that may partly explain the apparent dearth of insulin resistance loci contributing to genetic susceptibility to type 2 diabetes, rather than focus on traditional issues such as study design and sampling, which have been addressed elsewhere.

Keywords

Insulin resistance; Type 2 diabetes mellitus; Genome-wide association; Genetic association; Single nucleotide polymorphism; HOMA-IR; Euglycemic glucose clamp; Frequently sampled intravenous glucose tolerance test; Minimal model; Computer modeling

Introduction

The integration of advances in genomic technology, the sequencing of the human genome, and the cataloging of human variation have ushered in a new era of human genomic analysis, which has transformed the study of complex disease genetics. As of this writing, the Catalog of Genome-Wide Association Studies (http://www.genome.gov/26525384) has logged 2905 single nucleotide polymorphisms (SNPs) associated with a variety of human conditions from 599 publications. Genome-wide association studies of type 2 diabetes mellitus have been at the forefront of this new era of human genetics by forging collaborations across large studies, introducing new analytic approaches, and integrating genome-wide analysis of diabetes-related quantitative traits. This has resulted, to date, in the identification of 38 type 2 diabetes susceptibility loci [1•–5•,6–9,10••–13••,14]; the majority identified within the last 3 years. This is in striking contrast with the fact that only three susceptibility loci had been identified prior to 2007. As ever larger samples are assembled for further genome-wide analysis and next generation sequencing technology is increasingly

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applied to perform whole genome sequencing, additional susceptibility loci will be identified in the near future.

The susceptibility loci identified by genome-wide analysis have illuminated new biology underlying type 2 diabetes. For example, melatonin receptor 1B (*MTNR1B*) and cryptochrome 2 (photolyase-like) (*CRY2*) point to the regulation of insulin secretion by circadian rhythms as contributing components to the pathogenesis of type 2 diabetes. Insulin resistance and pancreatic β-cell dysfunction are the two physiologic hallmarks of type 2 diabetes and the a priori expectation was that the majority of type 2 diabetes susceptibility loci would map to either of these diabetes-related phenotypes. Yet, the majority of susceptibility loci can be directly mapped to the pancreatic β-cell or are of unknown biologic consequence, the latter opening exciting new avenues of research into the pathogenesis of type 2 diabetes. Interestingly, very few loci map directly to insulin resistance. So where are the insulin resistance loci? Where's Waldo?

This review will highlight the handful of loci identified by genome-wide association that appear to contribute to type 2 diabetes susceptibility through effects on insulin resistance. Furthermore, we will explore potential explanations for why larger numbers of insulin resistance loci have not been identified.

Known Insulin Resistance Loci

Although the majority of type 2 diabetes susceptibility loci have been identified from both large-scale genome-wide meta-analyses [1•–3•,6,14] and smaller-scale genome-wide association studies [4•,5•,7,8,11••] of case-control samples primarily of European ancestry, genome-wide analysis of type 2 diabetes–related quantitative traits in nondiabetic samples from these populations has also contributed to the discovery of additional type 2 diabetes susceptibility loci. In particular, the MAGIC (Meta-Analysis of Glucose and Insulin-related Traits Consortium), a consortium consisting of more than 120,000 nondiabetic samples derived from more than 50 individual studies, has identified novel type 2 diabetes susceptibility loci by performing genome-wide meta-analyses and replication for fasting glucose, fasting insulin, and related traits [10••,12••,13••,15••].

Peroxisome proliferator-activated receptor-γ (*PPARG*)

PPARG can be clearly identified as an insulin resistance locus from among the type 2 diabetes susceptibility loci. Deeb et al. [16] were the first to show association between rs1801282, which results in a proline to alanine conversion at codon 12, and type 2 diabetes. The rs1801282 G allele was also associated with reduced body mass index (BMI) and improved insulin sensitivity as assessed by frequently sampled intravenous glucose tolerance test (FSIGT) with minimal model analysis [16]. A subsequent large-scale meta-analysis confirmed the association with type 2 diabetes, such that *PPARG* along with potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*), and transcription factor 7-like 2 (T-cell–specific, high mobility group box) (*TCF7L2*) acted as positive controls in the first genome-wide association studies. The relative importance of *PPARG* as a type 2 diabetes susceptibility and insulin resistance locus is further enhanced by the fact that the thiazolidinedione class of diabetes medications act as PPARG agonists that improve insulin sensitivity.

Insulin receptor substrate 1 (*IRS1*)

Similar to *PPARG*, *IRS1* was clearly identified as an insulin resistance locus. IRS1 is phosphorylated by the insulin receptor and forms part of the complex intracellular insulin signaling pathway. Defects in IRS1 signaling have been shown to contribute to insulin resistance in both muscle and liver making *IRS1* an excellent candidate for genetic analysis.

Candidate gene studies have identified relatively rare coding variants showing varying levels of association between type 2 diabetes or measures of insulin resistance [17]. A genome-wide association study in a combined French and Danish case-control sample identified rs2943641 near *IRS1* to be associated with type 2 diabetes [11••]. Additional analyses showed that the rs2943641 C allele was associated with reduced insulin resistance assessed using the homeostasis model (HOMA-IR) approach. The HOMA-IR result was supported by additional analyses showing the same allele was associated with a higher fasting insulin and lower insulin area under the curve from the oral glucose tolerance test (OGTT). Similarly, the MAGIC observed modest evidence for association between rs4675095 in *IRS1* and HOMA-IR and although not genome-wide significant ($P = 4.6 \times 10^{-3}$), the result points to *IRS1* as a locus of interest given its biologic relevance to diabetes susceptibility [13••]. The MAGIC investigators noted that rs4675095 was not in linkage disequilibrium with rs2943641 in populations of European ancestry, making the association with rs4675095 an independent signal. Furthermore, the MAGIC investigators note that in their discovery meta-analysis, rs2943641 showed weak evidence for association with fasting insulin ($P = 0.02$) and HOMA-IR ($P = 0.04$) and would not have been selected for replication analysis.

Glucokinase (hexokinase 4) regulator (*GCKR*)

SNP rs780094 in *GCKR* was first shown to be associated with triglyceride levels in the genome-wide association study of type 2 diabetes [1•]. The T allele also showed trends for association with lower glucose concentrations, improved insulin resistance as reflected by HOMA-IR, and lower risk for type 2 diabetes. The associations with fasting glucose and HOMA-IR were subsequently confirmed in a follow-up study led by the same investigators [18]. MAGIC not only replicated these associations, but also demonstrated that rs780094 is associated with type 2 diabetes and therefore a diabetes susceptibility locus [13••].

GCKR regulates the activity of glucokinase (GCK) in the presence of fructose-6-phosphate (F6P). Although GCK is present in both the liver and pancreatic β cells, GCKR is nearly absent in the pancreas [19] and insulin secretion in isolated islets from $Gckr^{+/+}$ and $Gckr^{-/-}$ animals are nearly identical across a wide range of glucose levels [20], suggesting GCKR plays no role in regulating GCK activity in pancreatic β cells. In contrast, $Gckr^{-/-}$ and $Gckr^{+/-}$ animals had decreased hepatic GCK expression and enzymatic activity that was primarily due to loss of post-transcriptional regulation of GCK [20,21]. This suggests positive regulation of GCK by GCKR to maintain GCK levels and activity. Increased *GCKR* expression in high fat-fed diabetic mice resulted in reduced fasting glucose and insulin levels and a resultant improvement in glucose tolerance [22]. The changes in glucose and insulin levels were accompanied by lower leptin, reduced body weight, and decreased hepatic GCK activity. Thus, GCKR appears to play an important glucoregulatory role at the level of the liver, but not at the pancreas.

Beer et al. [23] assessed the biologic effect of the *GCKR* P446L variant (rs1260326) in vitro. Their results showed that F6P-dependent GCKR regulation of GCK was significantly reduced over a wide range of F6P concentrations, which led to concomitant increases in GCK activity. The increased GCK activity presumably results in increased glycolytic flux and hepatic glucose uptake. These observations form a mechanistic explanation for the observation of variation in *GCKR* being associated with higher triglyceride and lower glucose level in humans.

Insulin-like growth factor 1 (somatomedin C) (*IGF1*)

Like many diabetes candidate genes, *IGF1* had been subject to genetic analysis in multiple studies with inconsistent results across investigations [24]. IGF1 is a member of a family of proteins regulating growth and development and is similar to insulin in structure (~ 60%

amino acid homology) and function. IGF1 binds to specific receptors and subsequent signaling primarily regulates many of the growth-promoting effects of growth hormone. Mutations in *IGF1* cause insulin-like growth factor 1 deficiency (OMIM #608747), a condition characterized by reduced rates of growth or short stature in the presence of normal growth hormone and deficient IGF1 levels. Patients can be treated using recombinant DNA-derived IGF1, which restores normal growth and improves both glycemic control and insulin sensitivity.

Similar to *GCKR*, variation in *IGF1* was first shown to be associated with diabetes-related quantitative traits, in this case fasting insulin and HOMA-IR [13••]. The G allele of SNP rs35767 near *IGF1* was shown to be associated with both fasting insulin ($P = 7.8 \times 10^{-8}$) and subsequently HOMA-IR (2.2×10^{-9}). Subsequent testing in case-control samples showed association with type 2 diabetes [13••]. The known biologic effects of IGF1 coupled with the fact IGF1 is primarily secreted by the liver makes it a likely insulin resistance locus; however, one cannot exclude the possibility that variation in *IGF1* could alter the mitogenic effects of the protein and have subsequent implications for the development of the pancreas or β-cell mass.

Obesity Loci

Obesity, and more specifically body fat, is associated with insulin resistance and also a strong risk factor for type 2 diabetes. Therefore, it is reasonable to assume that some obesity loci would also be insulin resistance loci, and possibly type 2 diabetes susceptibility loci. A large number of loci underlying obesity, fat mass, BMI, and other anthropometric measures have been identified by genome-wide association [25–30]. However, most of these studies have not examined association between these loci and measures of insulin resistance. The fat mass and obesity associated (*FTO*) gene [25,26,31], first identified as a type 2 diabetes susceptibility locus [1•–3•], shows varying degrees of association with insulin resistance that appears to be dependent on the method used to assess insulin resistance. Studies in which HOMA-IR has been used tend to show evidence for association, whereas studies using more direct methods to assess insulin resistance tend not to show evidence for association. This dichotomy raises important questions regarding measures of insulin resistance used in genetic association studies. Studies examining association between obesity loci and insulin resistance are just now appearing in the literature. The overlap among obesity, insulin resistance, and type 2 diabetes loci will provide important clues regarding common biologic pathways that may explain obesity as a risk factor for type 2 diabetes.

Where Are the Other Insulin Resistance Loci?

One of the advantages of genome-wide association studies is the ability to interrogate a large proportion of the human genome for common genetic variants that may be contributing to susceptibility to disease in an unbiased fashion. Of course, the “unbiased” part refers to the fact that no a priori assumptions are made with regard to the location or identity of potential genetic loci; the genome-wide approach makes no specific accommodation for the underlying biology of the disease. So given that insulin resistance and β-cell dysfunction are the hallmarks of type 2 diabetes, why is there a dearth of insulin resistance loci? Where is Waldo?

Heritability of insulin resistance

Early heritability studies clearly established a genetic component to insulin resistance. Insulin resistance assessed by euglycemic glucose clamp data in Pima Indian families showed significant heritability (h^2) at different insulin levels ($h^2 = 0.38 \pm 0.061$ at ~ 130 μU/mL or $h^2 = 0.49 \pm 0.63$ at ~ 2000 μU/mL) [32]. Similar h^2 evidence was observed by Elbein

et al. [33], who examined affected sibling-pair families of European ancestry using the minimal model to estimate insulin sensitivity (S_I) from the FSIGT; $h^2 = 38 \pm 2\%$ for all family members, $h^2 = 29 \pm 2\%$ for only normal glucose tolerant family members. h^2 of similar magnitude was observed for S_I in a sample of Finnish families [34] and for the euglycemic glucose clamp in Finnish twins [35]. However, in these studies h^2 for insulin secretion or β-cell function was typically 1.5- to twofold higher [32–35]. These results suggest a stronger genetic contribution to components of insulin secretion or β-cell function compared with insulin resistance, which may partly explain the lack of insulin resistance loci, given the relatively limited statistical power of current genome-wide association samples.

Large-scale genetic association with direct measures of insulin resistance

The MAGIC examined by meta-analysis the 19 loci with primary associations with fasting glucose for association with other diabetes-related quantitative traits in an attempt to better understand the physiology underlying loci contributing to variation in fasting glucose [15••]. Among the traits examined was the largest collection of direct measures of insulin resistance/sensitivity; 2250 by euglycemic glucose clamp, 575 by FSIGT, and 370 by islet suppression test. In addition, insulin resistance/sensitivity was assessed by a variety of indirect methods in more than 15,000 nondiabetic subjects of European ancestry; Stumvoll index [36], Matsuda index [37], Belfiore index [38], and Gutt index [39]. The direct measures were combined in a single meta-analysis, whereas the individual indirect measures were meta-analyzed independently. None of the 19 loci showed evidence for association with the direct measures of insulin resistance, although *MTNR1B* and glucose-6-phosphatase, catalytic, 2 (*G6PC2*) showed trends for association ($P = 0.057$ and $P = 0.069$, respectively).

In contrast, 13 of the 19 loci showed marginal to strong evidence for association with one or more of the indirect measures of insulin resistance/sensitivity. However, it should be noted that these indices were not consistent in their evidence for association. For example, rs4607517 in *GCK* showed strong evidence for association with the Gutt index ($P = 8.13 \times 10^{-5}$), leading one to conclude that variation in *GCK* contributes to variation in insulin resistance, possibly through effects on hepatic glucose metabolism. However, the evidence for association with the other indirect indices were all nonsignificant; $P = 0.22$ for the Stumvoll index, $P = 0.59$ for the Matsuda index, and $P = 0.54$ for the Belfiore index. This would raise some doubts about the inference drawn from the association with the Gutt index. Such disparity in results can generate discussions of how one index may be more reflective of hepatic versus peripheral insulin resistance and that different information may be captured by the different indices.

Does the Measure of Insulin Resistance Matter?

The disparity in results from the MAGIC analysis of fasting glucose loci points to the limitation of using indirect measures of insulin resistance. Although each index has been shown to be correlated with one or more of the direct measures of insulin resistance, one should question whether a strong overall correlation is sufficient for genetic association studies. The reader is referred to the classic review by Bergman et al. [40] for a thoughtful discussion regarding the in vivo assessment of insulin sensitivity.

Characteristics of indirect measures of insulin resistance

An indirect measure of insulin resistance is only useful in genetic studies if it appropriately reflects the effect of genetic variation on insulin resistance. Computer modeling has been used to assess the ability of the indirect indices to appropriately reflect insulin resistance on

a physiologic level [41•]. The results suggest that many indirect indices are confounded by changes in insulin secretion and/or splanchnic glucose uptake, such that care is necessary in appropriately interpreting results based on such indices.

The modeling results are further supported by comparisons between HOMA-IR and S_I made by the Insulin Resistance and Atherosclerosis Study Family Study [42]. Their analysis showed that evidence for h^2 was stronger for S_I ($h^2 = 33.1 \pm 5.9$) compared with HOMA-IR ($h^2 = 17.4 \pm 5.3$) or fasting insulin ($h^2 = 18.6 \pm 5.3$). Furthermore, although the phenotypic correlation (r_P) between S_I and HOMA-IR was strong ($r_P = -0.478$), it was substantially weaker than that for fasting insulin and HOMA-IR ($r_P = 0.952$). More importantly, the same pattern of differences was observed for the genetic and environmental correlations. Thus, HOMA-IR does not appear to provide additional genetic or environmental information beyond that extracted from fasting insulin. Furthermore, the relatively weaker correlations (r_P, r_G, and r_E) between HOMA-IR and S_I, compared with HOMA-IR and fasting insulin suggests that although there are some common genetic determinants among these indices, there are clearly components that are different.

Testing direct versus indirect measures of insulin resistance

A small computer simulation study can be performed to gain additional insights into why more insulin resistance loci have not been identified. We take advantage of the glucoregulatory model previously created to test indirect measures of insulin resistance [41•]. See Hücking et al. [41•] for specific model details and equations. As an illustrative simulation example, two specific model parameters were manipulated to simulate the effects of genetic variation specifically contributing to variation in insulin resistance or β-cell function. A nondiabetic population was simulated to emulate genetic association studies of diabetes-related quantitative traits. The estimated population allele frequencies for *PPARG* rs1801282 and *KCNJ11* rs5215 were used to define genotype-specific parameter distributions for an “insulin resistance” and “β-cell function” gene, respectively, assuming an additive genetic model.

Individual simulations were performed by randomly selecting genotype-specific parameter pairs for the “insulin resistance” and “β-cell function” genes from their respective population distributions. These parameter values were then used to simulate paired OGTTs and FSIGTs to simulate a study sample and random error representing sampling and assay variation was added to the simulated glucose and insulin data. The Stumvoll index was calculated from the simulated OGTT data and the simulated FSIGT data were analyzed using the minimal model to estimate S_I. At each replicate analysis we computed the Pearson correlation coefficient between the Stumvoll index and S_I, performed a test of association between each index and each simulated genetic variant using standard regression models, and estimated the partial correlation coefficient (R^2) to assess the fraction of the variability in each index accounted for by each gene. A limited set of 20 replicates each of 1000, 2500, 5000, or 10,000 “subjects” were simulated to assess statistical power.

The median correlation between the Stumvoll index and S_I across all the simulations was 0.697 with a range of 0.589 to 0.779, similar in magnitude to the correlation reported in the literature [36]. A summary of the simulation results is shown in Table 1. Statistical power to detect association between the “insulin resistance” gene and S_I was 0.35, 0.60, 0.65, and 0.58 across all sample sizes tested, whereas power to detect association using the Stumvoll index was similar or slightly lower (Table 1). Therefore, the simulation suggests that although there is slightly better power to detect association between the “insulin resistance” gene and S_I, using the Stumvoll index should provide relatively similar results.

However, there is an interesting dichotomy when results from the analysis of the "β-cell function" gene are examined. There is relatively lower power to detect association between S_I and the "β-cell function" gene across all sample sizes, suggesting that S_I is mainly reflective of insulin resistance and not confounded by changes in insulin secretion or β-cell function (Table 1). In contrast, the power to detect association between the "β-cell function" gene and Stumvoll index is equivalent to or even greater than the power observed for the test of association with the "insulin resistance" gene (Table 1). These results suggest the Stumvoll index is relatively nonspecific and may show evidence for association with variation underlying both insulin resistance and β-cell function.

Our simple computer simulation study demonstrates that an erroneous conclusion can be derived if one uses an indirect measure of insulin resistance and the association is primarily driven by a β-cell function locus. In contrast, the risk of an erroneous conclusion with a direct measure of insulin resistance is unlikely. These results are congruent with previous observations and indicate that careful consideration must be made when interpreting association results based on indirect measures of insulin resistance.

Biologic Mapping of Loci

Although the majority of type 2 diabetes susceptibility loci and loci underlying variation in fasting glucose map to the pancreatic β cell, mapping of loci to specific biologic functions is, at times, nebulous and dependent on the validity of previous biologic knowledge and the absence of bias. Furthermore, one needs to consider the possibility that a given locus could engender multiple biologic effects. Two examples are presented here to illustrate how loci mapped to the pancreatic β cell may also serve as insulin resistance loci.

Effect of one locus in more than one location

Gene expression analysis is often used to assist in deriving biologic interpretation for novel loci and tends to focus on tissues showing the largest levels of expression. However, one should not minimize the importance of gene expression at lower levels in other tissue targets. For example, KCNJ11 is a critical component of insulin secretion by pancreatic β cells. However, *KCNJ11* is also expressed, at lower levels, in cardiac and skeletal muscle. The *KCNJ11* rs5215 variant has been shown to be associated with differences in cardiovascular function [43] and adenosine triphosphate (ATP)–sensitive K^+ (K_{ATP}) channel activity in skeletal muscle [44]. In the latter study, variant-induced changes in K_{ATP} channel characteristics and regulation led to a near sevenfold increase in open-state probability, which can result in hyperpolarization of the sarcolemmal membrane, muscle fatigue, and reduced muscle glucose uptake. Thus, *KCNJ11* rs5215 may have independent effects at the level of the pancreas and muscle that both contribute to type 2 diabetes susceptibility.

Effect of interorgan signaling

Another consideration is the fact that type 2 diabetes is partly a consequence of the breakdown in the closed-loop feedback between glucose and insulin and changes in interorgan signaling could contribute to this breakdown. One such signal is pulsatile insulin secretion. Studies have clearly demonstrated that loss of insulin pulses is a characteristic of type 2 diabetes. In addition, experiments have shown that compared with constant exogenous insulin infusion, infusion in pulses results in more efficient stimulation of glucose uptake by peripheral tissues.

Variants in *GCK* [45,46] and *G6PC2* [47,48] have been shown to be associated with variation in fasting glucose concentrations and the former is also a type 2 diabetes susceptibility locus [13••]. These gene products regulate the rate-limiting step in glycolysis

in pancreatic β cells and presumably alter glycolytic flux, subsequent ATP production, and insulin secretion, which should result in differences in fasting glucose. Therefore, these loci form a logical pairing for joint genetic analysis. Furthermore, there is evidence that the counter-balancing effects of these two enzymes may contribute to the pulsatile nature of insulin secretion.

We examined the relationship between fasting glucose and genetic variation in *GCK* and *G6PC2* to better understand their physiologic effects [49•]. We hypothesized that the primary association should be with a measure of insulin secretion, with the observed fasting glucose association being a secondary consequence of the effect of insulin to regulate glucose concentrations. The relationship between glucose and insulin secretion was examined by stratifying diabetes-related phenotypes on *GCK*/*G6PC2* genotype combinations. We observed a complex pattern in which the glucose-raising allele for *GCK* resulted in lower insulin secretion, but the glucose-raising allele for *G6PC2* resulted in increased insulin secretion [49•]. This pattern suggests that the balance of effects provoked by variation in *GCK* and/or *G6PC2* may not directly alter absolute insulin secretion, but may alter a signaling characteristic of insulin secretion, such as pulsatility. The change in pulsatile characteristic may alter insulin signaling efficiency to peripheral tissues, resulting in insulin resistance, which results in modest hyperglycemia. The modest increase in glycemia then feeds back to the β cell, causing a compensatory increase in absolute insulin secretion [49•]. This potential mechanism is supported by animal studies in which disruption of pulsatile insulin secretion led to hepatic insulin resistance and impaired fasting glucose (A. Matveyenko, Personal communication). Thus, the complex interaction among two loci that map to the pancreatic β cell may, in fact, degrade interorgan signaling, resulting in insulin resistance in a peripheral tissue.

Some Thoughts

Additional genetic studies of type 2 diabetes quantitative traits will be required to better understand the biologic implications of the known and soon-to-be known susceptibility loci. In addition, the majority of type 2 diabetes susceptibility loci have been identified in populations of European ancestry. Thus, additional replication in other ethnic/racial populations is important to better understand the relative contributions of these loci to disease susceptibility. In these studies, it will be important to keep in mind two of the lessons of this review.

First, future genetic studies focusing on type 2 diabetes–related quantitative traits must carefully consider the phenotype being analyzed. The strong correlation between indirect and direct measures of insulin resistance may be sufficient rationale for their use in clinical and/or epidemiologic studies, but may be inadequate for genetic studies. In the past, avocation for direct measures of insulin resistance in genetic association was interpreted as a means to reduce phenotypic variability and improve statistical power. However, our small simulation study would suggest the true strength of using a direct measure comes from its specificity for the phenotype of interest and its reflection of the genetic variation contributing to that phenotype, which allows for ease of biologic interpretation.

Second, investigators need to begin taking a wider “systems” perspective when attempting biologic interpretation of association results. We presented the concepts of individual loci mapping to both insulin resistance and β-cell function through functional effects in relevant tissues or through defects in interorgan signaling. However, the complex relationship between genetic variation and measurable phenotypes goes beyond those concepts. Many genome-wide association studies have published figures that show increasing risk for disease or increasing phenotype values with number of risk loci an individual carries, the so-

called allelic or genotype score. However, those figures also hint at significant heterogeneity within a given allelic score, for if the actual individual values were plotted rather than the mean and standard error, a single allelic score would have a relatively wide range of possible phenotype values. Furthermore, any given allelic score would be comprised of a family of differing allelic combinations. Do these differing patterns of allelic combinations provide us with additional clues regarding the underlying biology of type 2 diabetes pathophysiology?

Conclusions

The new era of human genomics has transformed the study of type 2 diabetes. The discovery of novel loci have resulted in new views on diabetes pathophysiology and renewed interest in loci whose appeal had faded during the candidate gene era. The application of whole-genome sequencing is likely to identify new highly penetrant rare variants that will add to the complex nature of type 2 diabetes genetics. Additional insulin resistance loci are likely to emerge from the continue analysis of genome-wide data. MAGIC is currently assessing type 2 diabetes susceptibility loci for association with diabetes-related quantitative traits similar to their study of fasting glucose loci and the GIANT (Genetic Investigation of Anthropometric Traits) consortia have begun to examine association between obesity loci and indirect measures of insulin resistance. Genome-wide association studies specifically examining direct measures of insulin resistance are also in progress.

Where's Waldo? As in the famous children's book, Waldo is right under our noses, awaiting discovery if we look carefully.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1•. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, Novartis Institutes for Biomedical Research, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1331–1336. This paper is among the first genome-wide association studies for type 2 diabetes that collaborated with other studies to perform the first meta-analysis. [PubMed: 17463246]

2•. Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341–1345. This paper is among the first genome-wide association studies for type 2 diabetes that collaborated with other studies to perform the first meta-analysis. [PubMed: 17463248]

3•. Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in U.K. samples reveals risk loci for type 2 diabetes. Science 2007;316:1336–1341. This paper is among the first genome-wide association studies for type 2 diabetes that collaborated with other studies to perform the first meta-analysis. [PubMed: 17463249]

4•. Sladek R, Rocheleau G, Rung J, et al. A genome-wide association study identified novel risk loci for type 2 diabetes. Nature 2007;445:881–885. This paper discusses the first genome-wide association analysis for type 2 diabetes to appear in the literature. [PubMed: 17293876]

5•. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, et al. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nat Genet 2007;39:770–775. This paper is among the first genome-wide association analysis for type 2 diabetes to appear in the literature. [PubMed: 17460697]

6. Zeggini E, Scott LJ, Saxena R, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638–645. [PubMed: 18372903]

7. Yasuda K, Miyake K, Horikawa Y, et al. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. Nat Genet 2008;40:1092–1097. [PubMed: 18711367]

8. Unoki H, Takahashi A, Kawaguchi T, et al. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat Genet 2008;40:1098–1102. [PubMed: 18711366]

9. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet 2009;41:89–94. [PubMed: 19060909]

10••. Prokopenko I, Langenberg C, Florez JC, et al. Variants in MTNR1B influence fasting glucose levels. Nat Genet 2009;41:77–81. This paper is among the first studies to demonstrate that genome-wide association studies for diabetes-related quantitative traits can identify type 2 diabetes susceptibility loci. [PubMed: 19060907]

11••. Rung J, Cauchi S, Albrechtsen A, et al. Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nat Genet 2009;41:1110–1115. This paper is among the first studies to demonstrate that genome-wide association studies for diabetes-related quantitative traits can identify type 2 diabetes susceptibility loci. [PubMed: 19734900]

12••. Saxena R, Hivert MF, Langenberg C, et al. Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. Nat Genet 2010;42:142–148. This paper is among the first studies to demonstrate that genome-wide association studies for diabetes-related quantitative traits can identify type 2 diabetes susceptibility loci. [PubMed: 20081857]

13••. Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 2010;42:105–116. This paper is among the first studies to demonstrate that genome-wide association studies for diabetes-related quantitative traits can identify type 2 diabetes susceptibility loci. [PubMed: 20081858]

14. Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes susceptiblity loci identified through large-scale association analysis. Nat Genet 2010;42:579–589. [PubMed: 20581827]

15••. Ingelsson E, Langenberg C, Hivert MF, et al. Detailed physiologic characterization reveals diverse mechanisms for novel genetic loci regulating glucose and insulin metabolism in humans. Diabetes 2010;59:1266–1275. This is the first study to attempt to unravel the underlying physiology of loci underlying variation in fasting glucose by examining a comprehensive series of diabetes-related quantiative traits. This is the first study to also use large samples phenotyped using direct assessment of insulin resistance. [PubMed: 20185807]

16. Deeb SS, Fajas L, Nemoto M, et al. A Pro12Ala substitution in PPARγ2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. Nat Genet 1998;20:284–287. [PubMed: 9806549]

17. Mercado MM, McLenithan JC, Silver KD, Shuldiner AR. Genetics of insulin resistance. Curr Diab Rep 2002;2:83–95. [PubMed: 12643127]

18. Orho-Melander M, Melander O, Guiducci C, et al. Common missense variant in the glucokinase regulatory protein gene is associated with increased plasma triglyceride and C-reactive protein but lower fasting glucose concentrations. Diabetes 2008;57:3112–3121. [PubMed: 18678614]

19. Van Schaftingen E, Detheux M, Veiga da CM. Short-term control of glucokinase activity: role of a regulatory protein. FASEB J 1994;8:414–419. [PubMed: 8168691]

20. Grimsby J, Coffey JW, Dvorozniak MT, et al. Characterization of glucokinase regulatory protein-deficient mice. J Biol Chem 2000;275:7826–7831. [PubMed: 10713097]

21. Farrelly D, Brown KS, Tieman A, et al. Mice mutant for glucokinase regulatory protein exhibit decreased liver glucokinase: a sequestration mechanism in metabolic regulation. Proc Natl Acad Sci U S A 1999;96:14511–14516. [PubMed: 10588736]
22. Slosberg ED, Desai UJ, Fanelli B, et al. Treatment of type 2 diabetes by adenoviral-mediated overexpression of the glucokinase regulatory protein. Diabetes 2001;50:1813–1820. [PubMed: 11473043]
23. Beer NL, Tribble ND, McCulloch LJ, et al. The P446L variant in GCKR associated with fasting plasma glucose and triglyceride levels exerts its effect through increased glucokinase activity in liver. Hum Mol Genet 2009;18:4081–4088. [PubMed: 19643913]
24. Rodriguez S, Gaunt TR, Day IN. Molecular genetics of human growth hormone, insulin-like growth factors and their pathways in common disease. Hum Genet 2007;122:1–21. [PubMed: 17534663]
25. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889–894. [PubMed: 17434869]
26. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 2007;3:e115. [PubMed: 17658951]
27. Loos RJ, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 2008;40:768–775. [PubMed: 18454148]
28. Willer CJ, Speliotes EK, Loos RJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 2009;41:25–34. [PubMed: 19079261]
29. Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 2009;41:18–24. [PubMed: 19079260]
30. Lindgren CM, Heid IM, Randall JC, et al. Genome-wide association scan meta-analysis identifies three Loci influencing adiposity and fat distribution. PLoS Genet 2009;5:e1000508. [PubMed: 19557161]
31. Dina C, Meyre D, Gallina S, et al. Variation in *FTO* contributes to childhood obesity and severe adult obesity. Nat Genet 2007;39:724–726. [PubMed: 17496892]
32. Sakul H, Pratley R, Cardon L, et al. Familiality of physical and metabolic characteristics that predict the development of non-insulin-dependent diabetes mellitus in Pima Indians. Am J Hum Genet 1997;60:651–656. [PubMed: 9042926]
33. Elbein SC, Hasstedt SJ, Wegner K, Kahn SE. Heritability of pancreatic β-cell function among nondiabetic members of Caucasian familial type 2 diabetic kindreds. J Clin Endocrinol Metab 1999;84:1398–1403. [PubMed: 10199785]
34. Watanabe RM, Valle T, Hauser ER, et al. Familiality of quantitative metabolic traits in Finnish families with non-insulin-dependent diabetes mellitus. Hum Hered 1999;49:159–168. [PubMed: 10364681]
35. Lehtovirta M, Kaprio J, Forsblom C, et al. Insulin sensitivity and insulin secretion in monozygotic and dizygotic twins. Diabetologia 2000;43:285–293. [PubMed: 10768089]
36. Stumvoll M, Mitrakou A, Pimenta W, et al. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 2000;23:295–301. [PubMed: 10868854]
37. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470. [PubMed: 10480510]
38. Belfiore F, Iannello S, Volpicelli G. Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. Mol Genet Metab 1998;63:134–141. [PubMed: 9562967]
39. Gutt M, Davis CL, Spitzer SB, et al. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract 2000;47:177–184. [PubMed: 10741566]
40. Bergman RN, Finegood DT, Ader M. Assessment of insulin sensitivity in vivo. Endocr Rev 1985;6:45–86. [PubMed: 3884329]

41•. Hücking K, Watanabe RM, Stefanovski D, Bergman RN. OGTT-derived measures of insulin sensitivity are confounded by factors other than insulin sensitivity itself. Obesity 2008;16:1938–1945. This is the first study to use mathematical modeling to assess the quality of indirect measures of insulin resistance. [PubMed: 18670420]

42. Bergman RN, Zaccaro DJ, Watanabe RM, et al. Minimal model-based insulin sensitivity has greater heritability and a different genetic basis than homeostasis model assessment or fasting insulin. Diabetes 2003;52:2168–2174. [PubMed: 12882937]

43. Yi Y, Dongmei L, Phares DA, et al. Association between KCNJ11 E23K genotype and cardiovascular and glucose metabolism phenotypes in older men and women. Exp Physiol 2008;93:95–103. [PubMed: 17720745]

44. Li L, Shi Y, Wang X, et al. Single nucleotide polymorphisms in K(ATP) channels: muscular impact on type 2 diabetes. Diabetes 2005;54:1592–1597. [PubMed: 15855351]

45. Stone LM, Kahn SE, Fujimoto WY, et al. A variation at position -30 of the β-cell glucokinase gene promoter is associated with reduced β-cell function in middle-aged Japanese-American men. Diabetes 1996;45:428.

46. Weedon MN, Frayling TM, Shields B, et al. Genetic regulation of birth weight and fasting glucose by a common polymorphism in the islet promoter of the glucokinase gene. Diabetes 2005;54:576–581. [PubMed: 15677518]

47. Chen WM, Erdos MR, Jackson AU, et al. Variations in the *G6PC2/ABCB11* genomic region are associated with fasting glucose levels. J Clin Invest 2008;118:2609–2628. [PubMed: 18568074]

48. Bouatia-Naji N, Rocheleau G, Van Lommel L, et al. A polymorphism within the G6PC2 gene is associated with fasting plasma glucose levels. Science 2008;320:1085–1088. [PubMed: 18451265]

49•. Li X, Shu YH, Xiang AH, et al. Additive effects of genetic variation in *GCK* and *G6PC2* on insulin secretion and fasting glucose. Diabetes 2009;58:2946–2953. This study demonstrates the complex nature of combined gene effects, even under the assumption of additivity. The results suggest that interorgan signaling may play a role in gene variants exerting biologic effects. [PubMed: 19741163]

Table 1

Summary of computer simulation results

		Stumvoll index			Minimal model S_I		
	N	**Average β**	**Power**	**R^2**	**Average β**	**Power**	**R^2**
	1000						
“Insulin resistance” gene		-9.08×10^{-4}	0.40	0.0030	−0.062	0.35	0.0035
“β-cell function” gene		6.91×10^{-4}	0.40	0.0033	0.029	0.20	0.0019
	2500						
“Insulin resistance” gene		-1.03×10^{-3}	0.40	0.0041	−0.080	0.60	0.0056
“β-cell function” gene		7.94×10^{-4}	0.45	0.0050	0.030	0.30	0.0025
	5000						
“Insulin resistance” gene		-8.16×10^{-4}	0.45	0.0040	−0.082	0.65	0.0056
“β-cell function” gene		7.61×10^{-4}	0.60	0.0045	0.027	0.10	0.0020
	10,000						
“Insulin resistance” gene		-1.16×10^{-3}	0.68	0.0059	−0.082	0.58	0.0059
“β-cell function” gene		7.24×10^{-4}	0.42	0.0047	0.033	0.21	0.0030

R^2—partial correlation coefficient; S_I—insulin sensitivity.

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