

Minimal Model–Based Insulin Sensitivity Has Greater Heritability and a Different Genetic Basis Than Homeostasis Model Assessment or Fasting Insulin

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Insulin resistance is an important risk factor for development of type 2 diabetes as well as other chronic conditions, including hypertension, cardiovascular disease, and colon cancer. To find genes for insulin resistance it is necessary to assess insulin action in large populations. We have previously measured insulin action in a large cohort of subjects (Insulin Resistance and Atherosclerosis Study [IRAS] Family Study) using the minimal model approach. In this study, we compare sensitivity from the minimal model (insulin sensitivity index [S_I]) with the measure of insulin resistance emanating from the homeostasis model assessment (HOMA) approach. The former measure emerges from the glycemic response to endogenous and exogenous insulin; the latter is based solely on fasting measures of glucose and insulin. A total of 112 pedigrees were represented, including 1,362 individuals with full phenotypic assessment. Heritability of S_I was significantly greater than that for HOMA (0.310 vs. 0.163) and for fasting insulin (0.171), adjusted for age, sex, ethnicity, and BMI. In addition, correlation between S_I and either HOMA or fasting insulin was only ~50% accounted for by genetic factors, with the remainder accounted for by environment. Thus S_I , a direct measure of insulin sensitivity, is determined more by genetic factors rather than measures such as HOMA, which reflect fasting insulin. *Diabetes* 52:2168–2174, 2003

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FSIGT, frequently sampled intravenous glucose tolerance test; G_p , glucose concentration; h^2 , heritability; HOMA, homeostasis model assessment; I_p , insulin concentration; IRAS, Insulin Resistance and Atherosclerosis Study; QTL, quantitative trait locus; r_E , environmental correlation; r_G , genetic correlation.

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Insulin resistance is a risk factor for a variety of chronic diseases, including not only type 2 diabetes but also cardiovascular disease, hypertension, dyslipidemia, and colon cancer (1–3). It is now clear that chronic diseases, such as type 2 diabetes, can be delayed or even prevented by identification of subjects with a predisposition to insulin resistance and reversal of the predisposing risk factor profile with lifestyle changes (4) and/or pharmacological agents, such as insulin sensitizers (5).

Reversal of insulin resistance by identification of those “at risk” will be enhanced when genes for insulin resistance are identified. Identification of gene targets and their gene products may lead to better therapy design for individuals with similar genetic risk factor profiles of insulin resistance. While promising genetic loci for diabetes risk have been reported in various populations (6–8), specific loci for insulin resistance per se remain to be elucidated. Identifying susceptibility genes for insulin resistance itself can be based on the candidate gene approach or by positional cloning (scanning the entire genome to identify loci linked to or associated with insulin resistance). Either approach requires relating genetic information to phenotypic quantification of insulin sensitivity.

Various methods exist for measuring insulin sensitivity and have been extensively compared [c.f., (9–12)]. To date, comparisons between methods have been based on estimating the correlation between the widely accepted (but labor intensive) euglycemic clamp method and different (but less laborious) approaches. Some approaches are invasive, including the insulin injection method (13), pancreatic suppression test (14), or minimal model (15). In these methods, the biological responses to perturbations in plasma insulin are measured. Alternative methods are simply based on basal (i.e., fasting) measures of glucose and insulin. The basal approach was originally introduced by Sluiter et al. (16) (termed the “Bennett Index”), and that early effort has been followed by the homeostasis model assessment (HOMA) (17), as well as quantitative insulin sensitivity check index (QUICKI) (18). These latter basal-only based methods are attractive because of the relative ease of calculating a value simply from fasting measurements. However, it remains an important question whether the approaches based on basal concentrations reveal

information similar to that obtained from the more invasive methods in which dynamic changes in insulin are used.

The validity of any measure of insulin sensitivity (or resistance) is particularly critical to its application to genetic studies. Clearly, it is important that the design of genetic studies be based on accurate and precise indices that reveal the effect of insulin on tissue metabolic function. To date, different approaches have often been compared in populations and applied if correlation was significant (18–20). Simple correlation comparison of phenotype, however, does not reveal which method or methods are best suited for genetic studies. Insulin sensitivity (or insulin resistance) is determined by genetic and environmental factors. Some of the many environmental factors affecting insulin action are obesity, aging, pregnancy, puberty, infection, and/or physical fitness. It is clear that simple correlation among measures of insulin sensitivity can be determined by either shared genetic factors or shared environmental determinants. The primary measure of the strength of genetic determination is heritability (h^2), the proportion of the variance of a phenotype that is attributed to additive effects of genes. Examination of family members in a large number of pedigrees allows for precise calculation of h^2 for different sensitivity measures.

In this study, we explored the information obtained from the Insulin Resistance and Atherosclerosis Study (IRAS) Family Study (21) to estimate genetic as well as environmental contribution of two widely used measures of insulin sensitivity: the insulin sensitivity index (S_I), from the minimal model, and the surrogate fasting measure-based insulin resistance measure, HOMA. It was determined that the heritability of S_I was twice that of HOMA among the IRAS families. Furthermore, the contribution of shared genetic and environmental risk factors to the variance of the two measures of insulin resistance was also markedly different. Surrogate markers such as HOMA may not be appropriate for studies of insulin resistance in human populations. They may not reflect the same physiological process as indices from more complex protocols, such as the frequently sampled intravenous glucose tolerance test (FSIGT) and the minimal model.

RESEARCH DESIGN AND METHODS

Clinical methods. The details of the IRAS Family Study design and methods have been described elsewhere (21). Briefly, the IRAS Family Study is an extension of the IRAS, an epidemiological investigation of the correlates and predictors of insulin resistance and atherosclerosis (22). Probands for the Family Study were selected from three of the four original IRAS clinics or clinical sites (San Antonio, TX; San Luis Valley, CO; and Los Angeles, CA). Ascertained families were chosen on the basis of an “optimal” pedigree structure in which a pedigree contained at least 12–13 family members available for study, including ≥ 9 members for full phenotyping and genotyping. When possible, additional siblings and offspring were studied to obtain additional phenotypic data. Blood for genotyping was collected from parents of the proband and from spouses. The clinical examination was completed in one or two visits and included an insulin-modified FSIGT, height, weight, waist and hip circumferences, fasting blood draw, and medical history interviews. Insulin resistance was determined with minimal model analysis of insulin and glucose obtained during the insulin-modified FSIGT using the reduced sampling protocol (9,15,23).

One-hundred and twelve pedigrees formed the basis for these analyses. Although there were 1,605 individuals (637 men and 968 women) in the pedigrees, not all individuals had complete phenotypic data. Some individuals were included to permit complete enumeration of the pedigree for determining correct genetic relations among relatives. For these analyses, there were

TABLE 1
Descriptive statistics for IRAS Family Study participants

	Total	Diabetic subjects	Nondiabetic subjects
<i>n</i>	1,605	205	1,400
Age (years)	43.3 ± 14.3	55.4 ± 12.1	41.6 ± 13.8
Sex (% female)	968 ± 58.6	147 ± 61.0	968 ± 58.6
Ethnicity (% AA)	494 ± 29.9	69 ± 28.6	425 ± 30.1
BMI (kg/m ²)	29.2 ± 6.3	33.4 ± 6.9	28.6 ± 6.0
S_I	1.83 ± 1.71	0.59 ± 1.16	1.95 ± 1.71
Fasting insulin	16.0 ± 12.7	23.2 ± 18.4	15.1 ± 11.4
Fasting glucose	103.0 ± 32.4	168.8 ± 55.2	93.9 ± 9.6
HOMA	77.4 ± 79.3	170.7 ± 146.8	64.5 ± 53.1

Data are means ± SD and *n* (%). AA, African American.

between 1,362 and 1,365 individuals with phenotypic data, depending on the variable analyzed (Table 1). The pedigrees represented ascertainment at three sites (San Antonio, *n* = 46; San Luis Valley, *n* = 29; and Los Angeles, *n* = 37) and two ethnic groups (African Americans from Los Angeles, *n* = 37; and Hispanic Americans from San Antonio and San Luis Valley, *n* = 75).

Indices of insulin sensitivity. In this study we compared insulin resistance from the HOMA approach with S_I from the minimal model. As these methods have been described in detail elsewhere (15,17), we shall outline them here in brief. The HOMA index is simply calculated from the basal insulin (I_f) and glucose (G_f) concentrations:

$$\text{HOMA} = \frac{G_f \cdot I_f}{22.5},$$

where I_f and G_f are the values determined after an overnight fast.

S_I was calculated with the MM3 program (copyright R.N.B., 1996). The minimal model is implemented on the digital computer. The protocol used in each subject was the FSIGT. Measurements from the test are plasma glucose and insulin before and after injection of glucose (0.3 g/kg), followed by insulin 20 min later (0.03 units/kg). The test is performed under fasting conditions. S_I has been shown to reflect the effect of incremental changes in plasma insulin upon the net fractional clearance rate of glucose from the plasma compartment.

Variables were transformed to logs to approximate normal distributions. In addition, as previously discussed (24), we used the variable ($S_I + 1$) to avoid values of $S_I = 0$ and allow for logarithmic transformation. Since there were few diabetic subjects in the analysis (~200) and since hyperglycemia per se can result in insulin resistance (28), we limited our analysis to the large plurality of family members without diabetes.

Statistical genetic analysis. Heritability (h^2) was determined for each phenotype to characterize the contributions of genes and environmental factors using a genetic variance component approach (25,26) as programmed in the SOLAR software (27). This approach is likelihood based, so that the phenotypic variance can be partitioned into that attributable to individual-specific covariates (e.g., age, sex, ethnicity, and BMI), while estimating the additive polygenic and residual environmental components. Since the relation between the phenotypes (S_I , fasting insulin, and HOMA) and BMI may not be linear, a quadratic term (BMI^2) was also included as a covariate. The heritability of the trait can be estimated as the ratio of additive genetic variance to the total (residual) phenotypic variance. This estimate of heritability is considered “narrow sense,” in that it does not include the (nonpredictable) interaction effects of genes (dominance, epistasis) that are included in many estimates derived from twin studies. Significance of estimates is provided using a standard likelihood ratio test based on models with and without the covariates of interest.

Genetic and environmental correlations were estimated using a bivariate extension of SOLAR. The genetic correlations indicate the degree to which two traits have a common genetic basis, while environmental correlations indicate the degree to which they are due to common environmental factors. In addition to the estimated genetic and environmental correlations, trait-specific additive and environmental variances are estimated, allowing the derivation of the phenotypic correlation between traits. Bivariate correlations were determined for the following pairs of traits: S_I and fasting insulin, S_I and fasting glucose, S_I and HOMA index, and fasting insulin and fasting glucose. Significance of the genetic and environmental correlations were determined by a likelihood ratio test, using the model with the estimated correlation compared with a model with that correlation set at zero (resulting in a χ^2 distribution with one degree of freedom).

TABLE 2
Heritability estimates for measures of insulin sensitivity

Phenotype	h^2	SE (h^2)	P	Covariates	% σ^2 (cov)
Log($S_I + 1$)	0.293	0.057	<0.001	None	—
	0.298	0.057	<0.001	Age, sex, age* sex	7.3
	0.279	0.057	<0.001	+ Ethnicity	8.1
	0.329	0.059	<0.001	+ BMI	35.4
	0.331	0.059	<0.001	+ BMI ²	36.3
Log(fasting insulin)	0.139	0.049	<0.001	None	—
	0.142	0.049	<0.001	Age, sex, age* sex	0.5
	0.134	0.048	<0.001	+ Ethnicity	0.8
	0.171	0.053	<0.001	+ BMI	24.6
	0.186	0.053	<0.001	+ BMI ²	25.2
Log(HOMA)	0.123	0.048	<0.001	None	—
	0.130	0.049	<0.001	Age, sex, age* sex	1.0
	0.125	0.048	<0.001	+ Ethnicity	1.1
	0.163	0.053	<0.001	+ BMI	26.8
	0.174	0.053	<0.001	+ BMI ²	27.4

RESULTS

Descriptive statistics for the individuals in this sample of pedigrees are shown in Table 1. The mean age of participants was 43.3 ± 14.3 years, with diabetic family members somewhat older (aged 55.4 ± 12.1 years) than the nondiabetic family members (aged 41.6 ± 13.8 years). There were more women participating than men (~60% female) and, by study design, more Hispanic Americans (~70%) than African Americans. There were no differences in either sex or ethnicity between the diabetic and nondiabetic group. As expected, the BMI in the diabetic subjects was higher (33.4 ± 6.9 kg/m²) than that of the nondiabetic subjects (28.6 ± 6.0 kg/m²). Fasting glucose was higher in diabetic subjects (168.8 ± 55.2 mg/dl) than in nondiabetic subjects (93.9 ± 9.6 mg/dl). Direct measure (S_I) and fasting-based indices (fasting insulin and HOMA) of insulin resistance were also consistent with diabetes status. S_I was lower in diabetic (0.59 ± 1.16) than in nondiabetic family members (1.95 ± 1.71), and as expected, fasting insulin and HOMA were higher in diabetic subjects (23.2 ± 18.4 μ U/ml and 170.7 ± 146.8 units, respectively) than in nondiabetic subjects (15.1 ± 11.4 μ U/ml and 64.5 ± 53.1 units, respectively).

Estimates of heritability of measures of insulin action are provided in Table 2. A series of hierarchical models was developed to determine the impact of covariates on the estimates of heritability. The first model included no covariates, the second model included age and sex as covariates, the third model added ethnicity as a covariate, and the final model included BMI as a covariate. In all cases, the estimated heritability for each measure of insulin action (S_I , fasting insulin, and HOMA) was significantly greater than zero ($P < 0.001$). Not surprisingly, the covariate that had the largest contribution to the variance of the measures of insulin sensitivity was BMI. As a covariate, BMI contributed 35.4, 24.6, and 26.8% to the variance in S_I , fasting insulin, and HOMA, respectively. The effects of age, sex, and ethnicity were small in comparison.

The largest heritability for measures of insulin sensitiv-

ity was found for S_I . Unadjusted for covariates, the heritability of S_I ($h^2 = 0.293$) was more than double that for the fasting-based indices of insulin resistance (fasting insulin, $h^2 = 0.139$; HOMA, $h^2 = 0.123$). Even after adjustment for age, sex, ethnicity, and BMI, the magnitude difference for S_I (residual $h^2 = 0.310$) was maintained (fasting insulin, $h^2 = 0.171$; HOMA, $h^2 = 0.163$). Based on heritability alone, the most “familial” phenotypic measurement of insulin sensitivity is S_I . Furthermore, these data suggest that there is virtually no difference in the heritability of fasting insulin versus HOMA as an index of insulin sensitivity. Each estimate of heritability was significantly lower than that for S_I , and the inclusion of fasting glucose in the definition of HOMA added nothing to the heritability beyond the contribution of fasting insulin itself.

Estimation of heritability is a primary measure of familial (genetic) contribution to a phenotype. An additional consideration is the extent to which genetic factors contribute to the observed (phenotypic) correlation between two measures. Bivariate genetic and environmental correlations are shown in Table 3 for alternative measures of insulin sensitivity. The phenotypic correlation between S_I and fasting insulin or S_I and HOMA are, as expected, negative. From these analyses, strong genetic and environmental components exist that account for the observed correlation between S_I and either HOMA or fasting insulin. The genetic correlation (r_G) between S_I and fasting insulin is $r_G = -0.539$, and the environmental correlation (r_E)

TABLE 3
Phenotypic, genetic, and environmental correlations of measures of insulin sensitivity

Trait 1	Trait 2	r_P	r_G	r_E
ln($S_I + 1$)	ln(fast ins)	-0.462	-0.539	-0.445
ln($S_I + 1$)	ln(HOMA)	-0.478	-0.567	-0.462
ln($S_I + 1$)	BMI	-0.546	-0.521	-0.590
ln(fast ins)	ln(HOMA)	0.952	0.968	0.948

r_P , phenotypic correlation; r_G , genetic correlation; r_E , environmental correlation

between S_I and fasting insulin is $r_E = -0.445$. The genetic correlation between S_I and HOMA is $r_G = -0.567$, and the environmental correlation is $r_E = -0.462$. The phenotypic correlation between fasting insulin and HOMA (and the genetic and environmental components of the correlation) are almost identical, suggesting that the sum of fasting insulin or HOMA as a measure of insulin sensitivity likely reflects the same set of genes and environmental risk factors.

DISCUSSION

Type 2 diabetes in the U.S. has been increasing at an alarming rate (29), and with the availability of western diets has become a major health problem in third world countries. While finding a cure for the disease is a laudable goal, prevention is an alternative strategy that has had important successes of late. Specifically, improvements in lifestyle (e.g., weight reduction and exercise) (4) as well as pharmacological intervention (e.g., insulin sensitizers) (5) have been demonstrated to exert profound reductions in diabetes incidence, at least in the short term (≤ 5 years of observation). Thus, we foresee the day when significant type 2 diabetes may be prevented, at least in younger individuals.

Prevention strategies entail significant costs for counseling or pharmacological therapy. It is necessary to identify individuals at risk for disease for whom intervention will be effective. One approach to such identification is to specify risk alleles for insulin resistance and/or β -cell defects, and identify those individuals via genotype who have the greatest risk and who would gain the most with intervention.

There are at least 20 population studies designed to find genes for type 2 diabetes. In many of these studies, quantitative trait analysis is used in which phenotyping can be used to identify individuals who do not yet have diabetes but may be at great risk for the disease. Exploitation of the phenotype can enhance the ability to find risk alleles. There are often practical limitations to the ability to phenotype within at-risk families. Yet, to have the greatest power to find genes, phenotypic markers that reflect the risk factor of importance should be chosen. Surrogate markers, such as fasting insulin or the HOMA resistance index, have been used. However, the present study indicates that these parameters do not appear to adequately measure the genetic aspects of insulin resistance.

Although S_I has been used increasingly in studies of association of insulin resistance and cardiovascular disease risk, few reports have presented evidence of familial aggregation of S_I . Hong et al. (30) presented estimates of heritability of S_I separately for Caucasian ($h^2 = 0.44$) and African American ($h^2 = 0.38$) sedentary families in the HERITAGE study. In a collection of Caucasian pedigrees ascertained with multiple cases of type 2 diabetes from Utah, Elbein et al. (31) estimated heritability of S_I in the same range ($h^2 = 0.38$) as in the IRAS Family Study ($h^2 = 0.31$). A slightly lower estimate of heritability of S_I ($h^2 = 0.28$) was observed in the FUSION study (32), in which families were ascertained having at least two siblings with type 2 diabetes. In contrast, a much higher estimate ($h^2 = 0.52$) was seen in families with two type 2 diabetic parents (33), while a much lower estimate ($h^2 = 0.16$) was

observed in families with polycystic ovary syndrome (34). Whereas the IRAS Family Study ascertained families on the basis of family size, other studies emphasized ascertainment on the basis of type 2 diabetes, a phenotype highly associated with insulin resistance (S_I). Despite the difference in ascertainment, the estimates of heritability of S_I remain relatively constant, in the 30–40% range.

In contrast to S_I , numerous studies have estimated heritability of fasting insulin and HOMA. Both fasting glucose and HOMA have been reported to be heritable, but the estimates vary widely depending on study design and population. In most studies, the heritability estimates for HOMA and fasting insulin are not significantly different, as the range of fasting glucose in a nondiabetic population has little variation. Thus, HOMA has the same distribution (and familial aggregation) as fasting insulin. In the IRAS Family Study, the heritability of fasting insulin (and HOMA) was low ($h^2 = 0.17$). In a study of female adult twins (35), fasting insulin and fasting glucose concentrations had heritability estimates at 57–90%. In the Pima Indians (36) a lower estimate of heritability of fasting insulin was observed ($h^2 = 0.46$), which is similar to that estimated in families ascertained with hypertensive sibling pairs (37) ($h^2 = 0.48$). In contrast, a recent study of the Old Order Amish (38) reported much lower heritability of fasting insulin ($h^2 = 0.11$). Unlike other studies, the IRAS Family Study differed in that ascertainment was not based on extreme phenotype (type 2 diabetes) that could influence the distribution and familial aggregation of fasting insulin and fasting glucose (HOMA). Thus, the estimates of familial aggregation (heritability) may be less influenced by correlations with other (selected) traits.

This study demonstrates the higher heritability of a direct measure of insulin resistance, S_I , based on the minimal model compared with the indirect HOMA measure. As expected, we found a significant correlation between S_I and HOMA indices, confirming previous studies that documented correlation among various sensitivity indices. However, the heritability of S_I was about twice that of the HOMA measure. The same result was seen when comparing S_I with fasting insulin. In fact, HOMA and fasting insulin behave virtually identically, suggesting that in nondiabetic individuals there is little additional information gained by the addition of fasting glucose to the HOMA measure, i.e., measuring fasting insulin may be just as useful as HOMA itself. However, using either of the latter two surrogates will be in principle much less powerful than using a direct assessment of insulin action, namely S_I . What distinguishes the minimal model-based approach from the surrogates is that the biologic response to exogenous insulin is measured with the model method. Because biological response to insulin can also be measured with the glucose clamp procedure, and since exogenous insulin is also administered in the clamp, it seems likely that the clamp method would be similar to the minimal model for assessment of genetic aspects of insulin resistance, and that the clamp method would be much better compared with HOMA. The utility of the clamp in genetic studies remains to be tested.

Additional support for a direct measure of insulin action in genetic studies is that the correlation between S_I and HOMA measure was not only caused by familial factors,

but also to an equivalent degree by environmental factors, independent of genes. Variation among family members is due to a variety of components, the most notable of which is obesity. Obesity itself has an important genetic component (39). Not surprisingly, we found that almost one-third of the variance of insulin sensitivity was due to BMI. However, adjusting for adiposity (BMI in the model as a covariate) did not alter the apparent overall superiority of S_I to reflect the genetic component of insulin sensitivity compared with HOMA. When S_I and BMI were included in a bivariate analysis, the genetic correlation was high ($r_G = -0.52$), as was the environmental correlation ($r_E = -0.59$); however, including correlations to BMI only slightly reduced the heritability of S_I ($h^2 = 0.28$). Thus, while BMI is an imperfect measure of obesity, it appears unlikely that the difference in heritability of S_I versus HOMA would be changed if other indices of adiposity were applied.

Differences between S_I and HOMA in reflecting genes may be explained by differences in what these two indices actually measure. The heritability of HOMA and of fasting insulin were similar, regardless of the adjustments made. Thus, it is likely that it is the component of fasting insulin in the numerator that accounts for the heritability of HOMA. Insulin sensitivity is not the only or even primary determinant of the fasting insulin concentration (or of HOMA). A primary determinant of fasting insulin is basal insulin secretion. It is the stereotypical hyperbolic relation between insulin secretion and action (40) that may account for the reflection of insulin sensitivity in the fasting insulin measure. Additionally, the concentration of insulin at fasting is determined by the metabolic clearance rate of the hormone. Any factors that determine secretion or clearance will affect fasting insulin and thus the HOMA measure. Among these factors are a variety of plasma-borne molecules, such as glucose itself, amino acids, free fatty acids, and glucagon. Clearance of insulin will change as a function of hyperinsulinemia per se (41), as well as visceral adiposity and/or free fatty acids (42,43). Variations in β -cell mass will be expected to yield differing fasting insulin for a similar degree of insulin resistance.

Given the many factors that can influence the fasting plasma insulin concentration, it may not be surprising that metrics that depend primarily on this single concentration may not reflect the genetic pattern of insulin resistance. Other indices that are determined by fasting insulin concentration are Bennett's Index and QUICKI. In fact, the relation between these indices and S_I is virtually identical to that of HOMA and fasting insulin: half the heritability of S_I and determination by both genetic and environmental factors (data not included). If only one quantitative trait locus (QTL) contributed to variation in S_I and one QTL contributed to variation in HOMA, then the phenotype with greater heritability (S_I) requires fewer families for detection (i.e., has greater power). However, for complex phenotypes like S_I and fasting insulin, there will likely be multiple QTLs contributing to the observed variation, so that magnitude of heritability may not correspond to the likelihood of detecting QTLs. Thus, while heritability can provide evidence regarding the degree by which variation in genetic factors influences phenotypic variation, it has

no ability to predict the number of QTLs, their mode of action, or their genomic location.

Previously, the (phenotypic) correlation among different parameters of insulin sensitivity has been used to compare measures. The exploitation of family studies has revealed that another statistic could also be applied—the propensity for inheritance of a given insulin resistance measure. Numerous studies of a strong correlation between S_I and insulin sensitivity measured with the euglycemic clamp, taken together with the present study, suggest alternatively that S_I truly reflects insulin action and the genetic transmission of that physiological process.

While use of fasting-based methods may not be appropriate for studies in which genetic causes of insulin resistance are being assessed, it may not be possible to extrapolate this weakness to all studies of insulin action. It is not clear which approach is best for environmentally caused alterations in insulin action. However, to the extent that the changes in insulin action due to environment are pleiotropic with specific genes, fasting-based methods such as HOMA, QUICKI, and Bennett's Index may not be appropriate. In addition, there is growing recognition that for complex diseases with correlated associated phenotypes, the use of statistical data reduction methods could provide both increased heritability over the original phenotype (disease) and increased power to detect QTLs. In the Pima Indians, a factor analysis was performed (44), identifying four factors: insulinemia, body size, blood pressure, and lipid metabolism. The insulinemia factor was associated with incidence of type 2 diabetes and could therefore be used as a quantitative trait in a linkage study. In a study of autism (45), a factor analysis identified several features that were used in gene mapping. Fifteen associated qualitative traits were reduced to two factors, one of which (Insistence on Sameness, IS) was mapped to a location with a strong candidate gene (*GABRB3*). Other uses of multivariate methods, including principal components, have been applied in the same context. Thus, combinations of direct measures of homeostatic variables (such as S_I , glucose effectiveness index, acute insulin response, and disposition index, a measure of β -cell function [40]) may provide a composite phenotype that has greater heritability and better distributional characteristics for gene mapping than any single measurement.

There is little doubt that type 2 diabetes is an inherited disease. Transmission among families, very different prevalence among different ethnic groups, as well as concordance between monozygotic twins confirms the heritability of this disorder. Insulin resistance is a risk factor for diabetes, although it must be coupled with β -cell dysfunction to cause the disease. Approaches for prevention now exist, justifying the search for genetic markers, which may indicate at-risk individuals. Because subjects at risk for diabetes are insulin resistant, the latter defect can be a characteristic that may suggest early intervention. The present study suggests that minimally invasive procedures, such as the FSIGT, will empower the search for the genes for insulin resistance and help identify subjects where intervention may be indicated. Additionally, newly discovered genes may provide a more productive approach to identification of the defective alleles leading to insulin resistance than has currently been available. Identification of these genes may lead to new and more

effective therapies for the prevention of diabetes and other syndromes associated with insulin resistance.

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