Original Paper

Human Heredity

Hum Hered 1999;49:159–168

Received: October 1, 1998
Accepted: October 16, 1998

Familiality of Quantitative Metabolic Traits in Finnish Families with Non-Insulin-Dependent Diabetes mellitus

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Key Words

Heritability · Variance components · Pedigree analysis · Genetics · Glucose tolerance

Abstract

Type 2 diabetes mellitus (NIDDM) is a complex disorder encompassing multiple metabolic defects. There exists strong evidence for a genetic component to NIDDM; however, to date there have been few reports of linkage between genetic markers along the genome and NIDDM or NIDDM-related quantitative traits. We sought to determine whether individual quantitative traits which determine glucose tolerance exhibit familiality in Finnish families with at least one NIDDM-affected sibling pair. Tolbutamide-modified frequently sampled intravenous glucose tolerance tests (FSIGT) were performed on unaffected offspring (n = 431) and spouses (n = 154) of affected sibling pairs sampled for the Finland-United States Investigation of NIDDM Genetics (FUSION) study. FSIGT data were analyzed using the Minimal Model to obtain quantitative measures of insulin sensitivity (S_I), glucose effectiveness (S_G), and insulin secretion assessed as the acute insulin response to glucose (AIR). The disposition index (DI), a measure of insulin resistance-corrected β-cell function, was also derived as the product of S_I and AIR. Variance components analysis was used to determine for each trait, the heritability (h^2), the proportion of the total trait variance accounted for by additive genes. After adjustment for age, gender, and body mass index, h^2 estimates were: S_G: 18 ± 9%, S_I: 28 ± 8%, AIR: 35 ± 8%, and DI: 23 ± 8%. We conclude that there is strong evidence for modest heritability of Minimal-Model-derived NIDDM-related quantitative traits in unaffected spouses and offspring of Finnish affected sibling pairs.

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Introduction

Type 2 diabetes mellitus (NIDDM) is a complex disease characterized by fasting hyperglycemia primarily due to insulin resistance and β-cell dysfunction [1–3]. NIDDM is also a risk factor for cardiovascular disease and hypertension [4] and therefore contributes significantly to morbidity and mortality. While the clinical characteristics of NIDDM are well documented, the specific defects responsible for the pathogenesis of the disease are generally unclear. Identification of the genetic basis for NIDDM could lead to identification of the specific metabolic defects responsible for the pathogenesis of the disease. Early evidence for a strong genetic component to NIDDM came from twin studies where it was noted that monozygotic twins had a higher NIDDM concordance rate compared to dizygotic NIDDM twins [5] and family studies showing a higher NIDDM prevalence rate in relatives of NIDDM subjects [6, 7] than in the general population.

The evidence for a genetic component to NIDDM has led several groups to determine whether NIDDM-related quantitative traits exhibit familiality [8–12]. Highly heritable NIDDM quantitative traits may provide clues for identification of genes responsible for NIDDM. Several groups have shown familiality for fasting glucose [8, 9] and fasting insulin [11]. However, these phenotypes reflect the net effect of multiple metabolic defects such as insulin resistance and β-cell dysfunction [1, 3, 13]. This raises the question whether individual quantitative traits that determine fasting glucose or insulin themselves exhibit familiality. Familial clustering of insulin action and acute insulin response were demonstrated in Pima Indians suggesting significant heritability for these traits [10, 14]. Recently, Sakul et al. [12] reported heritability estimates for a wide range of diabetes-related quantitative traits in Pima Indians. Their results indicate relatively high levels of heritability for such quantitative traits as insulin action, acute insulin response, and percent body fat.

The Finland-United States Investigation of NIDDM Genetics (FUSION) Study is a multicenter effort to identify genes for NIDDM [15]. FUSION has recruited and tested over 2,000 Finnish volunteers comprising 533 families with affected sibling pairs. One of the unique characteristics of the FUSION study is that we directly assessed NIDDM-related quantitative metabolic traits in the nondiabetic spouses and offspring of our affected sibling pairs using the frequently sampled intravenous glucose tolerance test (FSIGT) with Minimal Model analysis [16]. The availability of these quantitative traits allows us the opportunity to estimate heritability for traits which contribute to the pathogenesis of NIDDM. We observed statistically significant, albeit modest, heritabilities for glucose effectiveness (S_G), insulin sensitivity (S_I), acute insulin response (AIR) and the disposition index (DI) which were measured in the FUSION study.

Methods

The study design and recruitment for FUSION are detailed elsewhere [15]. Briefly, we successfully recruited and tested 533 nuclear families consisting of an affected sibling pair, parents when available and additional affected siblings. We ascertained families through index cases who were identified from the Finnish National Hospital Discharge Registry or from previous studies performed at the National Public Health Institute. Two hundred and ten of these nuclear families were extended to include an unaffected spouse and one or more offspring of the affected individuals. Here we report results from 176 index cases, 157 spouses, and 450 offspring from these extended families.

Phenotyping

Fasting glucose, insulin, C-peptide, and glutamic acid decarboxylase antibody (GAD Ab) were measured in all affected individuals. An oral glucose tolerance test (OGTT) conforming to WHO standards was performed in all unaffected subjects to confirm glucose tolerance status and in those affected subjects whose affection status could not be readily confirmed, yielding 2-hour glucose and insulin measurements in these individuals. All unaffected spouses and offspring of an index case or affected sibling were also invited to undergo a tolbutamide-modified FSIGT with Minimal Model analysis [17] to derive quantitative estimates of S_G and S_I. The acute insulin response to glucose (AIR_G) was computed as the incremental integrated area under the insulin curve for the first 8 min of the FSIGT [18, 19] and used as an index of insulin secretion. We also computed the DI, the product of S_I and AIR_G, as a resistance corrected index of β-cell function [16, 20]. Additional traits we assessed include fasting lipids and blood pressure.

Exclusions

Because the goal of FUSION is the identification of genes for NIDDM, we made an effort to identify and exclude subjects who might have had late-onset insulin-dependent diabetes (IDDM) rather than NIDDM. Affected individuals were excluded as possible late-onset IDDMs if they fulfilled one of the following sets of criteria: (1) insulin treatment was started within 10 years of diabetes diagnosis, GAD Ab was ≥ 0.03 GAU, and fasting C-peptide was ≤ 0.30 n*M*, or (2) insulin treatment was initiated within 4 years of diagnosis, no presence of GAD Ab, and fasting C-peptide was ≤ 0.30 n*M*. For the assessment of familiality, first-degree relatives (parents, offspring, and siblings) of suspected late-onset IDDM subjects also were excluded from analyses.

Prior to clinical testing, all subjects were asked to refrain from taking any of their prescription medication on the day of clinic visits. Data for those subjects who on the morning of blood sampling took medications known to affect the outcome of interest were excluded

Table 1. Size of families and number of offspring per family

Family size		1	2	3	4	5	6	7	8	9	10	Total
Families		0	13	35	77	32	14	7	4	1	1	184
Offspring/family	0	1	2	3	4	5	6	7	8			Total
Families	5	23	93	34	16	7	3	2	1			184

from analyses. Finally, since 1 day is an inadequate washout period for the majority of medications, we repeated analyses excluding those subjects prescribed medications known to impact on the outcome of interest, regardless of when the medication was last taken.

Data Analysis

We assessed familiality for our NIDDM-related quantitative traits using the multivariate normal variance components approach of Lange et al. [21]. We modeled mean levels of each quantitative trait value as a linear function of age and gender. Because obesity is a known risk factor for NIDDM [3, 22] and genes for obesity may overlap with those for NIDDM, we tested models with and without a term for body mass index (BMI). For non-FSIGT-derived traits, we corrected for ascertainment by conditioning on the trait value of the index case [21]. Since we did not perform FSIGTs in our affected subjects, for analyses involving FSIGT-derived traits, we carried out an approximate ascertainment correction by assigning a constant trait value to each index case and conditioning on that value. We chose the mean of the lowest quartile from the FSIGT results in the nondiabetic spouses who, as a group, were well matched with the index cases in terms of age, gender distribution, and BMI. The following values were assigned: S_G: 1.03, S_I: 2.41, AIR_G: 765.3, DI: 3,552.87. We assessed the impact of this ascertainment correction by repeating the analyses with other imputed values for the index cases, and without imputed values and no ascertainment correction.

We assumed a polygenic model for our analyses in which each trait was determined by the summed effects of multiple unmeasured genes of small effect (polygenes), unmeasured individual specific environmental effects, and the measured effects of age, gender, and (in some cases) BMI. Given our model, the total variance (σ^2) for a given quantitative trait is partitioned into an additive genetic variance component (σ^2_g), a genetic dominance variance component (σ^2_d) that reflects nonadditivity within loci, and an individual specific environmental variance component (σ^2_e) [21]:

$$\sigma^2 = \sigma^2_g + \sigma^2_d + \sigma^2_e.$$

Similarly, the covariance between two noninbred individuals *i* and *j* may be written as:

$$COV(X_i,X_j) = \sigma^2_g 2\Phi_{ij} + \sigma^2_d \Delta_{7ij} + \sigma^2_e \delta_{ij}.$$

Here Φ_{ij} is the kinship coefficient which is the probability that an allele drawn at random from individuals *i* and *j* at a given locus are identical by descent (ibd) [23], Δ_{7ij} is the probability that *i* and *j* share both genes ibd, and $\delta_{ij} = 1$ if $i = j$ and $\delta_{ij} = 0$ if $i \neq j$.

All data were transformed to approximate univariate normality prior to analysis. Square root (diastolic blood pressure, DI) or natural logarithmic transformations (fasting and 2-hour glucose and insulin, S_I, total cholesterol, HDL cholesterol, systolic blood pressure) were used for most variables. Exceptions were S_G ($y^{0.25}$), AIR_G ($y^{0.185}$), and triglycerides ($y^{-0.3}$). Also, we used the log-transformed BMI value in the mean model since the distribution of BMI tended to be skewed. We used the computer program FISHER [24] to estimate the parameters of our model by maximum likelihood. Presence of a significant variance component was assessed by using the log-likelihood statistic (Λ) in which we compared the models with the variance component of interest set to zero to that in which the component was allowed to be positive. Because of the one-sided nature of this test, Λ is asymptotically distributed as a 50:50 mixture of χ^2 on one degree of freedom and a point mass at zero, resulting in p values half as large as in the usual two-sided case [25]. We estimated the narrow sense heritability $h^2 = \frac{\sigma^2_g}{\sigma^2}$ as a measure of trait familiality.

Table 2. Subject demographics (mean ± SD, median, number of subjects)

	Gender F:M	Age years	Body mass index kg/m^2
Index cases	62:114	63.3 ± 6.6 63.4 176	29.7 ± 4.4 29.2 176
Unaffected spouses	108:49	60.8 ± 7.4 60.7 157	28.5 ± 4.7 28.2 157
Unaffected offspring	215:235	34.7 ± 7.3 34.9 450	25.8 ± 4.3 25.3 450

Results

We restricted our analyses to those extended families for which we had complete FSIGT results. A total of 184 pedigrees were available for analyses after excluding late-onset IDDM families and those subjects who took medications on the day of blood draw (table 1). Pedigree sizes ranged from 2 to 10 members. Demographic characteristics of our subjects are shown in table 2. Table 3 shows

Table 3. Fasting and 2-hour plasma glucose and insulin levels (mean ± SD, median, number of subjects)

	Fasting glucose m*M*	2-Hour glucose m*M*	Fasting insulin p*M*	2-Hour insulin p*M*
No medication exclusion				
Index cases	10.8 ± 3.6	15.5 ± 4.8	112 ± 77	489 ± 285
	10.7	14.4	96	498
	169	10	169	10
Unaffected	5.3 ± 0.7	6.1 ± 1.8	78 ± 51	429 ± 328
spouses	5.2	5.8	66	345
	155	155	157	152
Unaffected	5.0 ± 0.6	5.3 ± 1.4	67 ± 34	322 ± 2,250
offspring	5.0	5.2	60	237
	441	441	442	442
Medication exclusion				
Index cases	9.0 ± 2.9	13.2 ± 2.8	100 ± 46	574 ± 268
	8.4	12.7	84	570
	13	6	13	6
Unaffected	5.3 ± 0.7	6.2 ± 1.8	78 ± 51	430 ± 329
spouses	5.2	5.8	66	345
	153	153	155	150
Unaffected	5.1 ± 0.6	5.3 ± 1.4	67 ± 34	323 ± 250
offspring	5.0	5.2	60	240
	439	439	440	440

Table 4. Minimal Model results (mean ± SD, median, number of subjects)

	S_G $\times 100\ min^{-1}$	S_I $\times 10^{-5}\ min^{-1}/pM$	AIR p*M* × 8 min	DI
Unaffected	1.66 ± 0.57	5.88 ± 3.39	2,373 ± 1,671	12,458 ± 8,872
spouses	1.60	5.41	1,874	10,190
	154	154	156	153
Unaffected	1.77 ± 0.58	7.58 ± 4.48	2,180 ± 1,526	14,140 ± 9,158
offspring	1.70	6.73	1,891	12,513
	431	431	447	428

mean and median values for fasting and 2-hour glucose and insulin values for the total sample and for those subjects who were not taking medications known to affect the measured trait. A large proportion of our affected individuals (92%) were taking a medication known to affect glucose and/or insulin (e.g., exogenous insulin, sulfonylureas), while very few spouses or offspring were on such medication.

Table 4 summarizes the FSIGT results for those 154 spouses and 431 offspring in whom FSIGTs were successfully completed and analyzed. There were only 2 individuals on medications known to affect the metabolic parameters and exclusion of these individuals has no impact on the mean values (data not shown). Lipid and blood pressure values are summarized in table 5. Thirty-five of our affected subjects were taking medications known to affect lipid values and 120 were taking antihypertensive medication. The proportion of spouses and offspring taking either type of medication was much smaller.

We estimated heritability of BMI in our families to be 55.9 ± 6.0% ($p < 0.0001$), illustrating that adiposity is a highly heritable trait. However, it is interesting to note that we did not detect a significant impact of BMI on any of our other heritability estimates, i.e., mean components models which included a term for BMI provided similar estimates of heritability as those models which did not.

Table 5. Lipid and blood pressure results (mean ± SD, median, number of subjects)

	Total cholesterol m*M*	HDL cholesterol m*M*	Triglycerides m*M*	Systolic BP mm Hg	Diastolic BP mm Hg
No medication exclusion					
Index cases	5.80 ± 1.21	1.10 ± 0.32	2.38 ± 1.74	151.4 ± 22.1	85.3 ± 11.2
	5.65	1.05	1.99	149	84
	172	172	172	172	172
Unaffected	5.84 ± 1.05	1.34 ± 0.37	1.44 ± 0.67	144.6 ± 21.1	84.9 ± 11.1
spouses	5.74	1.29	1.26	141	83
	156	156	156	153	153
Unaffected	5.12 ± 1.00	1.27 ± 0.31	1.33 ± 0.81	125.4 ± 13.8	79.2 ± 10.0
offspring	5.00	1.23	1.03	124	78
	441	441	441	448	448
Medication exclusion					
Index cases	5.80 ± 1.15	1.13 ± 0.33	2.11 ± 1.12	142.0 ± 20.1	82.8 ± 10.7
	5.69	1.09	1.86	142	83
	137	137	137	52	52
Unaffected	5.85 ± 1.04	1.35 ± 0.37	1.44 ± 0.67	141.7 ± 21.3	83.0 ± 10.2
spouses	5.72	1.29	1.25	140	82
	153	153	153	110	110
Unaffected	5.11 ± 1.00	1.27 ± 0.31	1.33 ± 0.81	125.0 ± 13.4	79.0 ± 9.9
offspring	5.00	1.24	1.03	124	78
	440	440	440	435	435

Table 6. Heritability estimates (± SE) for FSIGT-derived quantitative traits

Trait	Corrected for ascertainment					Not corrected for ascertainment $\hat{h}^2$, %
	proportion of trait variability			$\hat{h}^2$, %	p value	
	covariates %	polygenes %	environment %			
S_G	7.3	17.0	75.7	18.3 ± 8.7	0.0395	18.9 ± 8.5
S_I	27.3	20.1	52.6	27.7 ± 8.1	0.0021	27.8 ± 9.0
AIR	4.8	33.6	61.6	35.3 ± 8.1	<0.0001	35.3 ± 8.7
DI	8.1	21.5	70.4	23.4 ± 8.3	0.0048	21.3 ± 8.4

Therefore, we report results only for models that include BMI as a measured covariate. Also, we did not detect any difference in heritability estimates from analyses using all individuals and analyses excluding individuals taking medications with the exception of fasting plasma glucose where exclusion of subjects taking medications known to affect the glucose concentration resulted in an increase in our heritability estimate (see below). For all other traits we report results from analyses which include all individuals so as to maximize statistical power.

Heritability estimates for FSIGT-derived quantitative traits are shown in table 6. We did not detect a significant dominance variance component for any of the FSIGT-derived traits. This is consistent with our observation of similar parent-offspring and sibling-sibling correlations for these variables (data not shown). A small proportion (<10%) of the total variance in S_G and DI is accounted for by gender, age, and BMI, with an additional 20% accounted for by genes. Thus, about one-third of the variance in these two quantitative traits is accounted for by

Table 7. Heritability estimates (± SE) for other quantitative traits

Trait	Corrected for ascertainment		Not corrected for ascertainment	
	$\hat{h}^2$, %	p value	$\hat{h}^2$, %	p value
Fasting glucose	8.4 ± 3.2	0.0014	63.8 ± 7.5	<0.0001
2-Hour glucose	14.1 ± 6.7	0.0181	17.6 ± 8.0	0.0136
Fasting insulin	23.0 ± 5.2	<0.0001	30.8 ± 6.8	<0.0001
2-Hour insulin	47.3 ± 8.0	<0.0001	47.6 ± 8.1	<0.0001
Total cholesterol	50.0 ± 6.2	<0.0001	50.9 ± 6.3	<0.0001
HDL cholesterol	44.4 ± 6.1	<0.0001	50.3 ± 6.7	<0.0001
Triglycerides	38.9 ± 6.1	<0.0001	42.1 ± 6.4	<0.0001
Diastolic BP	32.9 ± 6.2	<0.0001	35.5 ± 6.5	<0.0001
Systolic BP	26.0 ± 5.2	<0.0001	29.6 ± 5.8	<0.0001

the combination of measured covariates and unmeasured genes. The relatively small proportion accounted for by genes translates into the modest heritability estimates shown in table 6.

In contrast, while the relative proportion of the total variance in S_I accounted for by genes is similar to those for S_G and DI (20.9%), measured covariates account for a substantially larger proportion of the total variance (27.3%) resulting in a still modest but somewhat greater estimate in heritability (27.7%). Of all the FSIGT variables, AIR_G demonstrated the strongest heritability (35.3%). The measured covariates had minimal impact on the heritability estimate.

When we recomputed the heritability estimates for FSIGT-derived quantitative traits without correcting for ascertainment, the estimates were not different from when we assigned a value for the index cases (see table 6). Similarly, assigning different fixed values to the index cases had essentially no impact on our estimates, suggesting robustness of our findings to ascertainment correction.

We also estimated heritability for fasting and 2-hour glucose and insulin concentrations (table 7) for comparison with previously reported estimates. We detected a significant dominance variance only for fasting glucose (36.8 ± 19.7%; p = 0.0092), consistent with our observation of higher sibling-sibling than parent-offspring correlation for fasting glucose values (data not shown). Our narrow-sense heritability estimate for fasting glucose (8.4 ± 3.2%) is considerably lower than previously published values, which range from 25–40% [8, 9], although addition of the genetic dominance term resulted in a broad-sense heritability of 45.2%. When we recomputed the heritability estimates without correcting for ascertainment, our narrow-sense heritability estimate for fasting glucose increased to 63.8 ± 7.5% and there was no longer evidence for a dominance variance component. Heritability estimates for 2-hour glucose and both fasting and 2-hour insulin did not change appreciably when ascertainment correction was ignored (see table 7). When subjects taking medications known to affect the plasma glucose concentration were excluded from the analysis (156 index cases, 2 spouses, and 2 offspring), the narrow-sense heritability estimate for fasting glucose was 31.6 ± 7.7% ($p < 0.0001$). The heritability estimate for 2-hour glucose increased to 23.9 ± 9.1% (p = 0.0033). Our heritability estimates for fasting and 2-hour insulin concentrations did not change appreciably when subjects taking medications known to affect insulin were excluded from the analyses.

Finally, we estimated heritability for lipids and blood pressure (table 7). We did not detect a significant dominance variance component for any of these traits. Our heritability estimates are similar to previously published values for these traits [26–30].

Discussion

Identification of genes for NIDDM using classical methodology is complicated by the complex nature of this disease. It is probable that NIDDM is the result of multiple genes of modest effect, rather than a small number of genes of large effect [31]. Therefore, qualitative linkage approaches may be usefully supplemented by quantitative trait linkage approaches to identify genes for NIDDM. In addition, once linkage for NIDDM is identified, information regarding NIDDM-related quantitative traits may help elucidate the mechanisms of gene action.

Because the classic diagnostic criteria for NIDDM are based on glucose measurements, many investigators have examined the familiality of fasting glucose to provide further evidence for a genetic basis for NIDDM [8, 9, 30]. Although significant estimates of heritability have been reported for fasting glucose, it is important to keep in mind that glucose concentration represents the net integrated effect of multiple metabolic defects and environmental factors. Thus, if the traits which determine the glucose concentration in and of themselves exhibit familiality, then they may reveal important clues for genetic susceptibility for NIDDM.

Although numerous groups have examined the heritability of various NIDDM-related quantitative traits in a variety of populations [8–12, 26–30, 32, 33], to our knowledge all these traits have not been examined simultaneously in a single cohort. We report significant, but modest heritabilities for a wide range of NIDDM-related quantitative traits in nondiabetic spouses and offspring of affected sibling pairs in our Finnish families.

Our observations of modest heritabilities for these NIDDM-related quantitative traits suggest that while these traits may have a genetic determinant, other factors such as measurement error and/or environmental factors play a greater role in the determination of these phenotypes. This would suggest that detection of NIDDM-related trait loci using quantitative trait linkage methods might be difficult. Our heritability results would seem to be consistent with the hypothesis that NIDDM may be determined by multiple genes of small effect [31] and the integrated effect of these traits is what determines disease penetrance.

We recognized that our ascertainment scheme could result in a biased estimate of heritability and therefore render our results incomparable to estimates derived from randomly selected populations. We therefore corrected for our nonrandom sampling by conditioning on the trait value of the index case and repeated our analyses ignoring ascertainment. For all the traits we examined, with the exception of fasting glucose, correcting for ascertainment resulted in slightly higher estimates of heritability, but not significantly different from the uncorrected estimates.

Our estimate of narrow-sense heritability for fasting glucose was substantially lower than previous estimates from nondiabetic populations [8, 9, 30]. When ascertainment correction was not performed, this estimate increased from 8.4 to 63.8% (table 7). One plausible reason for this behavior is the apparent lack of homogeneity in the variance of fasting glucose among the index cases, spouses, and offspring. The variance components approach we used assumes homogeneity of variance across the groups studied. After logarithmic transformation, index cases have a 6-fold higher variance in fasting glucose (0.116) compared to spouses (0.019) and a 9-fold higher variance compared to offspring (0.012). The higher variance in fasting glucose concentrations in the index cases might be attributable to their disease status and to the fact that the majority of these subjects were undergoing treatment for NIDDM. When we repeated the analyses excluding subjects taking medications known to affect glucose concentrations, our estimate of heritability for fasting glucose was similar to previously published values (31.6 ± 7.7%). We did not observe large heterogeneity of variance for the other quantitative traits.

For FSIGT-derived traits we did not phenotype the index cases and thus utilized an approximate ascertainment correction (see Methods). To assess the likely effect of our ascertainment scheme on our heritability estimates for S_I, we carried out a computer simulation in which we generated samples of 200 families under the polygenic model described in the Methods. Data kindly provided by the Insulin Resistance Atherosclerosis Study (IRAS) were used to estimate the probability of having diabetes for a given simulated S_I value. The IRAS study assessed S_I in a large cohort covering the entire spectrum of glucose tolerance [34] that allowed us to estimate these probabilities. For each member of the stimulated families, diabetes status was determined probabilistically; based on their simulated trait values and the estimates obtained from the IRAS data.

Samples of 200 simulated nuclear families in which the father was affected and the mother and three offspring were unaffected were then ascertained and analyzed using the variance components method described in the Methods. Trait information on the index case was excluded and random sampling was assumed for the analysis. Given true narrow-sense heritabilities of 20 and 40%, we obtained average heritability estimates of 14.5 ± 6.5 and 27.8 ± 7.0% for 1,000 replications each, respectively. Thus, our simulation results suggest that our estimates of heritability are likely to be conservative, in that they underestimate the true heritability for these traits.

Both S_I and AIR_G showed modest heritability, despite defects in these traits being known hallmarks of NIDDM. We also examined glucose effectiveness, which is hypothesized to play an important role in the transition from impaired glucose tolerance to NIDDM [13, 35]. Heritability for this trait was less strong than that for S_I and AIR_G.

The fact that AIR_G showed the highest heritability among these traits is noteworthy since it has been hypothesized that factors operating on β-cells may be primarily responsible for NIDDM in the Finnish population [36]. It is noteworthy that we also observed relatively higher heritability for 2-hour insulin (47.3%) as compared to fasting insulin (23.0%) in our subjects. Coupled with our observation for significant heritability for AIR_G, this suggests that examination of stimulated insulin responses can provide significant clues for identification of genes for NIDDM. There is some supporting evidence from the recent report of Mahtani et al. [37]. In their initial genome scan, Mahtani et al. did not find significant evidence for linkage with markers along the genome in their complete sample of 26 Finnish families. However, when they stratified families based on the 30-min insulin response from the OGTT, they found evidence for a susceptibility locus on chromosome 12 in those 6 families with the lowest insulin response.

Reports from clinical and epidemiologic studies suggest that correcting insulin secretion for the existing level of insulin resistance may be a more sensitive index of β-cell dysfunction than insulin secretion itself [16, 20, 38]. We therefore used the disposition index, first described by Bergman et al. [16], as an index of resistance corrected β-cell function to see if this trait exhibited greater heritability. However, our heritability estimate for the disposition index was lower than those for S_I or AIR_G alone.

The group studying the Pima Indians was the first to attempt to characterize the familiality of diabetes-related metabolic phenotypes [10, 14, 39]. Recently, Sakul et al. [12] reported heritability estimates from the Pima Indian population for quantitative measures of body fat, insulin resistance, and insulin secretion. Based on a sample of 509 nondiabetic Pima Indians, they reported significant heritability for insulin resistance (49%), AIR_G (80%), and percent body fat (76%). These estimates are markedly higher than those we obtained from our Finnish families.

There are several possible reasons that might explain the differences in heritability estimates between the FUSION sample and the study by Sakul et al. [12]. The population prevalence of NIDDM in adult Pima Indians exceeds 50%, compared to ~5.8% for the overall US population from 1991–1993 [7], ~5% for the middle-aged Finnish population [40], and up to 20% in elderly Finns [41]. The large difference in prevalence of disease suggests that the genetic architecture of disease may differ in the two populations.

Another difference between our study and that of Sakul et al. is the differential impact of adiposity on heritability estimates. Sakul et al. reported lower heritability estimates when percent body fat, a common and highly heritable trait itself, was included in their models. This is in contrast to our results where BMI had almost no impact on our heritability estimates. The differential impact adiposity had on the heritability estimates between our two studies suggest that adiposity may play a greater genetic role in NIDDM, or at least in NIDDM-related quantitative traits, in Pima Indians than in the Finnish population.

Other factors regarding the Pima Indian population may also contribute to the relatively high heritability estimates observed for the quantitative traits. The Pima population resides in the relatively isolated Gila River Indian Reservation, which may result in a relatively constant environment for this population. This would serve to minimize the relative contribution of environmental factors to the total variance of the trait, thus increasing the estimate of heritability. Also, the relative isolation of the Pima Indian population raises the possibility of greater inbreeding, which might also affect heritability estimates.

It is interesting to note that Sakul et al. computed multiple AIR_G indices for sequential time points following the infusion of glucose and noted a progressive increase in their heritability estimates (43% at 3 min up to 80% at 10 min). Therefore, we estimated heritability for an additional AIR_G index using the same 2-point difference method, choosing the time point from our FSIGT (8 min) coming closest to that which gave Sakul et al. their maximum heritability estimate. Our heritability estimate for this new AIR_G index was 39.4 ± 8.8%, not much different from our original estimate of 35.3% using the integrated response. We further examined the 22-min insulin sample which provided the peak response following the tolbutamide injection at 20 min. The 2-point AIR_G computed using this sample gave a heritability estimate of 41.4 ± 9.1%, again similar to our original estimate. Thus, we do not observe this temporal phenomenon in AIR_G heritability.

In summary, we assessed familiality for a wide variety of NIDDM-related quantitative metabolic traits in a sample of nondiabetic spouses and offspring of Finnish affected sibling pairs using a variance components approach. We found evidence for significant, but modest, heritability for glucose effectiveness, insulin sensitivity, acute insulin response, and the disposition index. Consistent with the hypothesis that insulin secretion may be a critical factor in the pathogenesis of NIDDM in Finland, acute insulin response had the highest heritability among

the FSIGT-derived quantitative traits. We did not detect any appreciable impact of BMI on our estimates of heritability, despite the fact that BMI itself was highly heritable.

Acknowledgments

The authors wish to thank the National Public Health Institute of Finland for funding the lipid assays. The authors gratefully acknowledge the hard work of Paula Nyholm, Juoko Sundvall, Tuula Tenkula, and Sanelma Vikkilä. Also we wish to acknowledge the assistance of Edna Ross, Lisa Taylor, and Elza Demirchyan for performing the glucose and insulin assays. We also thank the IRAS steering committee for allowing us access to their data. This project was made possible by intramural funds from the National Human Genome Research Institute (Project number OH95-C-N030) and by a NIH grant to M.B. (HG00376). Family studies were approved by IRBs at the NIH (Assurance number SPA S-5737-05) and at the National Public Health Institute in Helsinki, Finland. R.N.B. is supported by grants from the NIH (DK27619 and DK29867). R.M.W. was previously an NHGRI supported postdoctoral trainee (T32-HG00040) and is currently supported by an individual NRSA from the NIDDK (F32-DK09525).

References

1 DeFronzo RA: The triumvirate: B-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1997;37:667–687.
2 Bergman RN: Integration of pathogenic factors in impaired glucose tolerance and NIDDM; in Grill V, Efendic S (eds): Pathogenesis of Non-Insulin Dependent Diabetes mellitus. New York, Raven Press, 1988, pp 241–269.
3 Knowler WC, Pettitt DJ, Saad MF, Bennett PH: Diabetes mellitus in the Pima Indians: Incidence, risk factors and pathogenesis. Diabetes Metab Rev 1990;6:1–27.
4 Reaven GM: Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607.
5 Kaprio J, Tuomilehto J, Koskenvuo M, Romanov K, Reunanen A, Eriksson J, Stengard J, Kesaniemi Y: Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 1992;35: 1060–1067.
6 Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR: Role of glucose and insulin resistance in development of type 2 diabetes mellitus: Results of a 25-year follow-up study. Lancet 1992;340:925–929.
7 Kenny S, Aubert R, Geiss L: Prevalence and incidence of non-insulin-dependent diabetes; in Harris M (ed): Diabetes in America. Bethesda, National Institutes of Health, 1995, pp 47–67.
8 Beaty T, Fajans SS: Estimating genetic and non-genetic components of variance for fasting glucose levels in pedigrees ascertained through non-insulin dependent diabetes. Ann Hum Genet 1982;46:355–362.
9 Boehnke M, Moll P, Kottke B, Weidman W: Partitioning the variability of fasting plasma glucose levels in pedigrees. Am J Epidemiol 1987;125:679–689.
10 Lillioja S, Mott DM, Zawadzki JK, Young AA, Abbot WGH, Knowler WC, Bennett PH, Moll P, Bogardus C: In vivo insulin action is a familial characteristic in nondiabetic Pima Indians. Diabetes 1987;36:1329–1335.
11 Schumaker M, Hasstedt S, Hunt S, Williams R, Elbein SC: Major gene effect for insulin levels in familial NIDDM pedigrees. Diabetes 1992; 41:416–423.
12 Sakul H, Pratley R, Cardon L, Ravussin E, Mott D, Bogardus C: 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.
13 Bergman RN: Toward physiological understanding of glucose tolerance. Minimal Model approach. Diabetes 1989;38:1512–1527.
14 Thompson DB, Janssen RC, Ossowki VM, Prochazka M, Knowler WC, Bogardus C: Evidence for linkage between a region on chromosome 1p and the acute insulin response in Pima Indians. Diabetes 1995;44:478–481.
15 Valle T, Tuomilehto J, Bergman RN, Ghosh S, Hauser E, Eriksson J, Nylund S, Kohtamäki K, Tuomilehto-Wolf E, Toivanen L, Vidgren G, Ehnholm C, Blaschak J, Langefeld C, Watanabe RM, Magnuson V, Ally D, Hagopian W, Ross E, Buchanan T, et al: Mapping genes for non-insulin dependent diabetes mellitus: Design of the Finland-United States Investigation of NIDDM Genetics (FUSION) Study. Diabetes Care 1998;21:949–958.
16 Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981;68:1456–1467.
17 Bergman RN, Prager R, Volund A, Olefsky JM: Equivalence of the insulin sensitivity index in man derived by the minmal model method and the euglycemic glucose clamp. J Clin Invest 1987;79:790–800.
18 Chen M, Porte D Jr: The effect of rate and dose of glucose infusion on the acute insulin response in man. J Clin Endocrinol Metab 1976; 42:1168–1175.
19 McCulloch DK, Bingley P, Colman P, Jackson R, Gale E, The ICARUS Group: Comparison of bolus and infusion protocols for determining acute insulin response to intravenous glucose in normal humans. Diabetes Care 1993;16: 911–915.
20 Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr: Quantification of the relationship between insulin sensivitiy and B-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993;42:1663–1672.
21 Lange K, Westlake J, Spence M: Extensions to pedigree analysis. III. Variance components by the scoring method. Ann Hum Genet 1976;39: 485–491.
22 Lillioja S, Bogardus C: Obesity and insulin resistance: Lessons learned from the Pima Indians. Diabetes Metab Rev 1988;4:517–540.
23 Jacquard A: In The Genetic Structure of Populations. New York, Springer, 1974, p 102.
24 Lange K, Weeks D, Boehnke M: Programs for pedigree analysis: MENDEL, FISHER, and dGENE. Genet Epidemiol 1988;5:471–472.
25 Hopper J, Mathews J: Extensions to multivariate normal models for pedigree analysis. Ann Hum Genet 1982;46:373–383.
26 Boehnke M, Moll P, Lange K, Weidman W, Kottke B: Univariate and bivariate analyses of cholesterol and triglyceride levels in pedigrees. Am J Med Genet 1986;23:775–792.
27 Knuiman M, Divitini M, Welborn T, Bartholomew H: Familial correlations, cohabitation effects, and heritability for cardiovascular risk factors. Ann Epidemiol 1996;6:188–194.
28 Mitchell B, Kammerer C, Blangero J, Mahaney M, Rainwater D, Dyke B, Hixson J, Henkel R, Sharp R, Comuzzie A, Vandeberg J, Stern MP, MacCluer J: Genetic and environmental contributions to cardiovascular risk factors in Mexican Americans. Circulation 1996;94: 2159–2170.
29 Svetkey L, McKeown S, Wilson A: Heritability of salt sensitivity in black Americans. Hypertension 1996;28:854–858.

30 Edwards K, Newman B, Mayer E, Selby J, Krauss RM, Austin M: Heritability of factors of the insulin resistance syndrome in women twins. Genet Epidemiol 1997;14:241–253.
31 Rich SS: Mapping genes in diabetes. Diabetes 1990;39:1315–1319.
32 Elbein SC, Ward WK, Beard JC, Permutt MA: Familial NIDDM molecular-genetic analysis and assessment of insulin action and pancreatic β-cell function. Diabetes 1988;37:377–382.
33 Martin BC, Warram JH, Rosner B, Rich SS, Soeldner JS, Krolewski AS: Familial clustering of insulin sensitivity. Diabetes 1992;41:850–854.
34 Wagenknecht L, Mayer E, Rewers M, Haffner S, Selby J, Borok G, Henkin L, Howard G, Savage PJ, Saad MF, Bergman RN, Hamman R: The Insulin Resistance Atherosclerosis Study (IRAS) objectives, design, and recruitment results. Ann Epidemiol 1995;5:464–472.
35 Best JD, Kahn SE, Ader M, Watanabe RM, Ni T, Bergman RN: Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 1996;19:1018–1030.
36 Cerasi E, Efendic S, Luft R: Dose-response relation between plasma-insulin and blood-glucose levels during oral glucose loads in prediabetic and diabetic subjects. Lancet 1973;i:794–797.
37 Mahtani M, Lehto M, Thomas J, McCarthy M, Brayer J, Bryant B, Chan G, Daly M, Forsblom C, Kanninen T, Kirby A, Kruglyak L, Munnelly K, Parkkonen M, Reeve-Daly M, Weaver A, Brettin T, Duyk G, Lander E, Groop LC: Mapping of a gene for type 2 diabetes associated with an insulin secretion defect by a genome scan in Finnish families. Nat Genet 1996;14:90–94.
38 Byrne MM, Sturis J, Clement K, Vionnet N, Pueyo ME, Stoffel M, Takeda J, Passa P, Cohen D, Bell GI, Velho G, Froguel P, Polonsky KS: Insulin secretory abnormalities in subjects with hyperglycemia due to glucokinase mutations. J Clin Invest 1994;93:1120–1130.
39 Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. N Engl Med 1993;329:1988–1992.
40 Tuomilehto J, Korhonen H, Salomaa J, Stengard J, Aro A, Javela K, Uusitupa M, Pitkäniemi J: Prevalence of diabetes mellitus and impaired glucose tolerance in the middle-aged population of three areas in Finland. Int J Epidemiol 1991;20:1010–1017.
41 Tuomilehto J, Missinen A, Kvela S, Pekkanen J, Kaarsalo E, Wolf E, Aro A, Punsar S, Karvonen M: Prevalence of diabetes mellitus in elderly men aged 65 to 84 years in eastern and western Finland. Diabetologia 1986;29:611–615.