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Heritability of quantitative traits associated with type 2 diabetes mellitus in large multiplex families from South India

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Abstract

India is a major contributor to the global public health burden of diabetes. We have undertaken a family study of large multiplex families from Chennai, South India, and report on the familial aggregation of quantitative traits associated with type 2 diabetes mellitus in these pedigrees. Five hundred twenty-four individuals older than 19 years from 26 large multiplex pedigrees were ascertained. Detailed questionnaires and phenotype data were obtained on all participating individuals including fasting blood glucose, fasting insulin, lipid profiles, height, weight, and other anthropometric and clinical measures. Heritability estimates were calculated for all quantitative traits at the univariate level, and bivariate analyses were done to determine the correlation in genetic and environmental control across these quantitative traits. Heritability estimates ranged from 0.21 to 0.72. The heritability estimates for traits most directly related to type 2 diabetes mellitus were 0.24 ± 0.08 for fasting blood glucose and 0.41 ± 0.09 for fasting insulin. In addition, there was evidence for common genetic control for many pairs of these traits. These bivariate analyses suggested common genes for fasting insulin and central obesity measures (body mass index, waist, and hip), with complete genetic correlation between fasting insulin and waist. Quantitative traits associated with type 2 diabetes mellitus have heritabilities suggestive of some familial or genetic effect. The evidence for pleiotropic control of insulin and central obesity–related traits supports the presence of an insulin resistance syndrome in South Asians with a tendency for central obesity.
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Diabetes is a major public health concern; the World Health Organization and the International Diabetes Federation report global prevalence rates in individuals at least 20 years of age between 2.8% [1] and 5.1% [2]. Projected rates for the next 3 decades estimate 366 million diabetic persons in 2030 [1]. In India, the National Urban Diabetes Survey [3], in a stratified random sample of 11 216 individuals from 6 major cities, revealed high prevalence rates of diabetes (12%) and impaired glucose tolerance (IGT) (14%). This is a 6-fold increase in prevalence compared with around 2% in the 1970s [4]. Considering the rapid increase in its population size coupled with the high rates of disease, India is expected to add to the worldwide diabetes burden with an estimated prevalence of 80 million diabetic persons by 2030, accounting for one-fifth of the world's population of diabetic persons [1].

The etiology of type 2 diabetes mellitus is not yet fully understood, but it is likely that both genes and environmental components play a major role in its pathophysiology. The sibling relative risk for type 2 diabetes mellitus is 4- to 6-fold [5]. This finding, coupled with higher MZ concordance rates compared with DZ concordance rates [6,7], suggests an etiology based on both genes and environment.

With respect to Asian Indians, the risk for type 2 diabetes mellitus and premature coronary artery disease is increased compared with Europeans [8]. This has been explained by a higher frequency of hyperinsulinemia [9], insulin resistance [10], dyslipidemia with low high-density lipoprotein (HDL) cholesterol [11], and increased visceral fat despite lower body mass index (BMI) [12], features collectively referred to as the *Asian Indian phenotype or paradox* [12].

Epidemiologic studies conducted by our group and others [3,13] also support a strong role for genetics as evidenced by an increased risk for type 2 diabetes mellitus and IGT among

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subjects with positive family history. Mohan et al [13] showed that glucose intolerance was significantly higher in subjects with both parents affected compared with those with just 1 parent affected or those with no family history. Despite this evidence in support of genetic susceptibility, the relative importance of a potentially unique genetic effect vs lifestyle-related factors is as of yet not clear. In this report, we present an overview of large multiplex families from South India and calculate estimates of heritability to evaluate the contribution of genetic variation to quantitative traits related to type 2 diabetes mellitus.

1. Research design and methods

1.1. Subjects

Probands were selected from 3 sources: (1) subjects participating in the Chennai Urban Rural Epidemiology Study (CURES), (2) subjects participating in the Chennai Urban Population Study (CUPS), and (3) diabetic subjects visiting the outpatient clinic at Dr Mohan's Diabetes Specialities Centre, a tertiary referral center for diabetes that is located in Chennai. The CUPS and CURES are both ongoing epidemiologic studies conducted by the Madras Diabetes Research Foundation and are described in detail elsewhere [14,15]. Briefly, CURES is an epidemiologic study conducted on a representative population of 26 001 individuals (aged >20 years) in Chennai, the fourth largest city in India, with a population of 5 million. On the other hand, CUPS is composed of a selected sample of 1262 subjects from 2 residential areas in Chennai representing the middle and lower socioeconomic groups. As part of these 3 studies, detailed family history information was obtained on all individuals. Families were considered for inclusion into this study based on size, number of individuals with diabetes, and willingness to participate.

Probands and all willing first-, second-, and third-degree relatives were recruited to participate in this family study. Clinical phenotyping and questionnaire administration were generally conducted at the subject's residence, except where individuals preferred to visit the clinic. An oral glucose tolerance test using 75-g glucose load was performed on all study subjects, except self-reported diabetic subjects, for whom fasting venous plasma glucose and postprandial plasma glucose were measured. Fasting blood samples were obtained after an 8-hour overnight fast. Anthropometric measures including weight, height, waist circumference, and hip circumference were obtained using standardized techniques described elsewhere [14]. Blood pressure was recorded in the sitting position in the right arm to the nearest 1 mm Hg using the electronic OMRON machine (Omron, Tokyo, Japan). Two readings were taken 5 minutes apart, and the mean of the two was taken as the blood pressure. Informed consent was obtained from all study subjects as per a protocol approved by the Madras Diabetes Research Foundation Institutional Review Board.

1.2. Biochemical estimations

Fasting plasma glucose (glucose oxidase-peroxidase method; Roche Diagnostics, Mannheim, Germany), serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method, Roche Diagnostics), serum triglycerides (TGL) (glycerol phosphate oxidase-peroxidase-amidopyrine method, Roche Diagnostics), and HDL cholesterol (direct method polyethylene glycol–pretreated enzymes, Roche Diagnostics) were measured using a Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany). Serum insulin concentration was estimated by an electrochemiluminescence immunoassay using an immunoassay analyser (Elecsys 2010, Roche Diagnostics), and hemoglobin A_{1c} (HbA_{1c}) was measured by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA).The intra- and interassay coefficients of variation for the biochemical assays ranged between 3% and 7%. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

An individual was classified as diabetic if the subject (1) had physician-diagnosed diabetes, (2) was on drug treatment for diabetes (insulin or oral hypoglycemic agents), and/or (3) met the criteria laid by the World Health Organization Consultation Group report, that is, fasting plasma glucose of at least 126 mg/dL or 2-hour post-glucose value of at least 200 mg/dL [16]. Impaired glucose tolerance was diagnosed if the 2-hour post-glucose was at least 140 mg/dL ($\geq$7.8 mmol/L) and less than 200 mg/dL (<11.1 mmol/L), and normal glucose tolerance was determined if 2-hour postglucose was less than 140 mg/dL (<7.8 mmol/L) [16].

1.3. Statistical methods

Traits were $\log_{10}$ transformed where necessary (as determined by the Shapiro-Wilk test); and simple and multiple linear regression models were then used to assess the importance of measured covariates including age and sex for all traits. Residuals from these models were used in the heritability analyses described below; that is, traits were adjusted for covariates before heritability analyses. Fasting plasma glucose, HbA_{1c}, and fasting insulin levels were analyzed by (1) ignoring diabetes status, (2) adjusting for diabetes status, (3) adjusting for medication use, and (4) also trimming the data (ie, setting all observations >2.5 standard deviations from the mean to be missing). Pairwise phenotypic correlations (ρ_p) between all pairs of phenotypes were calculated with heritability estimates and correlations (further described below) using the following [17]:

$$\rho_p = [(\sqrt{h_1^2}) \times (\sqrt{h_2^2}) \times \rho_g] + [(\sqrt{1-h_1^2}) \times (\sqrt{1-h_2^2}) \times \rho_e].$$

Polygenic heritability is the proportion of total phenotypic variance that can be attributed to the additive effect of genes. Maximum-likelihood estimates of polygenic heritability were obtained for transformed and adjusted traits using variance-components models in Sequential Oligogenic

Linkage Analysis Routines [18,19]. Briefly, the variance-components model partitions the total phenotypic variance of the trait (σ_p^2) into components that correspond to additive genetic factors (σ_g^2) and unmeasured environmental factors including nonadditive genetic components (σ_e^2). Given the additive nature of the 2 components, the estimate of (narrow sense) heritability is given by σ_g^2/σ_p^2. The significance of the estimate of heritability is obtained using a likelihood ratio test comparing a model in which heritability is estimated to one in which it is set to 0. In addition, bivariate trait analysis [18] was performed with a maximum-likelihood procedure for pairs of quantitative traits to test for effects of pleiotropy, that is, the additive effects of common genes on the traits. In these bivariate models, 2 additional parameters are estimated: ρ_g and ρ_e—the additive genetic correlation and environmental correlation (including unmeasured environmental effects and nonadditive genetic effects [17]) for the pair of traits in the model, respectively. The additive genetic correlation here is a measure of pleiotropy. Formal tests were carried out to test the null hypotheses that $\rho_g = 0$ and $\rho_e = 0$. The rejection of $\rho_g = 0$ indicates significant additive effects of common genes on both traits. Tests to evaluate $\rho_g = 1$ were also performed to evaluate the evidence for complete pleiotropy.

2. Results

The sample was composed of 26 pedigrees totaling 1039 individuals. The pedigrees ranged in size from 18 to 70 individuals (average = 40), were 3 to 6 generations in depth (average = 4), and comprised 267 sibships with an average of 7 subjects affected with diabetes per pedigree (range, 1-16). Phenotype data were obtained on 524 individuals older than 19 years. An average of 20 subjects was phenotyped per pedigree (range, 3-41), resulting in 2362 relative pairs. There were 2061 relative pairs excluding the proband: 340 parent-offspring, 386 sibling, 91 grandparental, 706 avuncular, 3 half-sibling, and 535 cousin pairs. The clinical characteristics of the study subjects are presented in Table 1.

Table 1
Clinical characteristics of study subjects by proband status

Variable	Nonprobands (n = 498)
Male sex	256 (51%)
Diabetes status	
Diabetic	166 (33%)
IGT	39 (8%)
Normal	293 (59%)
Age (y)	42.65 ± 14.58
Height (cm)	161.82 ± 9.82
Weight (kg)	67.5 ± 13.17
BMI	25.84 ± 4.66
BPS	123.21 ± 17.55
BPD	76.36 ± 10.56
Waist (cm)	89.15 ± 10.89
Hip (cm)	99.53 ± 9.68
Waist-to-hip ratio	0.9 ± 0.08
Fasting blood glucose (mg/dL)	116.9 ± 52.97
2-h blood glucose (mg/dL)[a]	122.39 ± 67.08
Cholesterol (mg/dL)	177.05 ± 38.4
TGL (mg/dL)	141.02 ± 122.18
LDL (mg/dL)	108.24 ± 31.08
HDL (mg/dL)	41.07 ± 8.87
Cholesterol-to-HDL ratio	4.45 ± 1.12
HbA_{1c} (%)	6.63 ± 1.83
Fasting insulin (μIU/mL)	11.5 ± 9.47

[a] Two-hour blood glucose levels were available only on subjects free from diabetes when enrolled in the study.

Table 2
Heritability estimates of quantitative traits in 498 individuals from 26 pedigrees

Phenotype	Heritability ± SE*
Height	0.72 ± 0.09
Weight	0.40 ± 0.09
BMI	0.44 ± 0.09
Waist	0.28 ± 0.09
Hip	0.37 ± 0.10
Waist-to-hip ratio	0.21 ± 0.09
BPS	0.33 ± 0.09
BPD	0.35 ± 0.10
Cholesterol	0.40 ± 0.09
TGL	0.22 ± 0.09
LDL	0.58 ± 0.10
HDL	0.39 ± 0.10
Cholesterol-to-HDL ratio	0.40 ± 0.09
Fasting blood glucose	0.24 ± 0.08
2-h blood glucose	0.25 ± 0.15
HbA_{1c}	0.36 ± 0.08
Fasting insulin	0.40 ± 0.09

* All estimates were statistically significant ($P < .001$) with the exception of 2-hour blood glucose ($P = .027$).

To adjust for the ascertainment scheme, the probands were removed from each family; and only the 498 nonprobands were used in the heritability analyses. Using the log-transformed quantitative traits (with the exception of waist, which was normally distributed) adjusted for age and sex, the traits had heritability estimates ranging from 21% to 72% (all P values < .001 with the exception of 2-hour blood glucose, $P = .027$; Table 2). The heritability of the traits most directly related to type 2 diabetes mellitus was as follows: 24% for fasting blood glucose, 41% for fasting insulin, and 36% for HbA_{1c}. Trimming the data (ie, setting all observations >2.5 standard deviations from the mean to be missing) made little difference on the estimates for these phenotypes (data not shown). Adjusting for diabetes status or medication use had no effect on the heritability estimates for fasting insulin; and although they resulted in lower estimates for fasting glucose and HbA_{1c}, the confidence intervals for the estimates overlapped (data not shown). Height, weight, BMI, waist, and hip were generally on the higher end of the range of heritabilities, with height having the highest heritability (72%).

Tables 3 and 4 present the phenotypic correlations and the genetic and environmental correlations (including the nonadditive genetic component) in the quantitative traits,

Table 3
Phenotypic correlations between the diabetes-related quantitative phenotypes in 498 individuals from 26 pedigrees

	Height	Weight	BMI	Waist	Hip	BPS	BPD	Chol	TGL	LDL	HDL	FBG	HbA1c	Insulin
Height														
Weight	0.35													
BMI	-0.06	0.92												
Waist	0.15	0.83	0.82											
Hip	0.21	0.88	0.84	0.78										
BPS	0.09	0.31	0.31	0.28	0.28									
BPD	0.07	0.38	0.39	0.38	0.33	0.71								
Chol	0.02	0.15	0.14	0.15	0.05	0.11	0.17							
TGL	0.02	0.02	0.23	0.22	0.14	0.19	0.25	0.63						
LDL	0.00	0.04	0.05	0.06	0.03	0.03	0.07	0.60	0.16					
HDL	-0.02	-0.07	-0.06	-0.07	0.03	-0.04	-0.05	-0.59	-0.24	0.15				
FBG	0.04	0.07	0.05	0.11	0.02	0.14	0.13	0.19	0.29	0.10	-0.04			
HbAlc	-0.01	0.09	0.10	0.17	0.05	0.15	0.09	0.17	0.26	0.10	-0.02	0.87		
Insulin	0.04	0.10	0.41	0.37	0.33	0.22	0.28	0.20	0.27	0.02	-0.13	0.06	0.07	
2h BG	-0.10	0.19	0.20	0.21	0.20	0.17	0.17	0.23	0.29	0.11	-0.12	0.85	0.79	0.30

Chol indicates cholesterol; FBG, fasting blood glucose; 2h BG, 2-hour blood glucose.

respectively. As seen in Table 3, many of the quantitative traits appear to be correlated (14 pairs with $0.3 \leq \rho_p \geq 0.7$ and 10 pairs with $\rho_p > 0.7$). The traits cluster as 4 subtypes of phenotypically related variables: (1) anthropometric (height, weight, BMI, waist, and hip), (2) blood pressure (systolic [BPS] and diastolic [BPD]), (3) lipids (cholesterol, TGL, LDL, and HDL), and (4) traits most related to type 2 diabetes mellitus (fasting blood glucose, HbA_{1c}, fasting insulin, and 2-hour blood glucose). The strongest correlations are observed between variables within subtypes (Table 3; average ρ_p considering absolute value and ignoring direction was 0.52 for pairs within subtypes and 0.15 for pairs between subtypes). This phenotypic correlation is reflected in ρ_e (environmental and nonadditive genetic correlation), as is evident from Table 4 where the ρ_e for most pairs of traits is significantly different from 0, although the degree of this correlation varies greatly (absolute ρ_e = 0.2-0.96) and was stronger within subtypes (average absolute ρ_e = 0.67 vs 0.32 between subtypes). There is also evidence for genetic correlation for several pairs of these traits, and this is most seen within the subtypes once again (average absolute ρ_g = 0.77 vs 0.50). Interestingly, the genetic correlation between fasting blood glucose and HbA_{1c} is 0.85. Most noteworthy is the strong genetic correlation seen between fasting insulin levels and many of the anthropometric measures, that is, the obesity-related measures (weight = 0.67, BMI = 0.68, waist = 0.79, and hip = 0.62). Finally, strong evidence for pleiotropy (where ρ_g is not statistically different from 1) was only observed for 2 pairs of traits: (1) insulin and waist and (2) BMI and waist.

Table 4
Statistically significant genetic (ρ_g, upper right triangle) and environmental (ρ_e, bottom left triangle) correlations from bivariate analysis among diabetes-related quantitative phenotypes

	Height	Weight	BMI	Waist	Hip	BPS	BPD	Chol	TGL	LDL	HDL	FBS	HbA1c	Insulin	2h BS
Height		0.43													
Weight			0.85	0.84	0.92									0.67	
BMI		0.96		0.93*	0.93			-0.32						0.68	
Waist	0.26	0.84	0.78		0.86									0.79*	
Hip	0.34	0.86	0.78	0.75		0.33		-0.35			0.46			0.62	
BPS		0.31	0.34	0.24			0.82					0.58	0.5		
BPD		0.47	0.53	0.48	0.53	0.66								0.42	
Chol		0.5	0.5	0.40	0.35	0.2	0.33			0.76	-0.4				
TGL		0.36	0.33	0.29		0.2	0.29	0.73				0.3			
LDL			0.29					0.45							
HDL		-0.33	-0.32	-0.29	-0.28	-0.25		-0.72	-0.4						
FBS													85		0.79
HbAlc				0.20				0.24	0.31			0.89			0.62
Insulin		0.23	0.22			0.2	0.2	0.28	0.26		-0.41				
2h BS			0.24	0.24	0.26		0.36					0.87		0.33	

* Significant evidence for complete pleiotropy, that is, evidence that ρ_g is not significantly different from 1.

3. Discussion

Our investigation of large multiplex families with type 2 diabetes mellitus may provide insight into the role of genetic predisposition vs environmental influence on the escalating prevalence of diabetes in India. In this current work, we assessed the contribution of genetic effects to quantitative traits associated with type 2 diabetes mellitus. Wide ranges of heritability estimates have been reported for these traits in other populations. For example, in the Framingham Heart Study, an unascertained representative white population in the United States, estimates for these traits were as follows: (1) height: 0.52 ± 0.09 to 0.88 ± 0.06, (2) weight: 0.42 ± 0.10 to 0.56 ± 0.50, (3) BMI: 0.46 ± 0.10 to 0.49 ± 0.06, (4) BPS: 0.38 ± 0.09 to 0.44 ± 0.03, (5) cholesterol: 0.51 ± 0.04, (6) fasting blood glucose: 0.17 ± 0.04 to 0.39, (7) HDL: 0.62, and (8) TGL: 0.56 [20-22]. Here, we have found that all the traits showed moderate to high familial aggregation, with heritabilities ranging from 21% to 72%. The anthropometric measures had the highest heritability especially considering height, BMI, and weight; and although lower, the measures most directly related to the type 2 diabetes mellitus phenotype are also significant. We analyzed pairs of traits and found strong correlations for shared genes (ρ_g, the additive effect of genes) and shared environment (ρ_e, unmeasured environmental effects along with the nonadditive effects of genes). Significant genetic correlations (ie, where $\rho_g > 0$) were found for several pairs of traits (n = 25) and appear to be stronger within subtypes of traits. Our most noteworthy finding was the strong genetic correlations between fasting insulin and all the anthropometric measures, trends not observed with any of the other subtypes (ie, blood pressure and lipid measures). This is particularly interesting given that only 2 pairs of traits showed evidence for complete pleiotropy: BMI and waist, and insulin and waist. These results taken in entirety suggest that common genes may exert an influence on central obesity and insulin in these pedigrees.

Obesity is known to be related to insulin resistance; studies have shown that increased secretion of free fatty acids, inflammatory cytokines, and decreased secretion of adiponectin mediate obesity and insulin resistance [23,24]. Asian Indians are more prone to diabetes and cardiovascular disease because of increased waist circumference, visceral fat in particular, and insulin resistance (features described as the *Asian Indian phenotype*) [25]. This suggests a correlation between waist and insulin as observed in our data; and although environmental factors could certainly account for this correlation (eg, diet, physical inactivity), our study also suggests that common genetic factors may also play a role. Furthermore, waist circumference is an aggregate measurement of total and abdominal fat and is highly correlated with visceral adiposity, which has been shown to be more metabolically active than other adipose tissues, whereas BMI lacks the discriminatory power to differentiate between body fat and lean mass. Studies show that waist circumference also predicts the percentage of body fat quite accurately [26] and correlates well with metabolic syndrome and cardiovascular risk factors in Canadians [27], blacks and whites in the United States [28], and other ethnic groups (Chinese, Europeans, and South Asians) [29]. In a study among Asian Indians [30], we reported that waist circumference yields higher correlation coefficients for metabolic risk factors compared with BMI, suggesting waist circumference as a better index than BMI to identify metabolic risk factors.

Earlier studies from our group have shown important genetic differences in Asian Indians in the PPARγ gene [31], PGC-1 gene [32], and adiponectin gene [33], which help explain at least in part the Asian Indian phenotype with respect to insulin resistance, visceral adiposity, and diabetes. In addition, studies on the LPL gene have shown the −T93G single nucleotide polymorphism to be associated with obesity but not type 2 diabetes mellitus, whereas the −G53C single nucleotide polymorphism appears to be protective against both obesity and type 2 diabetes mellitus among Asian Indians [32]. In this same study, subjects with normal glucose tolerance who had the Thr54 allele in the intestinal fatty acid–binding protein gene (*FABP2*) showed significantly higher 2-hour plasma glucose, glycated hemoglobin, 2-hour insulin, and fasting LDL cholesterol levels compared with those with the Ala54 allele [34]. These candidate gene studies provide some support for the observed genetic correlation seen between anthropometric measures and fasting insulin levels in our study. Future studies by our group include both linkage in these pedigrees and large-scale case-control association studies at the candidate gene and, eventually, a genomewide association level to further explore these findings.

In summary, our results support a role for both environment and genes in the pathophysiology of type 2 diabetes mellitus and its related quantitative phenotypes in Asian Indian subjects. The evidence for common effects across multiple traits is not surprising given the underlying physiologic relationship between these phenotypes. In fact, the evidence in favor of common genes playing a role in obesity-related phenotypes and fasting insulin levels is similar to findings by others [35,36] and supports the observations of an insulin resistance syndrome prevalent in South Asian populations that is associated with a tendency for central obesity [37]. This is in accordance with our biological understanding that obesity, particularly abdominal obesity, increases insulin resistance, the predecessor for diabetes. This supports the observation of high heritability of central obesity in southern Indians reported earlier. Complete pleiotropic control of insulin and waist, but not insulin and BMI, suggests that waist may play a more major role in diabetes than BMI in Asian Indians. In conclusion, these 26 multiplex families from Chennai, South India, reveal strong familial aggregation of quantitative traits that are typically associated with type 2 diabetes mellitus. Further study of

these families may help identify potentially unique genetic loci among Asian Indians.

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