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Heritability Of Quantitative Traits Associated With Type II Diabetes In Large Multiplex Families From South India

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Abstract

Objective—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 in these pedigrees.

Research Design and Methods—524 individuals over the age of 19 from twenty-six 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.

Results—Heritability estimates ranged from 0.21 to 0.72. The heritability estimates for traits most directly related to Type 2 diabetes 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 and environmental control for many pairs of these traits (25 and 45 pairs, respectively). These bivariate analyses suggested common genes for fasting insulin and central obesity measures (BMI, waist and hip), with complete genetic correlation between fasting insulin and waist.

Conclusions—Quantitative traits associated with Type 2 diabetes 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.

Diabetes is a major public health concern; The World Health Organization (WHO) and International Diabetes Federation (IDF) report global prevalence rates in individuals 20 years of age between 2.8% (1) and 5.1% (2). Projected rates for the next three decades estimate 366 million diabetics in 2030 (1). In India, the National Urban Diabetes Survey (3), in a stratified random sample of 11,216 individuals from six major cities, revealed high prevalence rates of diabetes (12%) and impaired glucose tolerance (14%). This is a six-fold increase in prevalence, compared to around 2% in the 1970s (4). Considering the rapid increase in its population size coupled with high rates of disease, India is expected to add to the world-wide diabetes burden with an estimated prevalence of 80 million diabetics by 2030, accounting for one-fifth the world's population of diabetics (1).

The etiology of Type 2 diabetes 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 is four to sixfold (5). This finding, coupled with higher MZ concordance rates (0.34% (6) and 0.63% (7)) compared to DZ concordance rates (0.16% (6) and 0.43% (7), respectively) suggest an etiology based on both genes and environment.

With respect to Asian Indians, the risk for Type 2 diabetes and premature coronary artery disease (CAD) is increased compared to Europeans (8). This has been explained by a higher frequency of hyperinsulinemia (9), insulin resistance (10), dyslipidemia with low HDL cholesterol (11) and increased visceral fat despite lower body mass index (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 and impaired glucose tolerance (IGT) among subjects with positive family history. Mohan et al. (13) showed that glucose intolerance was significantly higher in subjects with both parents affected (55%) compared to those with just one parent affected (22.1%, $p = 0.005$) or those with no family history (15.6%, $p < 0.001$). Despite this evidence in support of genetic susceptibility, the relative importance of a potentially unique genetic effect versus life-style 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 of the contribution of genetic variation to quantitative traits related to Type 2 diabetes.

Research Design and Methods

Subjects

Probands were selected from three sources: 1) subjects participating in the Chennai Urban Rural Epidemiology Study (CURES); 2) subjects participating in the Chennai Urban Population Study (CUPS); and 3) subjects visiting the outpatient clinic at Dr. Mohan's Diabetes Specialties Centre. CUPS and CURES are both ongoing epidemiological studies conducted by the Madras Diabetes Research Foundation (MDRF) 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. CUPS on the other hand, is comprised of a selected sample of 1,262 subjects from two residential areas in Chennai representing the middle and lower socio-economic groups. As part of these three 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 was generally conducted at the subject's residence, except where individuals preferred to visit the clinic. An oral glucose tolerance test (OGTT) using 75gm glucose load was performed on all study subjects, except self-reported diabetic subjects, for whom fasting venous plasma glucose and post prandial plasma glucose were measured. Fasting blood samples were obtained after an 8-hour overnight fast. Anthropometric measures including weight, height, waist circumference, hip circumference, mid thigh girth, mid arm circumference, skinfold measurements such as biceps, triceps, subscapular and supra iliac measurements were obtained using standardized techniques described elsewhere (14). Informed consent was obtained from all study subjects as per a protocol approved by the Madras Diabetes Research Foundation Institutional Review Board.

Biochemical Estimations

Fasting plasma glucose (glucose oxidase - peroxidase method, Roche Diagnostics, Mannheim, Germany) serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method, Roche Diagnostics, Mannheim, Germany), serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method, Roche Diagnostics, Mannheim, Germany) and HDL cholesterol (direct method-polyethylene glycol-pretreated enzymes, Roche Diagnostics, Mannheim, Germany) were measured using a Hitachi-912 Autoanalyser (Hitachi, Germany). Serum insulin concentration was estimated by an electrochemiluminescence immunoassay using an immunoassay analyser (Elecsys 2010; Roche Diagnostics, Mannheim, Germany), and HbA1c was measured by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, Calif., USA). The intra- and inter-assay coefficients of variation for the biochemical assays ranged between 3% to 7%. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

An individual was classified as diabetic if 1) the subject had physician-diagnosed diabetes or 2) was on drug treatment for diabetes (insulin or oral hypoglycaemic agents) and/or 3) met criteria laid by the WHO Consultation Group report i.e. fasting plasma glucose (FPG) ≥ 126 mg/dl or 2 hour (hr) post glucose value ≥ 200 mg/dl (16). Impaired glucose tolerance (IGT) was diagnosed if the 2 hr post glucose was ≥ 140 mg/dl (≥ 7.8 mmol/l) and <200 mg/dl (<11.1 mmol/l) and normal glucose tolerance (NGT) if 2hr post glucose was <140 mg/dl (<7.8 mmol/l) (16).

Statistical Methods

Traits were $\log_{10}$ transformed and simple and multiple linear regression models were then used to assess the importance of measured covariates including age and gender for all traits, and residuals from these models were used in the heritability analyses described below, i.e. traits were adjusted for covariates prior to heritability analyses. Fasting plasma glucose, HbA1c and fasting insulin levels were analyzed by (1) ignoring diabetes status, (2) adjusting for diabetes status, (3) adjusting for medication use and (4) also by trimming the data (i.e. setting all observations > 2.5 standard deviations from the mean to be missing). Pair-wise correlations between all pairs of phenotypes were calculated using the Pearson product-moment correlation in STATA (v 9).

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 or SOLAR (17;18). Briefly, the variance components model partitions the total phenotypic variance of the trait (σ^2_p) into components that correspond to additive genetic factors (σ^2_g) and unmeasured environmental factors (σ^2_e). Given the additive nature of the two components, the estimate of (narrow sense) heritability is given by σ^2_g / σ^2_p . The significance of the estimate of heritability is obtained using a likelihood ratio test (LRT) comparing a model in which heritability is estimated, to one in which it is set to 0. In addition, bivariate trait analysis (17) was performed with a maximum likelihood procedure for pairs of quantitative traits to test for effects of pleiotropy, i.e. the additive effects of common genes on the traits. In these bivariate models, two additional parameters are estimated: ρ_g and ρ_e – the additive genetic correlation and environmental correlation (for unmeasured environmental effects) 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 which indicate significant additive effects of common genes and common environmental effects on both traits, respectively. Tests to evaluate $\rho_g=1$ were also performed to evaluate the evidence for complete pleiotropy.

Results

The sample was comprised of 26 pedigrees totaling 1,039 individuals. The pedigrees ranged in size from 18 to 70 individuals (average = 40) and 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 over the age of 19. An average of 20 subjects were phenotyped per pedigree (range: 3–41) resulting in 2,362 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.

To adjust for the ascertainment scheme, the probands were removed from each family and only the 498 non-probands were used in the heritability analyses. Using the log transformed quantitative traits adjusted for age and gender, the traits had heritability estimates ranging from 21% to 72% (all p -values <0.001). The heritability of the traits most directly related to Type 2 diabetes was: 24% for fasting blood glucose, 41% for fasting insulin and 36% for HbA1c. Trimming the data (i.e. setting all observations > 2.5 standard deviations from the mean to be missing) made little difference on the estimates for these phenotypes (see Table 2). Adjusting for diabetes status or medication use had no effect on the heritability estimates for fasting insulin, and while they resulted in lower estimates for fasting glucose and HbA1c, the confidence intervals for the estimates overlapped. 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 in the quantitative traits, respectively. As seen in Table 3, many of the quantitative traits appear to be correlated (14 pairs with correlation coefficients $\rho = 0.3$ – 0.7 and 8 pairs > 0.7). The traits cluster as four subtypes of phenotypically related variables: 1) anthropometric (height, weight, BMI, waist and hip); 2) blood pressure (BPS and BPD); 3) lipids (cholesterol, TGL, LDL and HDL); and 4) traits most related to Type 2 diabetes (fasting blood sugar, HbA1C and fasting insulin). The strongest correlations are observed between variables within subtypes (Table 3: average ρ considering absolute value and ignoring direction was 0.49 for pairs within subtypes and 0.15 for pairs between subtypes). This phenotypic correlation is largely environmental in nature as is evident from Table 4 where the environmental correlations for most pairs of traits are significantly different from 0, although the degree of environmental correlation varies greatly ($\rho = -0.72$ to 0.96) and was stronger within subtypes (average absolute $\rho = 0.71$ 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 $\rho = 0.78$ vs. 0.48). Interestingly, the genetic correlation between fasting blood sugar and HbA1c is 0.85 . Most noteworthy is the strong genetic correlation seen between fasting insulin levels and many of the anthropometric measures, i.e. the obesity-related measures (weight= 0.67 , BMI= 0.68 , waist= 0.80 and hip= 0.62). Finally, strong evidence for pleiotropy (where ρ_G is not statistically different from 1, was only observed for two pairs of traits: 1) insulin and waist; and 2) BMI and waist.

Discussion

Along with the high prevalence of diabetes in India, prediabetic conditions (impaired glucose tolerance and impaired fasting blood glucose) and Metabolic Syndrome are widely prevalent (19). Indians likely have a genetic makeup which is characterized by low body mass index, coupled with high upper body adiposity, body fat percentage and insulin resistance (12;19). Our investigation of large multiplex families with Type 2 diabetes may

provide insight into the role of genetic predisposition versus 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. Wide ranges of heritability estimates have been reported for these traits in other populations. For example, in the Framingham Heart Study, an unascertained representative Caucasian population in the United States, estimates for these traits were: 1) height: $0.52 \pm 0.09 - 0.88 \pm 0.06$; 2) weight: $0.42 \pm 0.10 - 0.56 \pm 0.50$; 3) BMI: $0.46 \pm 0.10 - 0.49 \pm 0.06$; 4) SBP: $0.38 \pm 0.09 - 0.44 \pm 0.03$; 5) Cholesterol: 0.51 ± 0.04 ; 6) fasting blood glucose: $0.17 \pm 0.04 - 0.39$; 7) HDL: 0.62; and 8) triglycerides: 0.56 (20–22). Here, we have found that all the traits showed moderate to high familial aggregation with heritabilities ranging from 21% – 72%, all of which were statistically significant ($p < 0.001$). The anthropometric measures have the highest heritability especially considering height (0.72 ± 0.09), BMI (0.44 ± 0.09) and weight (0.40 ± 0.09), and while lower, the measures most directly related to the Type 2 diabetes phenotype are also significant (fasting blood sugar = 0.24 ± 0.08 , HbA1c = 0.36 ± 0.08 , and fasting insulin = 0.41 ± 0.09). We analyzed pairs of traits and found strong correlations for shared genes and shared (unmeasured) environment. There appear to be environmental components that have effects across several of these traits as evidenced by significant estimates of ρ_E (i.e. where $\rho_E > 0$ for 45 pairs of traits). Environmental correlations appear to be stronger within subtypes of traits (i.e. between the various anthropometric measures and between the various lipid measures). Significant genetic correlations (i.e. where $\rho_G > 0$) on the other hand were found for fewer pairs of traits ($n = 25$) and once again 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 (0.67 with weight, 0.68 with BMI, 0.80 with waist and 0.62 with hip) trends not observed with any of the other subtypes (i.e. blood pressure and lipid measures). This is particularly interesting given that only two 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.

In summary, our results support a role for both environment and genes in the pathophysiology of Type 2 diabetes and its related quantitative phenotypes in Asian Indian subjects. The evidence for common environmental and genetic effects across multiple traits is not surprising given the underlying physiological 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 (23;24) and supports the observations of an insulin resistance syndrome prevalent in South Asian populations that is associated with a tendency for central obesity (25). 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 body mass index, suggests that waist may play a more major role in diabetes than body mass index 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. Further study of these families may help identify potentially unique genetic loci among Asian Indians.

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Table 1

Clinical characteristics of study subjects by proband status

Variable	Non Probands N=498
Male Gender	256 (51%)
Diabetes Status	
Diabetic	166 (33%)
IGT	39 (8%)
Normal	293 (59%)
Age	42.65 ± 14.58
Height (cm)	161.82 ± 9.82
Weight (kg)	67.5 ± 13.17
BMI	25.84 ± 4.66
BP systolic	123.21 ± 17.55
BP diastolic	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 sugar (mg/dl)	116.9 ± 52.97
Cholesterol (mg/dl)	177.05 ± 38.4
Triglycerides (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
HbA1c (%)	6.63 ± 1.83
Fasting insulin (μIU/ml)	11.5 ± 9.47

Table 2

Heritability estimates of quantitative traits in 498 individuals from 26 pedigrees

Phenotype	Heritability $\pm$ SE*
Height	0.72 $\pm$ 0.09
Weight	0.40 $\pm$ 0.09
BMI	0.44 $\pm$ 0.09
Waist	0.28 $\pm$ 0.09
Hip	0.37 $\pm$ 0.10
Waist to hip ratio	0.21 $\pm$ 0.09
BP systolic	0.33 $\pm$ 0.09
BP diastolic	0.35 $\pm$ 0.10
Cholesterol	0.40 $\pm$ 0.09
Triglycerides	0.22 $\pm$ 0.09
LDL	0.58 $\pm$ 0.10
HDL	0.39 $\pm$ 0.10
Cholesterol to HDL ratio	0.40 $\pm$ 0.09
Fasting blood sugar:	
All data	0.24 $\pm$ 0.08
Trimmed data	0.28 $\pm$ 0.09**
Adjusting for diabetes	0.11 $\pm$ 0.07
Adjusting for treatment	0.13 $\pm$ 0.08
HbA1c:	
All data	0.36 $\pm$ 0.08
Trimmed data	0.37 $\pm$ 0.09**
Adjusting for diabetes	0.26 $\pm$ 0.08
Adjusting for treatment	0.23 $\pm$ 0.08
Fasting insulin:	
All data	0.40 $\pm$ 0.09
Trimmed data	0.37 $\pm$ 0.10**
Adjusting for diabetes	0.41 $\pm$ 0.09
Adjusting for treatment	0.40 $\pm$ 0.09

* All estimates were statistically significant ($p < 0.001$)** Trimmed quantitative trait where all observations > 2.5 standard deviations from the sample mean were censored.

Table 3

Pearson product-moment 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	FBS	HbA1c
Height													
Weight	0.34												
BMI	-0.07	0.92											
Waist	0.14	0.83	0.82										
Hip	0.21	0.86	0.83	0.79									
BPS	0.07	0.30	0.31	0.27	0.27								
BPD	0.06	0.38	0.39	0.37	0.33	0.71							
Chol	0.03	0.16	0.14	0.16	0.06	0.07	0.15						
TGL	0.02	0.22	0.22	0.22	0.12	0.18	0.24	0.63					
LDL	-0.01	0.05	0.05	0.07	0.04	0.01	0.06	0.59	0.17				
HDL	-0.04	-0.08	-0.05	-0.06	0.02	-0.01	-0.02	-0.57	-0.22	0.17			
FBS	0.03	0.08	0.06	0.12	0.01	0.13	0.14	0.20	0.32	0.11	-0.02		
HbA1c	-0.03	0.08	0.10	0.15	0.03	0.16	0.11	0.16	0.27	0.11	0.01	0.85	
Insulin	0.03	0.39	0.40	0.36	0.32	0.22	0.29	0.19	0.25	0.02	-0.13	0.08	0.09

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
Height		0.43												
Weight			0.85	0.84	0.92									0.67
BMI				0.94 *	0.93			-0.32						0.68
Waist			0.85		0.85	0.24	0.48							0.80 *
Hip	0.34	0.86	0.78	0.76		0.33		-0.35			0.46			0.62
BPS		0.31	0.34				0.82					0.58	0.5	
BPD		0.47	0.53		0.53	0.66								0.42
Chol		0.5	0.5	0.43	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	-0.3	-0.28	-0.25		-0.72	-0.4					
FBS													0.85	
HbA1c				0.2				0.24	0.31			0.89		
Insulin		0.23	0.22			0.2	0.2	0.28	0.26		-0.41			

* significant evidence for complete pleiotropy, i.e. evidence that ρ_G is not significantly different from 1