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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