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Heritability of quantitative traits associated with type 2 diabetes in an extended family from the United Arab Emirates

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Abstract
The prevalence of Type 2 Diabetes Mellitus (T2DM) in the United Arab Emirates (UAE) is steadily increasing, posing a major public health problem. This study assessed the value of specific clinical markers for T2DM among five generations of an extended Arab family. This family included 319 members of 41 nuclear families; from which 178 individuals (86 males, 92 females; 66 diabetic, 112 healthy) formed the study sample set. The ages of the participants ranged from 4 to 88 years. All participants completed a questionnaire that focused on baseline factors that have previously been associated with T2DM such as diet, smoking, and family history of the disease. The quantitative traits, fasting glucose, glycated hemoglobin (HbA_{1c}), cholesterol, triglyceride, urea and creatinine levels were measured. Body mass index (BMI) and waist circumference were also recorded. The heritability of these eight quantitative traits were determined with values ranging from 6% to 48%. We found a significant relationship between T2DM diagnosis and waist circumference (p = 2.6, E-9) and BMI (p = 1.0, E-6). The estimated power for these two traits was 80% to 90%, respectively. Creatinine (p = 0.002) and cholesterol (p = 0.02) levels were also associated with T2DM. Our results support the link between environmental and genetic factors in the pathophysiology of T2DM and its related phenotypes in an Arab population.

Keywords: *Heritability, Quantitative Trait, Type 2 Diabetes*

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most widespread chronic diseases, contributing to the severe illness and ultimately leading to death of millions of people worldwide. According to the International Diabetes Federation, the number of people diagnosed with T2DM has risen over the past twenty years from 30 million to more than 246 million.[1,2] In the Middle East, 12% to 20% of the population suffers from diabetes. This incidence increases every year along with the rising costs associated with health care provision.[3] A Ministry of Health survey in 1999 and 2000 reported that 19.6% of people in the United Arab Emirates (UAE) were diagnosed with diabetes. More recent studies have estimated that 25% of adult Arabs suffer from T2DM, and the prevalence of the disease is increasing. In 2007, the UAE population had the second-highest incidence of diabetes in the world. In this country, an estimated one in five people aged between 20 to 79 years of age lives with diabetes, while a similar percentage of the population is at risk of developing the disease.

A range of risk factors contribute to being at risk to T2DM, particularly obesity, physical inactivity, age, ethnicity, history of gestational diabetes, weakened glucose tolerance, and a familial history of diabetes.[4] The prevalence of diabetes varies between different populations. Approximately 5% of Asian populations are affected, while almost 50% of the Pima Indian population suffers from diabetes[5-7] at the top end of this spectrum. Researchers have noted high rate of new T2DM cases among youth in the United State every year for; African-American (39 per 100,000), Hispanic-American (29 per 100,000), American Indian (45 per 100,000), and to a lesser extent Asian-American and Pacific Island populations (24 per 100,00).[8]

Multiple factors, both environmental and genetic, contribute to the incidence and distribution of T2DM. Urbanization and concordant changes in lifestyle have been linked to the prevalence of the disease.[9] For instance, the incidence of T2DM is very low in some rural populations such as the Mapuche Indians of Chile and rural Chinese groups, indicating the role of environmental factors.[10] Some of the highest incidences of T2DM, however, have been among the Pima Indians of Arizona and the Naura of Papua New Guinea, suggesting the importance of genetic factors in the development of the condition.[10]

The increasing prevalence of T2DM in the UAE appears to follow similar trends. Families among the indigenous tribes show varying degrees of predisposition to the disease. With widespread urbanisation in the Middle East over the past

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century, environmental factors increasingly exert an influence. In this report, we estimate the heritability of traits associated with T2DM in an extended family from the UAE. This assessment of phenotypic factors will be followed up with ongoing studies to evaluate the contribution of genetic polymorphisms that contribute to the prevalence of T2DM in Arab populations.

Research design and methods

Subjects

Major hospitals and primary care centers in the UAE were contacted to establish a collaborative recruiting network for this study. The study was performed with the approval of the ethical review committee of the United Arab Emirates Ministry of Health. Through this collaboration, doctor diagnosed data collected through one-on-one interviews of T2DM patients (and healthy controls) were evaluated. Clinical assessment and questionnaire completion were conducted at the clinic. Subsequently, 319 individuals belonging to one extended family of Bedouins origin were identified. Multigeneration family relationships were compiled for these individuals, and the pedigree of five generation extended family was constructed from 41 nuclear families. A total of 178 individuals from this sample agreed to participate in this study.

Physical attributes

The age, waist circumference and body mass index (BMI) for each volunteer was recorded.

Biochemical testing

All biochemical tests were performed at the Al-Baraha Hospital, Dubai, UAE, using the Cobas Integra 800 clinical chemistry system (Roche Diagnostics, Indianapolis, IN, USA). Peripheral blood was collected from the 178 individuals in EDTA, heparin and fluoride vacutainers. The heparin and fluoride tubes were centrifuged at 3,000 rpm for 5 minutes. Serum from the fluoride tubes was aspirated off to measure fasting glucose, cholesterol and impaired glucose tolerance, while serum from the heparin tubes was used to measure triglycerides, urea and creatinine levels. HbA_{1c} was measured with 25µl of blood from the EDTA tubes.

An individual was classified as diabetic if the subject: (1) was diagnosed with the disease by a qualified physician; (2) had been prescribed drug treatment for diabetes; and/or (3) met the fasting plasma glucose criterion of $\geq$ 126 mg/dl set by the World Health Organisation (WHO).

Statistical analysis

Raw phenotypic data was transformed and adjustment for age and sex. The transformation process, quantile-quantile (QQ) plots and histogram plots were generated by version 11 of STATA statistical software (College Station, TX, USA). To achieve normal distribution, the quantitative trait data were log-transformed. Heritability and power estimates were calculated for each trait using Solar version 4.[11] Pairwise correlations between all phenotypic pairs were calculated using STATA.

Results

The study population included 66 subjects with T2DM and 112 healthy subjects; 86 were male and 92 were female, ranging from 4 to 88 years of age. The mean age of the cohort was 37 years. The means and standard deviations of the eight quantitative traits used in this study are presented in Table 1.

Table 1: Phenotypic and clinical characteristics of 178 individuals belonging to an extended family of Arab origin.

Description		Number
Males		86
Females		92
Type 2 diabetes mellitus		66
Healthy		112
	Variable	Mean ± SD
Physical Appearance	Age (years)	37.35 ± 19.24
	Waist circumference (inches)	38.41 ± 7.75
	Body mass index (BMI)	29.48 ± 7.97
Biochemical Tests	Creatinine (mg/dl)	0.96 ± 0.25
	Cholesterol (mg/dl)	177.19 ± 62.23
	Triglyceride (mg/dl)	148.24 ± 83.04
	Fasting glucose (mg/dl)	117.32 ± 44.14
	Urea (mg/dl)	26.24 ± 8.21
	HbA_{1c} (%)	5.73 ± 1.38

Table 2 shows the estimated heritability and power for the eight traits used to evaluate the influence of genetic component on phenotypic variation by using Solar. All traits showed moderate to high familial aggregation, with heritability estimates ranging from 6% to 44%. Waist circumference, BMI, creatinine and cholesterol levels showed significant levels of heritability ($p < 0.05$), while the p-values were greater than 0.05 for triglyceride, fasting glucose, HbA_{1c} and urea levels. Waist circumference (44% heritability) and BMI (48% heritability) had the highest heritability rates among the eight traits, with powers of 80% to 90%. Fasting glucose (36% heritability) and HbA_{1c} (6% heritability) were the only traits that were directly related to T2DM.

Table 3 presents the pairwise phenotypic correlations of the eight quantitative traits. The highest phenotypic correlation observed in this study was that between fasting glucose and HbA_{1c} (0.89). Another significant pairwise correlation was between BMI and waist circumference (0.70), which is related to obesity. There was also a phenotypic correlation between waist circumference and both fasting glucose (0.52) and HbA_{1c} (0.41); both of which are related to obesity.

Table 2: Heritability and power estimation to obtain a suggested (LOD =3) of eight quantitative traits in 178 individuals. Values have been adjusted for sex and age. Significant p-values are indicated in bold.

Trait	H_2r[a]	p-value[a]	Chi-square[a]	Power estimate
Waist circumference	0.44	2.6, E-9	34.04	> 80%
Body mass index	0.48	1.0, E-6	28.01	> 90%
Creatinine	0.28	2.0, E-3	7.60	> 20%
Cholesterol	0.18	0.02	3.59	> 10%
Triglyceride	0.14	0.06	2.28	> 10%
Fasting glucose	0.36	0.10	1.63	> 50%
Urea	0.10	0.11	1.49	> 10%
HbA_{1c}	0.06	0.36	0.11	> 10%

[a] Heritability (H_2r), p and chi-square values were obtained with tests on transformed quantitative trait data. The chi-square and p-values relate to the likelihood ratio test comparing polygenic models to sporadic models.

Table 3: Pairwise correlation between diabetes-related phenotypic traits in 178 individuals.

	Waist circumference	BMI	Creatinine	Cholesterol	Triglyceride	Fasting Glucose	Urea	HbA_{1c}
Waist circumference	1							
BMI	0.70	1						
Creatinine	0.20	0.18	1					
Cholesterol	0.21	0.18	0.29	1				
Triglyceride	0.23	0.29	0.20	0.31	1			
Fasting Glucose	0.52	0.26	0.22	0.24	0.24	1		
Urea	0.01	0.09	0.29	0.13	0.07	0.14	1	
HbA_{1c}	0.40	0.28	0.22	-0.04	0.14	0.89	0.16	1

Discussion

Our study of T2DM in an extended family of Arab origin provides insights into the roles of genetic predisposition and environmental influence in the rising prevalence of T2DM in Arab populations. We found strong phenotypic correlations between fasting glucose levels and HbA_{1c}, and between these two traits and waist circumference. Our findings also indicate a heritable tendency for obesity in this family, indicated by waist circumference and BMI values. Therefore the heritability of these traits suggest the contribution of genetic factors to the prevalence of T2DM in this population Obesity results from a combination of genetic and environmental factors that appear to play a significant role in the development of T2DM in this sample. A major and prevalent public health problem, obesity is associated with numerous conditions such as hypertension, T2DM, coronary heart disease and cancer.

Wide ranges of heritability have been reported for these traits in other populations. Mathias and colleagues[12] found moderate to high familial aggregation for the traits tested in this study in a south Indian population, with heritability ranging from 21% to 72%. Anthropometric measures such as height, weight and BMI showed the highest heritability in their study, and the results in Arabs shown here are consistent with this finding. The researchers also found strong correlations between genetic and environmental effects for the measures most directly related to T2DM, especially between fasting insulin levels and anthropometric measures. However, only two pairs of traits showed evidence for complete pleiotropy: waist circumference was correlated with BMI and fasting insulin levels. These results suggest that common genes may exert an influence on obesity and insulin levels in these pedigrees.[12]

A study conducted by the Framingham Heart Study group estimated the heritability of anthropometric and biochemical traits in a Caucasian population.[13-15] There anthropometric trends of this Arabian study were familiar with those shown in the Framingham studies which found heritability rates for height (0.52 ± 0.09 to 0.88 ± 0.06), weight (0.42 ± 0.10 to 0.56 ± 0.50) and BMI (0.46 ± 0.10 to 0.49 ± 0.06). However, the heritability of cholesterol (0.51 ± 0.04) and triglyceride (0.56) levels was much higher than in the Arab population studied. Their heritability results for fasting blood glucose (0.17 ± 0.04 to 0.39) were similar to that observed in the Arab study.

In summary, this study supports the influence of both environmental and genetic factors in the pathophysiology of T2DM and its related phenotypes in an Arab population. Waist circumference and BMI may play a more prominent role in the development of diabetes in this population. The results presented show a strong familial aggregation of quantitative traits associated with T2DM. Further studies

are underway to identify potentially specific genetic loci in Arab populations.

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