Chapter 4

Some Genetic Determinants of Obesity, Type 2 Diabetes and Dyslipidemias in "Oman Family Study"

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Introduction

Complex polygenic diseases result from the interactions of genetic and environmental factors. However, genetic studies are complicated by phenomena such as genetic heterogeneity, variable age at onset and clinical expression, incomplete penetrance, and wide-ranging, ill-understood, environmental triggers (Rannala, 2001). Because genetic influences are less clear-cut, progress in identifying genes implicated in the pathogenesis has been slow and success limited (Frayling, 2007a; Frayling, 2007b; Frayling *et al*., 2007; DGI, 2007; Scott *et al*; Sladek *et al*., 2007; WTCCC; 2007; Zeggini *et al*., 2007; Zeggini, 2007). The main difficulties associated with studies of complex traits are to achieve the necessary statistical power and reproducibility. In heterogeneous populations, very large sample sizes are required for successful detection of effects of multiple genes, both for association and linkage studies (Frayling, 2007b; Zeginni, 2007; Groop and Lyssenko, 2008).

An ideal population to provide statistical power required to study complex diseases with confidence preferably consists of multigeneration1 pedigrees, descended from a small number of founders just a few generations ago, and with environmental homogeneity, restricted geographical distribution, detailed records, well-ascertained and validated pedigrees, and inbreeding as a norm (Arcos-Burgos and Muenke, 2002).

We have chosen to study a homogeneous population of families with very large pedigree sizes (160-325 subjects) in some inland villages of the Nizwa region of Oman. The families converge towards common descendents of Arab origin, and the founders date back to no more than 200 years. Traditionally, each individual is genealogically well defined within the family, and records are well maintained by individuals and their elders. Often fathers, grandfathers, and even great grandfathers are still alive. This population has maintained homogeneity by extremely high levels of inbreeding due to the tradition of encouraging consanguineous marriage, mostly between first cousins. Such unions occur in over 50% of marriages. The relative isolation of these families in small villages is due to rough terrain. Travel, education and other modernizations of the area only developed in the past 20-30 years.

We believe this model had a good chance of achieving the power required to examine the genetic elements of complex diseases. To add further precision, we have adopted very stringent criteria for defining

the phenotypes, which are dissected down to all possible components. Here we present results of heritability of quantitative traits for obesity, type 2 diabetes (T2D) and dyslipidemia. Hamodynamics are dealt with separately (Hassan *et al*., 2005; Hassan *et al*., 2007). We also present linkage analysis of quantitative trait loci (QTLs) that are possibly involved in the pathogenesis of these diseases.

The Model

"Oman Family Study" has been carried out on highly consanguineous extended families. It is a model for the study of the genetics of the four common polygenic diseases: obesity, T2D, hyperlipidemias and hypertension (Hassan *et al*., 2005; Bayoumi *et al*., 2007; Hassan *et al*., 2007). The study was carried out during 2002-2007, in the Interior (Dakhliya) region of Oman. The population sampled is composed of five, highly consanguineous pedigrees of Omani Arabs of 330, 160, 230, 280 and 280 individuals each; totaling 1280. On closer examination they all seem to be related to common ancestry and intermarriage is common between them. Polygamy is widely practiced with some men marrying up to 4 wives. Although the total number of founders ranges from 70-100 in each pedigree, most of these are due to marriages outside the pedigrees. The 5th–10th generation founders were usually very few and range between 10-15 individuals. The rapid population growth due to the oil boom made these fairly young isolates of 7-10 generations, each, with 60% below the age of 20 years.

Subjects

Apparently healthy adults, 16 to 80 years old, were sampled from the five Omani Arab pedigrees (Table 4.1). Of the total examined, only 1198 individuals (536 men and 662 women) had complete sets of data. Anthropometric, biochemical, and hemodynamic parameters of the whole population have been described previously (Hassan *et al*., 2005, 2007; Bayoumi *et al*., 2007; Lopez-Alvarenga *et al*., 2008; Albarwani *et al*., 2008).

The Phenotypes

All individuals have been phenotyped in detail. Anthropometric measurements included age, weight, height, waist and hip circumferences and per cent body fat. Biochemical tests included fasting blood glucose and blood glucose 2-hours after 75 grams oral glucose load. Serum insulin level was measured in fasting and 2 hrs after 75 g glucose. Serum growth

Table 4.1. Pedigree data of Oman Family Study.

Pedigree	1	2	3	4	5
Generations	9	7	9	12	8
Total closely related individuals	508	309	511	649	464
Individuals tested	327	160	230	279	281
Founders	14	3	3	17	11
Nuclear families	108	60	98	101	87
Mean Inbreeding Coefficient	0.0106	0.0092	0.0206	0.0180	0.0183

hormone, leptin, cortisol, thyroxine and thyroid stimulating hormone; serum albumin, total protein, alkaline phosphatase, uric acid, urea and creatinine; fasting blood lipids: total cholesterol, LDL and HDL cholesterol and triglycerides; were all measured (Table 4.2). Known gender differences in height, weight, HDL and TG were confirmed. Although men and women had the same BMI, women seemed to have a much higher percentage body fat, larger waist circumference (in relation to height and weight), and higher glucose intolerance. The waist circumference in these women appears to correlate directly with parity: the higher the parity, the larger the waist (Albarwani *et al*., 2008). The average parity in this population is 6 to 7.

The Genotypes

On obtaining an NIH grant, the Marshfield Mammalian Genome Service (MGS), sponsored by the National Heart, Lung and Blood Institute (NHLBI), USA, genotyped all 1280 individuals using the Marshfield 10cM, 400 microsatellite marker genetic map.

Prevalence of Morbidities

The anthropometric and biochemical characteristics of the study population is shown in Table 4.2. The prevalence of morbidities in the study population (n = 1198) is shown in Table 4.3 There is low prevalence of obesity and diabetes but much higher levels of dyslipidemias (Hassan *et al.*, 2005 and 2007, Bayoumi *et al*., 2007; Lopez-Alvarenga *et al*., 2008; Albarwani *et al*., 2008).

Statistics

The relative pairs of individuals used in the calculation of heritabilities (h^2) in the five pedigrees were 23,253

Table 4.2. Characteristics of the Omani Arab study group (n = 1198).

Variables	Total (n=1198)	Males (n=536)	Females (n=662)	P-Value
	Mean (± SD)	Mean (± SD)	Mean (± SD)	
Age (years)	33.8 (16.2)	33.0 (17.0)	34.5 (15.5)	0 .005
Height (cm)	158.3 (9.3)	165.8 (7.3)	152.2 (5.5)	<0 .001
Weight (kg)	62.9 (14.6)	68.1 (14.4)	58.7 (13.4)	< 0.001
BMI (kg/m2)	25.1 (5.4)	24.8 (5.0)	25.7 (5.7)	0.1
% Body fat	23.5 (10.5)	17.9 (8.4)	28.1 (9.8)	<0 .001
Waist circumference (cm)	81.0 (14.5)	81.1 (14.3)	80.0 (14.6)	0.9
LDL (mmol/L)	3.2 (1.0)	3.3 (1.1)	3.2 (1.0)	0.1
HDL (mmol/L)	1.1 (0.3)	0.9 (0.2)	1.2 (0.3)	< 0.001
TG (mmol/L)	1.1 (0.8)	1.2 (0.8)	1.0 (0.8)	< 0.001
FPG (mmol/L)	5.6 (1.5)	5.6 (1.3)	5.7 (1.6)	0.3
PG2 (mmol/L)	6.8 (3.3)	6.2 (2.7)	7.3 (3.6)	<0 .001
Insulin 0 (mIU/L)	5.6 (4.3)	5.6 (4.1)	5.7 (4.4)	0.9
HOMA- IR	1.39 (1.1)	1.37 (1.01)	1.41 (1.17)	0.6
HbAIC	5.5 (1.8)	5.4 (1.0)	5.6 (2.2)	0.3
Leptin (ng/mL)	26.9 (23.8)	13.1 (13.6)	38.1 (24.4)	<0.001
Growth Hormone (mIU/L)	4.6 (9.8)	2.0 (5.8)	6.7 (11.7)	<0.001

FPG: Fasting plasma glucose.
PG2: Plasma glucose 2Hrs after 75g oral glucose load

pairs (Table 4.4). The SPSS statistical package version 14.0 for personal computers (SPSS, Inc., Chicago: IL) was used for initial statistical analysis. Inbreeding level was calculated using the Quaas-Henderson algorithm (Boyce, 1983). The inbreeding coefficient for each subject was calculated on the probability that two genes at the same locus drawn at random, one from each parent, will be identical by descent. The mean inbreeding coefficient was the average for each pedigree (Sham, 1998). To compute the inbreeding coefficients, PEDSYS (Pedigree Data Management System, version 2.0; Southwest Foundation for Biomedical Research, San Antonio, TX) was used.

Heritability (h^2) has two definitions. The first is a statistical definition, which defines h^2 as the proportion of phenotypic variance attributable to genetic variance. The second definition is more "common sensical." It defines h^2 as the extent to which genetic individual differences contribute to phenotypic individual differences. Heritability (h^2) and Kullback-Leibler pseudo-R for categorical variables were calculated for variability of the trait as explained by the independent variables. For calculating heritabilities, phenotypes were considered as quantitative discrete traits. Computation was carried out, on related individuals using the variance components-based approach implemented in the software package SOLAR v. 4.0 (Almasy and Blangero, 1998). Heritability analysis was performed by decomposing the phenotypic variance into independent genetic and environmental components, assuming an additive model of gene action and expected kinship coefficients based on the observed intra-familial relationships.

Linkage analysis was carried out to map loci that influence the studied phenotypes, in the Southwest Foundation for Biomedical Research, Texas, USA, during the period 2004-2006. A model free non-parametric component analysis was adopted. The probabilities of identity-by-descent (IBD) allele sharing among pairs of related individuals were computed by the Markov chain Monte Carlo approach implemented in software package Loki (Heath, 1991) using the genotypes at all linked markers jointly in the computations. The software SOLAR was used to perform a multipoint linkage analysis of various phenotypes adjusted for sex and age. Maximum likelihood marker allele frequencies (Boehnke, 1991) were used, and the genetic map was based on the one developed by deCODE genetics.

Table 4.3. Prevalence of obesity, type 2 diabetes and dyslipidemia among individuals of the Oman Family Study.

	Number Tested	Positive	% Prevalence
BMI 30-35 [Over Weight]	1126	146	13.0%
BMI> 35 [Obese]	1126	34	3.0%
Diabetes Mellitus	1190	DM= 33 IGT= 144	5.5% 12.1%
Hypercholestrolemia	1198	442	36.9%
Hypertriglyceridemia	1196	214	17.9%

BMI: Body mass index
IGT: Impaired glucose tolerance

Heritability of Phenotypic Abnormalities

The relative pairs of individuals, used in the quantitative genetic analysis, in the 5 pedigrees were 23,253 pairs (Table 4.4). This large number of pairs is due to the very high degree of inbreeding and complexity of pedigrees. The heritability (h^2) estimates for anthropometric and biochemical parameters (Table 4.5) in a descending order were: Height (0.68); Weight (0.68); BMI (0.68); HDL level (0.63); Leptin (0.55); per cent body fat (0.53); total cholesterol level (0.53); fasting insulin level (0.51); HOMA-insulin resistance index (0.48), TG level (0.43); waist circumference (0.40); 2hr glucose level (0.17); HbA_{IC} (0.10) and FPG (0.07). Very high levels of statistical significance were obtained with even low heritabilities due to the unique structure of these Arab pedigrees.

The heritability (h^2) of anthropometric and biochemical phenotypes showed a wide spread (0.07–0.68). Some phenotypes such as weight, BMI, HDL level and insulin resistance appear to be under considerable genetic influence. Whereas, other phenotypes such as TG, abdominal obesity and FPG levels appear to be largely affected by unmeasured non-genetic factors; probably environmental. In general, our data is in agreement with previous studies, where heritability of determinants of these diseases were estimated in Caucasians (Martin *et al*., 2003; Mills *et al*., 2004), Hispanics (Lin *et al*., 2005), Chinese and Japanese (Austin *et al*., 2004; Wu *et al*., 2002a). Heritability estimates in Omani Arabs seem closer to Hispanics than Caucasians. No significant differences in heritability estimates were observed between Omani Arabs and the above ethnic groups in all phenotypes tested, except in FPG and PG2 where lower estimates were obtained for the Omani Arabs.

Linkage Analysis

Linkage analysis of quantitative trait loci (QTLs) for obesity, T2D and dyslipidemias, identified 6

Table 4.4. The relative pairs of individuals used in calculations of heritabilities (h^2) in the 5 Omani Arab Pedigrees.

Relationship	Size
Self	1851
Parent offspring	2482
Siblings	1278
Grandparent – grandchild	3774
Avuncular	2815
Half-siblings	322
Grand avuncular	2928
Half avuncular	918
1st cousins	2610
1st cousins, 1 rem	932
Half 1st cousins, 1 rem	441
2nd cousins	4363
Other relationships	390
Total Relative Pairs	25104

positive signals with LOD scores >3.0 and 12 positive signals with LOD scores ranging 2-3 (Table 4.6). QTLs for obesity showed linkage at chromosomes 1, 2, 3, 12, 13, 19 and 20. QTLs for T2D showed linkage at chromosomes 3 and 13; while QTLs for dyslipidemia at chromosome 10.

The results have confirmed some previously identified obesity loci in other ethnic groups, such as those for weight and BMI at 1p22-1q21 (Perusse *et al*., 2001; Feitosa *et al*., 2002; Adeyemo *et al*., 2003; Chen *et al*., 2004); weight, per cent body fat, waist circumference and leptin at 2q21-2q31 (Rice *et al*., 2002); and weight, BMI and waist circumference at 3q21-3q26 (Kissebah *et al*., 2000; Wu *et al*., 2002b; Luke *et al*., 2003; Moslehi *et al*., 2003). The two loci for waist circumference at 12p12-12q13 and 13q21-13q34 were also previously described (Chagnon *et al*., 2001; Perusse *et al*., 2001; Deng *et al*., 2002; Norris *et al*., 2005; Dong *et al*., 2005).

The loci for waist circumference at chromosome 19p13 and per cent body fat at 20q13 have also been described before (Lee *et al*., 1999; Engelmann *et al*., 2003; Saar *et al*., 2003; Dong *et al*., 2003).

Loci for determinants for T2D such as fasting insulin and the Insulin Resistance Index at chromosome 3q22-3q29 and fasting blood glucose at 13q32-13q34 have also been previously described (Vionnet *et al*., 2000; Luna, 2005). The locus for LDL cholesterol at chromosome 10q24-q26 seems to be a novel locus as it has not previously been described. These findings validated and proved the robustness of the Oman Family model. Yet, linkage analysis needs to be extended to narrow down the search for the areas in the genome where candidate genes may be located.

In recently concluded genome-wide association studies (DGI, 2007; Fayling *et al*., 2007; Frayling, 2007

Table 4.5. Age and sex adjusted heritability estimates (h^2) of anthopometric and biochemical parameters amongst 1198 individuals of Oman Family Study.

Trait	h2	SE	p-value	Covariate
Height (cm)	0.68	0.06	1.5*10-37	0.61
Weight (kg)	0.68	0.05	2.1*10-48	0.23
BMI (kg/m2)	0.68	0.05	1.03*10-51	0.16
% Body Fat	0.53	0.06	1.0*10-36	0.43
Waist circumference (cm)	0.40	0.06	3.2*10-21	0.31
Cholesterol (mmol/l)	0.53	0.06	5.8*10-34	0.23
LDL (mmol/l)	0.48	0.06	1.5*10-32	0.17
HDL (mmol/l)	0.63	0.06	6.9*10-44	0.20
TG (mmol/l)	0.43	0.06	5.3*10-25	0.22
FPG (mmol/l)	0.07	0.04	0.015	0.10
PG2 (mmol/l)	0.17	0.05	0.0000005	0.18
Insulin 0 (mIU/L)	0.51	0.05	1.3*10-43	0.02
HOMA - IR	0.48	0.06	5.8*10-37	0.03
Hb A1C (%)	0.10	0.03	1.9*10-5	0.03
Leptin (ng/ml)	0.55	0.06	4.1*10-40	0.35
Growth Hormone (mIU/L)	0.24	0.05	3.5*10-11	0.37

FPG: Fasting plasma glucose; PG2: Plasma glucose 2 hours after oral glucose; Insulin 0: Fasting insulin level; HOMA: Homeostasis Model Assessment of Insulin Resistance.

a and b; Sladek *et al*., 2007; WTCCC, 2007; Zeggini *et al*., 2008) several loci and susceptibility genes for T2D and obesity phenotypes have been identified. None of these loci coincided with the loci we have described, except the obesity locus in chromosome 1p13-p11 where NOTCH2 has been identified (Zeggini *et al*., 2008). Since a great deal of the genetic influence on T2D and obesity still remains uncovered, non-congruence of results obtained by linkage analysis and genome-wide association studies could be explained. It is possible that each method is describing a different set of loci or a different level of risk.

Summary

Our aim was to establish a suitable model for the study of the genetics of complex diseases, such as diabetes, obesity, dyslipidemia and hypertension, with the necessary statistical power to reveal possible candidate genes. Our Omani model consists of five multigenerational highly inbred pedigrees, descending from a small number of founders just a few generations ago with environmental homogeneity, restricted geographical distribution, detailed records and well-ascertained and validated pedigrees. Stringent criteria were adopted for defining the phenotypes of these diseases. The SOLAR genetic software package was used to draw the pedigree structure, calculate heritability and run multipoint linkage analysis. Linkage analysis yielded several loci that may be implicated in the pathogenesis of these diseases. However, the search needs to be extended to narrow down and the areas in the genome where candidate genes may be located. Fine SNP mapping and high throughput sequencing is our next goal to determine the exact location of these possible candidate genes and putative mutations associated with the disease or phenotypes. Our Omani Arab model is also very well suited for replication of findings made by genome-wide association studies.

Table 4.6. Linkage analysis of quantitative trait loci for obesity, diabetes and dyslipidemia among individuals of Oman Family Study.

Phenotype	Chromosome	Markers	Distance (cM)	LOD Score
Weight (Kg)	1p22-1q21	D1S1596-D1S3723	90-130	2.7882
BMI (Kg/m2)		D1S198-D1S3723	100-140	2.9165
Leptin (ng/ml)	2q21-2q31	D2S410-D2S1391	130-190	3.3287
Weight (Kg)		D2S410-D2S1353	130-170	2.3524
Body Fat (%)		D2S410-D2S1353	130-180	2.5188
Waist Circumference (cm)		D2S410-D2S1353	130-170	3.1632
Weight (Kg)	3q21-3q26	D3S4523-D3S1763	130-180	4.0289
BMI (Kg/m2)		D3S4523-D3S1763	130-180	3.3897
Waist Circumference (cm)		D3S4523-D3S1763	140-180	2.3018
Insulin	3q22-3q29	D3S3636-D3S3715	140-190	2.1724
Insulin resistance		D3S2326-D3S1617	140-190	2.2651
LDLCholesterol	10q24-10q26	D10S2470-D10S1230	90-140	3.6573
Cholesterol		D10S12470-D10S1230	100-140	2.3601
Waist Circumference (cm)	12p12-12q13	D12S1042-D12S372	20-50	2.3474
Waist Circumference (cm)	13q21-13q34	D13S1281-D13S1265	60-120	2.5493
Glucose (mmol)	13q32-3q34	D13S796-D13S113Z	100-122	2.2296
Waist Circumference (cm)	19p13-	D19S589-D19S559	60-80	2.3380
Body Fat (%)	20q13-Telemore	D20S1143-D20S269	60-80	3.6909

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