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A Genome-Wide Search for Type 2 Diabetes Susceptibility Genes in an Extended Arab Family

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Summary

Twenty percent of people aged 20 to 79 have type 2 diabetes (T2D) in the United Arab Emirates (UAE). Genome-wide association studies (GWAS) to identify genes for T2D have not been reported for Arab countries. We performed a discovery GWAS in an extended UAE family (N = 178; 66 diabetic; 112 healthy) genotyped on the Illumina Human 660 Quad Beadchip, with independent replication of top hits in 116 cases and 199 controls. Power to achieve genome-wide significance (commonly $P = 5 \times 10^{-8}$) was therefore limited. Nevertheless, transmission disequilibrium testing in FBAT identified top hits at Chromosome 4p12-p13 (*KCTD8*: rs4407541, $P = 9.70 \times 10^{-6}$; *GABRB1*: rs10517178/rs1372491, $P = 4.19 \times 10^{-6}$) and 14q13 (*PRKD1*: rs10144903, 3.92×10^{-6}), supported by analysis using a linear mixed model approximation in GenABEL (4p12-p13 *GABRG1/GABRA2*: rs7662743, $P_{adj\text{-}agesex} = 2.06 \times 10^{-5}$; *KCTD8*: rs4407541, $P_{adj\text{-}agesex} = 1.42 \times 10^{-4}$; *GABRB1*: rs10517178/rs1372491, $P_{adj\text{-}agesex} = 0.027$; 14q13 *PRKD1*: rs10144903, $P_{adj\text{-}agesex} = 6.95 \times 10^{-5}$). SNPs across *GABRG1/GABRA2* did not replicate, whereas more proximal SNPs rs7679715 ($P_{adj\text{-}agesex} = 0.030$) and rs2055942 ($P_{adj\text{-}agesex} = 0.022$) at *COX7B2/GABRA4* did, in addition to a trend distally at *KCTD8* (rs4695718: $P_{adj\text{-}agesex} = 0.096$). Modelling of discovery and replication data support independent signals at *GABRA4* (rs2055942: $P_{adj\text{-}agesex\text{-}combined} = 3 \times 10^{-4}$) and at *KCTD8* (rs4695718: $P_{adj\text{-}agesex\text{-}combined} = 2 \times 10^{-4}$). Replication was observed for *PRKD1* rs1953722 (proxy for rs10144903; $P_{adj\text{-}agesex} = 0.031$; $P_{adj\text{-}agesex\text{-}combined} = 2 \times 10^{-4}$). These genes may provide important functional leads in understanding disease pathogenesis in this population.

Keywords: Type 2 diabetes, family-based GWAS, association analysis, UAE

Introduction

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, insulin action or both (Leslie, 1993; Stumvoll et al., 2005). Diabetes is one of the most prevalent chronic diseases. It results in significant morbidity and contributes to the death of millions of people worldwide. Currently, over 170 million people globally suffer from Type 2 Diabetes (T2D; Alberti & Zimmet, 2006; Alberti et al., 2006; Keller, 2006; Unwin & Alberti, 2006; Zimmet & Alberti, 2006; Borch-Johnsen, 2007; Danaei et al., 2011; Farzadfar et al., 2011; Finucane et al., 2011). Most of these patients are middle aged. However, earlier age-of-onset is becoming more common as a result of changes in lifestyle and behavioural factors interacting with genetic predispositions (Keller, 2006). Ethnicity is

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also a risk modifier as people of certain ethnic backgrounds are more likely to develop diabetes than others. For example, it has been reported that African Americans (Cheng et al., 2012), Hispanic Americans (Lorenzo et al., 2012), Pima Indians (Lillioja & Bogardus, 1988a,b; Lillioja et al., 1988), some Asian Americans (Hsu et al., 2012; King et al., 2012; Tang et al., 2012) and Pacific Islanders (Hsu et al., 2012; King et al., 2012) and Sri-Lankan Moors (Katulanda et al., 2012) are at particularly high risk for T2D.

Genetic factors are known to play a role in T2D and an understanding of the genetic basis of T2D could lead to the development of new treatments (Frayling, 2007a,b; Frayling & Mccarthy, 2007; Frayling, 2008). With the increased prevalence of diabetes worldwide, the need for intensive research is of high priority. Sequencing of the human genome and development of a set of powerful tools has made it possible to find the genetic contributions to common complex diseases (Donnelly, 2011). Genome-wide association studies (GWAS) have been used to search for genetic risk factors for complex disease (Hindorff, Junkins et al., 2009; Hindorff, Sethupathy et al., 2009). Used in combination with the scaffold data of the human genome courtesy of the HUGO Project (2003) and the International HapMap Project (Thorisson et al., 2005), it is now possible to analyse the whole genome to identify genetic variants that contribute to common disease in a fast and efficient manner.

Large-scale GWAS and meta-analyses have been used to identify and replicate genes contributing to T2D and related traits in Caucasian populations (recently reviewed in (Kwak & Park, 2013). There are more than 30 T2D GWAS listed in the Catalogue of Published GWAS Web site (http://www.genome.gov/gwastudies, accessed on 1st April, 2013) and more than 64 genetic variants are identified as associated with T2DM at a genome-wide significance level of $P < 5.0 \times 10^{-8}$ (Saxena et al., 2007; Scott et al., 2007; WTCCC, 2007; Zeggini et al., 2007, 2008; Voight et al., 2010; Morris et al., 2012). Recent extension of this technology has begun to focus on identification of genetic risk factors for T2D and related traits in other ethnic groups, including African Americans (Murea et al., 2011; Cooke et al., 2012; Hester et al., 2012; Ng et al., 2012; Palmer & Freedman, 2012; Palmer et al., 2012), Amish (Rampersaud et al., 2007), Asian (Yasuda et al., 2008; Takeuchi et al., 2009; Kooner et al., 2011; Cho, Chen et al., 2012; Cho, Lee et al., 2012; Dastani et al., 2012), Indian (Chandak et al., 2007; Kooner et al., 2011), Mexicans (Hayes et al., 2007; Below et al., 2011; Parra et al., 2011) and Pima Indians (Hanson et al., 2007). Variants in some genes have been observed to be common and to show consistent directions of effect across multiple populations (Helgason et al., 2007; Haiman et al., 2012; Li et al., 2012). Other genes, or specific variants in them, may be unique to specific populations (Yasuda et al., 2008; Takeuchi et al., 2009; Been et al., 2011). This may reflect underlying phenotypic heterogeneity, racial/ethnic differences in susceptibility allele frequencies or differences in sample size, study design and analytical methods. Of particular interest has been the recent focus on the possible contribution of rare variants to susceptibility of common diseases such as T2D (Bonnefond et al., 2012). In terms of study design, large-scale deep resequencing projects have revealed an excess of rare variants that, whilst rare in the general population, may provide good phenotypic predictive ability within families (Coventry et al., 2010). Indeed, these studies, together with theoretical analysis of distribution of rare causal variants in genealogies (Dickson et al., 2010), suggest that family units in which diseased individuals have genomic regions of highly shared ancestry may provide the best scale for inference about the genetics of complex disease. Understanding the similarities in ethnicity-specific associations as well as differences in the genetic makeup of different ethnic groups, particularly for a disease that occurs globally, is important for unravelling the genetic architecture.

Unlike most major population groups, a lack of research on the Middle East populations has created a serious gap in understanding the trend of common diseases such as diabetes within these populations. Compounding the problem is the fact that T2D has become a major public health problem in the United Arab Emirates (UAE) as the level of affluence has increased. It has been estimated that 25% of UAE citizens suffer from T2D (Malik et al., 2005) and the prevalence of the disease is increasing (Wild et al., 2004).

Here, we report on a GWAS undertaken to identify the genes that may influence susceptibility to T2D in an extended Arab family originating from the UAE. The project focussed specifically on an indigenous Arab population where a high rate of consanguineous marriage, high birth rate and life style factors make them ideal for the study of complex, polygenic, multifactorial disorders such as T2D. Our results highlight specific genes that may carry risk alleles for T2D in this population and which we were able to replicate in a second case-control sample from an Arab population in the UAE.

Materials and Methods

Subjects

For the discovery GWAS, a total of 319 individuals belonging to one extended family of Arab origin were identified during their routine visit to clinics in the UAE. Multigeneration family relationships were compiled for these individuals, allowing a five-generation extended family pedigree to be constructed containing 41 nuclear families. Prevalence of T2D in this

Table 1 Characteristics of the family-based discovery and case-control replication samples. The discovery sample comprised a single five-generation pedigree (319 members) of Arab descent. Characteristics of the 178 sampled individuals are provided here. Individuals sampled for the case-control replication sample were also of Arab descent.

	Discovery sample			Replication sample		
	Male	Female	Total	Male	Female	Total
N° T2D cases	27	39	66	63	53	116
Age T2D cases	50.70 ± 14.76	48.54 ± 14.75	49.42 ± 14.68	48.16 ± 11.93	50.25 ± 13.50	49.11 ± 12.66
Mean ± SD range	20–72	17–74	17–74	22–72	14–75	14–75
N° unaffected	59	53	112	157	42	199
Age unaffected	28.86 ± 16.67	31.79 ± 19.58	30.25 ± 18.08	30.99 ± 12.88	35.5 ± 15.36	31.94 ± 13.53
Mean ± SD range	4–73	6–88	4–88	16–82	16–81	16–82
N° nuclear families	N/A	N/A	41	N/A	N/A	N/A
Total N in pedigree	86	92	178	N/A	N/A	N/A

N/A, not applicable.

pedigree was 37%. Heritability of T2D as determined using SOLAR (Almasy & Blangero, 1998) was 18%. A total of 178 individuals from this pedigree agreed to participate in this study (Table 1) including 66 T2D patients and 112 healthy unaffected individuals. Clinical assessment, questionnaire completion and sampling of all family members were conducted at the clinic. An individual was classified as T2D if the subject was: (1) diagnosed with T2D by a qualified physician; (2) on a prescribed drug treatment regimen for T2D; and (3) returned biochemical test results of a fasting plasma glucose level of at least 126mg/dl (=7 mmol/l in SI units) as based on the criteria laid by the World Health Organisation consultation group report (Alberti & Zimmet, 1998). Height and weight were recorded to facilitate measurement of Body Mass Index (BMI) according to the standard formula BMI = weight (kilogram)/height (metre^2). Each individual (or the parent or guardian of individuals less than 18 years of age) provided signed, informed consent according to criteria approved by the ethics committee of the United Arab Emirates Ministry of Health. The work was also approved by the University of Western Australia's Human Research Ethics Committee with reference number RA/4/1/443.

For the replication study, 315 unrelated individuals of Arab origin (Table 1; 220 males, 95 females; 116 diabetic, 199 healthy) agreed to participate, each of whom gave signed, informed consent according to criteria approved by the ethics committee of the United Arab Emirates Ministry of Health. The replication study was performed with approval from the Ethics Committee of the UAE Ministry of Health. Diagnosis of diabetes was as before.

DNA Extraction

After blood was drawn into EDTA tubes, genomic DNA was extracted using a DNA Isolation Kit for Mammalian Blood Kit (Roche Applied Science, Indianapolis, IN, USA) according to the manufacturer's recommendations. Briefly, 300 μl of whole blood from each sample was mixed with 200 μl of lysis buffer (50 mM Tris pH 8.0, 100 mM EDTA, 100 mM NaCl, 1% SDS) and 40 μl of Proteinase K, followed by addition of 100 μl of isoproponal and 500 μl of Inhibitor Removal Buffer (5M guanidine-HCl, 20 mM Tris-HCl pH 6.6). The DNA was washed with a buffer (20 mM NaCl; 2 mM Tris-HCl; pH 7.5), centrifuged twice at 2000 rpm, washed using cold 70% ethanol and centrifuged at 3000 rpm. The supernatant was discarded and the pellet containing purified genomic DNA was diluted in TE buffer (1 mM EDTA; 10 mM Tris-HCl, pH 7.5) to a concentration of approximately 50 ng/μl.

Genotyping

Genotyping using the Infinium Human 660 Quad Chip I-Scan (Illumina Inc., San Diego, CA, USA), which contained 640,663 autosomal SNPs, was performed according to the manufacturer's instructions. Whole-genome amplification was performed using 200 ng of genomic DNA at 37°C for 20 to 24 h using reagents provided by Illumina Inc. Products were fragmented, precipitated and resuspended in a proprietary hybridisation buffer (Illumina Inc.). The resuspended samples were denatured at 95°C for 20 min and loaded on Illumina Bead Chips. The chips were placed in a hybridisation chamber for 16 to 20 h at 48°C. After hybridisation, nonhybridised DNA was washed away. An allele-specific single-base extension of the oligonucleotides on the BeadChip was performed in a 48-position Slide Chamber Rack (Illumina Inc.), using labelled deoxynucleotides and the captured DNA as a template. After staining of the extended DNA, BeadChips were washed and scanned with I-Scan (Illumina Inc.) and raw

data were generated by BeadStudio 3.0 software (Illumina Inc.).

For the replication study, SNP genotyping was undertaken using the KASPar technology by KBiosciences (Hoddesdon, UK: http://www.kbioscience.co.uk).

Quality Control (QC)

Genetic integrity of the pedigree was checked using the PedCheck software package (O'Connell & Weeks, 1998). Data cleaning was performed using the PLINK software (Purcell et al., 2007). The average call rate was 98.99% for all the subjects. SNPs were excluded from the analysis based on the following criteria: (1) minor allele frequency <0.05, (2) missingness per SNP >5%, (3) significant ($P < 1 \times 10^{-6}$) deviation from the Hardy-Weinberg equilibrium in pedigree founders. Approximately, 70% of SNPs passed QC and were used in the association analysis. Checks were also made for individuals with >5% of Mendelian error rate within the family or with >10% missingness across all SNPs. No individuals were excluded.

Data Analysis

We analysed the association between individual SNPs and disease trait (T2D) using the family-based association test (FBAT; Laird et al., 2000), as well as the GenABEL (Aulchenko et al., 2007; Chen & Abecasis, 2007) and FaST-LMM (Lippert et al., 2011) for analysis of genome-wide association studies. FBAT was used as a traditional transmission disequilibrium test to look for a bias in transmission of alleles from heterozygous parents to affected offspring, under the null hypothesis of no association and no linkage and using the *-o option*, which changes the offset to make optimal use of unaffected and affected members of the families. The FAmily-based Score Test for Association (FASTA; Chen & Abecasis, 2007) in GenABEL used a linear mixed model approximation to model the trait outcome, with whole genome data used to estimate kinship (in order to account for relatedness) and take account of population substructure, when comparing all cases with all unaffected members of the pedigree. It also permitted adjustments to be made for age and sex, or for age, sex and BMI. FaST-LMM scales linearly with cohort size in both run time and memory use and was used to compare alternative models (additive, dominant, recessive) of inheritance. GenABEL (FASTA) and FaST-LMM use a normal distribution function with an identity link, analysing the 0/1 variable modelling disease status (control/case) as if it were a normally distributed quantitative variable, which has been shown (Kang et al., 2010) to produce a valid test with respect to testing the null hypothesis.

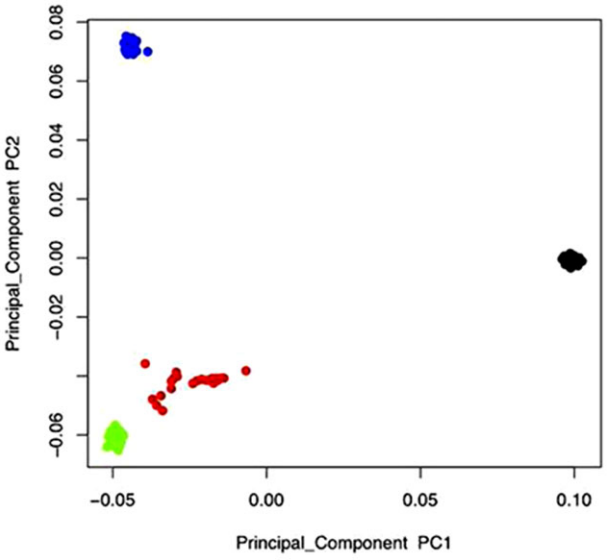

Figure 1 Principal components analysis of discovery GWAS genotype data. Scatter plot of principal components 1 and 2 for the UAE Arab study (red) compared with three HapMap populations representing Caucasian (CEU; green), Asian (CHB/JPT; blue) and African (YRI; black) ethnicities. The Arab population is closer to Caucasian than to Asian or African ethnicities.

Manhattan plots were generated using the mhtplot() function of 'gap', a genetic analysis package (Zhao and Tan, 2006) for use in R http://cran.r-project.org/web/packages/gap/. Quantile-quantile (Q-Q) plots were generated and inflation factors (often denoted λ) calculated in R version 2.15.0 (URL http://www.R-project.org/) by dividing the median of the observed distribution of the χ^2 statistic by the median of the theoretical χ^2 distribution. Regional plots of association were created using LocusZoom (Pruim et al., 2010) in which $-\log_{10}$(P-values) were graphed against their chromosomal location. Pairwise LD patterns between all regional SNPs and the top SNP were calculated specifically for this UAE study data using founders and unrelated members of the large pedigree. Multidimensional scaling, a form of principal components analysis (PCA), was undertaken in PLINK comparing founders of this Arab family with CEU, JPT+CHB and YRI HapMap populations. Linear mixed modelling was undertaken in R to test for independent effects in the discovery data by including pairs of SNPs simultaneously in a regression model and testing for an independent effect with a score test (results presented as P_{SCORE}).

For the replication study, association analysis under an additive model was undertaken using logistic regression analysis in Stata (version 8.0; http://www.stata.com/). Logistic regression modelling was undertaken in Stata to

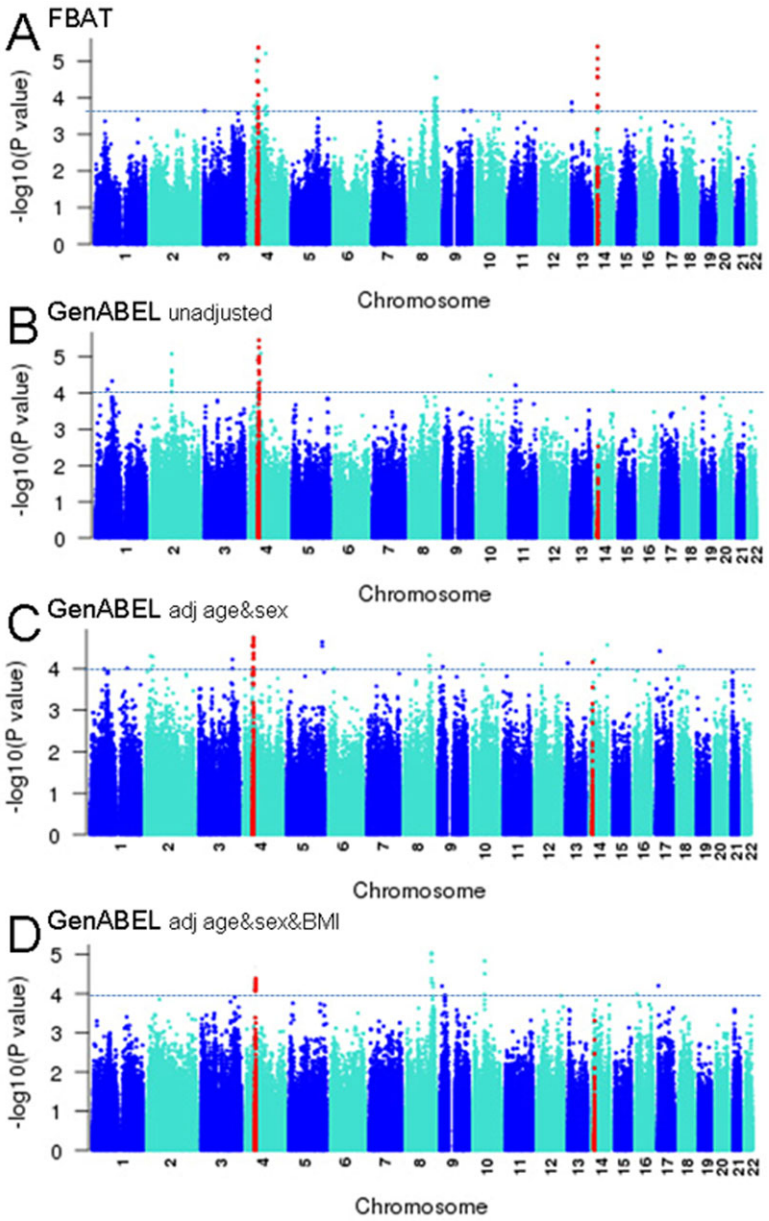

Figure 2 Manhattan plots for the discovery GWAS carried out in the single extended pedigree of 178 individuals of Arab descent. Plots are shown for association analyses using (A) FBAT or (B–D) GenABEL. GenABEL plots include analyses for (B) unadjusted, (C) adjusted for age and sex and (D) adjusted for age, sex and BMI data sets. Plots show $-\log_{10}$(P-values) of association on the *y*-axis ordered by chromosomal location on the *x*-axis. Red dots highlight the regions of the top hits initially identified at $P < 10^{-4}$ on Chromosomes 4 and 14 in the FBAT analysis. The apparent region of association at Chromosome 8 does not colocalise across analyses (see Table S1).

test for independent effects in the replication data by including pairs of SNPs simultaneously in a regression model and testing for an independent effect using a likelihood ratio test (results presented as P_{LRT}). Combined P-values across discovery and replication data sets were obtained using Fisher's Test calculated using MetaP (Whitlock, 2005; available at http://humangenome.duke.edu/software).

Results

Discovery GWAS

The study sample for the discovery GWAS (Table 1) comprised 178 individuals, 66 diabetes patients (39 females; 27 males) and 112 healthy individuals, from one extended family (319 members) of Arab descent. Male and female cases were well-matched for age, as were male and female unaffected members of the pedigree. However, the mean age of cases exceeded that of unaffected members of the pedigrees by ~20 years of age. This could reduce power since some controls could go on to get the disease. Therefore, where possible, results are presented for tests carried out with/without adjustment for age and sex. Given the strong association between T2D and BMI, we also adjusted for this covariate in selected analyses as indicated.

Following QC checks (see methods), Illumina 660W Quad Beadchip genome-wide data were available for 443,502 autosomal SNPs in the 178 individuals. Although from a single extended family, PCA comparing founders of this Arab family with CEU, JPT + CHB and YRI HapMap populations, provided evidence for some level of population substructure (Fig. 1). Scatter plots of the main axes of variation, PC1 and PC2, show that the Arab population is more closely related to populations of Caucasian descent than to Asian or African descent. However, our Arab data are less well-clustered than the data from the three HapMap populations, suggesting that there may be some population stratification within this Arab cohort. This was controlled for in the genetic analyses by using methods that are robust to population stratification: the traditional transmission disequilibrium test as implemented in FBAT, and the linear mixed model approximation implemented in GenABEL and FaST-LMM. The Q-Q plots (Fig. S1) show that there was little evidence of inflation of association test scores for FBAT (inflation factor $\lambda_{FBAT} = 1.041$; Fig. S1A) or GenABEL ($\lambda_{GenABEL:unadjusted} = 1.023$, Fig. S1B; $\lambda_{GenABEL:adj\text{-}agesex} = 1.073$, Fig. S1C; $\lambda_{GenABEL:adj\text{-}agesexbmi} = 1.070$; Fig. S1D) analyses. Inflation factors for FaST-LMM analyses were $\lambda_{FBAT} = 1.06$ for the additive model, $\lambda_{FBAT} = 1.24$ for the recessive model and $\lambda_{FBAT} = 1.12$ for the dominant model (Q-Q plots not shown). Manhattan plots for our genome-wide analyses for T2D susceptibility genes testing the additive effects of each SNP are presented in Figure 2 (FBAT and GenABEL) and Figure S2 (FaST-LMM). Analysis under a recessive model using FaST-LMM (see Manhattan plots comparing models, Fig. S2) did not provide evidence for additional genes not observed using FBAT or the additive model used in GenABEL. In this one extended family, no single variant achieved genome-wide significance, commonly accepted as $P < 5 \times 10^{-8}$ (Dudbridge & Gusnanto, 2008). Hits at nominal $P < 0.05$ in genes previously identified at $P < 5 \times 10^{-8}$ in other GWAS, as reported in the NCBI Catalogue of GWAS as accessed on April 1, 2013 and recently reviewed reference (Kwak & Park, 2013), are presented in Table S1. Whilst there was consistency between additive models analysed using GenABEL and FaST-LMM, there were few hits that provided evidence of association at $P < 10^{-3}$ after adjustment for age and sex (*VPS26A* $P_{GenABEL\_adj\text{-}agesex} = 8.56 \times 10^{-4}$; *DUSP8* $P_{GenABEL\text{-}adj\text{-}agesex} = 9.95 \times 10^{-4}$), or age, sex and BMI (*TLE4* $P_{GenABEL\_adj\text{-}agesexbmi} = 4.26 \times 10^{-4}$). *KLHDC5* ($P_{GenABEL\_unadj} = 9.07 \times 10^{-4}$; $P_{FaST\text{-}LMM\_additive} = 5.98 \times 10^{-4}$; $P_{FaST\text{-}LMM\_recessive} = 1.23 \times 10^{-4}$) provided evidence of association at $P < 10^{-3}$ under additive and recessive (with respect to the common allele) models, but not after adjustment for age, sex and BMI. Although we cannot be certain that associations observed in this UAE family were not due to type 1 error, we highlight here the top hits common to both FBAT and GenABEL analyses, which are of interest as novel biological candidates and for which replication data were obtained for our study population.

Analysis in FBAT showed two main top-scoring ($P < 1 \times 10^{-4}$) regions (Table 2 and Table S2A) with multiple SNPs associated with T2D on Chromosome 4 in the region of *KCTD8* (top SNP rs4407541; $P = 9.70 \times 10^{-6}$) and *GABRB1* (top SNP rs10517178/rs1372491; $P = 4.19 \times 10^{-6}$) genes, and on Chromosome 14 at *PRKD1* (top SNP rs10144903; $P = 3.92 \times 10^{-6}$). FBAT analysis relies on the presence of heterozygous parents to score numbers of transmissions of alternative alleles to affected offspring in trios from nuclear families. Only 13–16 out of 41 nuclear families (depending on the SNP) contributed to these associations (Table S2A). In order to improve power, we carried out analyses using a linear mixed model approximation in GenABEL, which compared all 66 T2D cases with all unaffected individuals in the pedigree, providing a total of 170–178 individuals contributing to association testing (Table 2; Table S2B–D). This analysis also facilitated adjustment for age and sex, or for age, sex and BMI. Support at $P < 10^{-4}$ was observed for the association in the region of *GABRG1* and *GABRA2* genes on Chromosome 4 (top SNP rs7662743: $P_{unadjusted} = 3.48 \times 10^{-6}$; $P_{adj\text{-}agesex} = 2.06 \times 10^{-5}$; $P_{adj\text{-}agesexbmi} = 4.56 \times 10^{-5}$). Support for associations distally at *KCTD8* (top SNP rs4407541: $P_{unadjusted} = 2.52 \times 10^{-3}$; $P_{adj\text{-}agesex} = 1.42 \times 10^{-4}$; $P_{adj\text{-}agesexbmi} = 1.56 \times 10^{-3}$) and proximally at *GABRB1* (rs1372491: $P_{unadjusted} = 0.051$; $P_{adj\text{-}agesex} = 0.027$; $P_{adj\text{-}agesexbmi} = 0.093$) was weaker. Similarly, association at *PRKD1* was only observed at $P < 10^{-4}$ after adjusting for age and sex (top SNP rs10144903: $P_{unadjusted} = 2.98 \times 10^{-3}$; $P_{adj\text{-}agesex} = 6.95 \times 10^{-5}$; $P_{adj\text{-}agesexbmi} = 4.90 \times 10^{-4}$). Associations were generally robust to adjustment for BMI, indicating that they are with T2D and not due to genes for obesity that are affecting T2D due to correlation between

Table 2 Comparison of association P-values for SNPs in the Chromosome 4p12-p13 and 14q12 region for FBAT and GenABEL analyses in the discovery families, and logistic regression analysis of the case-control replication sample. Combined P-values are for GenABEL discovery and the replication data.

			Discovery				Replication		$P_{combined}$	
		Bp position	FBAT	GenABEL						
Chr	Gene/SNP	(NCBI Build 36)	P_{FBAT}	$P_{unadjusted}$	$P_{adjagesex}$	$P_{adjagesexbmi}$	$P_{unadjusted}$	$P_{adjagesex}$	unadjusted	adjagesex
4	KCTD8_rs7675224	44049621	3.50×10^{-5}	3.02×10^{-3}	9.29×10^{-5}	4.11×10^{-4}	0.077	0.131	2.20×10^{-3}	1.20×10^{-3}
4	KCTD8_rs4407541	44076716	9.70×10^{-6}	2.52×10^{-3}	1.42×10^{-4}	1.56×10^{-3}	0.165	0.221	3.70×10^{-3}	4.00×10^{-4}
4	**KCTD8_rs4695718**	44107694	$\mathbf{3.50 \times 10^{-5}}$	$\mathbf{3.14 \times 10^{-3}}$	$\mathbf{1.31 \times 10^{-4}}$	$\mathbf{8.15 \times 10^{-4}}$	**0.029**	**0.096**	$\mathbf{9.00 \times 10^{-4}}$	$\mathbf{2.00 \times 10^{-4}}$
4	GABRG1_rs7692404	45570356	8.30×10^{-5}	7.38×10^{-3}	3.03×10^{-3}	7.50×10^{-3}	0.447	0.114	0.022	3.10×10^{-3}
4	GABRG1_rs1353642	45790488	2.11×10^{-3}	5.48×10^{-6}	1.75×10^{-5}	5.11×10^{-5}	0.936	0.285	6.76×10^{-5}	6.59×10^{-5}
4	GABRG1/GABRA2_rs7662743	45871585	2.34×10^{-3}	3.46×10^{-6}	2.06×10^{-5}	4.65×10^{-5}	ND	ND	-	-
4	GABRA2_rs279856	46012680	1.82×10^{-4}	1.20×10^{-4}	5.69×10^{-5}	1.25×10^{-3}	0.582	0.656	7.00×10^{-4}	4.00×10^{-4}
4	**COX7B2_rs7679715**	**46582873**	**0.010**	$\mathbf{3.00 \times 10^{-5}}$	$\mathbf{4.19 \times 10^{-5}}$	$\mathbf{4.09 \times 10^{-5}}$	$\mathbf{6.80 \times 10^{-3}}$	**0.030**	$\mathbf{3.34 \times 10^{-6}}$	$\mathbf{1.83 \times 10^{-5}}$
4	**GABRA4_rs2055942**	**46662807**	$\mathbf{5.96 \times 10^{-3}}$	$\mathbf{9.35 \times 10^{-5}}$	$\mathbf{1.11 \times 10^{-3}}$	$\mathbf{2.19 \times 10^{-3}}$	$\mathbf{8.00 \times 10^{-4}}$	**0.022**	$\mathbf{1.30 \times 10^{-6}}$	$\mathbf{3.00 \times 10^{-4}}$
4	GABRB1_rs10517178	46797750	4.19×10^{-6}	0.035	0.020	0.071	ND	ND	-	-
4	GABRB1_rs1372491	46804117	4.19×10^{-6}	0.051	0.027	0.093	0.812	0.914	0.173	0.116
14	PRKD1_rs1953722	29300389	8.00×10^{-5}	0.032	1.02×10^{-3}	3.50×10^{-3}	0.451	0.031	0.076	4.00×10^{-4}
14	PRKD1_rs10144903	29342060	3.92×10^{-6}	2.98×10^{-3}	6.95×10^{-5}	4.90×10^{-4}	ND	ND	-	-

Bold indicates SNPs that replicated across discovery and replication samples.

these two phenotypes. No other common regions of association at $P < 10^{-4}$ were observed across all analyses (Table S2A–D; apparent common associations at Chromosome 8 did not colocalise across analyses) and no other strong functional candidate genes were observed.

Detailed Analysis of the Chromosome 4 Association

Figure 3 (see also Fig. S3) provides regional plots comparing FBAT and GenABEL results for the discovery GWAS analysis across the region displaying the top hits at Chromosome 4p12-p13. As indicated above, there was stronger support for *KCTD8* in the FBAT analysis (Fig. 3A), while the GenABEL analyses (Fig. 3B; Fig. S3) showed a peak of association at rs7662743 in the intergenic region between *GABRG1* and *GABRA2*. After adjusting for rs7662743 in the GenABEL analysis (Fig. 3C), no signals remained at $P < 10^{-3}$, with only a weak signal at SNP rs12500815 ($P_{unadjusted} = 0.008$) in the intergenic region between *KCTD8* and *YIPF7*. Results of likelihood ratio tests (Table S3) suggest that the major genetic contribution across this region of Chromosome 4p12-p13 lies in the region of *GABRG1/GABRA2*, although a second effect at *KCTD8* is not discounted.

Replication of the Chromosome 4p12-p13 Association

To replicate, and to try to define, the association at Chromosome 4p12-p13, we genotyped a number of top SNPs across the region in a replication case-control sample of 116 cases and 199 controls (Table 1). As for the discovery sample, male and female cases were well age-matched to each other and to the discovery sample, while controls were ~20 years younger. Results are provided (Table 2) with and without adjustment for age and sex. Interestingly, SNPs rs7692404, rs1353642 (which acts as a proxy for rs7662743, $r^2 = 0.88$) and rs279856 in the *GABRG1/GABRA2* gene region did not replicate, whereas the more proximal SNPs rs7679715 ($P_{unadjusted} = 6.80 \times 10^{-3}$, $P_{adj\text{-}agesex} = 0.03$; $P_{unadj\text{-}combined} = 3.34 \times 10^{-6}$, $P_{adj\text{-}agesex\text{-}combined} = 1.83 \times 10^{-5}$) and rs2055942 ($P_{unadjusted} = 8.00 \times 10^{-4}$, $P_{adj\text{-}agesex} = 0.022$; $P_{unadj\text{-}combined} = 1.30 \times 10^{-6}$, $P_{adj\text{-}agesex\text{-}combined} = 3.00 \times 10^{-4}$) at *COX7B2/GABRA4* did. The latter two SNPs are in strong LD with each other ($D' = 0.96$; $r^2 = 0.76$) in the replication controls (data not shown). Results of likelihood ratio tests (Table S4) were again consistent with a second signal at *KCTD8* ($P_{adj\text{-}agesex\text{-}combined} = 2 \times 10^{-4}$ at rs4695718) that contributes to T2D in this population.

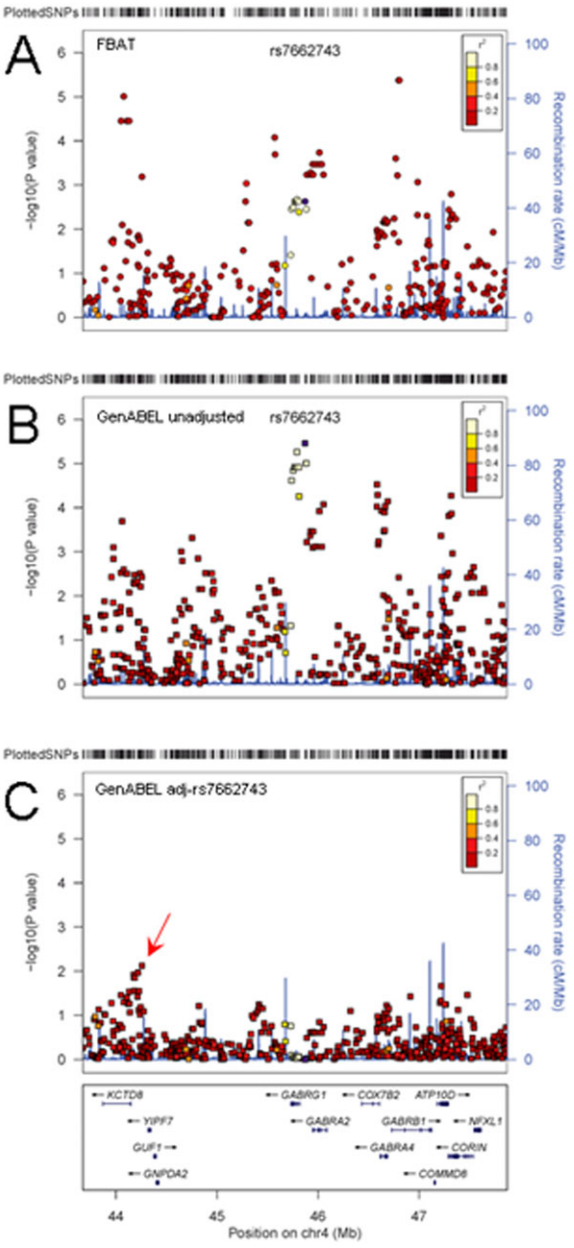

Figure 3 Regional plots for the Chromosome 4p12-p13 region. Locuszoom plots comparing $-\log_{10}$(P-values; $y1$-axis) across the region from 43.67 to 47.87 Mb (NCBI Build 36) on Chromosome 4p12-p13-encoding genes for *KCTD8* and the GABA-A receptors for (A) the FBAT analysis, (B) GenABEL unadjusted analysis, (C) the GenABEL unadjusted analysis after conditioning on the top SNP rs7662743. The key colour codes the degree of LD between rs7662743 (in purple) and all other SNPs on the plot. The blue line depicts local recombination rates ($y2$-axis). The arrow indicates SNP rs12500815. Regional plots for the GenABEL analysis adjusted for age and sex, and for age, sex and BMI, appear as Figure S2.

Replication of the Chromosome 14q13 Association

To replicate the association observed at PRKD1 (Fig. S4), we genotyped SNP rs1953722 (as a proxy for the top SNP rs10144903, which failed at assay design at KBiosciences) in the replication cohort (Table 2). Evidence for replication was observed after adjustment for age and sex ($P_{adj\text{-}agesex} = 0.031$), with $P_{adj\text{-}agesex\text{-}combined} = 4 \times 10^{-4}$ for age- and sex-adjusted analyses across discovery and replication cohorts.

Discussion

Results of the discovery GWAS and replication undertaken here provide the first hypothesis-free insights into genetic risk factors for T2D in an Arab population. Only modest support was obtained for T2D genes previously at genome-wide significance in other studies (see Table S1), including *VPS26A*, *DUSP8* and *KLHDC4* for which functional roles in relation to T2D have not been determined (Kwak & Park, 2013). No replication was observed at rs7903146, a variant at *TCF7L2* that has been strongly associated with T2D risk in most populations (Zeggini et al., 2008), including a Palestinian population (Ereqat et al., 2010). Other studies of rs7903146 in Arab populations of Saudi and Emirati origin also showed weak or no association with T2D (Alsmadi et al., 2008; Saadi et al., 2008). Whilst the power of our study may have limited our ability to replicate top hits found in conventional population-based case-control GWAS for T2D, there is increasing support (Coventry et al., 2010; Dickson et al., 2010) for the possibility that functional variants that are rare in the general population may be enriched through highly shared ancestry, identity-by-descent and linkage in the kind of extended pedigree that we have used in our discovery GWAS. Accordingly, our findings here, while requiring further definitive replication, highlight interesting novel association signals across the region of Chromosome 4p12-p13 encoding *KCTD8* and a number of subunits of the γ-aminobutyric acid (GABA) type-A (GABA-A) receptor, and at *PRKD1* on Chromosome 14q12 that might provide important clues to disease pathogenesis in this population.

In our discovery, GWAS signals of association were observed across the region ~45.5Mb to ~47Mb at 4p12 encoding *GABRG1*, *GABRA2*, *GABRA4* and *GABRB1* genes. *KCTD8* lies at ~44 Mb on 4p13, distal to this group of GABA-A receptors. Inability to narrow down the signal is likely to reflect the study design, in which analysis of associations in one large pedigree could provide a measure of genetic linkage rather than association. Nevertheless, there was evidence across both discovery and replication studies for an independent, albeit weaker, association at *KCTD8*. In the replication study, the signal within the GABA-A receptor gene cluster narrowed down to SNPs at *COX7B2* and *GABRA4* that were in strong linkage disequilibrium with each other, with evidence from the replication study favouring *GABRA4* as the aetiological gene. The signal at *PRKD1* was definitively within this gene.

GABRG1, *GABRA2*, *GABRA4* and *GABRB1* encode gamma 1, alpha 2, alpha 4 and beta 1 subunits of the GABA-A receptor. Functional GABA-A receptors are ionotropic receptors composed of five subunits arranged to form a central channel that conducts chloride ions. GABA-A receptors act as inhibitory neurotransmitters in the central nervous system. They are also present in the endocrine part of the pancreas at concentrations comparable to those in the central nervous system and colocalise with insulin in pancreatic beta cells (Rorsman et al., 1989). GABA, cosecreted with insulin from beta cells, can mediate part of the inhibitory action of glucose on glucagon secretion by activating GABA-A receptor chloride channels in pancreatic alpha 2 cells. GABA release from pancreatic beta cells inhibits the secretion of glucagon by 50% to 60% in both pancreatic mouse islets and murine alpha TC1–9 cell (Bailey & Nutt, 2008). Inhibition is glucose concentration-dependent, with increasing doses of glucose also increasing expression of GABA-A receptors.

GABA also acts through metabotropic (i.e. nonionotropic) GABA-B receptors. These are G-protein-coupled receptors that do not form ion channels but trigger other ion channels to open through second messengers. *KCTD8* encodes the potassium channel tetramerisation domain-containing protein 8. KCTD8, 12, 12b and 16 were recently identified as auxiliary GABA-B receptor subunits that increase agonist potency (Schwenk et al., 2010; Metz et al., 2011). Recent work has shown a role for both GABA-A and GABA-B receptors in regulating insulin secretion and glucagon release in pancreatic islet cells from normoglycaemic and T2D individuals (Taneera et al., 2012). Genes encoding GABA-A channel subunits are downregulated in islet cells from individuals with T2D. GABA originating within the islets evoked tonic currents in the cells that were inhibited by the GABA-A receptor antagonist, SR95531. Activation of GABA-A channels decreased both insulin and glucagon secretion. Of interest, the GABA-B receptor antagonist, CPG55845, increased insulin release in islets from normoglycaemic and T2D individuals. The authors (Taneera et al., 2012) conclude that interstitial GABA activates GABA-A channels and GABA-B receptors to modulate insulin release in islets from T2D and normoglycaemic individuals. These observations provide a model for feedback regulation of glucagon release, which may be of significance for the understanding of the hypersecretion of glucagon frequently associated with diabetes (Rorsman et al., 1989). Overall, the identification of polymorphisms in genes that affect both GABA-A and GABA-B receptor pathways

provides novel insight into the pathogenesis of T2D in our UAE population that might directly contribute to therapeutic strategies for diabetes care in this population.

The association with *PRKD1 (=PKD1)* is of interest as this gene is also thought to play a role in insulin secretion. The PKD family comprises a subclass of serine/threonine kinases, with structural and enzymological properties different from those of the PKC family (Valverde et al., 1994; Van Lint et al., 1995). PKD1 has been identified as a key regulator of insulin exocytosis stimulated by the mitogen-activated protein kinase p38δ (Sumara et al., 2009). Mice lacking this kinase exhibit improved glucose tolerance because of enhanced insulin secretion from the β cells of the pancreas (Sumara et al., 2009), suggesting that the signalling module of p38δ and *PRKD1* may be a potential therapeutic target for human diabetes.

In conclusion, this study has identified novel genetic associations for T2D at *KCTD8*, *GABRA4* and *PRKD1* in this Arab population from the UAE, providing interesting functional leads on disease pathogenesis that could translate into improved therapeutic interventions. Further replication and fine mapping in a larger Arab cohort will be essential to validate the results presented here.

Authors' Contributions

HS collected samples in UAE clinic centres under the supervision of OJ and KK. HS carried out the genotyping, data handling and some of the statistical analysis. HJC, DA, SEJ and MF provided statistical advice and carried out some of the analyses. HJC, GKT and JB supervised the work. HS and JB prepared the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

All the authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web site:

Table S1 Summary of the top SNP associations at nominal $P < 0.05$ for all analyses of the discovery GWAS data in the UAE family for genes previously shown in GWAS to be associated with T2D at $P < 5 \times 10^{-8}$ as reported in the NCBI Catalogue of GWAS (Hindorff, Junkins et al., 2009) accessed April 1, 2013.

Table S2A Summary of top SNP associations at $P < 10^{-4}$ for the FBAT analysis of the discovery GWAS data in the UAE extended family.

Table S2B-D Summary of top SNP associations at $P < 10^{-4}$ for the GenABEL analyses (B. unadjusted; C. adjusted for age and sex; D. adjusted for age, sex and BMI) of the discovery GWAS data in UAE extended family.

Table S3 Results of the score tests comparing 1-SNP versus 2-SNP models to determine independent effects across the Chromosome 4p12-p13 region in the discovery analysis.

Table S4 Results of the score and likelihood ratio tests comparing 1-SNP versus 2-SNP models to determine independent effects across the Chromosome 4p12-p13 region for SNPs typed in both the discovery and replication samples.

Figure S1 Quantile-quantile plots.

Figure S2 Regional plots for the Chromosome 4p12-p13 region.

Figure S3 Regional plots for the Chromosome 14q12 region.

Figure S4 Regional plots for the Chromosome 14q12 region.

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