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TYPE 2 DIABETES SUSCEPTIBILITY SNPS ARE NOT ASSOCIATED WITH PCOS

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Abstract

Two cohorts of women with PCOS (400 probands and affected sisters in 365 families and a case-control group including 395 women with PCOS and 171 healthy women with regular menstrual cycles) were studied to determine whether SNPs identified as susceptibility loci in genome-wide association studies of type 2 diabetes are also associated with PCOS. None of the 18 allelic variants in ten genes previously shown to be associated with type 2 diabetes were found to be associated with PCOS, but some were associated with indices of beta cell function.

Polycystic ovary syndrome (PCOS), a common endocrine disorder is characterized by hyperandrogenemia, chronic anovulation and infertility. Women with PCOS are at increased risk for insulin resistance and pancreatic β-cell dysfunction, resulting in a 5–10 fold greater risk of developing type 2 diabetes (1–4). Insulin resistance and beta cell dysfunction cluster in PCOS families and can occur independently of obesity (4–6). Given the frequent co-occurrence of insulin and glucose abnormalities and PCOS, we sought to determine whether

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genetic variants known to contribute to susceptibility to type 2 diabetes are also susceptibility loci for PCOS.

Large-scale studies identified or confirmed genes associated with type 2 diabetes: *CDKAL1*, *CDKN2A/B*, *HHEX/IDE*, *IGF2BP2*, *IRS1*, *KCNJ11* and *SLC30A8* (7–12), *PPARG* (13), *TCF7L2* (14) and *WFS1* (15,16). In addition, a variant near *IRS1* has been linked to insulin resistance associated with type 2 diabetes (17). In this report we examined the role in PCOS of 18 SNPs associated with type 2 diabetes based on findings from GWAS or large association studies.

PCOS families and case-control cohort: 365 families (400 probands and affected sisters) with PCOS were included in the family-based analysis. Diagnostic criteria for PCOS have been described in detail elsewhere (18,19). For analysis of SNPs associated with T2DM, women with self-reported diabetes or impaired fasting glucose levels (>100 mg/dl) were excluded they may carry diabetes-susceptibility allelic variants which would confound the assessment of the contribution these variants may make to the PCOS phenotype in the absence of diabetes. The offspring with PCOS and diabetes or IFG (N=77) were not analyzed separately as the number was too small to yield meaningful results. The self-identified ethnicities of probands in the families were: 87% white, 4% Hispanic, 1% black and 7% other or unknown. Probands and sisters were considered affected if they had 6 or fewer menses per year and elevated total testosterone (greater than 58 ng/dl) or elevated non-SHBG-bound testosterone (greater than 15 ng/dl); these thresholds are 2 SD greater than the mean of our normal controls. Clinical characteristics of the probands and sisters are presented in Supplemental Table 1.

The case-control cohort consisted of 395 unrelated Caucasian PCOS patients and 171 White control women recruited at two centers, the University of Alabama at Birmingham (248 PCOS and 147 controls) and Cedars-Sinai Medical Center (147 PCOS and 24 controls). Cases were premenopausal, non-pregnant, on no hormonal therapy, including oral contraceptives, for at least three months, and met 1990 NIH criteria for PCOS (20). Parameters for defining hirsutism, hyperandrogenemia, ovulatory dysfunction, and exclusion of related disorders were previously reported (21). Clinical characteristics of the case-control cohort are presented in Supplemental Table 1. Controls were healthy women, with regular menstrual cycles and no evidence of hirsutism, acne, alopecia, or endocrine dysfunction and had not taken hormonal therapy (including oral contraceptives) for at least three months. oral contraceptives) for at least three months. This study was approved by all of the authors' institutional review boards.

SNP genotyping: Eighteen SNPs in or near 10 genes found to be associated with type 2 diabetes in GWAS were genotyped: rs10946398 [proxy for rs7754840], rs7756992 and rs9465871 in *CDKAL1* (7,9–11), rs10811661 and rs564398 in *CDKN2A/B* (7,8,11), rs1111875, rs5015480 and rs7923837 in the region of *HHEX and IDE* (7–9,11), rs4402960 in *IGF2BP2* (7,8,11), rs2943641 in *IRS-1* (17), rs5215 and rs5219 in *KCNJ11* (7,8,12), rs1801282 in *PPARG* (7,8,11), rs13266634 in *SLC30A8* (7,8,10–12), rs7901695 and rs7903146 in *TCF7L2* (7–9,11) and rs10010131 and rs734312 in *WFS1* (11,15,16). In the family cohort, SNPs were genotyped using Applied Biosystems TaqMan SNP Genotyping Assays. Allelic PCR products were analyzed using the Applied Biosystems 7900HT Sequence Detection System and SDS 2.2 software. Genotypes were auto-called by SDS 2.2 software with quality value set at 0.95. Two CEPH individuals were typed on each of 16 96-well plates. No discrepancies were observed for any of the SNPs, and, except for two SNPs in KCNJ11 (which was deleted from the family cohort analysis), all genotypes were in Hardy-Weinberg equilibrium.

In the case-control cohort, genotyping was carried out using iSelect Infinium technology, following the manufacturer's protocol (Illumina, San Diego, CA) (22,23). Duplicate genotyping of 12 samples yielded a 100% concordance rate. The genotyping success rate was 99.97%. All SNPs were in Hardy-Weinberg equilibrium. SNPs were excluded if the genotyping failure rate was >10%; or if the minor allele frequency was <3%. Ultimately, of the 18 SNPs genotyped in the family cohort, 17 were genotyped in the case-control cohort.

Statistical analysis: Error-checking of genotypes in the family material was performed with Merlin software (24). Linkage and association between SNPs and PCOS was tested with the TDT (25). We corrected for multiple testing using Bonferroni adjustment based on testing of 14 independent SNPs or haplotype blocks; the corrected P-value corresponding to a nominal P of 0.05 was 0.0036. In the case-control cohort, genotypic association with PCOS status was evaluated using logistic regression, adjusting for recruitment site, BMI and age. Additive, dominant, and recessive models were examined. A $P<0.05$ was considered significant when there was evidence of association in the family cohort. For other SNPs, the Bonferroni-corrected P-value described above was utilized.

Genetic Power Calculator software (http://pngu.mgh.harvard.edu/~purcell/gpc/ (26)) was used to determine that with the sample size of each independent cohort there was approximately 80% power ($P = 0.05$) to detect a relative risk ratio of 3.7.

Among the 18 SNPs mapping associated with type 2 diabetes in previous studies that were genotyped in the family cohort, all were in Hardy-Weinburg equilibrium with the exception of two SNPs in KCNJ11 which were not included in the family-based analysis. None of the remaining 16 SNPs were associated with PCOS status in 365 families having at least one offspring with PCOS, but no history of diabetes or elevated IFG (Table 1). Results for TDT analysis of association between these SNPs and PCOS in all offspring with PCOS, including those with diabetes or IFG, are shown in Supplemental Table 2. Seventeen of these SNPs were also analyzed in the case-control study, none of which were significantly associated with PCOS after correction for multiple testing (Table 1).

This study was designed to address the question of whether the frequent co-occurrence of type 2 diabetes with PCOS might be due to common underlying genetic mechanisms or whether the genetic contributions are separate and independent. The initial phase of this study was a family-based analysis followed up by an independent analysis in a case-control cohort.

None of the SNPs that have been associated with type 2 diabetes in several GWAS were significantly associated with PCOS in either of our cohorts. A lack of association with PCOS has also been reported for SNPs associated with type 2 diabetes in *KCNJ11* (27) and *TCF7L2* (28,29). However, Biyasheva et al. (29) reported that two SNPs mapping approximately 100 kb centrometic to the most significant SNPs in the type 2 diabetes GWAS (rs7901695 and rs7903146 in *TCF7L2*; ref 7–9,11), were significantly associated with PCOS. Thus, our findings do not necessarily exclude the possibility of other variants in or near these 10 genes as loci for PCOS. Given the limited power in this study to detect SNPs with only a small effect (OR <3), we also cannot rule out the possibility that these, or other SNPs in the same genes, make lesser contributions to the risk for PCOS.

We also investigated whether any of the SNPs are associated with B-cell function as measured by HOMA-IR and HOMA-%B (see Supplemental material). Our finding that rs564398 and rs10811661, SNPs near CDKN2A and CDKN2B were significantly associated with HOMA-%B, despite the fact that subjects with diabetes and IFG were excluded, suggests a role for this locus in the metabolic abnormalities in PCOS, although it evidently does not contribute to the reproductive phenotype. Nominally significant association of

CDKAL1 rs7756992 and TCF7L2 rs7903146 in analysis including PCOS offspring with diabetes or IFG (Supplemental Table 2).

In contemporary genetic epidemiology, efforts to combine resources to increase sample sizes and/or provide replication cohorts have become increasingly common. Both cohorts were recruited and studied years ago. These cohorts are critical resources, each representing several years of effort to recruit and phenotype the subjects. All subjects were recruited employing full characterization of biochemical and clinical hyperandrogenism, and all cases meet 1990 NIH criteria. While there are manifest differences in BMI (and consequently, insulin-related parameters) between the two groups of cases we studied, we are confident that one cohort can serve to corroborate results found in the other. In terms of age differences, this reflects the subjects' age at recruitment, and should not influence or be influenced by genetic factors. In the case/control cohort, results are adjusted by age and BMI.

The frequent occurrence of abnormal insulin and glucose metabolism in a large percentage of women with PCOS and the known familial clustering of these phenotypes raises questions about the contributions of genetics to the spectrum of phenotypes. Non-overlapping sets of genes could predispose to each trait (e.g., the SNP 3’ of CDKN2A and CDKN2B influencing HOMA-%B, but not the reproductive phenotype of PCOS). Alternatively, one set of genes might contribute to two or more traits (i.e., the underlying genetic predisposition is the same) with different environmental factors or modifiers triggering disease progression down one path or another;. Finally, combination of the two scenarios described above, with genes predisposing for metabolic traits interacting or converging with genes determining reproductive traits to enhance the risk of PCOS and create the complex metabolic and reproductive phenotype. Each of these models is consistent with PCOS being an oligogenic or polygenic disorder. However, our findings in no way preclude the discovery of new genes or genetic variants that could account for the frequent occurrence of metabolic and reproductive phenotypes in PCOS.

In conclusion, 18 SNPs well-established as susceptibility loci for type 2 diabetes were not significant contributors to PCOS susceptibility, supporting the concept that these two conditions are largely genetically distinct.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Type 2 diabetes susceptibility loci identified in GWAS tested by TDT in 365 PCOS families (N=400 probands and sisters) and by logistic regression for association with PCOS in the case control cohort (395 cases, 171 controls).

Gene	SNP	Alleles[a]	MAF[b]	Over-transmitted Allele in TDT	T[c]	not T[c]	Total T[c]	Transmission Frequency	TDT χ^2	P
CDKAL1	rs10946398	A/C	0.318	C	161	137	298	0.540	1.93	0.164
	rs7756992	A/G	0.283	G	154	124	278	0.554	3.24	0.072
	rs9465871	T/C	0.197	C	119	105	224	0.531	0.88	0.350
CDKN2A/B	rs564398	T/C	0.395	C	185	168	353	0.524	0.82	0.365
	rs10811661	T/C	0.165	C	112	104	216	0.519	0.30	0.586
HHEX/IDE	rs1111875	C/T	0.403	C	174	169	343	0.507	0.07	0.787
	rs5015480	C/T	0.412	C	172	161	333	0.517	0.36	0.547
	rs7923837	G/A	0.365	A	159	150	309	0.515	0.26	0.609
IGF2BP2	rs4402960	G/T	0.316	T	161	156	317	0.508	0.08	0.779
IRS1	rs2943641	C/T	0.344	C	170	145	315	0.540	1.98	0.159
PPARG	rs1801282	G/C	0.108	C	55	45	100	0.550	1.00	0.317
SLC30A8	rs13266634	C/T	0.298	T	173	160	333	0.520	0.51	0.476
TCF7L2	rs7901695	T/C	0.314	T	179	151	330	0.542	2.38	0.123
	rs7903146	C/T	0.285	C	167	139	306	0.546	2.56	0.109
WFS1	rs10010131	G/A	0.394	A	191	166	357	0.535	1.75	0.186
	rs734312	A/G	0.469	G	186	169	355	0.524	0.81	0.367

PCOS status			ADDITIVE				DOMINANT				RECESSIVE			
Gene	SNP	Minor allele	N	OR	STAT	P	N	OR	STAT	P	N	OR	STAT	P
CDKAL1	rs10946398	C	571	0.771	−1.433	0.152	571	0.865	−0.629	0.529	571	0.412	−2.155	**0.031**
	rs7756992	G	571	0.835	−0.977	0.329	571	1.008	0.034	0.973	571	0.339	−2.438	**0.015**
	rs9465871	G	571	1.286	1.174	0.241	571	1.317	1.133	0.257	571	1.477	0.567	0.571
CDKN2A/B	rs564398	G	570	0.926	−0.473	0.636	570	0.647	−1.780	0.075	570	1.546	1.386	0.166
	rs10811661	G	571	1.114	0.492	0.623	571	1.134	0.499	0.618	571	1.139	0.188	0.851
HHEX/IDE	rs1111875	A	571	0.961	−0.230	0.818	571	0.753	−1.141	0.254	571	1.417	1.061	0.289

Gene	SNP		Alleles[a]	MAF[b]	Over-transmitted Allele in TDT		T[c]	not T[c]	Total T[c]	Transmission Frequency		TDT χ^2	P	
	rs7923837	A	571	1.095	0.519	0.604	571	0.958	−0.183	0.855	571	1.646	1.329	0.184
IGF2BP2	rs4402960	A	571	0.967	−0.189	0.850	571	0.899	−0.464	0.642	571	1.169	0.385	0.701
IRS1	rs2943641	A	571	0.810	−1.236	0.216	571	0.675	−1.679	0.093	571	1.001	0.004	0.997
KCNJ11	rs5215	G	569	1.457	2.198	**0.028**	569	1.489	1.713	0.087	569	2.081	1.983	0.047
	rs5219	A	571	1.439	2.135	**0.033**	571	1.471	1.671	0.095	571	2.021	1.914	0.056
PPARG	rs1801282	G	571	1.047	0.178	0.859	571	1.161	0.511	0.609	571	0.336	−1.057	0.291
SLC30A8	rs13266634	A	570	0.807	−1.232	0.218	570	0.861	−0.651	0.515	570	0.536	−1.634	0.102
TCF7L2	rs7901695	G	571	0.992	−0.044	0.965	571	0.946	−0.242	0.809	571	1.154	0.339	0.735
	rs7903146	A	571	1.015	0.080	0.937	571	0.974	−0.117	0.907	571	1.220	0.427	0.669
WFS1	rs10010131	A	571	1.048	0.282	0.778	571	1.147	0.577	0.564	571	0.934	−0.220	0.826
	rs734312	G	570	0.901	−0.638	0.524	570	0.771	−1.014	0.311	570	1.010	0.035	0.972

[a] SNP alleles, minor allele appears second.

[b] MAF, minor allele frequency for SNP

[c] T, number of transmissions to affected offspring in the TDT analysis.