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Article Review: Coloration Biochemistry and Molecular Biology Between Polycystic Ovary Syndrome and Diabetes Mellitus Type 2

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ABSTRACT

Polycystic ovarian syndrome is the most common reproductive endocrine disorder in premenopausal women Given the clinical overlap between PCOS and type 2 diabetes mellitus (T2DM), this research sought to investigate if genes associated with T2DM were similarly connected to PCOS vulnerability. In either the univariate or multivariate scenario, none of the 16 SNPs was significantly associated with Polycystic Ovarian Syndrome after Bonferroni correction for multiple testing. The nine T2DM genes investigated in this preliminary research may not be the main PCOS risk factors in Indian women. Our findings add to the absence of evidence of a link between T2DM genes and PCOS in Chinese and Caucasians, suggesting that this trend may be universal. To determine the exact significance of the diabetes genes, researchers will need to conduct extensive studies that involve women with T2DM and PCOS.

Keywords- T2DM, PCOS, Genes, Type 2 Diabetes.

I. INTRODUCTION

PCOS includes many components, including reproductive, metabolic, and cardiovascular issues, all of which have long-term health consequences. It is the most common cause of anovulatory infertility, with a complicated genetic basis. About 70 genes have been found related to PCOS in "genome-wide association studies", while 11 loci have been identified as connected with PCOS using the candidate gene method. Significant GWAS polymorphisms of PCOS, on the other hand, are not linked to risk phenotypes like diabetes and obesity[1-5]. PCOS is characterized by IR and hyperinsulinemia, in addition to reproductive abnormalities. As a result, several genes involved in insulin production and action have been investigated as potential PCOS candidate genes. A new variation in the INSR gene linked to the insulin pathway was discovered in a PCOS GWAS.

According to genetic research, PCOS and type 2 diabetic mellitus (T2DM) may share genetic susceptibility characteristics linked to both diseases. Several research has indicated that genes linked to T2DM may also have a role in Polycystic ovary syndrome pathogenesis, based on this theory, as evidenced by different meta-analyses. However, no significant relationship with Polycystic ovary syndrome was found for the GWAS-identified T2DM genes KCNJ11, TCF7L2, FTO, HHEX, CDKAL1, and SLC30A8[6-8]. IR is a metabolic trait that both PCOS and T2DM share. Women with PCOS reproductive anomalies were shown to have significant insulin resistance. However, some research has looked at the function of candidate and GWAS genes in the pathophysiology of T2DM[9-12]. The majority of PCOS research focused on clinical aspects, with just a few genetic studies conducted. Given the high incidence of T2DM and the common pathophysiology of T2DM and PCOS, it is critical to comprehend PCOS aetiology from T2DM genes[13-15]. As a result, the goal of this research was to see whether a panel of 15 single-nucleotide polymorphisms from nine distinct T2DM candidate/GWAS genes was linked to PCOS[16-20]. Despite the fact that a vast number of SNPs have been linked to T2DM in various groups, owing to a lack of resources, we were only able to genotype 15 SNPs that were most substantially and consistently linked to T2DM.

II. GROUPS OF CASES AND CONTROLS

Sampling criteria: "Identification of susceptibility genes linked with PCOS" is part of a bigger study. Only 210 of the 299 controls and 248 of the 250 cases were genotyped for the current research due to a lack of resources[21-23]. To be considered, two of the following conditions must be met, according to these criteria: An ovary with more than ten subcapsular follicles on ultrasonography in the context of polycystic ovaries has infrequent periods with an intermenstrual interval of more than 36 days. There were no androgen-secreting tumours or hyperprolactinemia in the research.

***Genotyping of T2DM genes*:** The phenol-chloroform technique was used to extract DNA. A total of fifteen well-replicated SNPs from nine T2DM genes were chosen from candidate and GWAS results[24-27]. The SNPs included were "rs7903146, rs11196205 and rs12255372 (*TCF7L2*), rs4402960 and rs1470579 (*IGF2BP2*), rs13266634 (*SLC30A8*), rs1111875 and rs7923837 (*HHEX*), rs7754840 and rs7756992 (*CDKAL1*), rs10811661 (*CDKN2A/B*), rs1801278 (*IRS1*), rs3792267 and rs5030952 (*CAPN10*) and

rs1801282 (*PPARG*)". The 15 SNPs were genotyped using the Sequenom MassARRAY platform. The raw data files generated by MassARRAY Sequenom were analyzed for the intensity peaks of calibrant to assess data quality. Overall, a call rate of more than 90% was maintained. The call rates were evaluated for concordance after four samples were duplicated for every 95 samples[28-33]. All runs were also checked for calls in the negative control (no DNA). Individual SNP genotype call rates ranged from 96 to 99 percent. Only one sample was eliminated from the 250 cases, with no call for all of the SNPs, while all of the samples in the controls functioned.

III. INTERACTION ANALYSIS

The individuals' clinical features have been previously reported. Given the young age of the PCOS patients, none of the PCOS cases was found to be diabetic. Except for rs5030952 of CAPN10 (P = 0.021), none of the 15 SNPs followed Hardy–Weinberg equilibrium. It also failed to meet the required level of significance under multiple testing (P = 0.003), resulting in its removal from further study[33-35]. After Bonferroni adjustment for multiple testing, none of the 15 SNPs were substantially related to PCOS, but PPARG (rs1801282) was discovered to be connected with the illness but in a protective function against developing PCOS[36-39]. In contrast, only after adjusting for BMI, the two SNPs of IGF2BP2 (rs4402960 and rs1470579) showed marginally significant association (P = 0.040 and 0.048, respectively), indicating that BMI may be a confounding factor in masking the protective role of this gene against the manifestation of PCOS. The pattern of genotype distribution in non-obese patients and controls offered empirical evidence for this.

Table 1: Single-nucleotide polymorphisms (SNPs) of T2DM susceptibility genes allele frequency distribution (in percent) in polycystic ovarian syndrome (PCOS) patients and controls.

Gene	SNP	Cases/controls (2 N)	Allele (major/ minor)	PCOS cases	Controls	*P* value	OR	95% CI for OR	
								Lower	Upper
TCF7L2	rs7903146	480/412	C	0.71	0.71	0.84	0.97	0.73	1.30
			T	0.29	0.29				
TCF7L2	rs11196205	482/410	G	0.61	0.63	0.28	0.88	0.66	1.13
			C	0.40	0.36				
TCF7L2	rs12255372	496/418	G	0.77	0.80	0.36	1.15	0.84	1.58
			T	0.23	0.20				
IGF2BP2	rs4402960	494/418	G	0.57	0.52	0.13	0.82	0.63	1.06
			T	0.43	0.48				
IGF2BP2	rs1470579	490/418	A	0.56	0.52	0.18	0.84	0.64	1.08
			C	0.44	0.48				
SLC30A8	rs13266634	496/418	T	0.78	0.78	0.94	0.99	0.72	1.35
			C	0.22	0.22				
HHEX	rs1111875	492/414	A	0.66	0.62	0.21	0.84	0.62	1.10
			G	0.34	0.38				
HHEX	rs7923837	492/418	A	0.63	0.59	0.20	0.84	0.64	1.10
			G	0.37	0.41				
CDKAL1	rs7754840	490/416	G	0.76	0.73	0.29	0.85	0.63	1.15

Table 2: Genotype frequency distribution (in percent) and logistic regression using body mass index as a covariate in a log-additive model.

Gene	SNP	Cases/controls (n)	Genotype	Cases	Controls	*P* value	OR	95% CI	*P* value
TCF7L2	rs7903146	240/206	CC	0.51	0.50	0.890	1.05	0.71-1.53	0.816
			CT	0.40	0.42				
			TT	0.09	0.08				
TCF7L2	rs11196205	241/205	GG	0.37	0.40	0.397	1.16	0.89-1.53	0.276
			GC	0.47	0.49				
			CC	0.16	0.12				
TCF7L2	rs12255372	248/209	GG	0.59	0.63	0.664	1.13	0.74-1.72	0.583
			GT	0.37	0.33				
			TT	0.04	0.04				
IGF2BP2	rs4402960	247/209	GG	0.34	0.28	0.328	0.69	0.49-0.99	0.040*
			GT	0.45	0.47				
			TT	0.21	0.24				
IGF2BP2	rs1470579	245/209	AA	0.34	0.28	0.405	0.71	0.50-1.00	0.048*
			AC	0.45	0.47				
			CC	0.22	0.25				
SLC30A8	rs13266634	248/209	CC	0.62	0.60	0.560	0.98	0.64-1.51	0.942
			TC	0.33	0.36				
			TT	0.06	0.04				

There was a significant LD between the SNPs of the genes on the same chromosome, "notably TCF7L2, IGF2BP2, CDKAL1, HHEX, and CAPN10", but no LD between the genes on the same chromosome, as anticipated[40-45]. Only nine SNPs from the nine genes were selected for the multivariate and interaction analyses based on the reported LD pattern, *i.e.* "(*TCF7L2* (rs7903146), *IGF2BP2* (rs1470579), *SLC30A 8* (rs13266634), *CDKAL1* (rs7756992), *CDKN2A/B* (rs1 0811661), *HHEX* (rs1111875), *IRS-1* (rs1801278), *CAPN10* (rs3792267) and *PPARG* (rs1801282)".

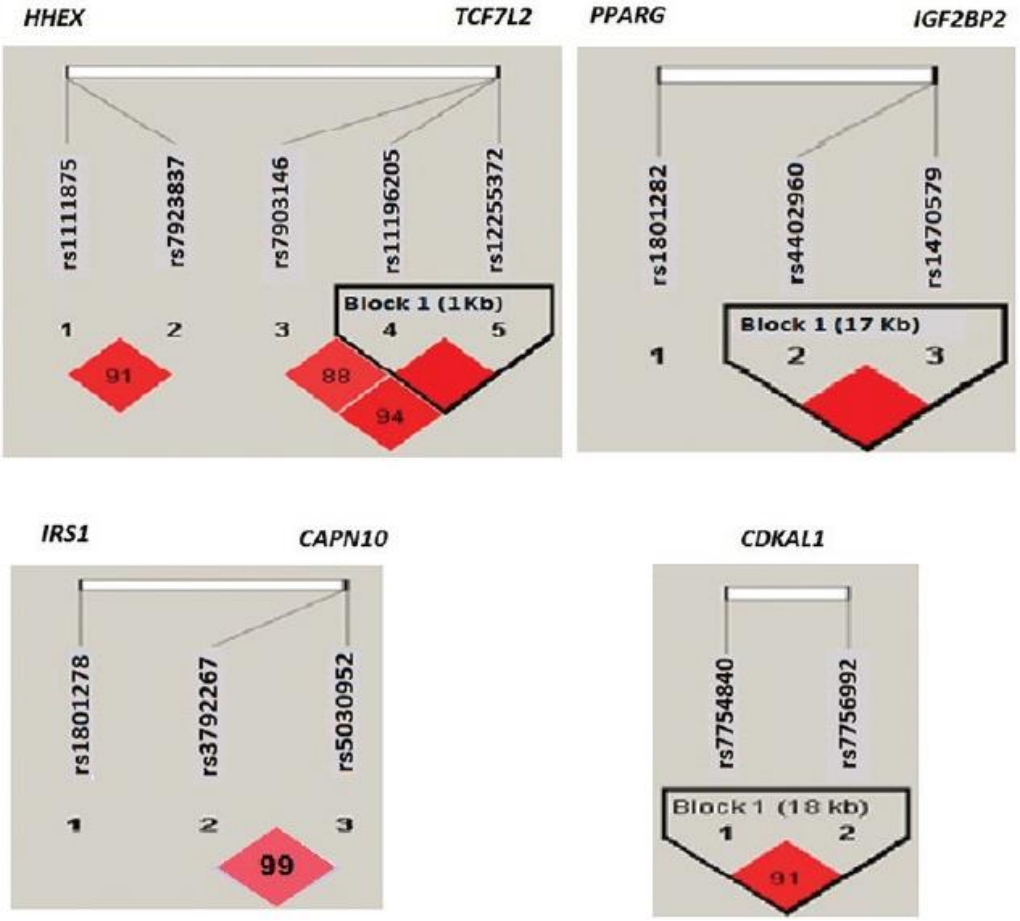

Figure 1: TCF7L2, HHEX; IGF2BP2, PPARG; IRS1, CAPN10; CDKAL1: LD plots of SNPs of genes on the same chromosome.

In the multivariate logistic regression analysis including confounders, none of the nine SNPs exhibited a significant relationship with PCOS after adjustment for multiple testing (results not presented). At the same time, PPARG SNP was significant in the allele-wise analysis (P = 0.036) and disappeared after adjusting for BMI, only CAPN10 genotype (GA) showed marginally significant (P = 0.049) association with PCOS after adjusting for BMI[46-50]. PPARG in one locus, IGF2BP2 and CDKAL1 in two, TCF7L2, IGF2BP2 and CDKAL1 in three, and TCF7L2, IGF2BP2, CDKAL1 and HHEX in four loci combinations were shown to have the optimal interactions utilizing multifactor dimensionality reduction (MDR). IGF2BP2 and CDKAL1 were also discovered to be shared by all three multilocus combinations[51-52]. The dendrogram revealed this, indicating a synergistic interaction between IGF2BP2 and CDKAL1. When permuted for 1000 iterations, however, none of the combinations seems to be noteworthy.

Table 3: Using multifactor dimensionality reduction, the findings of SNP-SNP interactions were summarised.

Combination	Balance Accuracy Training	Balance Accuracy Testing	CVC	*P* value
PPARG	0.5466	0.530	9/10	0.547
IGF2BP2, CDKAL1	0.5793	0.5235	8/10	0.608
TCF7L2, IGF2BP2, CDKAL1	0.6141	0.529	6/10	0.592
TCF7L2, IGF2BP2, CDKAL1, HHEX	0.6620	0.4634	6/10	0.381

CVC, cross-validation consistency; SNP, single-nucleotide polymorphism

Figure 2: Dendogram derived from the nine T2DM genes' multifactor dimensionality reduction interaction analysis, indicating potential synergistic interactions.

The gene-environment interaction analysis was performed using the R programme, and logistic regression analysis was used to assess the potential interaction of each of the individual SNP genotypes with BMI (environmental factor) and the Polycystic ovary syndrome phenotype as the binary response variable[53-58]. Despite BMI's very significant relationship with the phenotype (P 0.001), none of the genes exhibited significant interaction with BMI (results not shown). CDKAL1*BMI and CAPN10*BMI interactions were only significant at 10%.

IV. CONCLUSIONS

Diabetic diabetes (T2D) and polycystic ovarian syndrome (PCOS) are both prevalent diseases characterized by "Insulin Resistance(IR) and compensatory hyperinsulinemia". Type 2 diabetes have been reported to have a greater chance of having polycystic ovaries[59-66]. Is it possible that treating one illness will result in the treatment of the other disease? It is possible to increase insulin sensitivity, which may aid in the normalization of endocrine and reproductive diseases[67-69]. Clinical investigations have shown that insulin-sensitizing medications such as metformin and inositols may significantly enhance the endocrine and metabolic profiles of Polycystic ovary syndrome patients when used in conjunction with other treatments.

According to the researchers, despite one study indicating that Myo-inositol may have a role in the primary prevention of gestational diabetes in Polycystic ovary syndrome women[70-71], studies evaluating the preventative effects of type 2 diabetes in PCOS women are still missing. Because it has a better tolerability profile when compared to metformin[72-73], Myo-inositol is more likely to increase patient compliance and make it more appropriate for usage over a longer length of time. According to certain studies, treatment with liraglutide may be helpful, especially in the case of obese female patients. Studies on the effectiveness of SGLT2i should be carried out with more care and attention paid to detail[74-76]. The authors recommended additional study into the different PCOS phenotypes and whether they are associated with metabolic problems.

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