



Association of VDR Gene Variants with Polycystic Ovarian Syndrome in Arab Women

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Objectives

To determine whether VDR gene variants are associated with polycystic ovarian syndrome (PCOS) in women of Arab ethnicity in Oman and whether there are associations between clinical or biochemical parameters with these variants.

Background

PCOS is an endocrine disorder that affects women of reproductive age. It is associated with irregular menstrual cycles, hirsutism, hyperandrogenism and metabolic disorders. (Hong *et al.*, 2020) It is a multifactorial disorder which is associated with environmental and genetic factors. According to a study conducted among Egyptian women, VDR Taq-I gene polymorphism is associated with increased risk of PCOS in Egyptian women. It was found that there was a significant decrease of 25 hydroxy-vitamin D levels in carriers of haplotype Taq-I C/ Apa-I C (with variant alleles) compared to the non-carriers. (El-Shal *et al.*, 2013) The Vitamin-D receptor (VDR) regulates vitamin D levels and calcium metabolism in the body and these are known to be associated with endocrine dysfunctions, insulin resistance and type-2 diabetes in PCOS. (Dasgupta *et al*, 2015)

Study Design

Prospective case-control study.

Materials and Methods

A sample size of 49 cases and 49 controls was estimated for a significance level of 5% at 60% power, with minor allele frequencies of 12% and 1% with a 1:1 ratio. We recruited 50 cases and 50 controls (Omani women) in reproductive age from the Gynecology clinic at Sultan Qaboos University Hospital in Oman. Cases fulfilled the Rotterdam criteria for PCOS. Controls were non-pregnant reproductive aged women who were not diagnosed with PCOS. Genetic disorders, congenital adrenal hyperplasia, androgen secreting tumors, Cushing syndrome, and hyperprolactinemia were excluded. Clinical and biochemical data was collected and analyzed. SPSS was used for statistical analysis. Gene Panel Exome Sequencing was conducted on DNA extracted from blood samples for VDR gene and data analyzed using ANNOVAR software. Statistical analysis was performed using SPSS for descriptive statistics, Chi square test and Correlation analysis. SNPs were tested for Hardy-Weinberg Equilibrium.

Results

After whole exome sequencing, only one nonsynonymous single nucleotide polymorphism (SNP) was identified which was VDR rs2228570. It was tested for association with different clinical biochemical and physical parameters among PCOS cases. The VDR rs2228570 SNP followed the Hardy-Weinberg Equilibrium (HWE) and there was no association of VDR rs2228570 with PCOS (P value 0.7).

100% of cases with VDR/rs2228570(AG/GG) variant were within phenotype subtype D exhibiting all feature of PCOS. Cases with VDR rs2228570 (AG/GG) genotype compared to those that are (AA) genotype were found to have higher levels of testosterone (P value 0.22), more severe insulin resistance (P value 0.95) and have higher levels of fasting blood sugar (P value 0.66) but this did not reach statistical significance probably due to the small sample size. Cases with VDR rs2228570 (AA) genotype had a lower mean Vit D level than controls (P-value =<0.5).

Table 1. Sociodemographic Characteristics

CHARECTERISTICS		Case N=50 (%)	Control N=50 (%)	Chi-square (p-value)
Age	=<25	9(18.0%)	2(4.0%)	13.2 (0.001)
	26-34	31(62.0%)	23(46.0%)	
	>=35	9(18.0%)	25(50.0%)	
Family history of PCOS	yes	23(46.0%)	8(16.0%)	9.6 (0.002)
	No	26(52.0%)	42(84.0%)	
Marital status	single	3(6.0%)	4(8.0%)	0.0 (1.000)
	married	46(92.0%)	46(92.0%)	

Table 2. PCOS Phenotype Subtypes

Clinical findings	Number of cases (%)
Anovulation/oligo-ovulation (OA)	44 (88%)
Hyperandrogenism (HA)	43 (86%)
Poly-cystic ovary (PCO)	50 (100%)
Subtypes:	
A (OA+PCO)	44 (88%)
B (HA+PCO)	43 (86%)
C (HA+OA)	43 (86%)
D (HA+OA+PCO)	43 (86%)

Table 3. Hormonal Parameters Among the Participants (categorized)

VDR/rs2228570		Case (N=50)		Control (N=50)	
		Mean±SD	p-value	Mean±SD	P-value
Vit-D(ng/ml)	AA	42.0±38.0	0.024	81.0±53.0	0.6
	AG/GG	81.0±32.0		71.0±40.0	
HBA1C	AA	6.0±0.2	0.7	5.0±0.7	0.9
	AG/GG	7.0±10.0		6.0±0.4	
Insulin(umol/L)	GG	21.0±13.0	0.6	18.0±11.0	0.6
	GA/AA	18.0±10.0		16.0±9.0	
Fasting blood sugar(mmol/L)	GG	5.0±1.0	0.4	1.6±0.7	0.8
	GA/AA	5.0±1.0		1.2±0.2	
Testosterone(nmol/L)	GG	2.0±2.0	0.7	1.0±0.4	0.2
	GA/AA	2.0±2.0		0.9±0.1	
AMH	GG	16.6±21.6	0.4	12.1±7.5	0.9
	GA/AA	36.0±43.5		11.4±10.8	
FSH	GG	4.8±0.7	0.3	7.3±4.1	0.7
	GA/AA	5.7±1.8		6.7±2.8	
LH	GG	9.0±3.9	0.7	4.3±4.6	0.2
	GA/AA	10.4±6.0		6.5±4.0	

Chart 1. Symptoms & Signs of PCOS Among Participants

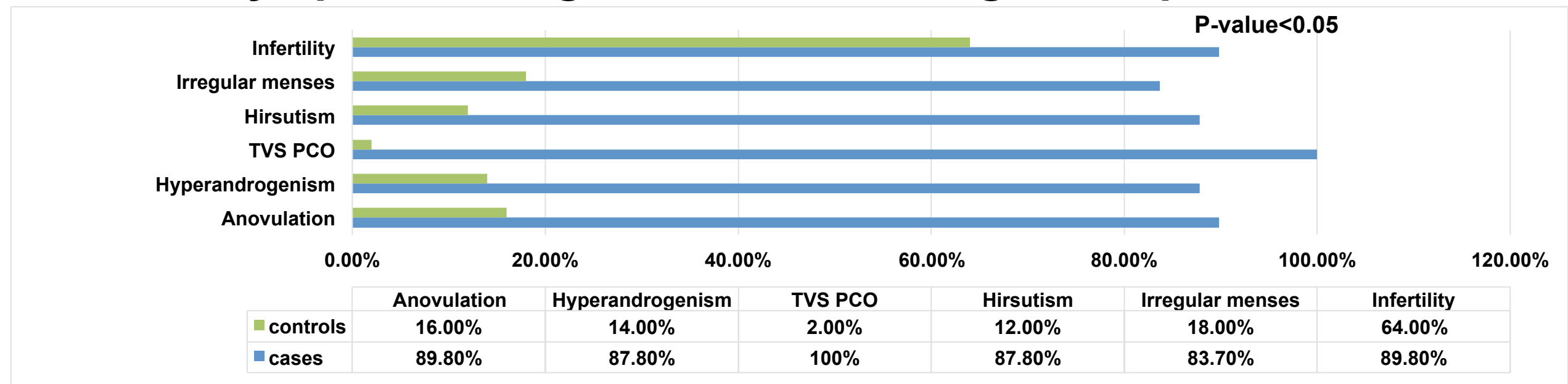


Table 4. Minor allele frequency and predicting factors of SNPs

SNP	Gene	location	Base change	GME allele frequency	SIFT prediction	MetaLR prediction	fathmm-MKL_coding_pred
rs2228570	VDR	Exon	A>G	0.7	D	T	D

T: tolerable, D: damaging

Table 5. Hardy-Weinberg Equilibrium for the selected SNPs

		0/0 (dominant homozygous allele)	0/1 (Heterozygous allele)	1/1 (recessive homozygous allele)	Chi square (p-value)
VDR/rs2228570	cases	4 (8.16%)	11 (22.4%)	34 (69.4)	1.90(0.20)
	controls	6 (12%)	12 (24.0%)	31 (62.0%)	5.20(0.07)

Conclusion

VDR rs2228570 SNP was not found to be associated with PCOS although there were higher levels of testosterone, fasting blood sugar and insulin in the AG/GG genotype cases compared to those that have AA genotype. Cases with VDR rs2228570 AA genotype had a lower mean Vit D level than controls.

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