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Secondary association of *PDLIM5* with paranoid schizophrenia in Emirati patients

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ABSTRACT

Schizophrenia is a clinically and genetically heterogeneous disorder of unknown etiology. *PDLIM5* variants have been linked to schizophrenia and other related neuropsychiatric disorders and upregulated in the brain of schizophrenia patients suggesting a possible pathogenic role in disease progression. The aim of this study is to examine the potential association of schizophrenia in Emirati patients with previously reported variants in *PDLIM5*, *PICK1*, *NRG3* or *DISC1* genes. Consequently, we found a secondary association between *PDLIM5* variants and the paranoid subtype of schizophrenia in Emirati Arabs suggesting that *PDLIM5* may represent a determinate/marker for schizophrenia subtype specification. However, no associations were found with variants in *PICK1*, *NRG3* or *DISC1* genes.

1. Introduction

Schizophrenia is a chronic and severe neuropsychiatric disorder that can trigger a range of positive and negative symptoms, including hallucinations, delusions, cognitive impairment, loss of motivation and impaired ability to manage emotions and relationships. The illness presents in several forms including paranoid symptoms.

Schizophrenia occurs in almost 1% of the population worldwide (National Institute of Mental Health/NIH, 2012). There is a genetic underpinning with other factors including viral and immunological factors, brain injury and drug abuse being implicated (Purcell et al., 2009; Bergen and Petryshen, 2012; The Schizophrenia Psychiatric Genome-Wide Association Study, 2011; 2014; Ripke et al., 2013; McAllister, 2014; Patterson, 2009; Glynn et al., 2011; Chacon and Boulanger, 2013; Stone JL and International Schizophrenia Consortium, 2008; Lee et al., 2012; Malhotra and Sebat, 2012; Giusti-Rodríguez and Sullivan, 2013). However, clinical and genetic heterogeneity and overlapping with other neurodevelopmental disorders complicate our understanding of the etiology of schizophrenia.

Both common and rare genetic variants have been associated with schizophrenia (Escudero and Johnstone, 2014). The major histocompatibility complex (MHC), an immune response gene locus on chromosome 6 is the most extensively associated locus for schizophrenia in GWAS (Purcell et al, 2009; The Schizophrenia Psychiatric Genome-Wide Association Study, GWAS Consortium, 2014). It has been postulated that MHC function may be affected by viral infection of the expectant mother in turn perturbing MHC's role in synaptogenesis in the unborn child (McAllister, 2014). The largest GWAS to date identified significant associations spanning 108 conservatively defined loci — enriched for synapse associated genes (The Schizophrenia Psychiatric Genome-Wide Association Study, GWAS Consortium, 2014). Rare variant association studies are also enriched for synapse-associated genes including *DISC1*, *ARC*, several calcium channel genes and the *NMDAR* (Thomson et al., 2014; McClellan et al., 2007; Wang et al., 2008; Purcell et al., 2014; Xu et al., 2012; Cukier et al., 2014).

To better understand the etiology of schizophrenia in a population of Emirati Arabs, we applied a candidate gene association approach to schizophrenia for previously implicated genes *DISC1*, *PICK1* and *NRG3* as well as *PDLIM5*, a gene upregulated in the brain of schizophrenia patients.

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Table 1
The analyzed single nucleotide variations (SNVs), their corresponding genes and primers.

Gene	SNV	HGVS names	Primers
PDLIM5	rs7690296	NM_001011513.3:c.814A>G NP_001011513.3:p.T272A	ggcaacaagagcgaaactct; cattacacatacttccaaatgcaaa
	rs14082	NM_001011513.3:c.*1006A>G NM_001011513.3:c.*1048delT	tttttgccttacagtggatca; tttaagagccggagtcttgc
	rs11339365		
	rs10590	NM_001011513.3:c.*1061T>C NM_001011513.3:c.292-212C>T	gctgctaacctgattgtgtttg; tggagactggtcagcactaaga
	rs2452600		
	rs12641023	NM_001011513.3:c.956 + 412G>A	aatgaaaggtaatacggaggtct; tcacgaagtgcaacaaggtc
PICK1	rs2076369	NM_001039583.1:c.283-59G>T	tctttgcctcagcctcct; ggacacccgtaactgctctg
	rs880669	NM_001039583.1:c.283-176C>T	
NRG3	rs2295933	NM_001010848.3:c.1986C>T	
	rs959317	NP_001010848.2:p.S662 = NM_001010848.3:c.1829T>G NP_001010848.2:p.V610G	aatgccagggatttctgaag; tcacttggtcaatgcagagtc ctgccatcagcagagttgag; ccagtgagggatccagagaa
DISC1	rs3738401	NM_001012957.1:c.791G>A NP_001012975.1:p.R264Q	

2. Patients and methods

2.1. Patient selection

Participants over the age of 18 were recruited from outpatient attendees at Al Ain Hospital, in Al Ain city, United Arab Emirates in accordance with the Al Ain Medical District Human Research Ethics Committee. Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR) clinical criteria (American Psychiatric Association, 2000) by way of a semi-structured interview, comprehensive medical and psychiatric history taking, mental state examination and collateral information from family members. Participants were excluded from the study if they had comorbid alcohol or drug dependence, depressive disorder, or bipolar affective disorder. Patients consisted of 71 males (58.7%) and 50 females (41.3%) with diagnosis of schizophrenia, aged 18–82 year old with a mean age of 37.1 (+/− 12.6) years. Eighty nine (73.6%) were diagnosed as paranoid schizophrenia (65.2% men and 34.8% women), ten (8.3%) with disorganized type, two (1.7%) with residual, one (0.8%) with schizoaffective, four (3.3%) undifferentiated type, and 15 (12.4%) as not otherwise specified. Paranoid schizophrenia was significantly more frequent among men (58, 65.2%) compared to women (31, 34.8%) ($\chi^2 = 12.18$, df = 5, P = 0.03).

Fifty one patients (42.5%) were married, 58 (48.4%) were single, one (0.8%) was separated, seven (5.8%) were divorced and three of the females (2.5%) were widowers. There was no statistically significant difference between genders in marital status. Seventy two (59.5%) patients were unemployed and 26 (21.5%) were housewives. Sixteen (13.2%) were employed in clerical positions, four (3.3%) were retired, 2 (1.7%) were students and one (0.8%) was working in the police. In this cohort

Table 2
Patient–control comparison of the studied variations in *PICK1*, *PDLIM5*, *NRG3* and *DISC1* genes.

SNV	Subjects (n = 295)	Genotype count (%)			χ^2	P
PICK1 rs880669		C/C	C/T	T/T	1.725	.422
	Patient (113)	70 (61.9)	39 (34.5)	4 (3.5)		
	Control (172)	107 (62.2)	53 (30.8)	12 (7.0)		
PICK1 rs2076369		G/G	G/T	G/T	4.476	.107
	Patient (114)	47 (37.6)	59 (45.4)	8 (25.8)		
	Control (172)	78 (62.4)	71 (54.6)	23 (74.2)		
*PDLIM5*rs7690296		A/A	A/G	G/G	.390	.823
	Patient (181)	30 (39.0)	61 (42.4)	27 (38.6)		
	Control (173)	47 (61.0)	83 (57.6)	43 (61.4)		
PDLIM5 rs7690464		C/C	C/T	T/T	1.471	.225
	Patient (118)	117 (40.3)	1 (100.0)	0 (0.0)		
	Control (173)	173 (59.7)	0 (0.0)	0 (0.0)		
PDLIM5 rs14082		A/A	A/G	G/G	.000	1.000
	Patient (112)	24 (40.0)	58 (40.0)	30 (40.0)		
	Control (168)	36 (36.0)	87 (60.0)	45 (60.0)		
*PDLIM5*rs11339365		T/T	T/−	−/−	2.771	.250
	Patient (116)	30 (35.7)	62 (45.9)	24 (36.9)		
	Control (168)	54 (64.3)	73 (54.1)	41 (63.1)		
*PDLIM5*rs10590		T/T	T/C	C/C	1.277	.528
	Patient (116)	49 (37.4)	55 (44.4)	12 (41.4)		
	Control (168)	82 (62.6)	69 (55.6)	17 (58.6)		
*PDLIM5*rs2452600		C/C	C/T	T/T	1.596	.450
	Patient (121)	76 (40.0)	38 (42.2)	7 (38.3)		
	Control (171)	114 (60.0)	52 (57.8)	5 (41.7)		
*PDLIM5*rs12641023		G/G	G/A	A/A	.217	.897
	Patient (121)	32 (42.1)	58 (42.3)	31 (39.2)		
	Control (171)	44 (57.9)	79 (57.7)	48 (60.8)		
*NRG3*rs2295933		C/C	C/T	T/T	.273	.873
	Patient (117)	40 (40.0)	60 (42.0)	17 (37.8)		
	Control (171)	60 (60.0)	83 (58.0)	28 (16.2)		
*NRG3*rs959317		T/T	T/G	G/G	1.973	.373
	Patient (117)	110 (39.9)	3 (50.0)	4 (66.7)		
	Control (171)	166 (60.1)	3 (50.0)	2 (33.3)		
DISC1 rs3738401		G/G	G/A	A/A	2.606	.272
	Patient (120)	79 (44.6)	39 (36.4)	2 (66.7)		
	Control (167)	98 (55.4)	68 (63.6)	1 (33.3)		

SNV = Single nucleotide variation.

the correlation between unemployment and schizophrenia was statistically significant ($\chi^2 = 43.45$, df = 6, P = 0.001).

2.2. Genotyping

121 patients with schizophrenia (SCZ) and 170 controls were genotyped using quality controlled primers (Table 1). PCR amplicons spanning SNPs from the respective genes were sequenced and analyzed using ClustalW2 against gene reference sequences NM_001039583.1 for *PICK1*, NM_006457.4 for *PDLIM5*, NM_001010848.3 for *NRG3* and NM_001012957.1 for *DISC1*.

3. Quality control and statistical analysis

Quality control (QC) was performed with PLINK software (Purcell et al., 2007). The chi square test was used to test for associations between SNVs and phenotypes. A logistic regression analysis was done with patients/control as dependent factor and SNVs as predictor factors.

3.1. Allelic association

Allelic association analysis was performed with PLINK software (5% of significance level). QQ plots were performed with the WGA-Viewer software (Ge and Goldstein, 2007; Ge et al, 2008), and Manhattan plot and linkage disequilibrium (LD) evaluation were performed with Haploview software (Barrett et al, 2005). Power analysis was performed with Quanto (http://hydra.usc.edu/gxe/), showing that for SNPs with MAF of P0.05, given our sample size, we had over 80% power to detect associations with odds ratio (OR) of P2.0; however, it showed much lower power to detect associations with smaller ORs (1.2).

4. Results

We evaluated a total of 295 Emirati individuals (121 with schizophrenia and 174 normal controls) for associations with variants in four genes (*DISC1*, *PICK1*, *NRG3* and *PDLIM5*) previously were shown to be associated with schizophrenia. Using the chi square test (95% confidence interval) none of the sequence variants were found to be significantly associated with schizophrenia in this Arab cohort. Table 2 shows comparison of patients and controls in single nucleotide variations (SNVs) for the four different genes tested.

Furthermore, the patients' group was divided into paranoid schizophrenia and non-paranoid schizophrenia. Chi square test was used to test for an association between SNVs and paranoid schizophrenia. The three *PDLIM5* SNVs; rs14082 ($\chi^2 = 7.807$, df = 2, P = 0.02), rs12641023 ($\chi^2 = 7.56$, df = 2, P = 0.023), and rs11339365 ($\chi^2 = 14.53$, df = 2, P = 0.001) were found significantly more frequent in paranoid schizophrenia group as well as *PICK1* SNV rs880669 ($\chi^2 = 6.317$, DF = 2, P = 0.042) (Table 3).

5. Subtypes of schizophrenia and association with genes

The chi square test was used to test for associations between SNVs of *PDLIM5* (rs14082, rs11339365, and rs10590) and subtypes of schizophrenia. There was significant association with rs14082 and rs11339365 but not with rs10590 (Tables 4, 5, 6).

A logistic regression analysis was done with patients/control as a dependent factor and SNVs as predictor factors (for *DISC1*, *PICK1*, *NRG3* and *PDLIM5*). The results showed that of these SNVs only rs11339365 from *PDLIM5* was a significant predictor of schizophrenia (Wald = 5.997, P = 0.014, CI = 1.080–1.995).

Table 3
paranoid/non-paranoid schizophrenia comparison of studied variations in *PICK1*, *PDLIM5*, *NRG3* and *DISC1* genes.

SNV	Subjects	Genotype count (%)			χ^2	P
PICK1rs880669		CC	C/T	T/T	6.32	.04
	Paranoid	56 (50.0)	23 (20.5)	4 (3.6)		
	Non-paranoid	14 (12.5)	15 (13.4)	0 (0.0)		
PICK1 rs2076369		G/G	G/T	T/T	1.76	.42
	Paranoid	33 (29.2)	46 (40.7)	5 (4.4)		
	Non-paranoid	14 (12.4)	12 (10.6)	3 (2.7)		
*PDLIM5rs*7690296		A/A	A/G	G/G	5.48	.06
	Paranoid	26 (22.)	44 (37.6)	16 (13.7)		
	Non-paranoid	4 (3.4)	16 (13.7)	11 (9.4)		
PDLIM5 *rs*7690464		C/C	C/T	T/T	.364	.55
	Paranoid	85 (72.6)	1 (0.9)	0		
	Non-paranoid	31 (26.5)	0 (0.0)	0		
PDLIM5 *rs*14082		A/A	A/G	G/G	7.81	.02
	Paranoid	14 (12.6)	45 (40.5)	27 (24.3)		
	Non-paranoid	10 (9.0)	12 (10.8)	3 (2.7)		
*PDLIM5*rs11339365		T/T	T/−	−/−	14.53	.001
	Paranoid	52 (45.2)	15 (13.0)	20 (17.4)		
	Non-paranoid	9 (7.8)	15 (13.0)	4 (3.5)		
*PDLIM5*rs10590		T/T	T/C	C/C	5.51	.06
	Paranoid	32 (27.8)	46 (40.0)	9 (7.8)		
	Non-paranoid	17 (14.8)	8 (7.0)	3 (2.6)		
*PDLIM5*rs2452600		C/C	C/T	T/T	1.21	.55
	Paranoid	54 (45.0)	29 (24.2)	6 (5.0)		
	Non-paranoid	22 (18.3)	8 (6.7)	1 (0.8)		
*PDLIM5*rs12641023		G/G	G/A	A/A	7.57	.02
	Paranoid	26 (21.7)	45 (37.5)	18 (15.0)		
	Non-paranoid	5 (4.2)	12 (10.0)	14 (11.7)		
*NRG3*rs2295933		C/C	C/T	T/T	.59	.75
	Paranoid	2 (1.7)	26 (21.8)	60 (50.4)		
	Non-paranoid	0 (0.0)	13 (10.9)	18 (15.1)		
*NRG3*rs959317		T/T	T/G	G/G	2.34	.31
	Paranoid	82 (70.7)	3 (2.6)	2 (1.7)		
	Non-paranoid	27 (23.3)	0 (0.0)	2 (1.7)		
DISC1 rs3738401		G/G	G/A	A/A	2.14	.34
	Paranoid	60 (50.4)	26 (21.8)	2 (1.7)		
	Non-paranoid	18 (15.1)	13 (10.9)	0 (0.0)		

SNV = Single nucleotide variation.

Table 4
Different types of schizophrenia among *PDLIM5 rs14082* genotypes.

Type of schizophrenia	Patients (n = 121) (%)	Genotype count (%)			χ^2	P
		A/A	A/G	G/G		
		33 (27.2%)	58 (47.9%)	30 (24.8%)		
Paranoid	89 (73.6)	14 (11.6)	45 (37.2)	27 (22.3)	25.42	.045
Disorganized	10 (8.3)	4 (3.4)	3 (2.5)	1 (0.8)		
Undifferentiated	4 (3.3)	1 (0.8)	1 (0.8)	0 (0.0)		
Residual	2 (1.6)	1 (0.8)	1 (0.8)	0 (0.0)		
Schizoaffective	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)		
Not otherwise specified	15 (12.4)	4 (3.4)	7 (5.8)	2 (1.7)		

A further logistic regression used paranoid/non-paranoid schizophrenia as a dependent factor and SNVs as predictor factors (for *DISC1*, *PICK1*, *NRG3* and *PDLIM5*). Again rs11339365 from *PDLIM5* was found to be a significant predictor of paranoid schizophrenia (Wald = 10.806, P = 0.002, CI = 1.885–17.508).

6. Discussion

The current study aimed to test the association of schizophrenia in Emirati Arabs with genetic variants in four schizophrenia candidate genes namely *DISC1*, *PICK1*, *NRG3* and *PDLIM5*. No such association was established in this relatively small cohort of patients. However, *PDLIM5* was found to be a significant secondary predictor of the paranoid subtype of schizophrenia in this Emirati Arab cohort.

PDLIM5 is localized to the postsynaptic density where it has an important role in limiting the size of dendritic spines — the small synaptic protrusions that serve as the primary sites of excitatory synaptic transmission in the CNS (Herrick et al., 2010; Bourne and Harris, 2008). Spine morphology is thought to play important roles in synaptic development and plasticity (Bourne and Harris, 2007) with larger spines possessing greater synaptic strength and stability and morphological derangements in spines correlating with several neurological disorders (Newey et al., 2005; Purpura, 1974). *PDLIM5* has been associated with schizophrenia, bipolar disorder and major depression and its expression is upregulated in the brain of schizophrenia patients suggesting a possible pathogenic role in the etiology of schizophrenia (Iwamoto et al., 2004; Horiuchi et al., 2006). The finding here of *PDLIM5* as a potential marker of schizophrenia subtype expands the role of synaptogenesis in neuropsychiatric disorders more generally (Clarke et al., 2012; Clarke and Eapen, 2014) thus beckoning further investigation of *PDLIM5* variant correlation in a larger study and their relationship to brain expression levels in patients post-mortem.

7. Conclusions

Our findings suggest that *PDLIM5* is a possible secondary determinate/marker for the paranoid schizophrenia subtype in Emirati Arabs.

Table 5
Different types of schizophrenia among *PDLIM5*rs11339365 genotypes.

Type of schizophrenia	Patients (n = 121) (%)	Genotype count (%)			χ^2	P
		T/T	T/−	−/−		
		30 (24.8)	67 (55.3)	24 (19.8)		
Paranoid	89 (73.6)	15 (12.4)	52 (43.0)	20 (16.5)	28.83	.017
Disorganized	10 (8.3)	6 (5.0)	2 (1.7)	2 (1.7)		
Undifferentiated	4 (3.3)	3 (2.5)	0 (0.0)	0 (0.0)		
Residual	2 (1.6)	1 (0.8)	1 (0.8)	0 (0.0)		
Schizoaffective	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)		
Not otherwise specified	15 (12.4)	5 (4.1)	6 (5.0)	2 (1.7)		

Table 6
Different types of schizophrenia among *PDLIM5 rs10590* genotypes.

Type of schizophrenia	Subjects (n = 295) (%)	Genotype count (%)			χ^2	P
		T/T	T/C	C/C		
		131 (44.4)	124 (42.0)	29 (9.8)		
Paranoid	89 (30.2)	32 (10.8)	46 (15.6)	9 (3.1)	22.54	.209
Disorganized	10 (3.4)	6 (2.0)	2 (10.7)	2 (0.7)		
Undifferentiated	4 (1.4)	2 (0.7)	0 (0.0)	1 (0.3)		
Residual	2 (0.7)	1 (0.3)	1 (0.3)	0 (0.0)		
Schizoaffective	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)		
Not otherwise specified	15 (5.1)	8 (2.7)	5 (1.7)	0 (0.0)		
Control	174 (59.0)	82 (27.8)	69 (23.4)	17 (5.8)		

Consanguinity is an established risk factor for schizophrenia (Dobrusin et al., 2009; Mansour et al., 2010; Britvić et al., 2010; Bener et al., 2012) and a study by Alkelai et al. (2011) demonstrated the utility of family-based studies for the identification of schizophrenia susceptibility genes. Therefore, our next step will be to carry out deeper genetic analysis involving whole-genome SNV genotyping and whole-exome sequencing to identify variants that are relevant to the development of schizophrenia in Emiratis.

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