Secondary association of PDLIM5 with paranoid schizophrenia in Emirati patients

Hamdy Moselhy, Valsamma Eapen, Nadia A. Akawi, Ali Younis, Badr Salih, Aws R. Othman, Said Yousef, Raymond A. Clarke, Bassam R. Ali

A R T I C L E   I N F O

Article history:
Received 14 April 2015
Revised 1 June 2015
Accepted 6 July 2015
Available online 21 July 2015

Keywords:
Schizophrenia
Genetics
PDLIM5
NRG3
DISC1

A B S T R A C T

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.

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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.

http://dx.doi.org/10.1016/j.mgene.2015.07.002
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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.

| 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 | gccaacaagcagccaacttc; cattacatactctcaagcagct |
| | rs14082 | NM_001011513.3:c.1006A→G | ttgctgccaggtgctca; tttaagcggagcgttgc |
| | rs1139365 | NM_001011513.3:c.1061T→C | tgggaatggtggttggag | tgggaatggtggttggag |
| | rs10590 | NM_001011513.3:c.292-212C→T | ggacaccgtaactgcttc | ggacaccgtaactgcttc |
| | rs2452600 | NM_001011513.3:c.283-176C→T | ctgcatcagctgag | ctgcatcagctgag |
| PICK1 | rs2076369 | NM_001011513.3:c.283-59G→T | ctctttgcctcagcctcct | ggacacccgtaactgcttc |
| | rs880669 | NM_001011513.3:c.283-176C→T | ggacacccgtaactgcttc | ggacacccgtaactgcttc |
| NRG3 | rs2295933 | NM_001010848.3:c.956 + 412G→A | aatgaaaggtaatacggaggtct | tcacgaagtgcaacaaggtc |
| | rs10590 | NM_001010848.3:c.1986C→T | tttaagagccggagtcttgc | tttaagagccggagtcttgc |
| DISCI | rs3738401 | NM_001012957.1:c.791G→A | gctgctaacctgattgtgtttg | tggagactggtcagcactaaga |

| Table 2 |
|---|
| Patient–control comparison of the studied variations in PICK1, PDLIM5, NRG3 and DISCI genes. |
| SNV | Subjects (n = 295) | Genotype count (%) | $\chi^2$ | P |
| PICK1 rs880669 | Patient (113) | C/C: 70 (61.9) | 1.725 | .422 |
| | Control (172) | C/T: 39 (34.5) | 12 (3.5) |
| PICK1 rs2076369 | Patient (114) | G/G: 47 (39.4) | 4.476 | .107 |
| | Control (172) | G/T: 39 (45.4) | 8 (25.8) |
| PDLIM5 rs7690296 | Patient (181) | A/A: 30 (39.0) | .390 | .823 |
| | Control (173) | A/G: 61 (42.4) | 27 (38.6) |
| PDLIM5 rs7690464 | Patient (118) | C/C: 117 (40.3) | 1.471 | .225 |
| | Control (173) | C/T: 1 (100.0) | 0 (0.0) |
| PDLIM5 rs14082 | Patient (112) | A/A: 24 (40.0) | .000 | 1.000 |
| | Control (168) | A/G: 58 (40.0) | 30 (40.0) |
| PDLIM5 rs11339365 | Patient (116) | T/T: 30 (35.7) | 2.771 | .250 |
| | Control (168) | T/C: 62 (45.9) | 24 (36.9) |
| PDLIM5 rs10590 | Patient (116) | T/T: 49 (37.4) | 1.277 | .528 |
| | Control (168) | T/C: 55 (44.4) | 12 (41.4) |
| PDLIM5 rs2452600 | Patient (121) | C/C: 36 (40.0) | 1.596 | .450 |
| | Control (171) | C/T: 38 (42.2) | 7 (38.3) |
| PDLIM5 rs12641023 | Patient (121) | G/G: 114 (60.0) | 5 (41.7) | .217 | .897 |
| | Control (171) | G/A: 52 (57.8) | 31 (39.2) |
| NRG3 rs2295933 | Patient (117) | C/C: 40 (40.0) | 1.973 | .373 |
| | Control (171) | C/T: 60 (42.0) | 17 (37.8) |
| NRG3 rs959317 | Patient (117) | T/T: 110 (39.9) | .273 | .873 |
| | Control (171) | T/C: 3 (50.0) | 2 (33.3) |
| DISCI rs3738401 | Patient (120) | G/G: 79 (44.6) | 2.606 | .272 |
| | Control (167) | G/A: 39 (36.4) | 2 (66.7) |

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% significance level). QQ plots were performed with the WGA-Viewer software (Ge and Goldstein, 2007; Ge et al., 2008), and Manhattan plot of significance level). The chi square test was used to test for an association between SNVs and paranoid 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).

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, 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).

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

| SNV        | Subjects | Genotype count (%) | $\chi^2$ | P   |
|------------|----------|--------------------|----------|------|
| PICK1 rs880669 | Paranoid | C/C | C/T | T/T | 6.32 | .04 |
|             | Non-paranoid | 56 (50.0) | 23 (20.5) | 4 (3.6) | |
|             |           | 14 (12.5) | 15 (13.4) | 0 (0.0) | |
| PDLIM5 rs7690296 | Paranoid | A/A | A/G | G/G | 5.48 | .06 |
|             | Non-paranoid | 26 (22.2) | 44 (37.6) | 16 (13.7) | |
|             |           | 4 (3.4) | 16 (13.7) | 11 (9.4) | |
| PDLIM5 rs7690464 | Paranoid | C/C | C/T | T/T | .364 | .55 |
|             | Non-paranoid | 85 (72.6) | 1 (0.9) | 0 | |
|             |           | 31 (26.5) | 0 (0.0) | 0 | |
| PDLIM5 rs14082 | Paranoid | A/A | A/G | G/G | 7.81 | .02 |
|             | Non-paranoid | 14 (12.6) | 45 (40.5) | 27 (24.3) | |
|             |           | 10 (9.0) | 12 (10.8) | 3 (2.7) | |
| PDLIM5 rs11339365 | Paranoid | T/T | T/T | 15 (13.0) | 20 (17.4) | 14.53 | .001 |
|             | Non-paranoid | 52 (45.2) | 15 (13.0) | 4 (3.5) | |
|             |           | 9 (7.8) | 15 (13.0) | 4 (3.5) | |
| PDLIM5 rs10590 | Paranoid | C/C | C/T | T/T | 5.51 | .06 |
|             | Non-paranoid | 32 (27.8) | 46 (40.0) | 9 (7.8) | |
|             |           | 17 (14.8) | 8 (7.0) | 3 (2.6) | |
| PDLIM5 rs2452600 | Paranoid | A/A | A/G | G/G | 7.57 | .02 |
|             | Non-paranoid | 54 (45.0) | 29 (24.2) | 6 (5.0) | |
|             |           | 22 (18.3) | 8 (6.7) | 1 (0.8) | |
| PDLIM5 rs12641023 | Paranoid | C/C | C/T | T/T | 1.21 | .55 |
|             | Non-paranoid | 26 (21.7) | 45 (37.5) | 18 (15.0) | |
|             |           | 5 (4.2) | 12 (10.0) | 14 (11.7) | |
| NRG3 rs2295933 | Paranoid | 2 (1.7) | 26 (21.8) | 60 (50.4) | |
|             | Non-paranoid | 0 (0.0) | 13 (10.9) | 18 (15.1) | |
| NRG3 rs959317 | Paranoid | T/T | T/T | T/T | 2.34 | .31 |
|             | Non-paranoid | 82 (70.7) | 3 (2.6) | 2 (1.7) | |
| DISC1 rs3738401 | Paranoid | G/G | G/A | A/A | 2.14 | .34 |
|             | Non-paranoid | 60 (50.4) | 26 (21.8) | 2 (1.7) | |

SNV = Single nucleotide variation.

Table 2 shows comparison of patients and controls in single nucleotide variations (SNVs) for the four different genes tested.
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., 2012). 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 determinant/marker for the paranoid schizophrenia subtype in Emirati Arabs.

### Table 4

| Type of schizophrenia | Patients (n = 121) (%) | Genotype count (%) | $X^2$ | P |
|-----------------------|-----------------------|-------------------|------|---|
| Paranoid              | 89 (73.6)             | A/A 33 (27.2%)    | 25.42 | .045 |
|                       |                       | A/G 58 (47.9%)    |      |    |
|                       |                       | C/G 30 (24.8%)    |      |    |
| Disorganized          | 10 (8.3)              | A/A 4 (3.3)       | 1 (0.8) | 0 (0.0) |
|                       |                       | A/G 3 (2.5)       | 0 (0.0) | 0 (0.0) |
|                       |                       | C/G 3 (2.5)       | 0 (0.0) | 0 (0.0) |
| Undifferentiated      | 4 (3.3)               | A/A 1 (0.8)       | 0 (0.0) | 0 (0.0) |
|                       |                       | A/G 1 (0.8)       | 0 (0.0) | 0 (0.0) |
|                       |                       | C/G 1 (0.8)       | 0 (0.0) | 0 (0.0) |
| Schizoffective        | 2 (1.6)               | A/A 1 (0.8)       | 0 (0.0) | 0 (0.0) |
|                       |                       | A/G 1 (0.8)       | 0 (0.0) | 0 (0.0) |
|                       |                       | C/G 1 (0.8)       | 0 (0.0) | 0 (0.0) |
| Not otherwise specified| 15 (12.4)             | A/A 4 (3.3)       | 1 (0.8) | 0 (0.0) |
|                       |                       | A/G 3 (2.5)       | 0 (0.0) | 0 (0.0) |
|                       |                       | C/G 7 (5.8)       | 2 (1.7) |    |

### Table 6

| Type of schizophrenia | Subjects (n = 295) (%) | Genotype count (%) | $X^2$ | P |
|-----------------------|------------------------|-------------------|------|---|
| Paranoid              | 89 (30.2)              | T/T 131 (44.4%)   | 22.54 | .009 |
|                       |                        | T/C 124 (42.0%)   |      |    |
|                       |                        | C/C 29 (9.8)      |      |    |
| Disorganized          | 10 (3.4)               | T/T 6 (2.0)       | 2 (0.7) | 0 (0.0) |
|                       |                        | T/C 2 (0.7)       | 0 (0.0) | 1 (0.3) |
|                       |                        | C/C 2 (0.7)       | 1 (0.3) | 0 (0.0) |
| Undifferentiated      | 4 (1.4)                | T/T 2 (0.7)       | 1 (0.3) | 0 (0.0) |
|                       |                        | T/C 1 (0.3)       | 0 (0.0) | 1 (0.3) |
|                       |                        | C/C 2 (0.7)       | 1 (0.3) | 0 (0.0) |
| Schizoffective        | 1 (0.3)                | T/T 1 (0.3)       | 0 (0.0) | 1 (0.3) |
|                       |                        | T/C 1 (0.3)       | 0 (0.0) | 1 (0.3) |
|                       |                        | C/C 0 (0.0)       | 0 (0.0) | 0 (0.0) |
| Not otherwise specified| 15 (5.1)              | T/T 8 (2.7)       | 5 (1.7) | 0 (0.0) |
|                       |                        | T/C 0 (0.0)       | 0 (0.0) | 0 (0.0) |
|                       |                        | C/C 0 (0.0)       | 0 (0.0) | 0 (0.0) |
| Control               | 174 (59.0)             | T/T 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; Britvic 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.

### Acknowledgments

We thank the subjects and volunteers for taking part in this study. The project was funded by United Arab Emirates University (grant no. 01-08-8-12/08).

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