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Association of GWAS and candidate gene loci of dopaminergic system with major depression, schizophrenia and bipolar disorder in the Pakistani population

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Abstract

The dopaminergic pathways control neural signals that modulate mood and behaviour along and have a vital role in the aetiology of major depression (MDD), schizophrenia (SHZ) and bipolar disorder (BD). Genome-wide association studies (GWAS) have reported several dopaminergic pathway's and other genetic loci's association with these disorders, therefore, the present study was conducted to analyse the GWAS and candidate gene loci of the dopaminergic and cognitive system genes in MDD, SHZ, and BD, in the Pakistani population. A total of 1237 subjects [MDD n = 479; BD n = 222; SHZ n = 146; and controls n = 390], were screened for eleven genetic variants through polymerase chain reaction (PCR) techniques. Univariant followed by multivariant logistic regression analysis were applied to determine the genetic association. Significant risk associations were observed for rs4532 and rs1799732 with MDD; and rs1006737 and rs2238056 with BD. However, after applying multiple test corrections rs4532 and rs1799732 association did not remain significant for MDD. Moreover, a protective association was found for three variants *DRD4*-120bp, rs10033951 and rs2388334 in the current cohort. Thus, in conclusion, the current study revealed the risk association of rs1006737 and rs2238056 with BD and the protective effect of *DRD4*-120bp in MDD and BD, of rs2388334 in BD and of rs10033951 in MDD, BD, and SHZ in the current Pakistani cohort.

1. Introduction

Psychiatric disorders are one of the leading causes of morbidity worldwide. Among common psychiatric conditions, major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SHZ) are categorised as the most complex psychiatric disorders, with overlapping clinical features and shared genetic determinants (Soares & Gershon, 2000; Torrey et al., 2000). These psychiatric conditions present with disruptive psychopathologies that involve behaviour, thought processing, perception, cognitive function, motor activity, mood, and emotions (Soares & Gershon, 2000; Torrey et al., 2000). Genetic factors are known to play an important role and influence the susceptibility to these psychiatric conditions but the elucidation of genetic factors is always challenging as these disorders are polygenic (Wang et al., 2017). The complex genetic heterogeneity of MDD, BD, and SHZ, predisposes the individuals to overlapping clinical conditions or features, thus making it hard to distinguish them clinically (Feczko et al., 2019).

A number of Genome-Wide Association Studies (GWAS), meta-GWAS and familial studies of psychiatric conditions have been conducted to unravel the genetic determinants of these disorders (Craddock & Sklar, 2013; Ikeda et al., 2018; Major Depressive Disorder Working Group of the Psychiatric et al., 2013). The GWAS identified genetic loci and candidate genes that are associated with MDD, BD and SHZ aetiology and which belong to multiple neuronal pathways regulating learning, memory, motor activity and cognitive functions (International HapMap, 2003; Liu et al., 2020; Major Depressive Disorder Working Group of the Psychiatric et al., 2013; Segurado et al., 2003; Sklar et al., 2008; Stahl et al., 2019).

However, it has also been reported that several loci, that are found to be associated with a higher risk of BD, were also associated with MDD and SHZ, similarly, genetic determinants of SHZ overlap with BD and MDD loci (Cross-Disorder Group of the Psychiatric Genomics, 2013). Some of the shared genetic markers between these psychiatric conditions (MDD, BD and SHZ), as reported by several GWAS and population-based association studies, regulate and belong to the dopaminergic neurotransmission (Allen et al., 2008; Cross-Disorder Group of the Psychiatric Genomics, 2013; Klein et al., 2019; Seifuddin et al., 2012; Stahl et al., 2019; Tunbridge et al., 2019).

The dopaminergic system is regulated by the excitatory neurotransmitter dopamine (DA), which is the most abundant neurotransmitter in the brain. This neurotransmitter is involved in regulating different brain functions such as behaviour, executive memory, reward, pleasure, decision, critical thinking, and voluntary motor movements of the body (Bombin et al., 2008; Chang et al., 2013; Klein et al., 2019). The DA hypothesis in mood disorders postulates that DA dysregulation and signalling abnormalities underlie, psychosis, SHZ, mood, and affective disorders such as MDD and BD (Kapur & Mann, 1992; Kesby et al., 2018; Singh, 1970; Tissot, 1975; Wittenborn, 1974). This defines DA signalling as of potential relevance in the pathophysiology and progression of psychiatric conditions like MDD, BD, and SHZ (Diehl & Gershon, 1992; Dunlop & Nemeroff, 2007; Fochtmann & Fink, 1992; Howes et al., 2012; Howes et al., 2013).

Therefore, the current case-control association study was conducted to replicate in the Pakistani population, the findings of selected GWAS identified and case-control association studies reported genetic variants of the dopaminergic system genes that have a direct or indirect role in the regulation of DA and cognitive functions, and to assess the potential genetic overlap in the aetiology of MDD, BD and SHZ.

2. Methodology

2.1. Subjects Recruitment

In total n = 1237 subjects, including MDD (n = 479), BD (n = 222), SHZ (n = 146), and healthy controls (n = 390), participated in the study. Patients were recruited from the Psychiatry department of Pakistan Institute of Medical Sciences (PIMS) hospital Islamabad, Pakistan. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), (American Psychiatric Association, 2013), by a qualified registered psychiatrist of the psychiatry department of PIMS. The healthy controls were also recruited from PIMS, conducting a questionnaire-based interview and were confirmed by psychiatrists, as not suffering from any psychiatric conditions.

2.1.1. Inclusion and Exclusion Criteria

To be included in the study, patients had to fulfil DSM-5 criteria for the relevant psychiatric illness, the participants (cases and controls) had to be between the ages of 18–65 years and not suffer from any metabolic disorders. In addition, controls with a positive family history of psychiatric disorders did not have any medical condition that potentially interferes with the brain function (thyroid disorder, uncontrolled hypertension, Hepatitis C, Human Immunodeficiency virus-HIV), and drug abusers were also not included in the current study.

2.1.2. Sample Collection and Processing

A blood sample of 3ml from each subject was collected in Ethylenediaminetetraacetic acid (EDTA) tube (1 Becton Drive, Franklin Lakes, NJ). The genomic DNA was extracted according to the standard phenol-chloroform DNA extraction protocol (Sambrook & Russell, 2001). The extracted DNA samples were stored at -20 ºC until further use.

2.2. Genetic Variants and Genotypying

Eleven genetic variants previously reported in GWAS and candidate gene studies in different psychiatric disorders were selected for association analysis. Ten single nucleotide polymorphism (SNP) and one variable number of tandem repeat (VNTR), belonging to ten genes, [Calcium voltage-gated channel subunit alpha1 C (*CACNA1c*), dopamine receptor 1(*DRD1*), dopamine receptor 2 (*DRD2*), dopamine receptor 3 (*DRD3*), dopamine receptor 4 (*DRD4*), dopamine receptor 5 (*DRD5*), phosphofurin acidic cluster sorting protein 1 (*PACS1*), tetratricopeptide repeat and ankyrin repeat-containing 1 (*TRANK1*), follistatin like 5 (*FSTL5*), and POU Class 3 Homeobox 2 (*POU3F2*)]. The selection criteria for the genes and variants were based on associations observed in GWAS, meta-analysis, and candidate gene studies in psychiatric disorders in different populations (Supplementary Table S1).

Seven variants [*CACNA1c* (rs1006737, rs2238056), *DRD1* (rs4532), *DRD2* (rs1799732), *DRD3* (rs6280), *DRD4* (120bp VNTR), *DRD5* (rs10033951)], were screened in MDD, SHZ and BD. While, an additional four variants [*PACS1* (rs10896090), *TRANK1* (rs9834970), *FSTL5* (rs11724116), *POU3F2* (rs2388334)], were selected from the recent GWAS in the BD cohort of European, North American, and Australian populations (Stahl et al., 2019), and were screened in the BD cohort of the present study.

The genotyping was performed by using different PCR techniques, 2 of the SNPs were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and 8 SNPs were genotyped by tetra- amplification refractory mutation system-PCR (TETRA-ARMS-PCR), while the VNTR was genotyped by standard polymerase chain reaction (PCR). The amplified fragments of less than 100 base pairs were analysed on a 2% agarose gel and fragments larger than 100 base pairs were visualized on 3% agarose gel. The details of primers and thermal profiles are mentioned in (Supplementary Table S2).

2.3. Statistical Analysis

All the statistical analyses were done using R (v 4.0.0), (R Core Team, 2020). Fisher *t*-test was applied for continuous variables and the χ^2 test was applied for categorical variables, in comparison between cases and controls. Hardy-Weinberg equilibrium (HWE), was also determined using the χ^2 test. Genotypes of variants were coded additively (Additive model) and univariate logistic regression analysis was applied to determine the association of each variant with the cases. All the results were adjusted for age and sex (multivariate logistic regression analysis). Quanto-v.1.2.4 (Gauderman, 2002) was used for the power calculation of the SNPs. The threshold significance was kept at a *P*-value ≤ 0.05 in all statistical tests, while the adjusted *P*-value after multiple testing was set at ≤ 0.007 in Tables 2 & 5 and ≤ 0.004 in Table 3.

2.3.1. Genotype and Allele Frequencies comparison with 1000 Genome and ALFA

The SNPs data of controls of the current study were also analysed in comparison to the 1000 Genome PJL (Punjabi in Lahore), data (The 1000 Genomes Project Consortium) and Allele Frequency Aggregator (ALFA) –data of South Asians (SAS), (L. Phan, 2020), and determine the differences and/or similarities between the genotype calls and allele frequencies.

3. Results

3.1. Descriptive Characteristics of the Subjects

The descriptive characteristics of all cases and controls are summarised in Table 1. The age of the cases was comparatively older than the healthy controls, MDD (*P* < 2.2e-16), SHZ (*P* = 7.51e-10), and BD (*P* = 1.47e-13). In the current cohort, the mean age at onset ± SD (AAO) was observed to be at a later age in MDD (28.89 ± 11.03) and at an earlier age in SHZ (23.43 ± 8.75) and BD (23.75 ± 9.81). Sex differences were only observed in MDD (*P* = 2.37e-08) and SHZ (*P* = 0.01), compared to the controls. Moreover, the majority of the participants in the present study were Punjabi in ethnicity (Punjab province of Pakistan), though a statistical difference has been observed in SHZ (*P* = 0.02), compared to the controls. In addition, more tobacco users were found in cases compared to controls, MDD (*P* = 4.60e-05), BD (*P* = 4.22e-10), and SHZ (*P* < 2.2e-16), and the cannabis users were only found in cases.

Table 1
Descriptive statistics of the studied cohort

Demographic Factors		CON	MDD	BPD	SHZ	MDD vs CON	BPD vs CON	SHZ vs CON
						P	*P*	*P*
Sr. no.	Total (n)	390	479	222	146			
1	Age (years)	24.06 ± 6.11	32.80 ± 11.50	30.47 ± 11.43	29.85 ± 10.12	< 2.2e-16	1.47e-13	7.51e-10
2	Age at onset (years)	NA	28.89 ± 11.03	23.75 ± 9.81	23.43 ± 8.75	NA	NA	NA
3	Sex (Male)	224(57.0%)	183(38.0%)	132(59.0%)	102(70.0%)	2.37e-08*	0.68*	0.01*
	(Female)	166(43.0%)	296(62.0%)	90(41.0%)	44(30.0%)			
4	Ethnicity (Punjabi)	267(68.50%)	321(67.01%)	166(75.00%)	115(79.00%)	0.70*	0.12*	0.02*
5	Tobacco users	29(7.43%)	81(16.91%)	58(26.13%)	52(35.62%)	4.60e-05*	4.22e-10*	< 2.2e-16*
6	Cannabis abusers	0	16(3.34%)	25(11.26%)	12(8.22%)	NA	NA	NA

Values are *n* (%), or mean ± SD; *P*-value from Welch Two Sample t-test and **P*-value from Pearson's Chi-squared test χ^2 with Yates' continuity correction. NA, not applicable; Con, Controls, MDD, Major depressive disorder, BPD, Bipolar disorder, SHZ, Schizophrenia

. **Genetic Association of the Variants**

In total 11 genetic variants were genotyped in the present cohort and the genotype of 3 of the SNPs was found in deviation from HWE, rs10033951 ($P = 0.02$), rs11724116 ($P < 0.0001$), and rs2388334 ($P = 0.03$), (Supplementary Table S4).

3.1.1. Association with MDD

Univariate logistic regression analysis did show significant association of rs1006737 [Odds Ratio (OR) (95% Confidence Interval (CI) = 1.05(1.00-1.11), $P = 0.040$], rs4532 [OR(95% CI) = 1.09(1.03–1.15), $P = 0.002$], and rs1799732 [OR(95%CI) = 1.10(1.01–1.18), $P = 0.029$], with higher risk of MDD susceptibility. The results remained consistent when adjusted for age and sex (multivariate logistic regression analysis), for rs4532 [OR(95%CI) = 1.06(1.01–1.11), $P = 0.039$], and rs1799732 [OR(95%CI) = 1.10(1.02–1.17), $P = 0.012$]. However, after applying multiple test correction (Bonferroni correction), the *P* values did not remain significant for any of the SNP (Table 2).

Table 2
Association of genetic variants with MDD

MDD							Univariate Analysis			Multivariate* Analysis		
Genes	**Variants**	**Allele change**	**Minor Allele**	**Genotype Call rate %**	**Control (n = 390) (AA, Aa, aa)**	**Cases (n = 479) (AA, Aa, aa)**	**OR**	**95% CI**	P-**value**	**OR**	**95% CI**	P-**value**
CACNA1c	rs1006737	G > A	A	91.0%	255 (137, 88, 30)	436 (203,163,70)	1.05	1.00-1.11	*0.040*	1.04	0.99–1.09	0.07
CACNA1c	rs2238056	T > C	T	95.0%	330 (33, 100, 197)	455 (64,63,328)	1.04	0.99–1.09	0.10	1.04	0.99–1.08	0.11
DRD1	rs4532	T > C	C	96.0%	348 (150, 171, 27)	460 (147,269,44)	1.09	1.03–1.15	*0.002*	1.06	1.01–1.11	*0.039*
DRD2	rs1799732	GG > G	DEL	96.6%	359 (309, 45, 5)	463 (371,82,10)	1.10	1.01–1.18	*0.029*	1.10	1.02–1.17	*0.012*
DRD3	rs6280	C > T	T	96.0%	370 (66,180,124)	460 (91,201,168)	1.00	0.96–1.05	0.832	1.01	0.97–1.05	0.57
DRD4	120bp VNTR	1R > 2R	2R	95.8%	359 (24,164,171)	459 (26,320,113)	0.85	0.80–0.90	3.68e-08	0.86	0.82–0.91	8.88e-08
DRD5	rs10033951	C > T	T	93.3%	353 (3,129,221)	447 (11,229,207)	0.85	0.80–0.91	2.14e-06	0.90	0.85–0.95	3.0e-04

*Multivariate (adjusted for sex and age); A, Major Allele; a, Minor Allele; *P*-value from Pearson's Chi-squared χ^2 test with Yates' continuity correction. OR, odd ratio; CI, confidence interval; MDD, Major Depressive Disorder. The threshold significance was kept at a *P*-value < 0.05 in all statistical tests and the adjusted *P*-value after multiple test corrections was set at ≤ 0.007. The significant values are bold and underlined.

In addition, 2 of the variants, *DRD4* (120bpVNTR), and rs10033951 were observed to have a significant protective effect towards MDD susceptibility in both univariate logistic regression analysis, *DRD4* (120bpVNTR) [OR(95%CI) = 0.85(0.80–0.90), *P* = 3.68e-08], rs10033951 [OR(95%CI) = 0.85(0.80–0.91), *P* = 2.14e-0], and in multivariate logistic regression analysis, DRD4 (120bpVNTR) [OR(95%CI) = 0.86(0.82–0.91), *P* = 8.88e-08], rs10033951 [OR(95%CI) = 0.90(0.85–0.95), *P* = 3.0e-04], (Table 2).

3.1.2. Association with BD

In BD, both of the *CACNA1c* SNPs [rs1006737, rs2238056], showed significant association with higher risk of susceptibility, univariate logistic regression analysis; rs1006737 [OR(95%CI) = 1.15(1.08–1.22), *P* = 7.52e-06], rs2238056 [OR(95%CI) = 1.12(1.05–1.19), *P* = 4.45e-4], and the results remained significant when adjusted for age and sex (multivariate logistic regression); rs1006737 [OR(95%CI) = 1.14(1.07–1.20), *P* = 1.3e-05], rs2238056 [OR(95%CI) = 1.11(1.05–1.18), *P* = 3.44e-4], (Table 3).

Table 3
Association of genetic variants with BD

BD							Univariate Analysis			Multivariate* Analysis		
Genes	Variants	Allele change	Minor Allele	Genotype Call rate %	Control (AA, Aa, aa)	Cases (AA, Aa, aa)	OR	95% CI	P value	OR	95% CI	P value
CACNA1c	rs1006737	G > A	A	73%	255 (137, 88, 30)	189 (65, 79, 45)	1.15	1.08–1.22	7.52e-06***	1.14	1.07–1.20	1.3E-05***
CACNA1c	rs2238056	T > C	T	88%	330 (33, 100, 197)	208 (19, 24, 165)	1.12	1.05–1.19	4.45E-4***	1.11	1.05–1.18	3.44E-4***
DRD1	rs4532	T > C	C	92%	348 (150, 171, 27)	215 (80, 127, 8)	1.01	0.95–1.08	0.72	1.01	0.95–1.08	0.77
DRD2	rs1799732	GG > G	DEL	94%	359 (309, 45, 5)	217 (186, 31, 00)	0.98	0.88–1.09	0.75	1.00	0.93–1.08	0.88
DRD3	rs6280	C > T	T	96%	370 (66,180,124)	216 (33, 106, 77)	1.02	0.97–1.08	0.43	1.02	0.97–1.07	0.45
DRD4	120bp VNTR	1R > 2R	2R	92%	359 (24,164,171)	206 (11, 137, 58)	0.89	0.83–0.94	4.30E-4***	0.9	0.84–0.96	9.02E-4***
DRD5	rs10033951	C > T	T	92%	353 (3,129,221)	208 (17, 113, 78)	0.79	0.74–0.85	2.72E-11***	0.81	0.76–0.86	1.98E-10***
PACS1	rs10896090	A > G	G	85%	307 (236, 64, 7)	215 (163, 49, 3)	1.00	0.92–1.09	0.97	1.01	0.93–1.09	0.94
TRANK1	rs9834970	T > C	C	85%	305 (132, 148, 25)	214 (112, 88, 14)	0.94	0.87-1.00	0.054	0.94	0.89–1.01	0.09
FSTL5	rs11724116	C > T	T	81%	287 (170, 56, 61)	210 (111, 75, 24)	0.98	0.93–1.04	0.62	0.97	0.92–1.02	0.27
POU3F2	rs2388334	A > G	G	84%	302 (51, 183, 68)	214 (42, 168, 4)	0.84	0.77–0.90	2.89e-06***	0.85	0.80–0.91	1.41e-05***

*Multivariate (adjusted for sex and age); A, Major Allele; a, Minor Allele; *P*-value from Pearson's Chi-squared χ^2 test with Yates' continuity correction. OR, odd ratio; CI, confidence interval; BD, Bipolar Disorder. The significant values are bold and underlined. The threshold significance was kept at a *P*-value < 0.05 in all statistical tests and the adjusted *P*-value after multiple test corrections was set at ≤ 0.004.

Three of the variants, rs2388334, *DRD4* (120bpVNTR) repeat and rs10033951, were found to afford a significant protective effect against BD susceptibility. Univariate logistic regression; rs2388334 [OR(95%CI) = 0.84(0.77–0.90), *P* = 2.89e-06], *DRD4*(120bpVNTR) [OR(95%CI) = 0.89(0.83–0.94), *P* = 4.30e-4], rs10033951 [OR(95%CI) = 0.79(0.74–0.85), *P* = 2.72e-11], multivariate logistic regression; rs2388334 [OR(95%CI) = 0.85(0.80–0.91), *P* = 1.41e-05], *DRD4* (120bpVNTR) [OR(95%CI) = 0.90(0.84–0.96), *P* = 9.02e-4], and rs10033951 [OR(95%CI) = 0.81(0.76–0.86), *P* = 1.98e-10].

3.1.3. Association with SHZ

In SHZ, only rs10033951 revealed protective association, univariate logistic regression analysis: [OR(95%CI) = 0.86(0.80–0.93), *P* = 1.60e-04] and multivariate logistic regression analysis: [OR(95%CI) = 0.89(0.83–0.95), *P* = 0.0013], (Table 4).

Table 5
Association of genetic variants with SHZ

SHZ							Univariate Analysis			Multivariate* Analysis		
Genes	**Variants**	**Allele change**	**Minor Allele**	**Genotype Call rate %**	**Control (n = 390) (AA, Aa, aa)**	**Cases (n = 146) (AA, Aa, aa)**	**OR**	**95% CI**	**P value**	**OR***	**95% CI**	**P* value**
CACNA1c	rs1006737	G > A	A	72%	255 (137, 88, 30)	130 (62,49,19)	1.04	0.97–1.11	0.24	1.03	0.97–1.09	0.37
CACNA1c	rs2238056	T > C	T	88%	330 (33, 100, 197)	139 (14,26,99)	1.05	0.99–1.12	0.09	1.04	0.98–1.10	0.15
DRD1	rs4532	T > C	C	91%	348 (150, 171, 27)	139 (63,74,2)	0.95	0.89–1.02	0.15	0.95	0.89–1.01	0.09
DRD2	rs1799732	GG > G	DEL	94%	359 (309, 45, 5)	144 (129,13,2)	0.95	0.86–1.05	0.36	0.96	0.88–1.06	0.47
DRD3	rs6280	C > T	T	96%	370 (66,180,124)	143 (30,74,39)	0.96	0.91–1.02	0.17	0.95	0.90-1.00	0.06
DRD4	120bp VNTR	1R > 2R	2R	94%	359 (24,164,171)	144 (10,73,61)	0.97	0.91–1.03	0.36	0.96	0.91–1.02	0.24
DRD5	rs10033951	C > T	T	93%	353 (3,129,221)	142 (4,74,64)	0.86	0.80–0.93	1.60e-04 ***	0.89	0.83–0.95	0.0013 **

*Multivariate (adjusted for sex and age); A, Major Allele; a, Minor Allele; *P*-value from Pearson's Chi-squared χ^2 test with Yates' continuity correction. OR, odd ratio; CI, confidence interval; SHZ, Schizophrenia. The threshold significance was kept at a *P*-value < 0.05 in all statistical tests and the adjusted *P*-value after multiple test corrections was set at ≤ 0.007. The significant values are bold and underlined.

3.2. Comparison with 1000 Genomes (PJL) and ALFA SAS data

The genotype and allele frequencies of the studied genetic variants were retrieved from the 1000 Genome PJL (Punjabi in Lahore) and compared with the current data (Supplementary Table S4).

Significant differences were observed with 7 of the 10 variants, in genotype frequencies; rs2238056 [χ^2(*P*) = 23.31(< 0.0001)], rs4532 [χ^2(*P*) = 12.21(0.02)], rs6280 [χ^2(*P*) = 13.50(0.001)], rs10033951 [χ^2(*P*) = 15.90(< 0.0001)], rs9834970 [χ^2(*P*) = 19.13(< 0.0001)], rs11724116 [χ^2(*P*) = 27.89(< 0.0001)], rs238833 [χ^2(*P*) = 64.40(< 0.0001)], and in 6 of the 10 variants in allele frequencies; rs2238056 [χ^2(*P*) = 43.68(< 0.0001)], rs6280 [χ^2(*P*) = 12.96(0.0003)], rs10033951 [χ^2(*P*) = 13.70(< 0.0001)], rs9834970 [χ^2(*P*) = 15.44(< 0.0001)], rs11724116 [χ^2(*P*) = 5.42(< 0.02)], rs2388334 [χ^2(*P*) = 47.71(< 0.0001)].

Allele frequencies were also compared with the ALFA SAS data, significant differences were observed in the same 6 variants, which showed differences with 1000 Genome PJL data, except rs4532, which did not show allele frequency difference with 1000 Genome PJL data while significant deviation was observed in comparison to the ALFA SAS allele frequency data of rs4532 [χ^2(*P*) = 195.9(< 0.0001)].

Additionally, the allele frequency data from 1000 Genome PJL were also compared to the ALFA SAS data to determine the differences in an allele frequency distribution between them. The significant differences were observed among 2 of the 10 variants, rs4532 [χ^2(*P*) = 48.15(< 0.0001)], and rs6280 [χ^2(*P*) = 53.24(< 0.0001)].

4. Discussion

The association analysis of GWAS and candidate gene loci belonging to dopaminergic system genes, in the current psychiatric cohort of the Pakistani population revealed a significant association for *CACNA1c* polymorphisms (rs1006737, rs2238056), *DRD1*-rs4532 *DRD2*-rs1799732, *DRD4*-

120bp, and *DRD5*-rs10033951. Among *CACNA1c* polymorphisms, rs1006737 was associated with a higher risk in both MDD and BD, while, rs2238056 was found to be associated with BD susceptibility only. However, the association did not survive for rs1006737 in MDD when the *P*-value was adjusted for age and sex, suggesting the possible impact of these demographic variables in this association with MDD, while the results remained significant in BD.

Similar to the current findings previously reported studies by He et al, (2014) in Chinese Han and Green et al, (2010) in the British populations, reported the rs1006737 association with MDD (Green et al., 2010; He et al., 2014), and in the European-British population, the association of both the polymorphisms; rs1006737, rs2238056 were reported with BD (Ferreira et al., 2008; Gershon et al., 2014; Green et al., 2010; Starnawska et al., 2016). However, studies conducted on Americans(Frazier et al., 2014), Germans(Kloiber et al., 2012), Europeans (Cross-Disorder Group of the Psychiatric Genomics, 2013) and Swedish population (Lavebratt et al., 2010) found contrasting results for rs1006737 association with MDD and in Southern Taiwanese population with BD (Jan et al., 2014). Whereas, a study of SHZ by Nie et al, (2015), reported the association of rs1006737 in European and Asian populations (Nie et al., 2015), while, the present study failed to establish a significant association of *CACNA1c* polymorphisms in SHZ, which points to the inconsistent association results of *CACNA1c* polymorphism in different populations and ethnicities.

CACNA1c is a calcium channel gene that encodes the alpha subunit (α1C) of the L-type voltage-gated calcium channel (LTCC). The function of the alpha subunit is to determine the kinetics, conductance, voltage dependence and pharmacology of the LTCC (Heyes et al., 2015). LTCC is involved in various aspects of neuronal development, signalling, and also in the establishment of maintenance of connectivity during and after neuronal development (Spitzer, 2006). The role of *CACNA1c* polymorphisms as a pathophysiological factor in the progression of psychiatric disorders has been reported by Yoshimizu et al, (2015) and Starnawska et al, (2016) in clinical and functional studies (Starnawska et al., 2016; Yoshimizu et al., 2015). Both polymorphisms (rs1006737 and rs2238056), are located in intron 3 of *CACNA1c*, which has important gene expression-regulatory functions, through interaction with the transcription start site. This intron also carries CpG islands which underwent a DNA methylation shift due to hypermethylation in the presence of rs2238056 (C > T), (Starnawska et al., 2016). This explains the impact of the polymorphisms (rs1006737 and rs2238056), and the role of intron 3 in the expression of *CACNA1c*, by regulating the 3D genomic architect associated with the chromosomal looping, in the presence of risk alleles of rs1006737 (A) and rs2238056 (T), (Starnawska et al., 2016). Thus the altered LTCC are unable to regulate the calcium influx and efflux which are important steps in neurotransmission, as calcium ions are also needed for the fusion of neurotransmitter vesicles to release neurotransmitters (dopamine, acetylcholine etc.) in the synaptic cleft (Imbrici et al., 2013), suggesting the contribution of *CACNA1c* polymorphisms in the genetic aetiology of psychiatric conditions by altering the functional activity of LTCC in different brain circuits and *CACNA1c* expression.

DRD1 is an extensively studied gene, yet very few reported association studies are available regarding rs4532, which is located on the 5' UTR (untranslated region) (Pan et al., 2014). This locus has been reported to be associated with the therapeutic response to antipsychotics (Potkin et al., 2003), the positive symptoms of SHZ (psychotic symptoms), and with the prefrontal cortex (PFC), related cognitive functions (Rybakowski et al., 2005; Williams & Castner, 2006). In the initial analysis, *DRD1*-rs4532 and *DRD2*-rs1799732 were found to be associated with the risk of MDD in the current cohort, however, the association did not survive for any of these SNPs in MDD, after applying multiple test corrections. The reported association studies in different populations have reported contrasting results to our current findings. A study in the Estonian population has reported no association of rs4532 with MDD (Koks et al., 2006), while, a study of the Sardinian population, reported a significant association of rs4532 with BD (Severino et al., 2005). Whereas in SHZ, the role of rs4532 is still controversial and its role in the manifestation of SHZ is yet to be established in different populations, however, a meta-analysis study conducted in 2014, reported no association of rs4532 in SHZ (Pan et al., 2014), which supports the current findings in SHZ of the present study.

DRD2 SNP rs1799732 is a functional polymorphism in a promoter region of the DRD2 gene, involving the insertion (INS)/deletion (DEL) of a cytosine (-141C INDEL), which affects the receptor density by modulating the transcription and transcription-binding-factors (TBF), and reduces DRD2 expression 20–40% (Arinami et al., 1997). This polymorphism has been reported for its association with MDD in the Chinese Han population (He et al., 2013), while a study in Caucasian populations reported contradictory results in MDD (Furlong et al., 1998; Leszczynska-Rodziewicz et al., 2005). In BD several association studies have reported a lack of risk association of rs1799732 in different ethnicities including Polish (Leszczynska-Rodziewicz et al., 2005), Asian (Han Chinese), and Caucasians (Furlong et al., 1998; Li et al., 1999; Stober et al., 1998). A meta-analysis by Zou et al, (2012), has also reported no association between rs1799732 and mood disorders (BD & MDD) in Caucasians (Zou et al., 2012). Whereas, studies in SHZ have reported risk association of this SNP, rs1799732 in Chinese Han (Xiao et al., 2013), British Caucasian (Breen et al., 1999), and Brazilian population (Cordeiro et al., 2009). Though an ethnicity-based meta-analysis for SHZ, revealed the significant association of rs1799732 with a higher risk of SHZ susceptibility in Asians (Wang et al., 2016), and in Chinese Han (Zhao et al., 2016), but not in Caucasian, Japanese and Indian populations. (Arinami et al., 1997; Zhao et al., 2016).

In the present study, we have also observed that 2 of the studied variants (*DRD4*-120bp repeat and *DRD5*-rs10033951), were found to be associated with a protective effect. *DRD4*-120bp (2R = longer repeat or 120bp duplication), showed a significantly lower risk association with MDD and BD susceptibility, while the association was not found with SHZ. The *DRD4* encodes dopamine receptor 4 (D4), which is involved in inhibitory neurotransmission (Andersen et al., 1990; Civelli et al., 1993; Missale et al., 1998; Niznik & Van Tol, 1992). The *DRD4*-120bp repeat is a promoter region tandem duplication polymorphism (functional polymorphism), having consensus binding sites for transcription factors. This suggests the role of the duplication sequence in conferring differential transcriptional activity (Seaman et al., 1999), by enhancing the binding capacity of certain

transcription factors such as Sp1 (specificity protein 1) in the duplicated form (2R), (Ronai et al., 2004). The Sp1 transcription factor binds to a GC-rich region and can activate or repress the transcriptional activity in response to the physiological or/and pathological stimuli (Infantino et al., 2011). However, functional studies by McCracken et al, (2000)d Souza et al, (2004) reported the lower transcriptional activity of longer repeat (2R), than the shorter allele (1R), suggesting that the duplication allele might have a regulatory role in *DRD4* expression providing an underlying biological mechanism in the aetiology of neuropsychiatric disorders (D'Souza et al., 2004; McCracken et al., 2000).

The *DRD4*-120bp repeat sequence is known to have a difference in allele frequencies in different populations. Significant risk association of duplication sequence (2R), in MDD, has been reported in the Chinese population (Lai et al., 2010) and in SHZ in the Chinese and North Indian populations (Li et al., 2004; Srivastava et al., 2006; Xing et al., 2003), while the non-significant results were reported in Danish SHZ patients (Olsen et al., 2005). The association of *DRD4*-120bp tandem duplication polymorphism has not been reported in case-control association studies of BD, however, an association study on novelty seeking (NS) behaviour analysis in BD patients has reported the association of shorter repeat (homozygous 1R) with higher NS scoring in BD (Rogers et al., 2004). In parallel, the *DRD5* variant, rs10033951 was found as a protective factor in all the studied groups, (MDD, BD and SHZ), in the present study. The literature on the *DRD5* variant is very limited and this locus has not been well studied in different ethinicities for MDD, BD and SHZ. However this variant has been explored in different antipsychotics analysis in psychiatric conditions (Hwang et al., 2012). In addition, DRD genetic variants specifically *DRD4*-48bp VNTR had shown differences in allelic distribution in different ethnic groups from Pakistan (Mansoor et al., 2008). Therefore further replication studies of *DRD4*-120bp and *DRD5* rs10033951 for psychiatric conditions in different population is suggested. On the contrary, the *DRD3* polymorphism rs6280 which is a missense variant (Ser9Gly), showed no risk association in either of the disorders (MDD, BD and SHZ), in our population. However, an association study by Chang et al., (2013) in Chinese BD patients, comorbid with or without anxiety disorders reported a significant association of rs6280 in BD comorbid with an anxiety disorder (Chang et al., 2013). Whereas association studies in SHZ did report a significant association of rs6280 with SHZ, however, all meta-analyses conducted for this variant failed to confirm a significant risk association with SHZ in different ethnicities (www.szgene.org, 2010), which comply with the current findings in SHZ.

Furthermore, 4 variants (*POU3F2*-rs2388334, *PACS1*-rs10896090, *TRANK1*-rs9834970, *FSTL5*-rs11724116), that were recently identified to be associated with BD cohorts of European, North American and Australian populations (Stahl et al., 2019), were screened in the present BD cohort of the Pakistani population. We observed that rs10896090 showed no risk association with BD in the present study, while it was reported to have a significant risk association with BD in a GWAS (Stahl et al., 2019). On the other hand, rs9834970, rs11724116 and rs2388334, were found with lower risk (protective-effect) in BD in the same GWAS (Stahl et al., 2019), however, in the present BD cohort of the Pakistani population, only rs2388334 was found to have a protective effect in BD susceptibility, which supports the previously reported GWAS findings (Stahl et al., 2019).

In the comparative analysis of the genotype and allele frequencies of all the studied genetic variants in the current study to the 1000 Genomes (PJL), significant differences were observed in genotype frequencies or allele frequencies of 6 variants (rs2238056, rs4532, rs6280, rs10033951, rs9834970, rs11724116 and rs2388334). All these variants were found in HWE except, rs10033951, rs11724116 and rs2388334. Similar differences were observed in comparison to ALFA SAS data, except rs4532, which did not show allele frequency differences with 1000 Genome Project PJL data but showed marked deviation in comparison to ALFA SAS allele frequency data. The deviation from 1000 Genome PJL reported frequencies might be due to the smaller sample size (n = 96), of that study as compared to the current study cohort size (n = 390) which was 3–4 folds larger than the 1000 genome PJL Pakistani data set, in addition, PJL included samples of Punjabi origin only from Lahore, which is g geographically separated (about 400–450 km apart) from Islamabad and Rawalpindi. As opposed to this the ALFA SAS reported frequencies were based on a larger sample size and included data of all South Asian populations but unlike the 1000 Genome, it did not describe the geographical location of the ethnicities they have included from Pakistan. In the present study, the majority of the participants, geographically belong to Rawalpindi and Islamabad, while the rest (20–33%) belongs to other geographical areas of Pakistan. Thus sample size and geographical differences might be the possible reasons for the observed deviation and differences.

The present study also had a few limitations, first, the majority of the participants of the current study were of Punjabi ethnic background, secondly, the control group that was collected was from the same geographical location as of the patients, therefore there are chances of overlooking the population stratification because three variants (rs10033951, rs11724116 and rs2388334) showed deviation from HWE of the control population. There is a chance of differences in the origins of the studied population. Thirdly, the sample size was relatively small in BD and SHZ groups. It is always very challenging with smaller cohort sizes, to decide on a genetic association study in multifactorial disorders, due to the diversity of population genetics. Since both the genetic and environmental backgrounds vary for different populations and ethnicities, thus the generalization of these current findings to other populations is limited. Despite all the reported association of the studied variants with the phenotypes, it must be admitted that most of the genetic association analyses in the present study were underpowered (See Supplementary Table 3), which might explain why some of the variants did not replicate the risk association observed in previous studies. Thus, the present study only provides preliminary explanations for the observed associations of the studied variants with MDD, BD and SHZ as these variants were screened for the first time in these psychiatric conditions in the Pakistani population. Future replication studies with larger cohort sizes in multiple ethnic populations are warranted to confirm these findings and functional studies may lead to a better understanding of the underlying genetic architectures of these psychiatric conditions (MDD, BD, and SHZ).

In conclusion, the present study was a replication study of the GWAS and association studies identified variants, in MDD, BD and SHZ in the Pakistani population. The present study explains evidence of some degree of genetic overlap between MDD, BD and SHZ, the underpinnings of susceptibility to these psychiatric conditions. We observed BD associated risk allele at *CACNA1c* polymorphisms (rs1006737), which also confers the risk of MDD susceptibility, whereas the risk allele at *DRD5* polymorphism (rs10033951), found to act as a protective factor in all the 3 psychiatric conditions (MDD, BD and SHZ), in the current Pakistani cohort. However, the role of studied variants in SHZ susceptibility remains elusive due to the contradictory findings on the association of these SNPs in SHZ. We did observe deviation of our results from previously reported findings thus explaining the contribution of divergent genetic and geographical backgrounds of the different populations in clinical heterogeneity in psychiatric illnesses.

Declarations

Statements and Declaration

The study conforms to the Helsinki Declaration and was approved by the Ethics Review Board of the Department of Biosciences, COMSATS University Islamabad, Pakistan. The study was supported by the Higher Education Commission of Pakistan (grant no. 3738), given to (Maleeha Azam) MA, and the Pakistan Academy of Sciences (grant no. 5-9/PAAS/1082) given to RQ. This research was supported by COMSATS University Islamabad (CUI), Pakistan's core grant to (Raheel Qamar) RQ.

Conflicts of Authors

None

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Conflicts of Authors

None

Ethical Approval

The current study conforms to the Helsinki Declaration and was approved by the Ethics Review Board of the Department of Biosciences, COMSATS University Islamabad, Pakistan. All the subjects were informed about the study objectives and written consent was obtained from the subjects or the family member of the patient. The privacy rights of all the participants were kept under consideration and their identity was anonymised.

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