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Original article

The association of MYD88 polymorphism with schizophrenia in the Tunisian population

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Abstract

Since abnormal inflammation triggered by Toll-like receptors was well described in schizophrenia pathophysiology, the altered activation of MyD88, the adaptor protein of the majority of these receptors, has gained attention. However, the genetic predisposition through MYD88 variants to schizophrenia is still unexplored. Therefore, we investigated the possible association between rs4988457 and schizophrenia in the Tunisian population. We performed a case-control study including 145 schizophrenic patients and 157 controls. All participants were genotyped for rs4988457 by PCR-RFLP. The genotypic and allelic frequencies were compared between patients and controls based on clinical characteristics. The statistical analysis of our results revealed a significant decrease of GG+CG genotypes and G allele frequencies in patients with the undifferentiated type of schizophrenia compared to controls (p-value=0.03; OR=0.4, p-value=0.02; OR=0.4, respectively) according to the dominant model. Further analyses showed that SANS and SAPS scores, before treatment, were significantly lower in patients carrying CC+CG compared to patients with CC (p-value=0.00007, p-value=0.003, respectively). After treatment, psychiatric scales scores decreased significantly in CC carriers (SANS: p-value=0.0001, SAPS: p-value=0.000002, BPRS: p-value=0.000001); meanwhile, these scores did not differ in CC+CG carriers (p-value=0.9, p-value=0.3, p-value=0.8, respectively). In addition, BPRS scores were significantly higher in CC+CG carriers compared to CC carriers (p-value=0.01) after treatment. In conclusion, the current study suggests that MYD88 rs4988457 could be associated with protection from the undifferentiated type and positive and negative symptoms of schizophrenia in the Tunisian population. Additionally, rs4988457 could be a pharmacogenetic marker of decreased efficiency of antipsychotic treatment against brief symptoms of schizophrenia.

Keywords: schizophrenia, MYD88, rs4988457, polymorphism

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1. Introduction

Schizophrenia (SCZ) is a chronic and severe psychiatric illness, which is characterized by a loss of contact with reality. SCZ symptoms are very heterogeneous and complex and usually appear in adolescence and last a lifetime [1]. The prevalence of this psychosis was estimated at 0.7% of the general population [2] and 0.6% of the hospitalized Tunisian population [3].

As a multifactorial disorder, SCZ was characterized by a very complex pathophysiology that includes interactions between environmental and genetic factors, causing neurological abnormalities. In the past decades, accumulating evidence suggested that the immune system could be one of the major underlying mechanisms. Thus, environmental stimulation of the innate immune system (infections, stress, etc.) during the perinatal period, in the presence of genetic alterations of immune genes, could lead to an altered neuroinflammatory response, causing structural and functional abnormalities in the brain response for the development of schizophrenia [4]. As one of the major families of innate receptors, the alteration of toll-like receptors' (TLR) activation and expression has been widely demonstrated in animal models and SCZ patients [5,6]. Hence, the investigation of the role of the signaling pathway of these receptors has gained attention. Indeed, previous studies have demonstrated an altered expression of the adaptor protein of most TLRs, the myeloid differentiation primary response 88 (MyD88), in schizophrenia patients [6]. Moreover, MyD88 activation upon TLR3 stimulation was associated with decreased expression of the gene Disrupted in schizophrenia 1 (Disc1) and impaired neurogenesis. Thus, DISC1 has been widely linked to SCZ and the neurological alterations of the disorder [7]. In mice, MyD88-deficiency was associated with altered brain development and neuronal activity, causing abnormal behavior [8,9]. Taking it all together, the alteration of MyD88 expression and activation could be caused by genetic variations. Indeed, the MYD88 gene is located on chromosome 3p21.3-p22; this region has been linked to schizophrenia [10]. However, only one study has investigated the predisposition of MYD88 polymorphisms such as 1944C>G to SCZ in the Spanish population. The

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polymorphism 1944C>G (rs4988457) consists of a substitution of C by G at position 1944 of a non-codifying exon [11].

Regarding the aforementioned findings, MYD88 could be a potential candidate gene for the genetic predisposition to SCZ. Therefore, we conducted a case-control study to investigate the possible association between the polymorphism rs4988457 of MYD88 and SCZ in the Tunisian population.

2. Materials and methods

Study population

We enrolled a case-control study composed of 145 schizophrenic patients and 157 healthy controls (HC). Patients were recruited from the Psychiatry Department of Fattouma Bourguiba University Hospital in Monastir, Tunisia. Their recruitment was controlled by strict inclusion and exclusion criteria. The inclusion criteria consist of including only volunteered SCZ patients who showed persistent symptoms for at least six months, with one month of active phase. However, patients showing blood relations and diagnosed with other psychiatric disorders and/or a metabolic medical condition are excluded.

Experienced psychiatrists from this department interviewed patients for their socio-demographic data, clinical characteristics (onset age, psychiatric scales, actual and annual adaptation, psychiatric antecedent, and psychopathologic scale), and substances' consumption. Moreover, psychiatrists diagnosed patients with SCZ and its different subgroups based on the Diagnostic and Statistical Manual of Mental Disorders-IV-TR. The classification of patients into the different SCZ subtypes was based on dominant symptoms: the paranoid subtype (delusions/ hallucinations), the disorganized subtype (speech/behavior/ affect), the catatonic subtype (motor immobility/ excitement), the undifferentiated subtype (mixed symptoms), and the residual subtype (history, minor current symptoms) [12].

On average, psychiatrists prescribed daily doses of 385.2 ± 260.2 mg of antipsychotics for each patient. The treatment included typical (haloperidol, fluphenazine, chlorpromazine) and/or atypical (risperidone, olanzapine, amisulpride) antipsychotics supplemented with anticholinergic treatment for 56.7% of these patients.

HC were recruited from the Regional Center of Blood Transfusion of Farhat Hached University Hospital of Sousse, Tunisia. The inclusion criteria consist of including only volunteered controls who do not show any mental illness. However, participants who are blood-related and diagnosed with inflammatory diseases and have a family history of mental illness were excluded from the study.

Socio-demographic and clinical characteristics of the studied populations are summarized in table 1.

Table 1. The studied populations' socio-demographic and clinical features

Variables	Populations	SCZ (N = 145)	HC (N = 157)	p-value
Gender	Male: n (%)	121 (83.5)	134 (85.4)	0.6
	Female: n (%)	24 (16.5)	23 (14.6)	
Age (years): (mean ± SD)		37.70 ± 10.40	36.10 ± 10.40	0.2
Onset-age (years): (mean ± SD)		26.20 ± 8.00	--	--
Clinical subgroups	Paranoid: n (%)	41 (28.30)	--	--
	Undifferentiated: n (%)	68 (46.90)	--	--
	Disorganized: n (%)	21 (14.50)	--	--
SANS 1 score (mean ± SD)		24.50 ± 12.80	--	--
SAPS 1 score (mean ± SD)		22.90 ± 11.60	--	--
BPRS 1 score (mean ± SD)		42.30 ± 14.50	--	--
SANS 2 score (mean ± SD)		14.70 ± 6.80	--	--
SAPS 2 score (mean ± SD)		12.50 ± 5.60	--	--
BPRS 2 score (mean ± SD)		31.50 ± 9.90	--	--
Alcohol consumption: n (%)		10 (7)	0	--
Smoking: n (%)		29 (20)	64 (40.80)	0.0004

SCZ: Schizophrenia, HC: healthy controls, SD: standard deviation, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, BPRS: Brief Psychiatric Rating Scale, 1/2: before/after antipsychotic treatment, the χ^2 test was applied to compare categorical variables, whereas quantitative variables were compared by the student-t test between SCZ and HC populations, $p<0.05$ is considered statistically significant.

Ethical aspects

After explaining the procedures and the aim of the study, written informed consent was obtained from each participant or his family. The ethical committee of research in life and health sciences of the Higher Institute of Biotechnology of Monastir, Tunisia, has validated the methodology conducted in the current study (N°: 005/2020).

MYD88 polymorphism genotyping by PCR-RFLP

Venous blood (5 ml) was collected from each participant in tubes with anticoagulant (EDTA). The salting-out method was applied to extract genomic DNA from leukocytes. We realized a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique for the detection of the single-nucleotide polymorphism (SNP) rs4988457 of MYD88. The following primers (forward: 5'-GAGATGATCCGGCAACTGGAA-3' and reverse: 5'-CTGGGAATAGCTTCAGGAAGGG-3') were used to amplify a sequence of 249 bp containing the polymorphism rs4988457. These primers were designed by Primer-Blast (https://www.ncbi.nlm.nih.gov/tools/primer-blast) based on the genetic sequence obtained from the dbSNP (https://www.ncbi.nlm.nih.gov/snp/). PCR products were digested with the restriction enzyme Cac8I after an overnight incubation at 55°C. The identification of this enzyme was performed using the online tool of New England Biolabs NEBcutter 3.0 (https://nc3.neb.com/NEBcutter/). Finally, the separation of restriction fragments using electrophoresis on a 3.5% agarose gel stained with ethidium bromide allowed us to identify each genotype after UV visualization. Thus, a single band with 249 bp indicated a CC genotype. Two bands of 195 and 54 bp indicated a GG genotype. The presence of the three bands indicated a heterozygous genotype CG. The genotype of 20% of the participants was randomly verified.

Statistical analysis

Qualitative variables were presented as frequency (percentage), while quantitative variables were presented as mean ± standard deviation (SD). For Hardy–Weinberg equilibrium (HWE) evaluation, the chi-square ($\chi 2$) test was applied to test genotypes' distribution among the studied population. The population is considered in HWE if $\chi 2$ calculated < 3.84 (degree of freedom = 1 and p-value > 0.05).

The possible association between the polymorphism of MYD88 and SCZ was explored by comparing genotypic and allelic frequencies between HC and patients. This association was tested based on different socio-demographic and clinical characteristics. Thus, the two-way contingency table with $\chi 2$ test or Fisher's exact test (if n<5) was applied for qualitative variables.

The estimation of the best-fit inheritance model was performed by the Akaike information criterion (AIC). The model with the lowest AIC score indicated the preferred inheritance model [13].

For quantitative variables, the Student's t-test is applied for means comparison between two independent groups or between two groups before and after antipsychotic treatment of the same patients using the paired Student-t test, if the normality test validated data distribution. Otherwise, nonparametric tests were applied.

The statistical difference is considered significant if a two-tailed p-value < 0.05. The relative risk of genotypes and alleles' associations with SCZ is defined by the odds ratio (OR) value at 95% confidence interval (CI). The power of statistical analyses is estimated for an α error = 0.05, a total sample size, and a medium effect size using the G*power software (version 3.1.9.7) [14].

All statistical analyses realized in the current study were performed using SPSS software (version 23, SPSS, Armonk, NY, USA) and the online version of OpenEpi (https://www.openepi.com/TwobyTwo/TwobyTwo.htm).

3. Results

In the current study, the distribution of genotypic frequencies of MYD88 SNP rs4988457 among the studied populations confirmed the HWE test for HC ($\chi 2 = 2.67 < 3.84$) and the patient group ($\chi 2 = 0.03 < 3.84$).

The distribution of MYD88 rs4988457 genotypes and allele frequencies between HC and SCZ patients according to inheritance models is summarized in Table 2. The AIC analysis of genotypes' distribution demonstrated that the recessive model (419) has the lowest score in comparison to the co-dominant (421) and the dominant (421) models. Thus, the comparison of genotypes' frequencies according to the recessive model between HC and SCZ patients revealed a similar distribution of the GG genotype in both groups (p-value = 0.2). Similarly, the comparison of allelic frequencies did not show any significant difference in minor allele G frequencies between controls and patients (p-value = 0.1) (Table 2). The statistical power of the genotypic and allelic frequencies analysis between HC and SCZ patients was estimated at 93%.

In order to investigate specific associations, the predisposition of the studied SNP to SCZ was also explored according to different clinical and socio-demographic features of the disorder.

First, the distribution of rs4988457 genotypes and alleles was analyzed according to SCZ subtypes. The AIC analysis of genotypes' distribution according to different inheritance models demonstrated that the dominant model (274) showed the lowest value compared to the codominant (276) and recessive (279) models. Thus, our results demonstrated significantly lower CG genotype frequencies in patients diagnosed with the undifferentiated subgroup (UDSCZ) (8.80%) compared to HC (19.80%) (p-value = 0.04; OR = 0.4) according to the co-dominant model. Moreover, the comparison of genotypic frequencies between the UDSCZ and the HC group according to the dominant model revealed a significant decrease of GG+CG genotypes frequencies in patients compared to controls (10.30% vs. 22.90%; p-value = 0.03; OR = 0.4, respectively). In the same way, the statistical analysis of the allelic frequencies' distribution revealed that the frequency of the minor allele G was significantly lower in UDSCZ compared to HC (p-value = 0.02; OR = 0.4) (Table 3). The statistical analysis of genotypic and allelic frequencies between the UDSCZ and the HC group showed a statistical power of 85%.

Second, the genetic predisposition of rs4988457 to SCZ

symptoms in response to antipsychotic treatment was investigated based on its association with psychiatric scales before and after treatment. Before antipsychotic treatment, patients carrying CC+CG genotypes demonstrated significant low SANS and SAPS scores in comparison to patients with the CC genotype (p-value = 0.00007, p-value = 0.003, respectively). After antipsychotic treatment, the scores of all psychiatric scales significantly decreased in patients carrying the CC genotype (SANS: p-value = 0.0001, SAPS: p-value = 0.000002, BPRS: p-value = 0.000001); however, patients carrying the CC+CG genotypes did not show any significant difference (p-value = 0.9, p-value = 0.3, p-value = 0.8, respectively). Moreover, CC+CG carriers demonstrated only significantly higher BPRS scores in comparison to CC carriers (p-value = 0.01) (Table 4).

Table 2. The distribution of MYD88 rs4988457 genotypes and allele frequencies between HC and SCZ according to inheritance models

Models		HC **N** = 157	SCZ **N** = 145	p-value	OR (95%CI)	AIC
	Genotypes	n (%)	n (%)			
Codominant	CC	121 (77.10)	120 (82.80)		1	421
	CG	31 (19.80)	24 (16.60)	0.4	0.8 (0.40-1.40)	
	GG	5 (3.2)	1 (0.7)	0.2	0.2 (0.004-1.80)	
Dominant	CC	121 (77.10)	120 (82.80)		1	421
	GG+CG	36 (22.90)	25 (17.20)	0.2	0.7 (0.40-1.20)	
Recessive	CC+CG	152 (96.80)	144 (99.3)		1	419
	GG	5 (3.20)	1 (0.7)	0.2	0.2 (0.004-1.90)	
	Alleles	n (%)	n (%)			
	C	273 (87)	264 (91)		1	
	G	41 (13)	26 (9)	0.1	0.6 (0.40-1.10)	

HC: healthy controls, SCZ: schizophrenia, p<0.05 is considered statistically significant, OR: Odds ratio, CI: Confidence interval, AIC: Akaike information criterion, comparison of genotypic and allelic frequencies between HC and SCZ was performed by the χ^2 test or Fisher's exact test (n<5)

Table 3. The distribution of MYD88 rs4988457 genotypes and allele frequencies between HC and Undifferentiated subgroup

Models		HC **N** = 157	UDSCZ **N** = 68	p-value	OR (95%CI)	AIC
	Genotypes	n (%)	n (%)			
Codominant	CC	121 (77.10)	61 (89.70)		1	276
	CG	31 (19.80)	6 (8.80)	**0.04**	0.4 (0.15-0.90)	
	GG	5 (3.20)	1 (1.50)	0.2	0.2 (0.004-1.80)	
Dominant	CC	121 (77.10)	61 (89.70)		1	274
	GG+CG	36 (22.90)	7 (10.30)	**0.03**	0.4 (0.16-0.90)	
Recessive	CC+CG	152 (96.80)	67 (98.50)		1	279
	GG	5 (3.20)	1 (1.50)	0.8	0.2 (0.01-4.20)	
	Alleles	n (%)	n (%)			
	C	273 (87)	128 (94)		1	
	G	41 (13)	8 (6)	**0.02**	0.4 (0.20-0.90)	

HC: Healthy Controls, UDSCZ: Undifferentiated Schizophrenia, OR: Odds ratio, CI: Confidence interval, AIC: Akaike information criterion, χ^2 test or Fisher's exact test (if n<5) was used to compare genotypic and allelic frequencies between HC and UDSCZ patients, p<0.05 is considered statistically significant.

Table 4. Comparison of psychiatric scales scores between MYD88 rs4988457 genotypes in SCZ patients according to the dominant model

	Genotypes		p-value		
	CC	GG+CG	CC vs. GG+CG	CC: 1 vs. 2	GG+CG: 1 vs. 2
SANS 1 score	26.0 ± 12.10	6.90 ± 4.0	**0.00007**		
SANS 2 score	15.30 ± 6.80	9.50 ± 3.40	0.1	**0.0001**	0.9
SAPS 1 score	24.10 ± 11.30	11.50 ± 7.30	**0.003**		
SAPS 2 score	12.70 ± 5.60	11.20 ± 6.10	0.6	**0.000002**	0.3
BPRS 1 score	42.80 ± 13.90	38.80 ± 18.50	0.3		
BPRS 2 score	30.20 ± 9.40	40.70 ± 9.70	**0.01**	**0.000001**	0.8

Results were expressed by mean ± standard deviation, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, BPRS: Brief Psychiatric Rating Scale, 1/2: before/after antipsychotic treatment, Shapiro-Wilk test was applied to test normality, the student-t test was used to compare means between genotypes, the paired Student-t test was used to compare means of psychiatric scales for the same patients before and after antipsychotic treatment, p<0.05 is considered statistically significant.

Finally, we explored possible associations of rs4988457 with other clinical and socio-demographic characteristics; however, we could not detect any statistical significance with genders, onset age, treatments, and substance abuse (alcohol and tobacco).

4. Discussion

Regarding the well-established role of TLR altered activation as one of the underlying mechanisms of abnormal inflammation in the pathophysiology of SCZ, the investigation of the potential implication of MyD88 as the major protein adaptor of these receptors has gained attention [5,6]. Indeed, MyD88 altered expression and activation could be implicated in SCZ pathophysiology [6,7]. Otherwise, the genetic dysfunction of MYD88 showed abnormal behavior in knockout mice caused by altered neuronal development and activity [8,9]. Furthermore, a previous study has demonstrated that the MYD88 gene could be associated with schizophrenia [10]. These promising findings prompt us to investigate the possible genetic predisposition of the MYD88 variant rs4988457 to SCZ in the Tunisian population.

The AIC analysis of the genotypic distribution of the MYD88 rs4988457 SNP among the studied populations estimated that the recessive model with the lowest AIC score compared to the two other models could be the best-fit transmission model. Thus, the comparison of genotypes' distribution between HC and SCZ patients according to the recessive model did not show any significant difference in GG genotype frequencies between both groups. Similarly, the distribution of allelic frequencies of rs4988457 was similar between controls and patients. These results suggest that rs4988457 could not be associated with SCZ in the Tunisian population. Corroborating with our results, a previous study has demonstrated the absence of any association of rs4988457 with SCZ in the Spanish population [11]. Similarly, rs4988457 did not show any association with sepsis, tuberculosis, and Hodgkin's lymphoma [15–17].

Schizophrenia is a very heterogeneous and complex disorder. Therefore, we investigated the possible association of rs4988457 with different socio-demographic and clinical characteristics of this disorder. Starting with the different subgroups of SCZ, our results revealed a significant increase in CG genotype frequencies in HC compared to patients diagnosed with the undifferentiated subgroup according to the co-dominant model. In addition, GG+CG genotypes of rs4988457 were significantly higher in controls compared to patients according to the dominant model. However, the AIC analysis showed that the dominant model with the lowest score is the preferred one for genotypes' analysis. Furthermore, the allelic distribution of rs4988457 revealed a significant decrease of the G allele frequency in UDSCZ patients compared to HC with OR (95%CI) = 0.4 (0.16-0.90). Hence, our results suggest that rs4988457 could be associated with protection from the undifferentiated subgroup of SCZ according to the dominant model. Since García-Bueno et al., 2016 did not explore the possible association of this variant with SCZ subgroups, this could be the first study demonstrating a protective genetic effect of MYD88 SNP rs4988457 against the undifferentiated subgroup.

Next, we examined the possible association between rs4988457 and the scales of assessment of negative, positive, and brief psychiatric symptoms (SANS, SAPS, and BPRS) before and after antipsychotic treatment of patients. Thus, CC+CG carriers showed significantly lower SANS and SAPS scores in comparison to CC genotype carriers, before treatment. Hence, the rs4988457 polymorphism could be associated with protection from negative and positive symptoms' onset. These findings support the aforementioned protective association from the undifferentiated type of SCZ, which is characterized by a mixture of various symptoms. After treatment, CC genotype carriers revealed a significant decrease in SANS, SAPS, and BPRS scores, while CC+CG carriers did not show any significant difference. Interestingly, only BPRS scores increased significantly in CC+CG carriers compared to CC carriers in response to treatment. Thus, rs4988457 could be associated with lower efficiency of antipsychotic treatment against brief psychiatric symptoms of SCZ. A previous study has demonstrated higher MyD88 expression in treated SCZ patients, which has been suggested to be associated with genetic modifications [11]. Moreover, we could previously demonstrate a possible genetic predisposition of functional TLR polymorphisms to the efficiency of antipsychotic treatment of SCZ [18,19]. Therefore, investigating pharmacogenetic markers is essential for more personalized and efficient antipsychotic treatment.

Despite the novel insights, it must be acknowledged that our study presented some limitations. Regarding the recent interest in the predisposition of MYD88 polymorphisms to SCZ, our discussion was limited to only one study, which did not investigate any socio-demographic or clinical parameters of SCZ. In addition, we could not explain the demonstrated associations because the effect of the studied SNP on MyD88 activation and on inflammation is still unexplored. Furthermore, the small size of the studied populations and the investigation of specific associations with SCZ subtypes caused smaller groups, which could be associated with false-positive results. Indeed, the small sample size of the UDSCZ subgroup (n = 86) was associated with a relatively low statistical power (85%). We acknowledge that this study is exploratory, and the suggested associations are subject to the limitations of our current sample size and should be interpreted as preliminary results. Therefore, further study with a larger sample size and investigating the functional effect of rs4988457 would be necessary to confirm and functionally explain our findings.

In conclusion, the current study could be the first to present the polymorphism rs4988457of MYD88 as a genetic protective factor against the undifferentiated type and positive and negative symptoms of SCZ in the Tunisian population. Moreover, rs4988457 could be associated with lower efficiency of antipsychotic treatment against brief psychiatric symptoms of schizophrenia.

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Declarations of interest

None.

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Author Contributions:

Besma Bel Hadj Jrad: Conceptualization, Supervision, Writing - review & editing. Youssef Aflouk: Methodology, Investigation, Writing - Original Draft. Nawres Maafi: Investigation, Data curation. Oumaima Inoubli: Formal analysis, Software. Saloua Yacoub: Resources. Ferid Zaafrane: Resources. Lotfi Gaha: Resources.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

The current study was approved by the ethical committee of research in life and health sciences of the Higher Institute of Biotechnology of Monastir, Tunisia (N°: 005/2020), according to the Helsinki Declaration of 2013.

Consent to participate

Written informed consent was obtained from all subjects included in the study or from patients' family members.

Consent to publish

All participants provide informed consent for the publication of the study.

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