Egyptian Journal of Medical Human Genetics

RESEARCH Open Access

Interleukin-1 receptor antagonist (IL-1RA) and interleukin-4 (IL-4) variable number of tandem repeat polymorphisms in schizophrenia and bipolar disorder: an association study in Turkish population

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Abstract

Background: Pro-inflammatory/anti-inflammatory cytokine imbalance in cerebrospinal fluid or plasma of schizophrenia (SCZ) and bipolar disorder (BD) patients has been documented over the last decade. We aim to examine the interleukin-1 receptor antagonist *(IL-1RA)* and *IL-4* variable number of tandem repeat (VNTR) polymorphisms in SCZ and BD patients by comparing them with healthy controls.

Methods: Two hundred and thirty-four unrelated patients (127 patients with SCZ, 107 patients with BD) and 204 healthy controls were included. The Structured Clinical Interview for DSM-IV Axis I Disorders was used to confirm the diagnosis. In addition, the polymerase chain reaction technique was used to investigate *IL-1RA* and *IL-4* VNTR polymorphisms.

Results: Our results showed that the distributions of *IL-1RA* and *IL-4* genotype and the allele frequencies of SCZ or BD patients were not significantly different from the healthy control group. *IL-1RA* allele 2 homozygous genotype and *IL-1RA* allele 2 frequencies were non-significantly higher among SCZ patients than in controls.

Conclusions: Our study indicates that the *IL-1RA and IL-4* VNTR polymorphisms are not considered risk factors for developing SCZ and BD among Turkish patients.

Keywords: Schizophrenia, Bipolar disorder, Inflammation, *IL-1RA*, *IL-4*, VNTR

Background

Schizophrenia (SCZ) and bipolar disorders (BD) are among the leading causes of disability worldwide, affecting around 1% of the population. However, biological mechanisms are still inadequately understood, where the interaction of environmental and genetic risk factors seems to play a prominent function in their etiology [1–3]. Moreover, expanding evidence has demonstrated that defects in immune-related genes present SCZ and BD susceptibility [4–8]. Numerous researchers have documented an imbalance in pro-inflammatory/anti-inflammatory cytokines or the level of their soluble receptors in plasma or cerebrospinal fluid of these patients over the last decade [9, 10]. Th1/Th2 imbalance with decreased levels of Th1-related cytokines and compensatory raised Th2-cytokine levels have been consistently observed in untreated SCZ patients [11]. In addition, IL-6 and TNF-alpha production of manic patients with BD was significantly higher than those of healthy participants, while

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IL-4 levels of the patients were significantly lower than controls [9].

The interleukin-1 receptor antagonist (IL-1RA) inhibits IL-1 activity by binding to the IL-1 receptors [12]. The IL-1RA encoding gene is found in chromosome 2q14, and the *IL-1RA* gene has a penta-allelic polymorphic region that contains variable numbers of an 86-bp tandem repeat (VNTR) (rs2234663) in intron 2 [13]. In addition, allele 2 of the *IL-1RA* VNTR variant is associated with elevated production of the IL-1β in vitro [14]. Plasma levels of IL-1RA and sTNF-R1 have been found to be related to general symptom severity and psychotic features of patients diagnosed with SCZ and BD [15]. Although documented results are contradictory, it has been shown that disease susceptibility in SCZ has been linked to the VNTR polymorphism in intron 2 of *IL-1RA* [16–18]. Besides, some results propose a relationship between BD and VNTR polymorphism in *IL-1RA* in literature [19].

IL-4 is a prototypic member of Th2 cytokines and has a potent anti-inflammatory feature [20]. It diminishes the production and effect of pro-inflammatory cytokines and concerns the isotype switching from immunoglobulin (Ig)M/IgG to IgE by B lymphocytes [21, 22]. IL-4 encoding gene is found in chromosome 5q31.1, and in its third intron, a 70 bp VNTR polymorphism (rs8179190) could alter the expression level of the *IL-4* gene. This VNTR polymorphism includes three alleles: RP1 allele, with three repeats, RP2 allele, with two repeats, and RP3 allele, with four repeats. The frequency of RP2 allele is lower than the RP1 alleles. Again, the RP3 allele is insufficiently detected in a few populations [23]. Besides the VNTRs sequence in the third intron, so far, more than 50 allelic variant polymorphisms have been described for *IL-4* gene, including − 33C/T (rs2070874), − 590C/T (rs2243250), 2979G/T (rs2227284), and + 3437C/G (rs2227282) [24]. Although we did not find any research on the relationship between *IL-4* VNTR polymorphism and SCZ or BD when we looked at the literature, some studies on the relationship between some peripheral cytokine levels, including IL-4, and these psychiatric disorders, drew our attention. Regarding BD, a meta-analysis and systematic review showed that levels of the soluble IL-2 receptor (sIL-2R), IL-4, sIL-6R, and TNF-α were significantly higher in BD patients than in healthy subjects [25]. Similarly, IL4 and IL-10 levels have been found to be associated with negative symptoms of SCZ [26]. Therefore, these studies might suggest that IL-4-related anti-inflammatory immunological processes may have a role in the SCZ and BD pathophysiology.

Although *IL-1RA* VNTR polymorphisms have been studied as potential susceptible markers for SCZ and BD, there is no published research about the relationship between *IL-4* VNTR polymorphism and SCZ or BD susceptibility. To the best of our knowledge, the present study is the first report investigating the possible association between *IL-4* VNTR polymorphism and the risk of SCZ or BD. Therefore, this research aims to investigate the connection between *IL-1RA* and *IL-4* VNTR polymorphisms in SCZ and BD by comparing the genotype distribution of these genes between Turkish patients and the healthy control group.

Methods

Study population

This case–control study included 234 unrelated patients (127 patients with SCZ, 107 patients with BD). Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) was used for the psychiatric clinical interview. They were consecutively accepted in Malazgirt State Hospital Psychiatry Outpatient Clinic for three months. The standardized, well-accepted drug regimen was applied to all patient groups. They were in remission and thus did not describe complaints that required hospitalization. Patients were excluded from the research if they had mental retardation, organic disorder, or psychiatric disorders other than SCZ or BD. We recruited age-, sex-, geographic area-, and ethnicity-matched 204 healthy participants who were well-matched with the patients' group. The Clinical Research Ethics Committee of the Istanbul Faculty of Medicine approved our study under the ethical standard for human experimentation established by the Declaration of Helsinki (29.01.2021-56267) [27].

DNA analyses

We collected peripheral blood into tubes with EDTA and extracted genomic DNA from the samples with the Quick-DNA Miniprep Plus Kit (Zymo Research). DNA samples were stored at − 20 °C. We investigated *IL-1RA* VNTR polymorphism by the PCR technique using the forward 5′-CTC AGC AAC ACT CCT AT-3′ and reverse 5′-TTC CAC CAC ATG GAA C-3′ primers. PCR products were separated by electrophoresis within a 2% agarose gel and visualized by ethidium bromide staining. Furthermore, we used the forward 5′AGG CTG AAA GGG GGA AAG C-3′ and reverse 5′-CTG TTC ACC TCA ACT GCT CC-3′ primers for *IL-4* amplification and examined the PCR products by gel electrophoresis [28, 29].

Statistical analyses

Statistical analysis was performed using IBM SPSS version 21.0 (IBM Corp. released 2012; Armonk, NY, USA). We analyzed genotype distributions in participants due to the Hardy–Weinberg Equilibrium (HWE).

Comparisons of genotype and allele frequencies between SCZ/BD patients and controls were performed using the Pearson chi-square or Fisher's exact test. The power analysis was performed with the "G*power" software (version 3.0.5, http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/). The possible presence of population stratification bias has been calculated, according to Lee and Wang [30]. Because two polymorphisms were included in this study, the significance level was set as 0.025 (0.05/2) after the Bonferroni correction.

Results

IL-1RA genotyping

According to the differences in 86-bp tandem repeat number, three types of alleles can be recognized through the study. *IL-1RA* allele 1 (4 repeats, 420-bp) and *IL-1RA* allele 2 (2 repeats, 240-bp) were the most common; meanwhile, *IL-1RA* allele 4 (3 repeats, 326-bp) was rare. Most of the patients and control subjects carried the *IL-1RA* allele 1. The participants were evaluated according to clinical characteristics, as shown in Table 1. When the *IL-1RA* genotype distributions of SCZ patients were compared with the control group, the genotype distributions were not significantly different between the SCZ patients and the control group (1/1 vs. 1/2+1/4+2/2) ($p=0.231$), (1/2 vs. 1/1+1/4+2/2) ($p=0.845$), (1/4 vs. 1/1+1/2+2/2) ($p=0.673$), and (2/2 vs. 1/1+1/2+1/4) ($p=0.086$). Again, the *IL-1RA* allele frequency distributions were not significantly different between SCZ patients and the control group (1 vs. 2+4) ($p=0.078$), (2 vs. 1+4) ($p=0.097$), and (4 vs. 1+2) ($p=0.676$). *IL-1RA* allele 2 homozygous genotype and *IL-1RA* allele 2 frequencies were non-significantly higher among SCZ patients than in controls (Table 2). When the *IL-1RA* genotype distributions of BD patients were compared with the control group, the genotype distributions were not significantly different between the BD patients and the control group (1/1 vs. 1/2+1/4+2/2) (p=0.571), (1/2 vs. 1/1+1/4+2/2) ($p=0.392$), (1/4 vs. 1/1+1/2+2/2) ($p=1.000$), and (2/2 vs. 1/1+1/2+1/4) ($p=0.676$). Additionally, the *IL-1RA* allele frequency distributions were not significantly different between BD patients and the control group (1 vs. 2+4) ($p=0.826$), (2 vs. 1+4) ($p=0.830$), and (4 vs. 1+2) ($p=1.000$) (Table 3).

Table 1 The clinical characteristics of participants

(Years)	BD (N:107) Mean ± SD	SCZ (N:127) Mean ± SD
Age	41.64 ± 11.75	40.91 ± 10.73
Age of onset	26.14 ± 9.05	24.75 ± 8.39
Duration of disorder	15.62 ± 10.38	16.20 ± 9.51
Number of hospitalization	3.20 ± 4.16	3.51 ± 4.58

Table 2 Comparison of frequencies of *IL-1RA* VNTR polymorphism between SCZ patients and healthy controls

Genotype	SCZ $n=$ [a] (%)	Healthy control $n=182$ (%)	OR	95% CI	p
IL-1RA					
1/1	48 (38.7)	83 (45.6)	0.753*	0.473–1.199*	.231*
1/2	47 (37.9)	71 (39.0)	0.954*	0.597–1.526*	.845*
1/4	6 (4.8)	7 (3.8)	1.271*	0.417–3.877*	.673*
2/2	23 (18.5)	21 (11.5)	1.746*	0.919–3.317*	.086*
Allele					
1	149 (60.1)	244 (67.0)	0.740*	0.529–1.035*	.078*
2	93 (37.3)	113 (31.0)	1.333*	0.949–1.872*	.097*
4	6 (2.4)	7 (1.9)	1.264*	0.420–3.808*	.676*

[a] $n=124$

*Pearson chi-square

IL-4 genotyping

The distribution of intron 3 VNTR *IL-4* genotype frequencies, allele frequencies, and risk association were compared between SCZ patients and controls and summarized in Table 4. When the *IL-4* genotype distributions of SCZ patients were compared with the control group, the genotype distributions were not significantly different between the SCZ patients and the control group (P1/P1 vs. P1/P2+P2/P2) ($p=0.346$), (P1/P2 vs. P1/P1+P2/P2) ($p=0.383$), and (P2/P2 vs. P1/P1+P1/P2) ($p=0.198$). Likewise, the *IL-4* allele frequency distributions were not significantly different between SCZ patients and the control group (P1 vs. P2) ($p=0.129$). When the *IL-4* genotype distributions of BD patients were compared with the control group, the genotype distributions were not significantly different between the BD patients and the control group (P1/P1 vs. P1/P2+P2/P2) ($p=0.321$), (P1/P2 vs. P1/P1+P2/P2) ($p=0.476$), and (P2/P2 vs. P1/P1+P1/P2) ($p=0.270$). Similarly, the *IL-4* allele frequency distributions were not significantly different between BD patients and the control group (P1 vs. P2) ($p=0.182$) (Table 5).

Discussion

Our results demonstrated that the functional VNTR polymorphism distributions of the *IL-1RA* and *IL-4* of SCZ and BD patients were not significantly different from the control group. The functional VNTR polymorphism of the *IL-1RA* has also been considerably analyzed in the literature. For example, Kim et al. reported that allele 2 was associated with SCZ in a Korean population [16], while Zanardini et al. documented that *IL-1RA* allele 1

Table 3 Comparison of frequencies of *IL-1RA* VNTR polymorphism between BD patients and healthy controls

Genotype	BD $n=^{a}$ (%)	Healthy control $n=182$ (%)	OR	95% CI	*p*
IL-1RA					
1/1	52 (49.1)	83 (45.6)	1.149*	0.711–1.856*	.571*
1/2	36 (34.0)	71 (39.0)	0.804*	0.488–1.326*	.392*
1/4	4 (3.8)	7 (3.8)	0.980[&]	0.280–3.430[&]	1.000[&]
2/2	14 (13.2)	21 (11.5)	1.167*	0.566–2.404*	.676*
Allele					
1	144 (67.9)	244 (67.0)	1.041*	0.725–1.496*	.826*
2	64 (30.2)	113 (31.0)	0.961*	0.665–1.388*	.830*
4	4 (1.9)	7 (1.9)	0.981[&]	0.284–3.390[&]	1.000[&]

[a] $n=106$

[*] Pearson chi-square

[&] Fisher's Exact Test

Table 4 Comparison of frequencies of the *IL-4* VNTR polymorphism between SCZ patients and healthy controls

Genotype	SCZ $n=^{a}$ (%)	Healthy control $n=204$ (%)	OR	95% CI	*p*
IL-4					
P1/P1	6 (4.7)	5 (2.5)	1.974[&]	0.590–6.606[&]	.346[&]
P1/P2	34 (26.8)	46 (22.5)	1.256*	0.753–2.095*	.383*
P2/P2	87 (68.5)	153 (75)	0.725*	0.444–1.184*	.198*
Allele					
P1	46 (91.9)	56 (93.5)			
P2	208 (8.1)	352 (6.5)	1.390*	0.908–2.128*	.129*

[a] $n=127$

[*] Pearson chi-square

[&] Fisher's Exact Test

Table 5 Comparison of frequencies of the *IL-4* VNTR polymorphism between BD patients and healthy controls

Genotype	BD $n=^{a}$ (%)	Healthy control $n=204$ (%)	OR	95% CI	*p*
IL-4					
P1/P1	5 (4.7)	5 (2.5)	1.951[&]	0.552–6.894[&]	.321[&]
P1/P2	28 (26.2)	46 (22.5)	1.217*	0.708–2.093*	.476*
P2/P2	74 (69.2)	153 (75)	0.747*	0.445–1.255*	.270*
Allele					
P1	38 (17.8)	56 (13.7)			
P2	176 (82.2)	352 (86.3)	1.357*	0.865–2.128*	.182*

$n=107$

[*] Pearson chi-square

[&] Fisher's Exact Test

frequency was significantly higher in Italian patients with SCZ than in the control participants [17]. Other studies, including ours, failed to find any difference [31, 32]. When we carefully examined the p values obtained as a result of statistical analyzes, *IL-1RA* allele 2 homozygous genotype and *IL-1RA* allele 2 frequencies were non-significantly higher among SCZ patients than in controls. The *IL-1RA* allele 2 was known to be related to severe clinical outcomes in chronic inflammatory diseases [33, 34]. Furthermore, it was documented that the presence of the *IL-1RA* allele 2 is associated with enhanced IL-1β production [35]. Therefore, it is likely that diminished IL-1RA production in the SCZ and BD patient's brain cells that carry the *IL-1RA* allele 2 by dysregulating IL-1β production is related to pro-inflammatory situations in the brain tissue damage [36]. For example, it has been documented that a higher expression of the *IL-1RA* allele 2 was related to bifrontal-temporal gray matter volume and generalized white matter tissue deficits in allele 2 carrier SCZ patients [37].

There are minimal data regarding the function of *IL-1RA* polymorphism in BD, unlike SCZ. Papiol et al. reported a significant excess of the haplotypic combination -511 allele*1/VNTR allele*2 in Spanish BD patients compared with controls [38]. Furthermore, Hosseini et al. documented that the IL1RN*1/2 genotype was more prevalent in BD patients than in controls [19]. In a recent published case–control study, genotyping of *IL-1RA* (VNTR; rs2234663), *IL-1α* (rs1800587), *IL-1β* + 3954 (rs1143634), and *IL-1β* − 511 (rs16944) loci revealed that three haplotypes including two SNPs of C-T (rs1800587-rs16944), T-C (rs1143634-rs16944), T-A1 (rs16944-rs2234663) and one haplotype including three SNPs of C-C-T (rs1800587-rs1143634-rs16944) were related to

the BD [39]. However, Kim et al. documented contradictory reports indicating that VNTR genetic variation in *IL-1RA* was not related to BD in a Korean population like our study [16]. Papiol et al. analyzed the influence of the IL-1 cluster on brain morphology in BD. They documented that while −511C/T polymorphism of the *IL-1β* gene was related to whole-brain gray matter and left dorsolateral prefrontal cortex gray matter deficits in BD patients, the *IL-1RA* genetic variability did not have any influence on the brain morphology [40].

In the present study, we showed no association between *IL-4* VNTR polymorphism and risk for SCZ and BD in the Turkish population. To the best of our knowledge, there is no study on *IL-4* gene VNTR polymorphism and SCZ or BD in the literature. There are, however, several studies on *IL-4* VNTR gene polymorphism and other autoimmune and inflammatory diseases from Turkey. Their associations with alopecia areata [41], coronary artery disease [42], diabetic peripheral neuropathy [43], knee osteoarthritis [44], multiple sclerosis [45], and recurrent aphthous stomatitis [46] have been studied in the Turkish population previously. Additionally, *IL-4* and *IL-1RA* VNTR gene polymorphisms have been found related to type 2 diabetes mellitus and frailty syndrome together [47, 48]. The *IL-4* coding gene is located within the cytokine gene cluster on chromosome 5q31.1, a chromosomal region identified by linkage analyses containing a susceptibility gene for SCZ [49, 50]. Schwarz et al. reported a significant association of the *IL-4* −590 CC genotype with SCZ [51]. However, Jun et al. study results showed no significant difference in the genotypic and allelic frequencies of *IL-4 Rα* + 1902 and *IL-4* − 590 gene polymorphism between patients with SCZ and normal controls [52]. Although in the literature, no study on this subject has examined the role of the *IL-4* gene polymorphism in BD, a study by Brietzke et al. on the cytokine levels (IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ) of patients with BD demonstrated that only IL-4 levels were increased in euthymic BD patients compared with healthy controls. This research also showed higher serum levels of IL-2, IL-4, and IL-6 in manic episodes compared to healthy participants [53]. Again, a meta-analysis of 10 studies (428 patients and 397 healthy controls) showed significantly higher IL-4 levels in BD patients than in controls [54]. Since we did not simultaneously investigate blood peripheral cytokine values in our study, we do not know outcomes regarding the relationship between *IL-4* VNTR polymorphism and blood IL-4 cytokine levels and the correlation with these studies in the literature.

Our study's strength is that the first research investigating the possible association between *IL-4* VNTR polymorphism and the risk of SCZ or BD, though *IL-1RA* VNTR polymorphism has been studied as a potential susceptible marker before. Secondly, our findings were more beneficial since SCZ or BD patients and healthy participants were gathered from the same geographic area. However, besides the strengths of the present research, our study has some drawbacks. The first limitation was the small sample size, limiting the statistical power. Secondly, examination of additional clusters of genes and polymorphic sites related to *IL-4* and *IL-1RA* would be needed to establish the contribution of *IL-4* and *IL-1RA* VNTR gene polymorphisms to the etiology of SCZ and BD.

Conclusions

In summary, the etiopathogenesis of SCZ and BD is still an unsolved puzzle of psychiatry. Moreover, the theories that try to enlighten the exact mechanism for chronic inflammation become more complicated every day. Therefore, we investigated anti-inflammatory cytokine VNTR polymorphisms of *IL-4* and *IL-1RA* in the remitted SCZ and BD patients in the present study. Although these biological markers do not seem to be used to diagnose SCZ and BD in the Turkish population, the finding that different inflammatory patterns exist in these psychiatric disorders can provide a hint for further examinations exploring candidate biomarkers for determining these two disorders. In addition, the association observed between cytokines and prognoses may provide some clues for new therapeutic medications and personal strategies in the future.

Abbreviations

SCZ: Schizophrenia; BD: Bipolar disorder; IL-1RA: Interleukin-1 receptor antagonist; IL-4: Interleukin-4; VNTR: Variable number of tandem repeat; SCID-I: Structured Clinical Interview for DSM-IV axis I disorders; PCR: Polymerase chain reaction; Ig: Immunoglobulin; DSM-IV-TR: Diagnostic and statistical manual of mental disorders, fourth edition, text revision; HWE: Hardy–Weinberg equilibrium.

Acknowledgements

We want to thank all patients and healthy controls for their willingness to participate in the present study.

Author contributions

SP, HMA, and YO are responsible for developing overarching research goals and aims, data integrity, and data analysis accuracy. YO, HMA, SP, and FCT conceived and designed the study. FCT and YO are the responsible provisions of study materials and laboratory samples. HMA drafted the manuscript. All authors critically revised the manuscript. SP and HMA supervised the study. All authors read and approved the final manuscript.

Funding

We received no specific funding for this research.

Availability of data and material

The authors confirm that all relevant data are included in the article, which does not contain any supplementary material.

Declarations

Ethics approval and consent to participate

The study was approved by the Clinical Research Ethics Committee of Istanbul Faculty of Medicine, under the ethical standard for human experimentation established by the Declaration of Helsinki (29.01.2021–56267).

Consent for publication

We give our consent for the publication of identifiable details, which can include photograph(s) and/or videos and/or case history and/or details within the text to be published in the your journal.

Competing interests

The author declares not to have any conflicts of interest that might be interpreted as influencing the manuscript's content.

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Received: 3 March 2022 Accepted: 17 August 2022
Published online: 24 August 2022

References

1. Aytac HM, Oyaci Y, Pehlivan M, Pehlivan S (2021) DNA Methylation Pattern of Gene Promoters of MB-COMT, DRD2, and NR3C1 in Turkish Patients Diagnosed with Schizophrenia
2. Avramopoulos D, Pearce BD, McGrath J, Wolyniec P, Wang R, Eckart N et al (2015) Infection and inflammation in schizophrenia and bipolar disorder: a genome wide study for interactions with genetic variation. PLoS ONE 10(3):e0116696
3. Aytac HM, Yazar MS, Erol A, Pehlivan S (2021) Investigation of inflammation related gene polymorphism of the mannose-binding lectin 2 in schizophrenia and bipolar disorder. Neurosci J 26(4):346–356
4. Aytac HM, Oyaci Y, Yazar MS, Pehlivan S (2021) Macrophage migration inhibitory factor-173 G/C polymorphism is associated with the age of onset and insight in Schizophrenia in the Turkish population. Neurol Res 43(12):977–984
5. Nursal AF, Aytac HM, Ciftci HS, Sila M, Oyaci Y, Pehlivan M et al (2021) TNF-α-308 G/A variant may be associated with bipolar disorder in a Turkish population. Arch Clin Psychiatry (São Paulo) 47:176–179
6. Aytac HM, Ozdilli K, Tuncel FC, Pehlivan M, Pehlivan S (2020) Tumor necrosis factor-alpha (TNF-α) −238 G/A polymorphism is associated with the treatment resistance and attempted suicide in Schizophrenia. Immunol Investig 51(2):368–380. https://doi.org/10.1080/08820139.2020.1832115
7. Pehlivana S, Aytacb HM, Ciftcia HS, Oyacia Y, Pehlivanc M, Nursal AF (2020) Investigating the eNOS and IFN-γ gene variants susceptible to bipolar disorder or Schizophrenia in a Turkish cohort. Psychiatry Clin Psychopharmacol 30(4):354–361
8. Aytac HM, Pehlivan S, Pehlivan M, Oyaci Y (2022) Quantitative detection of methylated SOCS-1 in schizophrenia and bipolar disorder considering SOCS-1 -1478CA/del polymorphism and clinical parameters. Irish J Med Sci (1971 -). https://doi.org/10.1007/s11845-022-03030-w
9. Kim Y-K, Jung H-G, Myint A-M, Kim H, Park S-H (2007) Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord 104(1–3):91–95
10. García-Bueno B, Bioque M, Mac-Dowell KS, Barcones MF, Martínez-Cengotitabengoa M, Pina-Camacho L et al (2014) Pro-/anti-inflammatory dysregulation in patients with first episode of psychosis: toward an integrative inflammatory hypothesis of schizophrenia. Schizophr Bull 40(2):376–387
11 Reale M, Costantini E, Greig NH (2021) Cytokine imbalance in schizophrenia. From research to clinic: potential implications for treatment. Front Psychiatry. https://doi.org/10.3389/fpsyt.2021.536257
12. Arend WP, Malyak M, Guthridge CJ, Gabay C (1998) Interleukin-1 receptor antagonist: role in biology. Annu Rev Immunol 16(1):27–55
13. Katila H, Hänninen K, Hurme M (1999) Polymorphisms of the interleukin-1 gene complex in schizophrenia. Mol Psychiatry 4(2):179–181
14. Santtila S, Savinainen K, Hurme M (1998) Presence of the IL-1RA allele 2 (IL1RN* 2) is associated with enhanced IL-1beta production in vitro. Scand J Immunol 47(3):195–198
15. Hope S, Ueland T, Steen NE, Dieset I, Lorentzen S, Berg AO et al (2013) Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophr Res 145(1–3):36–42
16. Kim S, Lee H, Koo H, Kim J, Song J, Kim M et al (2004) Impact of IL-1 receptor antagonist gene polymorphism on schizophrenia and bipolar disorder. Psychiatr Genet 14(3):165–167
17. Zanardini R, Bocchio-Chiavetto L, Scassellati C, Bonvicini C, Tura GB, Rossi G et al (2003) Association between IL-1β-511C/T and IL-1RA (86bp) n repeats polymorphisms and schizophrenia. J Psychiatr Res 37(6):457–462
18. Watanabe Y, Nunokawa A, Kaneko N, Muratake T, Koizumi M, Someya T (2007) Lack of association between the interleukin-1 gene complex and schizophrenia in a Japanese population. Psychiatry Clin Neurosci 61(4):364–369
19. Hosseini S, Taheri M, Hosseni-khah Z, Hajilooi M, Mazaheri Z (2013) Influence of IL-1RN intron 2 variable number of tandem repeats (VNTR) polymorphism on bipolar disorder. Neuropsychobiology 67(2):116–121
20. Kubo M, Yamashita M, Abe R, Tada T, Okumura K, Ransom JT et al (1999) CD28 costimulation accelerates IL-4 receptor sensitivity and IL-4-mediated Th2 differentiation. J Immunol 163(5):2432–2442
21. Coffman R, Ohara J, Bond M, Carty J, Zlotnik A, Paul W (1986) B cell stimulatory factor-1 enhances the IgE response of lipopolysaccharide-activated B cells. J Immunol 136(12):4538–4541
22. Del Prete G, Maggi E, Parronchi P, Chretien I, Tiri A, Macchia D et al (1988) IL-4 is an essential factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. J Immunol 140(12):4193–4198
23. Mout R, Willemze R, Landegent J (1991) Repeat polymorphisms in the interleukin-4 gene (IL4). Nucleic Acids Res 19(13):3763
24. Elghoroury EA, Fadel FI, Farouk H, Elshamaa MF, Kamel S, Kandil D, Mahmoud E (2018) Association of variable number tandem repeats polymorphism in the IL-4 gene with end-stage renal disease in children. Egypt J Med Human Genet 19(3):191–195. https://doi.org/10.1016/j.ejmhg.2017.08.009
25 Munkholm K, Braüner JV, Kessing LV, Vinberg M (2013) Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J Psychiatr Res 47(9):1119–1133. https://doi.org/10.1016/j.jpsychires.2013.05.018
26. Şimşek Ş, Yıldırım V, Çim A, Kaya S (2016) Serum IL-4 and IL-10 levels correlate with the symptoms of the drug-naive adolescents with first episode, early onset schizophrenia. J Child Adolesc Psychopharmacol 26(8):721–726
27. Association WM (2013) World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310(20):2191–2194
28. Vasudevan R, Norhasniza M, Patimah I (2011) Association of variable number of tandem repeats polymorphism in the IL-4 gene with end-stage renal disease in Malaysian patients. Genet Mol Res 10(2):943–947
29. Singh M, Mansuri M, Jadeja S, Marfatia Y, Begum R, Mansuri MS et al (2018) Association of interleukin 1 receptor antagonist intron 2 variable number of tandem repeats polymorphism with vitiligo susceptibility in Gujarat population. Indian J Dermatol Venereol Leprol. https://doi.org/10.4103/ijdvl.IJDVL_1_17
30. Lee W-C, Wang L-Y (2008) Simple formulas for gauging the potential impacts of population stratification bias. Am J Epidemiol 167(1):86–89
31. Mata I, Crespo-Facorro B, Pérez-Iglesias R, Carrasco-Marín E, Arranz MJ, Pelayo-Terán JM et al (2006) Association between the interleukin-1 receptor antagonist gene and negative symptom improvement during antipsychotic treatment. Am J Med Genet B Neuropsychiatr Genet 141(8):939–943
32. Chowdari KV, Xu K, Zhang F, Ma C, Li T, Xie BY et al (2001) Immune related genetic polymorphisms and schizophrenia among the Chinese. Hum Immunol 62(7):714–724
33. Alvarez-Rodriguez L, Carrasco-Marin E, Lopez-Hoyos M, Mata C, Fernandez-Prieto L, Ruiz-Soto M et al (2009) Interleukin-1RN gene polymorphisms in elderly patients with rheumatic inflammatory chronic

conditions: association of IL-1RN* 2/2 genotype with polymyalgia rheumatica. Hum Immunol 70(1):49–54
34. Rezaii AA, Hoseinipanah SM, Hajilooi M, Rafiei AR, Shikh N, Haidari M (2009) Interleukin-1 receptor antagonist gene polymorphism and susceptibility to ischemic stroke. Immunol Invest 38(3–4):220–230
35 Chourasia D, Achyut B, Mittal S, Mittal RD, Ghoshal UC (2009) Genotypic and functional roles of IL-1B and IL-1RN on the risk of gastroesophageal reflux disease: the presence of IL-1B—511*T/IL-1RN*1 (T1) Haplotype may protect against the disease. Am J Gastroenterol 104(11):2704–2713. https://doi.org/10.1038/ajg.2009.382
36. Luheshi NM, Kovács KJ, Lopez-Castejon G, Brough D, Denes A (2011) Interleukin-1α expression precedes IL-1β after ischemic brain injury and is localised to areas of focal neuronal loss and penumbral tissues. J Neuroinflammation 8(1):1–5
37. Meisenzahl EM, Rujescu D, Kirner A, Giegling I, Kathmann N, Leinsinger G et al (2001) Association of an interleukin-1β genetic polymorphism with altered brain structure in patients with schizophrenia. Am J Psychiatry 158(8):1316–1319
38. Papiol S, Rosa A, Gutierrez B, Martin B, Salgado P, Catalan R et al (2004) Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. J Med Genet 41(3):219–223
39. Talaei A, Afzaljavan F, Talaei A (2021) IL-1α, IL-1β and IL-1RN haplotypes are associated with bipolar I disorder and its characteristics: a pilot case-control study. Meta Gene 30:100977
40. Papiol S, Molina V, Desco M, Rosa A, Reig S, Sanz J et al (2008) Gray matter deficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13). Genes Brain Behav 7(7):796–801
41. Kalkan G, Karakus N, Baş Y, Takçı Z, Özuğuz P, Ateş Ö et al (2013) The association between Interleukin (IL)-4 gene intron 3 VNTR polymorphism and alopecia areata (AA) in Turkish population. Gene 527(2):565–569
42. Basol N, Celik A, Karakus N, Ozsoy SD, Yigit S (2014) The evaluation of angiotensin-converting enzyme (ACE) gene I/D and IL-4 gene intron 3 VNTR polymorphisms in coronary artery disease. In Vivo 28(5):983–987
43. Basol N, Inanir A, Yigit S, Karakus N, Kaya SU (2013) High association of IL-4 gene intron 3 VNTR polymorphism with diabetic peripheral neuropathy. J Mol Neurosci 51(2):437–441
44. Yigit S, Inanir A, Tekcan A, Tural E, Ozturk GT, Kismali G et al (2014) Significant association of interleukin-4 gene intron 3 VNTR polymorphism with susceptibility to knee osteoarthritis. Gene 537(1):6–9
45. Karakus N, Yigit S, Kurt GS, Cevik B, Demir O, Ates O (2013) Association of interleukin (IL)-4 gene intron 3 VNTR polymorphism with multiple sclerosis in Turkish population. Hum Immunol 74(9):1157–1160
46. Kalkan G, Yigit S, Karakus N, Baş Y, Seçkin HY (2013) Association between interleukin 4 gene intron 3 VNTR polymorphism and recurrent aphthous stomatitis in a cohort of Turkish patients. Gene 527(1):207–210
47. Pérez-Suárez TG, Gutiérrez-Robledo LM, Ávila-Funes JA, Acosta JL, Escamilla-Tilch M, Padilla-Gutiérrez JR et al (2016) VNTR polymorphisms of the IL-4 and IL-1RN genes and their relationship with frailty syndrome in Mexican community-dwelling elderly. Aging Clin Exp Res 28(5):823–832
48. Bid H, Konwar R, Agrawal C, Banerjee M (2008) Association of IL-4 and IL-1RN (receptor antagonist) gene variants and the risk of type 2 diabetes mellitus: a study in the north Indian population. Indian J Med Sci 62(7):259–266
49. Paunio T, Ekelund J, Varilo T, Parker A, Hovatta I, Turunen JA et al (2001) Genome-wide scan in a nationwide study sample of schizophrenia families in Finland reveals susceptibility loci on chromosomes 2q and 5q. Hum Mol Genet 10(26):3037–3048
50. Schwab S, Hallmayer J, Albus M, Lerer B, Eckstein G, Borrmann M et al (2000) A genome-wide autosomal screen for schizophrenia susceptibility loci in 71 families with affected siblings: support for loci on chromosome 10p and 6. Mol Psychiatry 5(6):638–649
51. Schwarz MJ, Krönig H, Riedel M, Dehning S, Douhet A, Spellmann I et al (2006) IL-2 and IL-4 polymorphisms as candidate genes in schizophrenia. Eur Arch Psychiatry Clin Neurosci 256(2):72–76
52. Jun TY, Lee KU, Pae CU, Chae JH, Bahk WM, Kim KS et al (2003) Polymorphisms of interleukin-4 promoter and receptor gene for schizophrenia in the Korean population. Psychiatry Clin Neurosci 57(3):283–288
53. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'Anna M, Mascarenhas M, Vargas AE et al (2009) Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord 116(3):214–217
54. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M (2013) Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiat 74(1):15–25

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