Evaluation of gene-gene interaction between the interleukin (IL)-2 and IL-2RA gene polymorphisms in schizophrenia patients in the Turkish Population

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ABSTRACT

الأهداف: تقييم الأشكال الجينية المتعددة في جينات *IL-2* و*IL-2RA* لدى مرضى الفصام ومقارنتها مع الأصحاء.

المنهجية: اشتملت الدراسة على عينة من 127 مريضا يعانون من SCZ و 100 متطوع أصحاء في دراسة الحالات والشواهد. اخترنا هؤلاء الأفراد على التوالي من العيادة الخارجية للطب النفسي بمستشفى مالازجيرت الحكومي في موس، تركيا، خلال ثلاثة أشهر من أكتوبر 2020م إلى ديسمبر 2020م. وتم استخدام المقابلة السريرية المنظمة لاضطرابات DSM-5، إصدار الطبيب السريري (SCID-5-CV). لتأكيد التشخيص وفقًا لمعايير DSM-5. بالإضافة إلى ذلك، تم استخدام تعدد أشكال طول الجزء المقيّد لتفاعل البوليميراز (PCR-RFLP) لتحديد تعدد أشكال الجينات من مادة الحمض النووي.

النتائج: أشارت النتائج التي توصلنا إليها إلى وجود اختلافات كبيرة في النمط الوراثي *IL-2* وترددات الأليل بين مرضى SCZ والمجموعة الضابطة الصحية. على وجه التحديد، كان تواتر النمط الجيني المتماثل GG أعلى بشكل ملحوظ في مرضى SCZ مقارنة بالمجموعة الضابطة. على العكس من ذلك، عند مقارنة النمط الجيني *IL-2RA* وترددات الأليل لمرضى SCZ مع المجموعة الضابطة، لم يلاحظ أي فروق ذات دلالة إحصائية بين المجموعتين. عند مقارنتها بالأفراد ذوي الأنماط الجينية الأخرى، أشار تحليل التفاعل إلى أن حاملي النمط الجيني GG/AG *(IL-2/IL-2RA)* أظهروا زيادة كبيرة في خطر الإصابة بـSCZ.

الخلاصة: في ضوء التحليلات، تشير دراستنا إلى أنه حين تعدد أشكال النمط الجيني IL-2 يمكن اعتباره عامل خطر لتطوير SCZ، فإن متغير *IL-2RA* لم يرتبط بـ SCZ بين المرضى الأتراك.

Objectives: To evaluate the genetic polymorphisms in *IL-2* and *IL-2RA* genes in schizophrenia (SCZ) patients by comparing them with healthy controls.

Methods: A sample of 127 patients with SCZ and 100 healthy volunteers were included in the case-control study. These individuals were consecutively selected from the Malazgirt State Hospital Psychiatry Outpatient Clinic in Mus, Turkey, over the three months from October 2020 to December 2020. The Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV) was used to confirm the diagnosis according to the DSM-5 criteria. In addition, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to determine gene polymorphisms from DNA material.

Results: Our findings indicated significant differences in the *IL-2* genotype and allele frequencies between SCZ patients and the healthy control group. Specifically, the frequency of the homozygous GG genotype was notably higher in SCZ patients compared to the control group. Conversely, when comparing the *IL-2RA* genotype and allele frequencies of SCZ patients with the control group, no statistically significant differences were observed between the 2 groups. When compared to individuals with other genotypes, interaction analysis indicated that carriers of the GG/AG (*IL-2/IL-2RA*) genotype demonstrated a significantly increased risk of SCZ.

Conclusion: In light of the analyses, our study indicates that while the *IL-2* genotype polymorphism may be considered a risk factor for developing SCZ, the *IL-2RA* variant was not associated with SCZ among Turkish patients.

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Schizophrenia (SCZ) is a persistent and severe mental disorder affecting approximately 1% of the general population. While the complete pathophysiology of SCZ remains unclear, an escalating number of studies are now concentrating on the involvement of the immune system in this disorder.[1-3] Recent studies suggest that uncontrolled activation of microglia and heightened inflammation due to proinflammatory cytokines may contribute to the development of SCZ, particularly in individuals with a genetic predisposition.[4] Moreover, infections experienced during embryonic and early childhood stages can hinder fetal brain development, while excessive synaptic pruning during adolescence has been identified as another potential risk factor for psychosis.[5] Numerous linkage and association studies have demonstrated the involvement of multiple genes in the development of SCZ.[6-8] A thorough examination of 118 meta-analyses revealed an association between SCZ and a set of 24 genetic variants situated in 16 different genes (HP, DRD4, SLC6A4, TPH1, IL1B, DRD2, MTHFR, TP53, GABRB2, DAO, DRD1, APOE, DTNBP1, COMT, PLXNA2, and GRIN2B).[9] Among the potential candidate genes for SCZ, those encoding cytokines appear promising. Cytokines play crucial roles in the central nervous system (CNS), acting as essential mediators in the communication between the brain and immune system and participating in neuroinflammatory processes.[10-12]

Interleukin-2 (*IL-2*) is a growth factor that regulates the autocrine function of T-cells, specifically regulatory T-cells (Treg), and plays a crucial role in the immune response.[13] The *IL-2* gene is located on chromosome 4q26-q27, and its various variants can lead to functional differences in activation.[14] Several linkage studies have suggested the possibility of a susceptibility gene for SCZ in this chromosomal region, such as 4q22–23 or 4q31,[15,16] although conflicting data exist.[17] Notably, 2 variants in the IL-2 gene, -330 T/G (rs2069762) and +114 G/T (rs2069763) have been identified as having an impact on IL-2 levels.[18] While prior investigations have explored the association between the *IL-2* -330 T/G (rs2069762) polymorphism and SCZ in German and Polish populations, no similar research has been identified concerning the Turkish population diagnosed with SCZ and its relationship with this *IL-2* polymorphism.[19,20]

The *IL-2RA* gene, or interleukin 2 alpha-receptor gene, is located on chromosome 10p15.1. It encodes CD25, a protein recognized as the alpha-receptor chain for interleukin 2, constituting the high-affinity alpha subunit of the interleukin receptor. The CD25 is vital for the T lymphocyte response to IL-2, the primary growth factor for these cells. CD25 expression is crucial for fostering proliferation, extending lifespan, and ensuring optimal T-cell function.[21,22] Upon evaluating 265 Irish families with SCZ alongside genome scan results, the findings indicate the potential presence of a vulnerability locus for SCZ within region 10p15-p11 in these specific Irish families.[23] However, there has been no prior investigation into the genetic polymorphism of *IL-2RA* genes in SCZ patients by comparing them with healthy controls. Moreover, association studies examining polymorphisms of *IL-2* genes in SCZ have been limited. Considering the potential association of immune-related genes with SCZ susceptibility, we hypothesized that polymorphisms in the *IL-2* (rs2069762) and *IL-2RA* (rs2104286) genes might show notable distinctions in Turkish individuals with SCZ compared to healthy individuals. Furthermore, the exploration of gene-gene interactions between *IL-2* and *IL-2RA* gene polymorphisms could offer valuable insights into the progression of this disorder. Hence, our objective was to examine genetic polymorphisms in *IL-2* and *IL-2RA* genes among SCZ patients, drawing comparisons with a healthy control group.

Methods.

Participant selection. In this case-control investigation, 127 individuals diagnosed with SCZ were included. The psychiatric clinical interview utilized the Structured Clinical Interview for the Diagnostic and Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV). These patients were consecutively selected from the Malazgirt State Hospital Psychiatry Outpatient Clinic from October 2020 to December 2020 for three months. For comparison, we recruited 100 healthy participants who were age-, sex-, geographic area-, and ethnicity-matched with the patient group. The participants were given details about the study's objectives, materials, and procedures, and their written informed consent was obtained. The study received approval from the Clinical Research Ethics Committee of the Istanbul Faculty of Medicine, in accordance with the ethical standards for human experimentation outlined in the Declaration of Helsinki (Approval date: 29.01.2021-56267).

DNA analyses. The DNA extraction from blood samples obtained from participants was performed in accordance with the manufacturer's instructions, utilizing the Quick-DNA Miniprep Plus Kit by Zymo Research. The extracted DNA samples were stored at -20 °C. Genotyping of *IL-2RA* rs2104286 and *IL-2* rs2069762 variants was carried out using polymerase chain reaction-restriction fragment length polymorphism

(PCR-RFLP) analysis, following established methods. The *IL-2RA* rs2104286 polymorphism was investigated through PCR with the forward primer 5'-GCAGGTGTCAACGCAAAAAC-3' and reverse primer 5′-TCCCTGGAATGTCACTGATG-3'. Additionally, *IL-2* rs2069762 amplification was performed using the forward primer 5'-ATTCACATGTTCAGTGTAGTTCT-3' and reverse primer 5'-GTGATAGCTCTAATTCATGC-3', and the resulting PCR products were examined through gel electrophoresis.[24,25]

Statistical analyses. Statistical analysis was carried out using IBM SPSS version 21.0 (IBM Corp., released 2012; Armonk, NY, USA). The adherence of genotype distributions in participants to the Hardy-Weinberg Equilibrium (HWE) was assessed. Genotypic distribution of *IL-2* (rs2069762) and *IL-2RA* (rs2104286) in SCZ patients, as well as the potential interaction between *IL-2* (rs2069762) and *IL-2RA* (rs2104286) polymorphisms concerning SCZ risk, were evaluated using the Pearson chi-square test or Fisher's exact test. Various models, including dominant, over-dominant, recessive, and additive, were employed to assess the relationship between single nucleotide polymorphisms and SCZ, providing 95% confidence intervals (CI) and odds ratios (OR). Statistical significance was considered for a *p*-value less than 0.05. Power analysis was conducted using "G*power" software (version 3.0.5, http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/). Additionally, we employed the approach proposed by Lee and Wang to evaluate the potential presence of population stratification bias.[26]

Table 1 - The clinical characteristics of SCZ patients.

SCZ (N=127)	n (%)
Sex	
Female	35 (27.6)
Male	92 (72.4)
IL-2	
GG	25 (19.7)
GT	13 (10.2)
TT	89 (70.1)
1L-2RA	
AA	22 (17.3)
AG	104 (81.9)
GG	1 (0.8)
	Mean±SD
Age	40.86±10.70
Age of onset (year)	24.57±8.26
Duration of dis. (year)	16.11±9.52
Number of hospt	3.51±4.61

SCZ - schizophrenia, SD - standart deviation, dis. - disease, hospt. - hospitalization

Table 2 - Comparison of frequencies of *IL-2* (rs2069762) gene variants between patients with SCZ and healthy controls.

IL-2	Genotype	SCZ	Healthy control	OR	95% CI	*P*-value
		n=[a] (%)	n=100 (%)			
Recessive	GG	25 (19.7)	10 (10)	0.453*	0.207-0.995*	0.045*
Over-dominant	GT	13 (10.2)	12 (12)	0.836*	0.364-1.923*	0.673*
Dominant	TT	89 (70.1)	78 (78)	0.661*	0.360-1.212*	0.179*
Additive	GG vs TT			2.191*	0.991-4.846*	0.049*
	G	50 (19.7)	32 (16)			
	T	204 (90.3)	168 (84)	1.287*	0.790-2.097*	0.311*

[a]n= 127, SCZ - schizophrenia, OR - odd ratio, CI - confident interval, *Pearson chi-square

Table 3 - Comparison of frequencies of *IL-2RA* (rs2104286) gene variants between patients with SCZ and healthy controls.

IL-2RA	Genotype	SCZ	Healthy control	OR	95% CI	*P*-value
		n=[a] (%)	n=100 (%)			
Recessive	AA	22 (17.3)	13 (13)	1.402*	0.668-2.945*	0.371*
Over-dominant	AG	104 (81.9)	86 (86)	0.736*	0.357-1.517*	0.405*
Dominant	GG	1 (0.8)	1 (1)	0.786[&]	0.049-12.719[&]	1.000[&]
Additive	AA vs GG			1.692[&]	0.097-29.413[&]	1.000[&]
	A	148 (58.3)	112 (56)			
	G	106 (41.7)	88 (44)	1.097*	0.754-1.595*	0.628*

[a]n= 127, SCZ - schizophrenia, OR - odd ratio, CI - confident interval, *pearson chi-square, &Fisher's exact test

Table 4 - Interaction of *IL-2* (rs2069762), and *IL-2RA* (rs2104286) polymorphisms on SCZ risk.

IL-2 (rs2069762)	*IL-2RA* (rs2104286)	SCZ (%)	Control (%)	OR (95%CI)	*P*-value
GT	AG	9 (7.1)	10 (10.0)	0.686 (0.268 – 1.760)*	0.431*
GT	AA	4 (3.1)	2 (2.0)	1.593 (0.286 – 8.881)&	0.697&
GT	GG	0 (0.0)	0 (0.0)	-	-
TT	AG	72 (56.7)	67 (67.0)	0.645 (0.374 – 1.112)*	0.114*
TT	AA	16 (12.6)	11 (11.0)	1.116 (0.515 – 2.639)*	0.712*
TT	GG	1 (0.8)	0 (0.0)	1.794 (1.597 – 2.015)*	1.000*
GG	AG	23 (18.1)	9 (9.0)	2.236 (0.984 – 5.079)*	0.050*
GG	AA	2 (1.6)	0 (0.0)	1.800 (1.601 – 2.023)&	0.505&
GG	GG	0 (0.0)	1 (1.0)	2.283 (1.969 – 2.642)&	0.441&

SCZ - schizophrenia, OR - odd ratio, CI - confident interval, *Pearson chi-square, & - Fisher's exact test

Results. The sociodemographic characteristics and clinical parameters of SCZ patients were analyzed (**Table 1**). A total of 227 individuals, including 127 SCZ patients and 100 healthy controls, underwent assessment for the *IL-2* rs2069762 and *IL-2RA* rs2104286 variants. The *IL-2* rs2069762 variant's genotype distribution is detailed in **Table 2**. Notably, our findings indicated significant statistical differences in IL-2 genotype and allele frequency distribution between SCZ patients and the healthy control group. The homozygous GG genotype frequency was significantly elevated in the SCZ patient group compared to the control group (OR: 0.453; 95% CI: 0.207–0.995; p=0.045). The additive model revealed a significant difference in the frequency distribution of GG and TT genotypes between the 2 groups (OR: 2.191; 95% CI: 0.991–4.846; p=0.049).

Furthermore, the genotype distribution of the *IL-2RA* rs2104286 variant is outlined in **Table 3**. When comparing the distribution of *IL-2RA* genotype and allele frequency in SCZ patients to the control group, no statistically significant differences were observed between the 2 groups. Compared with other genotypes, interaction analysis indicated that carriers of GG/AG *(IL-2/IL-2RA)* (OR: 2.236; 95% CI: 0.984–5.079; p=0.050) genotype demonstrated a significantly increased risk of SCZ (**Table 4**).

Discussion. According to our findings, the distributions of *IL-2* polymorphisms in SCZ patients were significantly different from those in the control group. However, no significant association was found between *IL-2RA* gene polymorphism and SCZ. Numerous extensive studies have been carried out to investigate alterations in *IL-2* levels among patients with SCZ. However, the findings from these studies display significant variation, with some indicating increased IL-2 levels in patients with SCZ,[27,28] while others report decreases[29,30] or no changes.[31] IL-2 appears to exhibit a specific association with the negative and cognitive symptoms observed in SCZ. Asevedo conducted a study that explored potential connections between peripheral *IL-2* levels and both negative symptoms and cognitive functioning in individuals with SCZ.[29] Again, O'Donnell et al's[23] published research investigated immune activation in SCZ and schizophreniform disorder, specifically the production of IL-2 and sIL-2R from stimulated lymphocytes. Their study revealed increased production of IL-2 in unmedicated patients with SCZ and schizophreniform disorder, but no significant changes in sIL-2R were observed in parallel with our study. Nevertheless, it is important to note that changes in IL-2R and sIL-2R levels in patients with SCZ exhibit a consistent pattern across the majority of studies. Specifically, sIL-2R levels consistently appear higher in patients with SCZ compared to healthy controls across diverse studies, indicating its potential as a diagnostic marker for SCZ.[33]

In the current study, we found a significant difference in the genotype distribution of *IL-2* (rs2069762) between SCZ patients and healthy controls. Notably, the frequency of the homozygous GG genotype was significantly higher in the SCZ patient group compared to the control group. Again, interaction analysis indicated that carriers of the GG/AG (*IL-2/IL-2RA*) genotype demonstrated a significantly increased risk of SCZ. Upon reviewing the literature, it was evident that several studies investigating the association between *IL-2* polymorphism and SCZ had been published. For instance, Schwarz et al[20] reported a significant association between the *IL-2* –330 TT genotype and the *IL-4* –590 CC genotype with SCZ.[20] Likewise, Palacz et al[34] reported that individuals with GT and GG genotypes have a reduced risk of developing SCZ compared to

those with the TT genotype.[34] In a recent study, the genotype TT and allele T for *IL-2* polymorphism were discovered to be significantly associated with paranoid SCZ in the Polish population.[19] Contrary to the results of these studies, our research revealed a significantly elevated vulnerability to the occurrence of SCZ among participants who carried the GG genotype. According to Hoffmann et al., the GG genotype is correlated with elevated levels of *IL-2*, while the TT and GT genotypes are associated with a decrease in the production of this cytokine.[35] As a result, our findings suggest the detrimental consequences of excessive cytokine production in individuals with SCZ.

The uniqueness of our study lies in being the first to investigate the potential connection between *IL-2RA* polymorphism and the susceptibility to SCZ. Furthermore, our findings were enriched by the fact that both SCZ patients and healthy participants were sourced from the same geographical area, thus minimizing potential environmental influences. Nevertheless, alongside these strengths, our study does exhibit certain limitations. Firstly, the small sample size restricted the statistical power of our analysis. Secondly, the cross-sectional design precluded us from making causal inferences regarding the relationship between *IL-2*, *IL-2RA* polymorphisms, and the development of SCZ. Thirdly, due to the timing constraints of our study, we were unable to concurrently measure serum IL-2 and IL-2R levels while investigating *IL-2* and *IL-2RA* gene polymorphisms.

In summary, while the *IL-2* rs2069762 polymorphism could potentially exhibit an association with SCZ, the *IL-2RA* rs2104286 polymorphism did not show any correlation with SCZ. The presence of the *IL-2* GG genotype might confer a disadvantage in terms of SCZ diagnosis within the Turkish population. These findings provide insights into the underlying causes of SCZ and underscore inflammation as a crucial factor in the progression of its pathophysiology. Currently, a significant gap remains in the availability of reliable markers for diagnosing and guiding the treatment of SCZ. Exploring drug repurposing, a strategy involving the utilization of existing treatments for new disease contexts, offers a promising avenue to address the limitations of current antipsychotic medications that primarily target dopaminergic pathways.[36] The dopamine hypothesis falls short in comprehensively explaining all symptoms, and neuroinflammation is increasingly gaining recognition as an additional contributing factor. The conclusions drawn from ongoing trials imply that supplementary anti-inflammatory strategies could hold potential advantages in alleviating clinical symptoms in individuals with SCZ. Consequently, the use of anti-inflammatory medications (such as aspirin, celecoxib, NAC, minocycline, etc.) could potentially be explored for alleviating psychotic symptoms. Furthermore, there has yet to be an antipsychotic medication developed with IL-2 as its target, opening up a potential avenue for future research in this direction.

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