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Computer modeling of the peculiarities in the interaction of IL-1 with its receptors in schizophrenia

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Abstract. One of the primary theories regarding the development of schizophrenia revolves around genetics, indicating the involvement of hereditary factors in various processes, including inflammation. Research has demonstrated that inflammatory reactions occurring in microglia can impact the progression of the disease. It has also been established that genetically determined changes in IL-1 can contribute to schizophrenia, thereby confirming the role of the IL-1 gene cluster in disease susceptibility. The aim of this study is a computer-based assessment of the structural interactions of IL-1 proteins with their receptors in schizophrenia. The study utilized the DisGeNET database, enabling the assessment of the reliability of identified IL-1 polymorphisms. Polymorphisms were also sought using NCBI PubMed. The NCBI Protein service was employed to search for and analyze the position of the identified polymorphisms on the chromosome. Structures for modeling were extracted from the Protein Data Bank database. Protein modeling was conducted using the SWISS-MODEL server, and protein interaction modeling was performed using PRISM. Notably, this study represents the first prediction of the interactions of IL-1α, IL-1β, and IL-1RA proteins, taking into account the presence of single-nucleotide polymorphisms associated with schizophrenia in the sequence of the corresponding genes. The results indicate that the presence of SNP rs315952 in the IL-1RA protein gene, associated with schizophrenia, may lead to a weakening of the IL-1RA binding to receptors, potentially triggering the initiation of the IL-1 signaling pathway by disrupting or weakening the IL-1RA binding to receptors and facilitating the binding of IL-1 to them. Such alterations could potentially lead to a change in the immune response. The data obtained contribute theoretically to the development of ideas about the molecular mechanisms through which hereditary factors in schizophrenia influence the interactions of proteins of the IL-1 family, which play an important role in the processes of the immune system.

Key words: IL-1; schizophrenia; molecular modeling; SNP; single-nucleotide polymorphisms; PRISM.

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Компьютерное моделирование особенностей взаимодействий IL-1 с его рецепторами при шизофрении

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Аннотация. Одной из основных теорий развития шизофрении является генетическая, свидетельствующая о вовлечении наследственных факторов в различные процессы, в том числе воспаление. Показано, что воспалительные реакции, протекающие в микроглии, могут влиять на развитие заболевания. Также установлено, что генетически обусловленные изменения IL-1 могут способствовать шизофрении, подтверждая роль кластера генов IL-1 в восприимчивости к болезням. Целью работы была компьютерная оценка структурных взаимодействий белков IL-1 с их рецепторами при шизофрении. Использовалась база данных DisGeNET, позволяющая оценить достоверность выявленных полиморфизмов IL-1. Проведен поиск полиморфизмов с помощью NCBI PubMed. Сервис NCBI Protein использовался для поиска и анализа положения на хромосоме найденных полиморфизмов. Из базы данных Protein Data Bank были извлечены структуры для проведения моделирования. Моделирование белков выполнялось с помощью сервера SWISS-MODEL, а моделирование белковых взаимодействий – с помощью PRISM. В настоящем исследовании впервые проведено прогнозирование взаимодействий белков IL-1α, IL-1β и IL-1RA с учетом наличия в последовательности соответствующих генов однонуклеотидных полиморфизмов, ассоциированных с шизофренией. Показано, что наличие ассоциированного с шизофренией полиморфизма rs315952 гена белка IL-1RA может привести к ослаблению связи IL-1RA с рецепторами и, предположительно, к запуску сигнального пути IL-1 путем разрыва либо ослаб-

ления связи IL-1RA с рецепторами и связыванием IL-1 с ними, что, возможно, вызовет изменение иммунного ответа. Полученные данные вносят теоретический вклад в развитие представлений о молекулярных механизмах влияния наследственных факторов шизофрении на взаимодействия белков семейства IL-1, играющих важную роль в процессах иммунной системы.
Ключевые слова: IL-1; шизофрения; моделирование; SNP; однонуклеотидные полиморфизмы; PRISM.

Introduction

The investigation of the causes of multifactorial diseases, characterized by complex inheritance and associated with the action of multiple genes (Bochkov, 2011), is a current challenge in contemporary medical biological science. When studying such diseases, special attention is given to their potential associations with single nucleotide polymorphisms (SNPs), as well as the involvement of the corresponding genes in the implementation of molecular mechanisms underlying pathologies.

Currently, a pressing issue is the exploration of the mechanisms underlying the development of such a prevalent disorder as schizophrenia. This condition has several etiopathogenetic concepts, with one of the main theories being genetic. It suggests the involvement of genetic factors in various physiological processes of the body, including inflammatory processes. The activation of the inflammatory response system, associated with the pathophysiology of schizophrenia, has been demonstrated in numerous studies (Xu, He, 2010; Sommer et al., 2015; Kapelski et al., 2016; Miyaoka et al., 2017; Müller, 2019). Studies on animal models of schizophrenia, including mice and primates, indicate that inflammatory reactions during pregnancy may influence brain development and contribute to the etiology of this disorder (Frodl, Amico, 2014). It has been shown that microglial cells are activated in schizophrenia and play a crucial role in inflammatory processes (Müller, 2019). Additionally, the nonsteroidal anti-inflammatory drug Celecoxib has been found to exert therapeutic effects on patients with schizophrenia. Considering these findings, immunomodulation is currently widely discussed as a potential approach to the treatment of this disorder (Müller, 2019).

Clinical case descriptions of patients undergoing bone marrow transplantation demonstrate the inflammatory nature of schizophrenia. For instance, T. Miyaoka et al. (2017) presented the case of a 24-year-old man with treatment-resistant schizophrenia who underwent bone marrow transplantation for acute myeloid leukemia. After the procedure, he showed a significant reduction in schizophrenia symptoms without the use of neuroleptics. I.E. Sommer et al. (2015) described a reverse case where schizophrenia was transmitted from a sibling. At present, the mechanism of changes introduced by bone marrow transplantation from a healthy individual influencing the development of schizophrenia is not fully understood. However, it has been shown that this process normalizes microglial changes, which are significant for this disorder (Miyaoka et al., 2017). While the examination of individual cases cannot definitively confirm the immune pathogenesis of schizophrenia, the involvement of the immune system may be one of the key factors in the development of this disorder (Sommer et al., 2015).

It has been demonstrated that genetically determined changes in the regulation of IL-1 metabolism, one of the key components of the immune response, may contribute to schizophrenia, thereby supporting the role of the IL-1 gene cluster in disease susceptibility (Zanardini et al., 2003). Pro-inflammatory cytokines can modify neurotransmitter metabolism, influencing the development of the nervous system. IL-1 participates in both acute and chronic neurodegeneration, suggesting that cytokines induced by the activation of the IL-1 signaling pathway may play a pivotal role both in the acute phase of the disease and during developmental stages of the brain that affect an individual's susceptibility to schizophrenia-related factors in later life (Katila et al., 1999).

Accumulated data to date provide an opportunity for a more detailed examination of the influence of individual cytokine genes, particularly IL-1, on the mechanisms underlying schizophrenia development. Bioinformatic methods enable the exploration of changes in gene sequences associated with this disorder and an assessment of the properties of the corresponding protein molecules. This includes their involvement in interleukin receptor interactions, impacting the realization of the pro-inflammatory effects of IL-1. This will expand theoretical knowledge and identify approaches for further investigations into potential mechanisms of the immune system's involvement in schizophrenia development.

The objective of this study is a computer-based assessment of the interactions between IL-1 proteins and their receptors in the context of schizophrenia.

Materials and methods

We investigated the genetic factors associated with schizophrenia using the DisGeNET platform renowned for hosting one of the largest publicly available collections of genes and variants linked to human diseases (Piñero et al., 2020). The search for SNPs and proteins related to the IL-1 family was conducted through the NCBI (National Center for Biotechnology Information) PubMed service and the Protein database (Sayers et al., 2021).

To ensure the reliability of the data obtained from the DisGeNET platform, we assessed the identified polymorphisms using the Evidence Index. An Evidence Index (EI) of 1 signifies unanimous support for Gene-Disease Associations (GDA) or Variant-Disease Associations (VDA) across all publications. A value of EI < 1 indicates the absence of a correlation between the gene/variants and the disease (Piñero et al., 2020).

Following the selection of polymorphisms in genes encoding proteins associated with the IL-1 family, we analyzed their chromosomal positions using the NCBI resource functionality (Sherry et al., 2001). It was imperative to locate the polymorphisms within the coding region for modeling the corresponding proteins.

The amino acid sequences for protein modeling were sourced from the NCBI Protein database (Sayers et al., 2021). Subsequently, we manually replaced the amino acids in the sequences based on the positions of the polymorphisms. Pro-

tein modeling using the obtained sequences was carried out using the SWISS-MODEL protein structure modeling server (Waterhouse et al., 2018).

We extracted the IL-1R1+IL-1RAP+IL-1β complex from the Protein Data Bank (PDB) database, which houses known spatial structures of proteins. Subsequently, IL-1β was removed from this structure as our analysis focused on the receptor complex without interleukin.

The receptor complexes obtained were imported into Protein Interactions by Structural Matching (PRISM) (Baspinar et al., 2014), where their surfaces underwent structural comparison with template interfaces – previously identified binding regions. An interface (binding region) is defined as a pair of sets of amino acid residues $\{(A_1, ..., A_N), (B_1, ..., B_M)\}$, where for any amino acid residue A_i from protein A, there is at least one amino acid residue B_i from protein B. This occurs in such a way that the distance between these residues does not exceed a specified threshold (typically ranging from 6 to 12 Å) (Hadarovich et al., 2020). Within the binding region, hot spots exist – amino acid residues contributing significantly to binding energy (Tuncbag et al., 2012).

PRISM operates as an algorithm for predicting and modeling protein interactions through structural matching, encompassing four key stages: extraction of the target protein surface; assessment of structural similarity with template interface partners; superimposition of protein surface areas resembling the template interface on the template; flexible refinement of the obtained complexes, and energy calculation (Aytuna et al., 2005; Tuncbag et al., 2011).

Through the modeling of molecular interactions, the PRISM service provides an interface for forecasting, the complex structure, and an energy indicator. The latter signifies binding energy, denoting the minimum work required to separate the system into its constituent particles. It characterizes system stability and consistently carries a negative value, with the system boasting the lowest binding energy considered the most stable (Acuner Ozbabacan et al., 2014).

An energy threshold value of –10 kJ/mol was employed to identify energetically favorable predictions. Interactions demonstrating conformational advantage, backed by experimental data and IS-assessment (interface similarity assessment), with an output energy less than –10 kJ/mol were deemed favorable (Gao, Skolnick, 2011; Kuzu et al., 2013). The IS score, a metric for evaluating protein-protein interaction predictions, takes into account not only geometric distances but also the preservation of interfacial contacts. For the PRISM algorithm, an IS score greater than 0.12 is considered acceptable (Gao, Skolnick, 2011).

To visualize the localization of amino acid substitutions and interactions of IL-1 with receptors in the obtained protein complexes, the YASARA program (Krieger, Vriend, 2014) was utilized.

Results

Identification of molecules initiating the IL-1 signaling pathway

The structures of IL-1α, IL-1β, and IL-1RA proteins, crucial for initiating the IL-1 pathway, underwent examination (Dinarello, 1994). These proteins interact with specific receptors IL-1R1 and IL-1RAP (Acuner Ozbabacan et al., 2014). Subsequently, we evaluated the presence of polymorphisms in the genes of IL-1α, IL-1β, IL-1RA, IL-1R1, and IL-1RAP proteins, modeling their interactions according to the scheme presented in Figure 1.

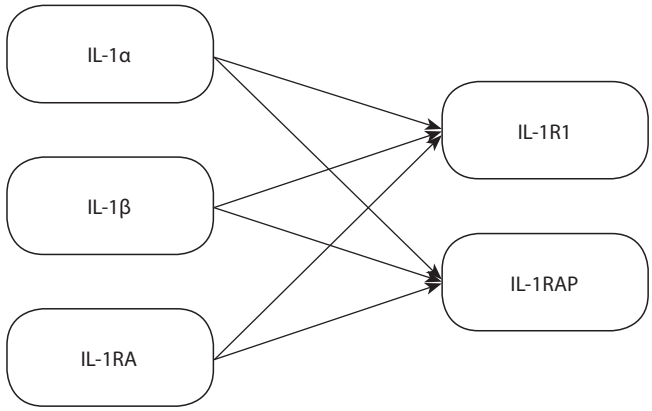

Fig. 1. IL-1 molecules and their interaction with cell receptors (based on Acuner Ozbabacan et al., 2014; Dinarello, 2018).

Search for SNPs in IL-1 genes associated with schizophrenia

A search in the DisGeNET catalog identified four single-nucleotide polymorphisms in genes initiating the IL-1 pathway associated with schizophrenia.

For IL-1α, SNPs rs113129609 and rs1800587 were found. While the EI for rs113129609 was 1, the corresponding article did not confirm its presence. For rs1800587, with an EI index less than 0.001, evidence was lacking. The rs16944 polymorphism in IL-1β, with an EI of 1, was supported by several studies (Shirts et al., 2006; Xu, He, 2010; Fatjó-Vilas et al., 2012), and the polymorphism was included in the list for further investigation. The rs1794068 polymorphism for IL-1RA had an EI less than 0.001, and further investigation was not pursued.

A PubMed search yielded 39 articles, and polymorphisms were extracted and listed in Table 1.

Analysis of the localization of SNPs of genes initiating the IL-1 signaling pathway

Localization and information on amino acid substitution for each polymorphism were analyzed using the dbSNP resource (Sherry et al., 2001) (Table 1). The IL-1RA rs315952 polymorphism, involving the substitution of serine with arginine, was identified for further modeling.

Modeling of proteins initiating the IL-1 signaling pathway

Since the rs315952 polymorphism is located in the *IL-1RA* amino acid sequence, it was selected for modeling. The original sequence was extracted from the NCBI Protein sequence database: >NP_776214.1 interleukin-1 receptor antagonist protein isoform 1 precursor [Homo sapiens].

Three-dimensional structures of IL-1RA were modeled with and without the polymorphism using the SWISS-MODEL service. The obtained molecular models were saved as ".pdb" files.

Table 1. Analysis of the localization and substitution of an amino acid in the sequence

Polymorphism	Gene name	Publication	Type of amino acid substitution	Localization of the polymorphism
rs16944	*IL-1B*	Papiol et al., 2007; Xu, He, 2010	No information on amino acid substitution is available	The polymorphism is located outside the protein coding region
rs1794068	*IL-1RA*	Ben Nejma et al., 2013		Intron
rs1143627	*IL-1B*	Hudson, Miller, 2018		Intron
rs1143623	*IL-1B*	Kapelski et al., 2015		The polymorphism is located outside the protein coding region
rs4848306	*IL-1B*	Yoshida et al., 2012; Kapelski et al., 2015	No information	No information
rs4251961	*IL-1RA*	Kapelski et al., 2015	No information on amino acid substitution is available	The polymorphism is located outside the protein coding region
rs9005	*IL-1RA*	Kapelski et al., 2016		No information
rs1143633	*IL-1B*	Sasayama et al., 2011		Intron
rs11677416	*IL-1A*	McClay et al., 2011	No information	No information
rs315952	*IL-1RA*	Kapelski et al., 2016	Serine is replaced by arginine	Position 130
rs419598	*IL-1RA*	Kapelski et al., 2016	A synonymous variant, thymine to cytosine substitution (T>C), does not result in a change of the amino acid alanine	Position 57
rs1143634	*IL-1B*	Xu, He, 2010	The alteration does not lead to the replacement of the amino acid phenylalanine	Position 27

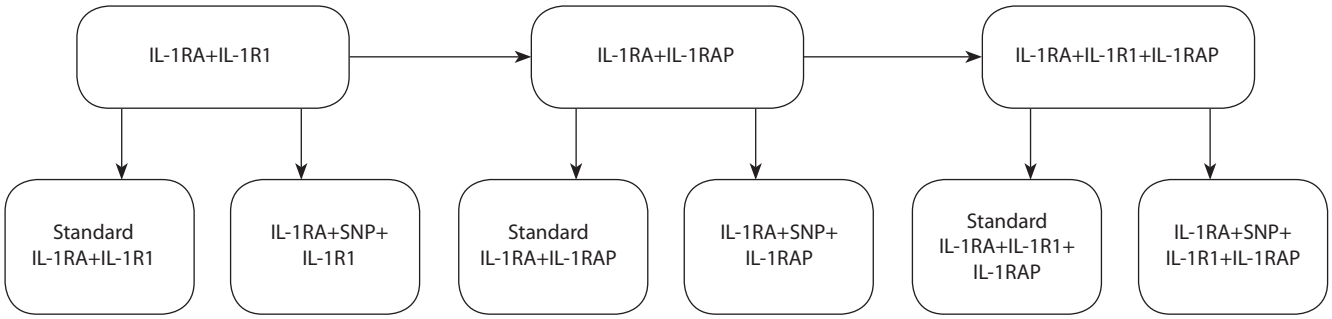

Fig. 2. Stages of protein interactions modeling.

Since IL-1RA interacts with IL-1R1, IL-1RAP, and the IL-1R1+IL-1RAP complex (Fig. 1), three-dimensional structures of the corresponding proteins were required for modeling and analysis. The PDB structure of the IL-1β signaling complex was obtained, including IL-1β (chains A, D), IL-1R1 (chains B, E), and IL-1RAP (chains C, F). The IL-1R1+IL-1RAP complex, IL-1RAP, and IL-1R1 were obtained using the PyMol program.

Modeling protein interactions initiating the IL-1 pathway

Modeling of interactions followed the scheme presented in Figure 2. Interactions of standard (non-polymorphic) IL-1RA with IL-1R1, IL-1RAP, and the IL-1R1+IL-1RAP receptor complex were modeled and analyzed sequentially. Subsequently, interactions with IL-1RA rs315952 were also modeled.

Modeling IL-1RA interactions with IL-1R1

Modeling interaction of standard IL-1RA with IL-1R1. In the obtained models, the minimum energy indicators demonstrated interaction according to the 1itbAB template, characterizing the most probable interaction where the structure is maximally stable (Table 2).

Considering the rs315952 polymorphism (Table 1) involving the replacement of serine by arginine at position 130, the interaction at this point was evaluated under normal and polymorphic conditions. According to the contact list of template residues, serine at position 130 of the IL-1RA molecule binds to leucine at position 237 of IL-1R1 (see Table 4).

Modeling interaction of IL-1RA with the rs315952 polymorphism with IL-1R1. The structures of IL-1RA molecules with the rs315952 polymorphism and IL-1R1 were utilized for modeling.

Table 2. Interfaces (binding regions) and interaction energies of standard IL-1RA with IL-1R1

Interface (binding region)	Decoding of the binding domain name	Energy, kJ/mol
1itbAB	Interaction of chains A (IL-1β) and B (IL-1β type 1 receptor) in the 1itb structure from the PDB database	–29.35
3kxyGH	Interaction of chains G (Protein C exoenzyme S synthesis) and H (Protein C exoenzyme S synthesis) in the 3kxy structure from the PDB database	–13.68
1iraXY	Interaction of chains X (IL-1 receptor antagonist) and Y (IL-1 receptor) in the 1ira structure from the PDB database	–5.03
1itbAB	Interaction of chains A (IL-1β) and B (IL-1β type 1 receptor) in the 1itb structure from the PDB database	–4.62

Table 3. Interfaces (binding regions) and interaction energies of IL-1RA with the rs315952 polymorphism with IL-1R1

Interface (binding region)	Decoding of the binding domain name	Energy, kJ/mol
1iraXY	Interaction of chains X (IL-1 receptor antagonist) and Y (IL-1 receptor) in the 1ira structure from the PDB database	–30.08
1itbAB	Interaction of chains A (IL-1β) and B (IL-1β type 1 receptor) in the 1itb structure from the PDB database	–28.18
1iraXY	Interaction of chains X (IL-1 receptor antagonist) and Y (IL-1 receptor) in the 1ira structure from the PDB database	–18.28
3kxyGH	Interaction of chains G (Protein C exoenzyme S synthesis) and H (Protein C exoenzyme S synthesis) in the 3kxy structure from the PDB database	–6.62
1itbAB	Interaction of chains A (IL-1β) and B (IL-1β type 1 receptor) in the 1itb structure from the PDB database	–6.38

In the results of modeling this interface, minimum energy values were found for the 1iraXY template (Table 3). However, as the interaction without the polymorphism in the IL-1RA structure (IL-1RA+IL-1R1) showed minimal interaction energy according to the 1itbAB template, the energy should be compared using the same template.

Comparison between Tables 2 and 3 suggests that the interaction of IL-1RA with the rs315952 polymorphism with IL-1R1 (–30.08 kJ/mol) is the most energetically advantageous. However, when comparing energies using the same 1itbAB template, this interaction becomes less energetically favorable (–29.35 kJ/mol and –28.18 kJ/mol, respectively). This suggests that in the presence of the rs315952 polymorphism in IL1-RA (serine substitution at position 130 for arginine (Table 4)), the interleukin-receptor interaction complex weakens, becoming less stable and more susceptible to decay.

Thus, based on the interactions of IL-1RA with the rs315952 polymorphism with IL-1R1, we cannot draw a definitive conclusion regarding the polymorphism's impact on its involvement in initiating the IL-1 signaling pathway. However, the modeled interactions indicate that the polymorphism participates in the formation of the protein-protein complex.

Modeling interactions of IL-1RA with IL-1RAP

Two investigations were conducted for modeling interactions: the interaction of standard IL-1RA with IL-1RAP and IL-1RA with the rs315952 polymorphism with IL-1RAP. In both cases, the algorithm did not create a model of protein interaction.

Modeling interactions of IL-1RA with the IL-1R1+IL-1RAP complex

Modeling interaction of standard IL-1RA with the IL-1R1+IL-1RAP complex. The interaction of IL-1RA with the receptor complex using the 1iraXY template showed a stable interaction (–34.27 kJ/mol) (Table 5). However, analyzing the interaction using the 1itbAB template revealed a very weak interaction (–2.67 kJ/mol).

According to the contact list of template residues, serine at position 130 is also a hotspot (Table 7).

The results in Table 5 indicate that the 1itbAB template is suitable for interaction with the added IL-1RAP protein, but its stability is almost minimal, implying the formed complex will quickly break down. Therefore, for further interaction analysis, we use the 1iraXY template.

Modeling interaction of IL-1RA with the rs315952 polymorphism with the IL-1R1+IL-1RAP complex. According to the contact list of template residues, arginine is also a hotspot. The simulation results presented in Table 6 show that the minimum energy of the complex is observed with the 1iraXY template at –25.27 kJ/mol.

Comparing interactions with the complex without polymorphism using the 1iraXY template, it is evident that the

Table 4. Contacts of interface residues of 1itbAB IL-1RA and IL-1R1 and 1itbAB IL-1RA with SNP rs315952 and IL-1R1

1itbAB IL-1RA and IL-1R1		1itbAB IL-1RA with SNP rs315952 and IL-1R1	
IL-1RA	IL-1R1	IL-1RA with SNP	IL-1R1
SER_97	ASN_30	ARG_51	GLU_11
VAL_95	PRO_31	ASN_64	GLN_108
GLU_100	PRO_28	GLN_154	PRO_31
PRO_132	SER_263	GLN_61	TYR_127
LYS_121	ARG_163	ARG_117	ASP_251
LYS_121	ASP_162	ARG_117	GLU_252
TRP_144	ILE_13	ARG_117	ASP_253
GLY_131	LEU_237	**ARG_130**	**THR_300**
GLN_119	ARG_163	GLU_77	ILE_250
ASP_99	LEU_15	ARG_51	ILE_13
PRO_142	VAL_124	GLN_45	LEU_123
TRP_144	TYR_127	GLN_45	VAL_124
LYS_96	GLU_129	LYS_34	LEU_237
ASP_120	ARG_163	LEU_60	TYR_127
SER_97	CYS_27	LYS_34	SER_263
CYS_141	LEU_115	GLU_77	VAL_249
ASP_120	VAL_124	GLU_77	ILE_240
SER_97	PRO_28	TYR_59	GLN_113
SER_97	LEU_29	PRO_78	ILE_240
GLY_98	CYS_27	GLY_131	THR_300
GLY_98	PRO_26	GLN_61	LEU_15
GLU_100	ILE_13	GLN_61	ILE_13
GLY_98	LEU_29	PRO_63	ILE_13
GLY_98	PRO_28	GLY_62	ILE_13
PRO_142	GLN_113	PRO_63	ILE_14
SER_130	**LEU_237**	GLN_45	GLN_113
ASP_99	PRO_28		
ASN_160	ILE_13		
ASP_99	PRO_26		

minimum energy without polymorphism is –34.27 kJ/mol, while with polymorphism it is –25.27 kJ/mol. Thus, it can be hypothesized that the studied rs315952 polymorphism affects the formation of IL-1RA binding with the IL-1R1+IL-1RAP receptor complex, creating a less stable complex more prone to decay.

The study results allow us to make an assumption that the p.Ser130Arg mutation in the IL-1RA protein gene may lead to the formation of a weakened complex between IL-1RA and the associated receptors IL-1R1+IL-1RAP, which could impact schizophrenia mechanisms.

Discussion

The functions of IL-1 family molecules are primarily associated with innate immunity. While inflammation normally acts as a protective mechanism, it can cause damage to the body when it becomes uncontrollable (Dinarello, 2018). IL-1 has been implicated in neuronal cell damage (Allan et al., 2005), and excessive phagocytosis may contribute to pathologies in Alzheimer's disease, schizophrenia, and aging (Vilalta, Brown, 2018). IL-1 triggers phagocytosis in the brain by acting as a chemoattractant for neutrophils. Initiating the IL-1 signaling pathway also leads to the release of cytokines

Table 5. Interfaces (binding regions) and interaction energies of standard IL-1RA with the IL-1R1+IL-1RAP protein complex

Interface (binding region)	Decoding of the binding domain name	Energy, kJ/mol
1iraXY	Interaction of chains X (IL-1 receptor antagonist) and Y (IL-1 receptor) in the 1ira structure from the PDB database	–34.27
3fmpCD	Interaction of chains C (Nuclear pore complex protein Nup214) and D (ATP-dependent RNA helicase DDX19B) in the 3fmp structure from the PDB database	–15.92
1itbAB	Interaction of chains A (IL-1β) and B (IL-1β type 1 receptor) in the 1itb structure from the PDB database	–2.67

Table 6. Interface (binding region) and interaction energies of IL-1RA with the rs315952 polymorphism with the IL-1R1+IL-1RAP protein complex

Interface (binding region)	Decoding of the binding domain name	Energy, kJ/mol
1iraXY	Interaction of chains X (IL-1 receptor antagonist) and Y (IL-1 receptor) in the 1ira structure from the PDB database	–25.27
1iraXY	Interaction of chains X (IL-1 receptor antagonist) and Y (IL-1 receptor) in the 1ira structure from the PDB database	–19.03
1iraXY	Interaction of chains X (IL-1 receptor antagonist) and Y (IL-1 receptor) in the 1ira structure from the PDB database	–15.47
1itbAB	Interaction of chains A (IL-1β) and B (IL-1β type 1 receptor) in the 1itb structure from the PDB database	–12.36

TNFα and IFN-γ, which activate macrophages (Sasayama et al., 2011).

Studies confirm an increase in the level of IL-1 in the blood of individuals with schizophrenia (Chu et al., 2018; Zhou et al., 2019). The reporter system of genetic knockout in mice, used to track the reciprocal deletion or expression of the IL-1 receptor (IL-1R1) in endothelial cells, ventricles, peripheral myeloid cells, microglia, astrocytes, and neurons, revealed that endothelial IL-1R1 is necessary and sufficient for mediating pain behavior. It is also shown to stimulate the proliferation of leukocytes in the central nervous system (CNS) and attenuate neurogenesis. Ventricular IL-1R1 is critical for the proliferation of monocytes in the CNS. Although microglia does not express IL-1R1, stimulation of endothelial cells with IL-1 leads to the induction of IL-1 in microglia (Liu et al., 2019).

The IL-1RA protein, which is an antagonist of IL-1 receptors and has an anti-inflammatory function (Dinarello, 1994), has also been found to be associated with schizophrenia (Kim et al., 2004). Preliminary results suggest that the IL-1RA protein gene may contribute to the ventricular changes observed in patients with this disease (Papiol et al., 2005).

An association has been found between single nucleotide polymorphisms in proteins involved in the IL-1 pathway and the risk of developing schizophrenia (Xu, He, 2010). There is a tendency for the association of the GAGG haplotype (rs1143627, rs16944, rs1143623, rs4848306) of the *ILB* gene; TG haplotypes (rs315952, rs9005) and TT61 rs5254 (rs4) of *IL1RN*, and CT haplotype (rs4251961, rs419598) in *IL1RN* with the risk of schizophrenia. Statistically significant association is shown for rs1143634 (*IL1B* gene; T3953C). This suggests a connection between pro-inflammatory factors, specifically polymorphisms in genes initiating the IL1 pathway, and the development of this disorder (Xu, He, 2010; Kapelski et al., 2016).

IL-1RA, acting as an antagonist to the IL-1 receptor, exhibits anti-inflammatory properties. In turn, IL-1α and IL-1β, by binding to the IL-1 receptor, initiate the IL-1 signaling pathway, participating in the implementation of the inflammatory response. Elevated synthesis of IL-1RA blocks this pathway, leading to inhibition of the immune response and weakening of the inflammatory process.

In the analysis of the interaction of the studied proteins, no differences in energy outputs were observed between standard IL-1RA and IL-1RA with rs315952 interacting with IL-1R1. When standard IL-1RA interacts with the IL-1R1+IL-1RAP complex, a lower energy value is observed compared to the case with the polymorphism, presumably indicating a weakening of the interaction between IL-1RA and IL-1R1+IL-1RAP. Notably, IL-1RA does not interact separately with IL-1RAP.

IL-1RA protein, upon binding to IL-1R1 and IL-1R1+IL-1RAP, inhibits the binding of IL-1 and, consequently, the activation of the IL-1 signaling pathway (Weber et al., 2010). In schizophrenia, the appearance of a single nucleotide polymorphism in the *IL-1RA* gene (p.Ser130Arg) may lead to the formation of a weakened complex between IL-1RA and associated receptors IL-1R1+IL-1RAP. This, presumably, could subsequently trigger the IL-1 signaling pathway and, as a result, the development of an uncontrolled immune response.

The results of the study showed that the functions of interleukin-1, namely the interactions of IL-1 family proteins, may be associated with structural changes in the corresponding genes. The analysis of SNP associations of these genes with

Table 7. Contacts of residues in the interface of 1itbAB standard IL-1RA with the complex of IL-1R1+IL-1RAP proteins and 1itbAB IL-1RA with the rs315952 polymorphism with the complex of IL-1R1+IL-1RAP proteins

1itbAB standard IL-1RA with the complex of IL-1R1+IL-1RAP proteins		1itbAB IL-1RA with the rs315952 polymorphism with the complex of IL-1R1+IL-1RAP proteins	
IL-1RA	IL-1R1+IL-1RAP	IL-1RA with the rs315952 polymorphism	IL-1R1+IL-1RAP
pdb1_A_SER_130	pdb2_C_ILE_184	pdb1_A_ARG_130	pdb2_C_ILE_184
pdb1_A_ARG_51	pdb2_B_GLU_11	pdb1_A_ARG_51	pdb2_B_GLU_11
pdb1_A_MET_150	pdb2_C_ASN_168	pdb1_A_ARG_51	pdb2_B_ILE_13
pdb1_A_MET_150	pdb2_B_ARG_163	pdb1_A_ASN_64	pdb2_B_ALA_109
pdb1_A_ASN_116	pdb2_B_GLU_252	pdb1_A_ASN_64	pdb2_B_ALA_107
pdb1_A_GLY_165	pdb2_C_PHE_167	pdb1_A_ASN_44	pdb2_B_VAL_124
pdb1_A_MET_161	pdb2_C_TYR_162	pdb1_A_GLN_154	pdb2_B_PRO_31
pdb1_A_TYR_59	pdb2_B_TYR_127	pdb1_A_PRO_63	pdb2_B_ILE_110
pdb1_A_ARG_117	pdb2_B_ASP_251	pdb1_A_PRO_63	pdb2_B_PHE_111
pdb1_A_GLN_154	pdb2_B_PRO_31	pdb1_A_ARG_117	pdb2_B_ASP_251
pdb1_A_SER_130	**pdb2_B_THR_300**	pdb1_A_ARG_117	pdb2_B_GLU_252
pdb1_A_LYS_170	pdb2_C_SER_185	pdb1_A_GLU_77	pdb2_B_GLU_259
pdb1_A_ASP_129	pdb2_B_THR_300	pdb1_A_ARG_130	pdb2_B_THR_300
pdb1_A_ASP_163	pdb2_C_MET_159	pdb1_A_GLU_77	pdb2_B_ILE_250
pdb1_A_ASP_163	pdb2_C_SER_185	pdb1_A_LYS_170	pdb2_C_SER_185
pdb1_A_VAL_43	pdb2_B_LYS_114	pdb1_A_ASP_129	pdb2_B_THR_300
pdb1_A_GLU_164	pdb2_C_MET_159	pdb1_A_ASN_64	pdb2_B_GLN_108
pdb1_A_LYS_170	pdb2_C_LEU_183	pdb1_A_GLU_164	pdb2_C_TYR_162
pdb1_A_GLU_164	pdb2_C_TYR_162	pdb1_A_GLN_45	pdb2_B_VAL_124
pdb1_A_GLU_77	pdb2_B_VAL_249	pdb1_A_GLN_45	pdb2_B_PRO_126
pdb1_A_TYR_59	pdb2_B_PHE_111	pdb1_A_GLU_175	pdb2_B_LEU_237
pdb1_A_LEU_67	pdb2_B_ILE_13	**pdb1_A_ARG_130**	**pdb2_C_ARG_286**
pdb1_A_GLU_77	pdb2_B_TYR_242	pdb1_A_LYS_34	pdb2_B_LEU_237
pdb1_A_GLY_131	pdb2_B_THR_300	pdb1_A_ASN_64	pdb2_B_ILE_110
pdb1_A_GLY_165	pdb2_C_MET_159	pdb1_A_LYS_34	pdb2_B_SER_263
pdb1_A_GLN_61	pdb2_B_GLU_11	pdb1_A_VAL_43	pdb2_C_LEU_183
pdb1_A_GLN_61	pdb2_B_ILE_13	pdb1_A_GLU_77	pdb2_B_VAL_249
pdb1_A_PRO_63	pdb2_B_LYS_12	pdb1_A_ASP_153	pdb2_B_PRO_31
pdb1_A_PRO_63	pdb2_B_ILE_13	pdb1_A_GLU_77	pdb2_B_TYR_261
pdb1_A_ARG_30	pdb2_B_ASP_260	pdb1_A_GLU_77	pdb2_B_ILE_240
pdb1_A_GLY_62	pdb2_B_ILE_13	pdb1_A_PRO_78	pdb2_B_ILE_240
pdb1_A_LYS_170	pdb2_C_ASN_168	pdb1_A_GLY_131	pdb2_B_THR_300
pdb1_A_PRO_63	pdb2_B_ILE_14	pdb1_A_HIS_79	pdb2_B_ILE_240
pdb1_A_GLN_45	pdb2_B_PHE_111	pdb1_A_GLN_61	pdb2_B_ILE_13
pdb1_A_GLN_45	pdb2_B_LYS_112	pdb1_A_VAL_65	pdb2_B_LYS_112
pdb1_A_GLN_45	pdb2_B_GLN_113	pdb1_A_PRO_63	pdb2_B_ILE_13
		pdb1_A_GLY_62	pdb2_B_ILE_13
		pdb1_A_PRO_63	pdb2_B_ILE_14
		pdb1_A_ASN_44	pdb2_C_ASN_168
		pdb1_A_GLN_45	pdb2_B_GLN_113
		pdb1_A_GLY_165	pdb2_C_TYR_162

schizophrenia, together with information about the influence of inflammation on the mechanisms of its development, can serve as a theoretical basis for a more detailed and careful study of the mechanisms of the inflammatory response.

Conclusion

It is known that *in silico* mutagenesis and the comparison of changes in interaction energies between the standard and mutated variants shed light on the mechanisms underlying the development of several diseases. The results obtained in this study demonstrate that in schizophrenia, structural changes in genes may influence the functions of interleukin-1 (protein interactions within the IL-1 family). This, in turn, allows correlating existing data on the impact of inflammation on the development of schizophrenia with associations of SNPs in genes related to the IL-1 family. The conducted research makes a theoretical contribution to the understanding of the details of the mechanisms involved in the inflammatory response in schizophrenia, and the results may serve as a basis for further studies (both *in silico* and experimental) in this field.

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