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EFFECTS OF CCL2 CHEMOKINE MISSENSE MUTATIONS ON CCR5 RECEPTOR AFFINITY: A COMPUTATIONAL STUDY IN THE CONTEXT OF HIV INFECTION REGULATOR DISCOVERY

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ВЛИЯНИЕ МИССЕНС-МУТАЦИЙ ХЕМОКИНА CCL2 НА АФФИННОСТЬ С РЕЦЕПТОРОМ CCR5: ВЫЧИСЛИТЕЛЬНОЕ ИССЛЕДОВАНИЕ В КОНТЕКСТЕ ПОИСКА РЕГУЛЯТОРОВ ВИЧ-ИНФЕКЦИИ

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Abstract

Introduction

HIV entry into host cells requires CD4 receptors and CCR5 co-receptors. Natural CCR5 ligands can inhibit HIV through steric blocking and receptor internalization. Although CCL2 is primarily a CCR2 ligand, emerging evidence suggests possible CCR5 interaction, challenging conventional views of chemokine specificity. Natural CCL2 missense mutations provide valuable insights into receptor interaction mechanisms and their potential role in HIV infection modulation, offering new perspectives on viral entry inhibition strategies.

Methods. The wild-type complex was modeled using AlphaFold Server with rigorous validation. From UniProt database, we selected 41 CCL2 mutations within predicted CCR5 binding sites based on structural analysis. For each variant, we generated mutant protein structures and complex models using FoldX algorithm in YASARA environment. We calculated binding energies, complex stability, and interaction energy parameters, while conducting detailed analysis of atomic contacts and hydrogen bonding patterns. Functional impact of mutations was assessed using PolyPhen-2 algorithm.

Results. Molecular modeling identified 35 CCL2 residues forming the comprehensive CCR5 interface. Five specific mutations (P78H, S57C, I28V, N29A, K79A) significantly enhanced CCR5 binding affinity, reducing interaction energy compared to wild type. P78H and S57C variants showed the strongest effects and were consistently predicted as "probably damaging". K79A demonstrated substantially improved binding while maintaining reasonable interfacial contacts. Detailed structural analysis revealed these mutations optimize the binding interface through strategic reorganization of molecular interactions and improved complementarity.

Discussion. Our findings demonstrate that specific natural CCL2 mutations can substantially enhance CCR5 binding affinity, revealing unexpected plasticity in chemokine-receptor recognition systems. The most impactful mutations suggest

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evolutionary mechanisms for modulating HIV entry pathways through natural genetic variation. These results provide structural insights into how sequence variations might influence viral pathogenesis through altered receptor specificity and binding kinetics.

Conclusion. This computational study identifies key CCL2 mutations that significantly enhance CCR5 binding, expanding our understanding of chemokine system flexibility and evolutionary adaptation. The results support further experimental investigation of natural CCL2 variants as potential modulators of HIV infection and contribute to fundamental knowledge of virus-host interactions at molecular level.

Keywords: HIV, chemokine CCL2, CCR5 receptor, missense mutations, molecular modeling, binding energy, virus attachment, *in silico*.

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Резюме

Введение. Фундаментальные механизмы взаимодействия ВИЧ с клеткой-хозяином остаются областью интенсивного изучения, где особое значение имеет проникновение вируса через рецепторы CD4 и корецепторы семейства хемокиновых рецепторов. Известно, что естественные лиганды рецептора CCR5, такие как RANTES, MIP-1α и MIP-1β, способны ингибировать проникновение ВИЧ-1 посредством стерического блокирования и интернализации рецептора. Хемокин CCL2, классически считающийся селективным лигандом CCR2, по данным компьютерного моделирования, потенциально может обладать способностью к взаимодействию с CCR5, что противоречит устоявшимся представлениям о строгой селективности хемокинов. Природные миссенс-мутации CCL2 представляют особый интерес для изучения молекулярных основ изменения рецепторной специфичности и потенциальной модуляции восприимчивости к ВИЧ-инфекции.

Цель. Моделирование и оценка влияния естественных миссенс-мутаций хемокина CCL2 на его способность к формированию стабильного комплекса с рецептором CCR5 в контексте фундаментальных механизмов взаимодействия "вирус-хозяин" и потенциального ингибирования проникновения ВИЧ-1.

Материалы и методы. Исследование выполнено методами структурной биоинформатики. Модель комплекса CCL2 дикого типа с рецептором CCR5 построена с использованием алгоритма AlphaFold Server. Из базы данных UniProt идентифицирован 41 полиморфизм CCL2, локализованных в предсказанном сайте связывания с CCR5. Для каждого варианта построены модели изолированного мутантного белка и комплекса с CCR5. Расчет свободной энергии проводили с использованием алгоритма FoldX в пакете YASARA. Определяли энергию стабильности изолированного белка, энергию стабильности комплекса и энергию взаимодействия. Дополнительно анализировали изменения в количестве атомарных контактов

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и водородных связей. Функциональная значимость мутаций оценена с помощью алгоритма PolyPhen-2.

Результаты. Молекулярное моделирование выявило 35 аминокислот CCL2, формирующих интерфейс взаимодействия с CCR5. Среди 41 проанализированной формы идентифицированы варианты (P78H, S57C, I28V, N29A, K79A), демонстрирующие значительное улучшение энергии связывания с CCR5 - снижение на 15-29 ккал/моль по сравнению с диким типом. Мутации P78H и S57C показали наибольшее снижение энергии взаимодействия (-29,14 и -20,18 ккал/моль соответственно) при прогнозе PolyPhen-2 как "probably damaging". Вариант K79A, требующий двух нуклеотидных замен, продемонстрировал сбалансированное сочетание улучшенной энергии связывания (-23,91 ккал/моль) и умеренного сокращения количества контактов.

Выводы. Показано, что ряд миссенс-мутаций хемокина CCL2 способен изменять энергетический профиль его взаимодействия с рецептором CCR5. Выявленные мутантные формы, демонстрирующие увеличение стабильности комплекса CCL2-CCR5, представляют фундаментальный интерес для понимания пластичности хемокиновой системы и механизмов молекулярного узнавания. Полученные данные расширяют представления о потенциальных естественных механизмах модуляции взаимодействия ВИЧ с клеткой-хозяином и заслуживают проверки в контексте фундаментальных основ патогенеза ВИЧ-инфекции.

Ключевые слова: ВИЧ, хемокин CCL2, рецептор CCR5, миссенс-мутации, молекулярное моделирование, энергия связывания, прикрепление вируса, in silico.

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1 Introduction

HIV infection, caused by the human immunodeficiency virus (HIV), is a chronic disease that, in the absence of antiretroviral therapy (ART), leads to the development of acquired immunodeficiency syndrome (AIDS). The widespread implementation of ART has allowed the infection to be reclassified as a manageable chronic condition; however, it is not a panacea. A key problem in long-term treatment remains the pervasive prevalence of viral mutations leading to the development of drug resistance, which compromises the efficacy of existing treatment regimens and necessitates the continuous development of new drug classes and therapeutic strategies [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]. Consequently, despite significant treatment advances, this infection remains a major global public health and modern medical challenge [**Ошибка! Источник ссылки не найден.**], underscoring the need for a detailed understanding of the fundamental basis of its pathogenesis—primarily, the mechanism of viral entry into the target cell.

This process represents a complex cascade of sequential molecular events, where each stepwise interaction serves as a precisely calibrated prerequisite for the next, ultimately enabling the viral genetic material to enter the target cell's cytoplasm [**Ошибка! Источник ссылки не найден.**]. The initial stages of this process critically depend on the interaction between the viral envelope glycoprotein gp120 and the cellular CD4 receptor alongside a co-receptor, often the chemokine receptor CCR5 [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]. The importance of CCR5 is highlighted by its role as the primary co-receptor for macrophage-tropic (R5-tropic) HIV-1 strains, which dominate during early infection stages. Furthermore, the presence of a natural mutation, CCR5-Δ32, which leads to a lack of the functional receptor on the cell surface, is associated with near-complete resistance to infection by these viral strains.

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It is known that natural ligands of the CCR5 receptor, including the chemokines RANTES, MIP-1α, and MIP-1β (CCL5, CCL3, CCL4), can partially or completely inhibit HIV-1 entry into the cell [**Ошибка! Источник ссылки не найден.**]. This effect is achieved through their ability to bind CCR5, leading to steric blocking of the viral binding site and, in some cases, inducing receptor internalization [**Ошибка! Источник ссылки не найден.**]. This natural mechanism is of interest for fundamental research aimed at understanding the molecular basis of ligand interactions with CCR5.

In our previous computationally-driven studies, a hypothesis was put forward regarding the potential ability of the chemokine CCL2—classically known as a selective chemoattractant for the CCR2 receptor—to interact with the CCR5 receptor [**Ошибка! Источник ссылки не найден.**]. This assumption challenges the established view of CCL2's strict selectivity for CCR2 and requires thorough experimental and theoretical validation [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**].

The central paradox requiring resolution is that if such an interaction exists, its energy and specificity appear insufficient for effective engagement with CCR5, consequently failing to block viral infection in vivo. However, natural genetic variants of chemokines and their receptors arising from missense mutations are of particular interest in this context. When such variants impact the affinity and specificity of ligand-receptor interactions, they offer unique opportunities. Firstly, they serve as an indispensable tool for studying the fundamental principles of molecular recognition. Secondly, and most importantly in the context of HIV infection, functionally active variants, analogous to the CCR5-Δ32 polymorphism, could potentially modulate susceptibility to the virus or disease progression. Therefore, their targeted search and analysis open new prospects for identifying natural mechanisms of resistance to infection [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**].

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The primary objective of this study was to model and comprehensively evaluate the impact of natural missense mutations in the chemokine CCL2 on its ability to interact with the CCR5 receptor, within the context of potentially inhibiting HIV entry into the cell.

2 Materials and Methods

The three-dimensional structure of the wild-type chemokine CCL2 (AAP35993.1| chemokine (C-C motif) ligand 2 [Homo sapiens]) complexed with the CCR5 receptor (NP_001381712.1| C-C chemokine receptor type 5 [Homo sapiens]) was modeled using the AlphaFold Server algorithm (https://alphafoldserver.com/) [**Ошибка! Источник ссылки не найден.**]. Visual analysis of the model, identification of intermolecular contact zones, and quantification of atomic contacts, steric clashes, and hydrogen bonds between the proteins were performed using UCSF ChimeraX [**Ошибка! Источник ссылки не найден.**].

Data on non-synonymous single nucleotide polymorphisms resulting in single amino acid substitutions without a reading frame shift for the CCL2 protein were obtained from the UniProt database [**Ошибка! Источник ссылки не найден.**]. Mutations for further analysis were selected based on their localization within the predicted CCR5 contact sites identified during the initial model analysis. Additionally, known polymorphic non-single nucleotide variants with documented effects on CCL2 function, as well as non-synonymous polymorphisms without a frame shift, were included in the study.

For each selected variant, models of the isolated mutant CCL2 protein and the complex of the mutant CCL2 variant with the CCR5 receptor were constructed using the AlphaFold algorithm. The prediction reliability for each variant's structure was assessed.

To quantitatively evaluate the effects of the mutations, the free energy for all obtained models was calculated using the FoldX algorithm [**Ошибка! Источник ссылки не найден.**], integrated into the YASARA molecular modeling package

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[**Ошибка! Источник ссылки не найден.**]. For each model, the stability energy of the isolated CCL2 protein structure, the stability energy of the CCL2-CCR5 complex, and the interaction energy between the partners in the complex were calculated. Based on these calculations, the energy difference between the mutant and wild-type for each parameter was determined.

For all modeled complexes, the interaction interface was analyzed in UCSF ChimeraX by counting the total number of atomic contacts and hydrogen bonds, and identifying steric clashes. The obtained values were compared to those of the wild-type complex.

For each polymorphic variant with the studied amino acid substitution, the functional significance and potential impact on protein function were predicted using the PolyPhen-2 algorithm [**Ошибка! Источник ссылки не найден.**]. This tool classifies substitutions as "probably damaging" (PolyPhen-score >0.85), "possibly damaging"(PolyPhen-score between 0.15 and 0.85), or "benign"(PolyPhen-score<0.15) [**Ошибка! Источник ссылки не найден.**].

A comprehensive criterion was applied to assess the potential impact of a mutation on the HIV-host interaction. A mutant CCL2 variant was considered potentially significant if it simultaneously met the following criteria: an increase in the free energy of the isolated CCL2 protein (indicating protein destabilization with a potential increase in affinity), a decreased energy of the complex with CCR5 (indicating increased complex stability), a number of atomic contacts comparable to the wild-type, an interaction binding energy comparable to the wild-type (preservation of the interaction interface), and a predicted damaging functional effect by PolyPhen-2 (potentially indicating reduced chemotactic activity while retaining the ability to bind CCR5).

3 Results

A model of the CCL2 complex with the CCR5 receptor was constructed and analyzed during the study. Molecular modeling revealed 302 atomic interactions on the protein surfaces, involving 35 amino acids of CCL2 that formed the contact

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zones. Analysis of the UniProt database identified 41 polymorphisms (in 27 contact zones) within the coding sequence of CCL2. Of these, one led to the formation of a stop codon, seven represented complex mutations, and the remaining 33 were missense mutations resulting in amino acid substitutions within the domain of potential interaction with CCR5.

For all variants, structures of the isolated mutant proteins and their complexes with CCR5 were built, resulting in a total of 82 molecular models. The individual protein models showed a comparable level of prediction reliability around pTM (predicted template modeling) 0.62-0.64 and ipTM score 0.80-0.82, as did the interaction models, for which the ipTM score was not below 0.7.

The stability of the single CCL2 molecule was 29.04 kcal/mol according to FoldX data, indicating an unstable or excited state of the molecule. 24 molecular variants showed a decrease in energy (increased molecular stability). The greatest reduction in the free energy of the monomer was observed for variants P19L (-10.64 kcal/mol) and Q20R (-9.15 kcal/mol), while an increase was observed for I28T (+3.49 kcal/mol) and E73X (+3.98 kcal/mol).

The difference in complex stability energy values ranged from an increase in complex stability compared to the wild-type with a change of -29.83 kcal/mol (S57C) to a decrease in stability of +32.24 kcal/mol (P60T).

In turn, the majority of amino acid substitutions (25 out of 41) increased the stability of the complex, manifested as a decrease in stability energy.

The difference in interaction energy values ranged from -29.14 kcal/mol (P78H) to +12.6 kcal/mol (N37D). The complete table of all energies is presented in Table 1.

Simultaneously with the energy calculations, an analysis of intermolecular contacts was conducted. This analysis revealed that the majority of amino acid substitutions led to a reduction in the number of potential contacts with the CCR5 molecule (Table 2).

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An *in silico* assessment of changes in protein function revealed that within the studied set of mutations, the number of variants predicted to impair protein function ("damaging") was approximately equal to the number of variants predicted to have no effect ("benign") (Table 3).

4 Discussion

This study presents a comprehensive *in silico* analysis of the impact of natural missense mutations in the chemokine CCL2 on its potential ability to interact with the CCR5 receptor. The obtained results require critical interpretation within the context of existing literature and theoretical concepts of the chemokine system.

It should be noted that CCL2 is presumed to interact selectively with the CCR2 receptor, while binding to CCR5 has not been demonstrated [**Ошибка! Источник ссылки не найден.**] and has in some cases been refuted [**Ошибка! Источник ссылки не найден.**]. However, our data show that specific amino acid substitutions can alter the structural and energetic parameters of CCL2, potentially enabling it to form a stable complex with CCR5. This aligns with modern understanding of protein structure plasticity and the potential for changes in their specificity under the influence of point mutations [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**].

Regarding the interaction, the most interesting mutations are those where both the complex energy and the interaction energy decreased, alongside a reduction in CCL2's functional activity as a chemoattractant. In biochemistry, a change in binding free energy of approximately ≈1 kcal/mol is already considered biologically significant [**Ошибка! Источник ссылки не найден.**]. In our study, many mutations demonstrated interaction energy changes > 5 kcal/mol (e.g., P78H: -29.14 kcal/mol; I28V: -22.43 kcal/mol), suggesting not just a statistically significant, but a drastic change in affinity. This indicates that the identified amino acid substitutions are capable of causing not fine regulation, but a qualitative change in the protein's functional profile.

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Concerning the correlation between complex stability and the efficiency of CCR5 blocking, two key mechanisms can be highlighted. First, increased stability of the CCL2-CCR5 complex (characterized by more negative values of interaction energy and complex stability) directly implies a longer lifetime for this complex [**Ошибка! Источник ссылки не найден.**]. For effective blocking of HIV attachment, this is critically important, as a viral particle encountering an occupied receptor will be unable to bind and initiate infection [**Ошибка! Источник ссылки не найден.**]. A CCL2 mutant with high affinity would act as a competitive antagonist. Second, increased complex stability often correlates with slower ligand dissociation [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]. Under physiological conditions, where chemokine concentrations can fluctuate, a slow "off-rate" from the receptor would provide more prolonged and reliable blocking of the CCR5 binding site for the viral gp120 protein, even if the mutant chemokine itself is not constantly present.

The interpretation of contact metrics and single-molecule stability energy is not straightforward. The stability energy of a single protein molecule – in the case of increased energy (decreased stability), the molecule should interact more actively with its environment, thus potentially losing interaction specificity [**Ошибка! Источник ссылки не найден.**]. In the opposite scenario (stability increases - energy decreases), the protein may have a lower propensity to interact [**Ошибка! Источник ссылки не найден.**], but the lifetime of the isolated protein could be prolonged [**Ошибка! Источник ссылки не найден.**].

A greater number of atomic or residue contacts within a molecule often contributes to increased molecular stability. However, not all contacts contribute equally to stability – some contacts can lead to local instability or misfolding [**Ошибка! Источник ссылки не найден.**]. For example, the I28V mutation shows a reduction in the number of contacts by 24, yet demonstrates one of the most significant improvements in binding energy (-22.43 kcal/mol).

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Thus, an ideal candidate for interacting with CCR5 should possess: lowered complex and interaction energy for structural stability; be functionally weaker (to avoid attracting lymphocytes to the site of viral activity and to interact less strongly with CCR2); have an increased or comparable number of contacts (without reducing the interaction energy); and have increased monomer energy to promote interaction with CCR5 (partially losing specificity for CCR2).

The analysis revealed that none of the studied mutations satisfied all criteria simultaneously. However, several variants demonstrated a promising combination of properties. The I18T mutation shows significant improvement in binding energy (-25.14 kcal/mol) and complex stability alongside an increase in contacts, although it is not predicted as functionally significant. The A23S mutation meets the energetic criteria but is accompanied by a decrease in contacts. The K79A variant is the most balanced, showing only a minor reduction in contacts and a predicted damaging effect on protein function. The main limitation of this mutation is its complexity, as it requires at least two nucleotide substitutions.

A cluster of mutations at positions 28-29 (I28T, I28V, N29K, N29A) is of particular interest, as they consistently improve affinity and complex stability. Importantly, for some of these variants (I28A, N29A), experimental data exist showing reduced functional activity of CCL2, which, combined with our calculations, makes them promising candidates for the role of CCR5 blockers, despite their PolyPhen-2 prediction as "benign".

The I65N mutation forms one of the most stable complexes; however, its association with gliomas requires extremely cautious interpretation and further study.

The most balanced profile is demonstrated by the S57C, P78H, and P78S mutations. They combine a significant improvement in binding energy (up to -29.14 kcal/mol for P78H) and complex stability with a minor decrease in monomer stability and a "probably damaging" prediction, suggesting retained ability to bind CCR5 alongside potentially reduced chemotactic function.

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An important limitation of the study is the lack of a direct correlation between the number of atomic contacts and the binding energy, underscoring the predominant role of the quality of interactions over their quantity. This indicates the need for a more detailed analysis of the nature of contacts in future work.

5 Conclusions

This study identified a range of natural genetic variants of CCL2 that demonstrate, *in silico*, the potential to interact with CCR5. The conducted molecular modeling suggests that natural missense mutations in the CCL2 chemokine can significantly modify its interaction with the CCR5 receptor. We successfully identified specific mutant forms (P78H, S57C, I28T/V, N29K/A, K79A) that exhibit an improvement in binding energy of 15-29 kcal/mol compared to the wild type. Such substantial changes in interaction energy indicate a potential significant increase in affinity. Although the S57C, P78H, and K79A variants did not show an increase in the number of atomic contacts, they demonstrated the greatest reduction in binding energy and were functionally predicted as "probably damaging." This combination of features makes them the most promising candidates.

The obtained data provide a basis for the targeted experimental validation of the ability of these mutant forms to competitively inhibit HIV binding to CCR5 without concurrently activating pro-inflammatory chemotactic pathways.

In conclusion, our research does not refute the existing understanding of CCL2 selectivity but rather expands upon it by demonstrating the potential for altering this chemokine's specificity under the influence of natural genetic variation. The identified mutant forms open new avenues for investigating the principles of molecular recognition within the chemokine family and warrant close attention in further experimental studies, particularly in the context of HIV infection.

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ТАБЛИЦЫ

Table 1. Stability energies of monomers and the complex, interaction energies, and differences from the wild-type (wt) CCL2 molecule energy.

Таблица 1. Энергии стабильности мономеров и комплекса, энергии взаимодействия и отличия от энергии молекулы CCL2 дикого типа (wt).

Polymorphism Полиморфизм	Mono Stability Энергия стабильность монобелка	ΔMono Stability Δэнергии стабильности монобелка	Complex Stability Энергия стабильности комплекса	ΔStability Δстабильности комплекса	Connection energy Энергия связи	ΔConnection Δэнергии связи
wt	29,04	0	-36,91	0	-5,29	0
A15P	28,56	-0,48	-28,93	7,98	-5,87	-0,58
T16S	30,5	1,46	-31,55	5,36	-10,61	-5,32
I18N	26,95	-2,09	-10,41	26,5	-1,37	3,92
I18T	28,85	-0,19	-50,09	-13,18	-30,43	-25,14
P19L	18,4	-10,64	-29,88	7,03	-12,5	-7,21
Q20P	25,98	-3,06	-52,32	-15,41	-11,21	-5,92
Q20R	19,89	-9,15	-42,1	-5,19	-22,52	-17,23
A23S	29,26	0,22	-45,75	-8,84	-21,7	-16,41
A23T	27,59	-1,45	-46,89	-9,98	-21,73	-16,44
Q24R	26,52	-2,52	-25	11,91	-5,86	-0,57
D26A	21,47	-7,57	-41,32	-4,41	-18,49	-13,2
A27G	28,77	-0,27	-43,37	-6,46	-20,74	-15,45
A27V	24,46	-4,58	-36,76	0,15	-16,85	-11,56
I28T	32,53	3,49	-48,16	-11,25	-25,79	-20,5

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I28V	24,94	-4,1	-57,13	-20,22	-27,72	-22,43
I28A	27,35	-1,69	-47,85	-10,94	-12,57	-7,28
N29K	23,43	-5,61	-55,18	-18,27	-28,35	-23,06
N29A	21,66	-7,38	-65,07	-28,16	-26,63	-21,34
P31A	27,82	-1,22	-55,42	-18,51	-18,73	-13,44
V32A	28,96	-0,08	-56,15	-19,24	-28,92	-23,63
V32E	25,03	-4,01	-32,99	3,92	-18,49	-13,2
T33A	29,36	0,32	-36,98	-0,07	-16,56	-11,27
T33E	23,52	-5,52	-52,3	-15,39	-23,53	-18,24
Y36C	28,18	-0,86	-36,4	0,51	-33,46	-28,17
Y36A	27,97	-1,07	-13,08	23,83	5,02	10,31
N37D	30,96	1,92	-23,45	13,46	6,87	12,16
T39A	24,59	-4,45	-54,61	-17,7	-16,49	-11,2
T39I	25,88	-3,16	-41,55	-4,64	-15,72	-10,43
S57C	26,59	-2,45	-66,74	-29,83	-25,47	-20,18
C59G	22,77	-6,27	-35,26	1,65	-9,94	-4,65
P60T	29,98	0,94	-4,67	32,24	6,51	11,8
K61I	25,1	-3,94	-25,13	11,78	-10,43	-5,14
I65N	30,79	1,75	-50,45	-13,54	-22,75	-17,46
E73X	33,02	3,98	-24,16	12,75	-21,24	-15,95
E73G	26,59	-2,45	-20,33	16,58	-3,78	1,51
I74N	30,29	1,25	-26,38	10,53	-2,68	2,61
P78H	27,74	-1,3	-56,41	-19,5	-34,43	-29,14
P78S	27,11	-1,93	-49,26	-12,35	-28,96	-23,67
K79E	20,07	-8,97	-45,34	-8,43	-20,23	-14,94
K79R	28,9	-0,14	-51,62	-14,71	-24,64	-19,35
K79A	31,61	2,57	-62,49	-25,58	-29,2	-23,91

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Notes: Polymorphism with non-single nucleotide substitutions is highlighted in bold.

Примечания: Полиморфизм с неодиночной нуклеотидной заменой выделен жирным шрифтом.

Table 2. Atomic contacts, steric clashes, and hydrogen bonds of CCL2 mutant forms

Таблица 2. Атомные контакты, стерические столкновения и водородные связи мутантных форм CCL2

Polymorphism Полиморфизм	**Contacts Контакты**	**Clashes Столкновения**	**h-bonds Водородные связи**	**∑All_Contacts ∑Все_Контакты**	**ΔAll_Contacts ΔВсе_Контакты**
wt	302	23	26	305	0
A15P	285	28	25	282	-23
T16S	331	31	19	319	14
I18N	240	21	17	236	-69
I18T	305	17	21	309	4
P19L	230	14	19	235	-70
Q20P	322	28	21	315	10
Q20R	310	38	23	295	-10
A23S	277	21	18	274	-31
A23T	299	25	20	294	-11
Q24R	268	19	20	269	-36
D26A	276	39	19	256	-49
A27G	263	20	24	267	-38
A27V	308	29	24	303	-2

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I28T	291	17	22	296	-9
I28V	279	22	24	281	-24
I28A	331	64	18	285	-20
N29K	306	20	15	301	-4
N29A	338	53	19	304	-1
P31A	268	24	21	265	-40
V32A	317	53	19	283	-22
V32E	225	23	17	219	-86
T33A	282	29	27	280	-25
T33E	295	36	23	282	-23
Y36C	337	49	25	313	8
Y36A	353	72	21	302	-3
N37D	244	34	17	227	-78
T39A	313	35	21	299	-6
T39I	316	47	22	291	-14
S57C	286	36	23	273	-32
C59G	359	44	21	336	31
P60T	329	47	17	299	-6
K61I	243	33	21	231	-74
I65N	312	46	21	287	-18
E73X	274	29	24	269	-36
E73G	310	39	26	297	-8
I74N	295	42	27	280	-25
P78H	328	48	21	301	-4
P78S	293	33	23	283	-22
K79E	171	28	7	150	-155
K79R	292	46	26	272	-33

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K79A	331	52	20	299	-6

Notes: ∑All_Contacts was calculated using the formula: Contacts - Steric Clashes + Hydrogen Bonds. Polymorphism with non-single nucleotide substitutions are highlighted in bold.

Примечания: ∑Все_Контакты рассчитаны по формуле Контакты-стерические столкновения + водородные связи. Полиморфизм с не-одиночной нуклеотидной заменой выделен жирным шрифтом.

Table 3. Summary of predicted functional effects of mutations according to PolyPhen-2(PP) and functional characteristics based on literature sources

Таблица 3. Сводка прогнозируемых функциональных эффектов мутаций в соответствии с PolyPhen-2(PP) и функциональные характеристики на основе литературных источников

Polymorphism Полиморфизм	PP-Score PP-значение	PP-sensitivity PP-чувствительность	PP-Specificity PP-специфичность	Functional data from literature Функциональные данные из литературы
A15P	0,997	0,41	0,98	None Не обнаружено
T16S	0,126	0,93	0,86	None Не обнаружено
I18N	0	1	0	None Не обнаружено
I18T	0	1	0	None Не обнаружено
P19L	0,002	0,99	0,3	None Не обнаружено

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Q20P	0,096	0,93	0,85	None Не обнаружено
Q20R	0,957	0,78	0,95	None Не обнаружено
A23S	0,966	0,78	0,95	None Не обнаружено
A23T	0,864	0,83	0,93	None Не обнаружено
Q24R	0,988	0,73	0,96	Adenomas and Adenocarcinomas Аденомы и аденокарциномы[**Ошибка! Источник ссылки не найден.**]
D26A	0,949	0,79	0,95	Reduction in activity Снижение активности[**Ошибка! Источник ссылки не найден.**]
A27G	0,01	0,96	0,77	None Не обнаружено
A27V	0,963	0,78	0,95	None Не обнаружено
I28T	0,061	0,94	0,84	Adenomas and Adenocarcinomas Аденомы и аденокарциномы[**Оши**

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				бка! Источник ссылки не найден.]
I28V	0,001	0,99	0,15	None Не обнаружено
I28A	0,001	0,99	0,15	Slight reduction in activity Незначительное снижение активности[**Ошибка! Источник ссылки не найден.**]
N29K	0,1	0,93	0,85	Adenomas and Adenocarcinomas Аденомы и аденокарциномы[**Ошибка! Источник ссылки не найден.**]
N29A	0,44	0,89	0,9	50% reduction in activity 50% снижение активности[**Ошибка! Источник ссылки не найден.**]
P31A	0,08	0,93	0,85	Loss of dimerization; slight reduction of activity Потеря димеризации; незначительное

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				снижение активности[14, **Ошибка! Источник ссылки не найден.**]
V32A	0,1	0,93	0,85	Slight reduction in activity Незначительное снижение активности [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]
V32E	0,655	0,86	0,91	Slight reduction in activity Незначительное снижение активности [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]
T33A	0,041	0,94	0,83	Slight reduction in activity Незначительное снижение активности [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]

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T33E	0,97	0,77	0,96	Slight reduction in activity Незначительное снижение активности [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]
Y36C	0,999	0,14	0,99	None Не обнаружено
Y36A	0,992	0,7	0,97	Loss of activity Потеря активности [**Ошибка! Источник ссылки не найден.**]
N37D	0,271	0,91	0,88	None Не обнаружено
T39A	0,002	0,99	0,3	None Не обнаружено
T39I	0,005	0,97	0,74	None Не обнаружено
S57C	0,998	0,27	0,99	None Не обнаружено
C59G	1	0	1	None Не обнаружено
P60T	0,976	0,76	0,96	Squamous Cell Neoplasms Плоскоклеточные новообразования

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				[**Ошибка! Источник ссылки не найден.**]
K61I	0,589	0,87	0,91	None Не обнаружено
I65N	1	0	1	Gliomas Глиомы[**Ошибка! Источник ссылки не найден.**]
E73G	0,186	0,92	0,87	None Не обнаружено
I74N	0,997	0,41	0,98	None Не обнаружено
P78H	1	0	1	None Не обнаружено
P78S	0,998	0,27	0,99	None Не обнаружено
K79E	0,045	0,94	0,83	None Не обнаружено
K79R	0,314	0,9	0,89	None Не обнаружено
K79A	0,81	0,81	0,93	No effect on heparin binding Отсутствие эффекта на связывание гепарина [**Ошибка! Источник ссылки не найден.**]

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Notes: Polymorphism with non-single nucleotide substitutions is highlighted in **bold**. The CCL2-E73X variant is not included in the table due to the inability to assess it (presumably as it is a stop-gain mutation). PolyPhen-2 classifies substitutions as "probably damaging" if PP-score>0,85, "possibly damaging" if PP-score between 0,15 and 0,85), and "benign if PP-score <0,15 [**Ошибка! Источник ссылки не найден.**].

Примечания: Полиморфизм с неодиночной нуклеотидной заменой выделен **жирным шрифтом.** CCL2-E73X не включена в таблицу по причине невозможности ее учета. PolyPhen-2 классифицирует замены как «вероятно опасные», если PP-балл>0,85, «возможно опасные», если PP-балл от 0,15 до 0,85, и «нейтральные», если PP-балл <0,15 [**Ошибка! Источник ссылки не найден.**].

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Блок 3. Метаданные статьи

EFFECTS OF CCL2 CHEMOKINE MISSENSE MUTATIONS ON CCR5 RECEPTOR AFFINITY: A COMPUTATIONAL STUDY IN THE CONTEXT OF HIV INFECTION REGULATOR DISCOVERY

ВЛИЯНИЕ МИССЕНС-МУТАЦИЙ ХЕМОКИНА CCL2 НА АФФИННОСТЬ С РЕЦЕПТОРОМ CCR5: ВЫЧИСЛИТЕЛЬНОЕ ИССЛЕДОВАНИЕ В КОНТЕКСТЕ ПОИСКА РЕГУЛЯТОРОВ ВИЧ-ИНФЕКЦИИ

Сокращенное название статьи для верхнего колонтитула:

ПОЛИМОРФИЗМ CCL2 И АФФИННОСТЬ СВЯЗЫВАНИЯ С CCR5 IN SILICO

IN SILICO ANALYSIS OF CCL2 POLYMORPHISMS AND CCR5 BINDING AFFINITY

Keywords: HIV, chemokine CCL2, CCR5 receptor, missense mutations, molecular modeling, binding energy, virus attachment, *in silico*.

Ключевые слова: ВИЧ, хемокин CCL2, рецептор CCR5, миссенс-мутации, молекулярное моделирование, энергия связывания, прикрепление вируса, in silico.

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Порядковый номер ссылки	Авторы, название публикации и источника, где она опубликована, выходные данные	Авторы, название публикации и источника на английском	Полный интернет-адрес (URL) цитируемой статьи
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