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BIOINFORMATICALLY ANALYZED RELATIONSHIPS BETWEEN SPECIFIC HUMAN GENES ASSOCIATED WITH HIV ATTACHMENT

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БИОИНФОРМАТИЧЕСКИЙ АНАЛИЗ ВЗАИМОСВЯЗЕЙ МЕЖДУ СПЕЦИФИЧЕСКИМИ ГЕНАМИ ЧЕЛОВЕКА, АССОЦИИРОВАННЫМИ С ПРИКРЕПЛЕНИЕМ ВИЧ

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Abstract

Introduction. Assessing interaction between the human immunodeficiency virus (HIV) and human factors is crucial for understanding the disease pathogenesis. HIV triggers an immune response that involves numerous cellular and molecular processes related to inflammation, cell migration, and disrupted tissue barrier functions. Such reactions build up a cascade in which chemokines and cognate co-receptors, as well as other molecules regulating the immune response, play a key role. However, the interaction between HIV and the human organism cannot be reduced to a simple mechanism because it represents a multilayered system where crucial molecules and events may be unknown or require further study.

Objective: to assess a significance of candidate genes potentially involved in the pathogenesis of HIV infection during the phase of viral attachment to cell, based on assessing gene expression, localization, and involvement in biological pathways and processes.

Materials and methods. The study compared the characteristics of the 100 most promising candidate genes (CG) according to the HumanNet web resource with background genes (CCR5, CXCR4, CCR2, CD4), known to be reliably linked to HIV attachment. Expression data, localization, and involvement in various cellular pathways and processes for the candidate and background genes were analyzed. A scoring system was developed to assess the significance of each gene in the context of its role in immune and inflammatory responses.

Results. A total of 100 candidate genes were analyzed. Using the developed scoring system, a number of genes were identified as significant based on the analyzed parameter: 17 candidates – significant by expression profile; 7 – by localization; 17 – by involvement in biological pathways; and 25 – by involvement in biological processes. The final ranking revealed 55 candidate genes. The identified candidate genes were classified into the following functional groups: chemokine co-receptors and their ligands; genes and proteins associated with G-

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proteins; and a group for which a common functional role or family could not be established.

Conclusions. The identified correlations between the candidate genes and background genes highlight the need to further investigate CG interactions in HIV pathogenesis allowing for a more detailed assessment of the contribution of both individual genes and entire systems, which, in the future, will expand our understanding of the molecular mechanisms behind HIV infection and, hypothetically, accelerate the discovery of new (or the expansion of existing) therapeutic models.

Keywords: human immunodeficiency virus, virus-host interaction, protein-protein interactions, candidate genes, in silico, CD4, CCR5, CXCR4, CCR2.

Резюме

Введение. Изучение взаимодействия вируса иммунодефицита человека (ВИЧ) с факторами человеческого организма имеет ключевое значение для понимания патогенеза заболевания. ВИЧ вызывает иммунную реакцию, которая включает в себя множество клеточных и молекулярных процессов, связанных с воспалением, миграцией клеток и нарушением барьерных функций тканей. Эти реакции образуют каскад, в котором важную роль играют как хемокины и их корецепторы, так и другие молекулы, регулирующие иммунный ответ. Проблема состоит в том, что взаимодействие ВИЧ с человеческим организмом невозможно свести к простому механизму — это сложная система, в которой ключевые молекулы и механизмы могут быть неизвестны и требуют дальнейшего изучения.

Цель. Оценка значимости генов-кандидатов, потенциально участвующих в патогенезе ВИЧ-инфекции на стадии прикрепления вируса к клетке, на основании оценки экспрессии, локализации и участии в биологических путях и процессах.

Материалы и методы. В работе было проведено сравнение характеристик 100 наиболее перспективных генов-кандидатов (ГК) согласно веб-ресурсу HumanNet с фоновыми генами (CCR5, CXCR4, CCR2, CD4), для которых достоверно показана связь с прикреплением ВИЧ к клетке. Были проанализированы данные экспрессии, локализации, а также вовлечённости в различные клеточные пути и процессы генов-кандидатов и фоновых генов. В ходе работы была разработана система баллового ранжирования, которая позволила оценить значимость каждого гена в контексте его участия в иммунных и воспалительных реакциях.

Результаты. Проанализировано 100 генов-кандидатов. С использованием разработанного метода баллового ранжирования ряд генов был определен, как значимый в зависимости от анализируемой характеристики: значимые по профилю экспрессии – 17 кандидатов,

локализации – 7, участие в биологических путях – 17, в биологических процессах – 25. По результатам итогового ранжирования выявлено 55 генов-кандидатов. Выявленные ГК были отнесены к следующим функциональным группам: хемокиновые корецепторы и их лиганды, гены и белки, связанные с G-белками, а также группа, для членов которой не удалось установить общую функциональную роль или семейство.

Выводы. Выявленные корреляции между ГК и фоновыми генами акцентируют внимание на необходимости дальнейшего изучения взаимодействий ГК в патогенезе ВИЧ. Это позволит более детально оценить вклад как отдельных генов, так и целых систем, что, в дальнейшем, расширит наше понимание молекулярных механизмов ВИЧ-инфекции, а также, гипотетически, ускорит обнаружение новых или расширение существующих терапевтических моделей.

Ключевые слова: Вирус иммунодефицита человека, взаимодействие вирус-хозяин, белок-белковые взаимодействия, гены-кандидаты, *in silico*, CD4, CCR5, CXCR4, CCR2.

1 Introduction

The disease caused by the human immunodeficiency virus (HIV) remains one of the most serious public health challenges worldwide. According to recent data, the number of people living with HIV reaches nearly 40 million [**Ошибка! Источник ссылки не найден.**]. HIV infection is characterized by a progressive destruction of the immune system, ultimately leading to acquired immunodeficiency syndrome (AIDS). The primary methods for combating HIV infection remain the suppression and management of the infection through antiretroviral therapy (ART) [**Ошибка! Источник ссылки не найден.**].

ART involves the use of different classes of drugs that act on key stages of the viral life cycle, including cell entry, replication, integration into the genome, and the assembly of new viral particles [0]. Drug resistance mutations in HIV, resulting from its high genetic variability, remain a major challenge for antiretroviral therapy. These mutations can reduce the efficacy of drugs and contribute to multidrug resistance, necessitating constant adaptation of treatment regimens and the search for new approaches [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]. The use of combination therapy involving multiple drugs helps reduce the risk of resistance, but the lifelong nature of therapy leaves a risk of disease recurrence even with full adherence by the patient [**Ошибка! Источник ссылки не найден.**].

Progression of the disease is influenced not only by viral characteristics, but also by individual human host features, primarily those that are genetically determined. HIV attachment to the cell occurs by binding to the CD4 receptor and chemokine co-receptors CCR5 and CXCR4. A well-known mutation in the CCR5 gene, CCR5-Δ32, has a prevalence ranging from 7.8% to 25% in different Russian regions [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**]. This deletion provides partial, or complete, resistance to HIV infection by preventing viral entry into cells [**Ошибка! Источник ссылки не найден.**]. Based on this data, a group of drugs has been developed that target

interactions between human and viral proteins, aimed at blocking co-receptors, which plays a key role in preventing viral entry into cells.

In contrast, no mutations analogous to delta 32 have been found in the CXCR4 gene. However, it has been shown that several mutations in this gene are presumably linked to the development of certain diseases, such as WHIM syndrome (rs104893625, rs104893624) [**Ошибка! Источник ссылки не найден.**], while the effects of other mutations on the human body remain to be elucidated.

Although these proteins are reliably linked to HIV attachment to the cell, it should be noted that the virus with specific tropism attaches only to one of the two co-receptors, although dual-tropic variants of HIV also exist. During the progression of infection, a shift in the primary tropism of the virus occurs through a mechanism whereby HIV-1 variants using CXCR4 suppress the replication of CCR5-dependent HIV-1 variants, whereas CCR5-dependent variants do not affect the replication of CXCR4-dependent HIV [**Ошибка! Источник ссылки не найден.**].

An additional co-receptor involved in viral attachment is CCR2 [**Ошибка! Источник ссылки не найден.**]. Genetic variations in the CCR2 gene may influence the rate of HIV progression, making it an important target for study [**Ошибка! Источник ссылки не найден.**].

The described proteins are involved in inflammatory processes through chemotaxis and recruitment of other cells. CXCR4 also plays a role in embryo attachment to the uterine wall. Given that these proteins are receptors involved in significant signaling cascades in the body, understanding their function is crucial. Given the vast number of human genes, experimental identification of key genes, and their polymorphic variants, is an extremely challenging task. In this regard, a preliminary search for candidate genes (CGs) using bioinformatic analysis is a necessary and effective approach, which allows narrowing down the potential targets for further study.

To date, a significant amount of information has been collected regarding the functioning of individual immune system components and their interaction with the

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virus. Integrating them into unified models, however, remains a complex challenge. Studying the links between genes encoding chemokine co-receptors associated with viral attachment to the cell and other human genes is important. The results of such studies will not only help to better understand the pathogenesis of HIV infection, but also facilitate further research into polymorphic variants of these genes that may either accelerate disease progression or, conversely, slow it down.

Modern bioinformatic methods significantly accelerate the analysis of large volumes of data and identification of key molecular mechanisms. Building and analyzing complex interaction networks between the virus and host cells can reveal new patterns, shift the focus to underexplored elements, and assess their contribution to the development and progression of HIV infection [**Ошибка! Источник ссылки не найден.**].

Thus, the identification of candidate genes interacting with chemokine co-receptors and associated with HIV progression could become an important step towards creating new treatment and prevention strategies for the disease. The objective of the study was to assess the significance of candidate genes potentially involved in the pathogenesis of HIV infection during the phase of viral attachment to the cell, based on evaluation of gene expression, localization, and involvement in biological pathways and processes.

Materials and Methods

Given the significance of the process of viral entry into the cell for the pathogenesis of HIV infection, the focus was on genes encoding proteins that are reliably associated with human infection at the stage of viral entry. In particular, the CD4 receptor in addition to chemokine co-receptors CCR5, CXCR4, and CCR2 (hereafter referred to as background genes, BG) were a focus since the proteins encoded by these genes play a crucial role in cell infection (specifically at the stage of viral attachment) and are involved in regulatory processes of the HIV life cycle [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**].

The HumanNetv3 web application was used to analyze genetic and protein-protein networks. Three types of networks were analyzed during the study: the physical protein interaction network (HumanNet-PI); the functional gene network (HumanNet-FN); and the functional network expanded by co-citation (HumanNet-XC). As of 2023, the physical interaction network included 17,849 genes and 633,460 connections [**Ошибка! Источник ссылки не найден.**].

To identify the biological context of the selected candidate genes (CG), the functional mapping and gene annotation web resource FUMA GWAS in GENE2FUNC mode (https://fuma.ctglab.nl/gene2func) was used. The FUMA GWAS application was used under the following conditions: Ensembl version 92, GTEx v8 expression dataset, 30 major tissue types, Benjamini–Hochberg correction method for gene set enrichment testing (FDR), maximum adjusted gene set association P-value < 0.05, and minimum number of overlapping genes with gene sets ≥ 2.

Additionally, statistical correlation analysis (using Pearson's criterion at p-value 0.05) was performed for gene representation relative to each other in protein localization and other genetic products of the studied genes, as well as their involvement in biological pathways.

For individual CGs that demonstrated a significant functional, spatial, or other type of association with BG (according to FUMA GWAS analysis), available scientific literature was reviewed to investigate and confirm their significance in the context of the detected associations.

As part of the research methodology, an analysis was conducted to identify CGs potentially related to HIV pathogenesis. At the initial stage, the HumanNet resource was used for the preliminary search of CGs, followed by evaluation of the reliability of the identified relationships using AUROC analysis. The FUMA GWAS tool in GENE2FUNC mode was used to perform a comprehensive analysis of the identified CGs, which included an assessment of gene expression level and tissue

specificity, product localization, and their involvement in various biological pathways and processes.

Scoring System

Expression

The expression profile of BG was evaluated in various bodily tissues. The inclusion criterion for a tissue in the analysis was a gene expression level log2 of no less than 2.51 (average expression level). Tissues with low BG expression levels were excluded from analysis. For CGs, the proportion of instances of co-expression of the genes with BG in selected tissues was evaluated.

The candidate gene score (CGS) was calculated using the following formula:

$$\mathrm{CGS}(EXP) = f_{eCCR5} + f_{eCXCR4} + \frac{(f_{eCCR2} + f_{eCD4)}}{2} + f_{eCCR5} * f_{eCXCR4}$$

where f represents the frequency of matching CG expression profiles with BG. The formula accounts for the contribution of the relationship with each BG, as well as the combined contribution of CG association with the two main co-receptors for HIV-1 attachment. CCR5 and CXCR4 are the main co-receptors for attachment, so the relationship with them has greater weight than with CD4 and CCR2.

Localization, Biological Pathways, and Biological Processes

To assess the contribution of CGs to BG based on intersections in localization, participation in the same biological pathways, and biological processes (hereafter 'characteristics'), based on FUMA GWAS data in GENE2FUNC mode, tables of localization/participation in biological pathways or processes were constructed for each analysis. In binary format (1-present, 0-absent), the participation/localization of CG and BG was indicated. Based on the resulting table, a correlation table was built using the four-point phi correlation method (analogous to the Pearson method for dichotomous variables), and correlations with BG were considered. The total score for each individual analysis was calculated using the following formula:

$$\mathrm{CGS}(\mathrm{loc.\,or.\,proc.\,or\,path}) = k_{CCR5} + k_{CXCR4} + \frac{k_{CCR2} + k_{CD4)}}{2} + k_{CCR5} * k_{CXCR4}$$

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where k represents the correlation level of the candidate gene with the background gene at p-value < 0.05. At p-value > 0.05, the correlation value was considered to be 0. The formula also accounts for the contribution of the relationship with each BG and the combined contribution of CG association with the two main co-receptors for HIV-1 attachment.

Final Scoring System

Based on the results of each scoring stage, given that specific contributions (expression, localization, participation in biological pathways, participation in biological processes) were assessed equally, the final CG score was considered to be the sum of the points obtained from each scoring stage. The maximum score for each stage was 4, and the maximum total score was 16. To enhance the significance of CGs with common characteristics, additional points were assigned: for scores in 2 characteristics, CGs received 2 points; in 3 characteristics, 3 points; and in 4 characteristics, 4 points. The threshold value for the total score was set at 2, as this value corresponds to two established relationships with key BG co-receptors CCR5 and CXCR4. Thus, CGs with this score, or higher, were evaluated as significant for the pathogenesis of HIV infection. The design of the analysis is presented in Figure 1.

Results

Candidate Genes

Based on the analysis of HumanNetv3, 659 genes potentially associated with the function of background proteins were identified. Using ROC analysis, false-positive results were reduced to 1% (Fig. 2).

Based on the final results, false-positive candidates were filtered out, and the selected genes were ranked according to evaluation of their association levels. The threshold value used to identify the most probable candidate genes, reflecting their proximity to other genes according to the neighbor relationship ranking rule, was set

at 5.844. This resulted in a list of 100 genes, ranked by association scores ranging from 5.844 to 8.589, which potentially impact the course of HIV infection. The identified candidate genes, and their encoded proteins, can be classified into general functional groups as shown in Table 1.

Expression

For the identified candidate genes, a tissue-specific expression map was generated using the FUMA GWAS web resource. The map is shown in Figure 3.

For assessment of expression levels, the following scale was used: Maximum (5.672), High (from 3.51 to 5.671), Medium (from 2.51 to 3.5), Low (from 1.51 to 2.5), and Minimal (from 0 to 1.5). For CCR5, the average expression level in the spleen is 3.361. It is low in the lungs (2.479), small intestine (terminal ileum) (2.359), and whole blood (1.994). In other tissues, the expression level is minimal. For CXCR4, there is a broad representation of tissues with varying expression levels. The maximum expression level is observed in the spleen (5.672). A high level of expression is shown in 32 tissues, including whole blood (5.671), lungs (5.650), and the small intestine (5.375).

According to the heat map data, the highest expression levels for the background genes (BGs) were found in the following tissues and organs: lungs, terminal ileum, spleen, and whole blood. It is worth noting that for the CCR5 gene, expression is found in fewer tissues at lower levels compared to CXCR4 expression.

When performing scoring ranking for CCR5 and CCR2, due to the small number of tissues with medium expression levels, four tissues with the highest expression were selected. For CCR5, the cutoff expression level was 1.994, corresponding to the expression level in whole blood. For CCR2, the cutoff was 2.394 (small intestine - terminal ileum).

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Based on the evaluation of expression profiles and levels, the following candidate genes (CGs) were identified with the highest co-expression with background genes (BGs):

CCR5: ANXA1, CCR7, GNA13, GNAI2, HEBP1, OXER1, P2RY13 (all 100%)

CXCR4: GNA13 (100%), GNAI2 (100%), HEBP1 (98%), ACKR3 (96%), ANXA1 (93%), GNAI1 (93%)

CCR2: ANXA1, GNA13, GNAI2, HEBP1, P2RY13 (all 100%)

CD4: GNA13 (100%), GNAI2 (100%), HEBP1 (100%), ACKR3 (96%), ANXA1 (96%), GNAI1 (96%)

As a result of this analysis, the following candidate genes were identified with the highest biological gene co-expression scores: **GNA13** (4.00), **GNAI2** (4.00), **HEBP1** (3.96), **ANXA1** (3.84), **ACKR3** (3.28), **GNAI1** (3.24), **CXCL12** (3.01), **CCL2** (2.88), **GPER1** (2.86), **CXCL2** (2.63), **ADRA2C** (2.54), **OXER1** (2.53), **S1PR3** (2.53), **S1PR2** (2.48), **CCL19** (2.48), and **ADRA2A** (2.43).

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Localization of Gene Products

In addition to the expression localization of candidate genes, it is important to evaluate the localization of the products of these genes. The products of candidate genes may interact with chemokine coreceptors and initiate a cascade of reactions. On the other hand, gene expression products do not necessarily "reside" in the same cell where the expression occurs, and their influence can extend to areas where their products are localized. The cellular localization of candidate gene products is shown in Figure 4.

For a significant number of candidate genes (HTR1D, GNAI2, HTR1F, NPY1R, NPY5R, HTR1A, HTR1E, etc.), multiple localization points of their products are shown.

For the products of the genes CXCR4, CD4, and CCR5, only localization in the cell

membrane is shown, approaching the level of significance. To rank the significance of the candidate gene products, a correlation analysis between gene pairs was performed. Since the products of CCR5, CXCR4, and CD4 do not have a shared localization with the products of other genes, the correlation assessments were conducted with respect to CCR2.

The products of the CCR2 gene, in combination with the products of other genes, have a broad spectrum of cellular localization, but they are also localized in structures associated with neurons and dendritic cells. The majority of gene products from the candidate genes studied are localized in the following cells: neurons, somatodendritic, and dendritic cells.

The list of candidate genes for which correlations of gene product localization with CCR2 were identified ($p<0.05$) includes HTR5A (0.87), with high correlation. It also includes those with moderate correlation: HTR1D (0.55), HTR1F (0.55), HTR1A (0.55), HTR1E (0.55), HRH4 (0.55), and OPRK1 (0.54). The candidate genes with their ranking scores for this stage were: HTR5A (0.44), HTR1D (0.28), HTR1F (0.28), HTR1A (0.28), HTR1E (0.28), HRH4 (0.28), and OPRK1 (0.27).

Biological Pathways

A biological pathway analysis was conducted in which the functional groups, candidate genes, and their products are involved. The analysis is shown in Figure 5.

The main functional groups of genes, their proteins, and metabolites are associated with G-proteins, peptide signaling pathways of G-proteins, chemokine signaling pathways that influence inflammatory processes, as well as those related to monoamine receptors. The three biological pathways with the highest p-values were: WP_GPCRS_CLASS_A_RHODOPSINLIKE (rhodopsin-like receptors, G-protein coupled class A) with the highest p-value; WP_PEPTIDE_GPCRS (peptide receptors, G-protein coupled); and WP_CHEMOKINE_SIGNALING_PATHWAY (chemokine signaling pathways).

The presence of CCR2, CXCR4, and, partially, CCR5 in these pathways indicates their important role in these biological processes.

Based on the assessment of the participation of candidate genes and their products, in combination with genes/products of BG in biological pathways, the following candidate genes were identified for each BG with the highest level of correlation ($p<0.05$):

CCR5: CXCR3 (0.77), NPY5R (0.52), OPRK1 (0.52), GPR18 (0.52), SSTR5 (0.52), GALR2 (0.52), GALR1 (0.52), FPR3 (0.52), SSTR4 (0.52), SSTR3 (0.52), GALR3 (0.52), SSTR2 (0.51).

CXCR4: CCR7 (0.89), CXCR3 (0.77), CCR10 (0.65), CCR9 (0.65), CXCR5 (0.65), FPR3 (0.52), GALR1 (0.52), GALR2 (0.52), GALR3 (0.52), NPY5R (0.52), OPRK1 (0.52), SSTR3 (0.52), SSTR4 (0.52), SSTR5 (0.52), CXCR6 (0.52).

CCR2: CXCR3 (0.68), CCR7 (0.57), CCR10 (0.59), CCR9 (0.59), FPR3 (0.47), GALR1 (0.47), GALR2 (0.47), GALR3 (0.47), NPY5R (0.47), OPRK1 (0.47), SSTR3 (0.47), SSTR4 (0.47), SSTR5 (0.47), CXCR6 (0.47).

No significant correlations were found for CD4. The scoring summary for the participation of CG in biological pathways in combination with BG was: CXCR3 (2.49), CCR7 (1.17), CCR10 (0.95), CCR9 (1.54), CXCR5 (0.65), FPR3 (1.54), GALR1 (1.54), GALR2 (1.54), GALR3 (1.54), NPY5R (1.54), OPRK1 (1.54), SSTR3 (1.54), SSTR4 (1.54), SSTR5 (1.54), CXCR6 (0.75), GPR18 (0.52), and SSTR2 (0.51).

Biological Processes

In functional mapping of the analyzed genes, their involvement in 343 biological processes was determined. Those shown only include processes in which functional groups and/or their products participate (Table 2).

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Evaluation of the Participation of Candidate Genes and Their Products in Biological Processes

Based on assessment of the participation of candidate genes (CG) and their products in combination with genes/products of BG in biological processes, the following CG were identified for each BG with the highest level of correlation ($p<0.05$):

CCR5: CXCL3 (0.57), CCL8 (0.48), CXCR6 (0.40), CXCR5 (0.37), CCL7 (0.36), CCL5 (0.35), CCL27 (0.35), CCR7 (0.35), CXCR3 (0.34), CCR9 (0.32), CCR10 (0.32), CCL2 (0.31).

CXCR4: CXCR3 (0.43), CXCL12 (0.41), SUCNR1 (0.34), CXCR6 (0.32), ACKR3 (0.31).

CCR2: CCL5 (0.38), CXCL12 (0.38), CCL2 (0.37), CXCL13 (0.35), ANXA1 (0.34), CXCR3 (0.32), CCL7 (0.31), CCL19 (0.31).

CD4: CCL2 (0.44), CCR7 (0.38), CCL19 (0.38), CCL5 (0.36), CCL25 (0.30).

The scoring summary for CG 'Participation in Biological Processes in Combination with Functional Groups and Scores Above 0.5' was: CXCR3 (1.14), CCL2 (1.074), CCL8 (1.047), CXCR6 (1.03), CXCL3 (1.02), CCL5 (0.97), CCR7 (0.962), CXCR5 (0.93), CCL19 (0.92), CXCL12 (0.91), CCR9 (0.89), CCL7 (0.84), CCR10 (0.82), CXCL13 (0.81), CCL20 (0.76), ACKR3 (0.76), CCL27 (0.74), SUCNR1 (0.74), CCL16 (0.68), FPR3 (0.63), CCL25 (0.62), ANXA1 (0.58), PENK (0.54), GPER1 (0.53), and GPR18 (0.51).

Final Ranking

Table 3 presents the final ranking results for identified genes with an overall score of 2 or higher.

The number of candidate genes (CG) with a score above the threshold was 55. It is worth noting separately all CGs that received more than 1 point. Although these genes do not overlap in the results of intermediate ranking stages, they may interact

with several functional genes (BG) or their products on one studied parameter. In this case, they have a similar expression profile with several BGs and may be included as possible candidates for further consideration. The list of CGs with the specified threshold is: HCAR2 (1.68), P2RY13 (1.67), S1PR5 (1.63), SSTR5 (1.56), GALR1 (1.54), SSTR4 (1.49), and P2RY14 (1.19).

Discussion

Viral attachment to a cell via chemokine receptors and co-receptors initiates a cascade of responses. Individual elements of this cascade can influence the course of the infectious process and/or the viral life cycle [**Ошибка! Источник ссылки не найден.**]. Assuming that potential CGs may directly or indirectly affect viral processes by binding to chemokine receptors/co-receptors, they and/or their products must be in close proximity to interact with the receptors and have a sufficient product concentration for such interaction, indirectly reflected in gene expression levels. These characteristics are often exhibited by participants in the same biological process and/or biological pathway. However, this does not exclude the possibility of multifunctionality of individual genes, providing more opportunities for interaction between the products of the hypothetical CG and BG products.

According to HumanNetv3, a number of CGs potentially related to chemokine co-receptors and, accordingly, to the human immunodeficiency virus, were identified. When considering the detected genes from the perspective of human molecular-biological elements associated with BGs, the belonging of these genes to the following main functional groups was shown: chemokines and their receptors, G-proteins and their associated receptors, including serpentine receptors, as well as other receptors such as taste TAS2R, neuropeptide and neurotransmitter, adrenergic, purinergic, somatostatin, peptide, and other functionally significant proteins. The identified candidates are widely expressed in various tissues, although for all BGs, an increased level of expression was observed in four main tissues/organs (lungs, terminal ileum, spleen, whole blood), where immune processes are actively

occurring. The lungs contain specialized immune cells such as macrophages that ingest and destroy pathogens inhaled with air. These cells are found in the alveoli and on the surface of the airways, providing the first line of defense against infections. In the lungs, the maturation and activity of various types of leukocytes, such as lymphocytes and neutrophils, also occur, playing a key role in fighting infections and inflammation [**Ошибка! Источник ссылки не найден.**].

In the terminal ileum, Peyer's patches, which are essential components of the intestinal immune system, are located. These patches contain lymphoid cells that help protect the body from pathogens ingested with food. Specialized immune cells lining the ileum protect the body from bacterial infections and maintain the mucosal barrier function [**Ошибка! Источник ссылки не найден.**]. The spleen, specifically the white pulp, is responsible for the production and maturation of leukocytes (lymphocytes), which produce antibodies to fight infections. The white pulp plays a key role in the adaptive immune response [**Ошибка! Источник ссылки не найден.**]. The involvement of blood in the body's immunity as a transport system is unquestionable. Thus, all four of these tissues are crucial sites for immune system activity. Genes with high expression levels in these tissues (CCR7, GNA13, GNAI2, HEBP1, OXER1, P2RY13, ANXA1), along with background proteins, participate in immune processes, supporting the homeostasis of the immune system.

The search for intersections in the localization of gene products did not yield significant results due to the narrow localization spectrum of the products of the main BGs, which are localized in the cell membrane. The CCR2 protein, due to its expression in a large number of cells in the nervous system, has more opportunities for interaction with other host factors. Localization of genetic products in neuronal and dendritic cells is strongly associated with the progression of HIV infection, leading to neurological manifestations. Against the background of tropism switching, the virus can infect a larger number of tissues and cell groups, such as

macrophages. This, in turn, leads to the infection of macrophages in the brain, which is associated with the development of neurocognitive disorders mediated by HIV.

A different pattern was observed when evaluating the participation of BGs in biological pathways and processes, which is not surprising, as receptors are an active part of signaling pathways via G-proteins and/or chemokines, as well as chemotaxis processes in response to influencing factors. The multifunctionality and the potential of individual genes and their products to influence the activity of other genes, including BGs, allow these genes to be considered as possible candidates, provided their established connection, intersection by characteristics (localization, sufficient concentration, etc.), and functional roles with BGs.

It should be noted that biological pathways refer to a series of individual reactions rather than direct interactions between proteins or their localization in one place, although such events may also occur. Primarily, joint participation in pathways indicates a possible indirect nature of interaction. The analysis of biological pathways revealed the following. CXCR4 and CCR5 have strong positive correlations with CXCR3, NPY5R, and SSTR4, indicating their joint involvement in the same pathways. The product of the NPY5R gene is a neuropeptide receptor, while SSTR4 is one of the five known somatostatin receptors and is involved in both immune [**Ошибка! Источник ссылки не найден.**] and neuroendocrine processes [**Ошибка! Источник ссылки не найден.**]. In turn, SUCNR1 (Succinate Receptor 1), also known as GPR91, which has a moderate correlation with chemokine co-receptors, is a receptor activated by succinate (a metabolite of the tricarboxylic acid cycle). The SUCNR1 protein is involved in regulating immune reactions, including macrophage polarization and inflammatory diseases such as ulcerative colitis and endometriosis [**Ошибка! Источник ссылки не найден.**].

Thus, without considering the likely physical interaction of CGs and their products with BGs, the probability of the association of CGs and BGs with their products was evaluated by combining four characteristics: expression, cellular localization, pathways, and biological processes. The necessary condition for such

interaction, including the required sufficient concentration, and the similarity of functional roles were also considered.

Based on the combined data of the aforementioned characteristics, a scoring system was developed, which allows the identification of CGs with the hypothesized highest probability of interaction with BGs. This is important because of the known connection between BGs and HIV, suggesting that their involvement may influence the pathogenesis of the infection. For several genes, it was considered that in the case of altered homeostatic conditions, for example, during an infectious process, there would be an increase in the expression levels of certain genes in tissues where this does not normally occur.

Most of the CGs identified are chemokines of the C-C or C-X-C family, or their receptors. Since the discovery of the contribution of the chemokine co-receptors CCR5 and CXCR4 in the process of HIV attachment to cells, researchers have focused not only on related chemokines, specifically their suppressive action against the virus through receptor competition, but also on the receptors themselves, as alternative entry points for the virus. Among the CGs ranked in this group, the following stand out as having the highest total scores.

CCR7 receptor: This receptor helps mobilize dendritic cells and their interaction with various subsets of T cells, including naive, regulatory, and memory T cells [0]. It has also been shown to play an important role in the immune system, preventing autoimmune diseases, and is involved in immune surveillance and anti-tumor immunity [**Ошибка! Источник ссылки не найден.**]. Thus, the high expression of CCR7 in the lungs, intestines, spleen, and blood may be related to its function in attracting and activating immune cells in these tissues, which is essential for effective protection against pathogens [**Ошибка! Источник ссылки не найден.**].

ACKR3 receptor, also known as **CXCR7**, is an important protein involved in various physiological and pathological processes and primarily functions as a scavenger receptor. The main roles of this chemokine that may be linked to the

progression of HIV infection include chemokine scavenging and immune system regulation [**Ошибка! Источник ссылки не найден.**]. This protein also influences the distribution and function of immune cells, helps localize lymphocytes in lymphoid tissues, and modulates immune responses. There may be a lesser need for chemokine regulation through ACKR3 in circulating blood, as its primary function is to control local inflammatory processes in tissues, with an increase in expression levels likely during inflammation [25].

CXCR6 receptor: This receptor plays a role in chemotaxis by attracting lymphocytes to sites of tissue damage, helping the body respond quickly to infection by directing immune cells to inflammation sites. CXCR6 is also expressed on T cells, particularly natural killer cells and cytotoxic T lymphocytes, playing an important role in their migration and localization [**Ошибка! Источник ссылки не найден.**].

An exception in terms of low expression levels in the CXC family group is **CXCR3**. The tissue with low expression is the lungs. The functions of this gene and its products are related to the migration and activation of T cells in other tissues, such as lymph nodes and sites of inflammation. Several studies show an increase in the expression of this receptor in the lungs during inflammatory processes [**Ошибка! Источник ссылки не найден.**]. It has been shown that CXCR3 is important for the migration of antigen-specific effector CD4+ T cells to both the respiratory tract and lung parenchyma during the acute phase of respiratory viral infection [**Ошибка! Источник ссылки не найден.**].

Chemokines **CCL2, CXCL2, CXCL12, CCL19, CXCL13, CCL8, CCL25, CCL27, CCL20**, and **CXCL3** primarily function in chemotaxis, typically directing immune cells to sites of inflammation [**Ошибка! Источник ссылки не найден.**]. As such, they are involved in regulating immune responses and inflammatory processes [**Ошибка! Источник ссылки не найден.**]. Some of these chemokines are expressed in various tissues, including bone marrow, thymus, spleen, and lymph nodes [**Ошибка! Источник ссылки не найден.**], and play a role in maintaining

the homeostasis of specific systems in the human body, such as the bone marrow [**Ошибка! Источник ссылки не найден.**].

The second major functional group among the ranked CGs are genes associated with G-proteins, which play a crucial role in cellular signaling and may influence viral entry and spread [**Ошибка! Источник ссылки не найден.**]. The G-protein subunits **GNAI1** and **GNAI2** are involved in transmitting signals from various receptors into intracellular effects. Proteins **GNA13** and **GPR18** are less studied compared to their predecessors but have been shown to participate in signal transmission via G-proteins, regulating various cellular functions, including migration and cellular survival. High expression levels of these genes may be linked to their role in multiple signaling pathways that regulate immune system functions, including chemotaxis [**Ошибка! Источник ссылки не найден.**, **Ошибка! Источник ссылки не найден.**].

The protein **GPER1**, also known as **GPR30**, plays a significant role in various physiological and pathological processes, primarily performing protective functions such as anti-tumor and anti-inflammatory effects [**Ошибка! Источник ссылки не найден.**]. It is difficult to pinpoint the exact reasons for its low expression in whole blood, as most studies focus on its specific influences on particular processes.

Two other genes with low expression in whole blood are **S1PR2** and **S1PR3**. Among the five known GPCRs with high affinity for **S1P** (sphingosine-1-phosphate, a signaling lipid), types 1, 2, and 3 are predominantly expressed in cardiovascular tissues. **S1PR2** and **S1PR3** are involved in regulating cell migration and vascular tone, which explains their low expression in blood, although expression levels increase during inflammation [**Ошибка! Источник ссылки не найден.**].

Additionally, the protein **S1PR5** is present in the analyzed group, but with low expression in the small intestine. Unlike **S1PR2** and **S1PR3**, **S1PR5** is characteristic of the immune and nervous systems [**Ошибка! Источник ссылки не найден.**]. It is expressed in whole blood, but its low expression in the small

intestine may be explained by its more significant functions in the central nervous system and other tissues.

Among the group associated with G-proteins, special attention should be given to the receptors involved in two signaling pathways (OXER1, HCAR2/3). The **OXER1** protein is a receptor for oxo-eicosanoids, which are involved in inflammatory and immune responses. High expression in tissues may be related to their role in regulating these processes. For example, in the lungs and intestines, **OXER1** helps protect against infections and inflammation, while in the spleen and blood, it plays a role in immune cell mobilization and function [**Ошибка! Источник ссылки не найден.**].

The **HCAR2** and **HCAR3** proteins are associated with inflammatory conditions, such as Crohn's disease and ulcerative colitis, where they participate in recruiting innate immune cells and differentiating Th-17 cells, respectively [**Ошибка! Источник ссылки не найден.**]. They exhibit low expression in the small intestine. However, their functions may be more significant in other tissues, such as the skin and brain, where they regulate inflammatory processes and energy metabolism.

The third group includes chemokines that do not share a common functional role or belong to the same protein family. The protein annexin A1 (ANXA1) plays an important role in regulating inflammation and immune responses. High expression of ANXA1 in various tissues may be associated with its function in suppressing inflammatory processes and tissue repair. This is especially important in the lungs and intestines, which are frequently exposed to external agents [**Ошибка! Источник ссылки не найден.**]. ANXA1 ranks fourth in terms of significance due to its high expression profile matching the background genes, as well as its involvement in similar biological processes. However, its mechanism of interaction with background chemokine receptors requires clarification to understand its potential impact on HIV attachment and/or the development of infectious processes.

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The protein HEBP1, in this case, is an exception to the other genes presented. It is involved in heme metabolism and may play a role in regulating cell growth and survival. High expression of HEBP1 in these tissues may be associated with the need to regulate heme levels and prevent its toxic effects, especially in tissues with high metabolic activity and frequent inflammatory processes [**Ошибка! Источник ссылки не найден.**].

The receptor FPR3 is expressed in monocytes and dendritic cells, but not in neutrophils. It is located in intracellular vesicles rather than on the cell surface, unlike other FPR group receptors [**Ошибка! Источник ссылки не найден.**]. This group of receptors is involved in chemotaxis and immune cell activation, but FPR3 is less studied compared to others, making it difficult to explain the reason for its expression level in the blood.

The receptors ADRA2A and ADRA2C regulate vascular tone and the sympathetic nervous system [**Ошибка! Источник ссылки не найден.**], which is less significant for circulating blood cells compared to other background tissues [**Ошибка! Источник ссылки не найден.**].

Receptors TAS2R5, TAS2R14, TAS2R46, TAS2R4, and TAS2R20 are involved in taste perception and possibly in modulating inflammatory responses [**Ошибка! Источник ссылки не найден.**]. The functional roles of this group of receptors, aside from their role in sensory taste perception, are poorly studied, and it is currently difficult to explain the expression levels of these genes.

It is noteworthy that for most of the chemokine genes presented, low expression levels were found in tissues where their expression increases during an immune response to inflammation or infection. In the context of HIV infection, where immune response activation is observed, the interaction between these genes becomes more likely, and their potential interactions with each other may influence the infectious process. However, if interaction occurs only during the immune response, established interactions between the background genes (BGs) and CGs may be absent, or if they do occur, they may be random.

In conclusion, analysis of the expression and localization of CGs, as well as their potential participation in various immune processes and biological pathways, identified promising CGs that may play a role in the pathogenesis of HIV infection. A limitation of our study is the indirect nature of the link between the identified CGs and the course of HIV infection. The results of this study confirm the need for further investigation into the functional roles and interactions of CGs in the pathogenesis of HIV infection. This will deepen the understanding of the molecular mechanisms underlying the disease and lead to the development of new therapeutic strategies.

Conclusion

In the course of the study, candidate genes potentially associated with chemokine coreceptors and, consequently, with viral attachment to the cell, were analyzed. These genes may play a key role in regulating immune responses and maintaining homeostasis in the body, especially in important organs such as the lungs, intestines, spleen, and blood. Some of the identified genes are involved in the regulation of inflammatory processes, immune cell migration, and the maintenance of barrier functions in various tissues. The potential link between genes associated with neurotransmitters and neuropeptides and the pathogenesis of HIV infection deserves special attention.

The detected correlations suggest the probable involvement of many of the identified candidate genes in complex signaling pathways that regulate immune responses and inflammation. The presence of positive correlations between chemokine receptors and other proteins may indicate the complex interaction of immune and neuronal processes in the context of HIV infection. The results of the analysis emphasize the importance of further studying the genetic and molecular mechanisms influencing the course of HIV infection.

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Conflict of Interest: The authors declare no conflict of interest.

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ТАБЛИЦЫ

Table 1. The main functional groups of candidate genes.

Таблица 1. Основные функциональные группы ГК.

Functional group	**Genes**
Chemokines and their receptors	*CCL5, CCL8, CCL7, CCL2, CCL16, CCL27, CCL25, CCL20, CCL19, CXCL12, CXCL3, CXCL13, CXCL2, CCR7, CCR10, CCR9, CXCR5, CXCR3, CXCR6, ACKR3*
G-proteins and associated receptors, including serpentine receptors	*GNAI2, GNAI1, GNA13, S1PR5, S1PR3, S1PR2, GPR18, HCAR2, HCAR3, HCAR1, OXGR1, GPER1, OXER1*
Taste receptors	*TAS2R (TAS2R46, TAS2R43, TAS2R40, TAS2R30, TAS2R9, TAS2R3, TAS2R16, TAS2R4, TAS2R1, TAS2R39, TAS2R50, TAS2R20, TAS2R38, TAS2R13, TAS2R60, TAS2R8, TAS2R14, TAS2R10, TAS2R5, TAS2R31, TAS2R42, TAS2R7, TAS2R41, TAS2R19*
Neuropeptide and neurotransmitter receptors	*NPY5R, NPY1R, GALR2, GALR3, GALR1, HTR1F, HTR5A, HTR1D, HTR1E, HTR1A, HRH3, HRH4, OPRK1, FPR3, CHRM2*
Adrenergic receptors	*ADRA2B, ADRA2A, ADRA2C*
Purinergic receptors	*P2RY13, P2RY4, P2RY14*
Somatostatin receptors	*SSTR4, SSTR2, SSTR5, SSTR1, SSTR3*
Peptide receptors	*NPBWR1, NPBWR2, NPW, PPY, PYY, APLN, PENK, PDYN, PNOC, SST*
Receptors not included in the above groups	*SUCNR1, TMIGD3, RXFP3, RXFP4*
Functionally significant non-receptor type proteins	*ANXA1, HEBP1*

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Table 2. Participation of BG and CG in biological processes according to GENE2FUNC. Results are ranked by level of evidential significance. The items include processes with the presence of chemokine receptor genes (CCR5, CXCR4, CCR2, CD4) or processes related to viral activity.

Rank	Participation	Genes	P-value
1	G-protein-coupled receptor (GPCR) signaling pathway	*HTR1D, RXFP4, OXER1, ADRA2B,* ***CXCR4****, CCL20, ACKR3, CCR9, CXCR6,* ***CCR2****,* ***CCR5****, GNAI2, HTR1F, P2RY14, P2RY13, SUCNR1, SST, ADRA2C, NPY1R, NPY5R, TAS2R1, RXFP3, HTR1A, HTR1E, GPER1, NPY, GNAI1, TAS2R16, CHRM2, TAS2R3, TAS2R4, TAS2R5, TAS2R38, TAS2R39, TAS2R40, TAS2R60, TAS2R41, HTR5A, PNOC, NPBWR1, OPRK1, PENK, CCL19, ANXA1, S1PR3, CXCL12, ADRA2A, PTGDR2, CXCR5, TAS2R7, TAS2R8, TAS2R9, TAS2R10, TAS2R13, TAS2R14, TAS2R50, TAS2R20, TAS2R19, TAS2R31, TAS2R46, TAS2R43, TAS2R30, TAS2R42, HCAR1, HCAR2, HCAR3, OXGR1, GPR18, SSTR1, SSTR5, NPW, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCR10, PPY, PYY, GNA13, SSTR2, GALR2, HRH4, GALR1, CCL25, S1PR2, S1PR5, FPR3, PDYN, SSTR4, HRH3, NPBWR2, SSTR3, GALR3, P2RY4, CXCR3, APLN*	4.77e-123
2	Chemokine signaling pathway	***CXCR4****, CCL20, ACKR3, CCR9, CXCR6,* ***CCR2****,* ***CCR5****, CXCL3, CXCL13, CCL19, CXCL12, CXCR5, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCR10, CCL25, CXCR3*	1.03e-30
3	Leukocyte chemotaxis	***CXCR4****, CCL20,* ***CCR2****,* ***CCR5****, CXCL3, CXCL13, CCL19, ANXA1, CXCL12, CXCR5, GPR18, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCL25*	6.44e-18
4	Cellular chemotaxis	***CXCR4****, CCL20,* ***CCR2****,* ***CCR5****, CXCL3, CXCL13, CCL27, CCL19, ANXA1,*	2.98e-17

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Rank	Participation	Genes	P-value
		CXCL12, CXCR5, GPR18, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCL25	
5	Taxis	***CXCR4***, *CCL20, CCR9,* ***CCR2***, ***CCR5***, *SUCNR1, CXCL3, CXCL13, CCL27, CCL19, ANXA1, CXCL12, PTGDR2, CXCR5, GPR18, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCL25, FPR3, CXCR3*	4.47e-17
6	Cytokine-mediated signaling pathway	***CXCR4***, *CCL20, ACKR3, CCR9, CXCR6,* ***CCR2***, ***CCR5***, *CXCL3, CXCL13, CCL19, CXCL12, CXCR5,* ***CD4***, *CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCR10, CCL25, CXCR3*	6.01e-17
7	Locomotion	*HTR1D,* ***CXCR4***, *CCL20, ACKR3, CCR9,* ***CCR2***, ***CCR5***, *GNAI2, SUCNR1, SST, CXCL3, CXCL13, GPER1, OPRK1, CCL27, CCL19, ANXA1, CXCL12, ADRA2A, PTGDR2, CXCR5, GPR18, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, GNA13, CCL25, S1PR2, FPR3, CXCR3*	1.46e-16
8	Leukocyte migration	***CXCR4***, *CCL20,* ***CCR2***, ***CCR5***, *CXCL3, CXCL13, CCL19, ANXA1, CXCL12, CXCR5, GPR18, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCL25, CXCR3*	2.43e-15
9	Inflammatory response	***CXCR4***, *CCL20, CXCR6,* ***CCR2***, ***CCR5***, *SUCNR1, CXCL3, CXCL13, NPY5R, GPER1, NPY, CCL19, ANXA1, S1PR3, ADRA2A, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, HRH4, CCL25, FPR3, CXCR3*	4.66e-15
10	Mononuclear cell migration	***CXCR4***, *CCL20,* ***CCR2***, ***CCR5***, *CXCL13, CCL19, ANXA1, CXCL12, CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCL25*	4.70e-15
11	Immune response	***CXCR4***, *CCL20, ACKR3, CCR9, CXCR6,* ***CCR2***, ***CCR5***, *SUCNR1, CXCL3, CXCL13, NPY5R, GPER1, NPY, OPRK1, CCL27, CCL19, ANXA1, CXCL12, PTGDR2, CXCR5,* ***CD4***, *CCL2, CCL7, CCL8, CCL5, CCL16, CCR7, CCR10, CCL25, FPR3, CXCR3, APLN*	3.15e-14

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Rank	Participation	Genes	P-value
12	Response to organic cyclic compounds	*HTR1D*, ***CXCR4***, ***CCR5***, *HTR1F*, *P2RY13*, *SST*, *HTR1A*, *HTR1E*, *GPER1*, *GNAI1*, *CHRM2*, *HTR5A*, *OPRK1*, *PENK*, *ANXA1*, *SSTR1*, *SSTR5*, *CCL2*, *CCL5*, *SSTR2*, *HRH4*, *SSTR4*, *HRH3*, *SSTR3*, *P2RY4*	3.87e-14
13	Response to cytokines	***CXCR4***, *CCL20*, *ACKR3*, *CCR9*, *CXCR6*, ***CCR2***, ***CCR5***, *CXCL3*, *CXCL13*, *GPER1*, *CCL19*, *ANXA1*, *CXCL12*, *CXCR5*, ***CD4***, *SSTR1*, *CCL2*, *CCL7*, *CCL8*, *CCL5*, *CCL16*, *CCR7*, *CCR10*, *CCL25*, *CXCR3*	4.38e-14
14	Response to oxygen-containing compounds	*HTR1D*, ***CXCR4***, ***CCR5***, *GNAI2*, *HTR1F*, *SUCNR1*, *SST*, *CXCL3*, *CXCL13*, *HTR1A*, *HTR1E*, *GPER1*, *GNAI1*, *CHRM2*, *HTR5A*, *OPRK1*, *PENK*, *CCL19*, *ANXA1*, *CXCL12*, *ADRA2A*, *SSTR1*, *CCL2*, *CCL7*, *CCL5*, *CCR7*, *SSTR2*, *HRH4*, *HRH3*, *SSTR3*, *P2RY4*	3.46e-12
15	Cell motility	***CXCR4***, *CCL20*, *ACKR3*, ***CCR2***, ***CCR5***, *GNAI2*, *SST*, *CXCL3*, *CXCL13*, *GPER1*, *CCL27*, *CCL19*, *ANXA1*, *CXCL12*, *ADRA2A*, *CXCR5*, *GPR18*, *CCL2*, *CCL7*, *CCL8*, *CCL5*, *CCL16*, *CCR7*, *GNA13*, *CCL25*, *S1PR2*, *SSTR4*, *CXCR3*	3.35e-10
16	Chemotaxis of dendritic cells	***CXCR4***, ***CCR2***, ***CCR5***, *CCL19*, *CCL5*, *CCR7*	1.07e-9
17	Migration of dendritic cells	***CXCR4***, ***CCR2***, ***CCR5***, *CCL19*, *CCL5*, *CCR7*	5.05e-9
18	Calcium ion transport	***CXCR4***, ***CCR5***, *GNAI2*, *GPER1*, *CCL19*, *CXCL12*, *ADRA2A*, ***CD4***, *CCL2*, *CCL8*, *CCL5*, *CCR7*	3.69e-7
19	Transport of monatomic ions	***CXCR4***, ***CCR2***, ***CCR5***, *GNAI2*, *HTR1A*, *GPER1*, *OPRK1*, *CCL19*, *CXCL12*, *ADRA2A*, ***CD4***, *CCL2*, *CCL8*, *CCL5*, *CCR7*, *GALR2*, *HRH3*, *P2RY4*	2.73e-6
20	Biological processes related to interspecies interaction between organisms	***CXCR4***, *CCL20*, ***CCR5***, *CXCL3*, *CXCL13*, *GPER1*, *CHRM2*, *OPRK1*, *PENK*, *CCL19*, *ANXA1*, *CXCL12*, ***CD4***, *CCL2*, *CCL7*, *CCL8*, *CCL5*, *CCL16*, *CCR7*, *CCL25*	8.26e-6

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Rank	Participation	Genes	P-value
21	Homeostatic processes	***CXCR4***, ***CCR2***, ***CCR5***, *GNAI2*, *SUCNR1*, *GPER1*, *NPY*, *OPRK1*, *CCL19*, *ANXA1*, *CXCL12*, *ADRA2A*, *HCAR2*, *SSTR5*, *CCL2*, *CCL7*, *CCL8*, *CCL5*, *CCR7*, *P2RY4*	1.54e-5
22	Transport of monovalent cations	***CXCR4***, ***CCR5***, *GNAI2*, *GPER1*, *OPRK1*, *CCL19*, *CXCL12*, *ADRA2A*, ***CD4***, *CCL2*, *CCL8*, *CCL5*, *CCR7*, *GALR2*	1.00e-4
23	Response to virus	***CXCR4***, *CHRM2*, *OPRK1*, *PENK*, *CCL19*, *CXCL12*, *CCL8*, *CCL5*	2.41e-4
24	Viral life cycle	***CXCR4***, *CXCR6*, ***CCR5***, ***CD4***, *CCL2*, *CCL8*, *CCL5*	3.51e-4
25	Calcium ion-mediated signaling	***CXCR4***, *CCL20*, ***CCR5***, *PTGDR2*, ***CD4***	1.05e-3
26	Signaling mediated by second messengers	***CXCR4***, *CCL20*, ***CCR5***, *GNAI1*, *PTGDR2*, ***CD4***	1.34e-3
27	Viral processes	***CXCR4***, *CXCR6*, ***CCR5***, ***CD4***, *CCL2*, *CCL8*, *CCL5*	1.85e-3

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Table 3. Candidate gene ranking by subcategory and total score (threshold = 2). Genes are listed in descending order of candidate significance rank.

Gene	Expression	Localization	Pathways	Processes	Additional Points	Total
CXCR3	1.14	0	2.49	1.14	3	7.77
CCR7	1.64	0	1.17	0.96	3	6.77
FPR3	1.58	0	1.54	0.63	3	6.74
ANXA1	3.84	0	0	0.58	2	6.42
GNAI2	4.00	0	0	0.26	2	6.26
ACKR3	3.28	0	0	0.76	2	6.04
CCL2	2.88	0	0	1.07	2	5.95
CXCL12	3.01	0	0	0.91	2	5.93
CXCR6	1.05	0	0.75	1.03	3	5.83
CCR9	0.41	0	1.54	0.85	3	5.80
GNAI1	3.24	0	0	0.35	2	5.58
GPER1	2.86	0	0	0.53	2	5.39
CCL19	2.48	0	0	0.91	2	5.39
CXCR5	0.79	0	0.65	0.93	3	5.37
OPRK1	0	0.27	1.54	0.47	3	5.28
NPY5R	0.41	0	1.54	0.11	3	5.07
GPR18	0.96	0	0.52	0.51	3	4.99
CCR10	0.22	0	0.94	0.82	3	4.99
GALR2	0.03	0	1.54	0.23	3	4.81
ADRA2A	2.43	0	0	0.11	2	4.53
GNA13	4.00	0	0	0	0	4.00
HEBP1	3.96	0	0	0	0	3.96
HCAR3	1.43	0	0	0.27	2	3.70
CXCL13	0.88	0	0	0.81	2	3.69
HTR5A	0.07	0.44	0	0.18	3	3.68
GALR3	0	0	1.54	0.07	2	3.61
CCL20	0.84	0	0	0.76	2	3.60
HTR1D	0.28	0.28	0	0.04	3	3.59
CXCL3	0.53	0	0	1.02	2	3.55
CCL8	0.50	0	0	1.05	2	3.55
SSTR3	0	0	1.54	0.01	2	3.55
NPY1R	1.32	0	0	0.14	2	3.46

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Gene	Expression	Localization	Pathways	Processes	Additional Points	Total
TAS2R14	1.15	0	0	0.14	2	3.29
TAS2R5	1.15	0	0	0.13	2	3.28
SUCNR1	0.49	0	0	0.74	2	3.23
SST	0.83	0	0	0.40	2	3.22
CCL25	0.44	0	0	0.62	2	3.06
SSTR1	0.87	0	0	0.17	2	3.04
NPY	0.79	0	0	0.16	2	2.95
PTGDR2	0.49	0	0	0.42	2	2.91
PNOC	0.67	0	0	0.18	2	2.85
CCL27	0.09	0	0	0.74	2	2.83
PENK	0.19	0	0	0.54	2	2.73
CXCL2	2.63	0	0	0	0	2.63
HRH4	0	0.28	0	0.28	2	2.56
ADRA2C	2.54	0	0	0	0	2.54
OXER1	2.53	0	0	0	0	2.53
S1PR3	2.53	0	0	0	0	2.53
HTR1F	0	0.28	0	0.23	2	2.50
S1PR2	2.48	0	0	0	0	2.48
HTR1E	0	0.28	0	0.11	2	2.39
PDYN	0.21	0	0	0.18	2	2.39
OXGR1	0.01	0	0	0.27	2	2.28
CHRM2	0.17	0	0	0.06	2	2.22
TAS2R20	0.07	0	0	0.14	2	2.21

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РИСУНКИ

Figure 1. Study design.

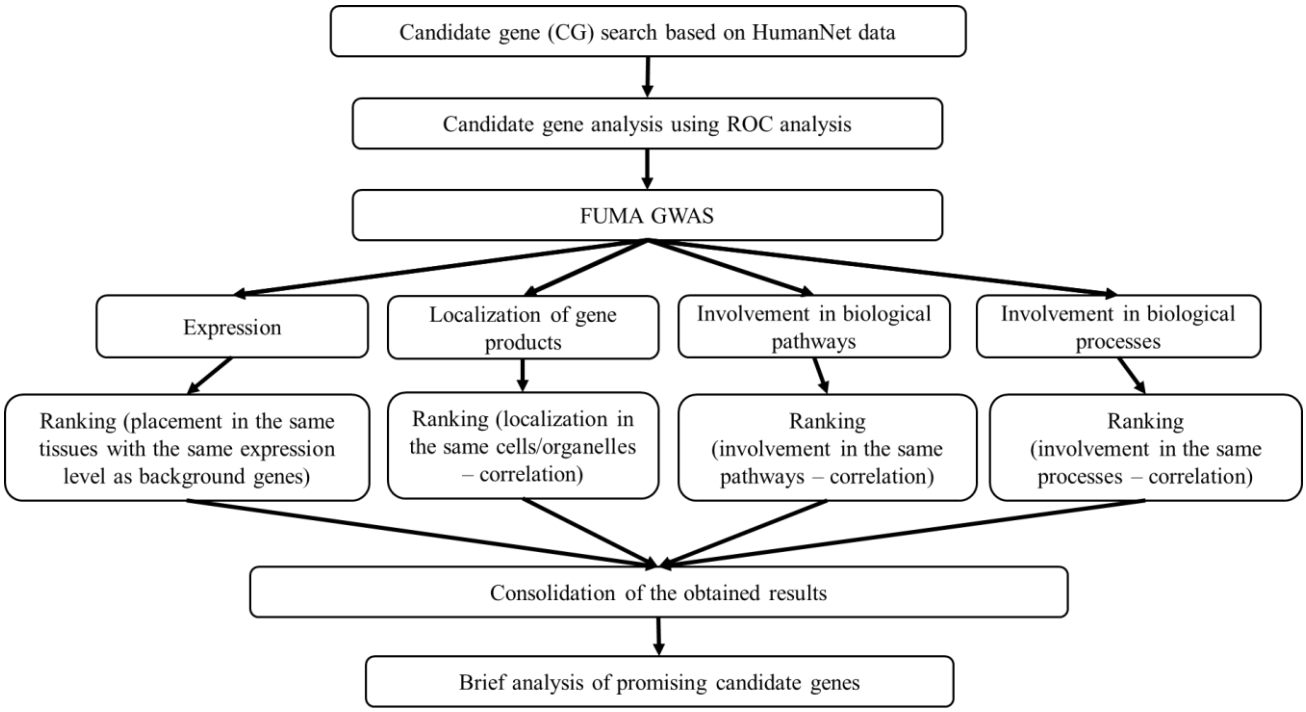

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Figure 2. AUROC prediction of identified HumanNet candidate genes, calculated relative to background genes (CCR5, CXCR4, CD4, CCR2) with a false-positive rate cutoff of 1%.

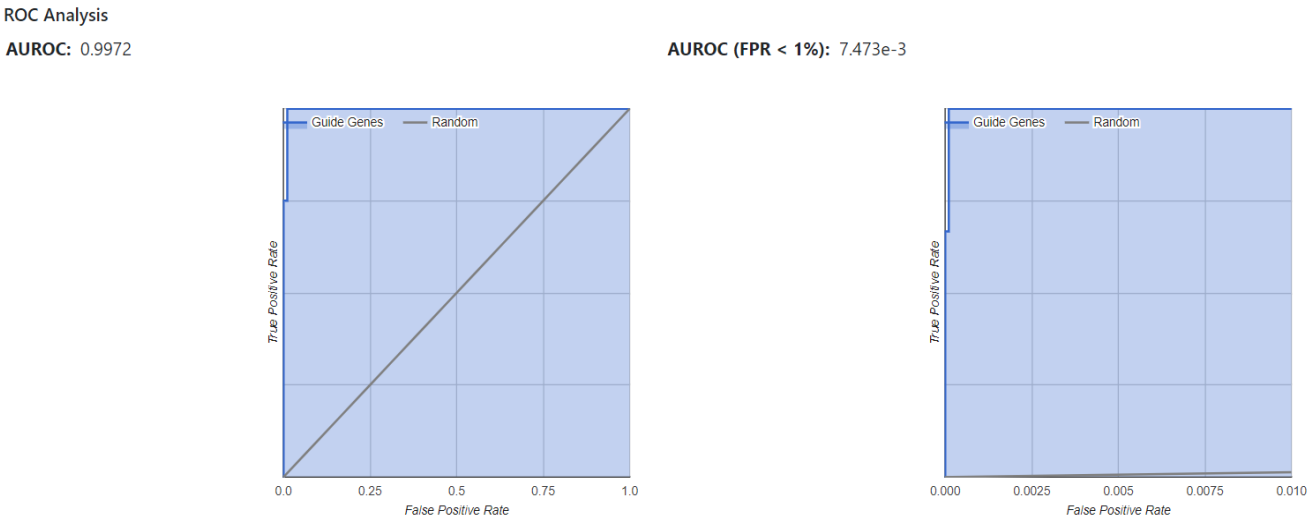

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Figure 3. Tissue-specific expression map for background genes (CCR5, CXCR4, CD4, CCR2) and candidate genes (CGs). CCR5, CXCR4, CD4, and CCR2 are highlighted with a red border.

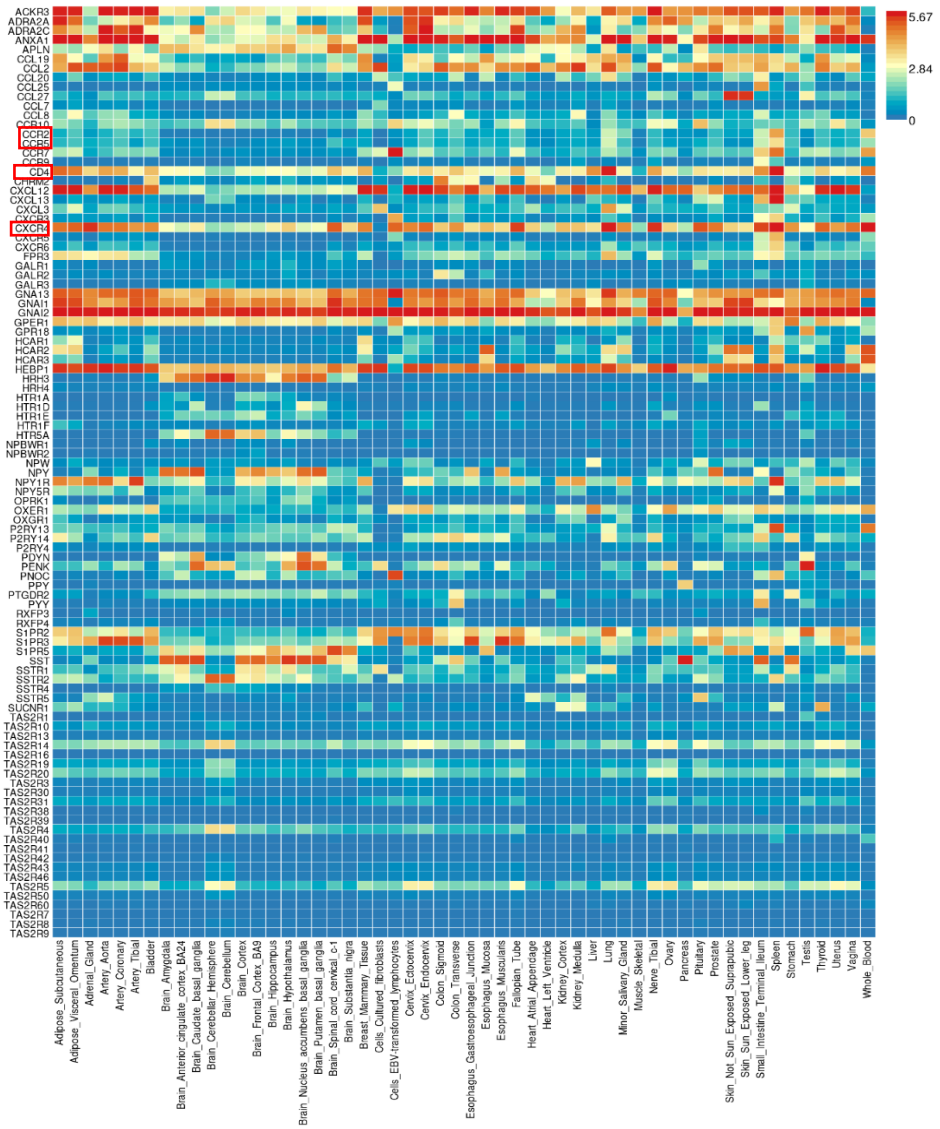

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Figure 4. Localization of gene products. Candidate genes (CGs) are presented along the horizontal axis, while cell types and/or their structures are on the vertical axis. Background genes (CCR5, CXCR4, CD4, CCR2) are marked with a red border.

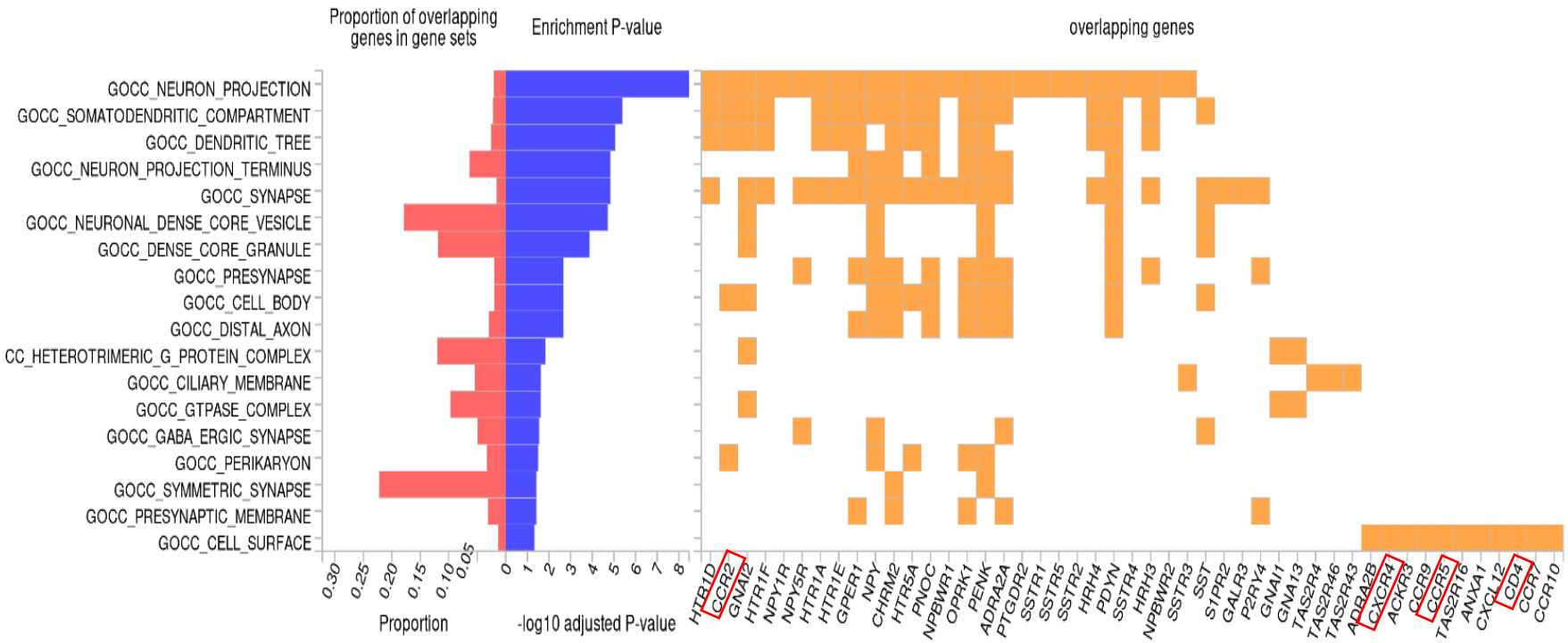

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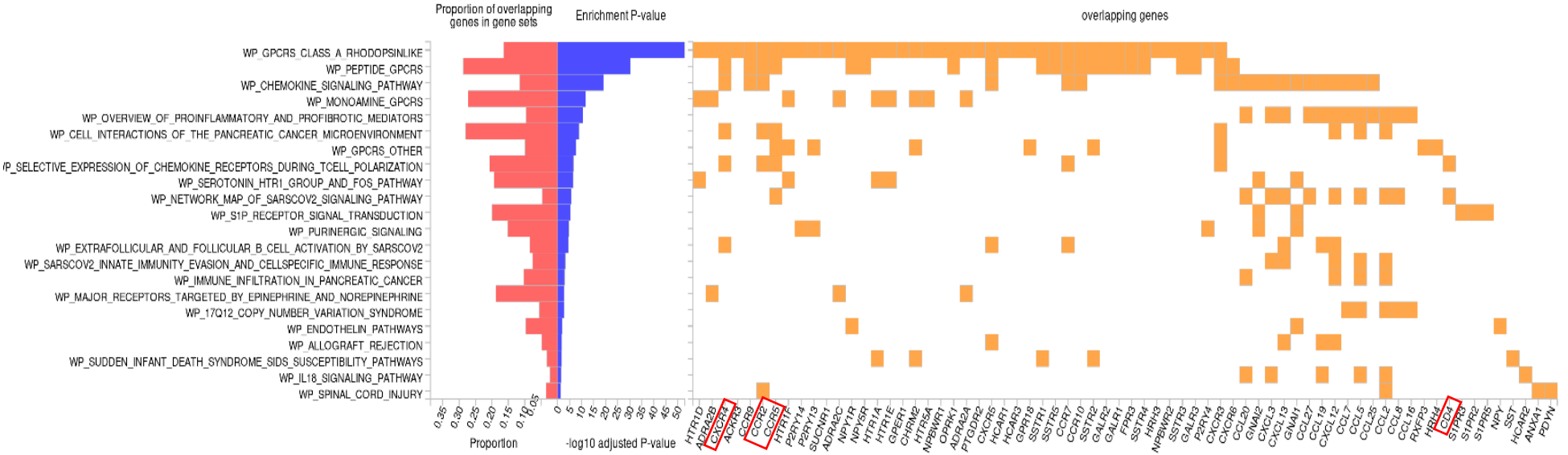
Figure 5. Biological pathway annotation for BG, CG, their proteins, and metabolites (p<0.05). CG are represented on the horizontal axis; biological pathways are on the vertical axis. BG (CCR5, CXCR4, CD4, CCR) are marked. Analysis obtained in GENE2FUNC mode using WikiPathways data.



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Блок 3. Метаданные статьи

BIOINFORMATIC ANALYSIS OF THE RELATIONSHIPS BETWEEN SPECIFIC HUMAN GENES ASSOCIATED WITH HIV ATTACHMENT

БИОИНФОРМАТИЧЕСКИЙ АНАЛИЗ ВЗАИМОСВЯЗЕЙ МЕЖДУ СПЕЦИФИЧЕСКИМИ ГЕНАМИ ЧЕЛОВЕКА, АССОЦИИРОВАННЫМИ С ПРИКРЕПЛЕНИЕМ ВИЧ

Сокращенное название статьи для верхнего колонтитула:

BIOINFORMATIC ANALYSIS OF HUMAN GENES LINKED TO HIV ATTACHMENT

БИОИНФОРМАТИЧЕСКИЙ АНАЛИЗ ГЕНОВ ЧЕЛОВЕКА, СВЯЗАННЫХ С ПРИКРЕПЛЕНИЕМ ВИЧ К КЛЕТКЕ.

Keywords: Human immunodeficiency virus, virus-host interaction, protein-protein interactions, candidate genes, in silico, CD4, CCR5, CXCR4, CCR2.

Ключевые слова: Вирус иммунодефицита человека, взаимодействие вирус-хозяин, белок-белковые взаимодействия, гены-кандидаты, *in silico*, CD4, CCR5, CXCR4, CCR2.

Оригинальные статьи.

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