Genetic and Molecular Insights into AIDS Progression: A Genome-Wide Association Data-Driven Analysis

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Abstract

AIDS progression varies widely among individuals, influenced by genetic and molecular factors affecting immune responses and viral replication. Identifying genetic variants associated with disease progression can reveal host-pathogen interactions and potential therapeutic targets. This study analyzes genome-wide association study (GWAS) data and performs functional enrichment analyses to explore key genetic determinants of AIDS progression. GWAS data were analyzed to identify single nucleotide polymorphisms (SNPs), significantly associated with AIDS progression. Functional enrichment through Gene Ontology (GO), KEGG pathways and CellMarker databases classified genes by biological functions, immune cell associations and metabolic pathways. Unsupervised machine learning algorithms, including hierarchical clustering and principal component analysis (PCA) were applied to validate patterns.

Significant SNPs were identified in genes such as PARD3B, LTF, CCRL2, NBPF14, DGKI, RPH3AL and H2AFY, linked to immune regulation, inflammation and viral replication control. PARD3B was associated with slower disease progression while DGKI highlighted metabolic involvement through phosphatidylinositol signaling. Hierarchical clustering revealed natural SNP groupings and PCA confirmed distinct genomic patterns influencing AIDS progression. This study highlights genetic variants influencing AIDS progression and identifies potential biomarkers for future therapeutic strategies. Validation and further exploration of personalized treatment approaches are recommended.

Keywords: AIDS progression, GWAS, immune regulation, lipid metabolism, genetic susceptibility

Introduction

There is significant variability in how individuals respond to HIV-1 infection, both in terms of susceptibility and disease progression. Some individuals exhibit a natural resistance to HIV-1 and remain uninfected despite repeated exposure while others contract the virus after a single exposure. Among those who do become infected, disease progression varies widely, some individuals advance to AIDS within just two years whereas others can remain asymptomatic for over 15 years. This variability is influenced by a combination of host genetic factors and viral characteristics.

One key viral factor affecting disease progression is the shift in HIV-1 coreceptor usage. The transition from viruses that use CCR5 to those that utilize CXCR4, is linked to a more rapid decline in CD4+ T-cell counts, leading to accelerated progression to AIDS.[1,9] Further evidence for the role of viral genetics in disease progression comes from studies of long-term nonprogressors (LTNPs) where individuals infected with an HIV-1 variant carrying a deletion in the nef gene exhibited slower disease progression due to the virus's reduced pathogenicity.[4]

The identification of host genetic factors influencing HIV-1 susceptibility and progression initially came from candidate gene studies which focused on genetic variants in host proteins known or suspected to be involved in HIV-1 pathogenesis and immune regulation. These studies uncovered several polymorphisms that significantly impact HIV-1 infection and disease course.[8,10,11,16-18,23,25-28] One of the strongest associations is with human leukocyte antigen (HLA) genes, which play a crucial role in immune defense. HLA-B*5701 and HLA-B27 are more frequently found in LTNPs, suggesting a protective role, whereas HLA-B35 is linked to faster disease progression and an increased risk of developing AIDS more quickly.[7,15,19]

Another well-documented genetic factor is a 32-base pair deletion in the CCR5 gene (CCR5Δ32), which affects the CCR5 coreceptor, a key entry point for HIV-1. Individuals who are homozygous for this deletion, lack functional CCR5 receptors on their cell surface, making them almost completely resistant to HIV-1 infection.[18-20] In contrast, individuals who are heterozygous for CCR5Δ32 still express some CCR5 receptors, allowing for infection; however, their disease progression is significantly delayed compared to those with the wild-type CCR5 genotype.[3,5,21]

The genome-wide association study (GWAS) by Troyer et al[24] investigated genetic factors influencing the progression of HIV infection to AIDS. Using a well-characterized cohort of 755 European American HIV sero converters, the researchers analyzed 700,022 single-nucleotide polymorphisms (SNPs) to identify genetic variations associated with the rate of disease progression.[23] The study identified a significant association between SNPs in the PARD3B gene and slower progression to AIDS. Among these, rs11884476 reached genome-wide significance, indicating a protective effect against disease progression.

The analysis revealed that PARD3B SNPs contribute approximately 4.52% of the variance in AIDS progression, a notable finding considering the complexity of host genetic interactions with HIV. A specific haplotype within PARD3B, defined by nine SNPs, also showed a significant protective effect. One of these SNPs, rs10185378, was located in an exon and was predicted to function as an exonic splicing enhancer. The study further confirmed functional relevance by demonstrating that different rs10185378 genotypes altered PARD3B gene expression and splicing patterns in lymphoblastoid cell lines.

The findings suggest that PARD3B, a gene involved in cell polarity and tight junctions, may play a role in HIV/AIDS pathogenesis through previously unrecognized mechanisms. PARD3B interacts with SMAD proteins which are involved in TGF-β signaling and have known roles in HIV replication and immune modulation. The study also highlights the broader implications of host genetic factors in influencing HIV progression and potential therapeutic targets.

Although the results were significant in the European American cohort, they did not replicate in an African American cohort, emphasizing the need for further validation in diverse populations. The study underscores the importance of genome-wide approaches in identifying novel genetic pathways that influence disease outcomes and suggest PARD3B as a potential candidate for future HIV research and therapeutic intervention.

Objectives

1. Utilize genome-wide association study (GWAS) data to identify and analyze genes associated with AIDS progression and host resistance mechanisms.
2. Perform Gene Ontology (GO) analysis to categorize identified genes based on their biological functions, molecular processes and cellular components involved in immune response and viral replication.
3. Conduct pathway analysis using KEGG and Reactome databases to identify molecular mechanisms associated with HIV pathogenesis, immune system modulation and inflammatory responses.
4. Analyse the mapped genes of AIDS progression with unsupervised models

Material and Methods

To investigate the genetic and molecular mechanisms underlying AIDS progression, we employed a multi-step bioinformatics approach integrating GWAS data analysis, functional enrichment assessments, pathway mapping and regulatory network exploration.

Data Acquisition and Processing: First, GWAS data were obtained from publicly available databases and HIV/AIDS cohort studies to identify genetic variants significantly associated with disease progression.[23] The dataset was curated and subjected to stringent quality control measures including minor allele frequency filtering, Hardy-Weinberg equilibrium testing and population stratification adjustments. Variants with strong statistical associations were prioritized for further functional analysis.

Functional Annotation and Enrichment Analysis: Gene ontology (GO) analysis was conducted to classify the identified genes into relevant biological processes (e.g. immune response, viral replication control), molecular functions (cytokine signaling, receptor interactions) and cellular components (lymphocyte activation, antigen presentation). Enrichment analysis was performed using established bioinformatics tools to determine overrepresented pathways involved in HIV progression and immune system interactions.

Pathway Analysis: To explore disease-associated molecular mechanisms, pathway analysis was performed using the KEGG and Reactome databases. This allowed us to assess whether the identified genes were enriched in key HIV-related pathways including T-cell activation, antigen presentation, chemokine signaling, inflammatory response and apoptosis. The findings provided a systems-level perspective on how genetic variations contribute to HIV disease progression and respond to antiretroviral therapy (ART).

Regulatory Network Analysis: To further investigate post-transcriptional and epigenetic regulation, miRNA enrichment analysis was conducted using miRTarBase and TargetScan to identify miRNAs that regulate key HIV-associated genes. This analysis provided insights into how miRNA-mediated gene silencing may influence immune responses, viral replication and resistance to infection.

Integration with Metabolomic Data: Lastly, GWAS findings were linked to metabolomic changes using MetaboAnalyst to assess whether identified genetic variants influence metabolic pathways associated with HIV/AIDS progression. This step aimed to uncover potential metabolic biomarkers that could serve as indicators of disease progression, ART response, or immune system alterations. By integrating genomic, regulatory and metabolomic data, this study provides a comprehensive approach in understanding HIV pathogenesis and in identifying novel therapeutic targets.

Results

This study extracted several genomic regions significantly associated with AIDS progression, revealing novel and previously implicated genetic factors that may influence immune response, inflammation and viral replication control.[23]

Two significant SNPs were identified within chromosome 3p21.31, mapping to Lactotransferrin (LTF) and C-C motif chemokine receptor-like 2 (CCRL2) genes. On chromosome 1q21.1, the study identified associations with NBPF14 and the RNVU1-8 - NBPF13P gene cluster. NBPF14

(Neuroblastoma Breakpoint Family Member 14) belonging to a family of genes involved in cell cycle regulation, neuronal differentiation and immune function. A strong association was observed at chromosome 7q33, mapping to DGKI (Diacylglycerol Kinase Iota). One of the most significant findings in this study was the association of PARD3B (Par-3 family cell polarity regulator beta) on chromosome 2q33.3 with slower AIDS progression. PARD3B is involved in cell junction integrity and immune signaling.

On chromosome 17p13.3, significant variants were mapped to RPH3AL (Rabphilin 3A-Like) and LINC02091, a long non-coding RNA (lncRNA). RPH3AL is known to regulate vesicle trafficking in neurons and immune cells. A notable SNP was also identified on chromosome 5q31.1, mapping to H2AFY (H2A Histone Family, Member Y) and PITX1-AS1 (PITX1 Antisense RNA 1).

The CellMarker data (table 2) for AIDS provides insight into the cellular components and immune cell types that are potentially implicated in the disease. Notably, the dataset highlights specific cell markers such as Tumor-infiltrating Regulatory T Cell Lung Human and T Helper 1 (Th1) Cell Stomach Human. The extremely high odds ratio (approximately 714 for the regulatory T cell marker) and combined score indicate a strong enrichment of these cells, suggesting that immune regulatory mechanisms are heavily involved.

The GO biological process enrichment data for AIDS reveals several key biological processes that appear to be disrupted in the disease context. In this dataset, processes such as establishment of centrosome localization and establishment or maintenance of epithelial cell Apical/Basal polarity emerge with exceptionally high odds ratios and combined scores, indicating a strong enrichment.

The GO Cellular Component enrichment for AIDS highlights the subcellular structures where key proteins implicated in the disease are localized (table 4). The top hits in this dataset, such as the Apical Junction Complex and Adherens Junction, are critical for maintaining cell–cell adhesion and the integrity of epithelial layers. The high odds ratios associated with PARD3B in these compartments suggest that disruption of cell polarity and junctional integrity may be an important aspect of AIDS pathology, potentially affecting barrier functions in tissues susceptible to opportunistic infections. In contrast, the components associated with DGKI, such as the nucleus and intracellular membrane-bound organelle, show very low odds ratios and combined scores, indicating that these more ubiquitous cellular structures may be less selectively affected. The GO molecular function enrichment for AIDS provides a window into the specific biochemical activities that are altered in the context of the disease (table 5). A striking finding in this dataset is the extremely high odds ratio associated with diacylglycerol kinase activity linked to DGKI. This suggests that enzymatic processes controlling diacylglycerol levels and thereby influencing signal transduction and lipid metabolism are highly enriched, which may have profound implications for cell signaling in immune cells.

The HMDB metabolite enrichment data for AIDS, derived from the human metabolome database, reveals a set of metabolites that are highly enriched in association with DGKI (table 6). All of the top 10 rows show consistent enrichment of various phospholipid species (including several phosphatidic acids and related compounds), with remarkably similar odds ratios and combined scores. This suggests that alterations in lipid metabolism, particularly those involving glycerolipid and glycerophospholipid intermediates, may be central to the metabolic dysregulation seen in AIDS.

The KEGG pathway enrichment analysis for AIDS (using 2019 Human data) underscores the importance of lipid metabolism and signaling in the disease context (table 7). The top pathways identified include Glycerolipid metabolism and Glycerophospholipid metabolism, both of which are critical for maintaining cellular membrane integrity and signaling functions. DGKI's consistent presence in these pathways reinforces its role in regulating the balance between diacylglycerol and phosphatidic acid, a key step in lipid signaling cascades. The identification of the phosphatidylinositol signaling system and choline metabolism in cancer pathways further suggests that perturbations in lipid-derived second messenger systems might contribute to immune dysregulation and altered cell survival in AIDS.

Additionally, the phospholipase D signaling pathway emerges as a significant pathway; this enzyme system is known to influence membrane trafficking, cell migration and even apoptosis, which are processes that can be disrupted during viral infections and chronic immune activation.

In K means clustering three SNP clusters were identified, suggesting different genetic patterns linked to AIDS progression. Hierarchical clustering reinforced the existence of natural SNP groupings, likely based on risk allele frequency and P-values. PCA successfully reduced the dataset to two principal components, preserving most variance. SNPs are well-separated in PCA space, indicating distinct genomic influences.

Discussion

Through GWAS analysis, key loci across different chromosomes were mapped to potential candidate genes, providing deeper insights into the genetic architecture of AIDS susceptibility and progression (table 1). LTF is an important component of innate immunity, known for its role in antiviral activity and immune modulation. Previous studies suggest that lactotransferrin can inhibit HIV replication by binding to viral particles and preventing cell entry.

Table 1
GWAS study results[23]

Region	CHR_ID	CHR_POS	Reported Gene (S)	Mapped Gene
3p21.31	3	46410189	LTF	CCRL2
1q21.1	1	1.47E+08	NBPF14	RNVU1-8 - NBPF13P
7q33	7	1.38E+08	DGKI	DGKI
2q33.3	2	2.05E+08	PARD3B	PARD3B
17p13.3	17	189133	RPH3AL	LINC02091
3p21.31	3	46386699	CCRL2	CCR5AS
5q31.1	5	1.35E+08	H2AFY	PITX1-AS1

The identification of CCRL2, a chemokine receptor-like protein, is particularly relevant as it is involved in immune cell trafficking and inflammatory responses, which play crucial roles in HIV disease progression and immune evasion mechanisms.

Role of NBPF14 in HIV progression remains unclear, it is possible that genetic variants in this region influence T-cell activation or neuronal protection in HIV-associated neurocognitive disorders. The NBPF gene family has been implicated in various immune-related disorders, suggesting a potential role in modulating immune responses against HIV infection. DGKI is involved in lipid metabolism and intracellular signaling, particularly in T-cell receptor (TCR) activation pathways. Since HIV-1 infection modulates TCR signaling to escape immune detection, variants in DGKI may influence T-cell activation, cytokine production and viral replication control. These findings suggest that lipid and signal transduction pathways could be key modulators of HIV progression.

The study found that a specific SNP within PARD3B (rs11884476) showed a strong protective effect, slowing disease progression. Further functional analysis suggested that PARD3B may influence TGF-β signaling pathways which interact with HIV replication and immune responses. This gene's association introduces a potential new mechanism of immune regulation in HIV progression, warranting further investigation into PARD3B's role in T-cell function and viral latency. RPH3AL could have implications for HIV viral trafficking, immune synapse formation, or neuronal dysfunction in HIV-associated neurocognitive disorders. LINC02091, as a lncRNA, could play a regulatory role in gene expression and immune modulation, possibly influencing HIV latency and immune escape mechanisms.

H2AFY is involved in epigenetic regulation and chromatin remodeling, which could impact HIV integration into host DNA and viral transcriptional activity. The PITX1-AS1 gene, an antisense RNA, may regulate gene expression at the post-transcriptional level, affecting host immune responses or viral replication dynamics. These findings indicate a potential role of epigenetic modifications in controlling HIV persistence and progression.

This study identified multiple genomic regions associated with HIV/AIDS progression, highlighting genes involved in immune regulation, viral replication control, inflammatory responses and epigenetic modifications[23]. The identification of PARD3B as a key genetic factor influencing slower AIDS progression is a particularly significant finding, suggesting novel immune pathways that may be targeted for therapeutic intervention. Additionally, genes related to chemokine signaling (CCRL2), lipid metabolism (DGKI) and epigenetic regulation (H2AFY, PITX1-AS1) suggest complex host-pathogen interactions that influence disease outcomes. Further functional studies are required to validate these associations and explore their potential for improving personalized medicine and therapeutic strategies for HIV/AIDS patients.

The presence of markers (table 2) for neutrophils, podocytes and hematopoietic stem cells points to a heterogeneous involvement of various cell types which may contribute to both the systemic immune dysfunction and tissue-specific pathology observed in AIDS. For instance, the involvement of CCRL2 in both the tumor-infiltrating regulatory T cell and neutrophil categories implies a recurring role of this receptor in immune modulation. In contrast, markers associated with PARD3B and DGKI hint at disruptions in cell polarity and lipid signaling pathways respectively which could affect barrier integrity and cellular metabolism in affected tissues. Overall, these data suggest that AIDS is not merely an immunodeficiency but also involves complex alterations in cellular phenotype and tissue microenvironments.

The enrichment of these cell markers provides valuable targets for further investigation and could guide future studies aimed at understanding the cellular basis of AIDS pathogenesis, as well as the development of targeted therapies to modulate these key cell populations.

The prominence of PARD3B in these processes suggests that cell polarity and organization play a pivotal role in the pathology of AIDS (table 3). In addition, processes related to lipid phosphorylation and diacylglycerol metabolism, linked to DGKI, highlight the involvement of lipid signaling and metabolic pathways. Such pathways can influence membrane dynamics and signal transduction in immune cells, potentially affecting how cells respond to viral

infection and inflammation. The dataset also includes regulation of synaptic transmission, glutamatergic and modulation of chemical synaptic transmission, hinting at potential impacts on neuronal communication, which may be relevant to neurocognitive disorders often associated with AIDS. Moreover, the enrichment of inflammatory response underscores the role of chronic inflammation in disease progression, particularly given the role of CCRL2, a chemokine receptor that can modulate immune cell trafficking.

Together, these processes paint a picture of AIDS as a disease that disrupts cellular organization, lipid metabolism and immune signaling. This multifaceted disturbance could contribute to both the immunodeficiency and the systemic complications seen in AIDS patients, suggesting new avenues for research and therapeutic intervention that target cell polarity, lipid signaling and inflammatory regulation.

Overall, the findings of table 4 imply that the disease process may involve selective targeting or dysregulation of specific cell–cell junctions that are essential for tissue organization. This disruption can lead to increased tissue permeability and might contribute to the systemic spread of infection and inflammation. The distinct patterns observed between PARD3B and DGKI further emphasize that while some proteins are mislocalized within specialized junctional complexes. Others maintain a more general cellular distribution. These insights could help direct future studies to examine how preserving junctional integrity might mitigate some of the tissue damage associated with AIDS.

Additionally, functions related to chemokine receptor binding (both CCR chemokine receptor binding and chemokine receptor binding) show significant enrichment for CCRL2 (table 5). Chemokine receptors are pivotal for directing immune cell migration and their dysregulation could lead to improper immune cell trafficking or excessive inflammation. The presence of terms such as phosphatidylinositol binding and G-protein coupled receptor binding further points to disturbances in membrane-associated signaling events. Such signaling pathways are essential for the coordination of immune responses and alterations may contribute to the immunopathogenesis of AIDS.

Cytokine receptor binding also appears enriched, emphasizing the role of cytokine-mediated communication in the disease.

Overall, this molecular function data suggests that both lipid signaling and immune receptor interactions are disrupted in AIDS. These abnormalities could affect how immune cells respond to infection and contribute to the progressive immunodeficiency characteristic of the disease. Targeting these altered molecular functions might offer new therapeutic strategies to restore proper signaling and improve immune function in AIDS patients.

Table 2
CellMarker Enrichment in AIDS

Term	Overlap	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds Ratio	Combined Score	Genes
Tumor-infiltrating Regulatory T Cell Lung Human	1/5	0.001998563431658992	0.015988507453271936	0	0	713.85714	4436.85532	CCRL2
T Helper 1(Th1) Cell Stomach Human	1/24	0.009561342717827156	0.03824537087130862	0	0	124.03106	576.74777	DGKI
Neutrophil Kidney Mouse	1/98	0.038540687309931360	0.10277516615981697	0	0	29.30044	95.40343	CCRL2
Schwalie Et al.Nature.P3 Adipose Tissue Mouse	1/191	0.073906750639935561	0.14781350127987122	0	0	14.88872	38.78439	PARD3B
Podocyte Kidney Mouse	1/263	0.100499905288096969	0.15235186099344833	0	0	10.75791	24.71735	PARD3B
Enteroendocrine Precursor Cell Intestinal Crypt Mouse	1/301	0.114263895745086626	0.15235186099344833	0	0	9.37714	20.34132	PARD3B
Hematopoietic Stem Cell Bone Marrow Mouse	1/565	0.204905145184836627	0.23417730878267	0	0	4.92097	7.80077	PARD3B
Monocyte Fetal Kidney Human	1/796	0.277448696266861976197	0.27744869626686197	0	0	3.44960	4.42279	CCRL2

Table 3
GO Biological Process Enrichment in AIDS

Term	Overlap	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds Ratio	Combined Score	Genes
Establishment Of Centrosome Localization (GO:0051660)	1/7	0.002797015027105056	0.021569452	0	0	475.85714	2797.66050	PARD3B
Lipid Phosphorylation (GO:0046834)	1/9	0.003594908666217628	0.021569452	0	0	356.85714	2008.47647	DGKI
Diacylglycerol Metabolic Process (GO:0046339)	1/23	0.009164554745730224	0.028593939	0	0	129.67532	608.49005	DGKI
Establishment Or Maintenance Of Apical/Basal Cell Polarity (GO:0035088)	1/26	0.010354501736256563	0.028593939	0	0	114.09714	521.46204	PARD3B
Establishment Or Maintenance Of Epithelial Cell Apical/Basal Polarity (GO:0045197)	1/40	0.015891074726793453	0.028593939	0	0	73.08791	302.72996	PARD3B
Acylglycerol Metabolic Process (GO:0006639)	1/41	0.01628550529596983	0.028593939	0	0	71.25714	293.39985	DGKI
Lipid Modification (GO:0030258)	1/42	0.016679797556906864	0.028593939	0	0	69.51568	284.56640	DGKI
Regulation Of Synaptic Transmission, Glutamatergic (GO:0051966)	1/55	0.02179302948367254	0.032689544	0	0	52.74603	201.81503	DGKI
Modulation Of Chemical Synaptic Transmission (GO:0050804)	1/123	0.048161911106035224	0.064215881	0	0	23.26698	70.57309	DGKI
Inflammatory Response (GO:0006954)	1/236	0.09060684636425971	0.108728216	0	0	12.01033	28.83952	CCRL2

DGKI, which encodes a diacylglycerol kinase, is known to be a key regulator of lipid signaling pathways (table 6). Its association with these metabolites implies that disruptions in the conversion of diacylglycerol to phosphatidic acid may lead to imbalances in membrane composition, signaling cascades and energy homeostasis. The consistency of the odds ratio (approximately 95) across these metabolites indicates a strong and reproducible enrichment. Given that lipid metabolism plays an essential role in both immune cell function and viral replication, these findings may reflect how AIDS perturbs metabolic pathways to influence disease progression.

Furthermore, such metabolic alterations could serve as potential biomarkers or targets for therapeutic intervention, offering insights into novel strategies to restore metabolic balance and improve cellular function in AIDS patients. Overall, the KEGG pathway enrichments (table 7) indicate

that alterations in lipid metabolism are not only a hallmark of AIDS-related metabolic disturbances but may also be directly involved in the mechanisms through which the disease impacts cellular functions. Understanding these pathways can provide new targets for metabolic intervention and might help in developing strategies to restore normal lipid signaling in affected patients.

Several genome-wide association studies (GWAS) have identified significant genetic variants associated with different aspects of HIV-1 infection, disease progression and treatment response across diverse populations. The HCP5 (rs2395029) variant has been repeatedly confirmed as a strong predictor of HIV control and progression, showing significant associations with plasma viral load, cellular HIV DNA levels and long-term nonprogression in Caucasian cohorts from the ANRS PRIMO (2008), GRIV (2009) and Euro-CHAVI, MACS (2009) studies.[2,6,13] Additionally, HLA-C (rs9264942) has been linked to viral load setpoint and HIV control, with strong statistical significance in multiple cohorts.[12,20] The clustering patterns suggest that AIDS progression risk SNPs may be divided into distinct genetic risk categories.

Table 4
GO Cellular Component Enrichment in AIDS

Term	Overlap	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds Ratio	Combined Score	Genes
Apical Junction Complex (GO:0043296)	1/106	0.041628695	0.146145285	0	0	27.05714	86.01373	PARD3B
Adherens Junction (GO:0005912)	1/150	0.058458114	0.146145285	0	0	19.02493	54.02023	PARD3B
Cell-Cell Junction (GO:0005911)	1/299	0.113544097	0.189240162	0	0	9.44104	20.53958	PARD3B
Nucleus (GO:0005634)	1/4487	0.869035379	0.908901567	0	0	0.49379	0.06931	DGKI
Intracellular Membrane-Bounded Organelle (GO:0043231)	1/5175	0.908901567	0.908901567	0	0	0.40913	0.03908	DGKI

Table 5
GO Molecular Function Enrichment in AIDS

Term	Overlap	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds Ratio	Combined Score	Genes
diacylglycerol kinase activity (GO:0004143)	1/10	0.00399365	0.03194917	0	0	317.19048	1751.85905	DGKI
CCR chemokine receptor binding (GO:0048020)	1/38	0.01510180	0.05182926	0	0	77.04633	323.05076	CCRL2
chemokine receptor binding (GO:0042379)	1/49	0.01943597	0.05182926	0	0	59.35714	233.90451	CCRL2
phosphatidylinositol binding (GO:0035091)	1/100	0.03931350	0.07135055	0	0	28.70563	92.89679	PARD3B
G-protein coupled receptor binding (GO:0001664)	1/133	0.05198675	0.07135055	0	0	21.49351	63.55128	CCRL2
cytokine receptor binding (GO:0005126)	1/137	0.05351291	0.07135055	0	0	20.85714	61.06622	CCRL2
phosphotransferase activity, alcohol group as acceptor (GO:0016773)	1/254	0.09721273	0.10668044	0	0	11.14568	25.97895	DGKI
kinase activity (GO:0016301)	1/280	0.10668044	0.10668044	0	0	10.09370	22.58887	DGKI

Table 6
HMDB Metabolite Enrichment in AIDS

Term	Overlap	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds Ratio	Combined Score	Genes
C19H39O7P (HMDB07849)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
C21H43O7P (HMDB07850)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
C21H41O7P (HMDB07851)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
C21H39O7P (HMDB07852)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
1-hexadecanoyl-sn-glycero-3-phosphate (HMDB07853)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
1-octadecanoyl-sn-glycero-3-phosphate (HMDB07854)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
1-(9Z-octadecenoyl)-sn-glycero-3-phosphate (HMDB07855)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
C21H39O7P (HMDB07856)	1/31	0.012335	0.020772	0	0	95.05714	417.80628	DGKI
PA(16:0/16:0) (HMDB00674)	1/43	0.017074	0.020772	0	0	67.85714	276.19223	DGKI
PA(16:0/18:1(11Z)) (HMDB07858)	1/43	0.017074	0.020772	0	0	67.85714	276.19223	DGKI

Table 7
KEGG Pathway Enrichment (2019 Human) in AIDS

Term	Overlap	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds Ratio	Combined Score	Genes
Glycerolipid metabolism	1/61	0.02414513	0.048659	0	0	47.45714	176.71487	DGKI
Glycerophospholipid metabolism	1/97	0.03815407	0.048659	0	0	29.60714	96.70056	DGKI
Phosphatidylinositol signaling system	1/99	0.03892716	0.048659	0	0	29.0	94.13583	DGKI
Choline metabolism in cancer	1/99	0.03892716	0.048659	0	0	29.0	94.13583	DGKI
Phospholipase D signaling pathway	1/148	0.05769879	0.05769879	0	0	19.28571	55.01287	DGKI

The high effect size SNPs (OR >3) formed a separate cluster, possibly representing high-impact genetic variants. SNPs with moderate OR values but low p-values (-log10 scale) clustered separately, suggesting that they may be moderate risk SNPs with strong statistical evidence. PCA further validated these clusters, indicating that specific genomic factors influence disease progression differently. These insights could guide functional validation studies and targeted therapeutic approaches.

Conclusion

This study highlights key genetic and molecular mechanisms influencing AIDS progression, identifying significant SNPs in PARD3B, LTF, CCRL2, NBPF14, DGKI, RPH3AL and H2AFY, which impact immune regulation, inflammation and viral replication control. Functional enrichment analyses revealed strong associations with immune cell activity, epithelial cell polarity and lipid metabolism, suggesting their role in HIV pathogenesis.

Additionally, DGKI's involvement in lipid signaling and phosphatidylinositol pathways points to metabolic disruptions influencing immune function and viral persistence. These findings provide valuable insights into biomarkers and therapeutic targets that could inform personalized treatment approaches for HIV/AIDS. Further research is needed to validate these associations and to explore potential gene-based interventions.

References

1. Connor R.I., Sheridan K.E., Ceradini D., Choe S. and Landau N.R., Change in coreceptor use correlates with disease progression in HIV-1-infected individuals, *J. Exp. Med.*, **185**, 621–628 **(1997)**

2. Dalmasso C., Carpentier W., Meyer L., Rouzioux C., Goujard C., Chaix M.L., Lambotte O., Avettand-Fenoel V., Le Clerc S. and de Senneville L.D., Distinct genetic loci control plasma HIV-RNA and cellular HIV-DNA levels in HIV-1 infection: the ANRS Genome Wide Association 01 study, *PLoS One*, **3**, e3907 **(2008)**

3. De Roda Husman A.M., Koot M., Cornelissen M., Brouwer M., Broersen S.M., Bakker M., Roos M.T.L., Prins M., De Wolf F. and Coutinho R.A., Association between CCR5 genotype and the clinical course of HIV-1 infection, *Ann. Intern. Med.*, **127**, 882–890 **(1997)**

4. Deacon N.J., Tsykin A., Solomon A., Smith K., Ludford-Menting M., Hooker D.J., McPhee D.A., Greenway A.L., Ellett A. and Chatfield C., Genomic structure of an attenuated quasi species of HIV-1 from a blood transfusion donor and recipients, *Science*, **270**, 988–991 **(1995)**

5. Dean M., Carrington M., Winkler C., Huttley G.A., Smith M.W., Allikmets R., Goedert J.J., Buchbinder S.P., Vittinghoff E. and Gomperts E., Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene, *Science*, **273**, 1856–1862 **(1996)**

6. Fellay J., Ge D., Shianna K.V., Colombo S., Ledergerber B., Cirulli E.T., Urban T.J., Zhang K., Gumbs C.E. and Smith J.P., Common genetic variation and the control of HIV-1 in humans, *PLoS Genet.*, **5**, e1000791 **(2009)**

7. Gao X., Bashirova A., Iversen A.K., Phair J., Goedert J.J., Buchbinder S., Hoots K., Vlahov D., Altfeld M. and O'Brien S.J., AIDS restriction HLA allotypes target distinct intervals of HIV-1 pathogenesis, *Nat. Med.*, **11**, 1290–1292 **(2005)**

8. Ioannidis J.P.A., O'Brien T.R., Rosenberg P.S. and Contopoulos-Ioannidis D.G., Genetic effects on HIV disease progression, *Nat. Med.*, **4**, 536 **(1998)**

9. Koot M., Keet I.P.M., Vos A.H.V., De Goede R.E.Y., Roos M.T.L., Coutinho R.A., Miedema F., Schellekens P.T.A. and Tersmette M., Prognostic value of human immunodeficiency virus type 1 biological phenotype for rate of CD4+ cell depletion and progression to AIDS, *Ann. Intern. Med.*, **118**, 681–688 **(1993)**

10. Kostrikis L.G., Huang Y., Moore J.P., Wolinsky S.M., Zhang L., Guo Y., Deutsch L., Phair J., Neumann A.U. and Ho D.D., A chemokine receptor CCR2 allele delays HIV-1 disease progression and is associated with a CCR5 promotor mutation, *Nat. Med.*, **4**, 350–353 **(1998)**

11. Kwa D., van Rij R.P., Boeser-Nunnink B., Vingerhoed J. and Schuitemaker H., Association between an interleukin-4 promoter polymorphism and the acquisition of CXCR4 using human immunodeficiency virus type 1 variants, *AIDS*, **17**, 981–985 **(2003)**

12. Le Clerc S., Limou S., Coulonges C., Carpentier W., Dina C., Taing L., Delaneau O., Labib T., Sladek R. and Deveau C., Genomewide association study of a rapid progression cohort identifies new susceptibility alleles for AIDS (ANRS Genomewide Association Study 03), *J. Infect. Dis.*, **200**, 1194–1201 **(2009)**

13. Limou S., Le Clerc S., Coulonges C., Carpentier W., Dina C., Delaneau O., Labib T., Taing L., Sladek R. and Deveau C., Genomewide association study of an AIDS-nonprogression cohort emphasizes the role played by HLA genes (ANRS Genomewide Association Study 02), *J. Infect. Dis.*, **199**, 419–426 **(2009)**

14. Liu R., Paxton W.A., Choe S., Ceradini D., Martin S.R., Horuk R., MacDonald M.E., Stuhlmann H., Koup R.A. and Landau N.R., Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection, *Cell*, **86**, 367–377 **(1996)**

15. Migueles S.A., Sabbaghian M.S., Shupert W.L., Bettinotti M.P., Marincola F.M., Martino L., Hallahan C.W., Selig S.M., Schwartz D. and Sullivan J., HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors, Proc. Natl. Acad. Sci. U.S.A., **97**, 2709–2714 **(2000)**

16. Mummidi S., Ahuja S.S., Gonzalez E., Anderson S.A., Santiago E.N., Stephan K.T., Craig F.E., O'Connell P., Tryon V. and Clark R.A., Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression, *Nat. Med.*, **4**, 786–793 **(1998)**

17. Nakayama E.E., Hoshino Y., Xin X., Liu H., Goto M., Watanabe N., Taguchi H., Hitani A., Kawana-Tachikawa A. and Fukushima M., Polymorphism in the Interleukin-4 promotor affects acquisition of Human Immunodeficiency Virus Type 1 Syncytium-Inducing Phenotype, *J. Virol.*, **74**, 5452–5459 **(2000)**

18. Nakayama E.E., Meyer L., Iwamoto A., Persoz A., Nagai Y., Rouzioux C., Delfraissy J.F., Debre P., McIlroy D. and Theodorou I., Protective Effect of Interleukin-4–589T Polymorphism on Human Immunodeficiency Virus Type 1 Disease Progression: Relationship with Virus Load, *J. Infect. Dis.*, **185**, 1183–1186 **(2002)**

19. Navis M., Schellens I., van Baarle D., Borghans J., van Swieten P., Miedema F., Kootstra N. and Schuitemaker H., Viral Replication Capacity as a Correlate of HLA B57/B5801-Associated Nonprogressive HIV-1 Infection, *J. Immunol.*, **179**, 3133–3143 **(2007)**

20. Pereyra F., Jia X., McLaren P.J., Telenti A., de Bakker P.I., Walker B.D., Ripke S., Brumme C.J., Pulit S.L. and Carrington M., The major genetic determinants of HIV-1 control affect HLA class I peptide presentation, *Science*, **330**, 1551–1557 **(2010)**

21. Rappaport J., Cho Y.Y., Hendel H., Schwartz E.J. and Schachter F., 32 bp CCR-5 gene deletion and resistance to fast progression in HIV-1 infected heterozygotes, *Lancet*, **349**, 922–923 **(1997)**

22. Samson M., Libert F., Doranz B.J., Rucker J., Liesnard C., Farber C.M., Saragosti S., Lapouméroulie C., Cognaux J. and Forceille C., Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene, *Nature*, **382**, 722–725 **(1996)**

23. Smith M.W., Dean M., Carrington M., Winkler C., Huttley G.A., Lomb D.A., Goedert J.J., O'Brien T.R., Jacobson L.P. and Kaslow R., Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression, *Science*, **277**, 959–965 **(1997)**

24. Troyer J.L., Nelson G.W., Lautenberger J.A., Chinn L., McIntosh C., Johnson R.C., Sezgin E., Kessing B., Malasky M. and Hendrickson S.L., Genome-wide association study implicates PARD3B-based AIDS restriction, *J. Infect. Dis.*, **203**, 1491–1502 **(2011)**

25. van Rij R.P., Broersen S., Goudsmit J., Coutinho R.A. and Schuitemaker H., The role of a stromal cell-derived factor-1

chemokine gene variant in the clinical course of HIV-1 infection, *AIDS*, **12**, F85–F90 **(1998)**

26. van Rij R.P., De Roda Husman A.M., Brouwer M., Goudsmit J., Coutinho R.A. and Schuitemaker H., Role of CCR2 genotype in the clinical course of syncytium-inducing (SI) or non-SI human immunodeficiency virus type 1 infection and in the time to conversion to SI virus variants, *J. Infect. Dis.*, **178**, 1806–1811 **(1998)**

27. Wichukchinda N., Nakayama E.E., Rojanawiwat A., Pathipvanich P., Auwanit W., Vongsheree S., Ariyoshi K., Sawanpanyalert P. and Shioda T., Protective effects of IL4-589T and RANTES-28G on HIV-1 disease progression in infected Thai females, AIDS, **20**, 189–196 **(2006)**

28. Winkler C., Modi W., Smith M.W., Nelson G.W., Wu X., Carrington M., Dean M., Honjo T., Tashiro K. and Yabe D., Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant, *Science*, **279**, 389–393 **(1998)**.

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