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Analysis of Genetic Diversity of Envelope Genes Obtained from Patients of HIV Positive

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Article History	*Abstract*
	Human immunodeficiency virus type 1 (HIV-1) is the retrovirus of human origin that has been responsible for the global HIV/AIDS pandemic, resulting in the loss of more than 30 million lives over a span of forty years. The global prevalence of HIV infection is estimated to affect roughly 40 million individuals, therefore rendering it a significant public health issue. Due to the implementation of antiretroviral medication (ART), HIV has transitioned into a chronic condition that may be effectively controlled and maintained. Regrettably, the present state of affairs reveals a lack of both a vaccine and a cure for HIV/AIDS, notwithstanding the significant advancements achieved through antiretroviral therapy (ART) in enhancing the well-being of individuals living with HIV.

1. Introduction

During the initial phases of the pandemic, it became evident that there is significant variability in the susceptibility of individuals to HIV infection. Certain demographic groups, such as individuals who engage in intravenous drug use and men who have sex with men (MSM), saw a disproportionate impact due to socioeconomic and behavioural characteristics that contributed to this variation. A minority of individuals, even within the population most heavily exposed to the virus, maintained a seronegative status for HIV. In a similar vein, it should be noted that age and co-morbidities, while recognized as significant determinants, only offer a partial explanation for the observed variations in the progression of HIV infection. These variations encompass the duration between infection and the diagnosis of AIDS, as well as the occurrence of opportunistic infections or malignancies. The integration of clinical and epidemiological observations indicates that genetic diversity in genes and pathways associated with the retroviral life cycle, as well as innate and adaptive immunity against HIV, contribute to the modulation of individual responses to the infection.

HIV gains access to its major target cell, the CD4+ T lymphocyte, via binding to CD4 and the co-receptor CC-chemokine receptor 5 (CCR5). The present connection instigates an intricate intracellular life cycle that ultimately results in the formation of novel viruses through the fusion of viral and human cell membranes. CD8+ T cells, sometimes referred to as cytotoxic T lymphocytes (CTLs), play a crucial role in the innate immune response to HIV infection. Upon first introduction of HIV into a host, there is a rapid replication process that results in a substantial increase in viral load within the plasma. This viral load is quantified as the number of copies of the HIV RNA genome per millilitre of plasma. The focused CD8+ T cell response plays a role in partially regulating this viral burden. HLA class I molecules, which exhibit considerable diversity, assume a pivotal role in the immune response by facilitating the presentation of epitopes, which are minute fragments derived from viruses, on the cellular membrane of infected cells. Cytotoxic T lymphocytes (CTLs) effectively eradicate cells that

are infected with the human immunodeficiency virus (HIV) by specifically identifying these cells as possessing a particular epitope. Although the immune system may not achieve total eradication of the virus, a more robust immune response is correlated with reduced viral load and decelerated disease progression during the chronic stage of an untreated infection.

HIV, a retrovirus, induces pathogenicity by impairing the genetic material of its host organisms. Indeed, the virus has the capacity to reproduce and disseminate by exploiting the molecular apparatus of the host cell. Additionally, it has a remarkable capability to integrate a DNA replica of its RNA genome into the chromosomal structure of a host cell. The long-term persistence of HIV within cellular reservoirs, resulting from its integration into the human genome, poses significant challenges for the development of therapeutic strategies aimed at achieving full eradication.

The reevaluation of the old Delphic maxim "know thyself" is crucial in the ongoing battle against HIV. The human immunodeficiency virus (HIV) has significant proficiency in infiltrating human cells and subduing the immune system. Consequently, there exists a pressing necessity to expand our comprehension of the human genome and the intricate mechanisms within the human body in order to effectively address this formidable challenge. The exploration of human genetic diversity at the DNA level has historically faced significant limitations due to technological constraints. However, the advancement of novel and enhanced instruments has recently invigorated the progress in this field. Recent progress in understanding human genetic diversity, as well as advancements in genotyping and sequencing technology, bioinformatics, and data science, have enabled the exploration of genetic factors that influence how individuals respond to HIV. This includes investigating factors related to resistance and susceptibility to infection, as well as the progression of the disease in people living with HIV.

The present review commences by providing a concise overview of the historical progression of scientific and theoretical breakthroughs that have propelled investigations into the HIV host genome. Subsequently, we delineate the HLA class I region and CCR5 locus as the two principal genetic factors that modulate the progression of HIV infection. Subsequently, a discussion ensues regarding the feasibility of conducting longitudinal evaluations of genetic interactions between hosts and pathogens, facilitated by recent advancements in the understanding of human and HIV genomes. The subsequent section of this discourse focuses on the potential advancements in translational research and clinical applications of human genomics in the context of HIV. We subsequently conclude by elucidating how the acquisition of genomic knowledge is positioned to yield favourable outcomes for People Living with HIV (PLWH). Notably, this will be achieved through the implementation of pharmacogenomic interventions and the stratification of care based on polygenic risk scores (PRS).

2. Literature Review

Aa **Yadav, S., Senapati, S., Kulkarni, S. S., & Singh, J. P. (2023).** This work aims to investigate the clinical application of surface-enhanced Raman scattering (SERS) for the detection of HIV-1 viral load and the prediction of disease prognosis. The reference provided is a citation for an article in the Journal of Photochemistry and Photobiology B: Biology, volume 239, with the identification number 112629. There is a pressing need for cost-effective point-of-care diagnostic tests capable of detecting even the smallest viral load of diseases such as human immunodeficiency virus (HIV)-associated acquired immune deficiency syndrome (AIDS) in resource-limited regions. This research paper presents an investigation into the application of surface enhanced Raman spectroscopy (SERS) in the identification and assessment of HIV-positive clinical samples, encompassing a broad spectrum of viral load levels spanning from 200 to 1 million copies/ml. The technology exhibits innovation, rapidity, and ease of deployment in practical settings.

Mandizvo, T., Gumede, N., Ndlovu, B., Ndlovu, S., Mann, J. K., Chopera, D. R., ... & Ndung'u, T. (2022). Subtle Longitudinal Alterations in Environmental Sequence This study investigates the potential amplification of variations in susceptibility to broadly neutralizing antibodies (bNAbs) subsequent to the onset of acute infection with HIV-1 subtype C. The citation provided is from the Journal of Virology, volume 96, issue 24, and corresponds to the article with the identifier e01270-22. The prevention and treatment strategies for HIV-1 require the utilization of broadly neutralizing antibodies (bNAbs) capable of inhibiting the transmission of both the initial viral strain and the viral

reservoir. The process of selecting rational broadly neutralizing antibodies (bNAbs) for clinical development can be facilitated by identifying genetic patterns that influence the variability of neutralization and by evaluating the sensitivity of circulating viruses to bNAbs. A total of 326 individual environmental genomes were examined in this study. These genomes were obtained from nine individuals who were monitored over a period of time after the initial identification of plasma viremia. The time span ranged from 300 to 1,709 days post-infection before the commencement of antiretroviral medication (ART), with a median duration of 724 days. Additionally, samples were collected from the same individuals after they had been on ART for a minimum of one year.

Parker, I., Khalil, G., Martin, A., Martin, M., Vanichseni, S., Leelawiwat, W., ... & Curtis, K. A. (2021). The antibody responses of individuals infected with HIV-1 are modified when they are concurrently utilizing preexposure prophylaxis. The citation provided is from the academic journal AIDS Research and Human Retroviruses, specifically volume 37, issue 3, and covers pages 189-195. The efficacy of preexposure prophylaxis (PrEP) in the prevention of HIV infection is contingent upon its consistent utilization. In order to comprehend the possible ramifications on the prompt identification and management, it is imperative to delineate the influence of Pre-Exposure Prophylaxis (PrEP) on the immune system's production of HIV antibodies in individuals who experience breakthrough infections. The Bangkok Tenofovir Study (BTS) observed the HIV-1-specific antibody responses of 42 people who inject drugs (PWID) participating in the study. Among these individuals, 28 were assigned to the placebo group and 14 were assigned to the pre-exposure prophylaxis (PrEP) group. These participants had infected HIV while on PrEP, and their antibody responses were tracked longitudinally. The plasma sample underwent testing to determine the existence of HIV-1 antibodies and their affinity towards three distinct envelope proteins (gp41, gp160, and gp120) using a customized Bio-Plex system manufactured by Bio-Rad Laboratories, located in Hercules, CA. The researchers conducted a time-to-event analysis for each biomarker to determine the frequency at which trial participants in the PrEP and placebo groups exceeded the predefined short- and long-term assay thresholds. The study employed mixed-effects models to investigate longitudinal fluctuations in antibody levels and avidity.

Mohabatkar, H., & Kar, S. K. (2004). Prediction of exposed domains of envelope glycoprotein in Indian HIV-1 isolates and experimental confirmation of their immunogenicity in humans. *Brazilian journal of medical and biological research*, *37*, 675-681. Here, we detail how variations in envelope glycoprotein subtypes affect the seroreactivity of linear antigenic epitopes among HIV-1 isolates from various regions. Potential antigenic sites in the envelope glycoprotein (gp120 and gp4l) of this virus were predicted using computational methods. Hydrophilicity, flexibility, accessibility, inverted hydrophobicity, and secondary structure parameters were taken into account after retrieving the protein sequences of interest from databases. We found multiple putative antigenic epitopes in the envelope glycoprotein of HIV-1 subtype B (IIIB) virus. Peptides were synthesized using Merrifield and Fmoc chemistry solid-phase peptide synthesis methods. These synthesized peptides largely mirrored the C2, V3, and CD4 binding sites of gp120, as well as a portion of gp41's ectodomain.

Andrade, V. M., Mavian, C., Babic, D., Cordeiro, T., Sharkey, M., Barrios, L., ... & Stevenson, M. (2020). A small subset of HIV-1 variations that specifically target macrophages has been detected during the resurgence of viral replication after the cessation of analytical treatment. The citation provided is from an academic journal, namely the Proceedings of the National Academy of Sciences. The article is found in volume 117, issue 18, and spans pages 9981-9990. The reactivation of HIV-1 from latent reservoirs inside cells can occur when the administration of antiretroviral medicine (ART) is discontinued. The occurrence of renewed viremia following the cessation of medication may offer insights into the composition of these reservoirs. Researchers successfully identified a subset of macrophage-tropic (M-tropic) viruses in a collection of recombinant viruses generated with distinct envelope genes, utilizing plasma samples from six patients undergoing analytic treatment interruption (ATI).

Power, C., McArthur, J. C., Nath, A., Wehrly, K., Mayne, M., Nishio, J., ... & Chesebro, B. (1998). The infection of the brain by Human Immunodeficiency Virus Type 1 (HIV-1) leads to the multiplication of the virus principally in macrophages and microglia. Although viral genome and proteins have been frequently detected in the brains of AIDS patients, both with and without HIV dementia, it is important to note that only a minority, specifically 20% of AIDS patients, develop

dementia. In order to explore the impact of viral envelope gene variation on the prevalence of dementia, we conducted an analysis on specific regions of variability within the viral envelope gene that were obtained from the brains of individuals diagnosed with AIDS. Significant sequence variations were observed in the brain-derived HIV-1 V1-V2 envelope sequences obtained from a cohort of seven AIDS patients with dementia and six AIDS patients without dementia.

Gao, F., Morrison, S. G., Robertson, D. L., Thornton, C. L., Craig, S., Karlsson, G., ... & Hahn, B. H. (1996). The existing understanding of the immunobiology of the envelope of human immunodeficiency virus type 1 (HIV-1) has primarily been obtained from the examination of subtype B viruses. However, it is important to note that these viruses constitute a minority of the strains that are currently being transmitted globally. In order to get a panel of envelope genes that accurately reflects genetic diversity, we employed PCR amplification, cloning, and sequencing techniques to analyse the full gp160 coding areas of 35 original HIV-1 isolates. These isolates were obtained from main epicentres of the ongoing AIDS pandemic and were grown in peripheral blood mononuclear cells. The examination of the inferred amino acid sequences yielded significant disparities from the standard subtype B strains. These disparities encompassed alterations in the quantity and arrangement of cysteine residues, notable variations in the lengths of hypervariable areas, and untimely terminations in the gp41 domain.

Hiv-Controlling Hla Variants

The genetic variability of the major histocompatibility complex (MHC) located on human chromosome 6 is significant. The extended major histocompatibility complex (MHC), comprising around 400 genes, has a crucial role in regulating both the innate and adaptive immune responses. This genomic region spans 7.6 megabases (Mb) inside the human genome. Recent studies using preprints have shown evidence of significant illness linkages in huge biobanks comprising diverse populations. These relationships are established by associating specific alleles at the classical class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DQ, HLA-DP) genes to a broad spectrum of autoimmune, inflammatory, and infectious disorders. These findings have been thoroughly addressed in the references cited. In order to initiate an adaptive immune response against an infectious disease, the immune system of the human body employs class I HLA proteins to exhibit endogenous peptides on the outer surface of infected cells. These peptides are subsequently identified by cytotoxic T lymphocytes (CTLs).

Irrespective of an individual's place of birth or familial lineage, research has demonstrated that the genotype at class I HLA genes plays a pivotal role as the primary host genetic factor influencing HIV set point viral load (spVL) and the course of the disease. The initial genome-wide association studies (GWAS) conducted on HIV set point viral load (spVL) and HIV controllers revealed that single nucleotide polymorphisms (SNPs) were identified alone in strong linkage disequilibrium with conventional HLA-B alleles. This observation places this discovery into the broader context of the entire genome. The utilization of computational techniques that exploit the linkage disequilibrium relationship between single nucleotide polymorphisms (SNPs) and sequence-based human leukocyte antigen (HLA) types in reference populations enables the precise estimation of classical HLA types from genome-wide association study (GWAS) data. This is achieved even though array-based genotyping methods for DNA samples do not provide direct identification of classical HLA alleles.

The amino acid position 97 underwent a significant alteration, exhibiting six distinct forms, one of which is the valine variant exclusive to the B*57 haplotype. The study detailed in a recent preprint identified specific amino acid locations in HLA-B (positions 67, 97, and 156) and HLA-A (position 77) that were found to be independently related with severe progressive viral load (spVL) in a multi-ethnic population of over 12,000 people living with HIV (PLWH). The impact of spVL is influenced by classical HLA alleles situated at the HLA-B loci, whereas the HLA-A locus suggests that HLA-A functions autonomously from HLA-B. The display of epitopes is considered to play a crucial role in the innate inhibition of HIV replication. It is noteworthy that all four sites are situated within the peptide-binding groove of the corresponding HLA protein. Furthermore, it should be noted that there was a lack of data suggesting any variation in the consequences of these polymorphic sites based on ancestry. This finding suggests that these sites hold biological significance across diverse populations globally.

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Various mechanisms have been proposed to elucidate the variations in the effects on HIV progression among different alleles of the identical HLA gene. Several protective alleles, including B*57:01 (which contains valine at position 97) and B*27:05 (which contains cysteine and asparagine at positions 67 and 97, respectively), have been demonstrated to induce compensatory mutations in the HIV genome. This leads to a reduction in viral fitness, as observed in epitope specificity studies. The proliferative ability of cytotoxic T lymphocytes (CTLs) is enhanced in individuals carrying certain protective HLA alleles. Additionally, these individuals exhibit stronger polyfunctional responses of CTLs. These findings indicate that the effector function of CTLs, resulting from epitope presentation, may contribute to the management of HIV infection, independent of variations in epitope specificity.

The Phenomenon of Epitope Presentation Heterogeneity Within the Host

The findings of a genome-wide association research provide evidence that individuals with varying HLA alleles at each class I gene exhibit significantly reduced viral load compared to persons who are homozygous. This reduction in viral load can be attributed to the cumulative effect of each allele. The heterozygote advantage, which supports the notion that a wide range of presentation is advantageous in preventing HIV development, is likely attributed to the capacity to display diverse HIV epitopes. In a recent study, an in-silico analysis was conducted to predict the binding affinity between 9-mer peptides in the HIV proteome and HLA proteins expressed by different class I alleles. This analysis aimed to get deeper insights into this particular topic. The relationship between the extent of the peptide repertoire bound by an individual's HLA protein isoforms and the spVL was determined by examining the association between these expected affinities and relevant clinical and genetic information. Furthermore, the HLA-B isoforms exhibited the most significant decrease in viral load and the broadest projected range of epitope recognition. However, it should be noted that subsets of epitopes, which are exclusively exhibited by protective HLA isoforms, account for a greater proportion of the observed variance in set point viral load (spVL) compared to the entire expected set. This implies that the protective capacity of an individual's HLA alleles cannot be solely attributed to the number of epitopes, indicating the presence of other factors at play. The observation is supported by both in silico and functional investigations, which have demonstrated that HIV epitopes containing structurally important residues are more likely to be targeted by protective HLA isoforms.
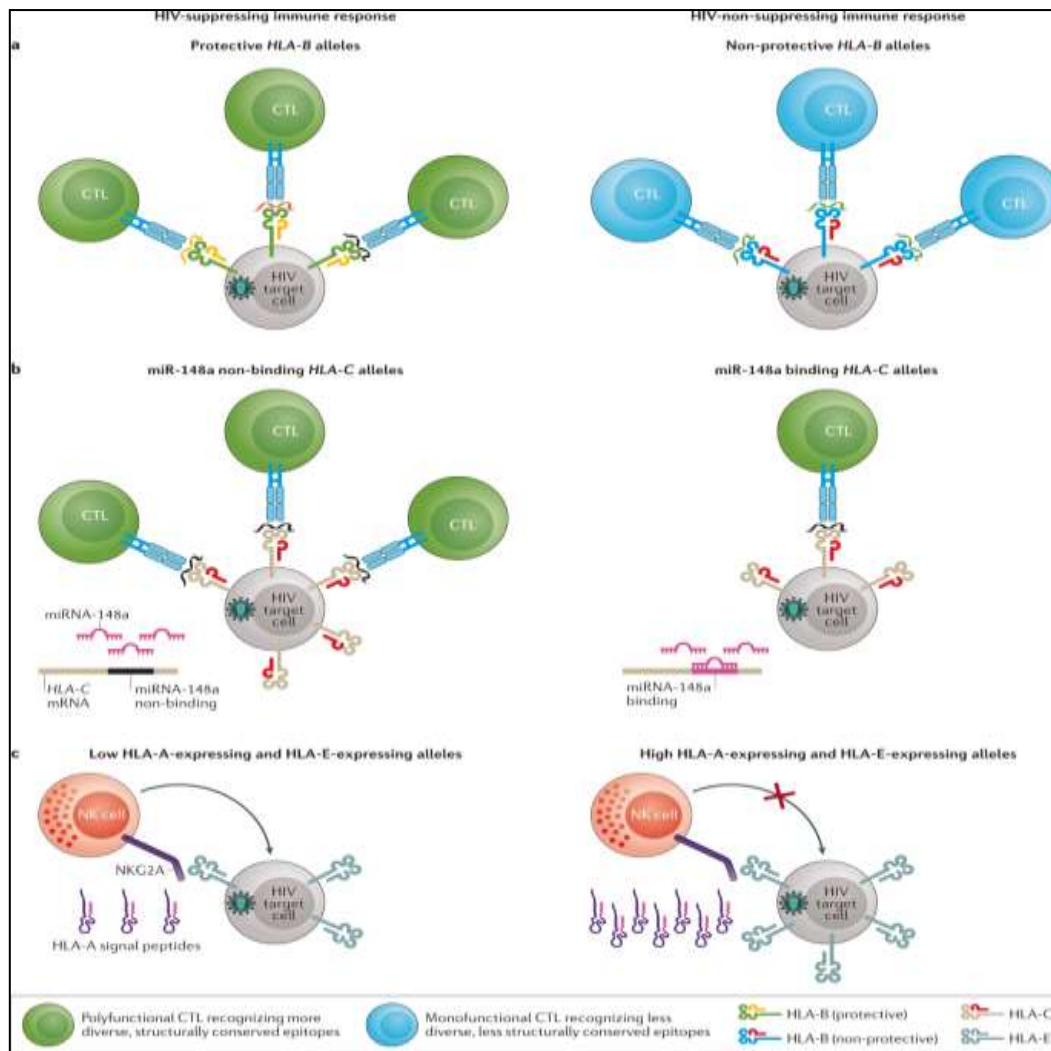
Figure 1: Impact of HLA Class on HIV Suppression: Traditional and Non-Classical Mechanisms

The Role of HLA Class Influence in HIV Suppression at the Molecular and Cellular Levels (a) More structurally diverse HIV epitopes are exhibited by HIV-infected cells in the presence of protective HLA-B alleles. Protective allele interactions are more likely to trigger polyfunctional cytotoxic T lymphocyte (CTL) responses. (b)There is a wide range of variation in the surface expression of HLA-C protein isoforms on infected cells. HLA-C alleles that are defective in their ability to display peptide on the cell surface and elicit robust CTL responses are those that lack a binding site for microRNA-148a (miRNA-148a) in the 3′ untranslated region of their mRNAs. (c)Across a broad spectrum of HLA-A alleles, there is a positive correlation between the amount of HLA-A signal peptide expressed and the amount of HLA-E peptide expressed. High levels of HLA-E prevent NK cells from eliminating infected cells through interfering with the NKG2A receptor.

The Ccr5 Polymorphism Associated With Hiv Infection

One of the most extensively disseminated instances of genetic variation in the human population impeding the transmission of diseases pertains to the discovery that individuals possessing two copies of a loss-of-function mutation in the gene responsible for encoding the cell receptor CCR5 exhibit resistance to HIV infection. CD4+ T cells, which belong to the monocytes and lymphocytes category, are the principal cellular targets of HIV infection. These cells carry a chemokine receptor known as CCR5 on their cell surfaces. During the initial phases of infection, the HIV envelope protein gp120 establishes contact with CD4 and CCR5 receptors located on the cellular surface. This interaction facilitates the fusion of the viral and host cell membranes, allowing for the subsequent release of viral DNA into the targeted cell. The original finding of resistance to infection in individuals with homozygous loss-of-function alleles at CCR5 was facilitated by the study of multiple-exposure non-

infected men who have sex with men (MSM). The individuals in question were discovered to possess a 32-base pair deletion inside the CCR5 gene, known as the CCR532 allele. This genetic alteration leads to the production of a protein that lacks functionality, resulting in the absence of functional CCR5 on the surface of cells. Consequently, the inability of HIV to enter target cells is observed. The allele CCR5Δ32 is observed in individuals of European ancestry at a prevalence of 10%, with homozygosity occurring at a frequency of 1%. Its occurrence is comparatively lower among southern Europeans as opposed to those residing in northern regions, and it is absent in populations from other continents. Individuals that possess compound heterozygosity, characterized by the presence of one copy of CCR5Δ32 in addition to another loss-of-function CCR5 variant, also exhibit resistance to infection. However, it is important to note that such occurrences are exceedingly rare.

Furthermore, the identification of individuals with diminished CCR5 expression as being impervious to HIV infection not only served as a catalyst for the initial morally challenging endeavour in human embryo manipulation, but also directly facilitated the development of Maraviroc, a pharmacological agent that acts as a CCR5 antagonist to combat viral infections. Bone marrow transplants conducted between donors and recipients with HIV infection, specifically those who are homozygous for the CCR5Δ32 mutation, have garnered significant interest due to their association with the only two documented instances of sustained HIV remission. There exists the potential for the upscaling of this impact to a magnitude that might effectively halt the spread of the pandemic. However, it is worth noting that the successful replication of this phenomenon in meticulously engineered autologous stem cell models has not been achieved to a satisfactory extent. There have been documented cases of infection in individuals homozygous for the CCR5Δ32 mutation, indicating that viruses that utilize the CXCR4 co-receptor or possess dual-tropic capabilities can overcome this protective mechanism.

The CCR5 polymorphism and its correlation with the innate ability to suppress HIV infection. The effectiveness of HIV entry into target cells is diminished when there are reduced quantities of CCR5 protein on the cell surface (Fig. 3a). This observation may provide an explanation for the lower set-point viral load (spVL) and delayed disease development observed in persons who possess a single copy of the CCR5Δ32 variant, as compared to individuals with two functioning copies. Furthermore, the identification of the CCR5 locus was achieved through the utilization of genome-wide association studies (GWAS). Initially, this investigation involved a cohort of 2,560 individuals living with HIV (PLWH) throughout Europe. Subsequently, the study was expanded to include a larger sample size of 6,300 participants from diverse geographical locations. The utilization of proxy single nucleotide polymorphisms (SNPs) was employed as a means to indirectly assess the presence of the CCR5Δ32 allele, as the genotyping platforms utilized in this study were unable to directly screen for its presence. Upon analysis of GWAS data in conjunction with direct CCR5Δ32 genotyping, it was observed that the CCR5Δ32 allele did not exhibit the highest level of association within the region. This finding suggests the existence of multiple distinct genetic factors exerting independent influences at this particular locus. Upon accounting for the confounding effect of CCR5Δ32, a subsequent genetic marker, rs1015164, shown a notable correlation with the set point viral load (spVL). The functional analysis of this variant has demonstrated its regulatory role in modulating the expression of the CCR5 gene, specifically in relation to the long non-coding RNA CCR5-AS. Moreover, the findings of this study indicate that the expression of CCR5 was increased in response to heightened CCR5-AS expression, which occurred as a result of interference with the degradation of CCR5 mRNA mediated by RALY. The aforementioned studies provide evidence that the inherent level of CCR5 expression in an individual has a substantial influence on the progression of untreated HIV infection in a clinical context. The inquiry of whether other functional variations of CCR5 have similar effects remains unresolved.
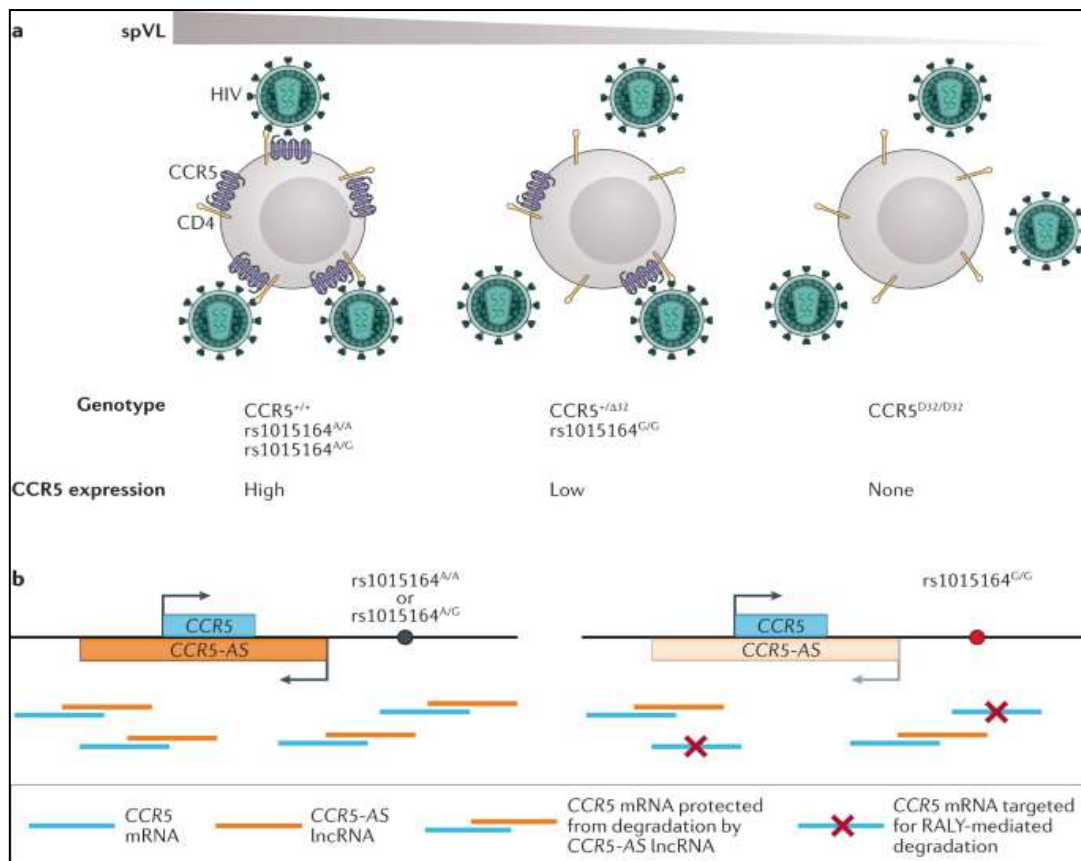
Figure 2: HIV Disease Development Is Affected by CCR5 Expression

The CCR5 receptor plays a significant role in modulating the progression of HIV infection. The user's text is already academic and does not require any rewriting.The diminished presence of CC-chemokine receptor 5 (CCR5) on the cellular surface is attributed to a 32-base pair deletion inside the CCR5 gene, commonly referred to as CCR5Δ32. Heterozygotes exhibit reduced CCR5 expression, which is associated with lower levels of viral load and a slower progression of disease. Individuals who possess two defective copies of the CCR5 gene have significantly reduced surface expression of the receptor, resulting in a heightened level of resistance against HIV infection. In addition, it has been observed that rs1015164, a specific variation in a single nucleotide downstream of the CCR5 gene, has an impact on the expression of CCR5 on the surfaces of cells. The expression of CCR5 on the cell surface is commonly observed in individuals with the reference genotype (A/A) and those who are heterozygous (A/G). However, those who are homozygous for the G/G genotype exhibit a reduction in CCR5 surface expression, which is also associated with lower levels of viral load in the blood.

The Genetic Factors Influencing HIV Drug Response

The impact of human genetic variability on both the course of HIV illness in untreated individuals and the responsiveness to treatment has been demonstrated. The development of a multitude of efficacious therapies that target various stages of the HIV life cycle signifies a significant triumph in combating the virus. The antiviral agents encompass a range of compounds that exhibit inhibitory effects on various stages of the viral replication cycle. For instance, entry inhibitors impede the binding of the viral spike protein gp120 to receptors on host cells, thereby hindering the fusion of the virus with the host cell membranes. Additionally, reverse transcriptase inhibitors, including both nucleoside and non-nucleoside variants, act to impede the activity of the reverse transcriptase enzyme. Integrase inhibitors function by preventing the integration of the viral DNA product into the genome of the host cell. Lastly, protease inhibitors are capable of inhibiting the activity of viral proteases. The impact of human genetic variability on the response to various anti-HIV therapies has been well-documented. This variability has been observed to occasionally lead to the occurrence of severe side effects and treatment stoppage, albeit in rare cases. The HLA-B allele B*57:01 is mostly associated with infection control; however, it

also confers a heightened susceptibility to a severe hypersensitivity reaction to the nucleoside reverse transcriptase inhibitor abacavir. The reason for this phenomenon is that abacavir has a strong affinity for binding, leading to alterations in the binding site of HLA-B*57:01. Consequently, this modification induces a response towards self-peptides. Variations in the genes responsible for encoding drug-metabolizing enzymes, namely CYP2B6, CYP2A6, CYP2C9, CYP2C19, CYP3A, and ABCC2, have been associated with the phenomenon of slow metabolization kinetics of their respective drugs. This can result in the accumulation of drugs in the brain, leading to psychiatric complications and the discontinuation of treatment. Certain populations have reduced pharmaceutical tolerance and efficacy due to variations in the incidence of certain SNPs across different ancestral backgrounds. For example, while comparing populations of Europeans and Africans, it has been observed that the prevalence of the CYP2B6*6 (rs3745274) allele is approximately twice as high in certain African communities. This particular genotype is associated with a reduced rate of metabolism for efavirenz and nevirapine, which are two non-nucleoside reverse transcriptase inhibitors that were formerly suggested by the World Health Organization (WHO) as first-line treatment options. In Zimbabwe, the transition to a treatment protocol consisting of a single pill resulted in a significant number of individuals discontinuing their prescription due to the escalating prevalence of adverse reactions. This underscores the necessity of tailoring treatment approaches to both individual patients and the broader community. Integrase inhibitors and enhanced nucleoside reverse transcriptase inhibitors represent contemporary pharmaceutical interventions for HIV treatment, characterized by increased pharmacokinetic properties and improved safety profiles. Nevertheless, there remains a dearth of understanding regarding the long-term ramifications of these pharmaceuticals and their potential interactions with the unique genetic makeup of individuals.

Genetics Of Complex Traits in HIV Treatment

A number of chronic diseases, including cardiovascular disease, metabolic syndrome, renal disease, and liver fibrosis, exhibit early onset among persons who are HIV-positive and undergoing long-term therapy. The amplification of genetic risk factors for type 2 diabetes mellitus and cardiovascular disease has been observed in people living with HIV (PLWH) who are on medication. It is worth noting that these three diseases, including HIV-uninfected individuals, are recognized to have a significant hereditary component. The extensive adoption of PRS has recently garnered heightened scrutiny. Highly accurate predictions of various metabolic, inflammatory, tumoral, and cardiovascular problems can be made using scores that are calculated by summing the combined effects of several genetic variants within an individual. The examination of predictive risk scores (PRS) in the population of individuals with HIV who are undergoing long-term antiretroviral therapy has only been conducted in recent times. This is despite the recent evidence indicating that PRS can effectively categorize people living with HIV (PLWH) who are at a heightened risk of developing cardiometabolic diseases, thus potentially benefiting from preventive treatments. Additionally, PRS has shown promise in enhancing the accuracy of predicting chronic kidney disease. It is imperative to consider diversity and equity in precision medicine methodologies, similar to other domains of genomics, as not all ancestral populations will exhibit identical polygenic risk scores (PRS).

The results of our study have demonstrated that the host genome has made a substantial contribution to our understanding of HIV biology. The recent findings regarding the impact of HLA diversity on HIV progression within the entirety of the genome have provided more support for the importance of T cell responses in the development of vaccines. In addition, the enhanced capacity to effectively deduce HLA allele types and protein-level diversity from genotyping array data has significantly advanced our comprehension of the role played by amino acid variety in HLA molecules in relation to many medically significant characteristics. The initial implementation of this approach was conducted in genomic investigations pertaining to HIV. Furthermore, in addition to the established influence of the CCR5Δ32 allele, extensive genotyping and large sample sizes have revealed numerous distinct signals within the CCR5 locus. These findings have significantly enhanced our comprehension of the regulatory mechanisms governing CCR5 expression and its role in modulating HIV infection. The availability of extensive genome-wide data for sizable populations of people living with HIV (PLWH) has facilitated the assessment of the accuracy of previous associations between candidate genes, thereby establishing a higher standard for identifying new genetic regions that play a role in restricting HIV infection.

4. Conclusion

In recent years, the advancement of our understanding of the impact of host genetics on HIV susceptibility and progression has encountered significant obstacles, leading to a stagnation in information acquisition. One primary concern pertains to the underrepresentation of individuals who are living with HIV (PLWH) from non-White racial backgrounds in existing studies, resulting in a predominantly European-descended participant pool. The absence of diversity within the field of genomics is a matter of concern in a broad sense. The imperative to extend investigations beyond European cohorts in order to explore potential population-specific effects is underscored by the case of the CCRΔ532 allele, which exclusively occurs within said community. In order to achieve the substantial sample numbers required for genetic discoveries, individuals from non-European backgrounds will require substantial investment in resources and capacity building. There is a need for a paradigm shift towards inclusivity within genomics databases, in order to facilitate a comprehensive understanding of the potential functional implications of genetic variants identified across diverse populations. Researchers have redirected their focus from the natural progression of infection phenotypes to intermediate phenotypes, the pharmacogenomics of long-term medication, comorbidities, and vaccination response, due to the progress in HIV treatment and the widespread adoption of test-and-treat policy. In order to gain a deeper understanding of the impact of genetic variation in crucial innate and adaptive immune genes on disease outcomes, it is imperative to investigate additional forms of genetic variation that are not adequately represented by genotyping arrays. These include the diversity of KIR alleles and T cell receptor usage, which play a significant role in the HLA interaction.

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