REVIEW PAPER

Genetic factors influencing HIV infection: a review

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Abstract

Patient's genetic background, especially in the HLA and CCR5 regions, strongly influences outcomes of HIV-1 infection. Understanding how host genetic factors can contribute to disease progression can help guide intervention strategies. To date, it has been estimated that HLA and CCR5 loci account for around 13% of variations in viremia set point. However, a key question in understanding all complex phenotypes, including HIV-1 progression, is what degree of influence different genetic variants can have.

Presence of a 32bp deletion in *CCR5* gene is associated with slower progression of HIV infection and positive effect on survival among cART untreated patients. Some studies have assessed CCR5-Δ32 as the most potent protective variant, both in immunological and viremic context, unrelated to HLA. Variants of CCR2 (rs1799864) are associated with slower progression to AIDS. CX3CR1 variant (rs3732378) may limit the shift in HIV-1 tropism from R5 to X4. This polymorphism may influence both disease progression and HIV tropism. HLA-C -35 (rs9264942) C/C variant is associated with a significant reduction in HIV viral load compared to T/T homozygote. Moreover, HLA-B*5701 has been confirmed to be more common in patients with slow disease progression to AIDS.

Patient's genetic background, especially in HLA and CCR5 regions, strongly influences the progression of HIV-1 infection as well as viremic and immunologic values.

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Introduction

Human immunodeficiency virus

HIV (human immunodeficiency virus) belongs to the genus of lentiviruses, the retrovirus family. It is a group VI RNA virus (ssRNA-RT) that causes acquired immune deficiency syndrome (AIDS). Most likely it evolved from simian immunodeficiency virus (SIV) [1]. HIV virion is spherical [2] in shape, with a double lipoprotein envelope with glycoproteins, including trans-membrane gp41 and extra-membrane gp120. Inside viral capsid, apart from genetic material, there are reverse transcriptase (RT), HIV protease, and integrase (IN) [3].

HIV is divided phylogenetically into HIV-1 and HIV-2, and both are morphologically indistinguishable from each other, but differ in their genetic sequence and antigenic structure. In Poland, practically, only HIV-1 infections are present. HIV-1 is differentiated into several types, such as M, N, O, and P, and type M is divided into several sub-types, including A-D, F-H, J. and K [4].

HIV infects cells that have a CD4 receptor on their surface. These are mainly T helper lymphocytes, but also macrophages, dendritic cells, microglia, monocytes, eosinophils,

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and thymus cells. Entry into host cell begins at the junction of gp120 glycoprotein with CD4 membrane receptor [5, 6]. The combination of gp120 with CD4 initiates changes in cell conformation revealing coreceptor target sites, of which the main role is played by CCR5 receptor (β-chemokine receptor) and CXCR4 (α-chemokine receptor) [7]. After the gp41 domain is exposed, the sheath fuses with the host cell membrane, and the virion enters the cell cytoplasm. Viral RNA is then reverse transcribed (viral enzyme: reverse transcriptase). Then, the viral DNA is transported to the cell nucleus and incorporated into genetic material of the host cell with the help of viral integrase enzyme. This is followed by translation of genetic material and later, formation of viral proteins. Resulting virions leave the cell by budding and lysing it [8].

The HIV infectious materials are blood, semen, preejaculate, vaginal and rectal secretions, mammary gland secretions, or unfixed human tissues. Routes of HIV infection are associated with infectious materials, i.e., intravenous injections with non-sterile equipment, transfusion of infected blood, occupational exposures, or sexual contacts as well as vertical transmissions (mother-to-child) [9].

Natural course of HIV infection

Natural course of HIV infection consists of early retroviral infection (described in 2003 by Fiebig *et al.* [10]), period of symptomatic HIV infection, and finally, acquired immunodeficiency syndrome (AIDS). According to Fiebig *et al.*, primary HIV-1 infection consists of 6 stages:

- Stage I: HIV in blood samples is only detected by molecular methods.
- Stage II: positive tests for p24 antigen and HIV-1 RNA, and non-reactive EIA antibodies.
- Stage III: RNA of HIV-1-positive, p24 antigen, IgM-reactive EIA-sensitive antibodies, but Western blot without HIV-1 specific bands.
- Stage IV: as stage III, but additionally undefined Western blot results, i.e. presence of HIV-1-specific Western blot bands that do not meet interpretation criteria for FDA-defined Western blot reactive test (reactivity of two of the following three bands: p24, gp41, gp120/160).
- Stage V: as stage IV, but reactive Western blot except for no p31 reactivity.
- Stage VI: as stage V, but complete Western blot reactivity, including p31 band.

From the moment of infection to the onset of full-blown AIDS, an average of about 10 years passes, during which infections associated with immunodeficiency caused by HIV not meeting criteria of opportunistic infections, may occur with varying frequency. The highest level of viremia is observed in patients with acute retroviral disease and later, in the phase of full-blown AIDS. Studies on natural history of HIV infection have estimated that during the first 8 years of follow-up, viremia increases by 0.04 log copies/ml/year [11]. It has been estimated that almost everyone with HIV would experience progression of infection if left untreated. Within this group, special cases of so-called 'elite and viremic controllers': people controlling HIV infection without ARV treatment are found. Elite controllers are patients who, despite being infected, maintain undetectable HIV viral load, and viremic controllers are patients who do not achieve a viral load higher than 50-2,000 copies/ml, despite no antiretroviral treatment [12]. Typical loss of CD4 lymphocytes during HIV infection is 30-40 CD4 lymphocytes/μl/year. It has been observed that, although patients who are elite controllers have undetectable viremia, they can lose CD4 lymphocytes as much as 53/μl/year [11].

Progression of immunodeficiency is inhibited by effective antiretroviral therapy. In addition to its' specific genetic variants, they may have a significant influence on both the immune and viremic response of the host.

Patient's genetic background, especially in the HLA and CCR5 regions, strongly influences the outcomes of HIV-1 infection. Understanding how host genetic factors can contribute to disease progression, can help guide intervention strategies. To date, it has been estimated that the HLA and CCR5 loci account for around 13% of the variation in viremia set point [13]. However, a key question in understanding all complex phenotypes, including HIV-1 progression, is what degree of influence different genetic variants can have [14].

Purpose

The aim of the study was to indicate the current state of knowledge of the impact of genetics on the clinical picture of HIV infection, and to indicate fields, in which further research and assessment of patients can be possible.

Brief description of the status of knowledge

Genetic variants influencing HIV infection

CCR5

CCR5 is one of the main coreceptors involved in HIV-1 entry into the cell. Polymorphisms in the coding gene as well as in the promoter of this gene cause changes in the expression of receptors on the cell surface, and therefore affect the progression of infection [15, 16]. CCR5, also known as CD195, is one of the β-chemokine receptors. The gene that encodes this receptor is found on chromosome 3, the p branch at position 21. CCR5 has many allelic variations, one of which is the delta32 mutation (rs333), which causes deletion of 32 bp, ultimately producing a non-functional receptor. HIV-1 requires the CCR5 and CXCR4 receptors of CD4 lymphocyte to bind to the viral gp120 glycoprotein to enter the cell. When a Δ32 mutation occurs, HIV-1 is unable to enter T cells. People who are homozygous, Δ32-Δ32, are in fact resistant to HIV-1 infection [17]. CCR5-Δ32 occurs in 5-14% of European citizens, but almost in none citizens of Asia and Africa [17, 18].

The presence of a 32 bp deletion in the *CCR5* gene is associated with slower progression of HIV infection and a positive effect on survival among cART untreated patients [19]. Various studies have assessed CCR5-Δ32 as the most potent protective variant, both in immunological and viremic context, unrelated to HLA [13, 20].

The CCR5 promoter (rs1799988) is one of the genetic variants influencing progression to HIV. Its' protective effect involves modifying the expression of CCR5 receptors on the surface of CD4 cells, which changes the ability of HIV to infect other cells [21].

CCR2

CCR2 is a chemokine receptor also known as CD192. It is encoded by the *CCR2* gene, which is responsible for encoding of two isoforms of monocyte chemoattractant-1 CCL2 receptor (responsible for monocyte chemotaxis). This protein is influencing migration of monocytes in inflammatory diseases, such as rheumatoid arthritis, and is also responsible for inflammatory response to tumors. Receptors encoded by this gene mediate agonist-dependent calcium mobilization and inhibit adenylate cyclase.

In an animal model, mice lacking CCR2 were more likely to develop disorders similar to Alzheimer's dementia [22], relatively more eosinophils were detected in their adipose tissue, and had a greater tendency to deposit this tissue with a high-fat diet [23]. HIV-1, in addition to using the CCR5 receptor to enter the cell, may use other receptors, including CCR2. Variants of this trans-membrane receptor are associated with slower progression to AIDS, while its' impact on susceptibility to HIV-1 infection is not fully understood till date [24].

CX3CR1

CX3CR1 is a gene encoding a protein of the same name (CX3CR1), also known as a fractalkine receptor, or a paired G-protein receptor 13 (GPR13), it is a CX3CL1 chemokine binding protein, including fractalkine or neurotactin [25]. In addition to the function of the CX3CL1 ligand for fractalkine, this protein has an influence on adhesion and migration of leukocytes. Moreover, CX3CR1 is also a co-receptor for HIV-1, and plays a role in the entry of the virus into the cell. Modifications of this gene may result in greater susceptibility to HIV-1 infection and faster progression to acquired immune deficiency syndrome (AIDS) [26].

For CX3CR1 variant (rs3732378), an allele of this SNP may limit the shift in HIV-1 tropism from R5 to X4. This effect may be related to the amount of co-receptors on the cell surface. Polymorphism of this chemokine receptor gene may influence both disease progression and HIV tropism [27].

HLA-C

Rs9264942 is a 5' region of the *HLA-C* gene 35kb from the beginning of transcription, which can occur in different genetic variants (T/T, C/T, and C/C). About 10% of European citizens carry the C/C variant, which is associated with a significant reduction in HIV viral load compared to T/T homozygote [28, 29]. HLA-C antigens play a key role in the control of HIV infection, both by acting as ligands for KIR presented on NK cells and directly by presenting the antigen to cytotoxic T lymphocytes [30-32]. Degree of NK lymphocyte activation depends on HLA-C expression [33]. This mechanism is most likely related to the level of HLA-C mRNA and surface expression depending on the given SNP. Among C/C homozygotes, the overall expression level of HLA-C was approximately 1.7 times higher than in cases with –35 T/T rs926494243 genotype. HLA-C influences immune activity in both chronic viral infections, i.e., HIV and HCV, and in autoimmune diseases, such as Crohn's disease, autoimmune liver disease, Graves' disease, and psoriasis [30, 34-37].

*HLA-B*5701*

HLA-B*57 is a split B17 antigen, and its' designation is widely used in care of HIV-infected patients, as it determines abacavir hypersensitivity reaction. Prior to a routine introduction of HLA-B*5701 in HIV testing, approximately 8% of patients receiving abacavir experienced hypersensitivity reactions, including the risk of developing a life-threatening anaphylactic reaction, if re-administered with the drug. Only determination of HLA-B*57 made it possible to reduce this risk, thanks to a positive prediction value (PV) of 61.2%, a negative PV of 95.5%, a sensitivity of 44%, and a specificity of 96% [38]. The prevalence of this genetic variant ranges from 1.53% to 7.75%. In Europe, it is around 4.98% [39]. Earlier studies by the Szczecin Center showed that it occurs in approximately 4.7% of infected Poles [28, 40]. Protective effect of HLA-B*5701 is presumed to result from more effective HLA I T cell response to HIV-1 antigens, which is associated with less mutational escape leading to a better replication control and lower viral load [29, 41-45].

One variant widely associated with a significant protective effect on HIV replication and delayed disease progression is HLA-B*5701 [42]. It has been confirmed that this allele is more common in patients with slow disease progression to AIDS, including elite HIV controllers [42]. HLA-B*5701 may also have a significant effect in diseases, such as psoriasis [46, 47] and drug-related liver injury (DILI) [48]. HLAB5701 is currently the only genetic variant that is routinely and extensively tested in HIV-infected patients.

Many genetic variants affect the course and progression of HIV infection, especially in the HLA and CCR5 regions. In addition, a number of other HLA variants, such as HLA-Cw0102 or HLA-B*2705 as well as allele combinations, including HLA-B*5701-Cw0602, HLA-B*2705-Cw0102, and HLA-B*3801-Cw1203, were associated with modification of HIV titre and differences in the rate of deterioration of immune system, which may affect survival among people living with HIV/ AIDS (PLWHA) [49]. A wide range of genetic variants influencing the progression of infection provides important opportunities in a detailed patient's assessment.

Conclusions

Patient's genetic background, especially in the HLA and CCR5 regions, strongly influences the progression of HIV-1 infection as well as viremic and immunologic values. Of the numerous variants affecting HIV infection, only HLA B5701 is widely performed in clinical practice, which makes it difficult to evaluate more widely some of these variants influencing HIV infection.

Conflict of interest

The authors declare no conflict of interest.

References

1. German Advisory Committee Blood (Arbeitskreis Blut), Subgroup 'Assessment of Pathogens Transmissible by Blood'. Human immunodeficiency virus (HIV). Transfus Med Hemother 2016; 43: 203-222.
2. Oxford JS, Collier LH, Kellam P. Human Virology. Oxford University Press, Oxford 2016. Available from: https://books.google.pl/books?id=rN0dDAAAQBAJ&printsec=frontcover&hl=pl#v=onepage&q&f=false (Accessed: 12.01.2020).
3. Campbell EM, Hope TJ. HIV-1 capsid: the multifaceted key player in HIV-1 infection. Nat Rev Microbiol 2015; 13: 471-483.
4. Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet 2014; 384: 258-271.
5. de Goede AL, Vulto AG, Osterhaus ADME, Gruters RA. Understanding HIV infection for the design of a therapeutic vaccine. Part I: Epidemiology and pathogenesis of HIV infection. Ann Pharm Fr 2015; 73: 87-99.
6. Chereshnev VA, Bocharov G, Bazhan S, et al. Pathogenesis and treatment of HIV infection: the cellular, the immune system and the neuroendocrine systems perspective. Int Rev Immunol 2013; 32: 282-306.
7. Mao Y, Wang L, Gu C, et al. Subunit organization of the membrane-bound HIV-1 envelope glycoprotein trimer. Nat Struct Mol Biol 2012; 19: 893-899.
8. Rossi E, Meuser ME, Cunanan CJ, Cocklin S. Structure, function, and interactions of the hiv-1 capsid protein. Life (Basel) 2021; 11: 100.
9. Shaw GM, Hunter E. HIV transmission. Cold Spring Harb Perspect Med 2012; 2: a006965.
10. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003; 17: 1871-1879.
11. Sabin CA, Lundgren JD. The natural history of HIV infection. Curr Opin HIV AIDS 2013; 8: 311-317.
12. Okulicz JF, Marconi VC, Landrum ML, et al. Clinical outcomes of elite controllers, viremic controllers, and long-term nonprogressors in the US department of defense HIV natural history study. J Infect Dis 2009; 200: 1714-1723.
13. Fellay J, Ge D, Shianna KV, et al. Common genetic variation and the control of HIV-1 in humans. PLoS Genet 2009; 5: e1000791.
14. McLaren PJ, Carrington M. The impact of host genetic variation on infection with HIV-1. Nat Immunol 2015; 16: 577-583.
15. Martin MP. Genetic acceleration of AIDS progression by a promoter variant of CCR5. Science 1998; 282: 1907-1911.
16. Mummidi S, Ahuja SS, Gonzalez E, et al. Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression. Nat Med 1998; 4: 786-793.
17. Samson M, Libert F, Doranz BJ, et al. Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 1996; 382: 722-725.
18. Sabeti PC, Walsh E, Schaffner SF, et al. The case for selection at CCR5-Δ32. PLoS Biol 2005; 3: e378.
19. Parczewski M, Bander D, Leszczyszyn-Pynka M, et al. Risk of all-cause mortality in HIV infected patients is associated with clinical, immunologic predictors and the CCR5 Δ32 deletion. PLoS One 2011; 6: e22215.
20. Ioannidis JPA, Contopoulos-Ioannidis DG, Rosenberg PS, et al. Effects of CCR5-delta32 and CCR2-64I alleles on disease progression of perinatally HIV-1-infected children: an international meta-analysis. AIDS 2003; 17: 1631-1638.
21. Knudsen TB, Kristiansen TB, Katzenstein TL, Eugen-Olsen J. Adverse effect of the CCR5 promoter –2459A allele on HIV-1 disease progression. J Med Virol 2001; 65: 441-444.
22. Gorelick PB. Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. Ann N Y Acad Sci 2010; 1207: 155-162.
23. Bolus WR, Gutierrez DA, Kennedy AJ, Anderson-Baucum EK, Hasty AH. CCR2 deficiency leads to increased eosinophils, alternative macrophage activation, and type 2 cytokine expression in adipose tissue. J Leukoc Biol 2015; 98: 467-477.
24. Singh KK, Barroga CF, Hughes MD, et al. Genetic influence of CCR5, CCR2, and SDF1 variants on human immunodeficiency virus 1 (HIV-1)-related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. J Infect Dis 2003; 188: 1461-1472.
25. Combadiere C, Salzwedel K, Smith ED, Tiffany HL, Berger EA, Murphy PM. Identification of CX3CR1. A chemotactic receptor for the human CX3C chemokine fractalkine and a fusion coreceptor for HIV-1. J Biol Chem 1998; 273: 23799-23804.
26. CX3CR1 C-X3-C motif chemokine receptor 1 [Homo sapiens (human)] – Gene – NCBI. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=1524 (Accessed: 04.12.2020).
27. Parczewski M, Urbańska A, Maciejewska K, Clark J, Leszczyszyn-Pynka M. Association of chemokine receptor gene variants with HIV-1 genotype predicted tropism. HIV Med 2014; 15: 577-586.
28. Leszczyszyn-Pynka M, Aksak-Was B, Urbańska A, Parczewski M. Protective effect of HLA-B*5701 and HLA-C-35 genetic variants in HIV-positive Caucasians from Northern Poland. PLoS One 2015; 10: e0127867.
29. Fellay J, Shianna KV, Ge D, et al. A whole-genome association study of major determinants for host control of HIV-1. Science 2007; 317: 944-947.
30. Blais ME, Dong T, Rowland-Jones S. HLA-C as a mediator of natural killer and T-cell activation: spectator or key player? Immunology 2011; 133: 1-7.
31. Alter G, Altfeld M. NK cells in HIV-1 infection: evidence for their role in the control of HIV-1 infection. J Intern Med 2009; 265: 29-42.
32. Blais ME, Zhang Y, Rostron T, et al. High frequency of HIV mutations associated with HLA-C suggests enhanced HLA-C-restricted CTL selective pressure associated with an AIDS-protective polymorphism. J Immunol 2012; 188: 4663-4670.
33. Tiemessen CT, Paximadis M, Minevich G, et al. Natural killer cell responses to HIV-1 peptides are associated with more activating KIR genes and HLA-C genes of the C1 allotype. J Acquir Immune Def Syndr 2011; 57: 181-189.
34. Suppiah V, Gaudieri S, Armstrong NJ, et al. IL28B, HLA-C, and KIR variants additively predict response to therapy in chronic hepatitis C virus infection in a European cohort: a cross-sectional study. PLoS Med 2011; 8: e1001092.
35. Elahi S, Horton H. Association of HLA-alleles with the immune regulation of chronic viral infections. Int J Biochem Cell Biol 2012; 44: 1361-1365.
36. Venkataramana NK, Kumar SKV, Balaraju S, et al. Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease. Transl Res 2010; 155: 62-70.

37. Majorczyk E, Matusiak Ł, Nowak I, et al. A single nucleotide polymorphism -35kb T > C (rs9264942) is strongly associated with psoriasis vulgaris depending on HLA-Cw*06. Hum Immunol 2014; 75: 504-507.
38. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-B*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis 2008; 46: 1111-1118.
39. Orkin C, Wang J, Bergin C, et al. An epidemiologic study to determine the prevalence of the HLA-B*5701 allele among HIV-positive patients in Europe. Pharmacogenet Genomics 2010; 20: 307-314.
40. Parczewski M, Leszczyszyn-Pynka M, Wnuk A, et al. Introduction of pharmacogenetic screening for the human leucocyte antigen (HLA) B*5701 variant in Polish HIV-infected patients. HIV Med 2010; 11: 345-348.
41. Gao X, O'Brien TR, Welzel TM, et al. HLA-B alleles associate consistently with HIV heterosexual transmission, viral load, and progression to AIDS, but not susceptibility to infection. AIDS 2010; 24: 1835-1840.
42. Migueles SA, Sabbaghian MS, Shupert WL, et al. 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 2000; 97: 2709-2714.
43. Carrington M, O'Brien SJ. The influence of HLA genotype on AIDS. Annu Rev Med 2003; 54: 535-551.
44. Gillespie GMA, Kaul R, Dong T, et al. Cross-reactive cytotoxic T lymphocytes against a HIV-1 p24 epitope in slow progressors with B*57. AIDS 2002; 16: 961-972.
45. Yu XG, Lichterfeld M, Chetty S, et al. Mutually exclusive T-cell receptor induction and differential susceptibility to human immunodeficiency virus type 1 mutational escape associated with a two-amino-acid difference between HLA class I subtypes. J Virol 2007; 81: 1619-1631.
46. Zhao YE, Ma JX, Hu L, Xiao SX, Zhao YL. Meta-analysis of the association between psoriasis and human leucocyte antigen-B. Br J Dermatol 2013; 169: 417-427.
47. Feng BJ, Sun LD, Soltani-Arabshahi R, et al. Multiple loci within the major histocompatibility complex confer risk of psoriasis. PLoS Genet 2009; 5: e1000606.
48. Ho SS, McLachlan AJ, Chen TF, Hibbs DE, Fois RA. Relationships between pharmacovigilance, molecular, structural, and pathway data: revealing mechanisms for immune-mediated drug-induced liver injury. CPT Pharmacometrics Syst Pharmacol 2015; 4: 426-441.
49. Salgado M, Simón A, Sanz-Minguela B, et al. An additive effect of protective host genetic factors correlates with HIV nonprogression status. J Acquir Immune Def Syndr 2011; 56: 300-305.