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Prevalence and the role of CCR5Δ32 heterozygosity in disease progression in HIV positive patients in the Czech Republic

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ABSTRACT

Background: Entry of human immunodeficiency virus type 1 (HIV-1) in target cells is enabled by CD4 receptor and one of two co-receptors, CXCR4 or CCR5. Deletion of 32 bp in CCR5 gene (CCR5Δ32) in both alleles provides strong but not absolute resistance to HIV-1 infection and deletion in one allele slows disease progression to AIDS. Here, we analyzed the prevalence and the role of CCR5Δ32 heterozygosity on the disease progression in HIV positive patients in the Czech Republic.
Patients and methods: A total of 92 HIV-1 seropositive subjects that included 80 Czech individuals from the AIDS center in the Hospital Na Bulovce in Prague were enrolled in CCR5 genotyping as a part of a study of the role of HIV fitness on disease progression. DNA was extracted from patient's peripheral blood mononuclear cells and subjected to real-time PCR with specific probes detecting wild-type and 32 bp-deleted CCR5 variants. A subgroup of 74 antiretroviral therapy-naive patients with more than one year of follow-up was used to determine the role of the CCR5Δ32 heterozygous phenotype in disease progression.
Results: CCR5Δ32 was found heterozygous in 23.8% of 80 Czech HIV-1 seropositive individuals which is very similar to 21% and 24% prevalence reported in HIV negative Czech population. Homozygous mutant variant was not detected. In CCR5Δ32 heterozygous group we observed slightly higher mean $CD4^+$ T-cell count and lower mean plasma viremia levels.
Conclusions: Overall, our study indicates no obvious benefit of CCR5Δ32 heterozygosity on HIV transmission and only small benefit on disease progression in the Czech HIV-1 cohort.

KEYWORDS

HIV-1 – CCR5 co-receptor – CCR5Δ32 – heterozygous polymorphism – disease progression

SOUHRN

Sácká L., Hodek J., Machala L., Malý M., Weber J.: Prevalence a role CCR5Δ32 v progresi onemocnění u HIV pozitivních pacientů v České republice
Úvod: Vstup viru lidské imunitní nedostatečnosti typu 1 (HIV-1) do cílových buněk je umožněn CD4 receptorem a jedním ze dvou koreceptorů CXCR4 nebo CCR5. Delece úseku 32 nukleotidů v genu pro CCR5 (CCR5Δ32) v obou alelách poskytuje silnou, avšak ne absolutní odolnost proti infekci HIV-1 a delece v jedné alele zpomaluje postup nemoci směřující k rozvinutí AIDS. Zde jsme analyzovali prevalenci a roli heterozygotního výskytu CCR5Δ32 na postup onemocnění u HIV pozitivních jedinců v České republice.
Metody: Celkem 92 HIV-1 séropozitivních osob včetně 80 Čechů z AIDS centra v Nemocnici Na Bulovce v Praze bylo zařazeno do genotypizace CCR5, která byla součástí studie role HIV fitness na průběh onemocnění. Z periferních mononukleárních buněk pacienta byla získána DNA, která byla použita k amplifikaci pomocí PCR v reálném čase použitím specifických sond, které detekovaly divokou variantu CCR5 a variantu s 32 nt delecí. Podmnožina 74 pacientů bez antiretrovirové léčby, kteří byli sledováni déle než jeden rok, byla použita k určení role heterozygotního fenotypu CCR5 na průběh nemoci.
Výsledky: Heterozygotní CCR5Δ32 varianta byla nalezena u 23,8 % z 80 českých HIV-1 séropozitivních osob, což je velmi podobné jako publikovaná 21 % a 24 % prevalence u HIV negativní české populace. Homozygotní mutovaná varianta nebyla nalezena. U skupiny osob s heterozygotním CCR5 fenotypem jsme pozorovali slabě zvýšený průměrný počet CD4-pozitivních T-lymfocytů a nižší průměrné hodnoty virémie v plazmě.
Závěr: Celkově, naše studie neukázala žádný zřejmý užitek přítomnosti heterozygotní CCR5Δ32 varianty na přenos HIV a pouze malý užitek na průběh nemoci u české HIV-1 pozitivní kohorty.

KLÍČOVÁ SLOVA

HIV-1 – koreceptor CCR5 – CCR5Δ32 – heterozygotní polymorfismus – progrese nemoci

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INTRODUCTION

Human immunodeficiency virus (HIV) entry into target cells is facilitated both by CD4 receptor and co-receptors. The CXCR4 and CCR5, members of the seven-transmembrane G protein-coupled receptor family, serve as the major co-receptors for T-cell line-tropic and macrophage-tropic HIV-1 strains, respectively (reviewed in [1, 2]). Soon after their discovery [3–5] it was shown that persons heterozygous for a 32 base pair deletion in gene encoding CCR5 (CCR5Δ32) have slower progress to AIDS than individuals with two wild type alleles [6–11]. Moreover, individuals homozygous for CCR5Δ32 showed

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high degree of resistance to HIV-1 infection but not absolute as already several cases of HIV infection in these subjects were documented ([12] and citations herein).
Population surveys showed highest prevalence of CCR5Δ32 deletion in persons of European descent, lower prevalence in people from western Asia, sporadic in individuals from northern Africa and almost no prevalence in native Africans and Asians [13–17]. In healthy unrelated Czech individuals the CCR5Δ32 was found heterozygous in 21% persons and only one individual out of 386 (0.3%) tested persons carried both mutant alleles [18]. Another study performed in the HIV-1 negative Czechs found in approximately double number of the subjects on average 24% individuals with mutant CCR5 allele [19]. To the best of our knowledge, the only report about prevalence of CCR5Δ32 deletion in HIV-1 positive persons was presented at 14th European Congress of Clinical Microbiology and Infectious Diseases in Prague in 2004. In this study homozygous mutant genotype was not found, but 18% of individuals carried one mutant CCR5 allele [20].
There is a clear benefit of homozygous deletion in CCR5 gene that results in absence of functional co-receptor on the cell surface and inability of CCR5-tropic HIV-1 to enter cells. Less evident is the advantage for HIV-1 infection and pathogenesis in the case of heterozygous deletion in CCR5. It was shown that in spite of considerable innate variability, CCR5 expression levels in peripheral blood mononuclear cells (PBMCs) are markedly reduced in CCR5-+/Δ32 heterozygous individuals compared to CCR5 wild type individuals [21]. In addition, lower infection of PBMCs from CCR5 heterozygous individuals with CCR5-tropic HIV-1 isolates was documented [22]. In contrast, another study demonstrated that overexpression of CCR5Δ32 did not markedly impair the cell surface density or function of co-expressed wild-type receptor either in human epithelial cells or Jurkat T cells [23]. Additional molecular mechanism was proposed where mutant CCRΔ32 protein is retained in endoplasmic reticulum and exert transdominant negative effect on wild-type CCR5, preventing exit from this compartment [24, 25]. Moreover, this mechanism is supported by showing that expression of recombinant CCR5Δ32 in human PBMCs provides protection against both CCR5- and also CXCR4-tropic HIV-1 strains [26]. It demonstrates ability of truncated CCR5 protein to form heterodimeric complexes with wild type CCR5 and CXCR4 resulting in reduced cell surface expression of both co-receptors [26].
Lower CCR5 co-receptor density on the cell surface and ability of truncated CCR5 protein to scavenge functional co-receptors is the best explanation to date for protective role of CCR5Δ32 heterozygosity. CCR5 co-receptor density was correlated with viral load and immunological progression [27, 28]. Controversial is the benefit of CCR5Δ32 heterozygosity for HIV transmission. Among studies reporting that CCR5Δ32 heterozygotes are more protected from HIV-1 infection than CCR5 wild type homozygous individuals is cross-sectional and longitudinal analysis in large MSM cohort [29], analysis in small group of heterosexual discordant couples [30], analysis in Caucasian cohorts [31], analysis in Greek [32], Italian [33] and Brazilian cohorts [34]. On the contrary, no beneficial effect on HIV transmission was observed in study on heterosexual transmission in Scotland [35], in several cohorts in the USA [8], in cohort of drug users and hemophiliacs in Italy [36], in analysis in Chinese [37] and Columbian population [38]. A larger meta-analysis of 18 studies on more than 12000 subjects found no significant effect of CCR5Δ32 heterozygosity on protection from HIV-1 infection [39]. Better consensus in the HIV field we find on slightly delayed progression to AIDS in HIV-1-infected individuals carrying single CCR5Δ32 allele. Immediately after discovery of Δ32 deletion in CCR5 gene, several studies showed 2-4 years delay in progression to AIDS, long-term nonprogression of HIV disease, survival advantage, and lower all-cause mortality [6–10, 40–43]. A large meta-analysis from 15 cohorts from Western Europe, Africa, USA and Australia quantified and expressed the benefit of CCR5Δ32 mutation as 25% slower progression to AIDS and 35% slower progression to death [44]. In this paper, we analyzed the prevalence and the role of CCR5Δ32 heterozygosity on the disease progression in HIV positive patients in the Czech Republic.

MATERIALS AND METHODS

Subjects and samples

The CCR5 genotype analyses were performed as a part of a study of The Role of HIV Fitness on Disease Progression in the Absence of Antiretroviral Treatment. Between May 2012 and June 2013 92 HIV-1 seropositive subjects were enrolled in the study at AIDS center in the Hospital Na Bulovce in Prague. Subjects signed an informed consent that included provision for genetic testing such as CCR5 genotype determination (6.2.2012/6015/EK-Z). Peripheral blood mononuclear cells (PBMCs) were separated from whole blood by gradient centrifugation on Ficoll Paque Plus (GE Healthcare Life Sciences, Chicago, Illinois, USA) and stored at -80 °C.

DNA extraction and real time PCR amplification

DNA was extracted from thawed PBMCs using QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany), eluted in 100 µl of deionized water and used as a template for real-time PCR. Primers and probes were designed based on the published CCR5 sequence (GenBank accession number NG_012637) and were as follows: CCR5 forward 5'-GGGTGGTGACAAGTGTGAT-3', CCR5 reverse 5'-CAGATGACCATGACAAGCA-3', probe detecting wild-type CCR5 variant ROX-CAGTCAGTATCAATTCTGGAAGAATTTC-BHQ (wild-type probe) and probe detecting 32 bp-deleted variant FAM-CTCATTTTCCATACATTAAAGATAGTCATC-BHQ (Δ32 probe). PCR was performed in 20 µl volume with 5 mM MgCl2, 200 mM dNTPs (both Thermo Fisher Scientific, Waltham, Massachusetts, USA), 0.3 µM forward primer, 0.3 µM reverse primer, 0.08 µM wt probe, 0.08 µM Δ32 probe, and 1.25 U Platinum DNA Taq polymerase (Thermo Fisher Scientific). PCR conditions consisted of one denaturation cycle (95 °C, 10 min), followed by 40 cycles of amplification (95 °C, 15 s and 60 °C, 1 min). Positive signal in FAM channel determined homozygous mutant CCR5-Δ32/Δ32 phenotype, positive signal in ROX channel determined homozygous wild type phenotype, and positive signal in both ROX and FAM channels determined heterozygous CCR5-+/Δ32 phenotype. Resolution on 2% agarose gel confirmed 206 bp long PCR product for wild type CCR5 allele and 174 bp long PCR product for Δ32 allele.

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Statistical analysis

CD4+ T lymphocyte counts were determined during routine patient visits in the Hospital Na Bulovce and viral loads were measured at the National Institute of Public Health in Prague. CD4+ T-cells and logarithms of HIV-1 viral load results are expressed as mean values and standard deviations. Differences in CD4+ T-cell slopes distribution between groups were analyzed using the Mann-Whitney test. Slopes were determined for each patient separately from all CD4+ T-cell values during the follow-up period up to the initiation of antiretroviral treatment. Mean CD4+ T-cell slopes are expressed as mean values and standard errors of the mean. All analysis and graphs were performed using GraphPad Prism v.8.0.2 (GraphPad Software, La Jolla, USA).

RESULTS

In the cohort of 92 HIV positive patients of Caucasian decent we detected 23.9% of heterozygous CCR5Δ32 genotype and no homozygous CCR5Δ32 genotype (Table 1). The removal of six Slovaks, two Ukrainians, one Slovenian, one Belorussian, one Armenian, and one Hungarian from the analysis led to almost identical percentage of heterozygous CCR5Δ32 genotype (23.8%) in the remaining 80 Czech patients. In our dataset there were only five women (one CCR5Δ32 heterozygous and four CCR5 wild-type homozygous), which reflects the

Table 1. Percentages of each CCR5 genotype among HIV-seropositive individuals in study population

	Number of CCR5 genotype (percentage)		
	Homozygous mutant	Heterozygous	Homozygous wild type
	CCR5-Δ32/Δ32	CCR5-+/Δ32	CCR5-+/+
All patients	0 (0%)	22 (23.9%)	70 (76.1%)
Czechs and Slovaks	0 (0%)	20 (23.3%)	66 (76.7%)
Czechs	0 (0%)	19 (23.8%)	61 (76.2%)

Table 2. Demographic, clinical and virological parameters for antiretroviral therapy-naive patients with more than 1-year of follow-up

	Heterozygous CCR5-+/Δ32	Homozygous wild type CCR5-+/+	p-value[e]
Number (percentage)[a]	18 (24.3%)	56 (75.7%)	-
Age range	21 - 50	20 - 59	-
Men	17	54	-
Women	1	2	-
Follow-up range (months)[b]	20 - 125	15 - 166	-
Mean CD4+ count (CD4+ T-cells/mm^3)[c]	762 ± 222	645 ± 201	0.055
Mean CD4+ slope (CD4+ T-cell decline/month)[d]	-4.0 ± 1.4	-3.5 ± 0.6	0.78
Mean CD4+ slope for patients with more than 4 years of follow-up (CD4+ T-cell decline/month)[d]	-0.3 ± 1.0 (n=10)	-2.2 ± 0.6 (n=25)	0.048
Mean HIV-1 RNA (log RNA copies/ml)[c]	4.04 ± 0.54	4.39 ± 0.58	0.023

[a]Number and percentage of patients for each group. [b]Range of months that the patients had been monitored up to the initiation of antiretroviral treatment. [c]Mean and standard deviation of CD4+ T-cell count and HIV-1 viral load from all available values determined during the follow-up period up to the initiation of antiretroviral treatment. [d]Mean and standard error of the mean of CD4+ T-cell count decline (slope) determined as average of individual patient's CD4+ T-cell slopes using all CD4+ count values determined during the follow-up period up to the initiation of antiretroviral treatment. [e]Mann-Whitney test, n number of patients.

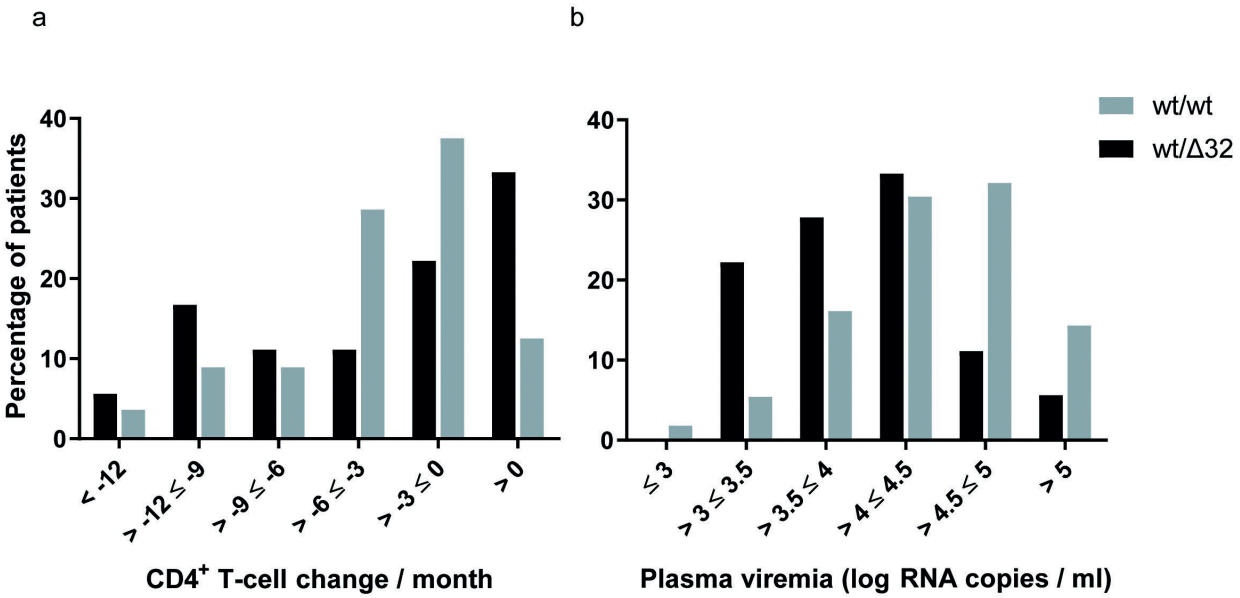


Figure 1. The CCR5 genotype and disease progression for antiretroviral therapy-naive patients with more than 1-year of follow-up
The probability distributions of the CD4+ T-cell change per month (a) and plasma viremia levels (b) are depicted for the wild-type homozygotes (n = 56; grey bars) and CCR5Δ32 heterozygotes (n = 18; black bars). n – number of patients.

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trend in the Czech Republic as almost 90% of new infections are in men.

To investigate the role of the CCR5Δ32 heterozygous phenotype in disease progression we selected a subgroup of antiretroviral therapy-naive patients with more than one year of follow-up (Table 2). This led to selection of 74 patients (71 men and three women) with the same distribution of Δ32 heterozygosity. Both groups, CCR5Δ32 heterozygotes and wild type homozygotes, had similar age range and follow-up range. There was slightly higher mean $CD4^+$ T-cell count ($p = 0.055$) and lower mean plasma viremia levels ($p = 0.023$) in heterozygotes. It is worth noting that the mean $CD4^+$ T-cell count decline was slightly lower in wild type homozygotes but this reduction did not reach statistical significance ($p = 0.78$). The trend was changing with increased follow-up. Consequently, analysis of patients with four and more years (total 35 patients) showed significantly lower decline of $CD4^+$ T-cell that led to loss of two cells each month more in wild-type persons than in heterozygous persons ($p = 0.048$). The overall trend is graphically evident by the small shift to the right in the distribution of slopes of $CD4^+$ T-cell change for CCR5Δ32 heterozygotes (Figure 1a). Similarly, the small reduction in mean plasma viremia level of 0.35 log RNA copies/ml in heterozygotes is better evident by the shift to the left in the distribution of viral loads for patients carrying Δ32 deletion (Figure 1b).

DISCUSSION

The only work presented on CCR5Δ32 allele in HIV-1 positive persons in the Czech Republic showed about 5% lower occurrence of CCR5 32-bp heterozygous deletion and with agreement with our study no homozygous mutant genotype was found [20]. Comparing the prevalence of CCR5Δ32 heterozygotes in HIV positive persons in our study with 21% and 24% prevalence reported in HIV negative Czech population indicates no obvious benefit of CCR5Δ32 heterozygosity on HIV transmission in the Czech Republic [18, 19].

In Slavic populations, there is large variability in reported prevalence of CCR5Δ32 heterozygotes between HIV negative and HIV positive population. In polish population Wasik et al reported higher, but not statistically significant, prevalence of CCR5Δ32 mutant allele among seronegative persons (13.6%) compared with HIV positive persons (9.7%) [45]. The small sample set of only 59 seronegative participants could explain the difference in comparison with study from 2000 where 861 individuals were examined that showed 10.9% frequency of Δ32 and 20.3% heterozygotes [46]. Interestingly, more recent study in the Polish population showed protective effect of CCR5Δ32 heterozygous phenotype in the case of heterosexual exposure [47]. Here, the prevalence of CCR5Δ32 heterozygosity in HIV-positive individuals infected through heterosexual contact (8.2%) was much lower than in the HIV-negative individuals (21.5%) as well as in heterosexually exposed uninfected group (25%). No significant differences in genotype representation and CCR5Δ32 allele frequencies between HIV-1 infected and uninfected were found in analyses in Slovakia [48], Russia [49, 50], and Slovenia [51].

One of the limitation of our study is the lack of knowledge of the approximate time of seroconversion. It was previously shown that difference in viremia between heterozygotes and wild type individuals reached significance in individuals with known time of seroconversion but the significance was lost in subjects with prevalent HIV-1 infection [10]. Moreover, large meta-analysis of the effect of CCR5Δ32 heterozygosity on HIV-1 disease progression has shown that heterozygous patients have diminished viremia early in the course of their disease. Compared with the HIV-1 RNA level at study entry or soon after seroconversion in wild type homozygotes, the viremia for CCR5Δ32 heterozygotes was lower by 0.18 log RNA copies / ml in seroconverters and by 0.21 log RNA copies / ml in seroprevalent patients [44].

Even slightly lower viremia can translate to slower decline of CD4+ T-cells over time [52, 53] and accordingly to lower risk of development of AIDS and death. Indeed, studies in six US cohorts, cohort of Danish homosexual men, in seroconversion SEROCO cohort, and in others showed significantly slower progression to AIDS and to death in CCR5Δ32 heterozygous group [8, 9, 44, 54]. However, CCR5Δ32 heterozygosity was not clearly associated with the risk for dying after progression to AIDS [44]. Despite the fact that with the wide use of combined antiretroviral treatment (cART) there is clear evidence of delayed disease progression and decline in mortality, the determination of patient´s CCR5Δ32 status is still clinically important. A recent study showed that CCR5Δ32 enhances the long-term survival also for those patients receiving cART [55]. Additional studies are necessary especially because previous reports did not find an association between CCR5Δ32 and survival in patients on cART [56, 57].

CONCLUSION

In conclusion, we found comparable incidence of CCR5Δ32 heterozygous genotype in HIV-1 infected persons with previously reported for HIV-1-negative Czech population, suggesting that this genotype does not protect against HIV-1 transmission. In addition, we showed small benefit of CCR5Δ32 heterozygous genotype for disease progression.

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Conflict of interest
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