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Review

The evolutionary history of the *CCR5*-Δ*32* HIV-resistance mutation

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Abstract

The CCR5 chemokine receptor is exploited by HIV-1 to gain entry into $CD4^+$ T cells. A deletion mutation (Δ*32*) confers resistance against HIV by obliterating the expression of the receptor on the cell surface. Intriguingly, this allele is young in evolutionary time, yet it has reached relatively high frequencies in Europe. These properties indicate that the mutation has been under intense positive selection. HIV-1 has not exerted selection for long enough on the human population to drive the *CCR5*-Δ*32* allele to current frequencies, fueling debate regarding the selective pressure responsible for rise of the allele. The allele exists at appreciable frequencies only in Europe, and within Europe, the frequency is higher in the north. Here we review the population genetics of the *CCR5* locus, the debate over the historical selective pressure acting on *CCR5*-Δ*32*, the inferences that can potentially be drawn from the geographic distribution of *CCR5*-Δ*32* and the role that other genetic polymorphisms play in conferring resistance against HIV. We also discuss parallel evolution that has occurred at the *CCR5* locus of other primate species. Finally, we highlight the promise that therapies based on interfering with the CCR5 receptor could have in the treatment of HIV.

Keywords: CCR5; Evolution; HIV; Population genetics

1. Introduction

Host–pathogen coevolution leaves a genomic signature by driving changes in polymorphism at loci involved in disease resistance. An important example that has received considerable attention over the last decade is the chemokine receptor 5 (CCR5) locus and its *CCR5*-Δ*32* allele. The role of *CCR5*-Δ*32* in HIV infection, resistance and therapy, coupled with its recent origin, unexpectedly high frequency and distinct geographic distribution, have captured the research interests of molecular biologists, epidemiologists and population geneticists.

The *CCR5* gene codes for a G protein-coupled chemokine receptor. Chemokines and their receptors form a regulatory network that controls the development, recruitment and activation of lymphocytes. Thus, chemokine receptors play a central role in the immune response against many pathogens, particularly in the inflammatory response. Most HIV-1 strains use the CCR5 chemokine receptor to enter $CD4^+$ T cells and macrophages [1]. CCR5 is the primary coreceptor in the initial phases of infection, and is thus fundamental in establishing HIV infection. Interference with the expression of the CCR5 receptor may also hold promise in the treatment of HIV [2,3].

Several studies have demonstrated that polymorphism at the *CCR5* locus in both the coding and regulatory regions affects susceptibility to HIV infection. The much-studied *CCR5*-Δ*32* allele is a 32-bp deletion that introduces a premature stop codon into the CCR5 chemokine-receptor locus and thus obliterates the receptor [4–6]. *CCR5*-Δ*32* is at average allele frequency of 10% across Europe, translating into a homozygote frequency of about 1%.

Individuals homozygous for the *CCR5*-Δ*32* allele do not express any of the CCR5 chemokine receptor on their cell surfaces, and in turn, they are largely resistant to infection by HIV-1. Heterozygote individuals exhibit elevated resistance relative to wild-type individuals, and if heterozygotes do become infected, they have reduced HIV-1 viral loads with slowed progression to AIDS by an additional 2–3 years [4,7–10].

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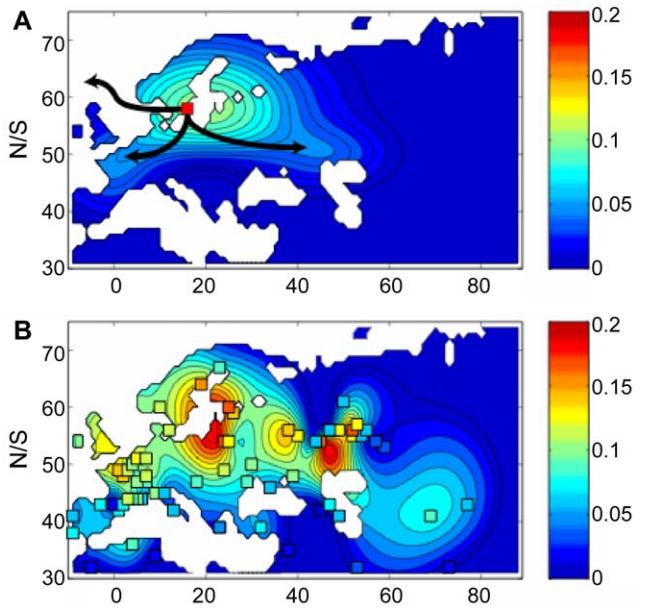

Fig. 1. A. A schematic representation of Viking hypothesis of Lucotte. The red square represents a Scandinavian origin of the allele. The black arrows represent dissemination of *CCR5-Δ32* by Vikings southwards towards France and the Mediterranean, eastwards towards Russia, and northwest towards Iceland. Contour lines and color represent the frequency in Europe at an intermediate stage of the allele's migration out of Scandinavia. B. The modern-day observed allele frequencies. Squares mark locations of sampled allele frequencies, and color within the squares denotes the observed frequencies. Contour lines represent interpolated allele frequencies. Data are from [66–75].

Clearly, the *CCR5-Δ32* resistance allele should be under intense positive selection in populations with a high prevalence of HIV [11]. Here we discuss the evolutionary history of the *CCR5-Δ32* deletion, including its origin, selective rise and current geographic pattern. We also review additional polymorphisms at the CCR5 locus and how patterns of variation in CCR5 vary among human populations and among primate species.

2. Single origin

Multiple lines of evidence indicate that the *CCR5-Δ32* allele is the result of a single unique mutation event. The high frequency of *CCR5-Δ32* in a number of Caucasian populations (Fig. 1B [4,7,8,12,13]) despite its virtual absence in Asian, Middle Eastern and American Indian populations [13] indicates that the mutation occurred only once after the divergence of Caucasians from their African ancestors [4,13,14]. Population-genetic assessment of the extent of linkage disequilibrium around the *CCR5-Δ32* corroborates this single origin [2]. Recurrent mutation is unlikely, given that the variant occurs in a predominately homogeneous haplotype background [13]. Furthermore, mutations as large as a 32-bp deletion occur at an extremely low probability, making it unlikely to occur more than once within the last couple 1000 years.

3. The age of the allele

Once it was established that the *CCR5-Δ32* allele arose as a single mutation, it became possible to inquire about when the mutation event occurred. Studying allele age has been important for our understanding of the evolutionary history of *CCR5-Δ* 32, because the allele age estimates have strongly supported the hypothesis of an intense historical selective pressure in favor of the deletion. The age of the *CCR5-Δ32* deletion has been inferred using three main approaches: linked genetic variation, the average frequency of the mutation, and patterns of geographic distribution.

Two studies have used patterns of linked genetic variation to estimate the age of the *CCR5-Δ32* deletion. The sources of the data and the methodologies differ between these two studies, but both approaches rely on the common principle that the amount of recombination and mutation observed on genomic regions surrounding the *CCR5-Δ32* deletion will be proportional to the age of the deletion. Stephens et al. adopted a coalescent analysis of the linkage disequilibrium between the CCR5 locus and surrounding microsatellite loci in a sample of 4000 individuals from 38 ethnic populations. They combined patterns of variation at two linked short-tandem repeat loci, and assumed a star-shaped gene genealogy [15] for the human population [13]. This led to an estimate for the origin of the *CCR5-Δ32* deletion of about 700 years ago, with a 95% confidence interval of 275–1875 years [13]. The second study used a Luria–Delbruck model for the genealogy [16,17] to make unique allele age estimates based on data at each of two linked microsatellite loci. Their estimates suggest that the *CCR5-Δ32* deletion arose around 2000 years ago with a plausabile range from 375 to 4800 years. The confidence intervals for the Stephens et al. approach were reduced by combining the data from both linked loci.

Additional inferences about the age of the *CCR5-Δ32* mutation have been drawn from the concentration of *CCR5-Δ32* in Northern Europe and Iceland. This data has been used to suggest that the mutation existed in Scandinavia before the Vikings dispersed 1000–1200 years ago, and was then spread towards Iceland, France, the Mediterranean coasts and Russia via Viking dispersal [18]. This hypothesis is illustrated in Fig. 1A, B.

While the estimated ages range over the last few millennia, these dates are all relatively young in evolutionary time, particularly for an allele with a 10% average frequency in Europe. Based on its frequency in Europe, the *CCR5-Δ32* deletion would be estimated to be 127,500 years old, if it had been unaffected by selection [13]. Thus, when neutrality is assumed, the age estimate is two orders of magnitude older than that obtained from inferences based on linkage disequilibrium and the geographic distribution data. This type of discrepancy between observed allele age and that estimated under the assumption of neutral drift is a population-genetic signature of natural selection. The data can be explained by his-

torical selective pressure in favor of the *CCR5-Δ32* allele that have rapidly increased its frequency to an average of 10% across Europe [13,16].

4. Historical selective pressures

HIV-1 has not exerted selection on the human population over a sufficient duration to account for the strong signature of selection. Thus, inferring the historical selection pressure that drove this allele to observed frequencies has drawn considerable attention. The coincidence of the age of the allele and the infamous bubonic plague Black Death pandemic led Stephens et al. (1998) to suggest that plague had been responsible for the selective rise of the allele. Indeed, the bubonic plague was responsible for the Black Death pandemic that killed an estimated 30% of Europe's population between 1346 and 1352 [19,20], a series of less severe intermittent epidemics [19–21] and the Great Plague of 1665–1666, which killed 15–20% of Europe's population [20,22], after which bubonic plague waned into extinction [23].

The plague hypothesis gained CCR5 attention as a classic example of a clinically important locus that shows a signature of historical selection. The hypothesis has become widely accepted in both the population-genetic and medical literature, as well as the scientific media. However, the hypothesis had not been assessed quantitatively. Therefore, Galuani and Slatkin investigated the likely cause of the selective rise of the resistance allele, using a model that combines population genetics and disease dynamics. Age-structuring can affect the selection of a resistance allele, particularly if disease dynamics are episodic [24], so Galvani and Slatkin [25] used an age-structured population-genetic framework. This model took into account the age-specific nature and temporal pattern of different diseases to identify the most likely cause of the selective rise of the resistance allele. We found that while plague was responsible for heavy mortality during epidemics such as the Black Death of 1348–1350, plague did not generate sufficient selection to drive the allele to a frequency of 10% [25].

Instead, it is more likely that a disease that persisted since the origin of the resistance allele drove its increase in frequency. For instance, smallpox was one such disease that caused significant mortality in Europe during both epidemic and inter-epidemic periods, until its recent eradication [26,27]. Because smallpox epidemics occurred frequently, children were the only immunologically naïve individuals in a population, making smallpox a childhood disease. The vast majority of Europeans were infected by smallpox before the age of 10 [26,28]. Smallpox also had a high case fatality rate of about 30% [29]. The cumulative number of deaths during the last 700 years from smallpox was greater than from plague. In addition, smallpox disproportionately affected younger people; a typical smallpox death removed greater reproductive potential than the average plague victim. Indeed, results from our population-genetic model that incorporated all of these factors demonstrated that smallpox could have posed sufficient selection to account for the rise of the *CCR5-Δ32* allele [25].

Model predictions pointing to smallpox as the selective agent are consistent with molecular evidence. Both HIV and smallpox are viruses, whereas the causative agent of plague is a bacterial pathogen. In addition, HIV and poxviruses both infect lymphocytes using chemokine receptors [30,31]. Gene products from poxviruses even inhibit chemokines [32,33], presumably to increase the availability of chemokine receptors for viral attachment. Thus, it is biologically plausible that the obliteration of the CCR5 chemokine receptor could confer resistance against both HIV and smallpox. These theoretical hypotheses have motivated experimental investigation of the role of CCR5-Delta24 in the resistance to particular pathogens. Recent research provided experimental confirmation that the *CCR5-Δ32* allele does not confer resistance against plague [34]. A following study further confirmed that CCR5-deficient mice do not survive better when infected by *Yersinia pestis*, but its results were ambiguous [35]. Donald Mosier and colleagues are currently investigating whether CCR5-deficient mice are resistant to smallpox (pers. comm.).

4.1. Selection coefficients

Selection coefficients are a quantitative measure of the intensity of selection that has acted on a locus, and a fundamental parameter in population-genetic analysis. As such, they determine the evolutionary dynamics of the alleles at a locus. Estimation of selection coefficients from human population-genetic data is a challenging task, but by fitting mathematical models to observed data, indirect estimates can be obtained.

Typically, estimates of selection coefficients depend on the assumptions made about the degree of dominance of the resistance allele. In this case, the assumption corresponds to the degree to which heterozygous carriers of *CCR5-Δ32* were resistant to the historical selective pressure in comparison to homozygous carriers of the allele. Under the assumption of complete dominance, both heterozygotes and resistant homozygotes are fully protected against disease mortality (though not necessarily infection). When an additive effect of the resistance allele is assumed, the case fatality rate of a heterozygote is half that of a susceptible homozygote. While the true degree of dominance for resistance to the historical disease is not known, it is worth noting that the resistance to HIV conferred by *CCR5-Δ32* is not dominant, because heterozygotes have intermediate levels of resistance. In fact, heterozygous carriers of the allele have a greater than 50% reduction of CCR5, which is lower than the reduction expected from gene dosage effects [36,37]. This non-additivity has been attributed to dimerization between wild-type and mutant gene products, interfering with the transport of CCR5 to the cell surface [37].

Stephens et al. used their estimates of allele age and the current frequency in Europe to infer an estimate of 23% with

dominance, and 37% with additivity. A likelihood-based method that accounted for population growth and genetic drift was subsequently applied to the linkage disequilibrium data of Slatkin [38]. This likelihood method generated an estimate of selection assuming additivity of approximately 20%, although the results suggested the data are also compatible with stronger selection coefficients.

A modeling study by Galvani and Slatkin showed that these estimates of strong selection are consistent with the selection that would be produced by smallpox. Assuming that the smallpox resistance conferred by *CCR5*-Δ*32* is additive, the effective selection coefficient was calculated to be 17%. Under the assumption of dominant resistance, a coefficient of 28% is generated via the action of smallpox epidemics [25]. Few polymorphic alleles have been revealed in humans to have undergone as strong selection as that estimated for *CCR5*-Δ*32*. As an example, the estimated selection in favor of *CCR5*-Δ*32* homozygotes is similar to, or even slightly greater than, that generated by malaria against homozygous carriers of the famous sickle-cell allele [39].

4.2. Cost of resistance

The central role that chemokine receptors play in the inflammatory immune response makes it likely that the obliteration of CCR5 would have negative fitness repercussions in the absence of a compensatory protective effect. Indeed, chemokines of the CCR5 receptor serve a role in the inflammatory responses to infection of *Mycobacterium tuberculosis* [40] and coxsackievirus [41]. Also, CCR5-knockout mice have poorer survival from *Cryptococcus neoformans* [42], reduced clearance of *Listeria donovani* [43] and increased susceptibility to *Toxoplasma gondii* [44].

Despite our understanding of the role that CCR5 plays in the inflammatory immune response, no ill effects associated with the Δ*32* deletion have been documented in clinical studies. Homozygous individuals are apparently healthy [4,6], possibly because the CCR5 chemokine receptor function is at least partially redundant, and thus its loss may be compensated for by other chemokine receptors. Alternatively, the failure to detect ill effects may be because studies exploring the cost of resistance have been conducted in communities where infection with pathogens that elicit an inflammatory response are currently rare. In contrast, pathogens such as helminth parasites are likely to have been more prevalent historically, as they are currently in developing countries. Indeed, comparative studies of CCR5 sequences among primates show that CCR5 transmembrane domains are well conserved among species, suggesting that on an evolutionary timescale, there is evidence for selective constraint at the CCR5 locus [45].

Any such cost of resistance further argues against the hypothesis that bubonic plague selected for *CCR5*-Δ*32*. Plague has not been an important source of mortality for at least the last 250 years in Europe. Mass vaccination against smallpox was not initiated until 1950 [46]. In the absence of plague-mediated selection during this time, a cost of resistance would be expected to drive down the frequency of the resistance allele. In contrast, smallpox was not eradicated until 1978, coincidental with the start of the AIDS epidemic. Thus, under the smallpox scenario, there has not been a long period without positive selection since the origin of *CCR5*-Δ*32*.

5. Geographical distribution

The geographical distribution of an allele provides insight into evolutionary history and the properties of selection that have acted on it. Across Eurasia, the allele frequency of *CCR5*-Δ*32* forms a north-to-south cline, with frequencies of over 15% in Iceland and Baltic countries to 4% in Sardinia (Fig. 1B) [12,13,16], with an average of 10% over Europe [6,12,13,16].

Assessment of the factors that have given rise to the geographic distribution of *CCR5*-Δ*32* is an important area for future research. One hypothesis, which was highlighted in the context of allele age above, is that *CCR5*-Δ*32* arose in Scandinavia 1000–1200 years ago and was then spread northward to Iceland, eastward to Russia, and southward to central and southern Europe by Viking dissemination. This intriguing hypothesis is qualitatively consistent with the age of *CCR5*-Δ*32* and its current geographic distribution (Fig. 1A, B). However, it remains to be seen if simpler hypotheses which do not invoke any special form of dispersal can explain the data. For instance, it is also possible that the allele arose in Scandinavia, from which point it spread outward by the ordinary background level of human dispersal in Europe, without requiring a contribution from long-range migrations by Vikings. An alternative hypothesis is that the allele arose in central or even southern Europe and was then spread northward along selective gradients. Limborska et al. 2002 have documented a negative correlation between *CCR5*-Δ*32* frequency and annual radiation balance, which may be a reflection of geographically variable selection pressures. Stronger selection pressure in the north may also have resulted from more intense and frequent smallpox epidemics in northern Europe, as has been documented historically [27] and with which the geographical data are consistent. Quantitative analysis using a spatially explicit model of the spread of *CCR5*-Δ*32* may be employed to determine which of these hypotheses alone or in combination is the most likely explanation for the geographic distribution.

Understanding the causes of the geographic distribution of *CCR5*-Δ*32* can be used to infer properties of the historical selective pressure. Plague was historically most active in central and southern Europe, so the high frequencies of the deletion allele in the north supports the hypothesis of smallpox as the historical selective agent. If driven by the spatial variation in the intensity of the epidemic, the gradient of allele frequency may provide an example of the impact of epi-

demic spatial dynamics on the geographic distribution of genetic polymorphism in the host population.

6. Other HIV-resistance alleles

There is extensive variation among individuals in susceptibility to infection and the rapidity of progression to AIDS [47]. While a range of socioeconomic factors contributes to this heterogeneity, a proportion of the heterogeneity can also be attributed to host genetics, particularly at loci associated with HIV cell entry, the expression of competing ligands, immune recognition and antigen presentation. It has been estimated that 30% of potential AIDS cases are averted by a combination of restriction alleles [48]. The intensity of the protective effect combined with the prevalence of the allele determine the number of AIDS cases prevented by a given restriction allele.

Polymorphisms associated with CCR5 and other HIV coreceptors CXCR4 and CCR2 and their ligands have been shown to affect HIV-resistance or progression [2]. *CCR5-Δ32* and *CCR2-64I* chemokine receptor alleles confer the most potent protection of known restriction alleles [48]. *CCR5-P1*, *CCR2-64I* and *SDF1-3′A* also play a role in the rate of HIV progression [2]. In addition, the HLA region influences the rapidity of progression to AIDS [47,49].

Polymorphism in the regulatory region of CCR5 also affects susceptibility to HIV [50,51], although the resistance conferred from regulatory region polymorphism is weaker than that conferred by the coding region of the *Δ32* mutation. Interestingly, the regulatory region of CCR5 has been found to have high levels of polymorphism [52], suggestive of balancing selection in which the heterozygote is selected more positively than either of the homozygotes. The allelic history of these regulatory haplotypes remains to be determined. Polymorphisms that affect the expression or activity of CCR5, either through regulation of transcription, translation or functional activation, can all be expected to influence susceptibility to HIV. In addition, these resistance alleles may be positively epistatic, such that the cumulative effect of these alleles is more protective than the sum of individual effects in terms of stalling progression to AIDS [53]. Human populations vary in the nature and extent of genetic resistance to HIV. For instance, the allele frequency of *CCR2-64I* in Nairobi is more than twice that in individuals of European descent [54].

7. CCR5 in other primate species

Parallel evolution has occurred at the CCR5 locus in primate species that are naturally infected by simian immunodeficiency virus (SIV). Most strains of HIV and SIV utilize the chemokine receptor CCR5 for viral attachment and entry into cells of the host immune system. In rhesus macaques, SIV leads to progressive decline in $CD4^+$ counts and AIDS-like symptoms. In contrast, SIV does not cause clinical symptoms in sooty mangabeys, despite maintaining viremia [55,56]. Sooty mangabeys are the natural hosts of SIV, while rhesus macaques are not [57].

One explanation for the reduced virulence of SIV in sooty manabeys is that the sooty mangabeys and the closely related red-capped mangabeys have evolved mechanisms to silence the CCR5 receptor. SIV-infected sooty mangabeys down-regulate expression of CCR5 on their $CD4^+$ T cells [55]. Red-capped mangabeys carry a 24-bp deletion in CCR5, which also prevents the expression of a functional CCR5 receptor at the cell surface and thus has a similar phenotypic effect as the *CCR5-Δ32* allele in humans. This *CCR5-Δ24* allele is widespread in red-capped mangabeys, such that 98% of individuals carry at least one copy [58]. Because CCR5 is an entry-point for various viruses including SIV, pathogen-mediated selection has likely driven the *CCR5-Δ24* allele nearly to fixation. These examples of parallel evolution of CCR5 inhibition in mangabeys and humans showcase the importance of the CCR5 receptor in the evolutionary response of primate hosts to SIV-like viruses.

The evolutionary history of the *CCR5-Δ24* allele in primates remains to be explored. The *CCR5-Δ24* allele is also found in sooty mangabeys, albeit at the much lower frequency of 4% [58,59]. The disparity in allele frequencies between the two subspecies is intriguing. The *CCR5-Δ24* allele may predate the separation of the two mangabey subspecies, suggesting the allele is more than 10,000 years old, and hence much older than *CCR5-Δ32*. This scenario of a comparatively ancient origin would require that the allele has remained in low frequency in one subspecies while being driven to a high frequency in the other. An explanation for such a trajectory would be that selection has been much stronger in red-capped mangabeys than in sooty mangabeys. An alternative scenario would be that the *CCR5-Δ32* allele arose within red-capped mangabeys and has spread to sooty mangabeys recently via a rare interbreeding event. Dating the age of the *CCR5-Δ32* allele in each subspecies using linkage disequilibrium data could provide the necessary information to evaluate these two hypotheses, and to determine whether we are observing the effects of species-specific selection or a unique example of a disease resistance genotype being spread across species boundaries.

Suggestive of a coevolutionary arms race, SIV adaptation to CCR5 inhibition: red-capped mangabeys harbor SIV strains that utilize CCR2 instead of CCR5 [58]. It appears highly plausible that originally, SIV, or an ancestral virus, in this primate species exploited CCR5. It is postulated that such a disease increased the frequency of a CCR5 resistance allele in red-capped mangabeys, in turn generating selection on SIV in favor of strains that used CCR2 instead. Currently, resistance to SIV does not confer a reproductive advantage to mangabeys, given that SIV is no longer pathogenic to mangabeys. Ancestral SIV may have been more virulent, but has

evolved to become avirulent. The factors affecting the evolution of the avirulence are difficult to determine, but could arise if CCR2 was a more challenging coreceptor through which to perpetuate within-host infection; for example, if CCR2 is more difficult for SIV to bind to or if CCR2 is less abundantly expressed. Overall, the signs of selection on CCR5 in other primates reveal the importance of CCR5 as a target of selection, not only in humans but across species. More generally, these instances of parallel evolution show that similar molecular mechanisms may apply to the dynamics of host–pathogen co-evolution in other primate species.

8. CCR5 and therapy

Research into the CCR5 receptor and the Δ*32* allele has prompted the development of therapies and vaccines targeting CCR5. Protease and reverse transcriptase inhibitors cannot eradicate HIV from infected individuals [60]. Side effects of drugs [61] and the emergence of drug resistance [62] add to the growing need for new classes of drugs. Understanding the molecular effect of *CCR5*-Δ*32* has galvanized efforts to develop intervention targeting the virus co-receptor interaction, thereby inhibiting HIV infection of $CD4^+$ T cells and stalling progression to AIDS [2]. Research documenting the parallel evolution of CCR5 and the effect of *CCR5*-Δ*32* among primates highlights the usefulness of the SIV system as a model for testing novel therapeutic treatments for HIV [63]. Several approaches to blocking HIV infection are promising and have entered clinical trials [64,65]. Combined therapy may also be beneficial, particularly given that *CCR5*-Δ*32* heterozygotes respond better to anti-retroviral therapy than do wild-type homozygotes [2]. Additionally, a number of pathogens exploit chemokine receptors, so therapies that interfere with chemokine receptors may also be used in the treatment of other diseases.

9. Discussion

Polymorphism at the CCR5 affects response to specific therapies, resistance to infection, rapidity of HIV progression and viral load and transmissibility to other hosts. The CCR5 locus shows that historical epidemics have been important in shaping the genomes of humans and other primate species. It has been projected [11] that if the HIV epidemic continues for another 100 years, it will leave a signature on the human genome at the CCR5 locus and related HIV-resistance loci. Thus, alleles that provided disease resistance during historical epidemics may continue to be positively selected by the current HIV epidemic.

A population-genetic model has yielded insights into the evolutionary history of *CCR5*-Δ*32* based on allele age and frequency. It is most likely that a disease that persisted since the origin of the allele in a continuous temporal pattern and had a high case fatality rate is responsible, particularly if younger age classes were disproportionately heavily affected. The geographic distribution of *CCR5*-Δ*32* may contain further information about its evolutionary history that remains to be tapped by a mathematical model. It is important to investigate whether the current geographic distribution may be the result of geographically variable selection or if the data can be explained by uniform selection intensity across Europe. Analysis of the geographic data will also provide insight regarding the speed at which genetically based disease resistance spreads among human populations and whether, in this case, the dispersal of Vikings may have greatly accelerated the dissemination of the resistance allele across Europe.

Integrating population genetics and epidemiology has the potential to yield insight into the dynamic interplay between hosts and their pathogens and the epidemiological history of humans and of other species. There is an abundance of future research possibilities for models that integrate population genetics with epidemiological dynamics. Such research is also becoming increasingly feasible with the ever-mounting abundance of genomic information for human populations. Melding population genetics with disease epidemiology is a powerful approach for inferring the evolutionary history of other clinically important loci, such as those that confer disease resistance or responsiveness to different treatments.

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