Letter to the Editor

Controversial role of smallpox on historical positive selection at the *CCR5* chemokine gene *(CCR5-Δ32)*

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The positive selection of the 32-bp (base pair) deletion in the chemokine receptor CCR5 (Figure 1a), a variant that confers resistance to HIV/AIDS, is hypothesized to have originated relatively recently in response to the strong selective pressure of smallpox [1]. However, based on our extensive studies in India, for the first time we have found that the theory of positive selection pressure of smallpox for *CCR5-Δ32* may not be as clear.

The *CCR5-Δ32* mutation determines the susceptibility of an individual to HIV/AIDS and is highly protective against infection with HIV-1 through the formation of a truncated receptor preventing viral entry [2,3]. The *CCR5-Δ32* mutation is common among Caucasians with an allelic frequency of 10%. The high incidence of this allele may be indicative of a positive selection event. With population genetic studies and mathematical models, it has been suggested that the *CCR5-Δ32* mutation has been under positive selection pressure of smallpox [1].

Smallpox, one of history's most contagious, devastating and disfiguring diseases, was present in India as early as 1000 B.C. and remained endemic until its final eradication in 1977. Approximately 95% of the population of the valley of the Ganges in India (which was an endemic area for smallpox since the origin of the disease had been attacked with smallpox at some period of their lives; in 60% of the population, the traces of the disease were on the face [4,5]. Smallpox was introduced to Europe sometime between the fifth and seventh centuries [4]. In unprotected populations of the eighteenth century, the smallpox case fatality rate was significantly higher in India (25–50%) as compared to that in Europe (10%) [5], so if the theory of selection pressure of smallpox on *CCR5-Δ32* is completely correct, then one should predict a higher frequency of *CCR5-Δ32* mutation in the various populations of the valley of the Ganges in India. Furthermore, the population there has a paternal lineage more similar with that of Europeans than Asians [6].

We have evaluated the frequency of the *CCR5-Δ32* mutation in the various ethnic populations of the valley of the Ganges in India, as well in rest of India. Our results presented in Figure 1b exhibit the presence of a low allelic frequency of the *CCR5-Δ32* mutation (1% heterozygote; $\chi^2 = 0.0802$; d.f. = 1; $P > 0.05$, not significant) in 8 out of the 15 studied populations of the valley of the Ganges in India (North India), while it is virtually absent in the rest of the 30 Indian populations (S.K.S. *et al*., unpublished data; The sequences were submitted in NCBI with accession numbers EF202087 and EF202088). *CCR5-Δ32* is at average allele frequency of 10% across Europe [1].

The presence of a low frequency of *CCR5-Δ32* mutation, in spite of having significantly higher cases of smallpox in India than estimated for unprotected populations in eighteenth-century Europe, does not support the hypothesis of positive selection pressure of smallpox for *CCR5-Δ32*. Restriction of the *CCR5-Δ32* mutation only in caste populations of North India and its virtual absence in rest of Indian populations agrees with the facts obtained from previous paternal lineage findings which suggest that these caste groups are primarily descendents of Indo-European speakers who migrated from Central Asia ~3,500 years ago [7] and have a higher affinity to Europeans than to Asians [6]. Thus it is evident that

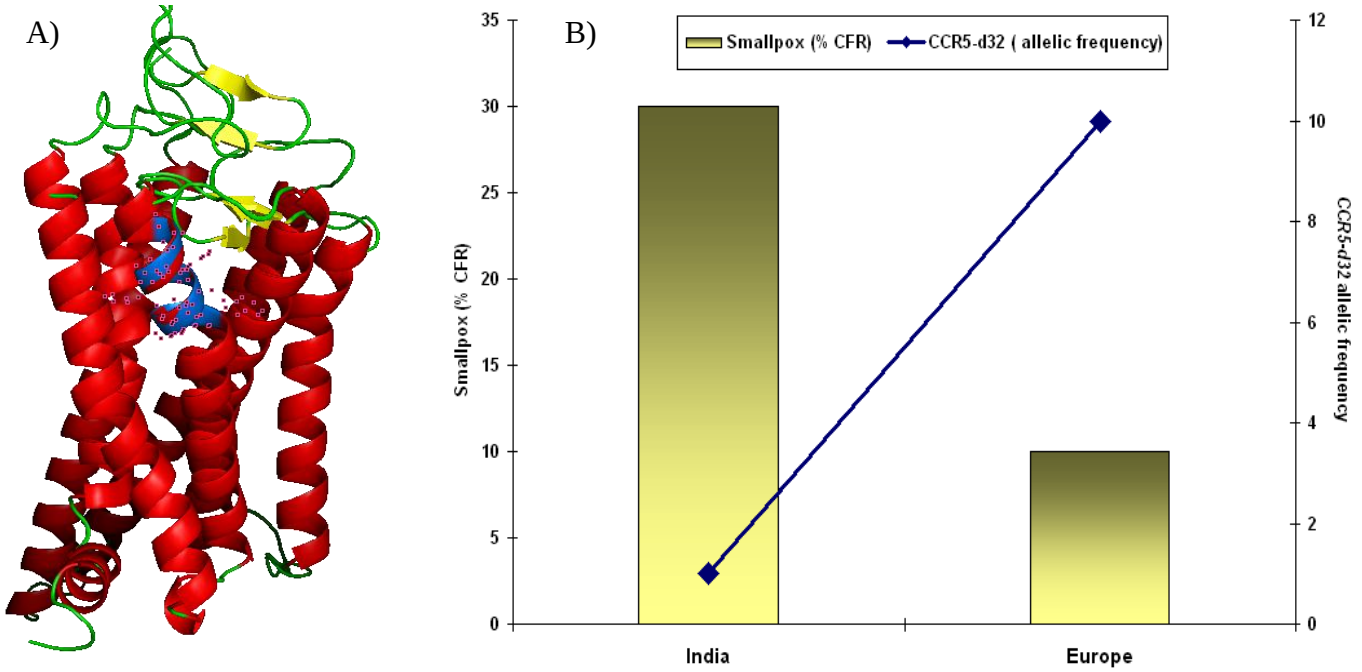

Figure 1. Structural model of CCR5 and correlation between allelic frequencies of *CCR5-Δ32* mutation and percent case fatality rate (CFR) of smallpox (in the 18th century) in Europe and India. (a) Ribbon representation of CCR5, which allows HIV entry and infection. (b) The figure represents the percent allelic frequencies of *CCR5-Δ32* mutation and percent case fatality rate (CFR) of smallpox (in the 18th century) in Europe and India. The bar indicates smallpox (% CFR 18th century) and the line indicates percent allelic frequencies of CCR5-Δ32 mutation. (Figure based on our study and referemces 1,5).

the age of mutation is definitely more than ~3,500 years and had its origin in European population. Moreover, ancient German DNA samples from 2,900-years-old Bronze Age skeletons revealed that frequency of the *CCR5-Δ32* mutation (11.8%) was similar to those in modern German DNA samples (9.2%), which also suggests lack of positive selection pressure of smallpox in Europe for last 2,900 years [8]. A recent ancient DNA (aDNA) study in Poland also presents a compelling case against historic pandemics acting as a historical positive selection pressure for *CCR5-Δ32* [9].

Therefore, based on our extensive studies in India, for the first time we have demonstrated that the positive selection of the 32-bp deletion in the chemokine receptor CCR5 may not be actually under the pressure of smallpox, and reconfirms the presence of the mutation ~3,500 years ago in Europe. Further studies are in progress in our laboratory to assess the accurate date of origin of the mutation and to elucidate the cause behind the selection of *CCR5-Δ32*. The clue may lie in search of a pathogen that was present and prevalent in Europe and absent in India at that time that may have activated the immunological response through CCR5. We should also evaluate the role of other selection pressures; furthermore, the possibility of neutral evolution cannot be ruled out. Apart from behavioral factors, host genetics also plays an important role in influencing the dynamics of HIV infection in India. Therefore, the studies on the evolution of HIV immunity may be a helpful tool in providing better prospects for those afflicted with the disease in this embattled continent.

References

1. Galvani AP, Slatkin M (2003) Evaluating plague and smallpox as historical selective pressures for the CCR5-Delta 32 HIV-resistance allele. Proc Natl Acad Sci USA 100: 15276–15279.
2. Nolan D, James I, Mallal S (2005) HIV: experiencing the pressures of modern life. Science 307: 1422–1424.
3. Mecsas J, Franklin G, Kuziel WA, Brubaker RR, Falkow S, Mosier DE. (2004) Evolutionary genetics: CCR5 mutation and plague protection. Nature 427: 606.

4. Fenner F, Henderson DA, Arita I, Ježek Z, Ladnyi ID. (1988) Smallpox and its Eradication. World Health Organization (Geneva). Available: http://whqlibdoc.who.int/smallpox/9241561106.pdf. Accessed 03 January 2009.
5. Banthia J, Dyson T (1999) Smallpox in Nineteenth-Century India. Popul Dev Rev 25: 649-680.
6. Bamshad M, Kivisild T, Watkins WS, Dixon ME, Ricker CE, Rao BB, Naidu JM, Prasad BV, Reddy PG, Rasanayagam A, Papiha SS, Villems R, Redd AJ, Hammer MF, Nguyen SV, Carroll ML, Batzer MA, Jorde LB (2001) Genetic evidence on the origins of Indian caste populations. Genome Res 11: 994–1004.
7. Cordaux R, Aunger R, Bentley G, Nasidze I, Sirajuddin SM, Stoneking M (2004) Independent origins of Indian caste and tribal paternal lineages. Curr Biol 14: 231–235.
8. Hummel S, Schmidt D, Kremeyer B, Herrmann B, Oppermann M (2005) Detection of the CCR5-Delta 32 HIV resistance gene in Bronze Age skeletons. Genes Immun 6: 371–374.
9. Zawicki P, Witas HW (2008) HIV-1 protecting CCR5-Delta32 allele in medieval Poland. Infect Genet Evol 8: 146-151.

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