Heredity (2006) 96, 280–281

www.nature.com/hdy

NEWS AND COMMENTARY

Evolutionary population genetics

Were the Vikings immune to HIV?

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Heredity (2006) **96,** 280–281. doi:10.1038/sj.hdy.6800806; published online 1 February 2006

Our hope is that understanding the genetic bases of disease resistance will help us to eradicate various diseases and, in particular, infectious diseases such as AIDS. However, this is not enough. We also need to understand its evolutionary history to identify the mechanisms and factors that have favoured the spread of these beneficial disease resistant alleles. This is no simple task; it requires large databases that include both genetic and nongenetic data (eg geographic coordinates of the samples) and complex statistical methods. In a recent paper, Novembre *et al* (2005) present an excellent example of an approach that provides valuable information about the spread of a mutation, CCR Δ32, that confers resistance to HIV-I infection. In particular, they provide compelling evidence indicating that the allele has spread rapidly via long-distance dispersal and intense selection. The restricted geographic distribution of this allele is likely due to the limited time to disperse rather than local selection pressures.

Disease follows humans wherever they go but sometimes a chance event, an error in DNA replication, help us to fight it back. The CCR5 Δ32 mutation is one of the many variants of the chemokine receptor gene, CCR5. This gene produces a molecule that serves as a major cell surface co-receptor for the HIV-1 virus. Individuals homozygous for the Δ32 allele do not produce a functional protein (Carrington *et al*, 1999) and are therefore almost completely immune to infection. Heterozygous individuals have reduced susceptibility to infection and delayed onset of AIDS (Carrington *et al*, 1999).

This mutation was originally identified in Caucasians and is mainly found across Europe and western Asia with frequencies that vary geographically but which average 10%. Its origin predates the emergence of HIV as a human pathogen but its current frequency and estimated age (between 700 and 2900 years but maybe older) suggest that it has been under strong selection throughout its history. Several studies suggest smallpox as the possible selective agent.

The observed allele frequency surface of Δ32 is noisy and multimodal, with a broad area of high frequency in the Baltic region and additional peaks in the northern coast of France and the extreme west and Volga-Ural region of Russia. This ragged frequency surface is compatible with multiple hypotheses concerning the geographical origin of the mutation and the factors that controlled its spread. In particular, it has been proposed that the high frequency in the Baltic region imply a Viking origin (Lucotte and Mercier, 1998). So in this interesting study, Novembre *et al* (2005) set out to model the effects of selection and dispersal on the geographic distribution of the allele.

They use as starting point a classic model for the spread of an advantageous mutation, the wave-of-advance model, first introduced by Sir Ronald Fisher (1937), one of the forefathers of evolutionary biology. Using a diffusion model that incorporated the joint effect of selection and dispersal, Fisher showed that, after a gene was established in a population, there would be a wave of advance for which the velocity of the wave is proportional to the selective advantage of the allele. Novembre *et al* (2005) use a two-dimensional version of this model that was slightly modified in order to incorporate geographical gradients in selection. With this approach they simulated the allele frequency distribution of Δ32 under various scenarios that considered different initial geographic positions for the mutation and various selection intensities and dispersal distances.

The first interesting result obtained by the authors is that, although allele frequency surfaces generated by this model can be unimodal and smooth, the sampling of genes from such a surface can generate noisy and multimodal surfaces similar to those observed for the Δ32 mutation. Thus, it is not necessary to invoke unusual local conditions or specific migration events to explain regions of high frequency. Using a maximum likelihood approach the authors evaluated the fit of the model under the various scenarios they considered. The maximum likelihood estimates coincided with scenarios involving strong selection and long-distance dispersal. Selection gradients did not need to be extreme but were steeper in the north–south direction than in the east–west direction. The most likely origin of the mutation is in Spain or northern Germany, contradicting the Viking hypothesis. The only scenarios where a Scandinavian origin was favoured involved spatially uniform selection but their likelihoods were lower than those of scenarios including selection gradients.

The fact that all this detailed information could be obtained using a slight modification of a classical model proposed by R Fisher a very long time ago is a reminder of the richness of the population genetics theory that was developed very early on by the field's founders. Indeed, much of their work is surprisingly modern. More complex models incorporating specific historical events could be envisioned and will certainly follow thanks to the help of modern statistical tools and increased computer power. However, the underlying genetic model will almost certainly be drawn from the 'ancient' population genetics theory that we should always revisit.

Although very innovative, this study rests on a rather stringent prerequisite, the existence of a well studied mutation whose implication in disease resistance has been well established. For the moment few such mutations have been well characterised, but the method could also be used to study adaptive traits other than disease resistance. In any case, this is a very welcome first step that will eventually be followed by more sophisticated methods to study the geographic spread of adaptive traits involving many genes. Some of the existing methods to detect loci under selection (eg Beaumont and Nichols 1996; Vitalis *et al*, 2001; Beaumont and Balding, 2004) could be combined with approaches that allow the integration of genetic and nongenetic data (eg Gaggiotti *et al*, 2002). This promises to be a difficult task but it could lead to a better understanding of the way in which complex traits spread across species ranges.

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Further Reading

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