Karolinska Institutet

Department of Microbiology, Tumor and Cell Biology

HIV Evolution:

Theoretical Framework and Practical Applications

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i MTC föreläsningssal, Theorells väg 1

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ABSTRACT

The human immunodeficiency virus (HIV) is one of the most important and interesting organisms to study today. This pathogen causes life-long infection that presently cannot be cured and the infection leads to development of opportunistic diseases and death if not treated. Finding the answers to the questions still remaining about the evolutionary dynamics of the virus may be crucial in order to develop new therapeutics and functional vaccines, as well as to achieve efficient prevention and surveillance of HIV spread. In terms of evolution, the virus has a remarkable ability to accumulate new mutations over short time. Hence, theoretical models can be applied to HIV data from which parameter estimations can be done directly, and consequently detailed inference of the evolutionary history of HIV can be done. In this thesis the evolution of HIV was studied from several different aspects, and both existing as well as newly developed methods were used.

The spread dynamics of HIV-1 among injecting drug users (IDUs) in Sweden were studied using genetic viral material from newly diagnosed patients and by comparing clinical and demographic data. We found several old lineages of subtype B that had been present at least since the 1990s and that have continued to spread up until late 2007, and we estimated the rate of spread in these lineages to have been generally slow. There have been additional introductions of subtype B into Sweden but these introductions appear to have caused no or limited spread. An introduction of CRF01_AE from Helsinki to Stockholm caused an outbreak in 2006-2007, probably in a standing social network of IDUs. We estimated the incidence rate to increase with a factor of 12 at the outbreak onset, but time from infection to diagnosis during the outbreak was estimated to be short, indicating a rapid discovery of infected individuals. However, both before and after the outbreak, newly HIV-1 infected individuals seem to have remained undiagnosed for longer time periods than during the outbreak.

Within-patient evolutionary rates of HIV were studied in HIV-2 and HIV-1 patients, matched according to viral load, CD4 count, antiretroviral treatment and sampling times. We found that the envelope gene evolved at a faster rate in HIV-2 than in HIV-1 in patients at similar disease stage. The faster rate was more pronounced at synonymous sites, probably a result of factors influencing the replication or mutation rate of the virus.

Finally, we investigated the evolutionary dynamics of HIV-1 in an asymptomatic patient during chronic infection. Through high-frequency sampling it was possible to perform detailed analyses of the processes influencing the short-time evolution of HIV-1 (up to months). We found that several subpopulations were present over time, whose fluctuations over longer time periods (~1.5 years) were consistent with a neutral model of evolution. However, signatures of positive selection were observed on the branches connecting the subpopulations. Thus, non-neutral evolution had likely influenced the formation of these subpopulations and is probably acting over longer time periods in chronic infection of HIV-1.

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