

## PE2

### HIV-1 integrase variants retarget proviral integration and are associated with disease progression

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**Background:** Distinct integration patterns of different retroviruses, including HIV-1, have puzzled virologists for over 20 years. A tetramer of the viral integrase (IN) assembles on the two viral cDNA ends, docks onto the target DNA (tDNA) to form the target capture complex (TCC) and catalyzes viral genome insertion into the host chromatin.

**Methods:** We combined structural information on the Prototype Foamy Virus TCC with conservation in retroviral IN protein alignments to determine aa-tDNA base contacts. We generated HIV-1 variants based on the observed variability at these positions, assessed replication capacities and performed integration site sequencing to reveal their integration preferences. Finally, we examined their effect on disease progression in a chronic HIV-1 subtype C infection cohort.

**Results:** We identified retroviral IN amino acids affecting molecular recognition in the TCC and resulting in distinct local tDNA nucleotide biases. These residues also determine the propensity of the virus to integrate into flexible tDNA sequences. Remarkably, natural polymorphisms IN119G and IN231G retarget viral integration away from gene dense regions. Precisely these variants were associated with rapid disease progression in a chronic HIV-1 subtype C infection cohort.

**Conclusions:** Our findings reveal how polymorphisms at positions corresponding to HIV IN119 and IN231 affect both local and global integration site targeting. Intriguingly, these findings link integration site selection to virulence and viral evolution but also to the host immune response and antiretroviral therapy, since HIV-1 IN119 is under selection by HLA alleles and integrase inhibitors.

**Under embargo until 11.00 on 21 July 2015**