

Abstract

Objectives: Characterization of HIV-1 from slow progressors (SP) is important to facilitate vaccine and antiviral drug development. In order to identify virus attenuations that may contribute to slower rates of disease progression, the full viral genomes from primary isolates of six slow progressing HIV-positive children were sequenced.

Methods: Primary virus biological phenotypes were determined by growth in CCR5- and CXCR4-expressing U87.CD4 cell lines. Proviral DNA was isolated from co-cultured PBMCs, and the near full-length genomes and LTR regions were PCR amplified, sequenced and analysed. Predicted amino acid (aa) sequences for all the HIV-1 proteins were extensively analyzed.

Results: All primary HIV-1 isolates utilized CCR5, and were determined to be HIV-1 subtype C by phylogenetic analysis. Predicted aa sequence analysis revealed open reading frames for all HIV-1 genes which encoded for proteins of the expected length, with several exceptions. For example, isolate LT5 had a 2 aa insertion in the Vpr mitochondriotoxic domain. Isolate LT21 contained an additional 5aa in the C-terminus of tat exon 2, while the integrase enzyme in isolate LT39 had an additional 3aa at the C-terminus. Rev from isolates LT45 and LT46 did not have the characteristic subtype C 16aa truncation, and in addition, had a further 3aa. In addition, altered functional domains was noted in several isolates, such as the cAMP-dependent kinase PKA phosphorylation site in Nef (LT5), a Vpr mutation involved in decreasing pro-apoptotic activity (LT42), and the Nef ExxxLL motif involved in the interaction with AP-1 and AP-2 (LT46).

Conclusions: The slower HIV disease progression in these six children may be attributed to altered protein functions. For example, LT46 Nef is unable to bind AP-1 and AP-2 and therefore inactive on CD4 endocytosis. The biological relevance of these findings requires further investigation.