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A novel mutation D404N in the connection sub-domain of reverse transcriptase of HIV-1 CRF08_BC subtype confers cross resistance to NNRTIs

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Growing evidence suggests that mutations in the connection domain of the HIV-1 reverse transcriptase (RT) can contribute to viral resistance to RT inhibitors. This work is designed to characterize a novel mutation D404N in the connection sub-domain of RT of HIV-1 CRF08_BC subtype on drug resistance, viral replication capacity (RC) and RT activity. Mutation D404N alone or together with the other reported mutations were introduced into an HIV-1 CRF08_BC subtype infectious clone by site-directed mutagenesis. The drug susceptibility to nine RT inhibitors, viral RC and the DNA polymerase activity of viral RT of the constructed virus mutants were investigated. Modeling study using the server SWISS-MODEL was conferred to speculate the possible structure-related drug resistance mechanism of the mutation D404N. Single mutation D404N and H221Y conferred low-level resistance to nevirapine, efavirenz, rilpivirine and zidovudine. Double mutations Y181C/D404N and Y181C/H221Y significantly reduced susceptibility to NNRTIs. The most pronounced resistance to NNRTIs was observed with the triple mutations Y181C/D404N/H221Y. The virus containing a single mutation D404N displayed approximately 50% of RC compared to the wild type (WT) virus. Modeling study suggested that the D404N mutation might abolish the hydrogen bonds between residue 404 and K30 in p51 or K431 in p66, leading to impaired RT subunit structure and enhanced drug resistance. These results indicate D404N to be a novel NNRTI-associated mutation in the HIV-1 CRF08_BC subtype which provides valuable information to monitor clinical RTI resistance.

Biography

Bojian Zheng has completed his PhD at The University of Hong Kong and Postdoctoral studies from McMaster University in Canada. He is currently a Professor working in Department of Microbiology, The University of Hong Kong. He has published more than 180 papers in reputed journals and has been serving as an Editorial Board Member of several international journals.

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