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Interpretation Approaches

Bayesian network analysis of resistance pathways in HIV-2 reverse transcriptase


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Introduction: HIV-2 antiviral resistance is a major cause of therapy failure and compromises future treatment options. Because of the high mutation rate of the virus, resistance mutations emerge under drug selective pressure. This is more problematic for HIV-2 than for HIV-1, because treatment options are more restricted and most drugs loose their efficacy with fewer mutations than for HIV-1. HIV-2 drug resistance pathways are still insufficiently understood. In this study, Bayesian Network probabilistic modeling was applied to investigate associations of mutations in the HIV-2 reverse transcriptase (RT), and infer resistance pathways against nucleoside RT inhibitors (NRTI).

Material & Methods: This study assessed 176 HIV-2 infected patients. 76 had never undergone antiretroviral therapy and constituted the control group, and 100 patients were treatment-experienced. All samples belonged to HIV-2 subtype-A. An in-house method was used to amplify and sequence an HIV-2 fragment comprising part of the RT. Sequences were analyzed with SeqScape® software using ROD HIV-2 strain as reference. χ² statistics and Bayesian Network analysis were used to identify mutations selected during therapy and investigated dependencies between them. Robustness of network features was assessed with non-parametric bootstrap and only interactions with bootstrap support over 70% were considered for analysis.

Results: The Bayesian network analysis indicated K65R, Q151M and M184V as the three main mutations directly associated to treatment in HIV-2 RT, also suggesting that they occur mostly independently from each other. The S215A/C/F/L/Y substitutions could not be excluded as additional primary mutations, since they were also directly connected to treatment, but the bootstrap support was < 70%. Several mutations appeared in the network as secondary, being selected in the presence of a primary mutation. It is the case of mutations R22K, T53S, A62V and V111I, which appear to be independently selected in the presence of K65R, and possibly represent four distinct pathways towards drug resistance. The Q151M mutation evidenced two alternative resistance pathways, one through accessory mutation F214L, with which it showed a very robust association, and another through the selection of V111I. Interestingly, the network suggested a weak association between K65R and Q151M.

Conclusions: This analysis suggests the existence of three main pathways implicated in the development of resistance to reverse transcriptase inhibitors in HIV-2, through mutations K65R, Q151M and M184V. K65R and Q151M are substantially more common in HIV-2 than in HIV-1. The association between Q151M, V111I and F214L may constitute a specific HIV-2 multi-NRTI resistance complex, and warrants further investigation. Accessory mutations are thought to compensate the virus for a loss of fitness due to the acquisition of primary mutations, but in vitro mutagenesis is required to corroborate their true phenotypic impact.

No conflict of interest