Title:	Small Conformational Changes Underlie Evolution of Resistance to NNRTI in HIV Reverse Transcriptase
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Abstract:	Despite achieving considerable success in reducing the number of fatalities due to acquired immunodeficiency syndrome, emergence of resistance against the reverse transcriptase (RT) inhibitor drugs remains one of the biggest challenges of the human immunodeficiency virus antiretroviral therapy (ART). Non-nucleoside reverse transcriptase inhibitors (NNRTIs) form a large class of drugs and a crucial component of ART. In NNRTIs, even a single resistance mutation is known to make the drugs completely ineffective. Additionally, several inhibitor-bound RTs with single resistance mutations do not exhibit any significant variations in their three-dimensional structures compared with the inhibitor-bound RT but completely nullify their inhibitory functions. This makes understanding the structural mechanism of these resistance mutations crucial for drug development. Here, we study several single resistance mutations in the allosteric inhibitor (nevirapine)-bound RT to analyze the mechanism of small structural changes leading to these large functional effects. In this study, we have shown that in absence of significant conformational variations in the inhibitor-bound wild-type RT and RT with single resistance mutations, the protein contact network analysis of their static structures, along with molecular dynamics simulations, can be a useful approach to understand the functional effect of small local conformational variations. The simple network analysis exposes the localized contact changes that lead to global rearrangement in the communication pattern within RT. Furthermore, these conformational changes have implications on the overall dynamics of RT. Using various measures, we show that a single resistance mutation can change the network structure and dynamics of RT to behave more like unbound RT, even in the presence of the inhibitor. This combined coarse-grained contact network and molecular dynamics approach promises to be a useful tool to analyze structure-function studies of proteins that show large functional changes with negligible variations in their overall conformation.
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