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Poster presentation

A bioinformatic approach to identify new potential resistance relevant amino acid substitutions (AAS) in HIV-1 protease (H1P)

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Background

Predicting potential drug resistance mutations are important when evaluating protein-drug interactions of potential new antiviral drugs. Here we used evolutionary data from the Retroviral Aspartyl Protease (RVP) family (PF00077, 54135 sequences) to estimate plausible PI resistant-associated AAS within the H1P.

Methods

Using a Hidden Markov Model (HMM) of the RVP family probabilities were extracted for each possible AAS limited to the 38 positions reported in the IAS drug resistance listing for H1P (December 2008 version). The HMM is a dynamic Bayesian network, modeling sequences of amino acids. The HMM is based on curated and representative sequences from the RVP family.

Results

Theoretically 760 AAS (20 × 38) are possible for the 38 evaluated positions within the H1P. Of these, the RVP-HMM detected a total of 229 AAS (30.1%) with a probability above 1/20 (0.05). Of the 229 AAS, 51 (70%) were among the 73 AAS included in the IAS listing as PI-resistant mutations, leaving 178 AAS with $P > 0.05$ as evolutionary plausible.

Conclusion

Based on exploration of the RVP family by HMM, 70% of the established PI-resistant associated AAS could be predicted to occur. Additional 178 AAS was identified as evolutionary plausible and potentially could allow for drug-resistance. In conclusion, we provide a probability landscape of plausible/unfavorable AAS based on inherited structure through evolution and genetic distance, which could prove useful for future drug design.