tary Figure 2). H110R is in close structural proximity to F154Y and the natural substrate of the protease (Supplementary Figure 3). Although it might be preferable when investigating BSVs to engineer swaps of the complete NS3 sequence into the background of a replication-competent clone, it is not clear how often this approach would fail due to sequence incompatibilities between the donor and recipient viruses. NS3 appears to interact with several other viral proteins.[28]

Our findings provide a molecular basis for ketoamide resistance among BSVs that exist naturally as dominant quasi-species in some patients before treatment with DAAs (Supplementary Table 3). Such natural variants might be of limited clinical significance at present because they are likely to be suppressed by Peg-IFN/RBV in current SOC regimens, but they can be expected to be of substantial importance to the outcome of future interferon-sparing, all-DAA combination therapies. These variants might also affect future generations of inhibitors depending on their chemical structures. Knowledge on the natural variability in structures targeted by antivirals, as presented in this study, can help guide the development of future generation PIs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.11.035.

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Conflicts of interest

These authors disclose the following: Stefan Zeuzem has served as a consultant for Abbott, Achillion, Anadys, BMS, Boehringer, Gilead, iTherX, Janssen, Merck, Novartis, Pfizer, Pharmasset, Roche, Santaris, Tibotec, and Vertex. Stanley M. Lemon has served as a consultant for Abbott, Hoffmann-LaRoche, Juvaris Biotherapeutics, Merck, Novartis, and Pfizer; research in his laboratory is supported by Merck and Tibotec. The remaining authors disclose no conflicts.

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