Single residue mutations may affect protein function without introducing detectable effects on structure. I will present multiple examples in which mutations have surprising effects in vitro, including the differential binding of a disease-associated Val66Met variant in a long intrinsically disordered region of BDNF and the temperature-dependent effects of the Lys289Met mutation in the GABA(A) receptor, which causes seizures with fever. None of these mutations has well-defined effects on the overall protein structure or conformation, but we find through molecular dynamics simulations that the in vitro observations can be explained through differential protein-solvent or intraprotein interactions. These are not the hydrogen-bonds or salt-bridges most commonly addressed in a structurally-focused analysis, but include specific methionine-methionine interactions, quasi-symmetric electrostatic repulsions, and differential interactions with lipid. Finally, I will provide general strategies for detecting these interactions, as well as caveats for their treatment in simulations.