Abstract

Predicting the impact of missense protein variants on drug binding would have a widespread impact on the practice of genomic medicine, and enable matching a molecular therapy and dosage to an individual’s genomic sequence. Using simulations of opioid binding to naturally occurring variants in opioid receptor mu 1 (OPRM1), the ligand specific changes to binding energy demonstrate how specific drug:variant predictions can inform clinical decisions.

Introduction

Genomic profiling studies of healthy individuals have revealed an enormous amount of naturally occurring variation, and understanding the functional significance of these differences presents a major challenge to genomic medicine. This is especially true for missense variants, which presumably persist in the population because the underlying change to the protein structure only minimally impacts the wildtype function. However, when these variants occur in the functional domains of small molecule drug targets it can alter the drug response.

Predicting the impact of genomic variation on ligand binding would help inform clinical decisions when selecting an appropriate molecular intervention and dosage. This is particularly important when adverse drug responses can lead to a public health crisis, as with opioid misuse. While the driving factors underlying tolerance, addiction, and abuse are complex, the responsible administration of these powerful interventions would benefit from insight into how specific drug:target interactions will be altered.

The combinatorial explosion that results from the limitless pool of potential variants and continuously expanding list of drug candidates necessitates the use of a computational method inform clinical decision making. Our previous work highlighted the translational potential of a simulation based approach for predicting the impact of drug resistant somatic variation on available kinase inhibitors, leading to an improved workflow (SNP2SIM) and its extension to G-protein-coupled receptors (GPCRs) using opioid receptor mu 1 (OPRM1) presented here.

Methods

Binding simulations were run using the drugSearch module of the SNP2SIM, a Python-based workflow built to enable large scale computational simulations of variant protein structures. The initial structure of active OPRM1 and variants to the binding interface were obtained from GPCRdb, and an opioid drug library was built from 27 opioid structures downloaded from DrugBank. SNP2SIM was used to run 10 independent simulations of AutoDock Vina for each of the variant:drug combinations, and results for prediction to the wildtype system were validated using experimental inhibitory constants (R^2 = 0.79, not shown).

Results

Comparing the predicted binding affinity of a variant to that of the wildtype provides a relative measure of the variant impact on drug binding (Figure 1). Increases in the relative binding energy correlate to

Figure 1. Predicted impact of variants in OPRM1. Increases in the binding energy relative to the wildtype indicate weaker binding.
decreased binding of the drug compared to the wildtype simulations. In general, variants show a similar impact across the opioid library, enhancing (238I, 302I) or diminishing (235M, 235N) the interactions of OPRM1 with the ligand. However, depending on the ligand, the 153V variant predicted both increased (morphine, fentanyl) and decreased (oxycodone, oxymorphine) compared to the wildtype structure.

These trends are highlighted in the plots for the variant impact on individual drugs (Figure 2). For some ligands, binding to variant structures did not drastically alter interactions compared to the wildtype, showing a similar pattern to endomorphin. The predicted robustness of this natural OPRM1 ligand to variation in the binding pocket seems reasonable, given that these variants are not associated with any adverse conditions and found in healthy individuals.

**Discussion**

The emerging discipline of genomic medicine will rely on an individual’s genome to guide treatment decisions. Robust, accurate models of how variants in the protein targets of molecular interventions can inform prioritization or dosage of a particular drug. The simulation results provide additional insight into structure based drug design. For example, drugs whose variant binding profile correlates with endomorphin (hydrocodone, mitragynine, PZM21) may be good candidates to seed the next generation of targeted therapeutics.

This current study is limited to variants that interact directly with the bound ligand, despite many more OPRM1 variants curated in GPCRdb. These changes to the proteins primary structure will influence conformational dynamics and spatial organization of binding residues. A structure based prediction would require simulating the variant protein structures using molecular dynamics. Additional modules of SNP2SIM enable these computationally intensive simulations for cytoplasmic or extracellular protein domains, and will be extend to membrane embedded structures in a future update.

The current guidelines for the clinical interpretation of variants (American College of Medical Genomics, Association for Molecular Pathology) justifiably do not allow for the sole use of computational evidence to make a strong assertion of a variants functional impact. But this is largely in part to the uncertainty of methods that only provide a generalized or non-ligand specific prediction. The ligand-dependent impact on binding observed in OPRM1 153V is lost when the prediction is categorical (pathogenic/disruptive or benign) or doesn’t explicitly consider differences in the biochemical nature of individual ligands. SNP2SIM enables the protein specific characterization of variants of unknown significance, providing a more robust form of computational evidence to support their clinical interpretation and translation to clinical practice.

**References**