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DrugFEATURE: Identifying Druggable Targets by Protein Microenvironments Matching

Druggability of a protein is its potential to be modulated by drug-like molecules. It is important in the target selection phase. We developed DrugFEATURE to quantify druggability by assessing the microenvironments in potential small-molecule binding sites. We benchmarked DrugFEATURE using two data sets. One data set measures druggability using NMR-based screening. DrugFEATURE correlates well with this metric. The second data set is based on historical drug discovery outcomes. Using the DrugFEATURE cutoffs derived from the first, we accurately discriminated druggable and difficult targets in the second. We further identified novel druggable transcription factors with implications for cancer therapy. DrugFEATURE provides useful insight for drug discovery, by evaluating druggability and suggesting specific regions for interacting with drug-like molecules.

Applications

- DrugFEATURE can be used systematically to estimate the potential of drug and drug-like molecules to modulate the network by quantifying the druggability of particular genes in a disease-associated network
- DrugFEATURE is able to quantify the druggability of individual transcription factors and identify most promising for early stages of drug discovery. It can also assist in developing therapeutic strategies that are more likely to be successful. Transcription factors are among the most intriguing targets for treating cancer, yet they (as a group) are considered difficult targets.

Advantages

- • DrugFEATURE is a simple and fast procedure that can evaluate druggability computationally. It provides an estimate of the difficulty of targeting a particular molecule and can highlight problematic microenvironments that are not seen in the database of pockets associated with successful drug binding.
- • DrugFEATURE predictions correlate well with both experimental results and drug discovery outcomes. DrugFEATURE achieves better performance in terms of discriminating druggable targets from undruggable ones, compared to other state-of-art methods, including F-pocket, SiteMap, and DLID.

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