

Binding site similarity analysis for the functional classification of the protein kinase family

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Methods for analysing complete gene families in the drug discovery process are becoming of increasing importance, because similarities and differences within a family are often the key to understanding functional differences that can be exploited in drug design. Constituting around 1.7% of the human genome, the protein kinase family is one of the largest enzyme families and plays key roles in almost all signalling pathways. Since the deregulation of these signalling pathways often leads to disease, the control of protein kinase activity is a principle focus of pharmaceutical research. The vast majority of kinase inhibitors target the ATP-binding site. However, the high degree of sequence and structural conservation amongst the protein kinases means that the design of potent, selective kinase inhibitors is a significant challenge.

We have developed a large online database for the retrieval of ligand binding site similarities¹. These are extracted automatically from the Macromolecular Structure Database using a geometric hashing algorithm². We have undertaken a large-scale comparison of protein kinase ATP-binding sites. This has allowed us to discover binding site similarity in different sub-families of protein kinase that are not evident from sequence similarity alone. It has also enabled us to quantify the effect of how different drug molecules bind to the same binding site and influence the local binding site conformation. We propose a relevant classification of the protein kinase family based on the similarity of their binding sites. Not only does this classification highlight features that are important for the potency and selectivity of kinase inhibitors, but it also allows us to predict possible cross-reactivity among the protein kinases.

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