

STRUCTURAL STUDIES OF WD REPEAT PROTEINS,
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WD repeats (also known as beta-transducin or WD40 repeats) are ~40 amino acid sequence motifs that are weakly conserved and have been found in hundreds of mostly eukaryotic proteins. In general, they appear to function by mediating the protein-protein interaction involved in a large and diverse number of physiologically relevant processes. WD repeat proteins are coded for by a significant portion of well-characterized genomes, more than 1% in the case of budding yeast and nearly 2% in other eukaryotes. The structure of the beta subunit of the G protein has previously defined the structure for this family of proteins as a beta-propeller. Each WD repeat effectively generates one blade of the propeller which is composed of a four-stranded beta-sheet. Structures of G-beta and several other proteins have demonstrated that seven of these repeats yield seven blades in the propeller. Examination of genomic data indicates that perhaps the majority of these proteins have fewer or more than seven repeats. Is the beta propeller motif able to accommodate a variable number of blades or are the sequences of some WD repeats unrecognizable within a stable, 7-bladed fold?

In order to understand the structural diversity of this family, we have determined the crystal structures of four WD-repeat proteins with greater and less than seven repeats as identified by sequence. Functionally, these proteins are completely unrelated, playing roles in the mitotic checkpoint (Bub3p), mRNA degradation (Ski8p), actin depolymerization (Aip1p) and histone deacetylation (Sif2p). Surprisingly, almost all of these contain domains that fold into the canonical seven-bladed motif implying that many of these repeats may not be identified by sequence using current criteria. Since similar structure often indicates similar function, the regions of the WD repeat proteins responsible for partner protein binding are being mapped using a variety of techniques. A common surface area seems to be emerging on the “top” of the propeller, a region that is composed of many loops. These loops are not as well conserved as the core of the propeller suggesting that modulation of the protein interaction surface specificity can be easily altered without affecting the overall structure, reminiscent of what is seen in antibodies.