

proteins bound hypophosphorylated isoforms, they were not efficient at stimulating ubiquitination. Thus, phosphorylation may play additional roles following substrate binding. Furthermore, binding of phosphorylated Sic1 may be more complex and additional positively charged residues distributed on the surface of Cdc4 might serve as additional phosphoacceptors. The situation might be even more complex *in vivo* because homologs of Cdc4 have been found to form oligomers (Kominami et al., 1998; Wolf et al., 1999). Nonetheless, by perturbing the CDP-Cdc4 interface, the authors strongly support the idea that the single CPD binding site is critical for setting the hexameric phosphorylation threshold for Sic1 binding. Thus, they illustrate the theory that binding of a polyvalent ligand to a single receptor site can create cooperative binding and an ultrasensitive transition.

The CPD-Cdc4 structure will certainly allow more detailed tests of how Cdc4 counts phosphorylation sites and may provide clues to the binding specificity of other WD40 containing F box proteins, including the highly studied β TrCP. Even so, the remaining questions of how substrates, once bound, are presented to the SCF ubiquitin ligase, the potential role of oligomerization, and the mechanism of ubiquitin chain assembly will keep us busy for more time to come!

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Visualizing Genetic Influences on Human Brain Functions

Egan and colleagues (2003), in this issue of *Cell*, integrate genetics and functional brain imaging by showing that variation in the human brain-derived neurotrophic factor (BDNF) gene is associated with variation in episodic memory ability and in hippocampal neurochemistry and function.

Over the last decade, two of the most exciting frontiers of human biology have been genetics and functional brain imaging. Genes that influence human behavior must logically do so through their effects in the brain at the level of neuronal functioning. The bridges from gene to brain to mind have, however, been studied by indirect inferences, such as twin studies that compare similarities in brain structures and mental abilities between unrelated people, dizygotic twins, and monozygotic twins (e.g., Thompson et al., 2001). These interesting studies, however, are limited by much-debated assumptions about heritability estimates and by an absence of specification of genetic and molecular mechanisms.

In a pioneering study that integrates genetics and functional imaging of the human brain, Egan et al. (2003) have linked genetic variation in humans to variation in both memory ability and hippocampal function. The hippocampus, located bilaterally in the medial temporal lobes, is essential for the formation of long-term memory in animals (Squire, 1992) and humans (Gabrieli, 1998). In humans, damage to the hippocampus and adjacent structures results in global amnesia, the inability to form new memories for events (episodic memory) and facts (semantic memory) despite otherwise intact mental abilities. The neural mechanisms underlying hippocampal plasticity have been investigated in detail, and long-term potentiation (LTP) has arisen as the predominant model of hippocampal learning mechanisms. *In vivo* and *in vitro* animal studies have shown that the BDNF protein plays an important role in hippocampal LTP, and this suggests that genetic variation associated with BDNF may affect hippocampal LTP and, thus, memory function.

Egan et al. (2003) divided subjects on the basis of a common, single nucleotide polymorphism that alters the amino acid sequence in the pro-region of the human BDNF gene. Subjects were divided into three BDNF alleles varying by a valine (val) to methionine (met) substitution. The met/met group demonstrated inferior performance on a test of episodic memory for short stories compared to the other two groups (val/val and val/met). Two *in vivo* imaging measures of the hippocampus were utilized to further compare differences between individuals with the val/met and met/met alleles. One measure involved proton magnetic resonance spectroscopic imaging (MRSI), which provides a measure of intracellular neurochemical integrity. MRSI revealed that val/met heterozygotes had lower levels of hippocampal NAA, an intracellular marker of neuronal function, than did val/val homozygotes.

The second brain measure utilized functional magnetic resonance imaging (fMRI), which provides a mea-

