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Crystal Structure of Human Dj-1, A Protein Associated with Early-Onset Parkinson's Disease. Xiao Tao, Liang Tong, Dept. of Biological Sciences, Columbia Univ., New York, NY 10027 USA.

Recently, it was discovered that three types of mutations in the DJ-1 gene are linked with autosomal recessive early onset familial Parkinson's disease. One is a deletion of several of its exons, which abolishes the production of the DJ-1 protein. The other two disruptions are single-point mutations, L166P and E64D. We determined the crystal structure of human DJ-1 at 1.8 Å resolution (1). The monomer of DJ-1 contains the α/β fold that is conserved among members of the DJ-1/ThiJ/PfpI superfamily. However, the structure also contains an extra helix at the C-terminus, which mediates a novel mode of dimerization for the DJ-1 proteins. A putative active site has been identified near the dimer interface, and the residues Cys106, His126 and Glu18 may play important roles in the catalysis by this protein. Studies with the disease-causing L166P mutant suggest that the L166P mutation has disrupted the C-terminal region and the dimerization of the protein. The DJ-1 proteins may function only as dimers. The other disease-causing mutation E64D does not affect the structure of DJ-1 itself, which, together with the observation that the loop containing residue E64 is highly flexible, indicates that this region of DJ-1 may be involved in binding another protein and the mutation causes deleterious effects by disrupting this interaction. We also showed that the Lys to Arg mutation at residue 130, the site of sumoylation of DJ-1, has minimal impact on the structure of the protein.

1. Tao, X. & Tong, L. (2003) *J. Biol. Chem.* 278, 31372-31379.