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Domain Flexibility and Catalysis in the Complex II Superfamily. Thomas M. Tomasiak[1,2,6], Elena Maklashina[7,8], Kristian Kaufmann[5,6], Eric Dawson[3,4,6], Jens Meiler[1,3,5,6], Gary Cecchini[7,8], Tina M. Iverson[1,2,3,4,6], [1]Dept. of Pharmacology, [2]Vanderbilt Inst. for Chemical Biology, [3]Center for Structural Biology, [4]Dept. of Biochemistry, [5]Dept. of Chemistry, [6]Vanderbilt Univ., Nashville, TN, 37232, [7]Molecular Biology Div., VA Medical Center, San Francisco, CA, 94121 [8]Dept. of Biochemistry and Biophysics, UCSF, San Francisco, CA 94143.

The catalytic subunits of integral membrane Complex II enzymes have a conserved fold comprising two domains: an FAD-binding domain and a capping domain. The capping domain covers the active site with multiple residues within hydrogen bonding distance of substrate. Of note is Thr 244, which has not been assigned a direct catalytic role, yet when substituted to Ala reduces catalytic activity by 97%. To establish the basis for this loss of activity, the structure of a T244A variant in the *Escherichia coli* Complex II homolog Quinol:Fumarate Reductase (QFR) was determined to 3.65Å resolution. In this structure, the capping domain significantly rotates to expose the active site to solvent. This domain shift combined with interface stability calculations suggests that the hydrogen bond between Thr 244 and substrate is critical for inducing capping domain closure and correct orientation of catalytic residues upon substrate binding.