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Structural Investigations of the Hydrophobic Core of the Flavin-Dependent Thymidylate Synthase. Irimpan I. Mathews¹, Heath Klock^{2,3}, Eileen Ambing^{2,3}, Scott A. Lesley, Ashley M. Deacon^{1,2}, ¹Stanford Synchrotron Radiation Laboratory, ²The Joint Center for Structural Genomics, Stanford Univ., 2575 Sand Hill Rd, SSRL MS 69, Menlo Park CA 94025, ³The Genomics Inst. of Novartis Research Foundation, 10675 John Jay Hopkins Dr., San Diego, CA 92121.

The functional role of two of the highly conserved residues from the hydrophobic core of flavin-dependent thymidylate synthase (thyX/Thymidylate Synthase Complementing Protein) has been analyzed by stability measurements and structural studies. We have solved five structures of the double mutants of the highly conserved residues from the hydrophobic core of FDTS. These results emphasize the importance of the rigidity of the hydrophobic core and its plasticity to accommodate small changes in the size of the contributing side chains. Interestingly, while the drastic changes in the sizes of the side chains affected the cofactor and substrate binding properties, enzyme was able to maintain its overall fold. In conclusion, the current study shows that small changes in the sizes of the hydrophobic residues do not affect the overall fold and supports the earlier suggestion of a common overall fold for the FDTS/TSCP family of enzymes.