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Structure and Function of the N-terminal 40 kDa Fragment of Human PMS2: a Monomeric GHL ATPase

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Human MutLa, a heterodimer of hMLH1 and hPMS2, is essential for DNA mismatch repair. Inactivation of the *hmlh1* or *hpms2* genes by mutation or epigenesis causes genomic instability and predisposition to hereditary non-polyposis cancer. We report here the X-ray crystal structures of the conserved amino-terminal 40 kDa fragment of hPMS2, NhPMS2 and its complexes with ATP_gS and ADP at 1.95, 2.7 and 2.7 Å resolution, respectively. The NhPMS2 structures closely resemble the ATPase fragment of *E. coli* MutL, which coordinates protein-protein interactions in mismatch repair by undergoing structural transformation upon binding of ATP. Unlike the *E. coli* MutL, whose ATPase activity requires protein dimerization, the monomeric form of NhPMS2 is active both in ATP hydrolysis and DNA binding. NhPMS2 is the first example of a GHL ATPase active as a monomer suggesting that its activity may be modulated by hMLH1 in MutLa and *vice versa*. The potential heterodimer interface revealed by crystallography provides a mutagenesis target for functional studies of MutLa.