# Investigation of ATP-induced global motions of the human DNA mismatch repair sensor complex using time-lapse crystallography

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Over 1 in 300 people in the US have Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC), which is caused by mutations in DNA mismatch repair (MMR) genes. Over 40% of the Lynch syndrome mutations are found in the human MSH2 gene, which is the common subunit that forms the key MMR lesion sensors MutSα (MSH2-MSH6) and MutSβ (MSH2-MSH3). MSH2 mutations are also identified in over ten other cancer types. The MutS proteins are members of the ABC ATPase family that undergo large conformational rearrangements upon binding/hydrolysis of ADP/ATP. Here we present our time-lapse X-ray crystallography studies to demonstrate the conformational changes of MSH2 as it transitions from ATP to ADP bound states. A dramatic and global conformational rearrangement is triggered after ATP hydrolysis, which spans over 150 Å and causes over 60-degree domain rotations. Time-lapse crystallographic results reveal a network of interactions that link the ABC ATPase center to the DNA binding domains. Moreover, a nascent globular domain formed only in specific nucleotide states has been identified, which is stabilized by residues that are variants of unknown significance in Lynch syndrome and other cancers. Our findings provide new insights into the mechanism of MMR and could aid the development of better colorectal cancer risk prediction models and personalized therapeutic strategies. These results may also extend the understanding of the mechanism of other ABC ATPase family proteins.