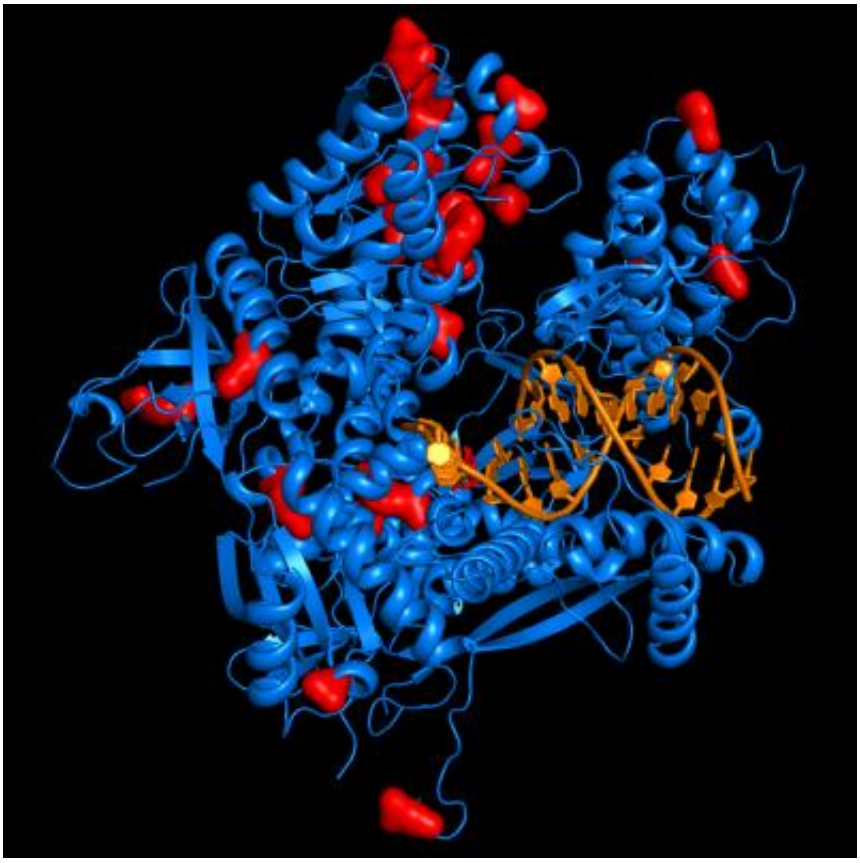
Detailed image shows how genomes are copied

December 2 2013



The image shows how mutations that can contribute to the development of colorectal cancer and cervical cancer lead to changes in the structure of the protein. Credit: Erik Johansson

For the first time, researchers at Umeå University have succeeded in showing how the DNA polymerase epsilon enzyme builds new genomes.

The detailed image produced by these researchers shows how mutations that can contribute to the development of colorectal cancer and cervical cancer lead to changes in the structure of the protein. This study will be published in the journal *Nature Structural and Molecular Biology*.

Genomes are built from pairs of long strands of DNA. In previous collaborations with American researchers, Umeå University scientists have shown that DNA polymerase epsilon is one of the three enzymes that build DNA strands in all higher-level organisms from yeast to humans. When the DNA of an organism's genome is copied, DNA polymerase epsilon is responsible for building about half of the DNA. This process occurs quickly and with very high accuracy to avoid producing mutations that can be detrimental to the cell and to the organism as a whole.

To understand on a molecular level how DNA polymerase epsilon builds new DNA so quickly and accurately, researchers at Umeå University have used X-ray crystallography techniques to produce a highly detailed picture of the protein caught in the act of building a new piece of DNA. They discovered that DNA polymerase epsilon has a unique protein structure – a domain that has never been seen in any other polymerase. This new domain suggests that DNA polymerase epsilon has developed a unique way of holding on to the DNA that it is copying without falling off and having to start over again.

The researchers performed further experiments to confirm their new model and showed that the new domain (that they have called the P-domain) is, indeed, critically important for the protein's ability to build long strands of DNA without falling off. This is an important property of DNA polymerase epsilon that allows it to fulfil its role in copying DNA and reproducing the genome as a cell divides.

The human genome has now been mapped. Today there are large on-

going international studies in which the DNA of tumour cells and of families with hereditary conditions are being sequenced to see if there are any special mutations that have caused the tumours to form or that have led to the hereditary conditions. As part of this work, a series of mutations within DNA polymerase epsilon have recently been discovered that can be directly linked to the development of colorectal and cervical cancers.

"The structure of the polymerase that we have solved makes it possible to see where these mutations lead to changes in the structure of DNA polymerase epsilon," says Erik Johansson, Professor at the Department of Medical Biochemistry and Biophysics, "This can help us to understand why a certain mutation contributes to the development of a certain cancer." Professor Johansson conducted the study in collaboration with others including Elisabeth Sauer-Eriksson, Professor at the Department of Chemistry.

More information: The article describing this work will be published in the January edition of the journal *Nature Structural and Molecular Biology*.

Provided by Umea University