Hereditary cancer risk

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(Medical Xpress) -- Medical researchers have discovered a new type of mechanism causing cancer susceptibility, showing that tiny changes in some anti-cancer genes can act as magnets to attract modifying "biochemical tags", effectively switching them off and predisposing families to an increased risk of the disease.

The study and its findings are reported in the leading international journal Cancer *Cell*.

The researchers, from the University of New South Wales (UNSW), believe a tiny spelling mistake involving a single letter in the DNA sequence near the start of the genes is what attracts the biochemical tag – known as methylation.

This biochemical tag directly impacts on our DNA, by switching genes off.

“Methylation sits on top of our DNA, and provides the instructions to turn the gene off,” explains study co-leader, Dr Megan Hitchins, from UNSW’s Lowy Cancer Research Centre.

In one well-known cause of hereditary cancer, changes in the cancer-prevention gene MLH1 are passed from parent to child creating up to 80 percent risk of developing bowel, uterine and other cancers. However, some families with hereditary cancer have no spelling mistakes in MLH1, but instead have methylation sitting on the gene.

“When the methylation attaches to the MLH1 gene in these families, it causes it to be completely switched off and as a consequence cancer develops,” says study co-leader and head of the adult cancer program at the Lowy Cancer Research Centre, Professor Robyn Ward. “But until now, we did not understand how these methylation tags were being passed from parent to child.”

In the study the researchers looked at three generations of a large family, who had cancer at a young age, but in whom no spelling mistakes typical of this hereditary cancer syndrome had been found. Strikingly several members of the family from all generations had methylation tags on their gene.

“In this family, biochemical tags attached to the MLH1 gene were present in all three generations. This was intriguing since these markers are usually removed during the production of eggs and sperm,” Dr Hitchins said.

“What we found was that a subtle change near the gene was acting like a magnet to attract methylation. So it was not the methylation itself that was being passed from parent to child, but rather the DNA change, and this acted as a methyl magnet,” she said.

The methylation was cleared away in the sperm and eggs and then recreated in each new generation, the researchers said.

Professor Ward said the discovery pinpointed the cause of cancer in this family and it offered new options for genetic diagnosis, counselling and early interventions in other families at risk of hereditary cancers.

The team is also exploring the use of certain drugs to clear away the methylation in cancer to switch the anti-cancer genes back on again. In the future these drugs may be used to create a more targeted approach to

cancer treatment and possibly prevention.

Other researchers involved in this study were the Genetic Services of Western Australia and School of Paediatrics and Child Health, University of Western Australia.

Provided by University of New South Wales