MedicalXpress

Study sheds new light on aggressive cancer in children

February 3 2015

A new study involving researchers at The University of Nottingham has revealed how children with an aggressive cancer predisposition syndrome experience a never before seen flood of mutations in their disease in just six months.

The syndrome, called 'biallelic mismatch repair deficiency' (bMMRD) causes multiple brain tumours, lymphomas and gastrointestinal cancers by the age of 10. As a result these children rarely survive into adulthood.

While most cancers grow progressively, developing genetic mutations over many years, researchers at The Hospital for Sick Kids in Toronto, Canada, the Wellcome Trust Sanger Institute and the Children's Brain Tumour Research Centre in Nottingham, were shocked to find that children with this syndrome develop more mutations than any human cancers by far—as many as 20,000 mutations in as little as six months.

The new paper, published online in *Nature Genetics*, suggests a previously undiscovered mechanism for cancer progression which could lead to more targeted treatment for these patients and indeed for more common cancers.

'Great flood'

Children with biallelic mismatch repair deficiency, or bMMRD, have mutations in the genes responsible for mismatch repair and therefore cannot fix mistakes in DNA while the cell is dividing (or replicating). This study identifies a secondary mutation which occurs only in tumour cells in an enzyme called polymerase, which is a second safeguard that helps to effectively repair mutations while the DNA replicates. The combination of these two mutations leaves patients with no ability to repair mistakes that may occur while DNA is replicating, and causes a rapid wave of cancer that the investigators have dubbed the "great flood."

Professor Richard Grundy from the University's Children's Brain Tumour Research Centre said: "This study provides a major step forwards in understanding why certain children are more susceptible to developing multiple cancers and can screen for this eventuality. In turn, this study allows us to begin to understand the steps that lead to cancer developing. Ultimately, we hope this leads to treatments to avoid the presently inevitable consequences of this predisposition syndrome"

Implications for diagnosis and treatment

Dr Uri Tabori, co-principal investigator of the study from Genetics & Genome Biology at SickKids, Toronto said: "In other cancer predisposition syndromes like BRCA1 and Li Fraumeni syndrome, we know that there is a genetic mutation that predisposes the individual to

cancer, but we do not know the secondary mutation, or genetic driver that actually causes the cancer to occur. Our findings indicate the genetic driver that causes this 'great flood' of cancer mutations in patients with bMMRD. The secondary mutation in the enzyme polymerase causes a unique signature of mutations that is present in 100 per cent of the cases. This has important implications for both diagnosis and targeted treatment of this devastating disease."

The Children's Brain Tumour Research Centre in Nottingham is part of an international consortium run by SickKids, Toronto, that offers free genetic testing, genetic counseling and surveillance of cancers in children and family members with bMMRD. Using genetic and clinical information and tumour samples gathered from each patient, the research team was able to take a deeper look at this cancer predisposition syndrome and for the first time they are able to tell the story of how this cancer develops.

"We were able to describe how many mutations develop, how fast they occur, how many mutations the tumour can sustain, and the type of mutation that occurs, which we found is unique to bMMRD cancers," says Dr Adam Shlien, lead author of the study and Associate Director of Translational Genetics and Scientist in Genetics & Genome Biology at SickKids.

"Additionally, by studying a rare cancer syndrome we were able to have an unobstructed view on how cancer develops and learn not only about how we can help these patients, but also about cancer progression in general."

Because the high number of mutations is so specific to bMMRD syndrome, researchers are now able to detect children who are carriers just by sequencing the tumour.

"If the child has a very high number of mutations then we know immediately that they have this cancer predisposition syndrome," said Dr Shlien.

Towards tumour cell death

The team may have also found a clue that may help to develop a novel treatment that promotes tumour cell death. The observation that tumour cells reach a threshold of 20,000 mutations and cannot overcome it suggests that the tumour cannot withstand any more, and more mutations may cause cell death. Future research may explore how certain pharmacological agents may push these cancer cells over the mutational edge and cause the tumour cells to die.

It's hoped findings from this study will also lead to more effective treatments for more common cancers such as colon, gynaecological cancers and recurrent malignant gliomas (cancer in the brain or spine) since they share the same mutations in the mismatch repair genes as bMMRD patients).

More information: *Nature Genetics*, www.nature.com/ng/journal/vaop … nt/full/ng.3202.html

Provided by University of Nottingham

Citation: Study sheds new light on aggressive cancer in children (2015, February 3) retrieved 8 April 2024 from https://medicalxpress.com/news/2015-02-aggressive-cancer-children.html