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Pioneering study may open door to first targeted treatment for common childhood brain tumour

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Scientists have found evidence to suggest that 'small molecule' drugs could offer the first effective chemotherapy for childhood low-grade astrocytomas, improving the prognosis for hundreds diagnosed with the disease - reveals research published today in *The Journal of Pathology*.

The team of British and American researchers, funded by Samantha Dickson Brain Tumour Trust, Cancer Research UK and ALSAC, has discovered that a specific set of genetic abnormalities may initiate and drive pilocytic astrocytomas, the most common childhood brain tumour.

Scientists say the study is significant because it suggests that the first successful chemotherapy for these tumours might be possible using drugs already being tested on other cancers.

Surgery is currently the best method of treatment for pilocytic astrocytomas, which affect about 145 children each year in the UK. However, the tumours grow slowly and those situated around critical brain structures are inoperable. They cause symptoms over many years and may ultimately be fatal because current anti-cancer drugs and radiotherapy may not control the disease successfully.

The team was led by Professor Denise Sheer, of Barts and The London School of Medicine and Dentistry, and Professor David Ellison, of St. Jude Children's Research Hospital, Memphis, USA. They analysed low-

grade astrocytomas from 50 patients aged 1-20, searching for common genetic changes. Their findings confirmed a high frequency of gene fusions involving BRAF, a gene thought to trigger cancer, in pilocytic astrocytomas. Another fusion event involving a related gene called RAF1 was found, and every one of the pilocytic astrocytomas tested contained either one of those fusions or a mutation in a gene called KRAS, also known to be linked with cancer. These genetic changes permanently activate the MAPK molecular pathway, allowing cells to multiply uncontrollably.

Professor Denise Sheer, said: “Our research could have important therapeutic implications. We found that the genetic abnormalities associated with children’s astrocytoma permanently activate the MAPK molecular pathway; this malfunction appears critical in the generation of pilocytic astrocytomas. There are now drugs being tested in various cancers, such as malignant melanomas, that specifically inhibit the MAPK pathway. We believe that these drugs may also be applied to treat paediatric low-grade astrocytomas, particularly pilocytic astrocytomas.”

Brain tumours are the leading cause of childhood cancer-related deaths. Understanding molecular pathway activation raises the possibility of targeted drug therapies for these tumours when surgical resection alone will not control the disease.

Professor Ellison added: “Our more detailed molecular understanding of pilocytic astrocytomas will also be useful in diagnosis, enabling pathologists to use genetic tests to distinguish among different types of childhood brain tumours to guide better treatment decisions.”

Paul Carbury, Chief Executive of Samantha Dickson Brain Tumour Trust said: “We are committed to collaborative funding of research that will lead to a better prognosis for this devastating disease; this study marks an advance in our understanding and we hope that it will lead to

the development of more effective treatments for childhood brain tumours."

Dr Lesley Walker, Director of Cancer Information at Cancer Research UK, said: "It's often more difficult to treat brain tumours successfully because of the sensitive position of the tumour. This research adds to our understanding of the cancer pathways that cause these tumours to form, and we think this study will be vital in guiding future research into targeted treatments for the disease."

Provided by Queen Mary, University of London (news : web)