Study splits incurable childhood brain tumors into 10 new diseases

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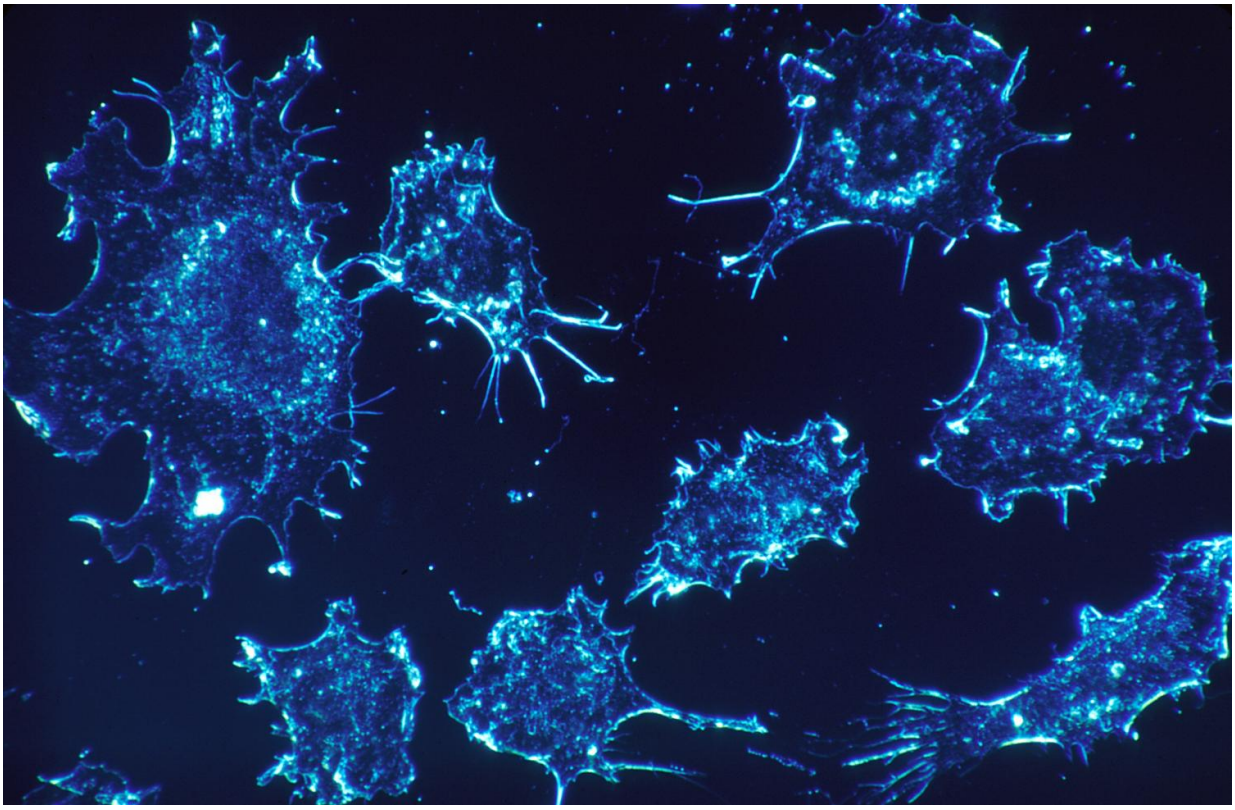

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Scientists have found that deadly childhood brain tumours are actually 10 different diseases that should each be diagnosed and treated based on their specific genetic faults.

The major new study has important implications for treatment, since personalising care for each type of brain tumour is likely to be much more effective than grouping them all together as one.

A team at The Institute of Cancer Research, London, found stark differences among children's 'high grade' brain tumours, or gliomas, and that they could be split into at least 10 different cancers.

Some types should be far more treatable than others using drugs under development or already on the market.

The study, published today (Thursday) in *Cancer Cell*, is the world's largest of these aggressive childhood brain cancers and should lead to more accurate diagnostic tests to ensure each child receives the best possible treatment.

Many of the children had mutations in their tumours that can be targeted by existing drugs approved for adult cancers, demonstrating the benefit of testing children for genetic mutations in their tumours at the point of diagnosis.

The research was funded by The Institute of Cancer Research (ICR) itself along with many different charitable funders - Cancer Research UK, CRIS Cancer Foundation, Abbie's Army, The Lyla Nsouli Foundation, Christopher's Smile and the INSTINCT network funded by The Brain Tumour Charity, Great Ormond Street Hospital Children's Charity and Children with Cancer UK.

Researchers gathered genetic data from 910 cases from 20 previously published analyses and 157 new cases, from children or young adults up to the age of 30 with high-grade glioblastoma or diffuse intrinsic pontine glioma (DIPG).

Although rare, these are the biggest cause of cancer-related death in people under 19 years of age because survival rates are so poor - children with these tumours are only expected to live an average of 9-15 months.

It is therefore vital to find out more about their biology, what makes them so deadly, and how they might be treated.

The tumours could be split into different subtypes based on different characteristics, such as age at diagnosis, area of the brain, the number of genetic mutations and - crucially - errors in key genes that drive the disease.

One of the striking findings from the study was that while some children's tumours were driven by a single genetic error in which two genes were fused together, others had tens of thousands of genetic errors - among the highest number of mutations in any human cancer.

Tumours with mutations in a gene called BRAF were found to be much less aggressive than some of the other cancers, and actually shouldn't be classified as 'high grade' at all. These tumours could be susceptible to several adult cancer drugs that target BRAF mutations.

Scientists at the ICR, a research institute and charity, found mutations in common cancer genes such as PDGFRA, KIT, MYCN, EGFR, CDK6, and genes involved in DNA repair - all of which can be targeted by existing drugs.

They also uncovered numerous new potential therapeutic targets within each subtype, such as the gene TOP3A - a gene involved in DNA replication - in tumours with a specific type of histone mutation called H3.3K27M.

Three of the subtypes were distinguished by the presence or absence of

different mutations in genes that produce histones - proteins that DNA is wrapped around to pack it tightly into cells. Histones are also involved in turning off and on certain genes - a role that can be very important in cancer.

Although there are currently no drugs that can target histone mutations, there are some in development and the presence or absence of these mutations gave clues about how aggressive the cancer is, and could point to future approaches to treatment.

The data produced by this study is now considered the definitive dataset on these cancers, and will be made available on a public data portal so the research community can use it to develop new tests and treatments.

Study leader Professor Chris Jones, Professor of Childhood Brain Tumour Biology at The Institute of Cancer Research, London, said:

"Our study uncovered a wealth of new information about children's brain cancers. We found that tumours that have historically been lumped together under one diagnosis are in fact comprised of many, remarkably different, diseases.

"Treating cancer based only on what we see down the microscope simply isn't good enough any more. We need to start thinking about these as completely different cancers and diagnosing and treating them based on their genetic faults. It's exciting that several types look like they could be clearly treatable using either existing drugs on the market or other treatments under development.

"We worked with colleagues across the world to gather enough data on these rare cancers to understand better what makes them so aggressive, and what mutations occur that might make them susceptible to different treatments."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"A diagnosis with one of these high-grade brain tumours in children is devastating for families. We desperately needed to understand the biology of the diseases better if we are ever to find ways of treating them effectively. This important study is a vital step forward.

"We really need to get much better at making modern, targeted cancer treatments available for children, which means improving access to genetic testing and changing regulations so more drugs get tested in paediatric clinical trials."

Jo Williams lost her son Lucas after he was diagnosed with a brain tumour in May 2015. Jo and her husband Andrew set up the charity Lucas' Legacy in their son's name, to fund research into, and raise awareness of, childhood brain tumours. Jo said:

"We lost Lucas, our beautiful only child, in August 2015 following a short battle with a brain tumour. Before this Lucas had never been ill, or had a day off school. After a roller coaster of desperate hope and extreme despair, Lucas died at home - 11 weeks and one day after first becoming ill, and just four weeks away from his seventh birthday.

"After Lucas died, we were so sad to find out how little is invested in developing treatments for children with brain cancer. The standard treatment regimes that children receive for high-grade brain tumours are brutal, and Lucas went through so much. He fought so hard, but he deserved so much more, to have better treatments in his brave and courageous fight against this devastating illness.

"Professor Jones and his team are working hard to understand children's brain tumours better and to develop personalised treatments for children

like Lucas, kinder treatments that will give them a better chance of survival.

"We are still so shocked that this happened to our seemingly healthy six-year-old boy. Lucas was a really kind, funny, clever, sporty boy and the centre of our world. We know that he would have grown up to be something really special. We know that he would have changed the world for the better. We still hope he will."

More information: *Cancer Cell* (2017). DOI: 10.1016/j.ccell.2017.08.017

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