Genetic abnormality offers diagnostic hope for children's cancer

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A chromosomal abnormality in children with a deadly form of brain cancer is linked with a poorer chance of survival, clinician scientists at The University of Nottingham have discovered.

The study led by experts at Nottingham's Children's Brain Tumour Research Centre as part of a European collaboration could potentially lead to a new diagnostic test to allow doctors to identify youngsters who are at the highest risk associated with an ependymoma tumour and may need aggressive life-saving treatments.

The research could also help them to decide which children with the tumour have a better prognosis and would benefit from less intensive therapies, reducing their exposure to a range of side effects which can cause permanent disabilities, having a debilitating impact on them for the rest of their lives.

The study, published in the April 1 edition of the journal Clinical Cancer Research, focused on looking at abnormal copies of chromosomes in the cells of ependymoma tumours and aimed to establish whether it was associated with a worse outlook for children suffering from the disease.

The research, led by Professor Richard Grundy and Dr John-Paul Kilday, found that increased copies of a specific region of a chromosome called 1q25 were associated with around 20 per cent of the 147 tumours they tested from European children with ependymoma and that it was associated with a worse outcome in younger children treated

with surgery and chemotherapy.

In addition, when combining the results for 1q25 copy gain with how much tumour was removed at the time of surgery, the scientists could accurately place the children into three risk groups — high, intermediate and standard.

Dr Kilday said: "This study is the first to assess copy number gain like this in groups of children with ependymoma who have been treated in a similar way and is an important step forward in being able to predict the future for children with these brain tumours"

"We are now hoping that these findings are reproduced in other studies currently underway in other countries, including the USA" added Professor Grundy, "If their results match ours, then the presence of 1q25 copy gain in childhood ependymoma could be introduced into future international treatment planning as a new marker of poor outcome which will in turn define treatment. We would intend that this should be something each patient's tumour is tested for at the time of diagnosis."

Ependymomas are brain tumours that can occur at any age but are more common in children. Despite improvements in therapy over recent years, the prognosis for children with this cancer remains poor — 40 per cent of affected children still die.

One of the reasons that survival for childhood ependymomas has not improved is that, until now, doctors have not been able to accurately predict which tumours will behave more or less aggressively than others. Factors that have helped the ability to predict outcomes in other cancers, such as patient sex, age, how much of the tumour is removed and how aggressive the tumour appears under the microscope, have not been found to be consistently reliable in previous studies.

In normal humans, the cells which make up our body tissue contain chromosomes made up of DNA and proteins — the building blocks of life. Normally, our cells have two copies of 23 chromosomes (numbered 1 to 22) plus two sex chromosomes, making a total of 46 chromosomes. Each chromosome has two arms — a short arm called the p arm and a long arm called the q arm.

In tumour cells the number of chromosomes can vary significantly from the normal cell numbers and in ependymoma a frequent finding from biological studies is increased copies of chromosome number 1, specifically increased numbers of the long arm of chromosome 1. This abnormality is termed 1q copy number gain.

For the Nottingham-led study, the scientists assessed the results from 147 brain ependymomas in young UK and French children who received tumour surgery followed by chemotherapy and older European children who received tumour surgery followed by radiotherapy.

Copy number gain of 1q in the ependymoma cells from each of the 147 patients was assessed using a technique called fluorescence in situ hybridisation (FISH) in which pieces of DNA called probes are made in the lab containing a fluorescent dye. This enables the tumour cells to be seen down a fluorescent microscope. In the Nottingham project, the scientists used a green probe that bound to a region within chromosome 1q of the tumour cells, called 1q25.

The team then linked which of the ependymomas had increased copies of the 1q25 probe in their cells to corresponding patient data to work out whether increased copy number gain was associated with a worse survival rate.

More information: A full copy of the paper is available to view online at tiny.cc/x1ivbw

Provided by University of Nottingham