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Test for single genetic fault can help tailor cancer treatment for children

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A study led by Dr Janet Shipley from The Institute of Cancer Research (ICR) in London in collaboration with Dr Mauro Delorenzi from the SIB Swiss Institute of Bioinformatics in Lausanne has shown that a simple genetic test could help predict the aggressiveness of rhabdomyosarcoma tumours in children. The test, which should be introduced into clinical practice, would lead to changes in treatment for many patients, allowing some children to escape potentially long-term side-effects whilst giving others the intense treatments they need to increase their chances of survival. The results of the study are published online today in the *Journal of Clinical Oncology*.

Until now, the PAX3/FOXO1 fusion gene only served as a classification agent for tumour histology but never as a prognostic indicator. The research team found that children who have a tumour called rhabdomyosarcoma with this particular genetic fault have significantly poorer survival rates than other rhabdomyosarcoma patients. This fusion gene can thus be very useful in the prognosis of patient's survival.

More than that, it can provide better information about how aggressively the tumour is likely to behave and help doctors to tailor treatment for each patient. So far, children diagnosed with rhabdomyosarcoma were treated with a combination of chemotherapy and surgery and sometimes radiotherapy. These treatments have helped improve survival rates, but they can also cause serious and long-term side-effects including the potential to develop another cancer later in life. But not all patients need such intense treatment. Dr Shipley says: "Our previous studies have

raised issues with the current system of predicting patients' risk, which is based on the appearance of patients' tumours. Our new study finds that a simple genetic test should be incorporated into standard clinical practice as it significantly improves our ability to predict tumour aggressiveness. This fusion gene test could be used alongside other standard clinical measures to divide patients into one of four risk-groups, so that treatment can be tailored accordingly. Importantly, this will mean some patients who were previously categorised as high-risk could be able to avoid the side-effects associated with intense treatment, while others should receive the intense treatment they need to increase their chance of survival."

The study required high level statistics expertise

To analyse the data for thousands of genes from 225 rhabdomyosarcoma samples, Dr Shipley called onto the expertise of the Bioinformatics Core Facility Group at the SIB Swiss Institute of Bioinformatics in Lausanne, which is led by Dr. Mauro Delorenzi. This group provides statistical and analysis support for either national and international academic and private teams. Dr. Edoardo Missiaglia and Dr. Pratyaksha Wirapati performed the analysis of the data provided in the frame of this study and constructed and evaluated systems to score the aggressiveness of the individual case of rhabdomyosarcoma. Their work allowed to identify a panel of 15 genes whose altered activity level could be used to predict how patients responded to treatment. However, it was also found that most of these gene changes are linked to the presence of the PAX3/FOXO1 fusion gene: the detection of which is much simpler and cheaper than that of altered gene activity levels. Dr Delorenzi says: "We showed that by making a good use of the information about the presence or absence of the fusion of the two gene PAX3 and FOXO1, alongside other standard clinical measures, we could create a risk scoring system that is very informative on the aggressiveness of a tumour; it is so good that the additional use of the complex gene activity information does not

appear to help to further improve it."

Using the new system, 31 per cent of patients in the study who would previously have been classified as intermediate risk would be reassigned to a lower risk group, while a further 29 per cent of intermediate-risk patients would be moved to a higher risk group. Combining the fusion gene test with two existing standard measures of risk for rhabdomyosarcomas – the patient's age at diagnosis and the tumour's stage of development – gave a simple but highly effective prognostic test.

The research team now intends to validate their findings using a larger European and independent data set. If confirmed, their method could be used in future clinical trials to assist clinicians in treatment decision. Dr Missiaglia adds: "In the same work we also show evidence that the gene activity information of 5 other genes might give important additional information in a subgroup, but since this is rare we do not yet have enough cases to be sure and this should be further tested on new data that are not yet available".

Provided by Swiss Institute of Bioinformatics