New study discovers genetic changes linked to leukaemia in children with Down's syndrome

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Researchers at the University of Oxford, in collaboration with colleagues from Hannover Medical School and Martin-Luther-University Halle-Wittenberg, have discovered the specific gene mutations that are required for the development of leukaemia in children with Down's syndrome. Children with Down's syndrome have a 150-fold increased risk of myeloid leukaemia, and while some of the genetic causes of this have been previously established, this is the first study to identify a wide range of mutations and how they functionally interact to lead to leukaemia. The study was published today in the journal *Cancer Cell*.

'We already knew that 30% of babies born with Down's syndrome have acquired a change in a gene called GATA1 in their blood cells. This is not an inherited genetic change, but one that occurs and will remain only in the baby's blood cells," says study author Professor Paresh Vyas, from the MRC Weatherall Institute of Molecular Medicine at the Radcliffe Department of Medicine, University of Oxford. "The abnormality in the GATA1 gene can be detected by a simple blood test at birth. Babies with an altered GATA1 gene have a predisposition to develop leukaemia, and we often refer to this as 'myeloid preleukaemia'.'

Of the 30% of children with Down's syndrome who are found to have 'myeloid preleukaemia', only 10% of those will go on to develop myeloid leukaemia (3% of all children with Down's syndrome). Until now, it was not understood why only some children with the GATA1 mutation were progressing to full leukaemia, while others were not.

'90% of babies with Down's syndrome do not go on to develop preleukaemia. But until now, we did not fully understand why some babies did develop leukaemia,' says Vyas, who is also a group leader at the MRC Molecular Haematology Unit. 'To answer this question, we carefully characterised the mutations in genes required for leukaemia to develop. We found that additional genetic changes are required in the altered GATA1 blood cells, and these additional changes transform the preleukaemic blood cells into leukaemic blood cells.' In total, 43 different altered genes were found.

The discovery of which specific genetic changes are required for leukaemia to develop has practical implications. While children with Down's syndrome are currently tested at birth for the GATA1 mutation, it may now become possible in the future to test for the additional mutations too. 'This would mean that we could identify the 10% of children who will develop leukaemia more quickly and easily, and importantly reassure 90% of families whose children will not develop leukaemia,' says Vyas. 'The identification of these genetic changes may also mean we can develop and test new treatments specifically targeting the genetic changes we now know are required by the leukaemia—and so develop more targeted treatments with less side effects.'

Current treatments for Down's syndrome children with leukaemia are already highly successful, and off the back of this research, another possible drug treatment has come to light. The drug Ruxolitinib, which is currently used to treat some blood conditions, could potentially be used to treat some of the specific genetic mutations found in the study. Clinical trials of the drug are a possibility for the future.

'The recent identification of a group of genes linked to leukaemia in children with Down's syndrome is an important first step towards developing early diagnostic tests and identifying effective treatments to help these patients,' says Dr. Mariana Delfino-Machin, Programme

Manager at the Medical Research Council (MRC). 'The MRC is proud to support the research undertaken at the MRC Molecular Haematology Unit, of which this early-stage study is a great example.'

More information: Maurice Labuhn et al, Mechanisms of Progression of Myeloid Preleukemia to Transformed Myeloid Leukemia in Children with Down Syndrome, *Cancer Cell* (2019). DOI: 10.1016/j.ccell.2019.06.007