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Mutations in leukemia gene linked to new childhood growth disorder

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Mutations in a gene associated with leukaemia cause a newly described condition that affects growth and intellectual development in children, new research reports.

A study led by scientists at The Institute of Cancer Research, London, identified mutations in the DNA methyltransferase gene, DNMT3A, in 13 children.

All the children were taller than usual for their age, shared similar facial features and had intellectual disabilities. The mutations were not present in their parents, nor in 1,000 controls from the UK population.

The new condition has been called 'DNMT3A overgrowth syndrome'.

The research is published today (Sunday) in the journal *Nature Genetics* and is a part of the Childhood Overgrowth Study, which is funded by the Wellcome Trust, and aims to identify causes of developmental disorders that include increased growth in childhood. The DNMT3A gene is crucial for development because it adds the 'methylation' marks to DNA that determine where and when genes are active.

Intriguingly, DNMT3A mutations are already known to occur in certain types of leukaemia. The mutations that occur in leukaemia are different from those in DNMT3A overgrowth syndrome and there is no evidence that children with DNMT3A mutations are at increased risk of cancer.

Researchers at The Institute of Cancer Research (ICR), with colleagues at St George's, University of London, The Royal Marsden NHS Foundation Trust, and genetics centres across Europe and the US, identified the mutations after analysing the genomes of 152 children with overgrowth disorders and their parents.

Study leader Professor Nazneen Rahman, Head of Genetics and Epidemiology at The Institute of Cancer Research, London, and Head of Cancer Genetics at The Royal Marsden NHS Foundation Trust, said: "Our findings establish DNMT3A mutations as the cause of a novel human developmental disorder and add to the growing list of genes that appear to have dual, but distinct, roles in human growth disorders and leukaemias."

The new discovery is of immediate value to the families in providing a reason for why their child has had problems. Moreover, because the mutations have arisen in the child and have not been inherited from either parent, the risk of another child in the family being similarly affected is very low. This is very welcome news for families.

Study co-leader Dr Katrina Tatton-Brown, Clinical Researcher at The Institute of Cancer Research, London, and Consultant Geneticist at St George's, University of London, said: "Having a diagnosis can make a real difference to families – I recently gave the result back to one of the families in which we identified a DNMT3A mutation and they greatly appreciated having a reason for their daughter's condition after many years of uncertainty."

More information: Mutations in the DNA methyltransferase gene DNMT3A cause an overgrowth syndrome with intellectual disability, DOI: 10.1038/ng.2917