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HAEMATOLOGICAL CANCER

DOWN SYNDROME LINKS TO CANCER

Children with Down syndrome (DS or trisomy 21), have a 20-fold increased risk of developing B-cell acute lymphoblastic leukaemia (B-ALL) as chromosome 21 is also the most frequently gained chromosome in patients with B-ALL without DS. However, the mechanisms underlying the role of chromosome 21 triplication in leukaemia development are unclear. A new study by Andrew Lane and colleagues reports that overexpression of the nucleosome remodeller non-histone chromosomal protein HMG-14 (HMGN1) and changes in chromatin methylation are key events in the development of DS-related B-ALL.

The researchers studied B-cell development and leukemogenesis in a mouse model of DS in which only 31 genes of the human chromosome 21 were triplicated. "This region overlapped with a recurrent intrachromosomal amplification that is seen in patients with B-ALL and is associated with a very poor prognosis," explains Lane. Mouse B cells and human B-ALL cells with trisomy 21 showed transcriptional upregulation of targets of the polycomb repressor complex 2 (PRC2). In addition, "trisomy 21 mouse B cells had decreased histone H3K27 trimethylation—the repressive mark normally placed by PRC2," says Lane. The researchers reported that inhibitors of H3K27 histone demethylases block the growth of trisomy 21 B cells, and treatment of wild-type B cells with a PRC2 inhibitor was sufficient to confer self-renewal activity. As Lane emphasizes, "these data suggest that progenitor B-cell growth is modulated by H3K27 methylation status, and that trisomy 21 may alter B-cell phenotypes by disrupting this epigenetic regulation."

The investigators further showed that HMGN1 protein was essential for growth of the trisomy 21 B cells. Lane concludes that "overexpression of HMGN1 itself could recapitulate some, but not all, of the features of the 'triplicated' cells, indicating that additional genes have yet to be identified." Importantly, this study describes new molecules and mechanisms that could be targeted in the treatment of DS-related B-ALL.

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Original article Lane, A. A. *et al.* Triplication of a 21q22 region contributes to B cell transformation through HMGN1 overexpression and loss of histone H3 Lys27 trimethylation. *Nat. Genet.* doi:10.1038/ng.2949

Futher reading Letorneau, A. *et al.* Domains of genome-wide gene expression dysregulation in Down's syndrome. *Nature* doi:10.1038/nature13200