It is ALL about the 6p22 histone gene cluster: characterizing the unique genetic features of Down’s syndrome patients

References


Genomic profiling in Down syndrome acute lymphoblastic leukemia identifies histone gene deletions associated with altered methylation profiles

Loudin et al. (2011)

Down syndrome (trisomy 21) is one of the most common chromosomal abnormalities, and patients with Down syndrome are at a significantly increased risk of developing acute lymphoblastic leukemia (ALL). These patients have been shown to experience poorer treatment outcomes and increased treatment-related toxicities as compared to non-Down syndrome-ALL (NDS-ALL) patients (1). This is partly because of the fact that Down syndrome-ALL (DS-ALL) patients exhibit unique cytogenetic abnormalities not found in NDS-ALL patients, which results in specific treatments tailored to NDS-ALL patients ineffective in DS-ALL.
Fig. 2. Hypothesized pathological mechanism resulting from 6p22 histone gene deletion in Down syndrome-acute lymphoblastic leukemia patients.

For example, an enrichment of mutations in the genes *JAK2* and *CRLF2* have been uniquely observed in DS-ALL patients, and while such mutations account for approximately half of DS-ALL cases, the genetic causes underlying DS-ALL in the remainder of patients have not been identified (3). Thus, there is an emerging need to specifically characterize the genetic features of individuals with Down syndrome that develop ALL in order to develop effective therapeutics for this specific group of patients.

In this study by Loudin et al., several genetic abnormalities present in DS-ALL patients are uncovered. Through genome-wide assessment of DNA copy number (CN), loss of heterozygosity, methylation profiles and gene expression on a cohort of 58 DS-ALL and 68 NDS-ALL subjects, a novel 6p22 histone gene deletion was discovered. The size and number of CN alterations as well as frequency of anomalies in the genes examined was found to be similar overall between the two groups, indicating genomic stability. However, novel CN alterations were identified, with one particular CN abnormality, a histone gene 33.8-kb deletion in the 6p22 cluster, occurring at a higher frequency (22%) in the DS-ALL group and absent in the NDS-ALL group (1).

Additionally, a neighboring region was found to contain deletions in several DS-ALL subjects, also occupied by histone genes. Lower histone gene expression levels were also found in the homozygous deletions. In addition to the observed deletions, sequencing revealed a non-synonymous HIST1H2BE mutation and a HIST1H4D two-base insertion in the conserved 3′-UTR sequence, which is essential for histone mRNA processing, suggesting a possible reduction in gene expression (1). Upon examination of epigenetic changes, the DS-ALL group containing histone deletions were found to possess significantly more highly methylated probe-sets than other DS-ALL cases, while the methylation levels were comparable between the deletion-lacking DS-ALL and NDS-ALL groups. These highly methylated sites were also found to be significantly associated with specific cytobands and hence have distinct spatial localization.

The functional consequences of the observed altered methylation levels were assessed by combining the methylation and gene expression data sets. Of the 109 genes found to be both highly methylated and lowly expressed, 11 genes significantly overlapped with defined canonical gene pathways, including cytokine–cytokine receptor interactions as well as neuroactive ligand receptor interactions (1). Another 29 genes were found to overlap with five transcription factor targets gene sets. Thus, it is possible that the presence of histone deletions associated with increased methylation and altered spatial localization, combined with an enrichment of particular pathways, may play a key role in leukemogenesis through the regulation of lymphoid production and differentiation (Fig. 2).

The identification of this specific genetic alteration associated with DS-ALL, and not NDS-ALL, further details the genetic differences between the two related conditions. Ongoing studies looking into the underlying genetic patterns and functional consequences of such differential abnormalities will contribute to the discovery of specific, tailored therapies for this subgroup so as to ensure a brighter outcome for Down syndrome patients suffering from ALL.

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