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AUTHOR'S VIEW

High hyperdiploid childhood acute lymphoblastic leukemia: Chromosomal gains as the main driver event

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ABSTRACT
High hyperdiploid childhood acute lymphoblastic leukemia is characterized by multiple chromosomal gains. Recent results show that this subtype harbors relatively few genetic abnormalities besides the extra chromosomes, which appear to arise early and are likely the main driver event. Secondary hits primarily target genes in the rat sarcoma (RAS) signaling pathway and histone modifiers.

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High hyperdiploid (51-67 chromosomes) acute lymphoblastic leukemia (ALL) is one of the most common childhood malignancies, constituting approximately 30% of all pediatric B-cell precursor ALL. It is associated with low white blood cell counts, age of 3-5 years, and a favorable prognosis, with overall survival rates >90% on current treatment protocols.[1] The characteristic genetic feature of high hyperdiploidy is chromosomal gains, mainly trisomies but also frequently tetrasomies; in contrast, monosomies and gain of more than 2 copies of a chromosome are extremely rare. The gains may involve any chromosome, but more than 70% of cases harbor +X, +4, +6, +10, +14, +17, +18, or +21.[1] Considering that most of the other leukemia subtypes are associated with specific fusion genes or mutations, it has been proposed that this hyperdiploidy is an epiphenomenon without any leukemogenic effect that is secondary to a hitherto cryptic event. However, numerous investigations using fluorescence in situ hybridization, PCR, array comparative genome hybridization, and single nucleotide polymorphism array analysis have failed to identify such a hidden primary somatic aberration.[1] We recently published a large next-generation sequencing (NGS) study of high hyperdiploid childhood ALL in which tumor/normal pairs were subjected to whole genome sequencing (WGS; n = 16) or whole exome sequencing (n = 35).[2] The data from this investigation confirmed that there is no cryptic fusion gene in high hyperdiploid childhood ALL, with only 3/16 cases displaying rearrangements resulting in chimeric genes by WGS and no recurrent rearrangements leading to fusion genes. Furthermore, high hyperdiploid cases were shown to harbor relatively few mutations in coding regions, with a median of only 7 non-silent mutations among the whole cohort of 51 cases, well in line with previously reported data for childhood malignancies, including other pediatric ALL subtypes. Two groups of mutations were identified as putative driver events: those occurring in genes involved in the rat sarcoma (RAS) signaling pathway, including fms-related tyrosine kinase 3 (*FLT3*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*), and protein tyrosine phosphatase, non-receptor type 11 (*PTPN11*), in 50% of the cases, and those occurring in histone modifier genes, primarily CREB binding protein (*CREBBP*) and Wolf-Hirschhorn syndrome candidate 1 (*WHSC1*), in 20% of cases. Although mutations in these genes were known to occur in high hyperdiploid childhood ALL,[3,4] the frequency was higher than reported previously, partly due to a high number of *KRAS* mutations outside the hotspot regions in codons 12, 13, and 61.[2] Notably, in a very recent study of relapsed high hyperdiploid childhood ALL, Malinowska-Ozdowy et al.[5] showed that *KRAS* and *CREBBP* mutations commonly co-occur at relapse, indicating that mutations in these genes have synergistic effects, in particular when the leukemic clones are subjected to selective pressures during chemotherapy. However, further studies are needed to delineate the exact role of the RAS signaling pathway and histone modifiers in the leukemogenesis of high hyperdiploid ALL.

Considering that mutations affecting RAS signaling and histone modifiers are also found in other genetic subtypes of childhood ALL and that half of high hyperdiploid cases lack these mutations, neither group of genes is likely to underlie the specific clinical features of high hyperdiploid ALL. Thus, available data point to chromosomal gains as the only common genetic aberration in high hyperdiploid childhood ALL, strongly suggesting that the aneuploidy in itself is the main driver event in these cases. To investigate this further, we mapped the temporal relationship between chromosomal gains and mutations in the trisomic chromosomes. This analysis showed that the vast majority of mutations occurred after the trisomies, suggesting that the latter were early events that probably preceded overt leukemia by an extended time period.[2] This agrees well with

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studies showing that high hyperdiploidy may sometimes be present already at birth based on twins with concurrent ALL, the presence of trisomic cells in cord blood, and backtracking of leukemia-specific immunoglobulin heavy locus (*IGH*) rearrangements in neonatal blood spots from children who developed leukemia years later.[6-8] Taken together with our results on trisomies and mutations, all available data point to chromosomal gains as an initiating early event in high hyperdiploid childhood ALL.

What is the leukemogenic effect of the chromosomal gains? Extra copies of chromosomes generally lead to increased expression of genes on that chromosome. Such dosage effects have also been reported in high hyperdiploid childhood ALL, but not all genes in the gained chromosomes are affected.[9,10] This is expected, as upregulation of a large proportion of genes will in turn affect the expression of genes on other chromosomes, leading to downstream effects that are difficult to untangle. Today, we are nowhere near an understanding of these complex processes. In the future, concurrent allele-specific gene expression analysis using NGS and proteomic characterization may finally reveal the functional outcome of high hyperdiploidy in the leukemogenesis of childhood ALL.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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