Chromosome gains drive childhood ALL.

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Published in:
Oncotarget

2015

Link to publication

Citation for published version (APA):

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High hyperdiploid (51-67 chromosomes) acute lymphoblastic leukemia (ALL), characterized genetically by a nonrandom gain of chromosomes, is one of the most common childhood malignancies. It is associated with a B-cell precursor immunophenotype and shows a distinct age peak at 2-4 years, with adult cases being much less common. The gained chromosomes generally forms a specific pattern of trisomies X, 4, 6, 10, 14, 17, and 18, and tri- or tetrasomy 21, with no concurrent monosomies [1]. In contrast to the majority of aneuploid solid tumors, which generally displays an increased rate of gains and losses of whole chromosomes termed chromosomal instability (CIN), there is no evidence of ongoing CIN in high hyperdiploid childhood ALL. Instead, these cases generally have no or few subclones, no clonal evolution between diagnosis and relapse samples as regards chromosomal content, and little cell-to-cell heterogeneity on the chromosomal level [1].

We recently published a whole genome and exome sequencing study of 51 cases of high hyperdiploid childhood ALL, characterizing the genomic landscape of this disease [2]. This investigation showed that high hyperdiploid cases harbored relatively few other genetic mutations, with no recurrent fusion gene and only 7.5 point mutations on average in coding regions. Putative driver events besides the aneuploidy comprised mutations in the RTK/RAS pathway, such as \textit{KRAS}, and in histone modifiers, in particular \textit{CREBBP}. Notably, such mutations have been shown to frequently be subclonal and to arise or disappear at relapse, whereas the chromosomal gains usually are stable [3;4]. Taken together with the fact that RTK/RAS and histone modifier mutations were only seen in a subset of high hyperdiploid cases, we concluded that the gained chromosomes are the primary driver event in this form of pediatric ALL [2].

How and when, then, do the chromosomal gains occur? As to the “how”, this process is still an enigma, considering the apparent lack of CIN in high hyperdiploid childhood ALL. Notably, both parental homologues are generally duplicated in chromosomes that have gained extra chromosomes relatively late in the temporal order, whereas the chromosomal gains usually are stable [3;4]. Taken together with the fact that RTK/RAS and histone modifier mutations were only seen in a subset of high hyperdiploid cases, we concluded that the gained chromosomes are the primary driver event in this form of pediatric ALL [2].

To see whether we could determine when this mitosis occurred, we looked at the mutant allele fractions of mutations in trisomic chromosomes, including both putative driver and passenger mutations. We assumed that a mutation that was present in two of the three chromosomal copies most likely arose before the duplication of one homologue, whereas mutations that were present in one of three chromosomal copies could have arisen either before (if the other homologue was subsequently duplicated) or after the duplication. In this way, we could study the temporal sequence of mutational events in high hyperdiploid childhood ALL. The analysis clearly showed that the trisomies, and hence most likely the high hyperdiploid pattern in its entirety, arose very early in most cases [2].

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Keywords: Chromosome Section, aneuploidy, hyperdiploidy, leukemia, chromosomal instability

Received: July 30, 2015
Published: August 10, 2015

REFERENCES