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Clinical Pediatrics 2017: Overexpression of tyrosine kinase and chromatin remodeling genes in the iAMP21 subtype of pediatric acute lymphoblastic leukemia

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In childhood acute lymphoblastic leukemia (ALL), detection of known cytogenetic markers at diagnosis is important for risk stratification and guides the choice of treatment intensity. In the Nordic Society of Pediatric Hematology and Oncology (NOPHO) treatment protocol, six genetic markers are used to upgrade risk stratification of patients because of association with risk for relapse and treatment resistance. Intrachromosomal amplification of chromosome 21 (iAMP21) is an intermediate risk marker present in 2% of pediatric BCP ALL; the subtype is associated with high age, low white blood cell count and a high relapse rate if treated according to standard risk protocols. A previous study demonstrated that iAMP21 patients treated according to high risk protocols had a reduced risk of relapse, however, data from the NOPHO 2008 protocol show that iAMP21 is associated with dismal prognosis despite intensive treatment. The iAMP21 subtype has been investigated extensively at the genomic level, with studies describing the composition of the amplified chromosome and the mechanisms of formation. Others and we have shown that iAMP21 is primary event associated with specific copy number alterations (CNAs), genomic fusions and mutations in RAS pathway genes. However, the only genetic alteration recurrent in all iAMP21 cases is an amplification of a 5 Mb region on chromosome 21q and although the leukemia promoting mechanism in iAMP21 is thought to originate from this region, no causative genes have thus far been identified in the region.

In this study, we use an integrated approach to investigate the structure and transcriptional effects of the iAMP21 rearrangement, and we show that the amplification of chromosome 21 affects several potential oncogenes involved in cell cycle regulation and chromatin remodeling.

Intrachromosomal amplification of chromosome 21 (iAMP21) is a cytogenetic subtype associated with relapse and poor prognosis in pediatric B-cell precursor acute lymphoblastic leukemia, however, the biological cause of the high relapse risk is still unknown. The only genetic alteration consistently present in all iAMP21 cases is additional copies of the region of amplification, and the minimal region of amplification (MRA) has been determined to a 5,1 Mb region on 21q22.3. The MRA encompasses several protein coding genes, including RUNX1, however, no causative oncogene or tumor suppressor has thus far been identified in the region. In this study, we used massively parallel sequencing in an integrated approach to investigate the structure and transcriptional effects of the iAMP21 rearrangement, with focus on the MRA, and we show that the iAMP21 subtype has several unique and recurrent alterations of genes involved in cell cycle and chromatin remodeling that could possibly explain the relapse tendency for this subtype.

In conclusion, this study has shown that the iAMP21 subtype has a heterogeneous genomic pattern but a unique transcriptional profile, with significant overexpression of biologically relevant genes in the amplified region on chromosome 21. We were able to identify three candidate genes, DYRK1A, CHAF1B and SON; each gene by its own right involved in malignant disease. DYRK1A and CHAF1B have expression level dependent functions and all three genes are involved in chromatin remodeling, pointing to chromatin modification as a possible contributing mechanism for the pathogenicity in iAMP21. The tyrosine kinase and quiescence functions of DYRK1A, and the leukemogenic properties of CHAF1B overexpression indicate that these genes are particularly strong candidates. Further studies are needed to elucidate the functional role of these genes in the pathogenesis and treatment response of iAMP21-positive ALL.

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