Diverse mutations and structural variations contribute to Notch signaling deregulation in paediatric T-cell lymphoblastic lymphoma

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Abstract

Background T-cell lymphoblastic lymphoma (T-LBL) is an aggressive neoplasm closely related to T-cell acute lymphoblastic leukaemia (T-ALL). Despite their similarities, and contrary to T-ALL, studies on pediatric T-LBL are scarce and, therefore, its molecular landscape has not been fully elucidated yet. Procedure To characterize the genetic and molecular heterogeneity of paediatric T-LBL, 33 patients were analyzed using an integrated approach, including targeted next generation sequencing, RNA-sequencing transcriptome analysis and copy-number arrays. Results Copy number and mutational analyses allowed the detection of recurrent homozygous deletions of 9p/CDKN2A (78%), trisomy 20 (19%) and gains of 17q24-q25 (16%), as well as frequent mutations of NOTCH1 (62%), followed by BCL11B (23%), WT1 (19%) and FBXW7, PHF6 and RPL10 genes (15%, respectively). This genetic profile did not differ to that described in T-ALL in terms of mutation incidence and global genomic complexity level but unveiled virtually exclusive 17q25 gains and trisomy 20 in T-LBL. Additionally, we identified novel gene fusions in paediatric T-LBL including NOTCH1-IKZF2, RNGTT-SNAP91 and DDX3X-MLLT10, the latter being the only one previously described in T-ALL. Moreover, clinical correlations highlighted the presence of Notch pathway alterations as a factor related to favorable outcome. Conclusions In summary, the genomic landscape of paediatric T-LBL is similar to that observed in T-ALL and Notch signaling pathway deregulation remains the cornerstone in its pathogenesis, including not only mutations but fusion genes targeting NOTCH1.

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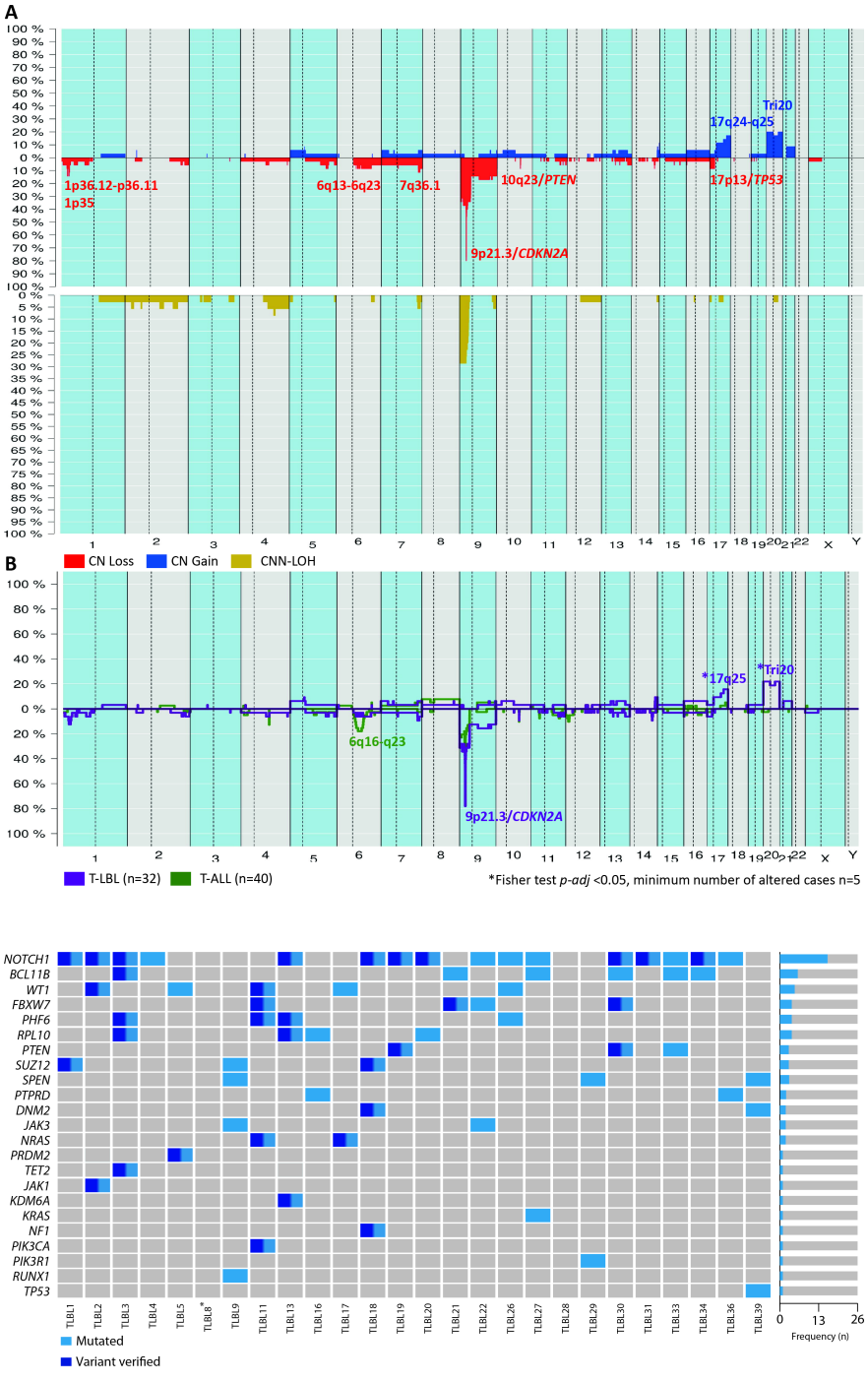

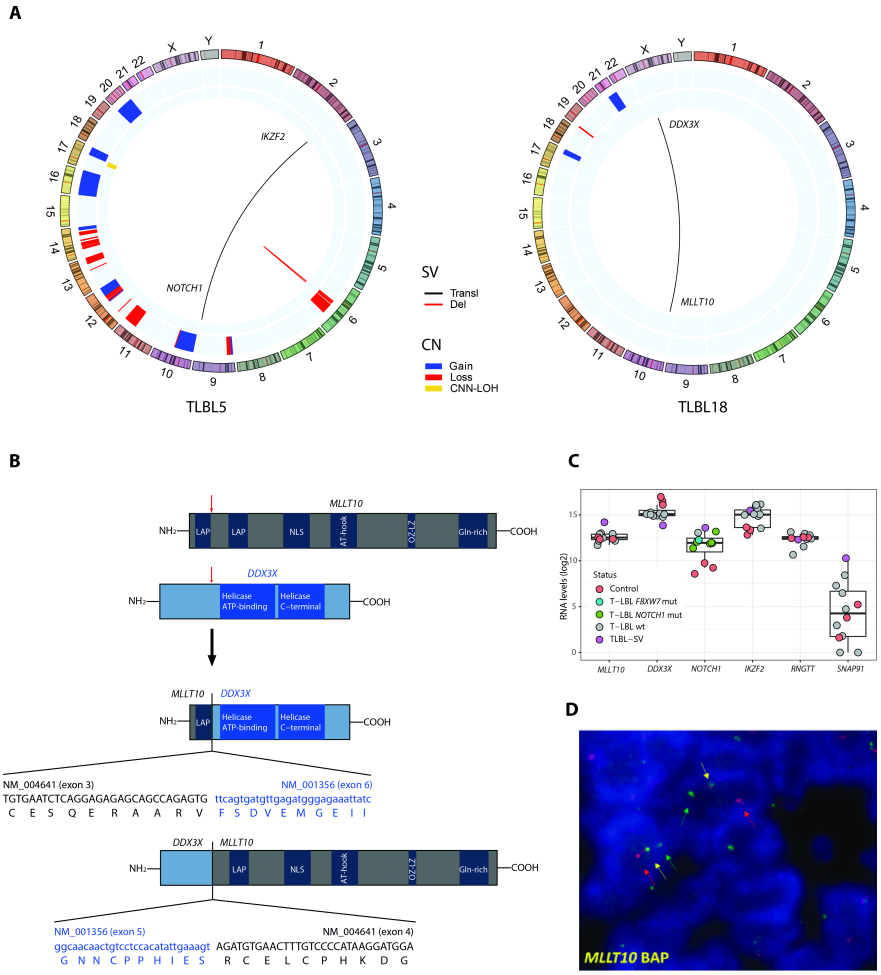

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