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Title: DECIPHER STRUCTURAL ABERRATIONS OF THE PAX5 GENE AND THEIR CORRELATION WITH DIAGNOSTIC CLASSIFICATION AND TREATMENT OUTCOME IN B CELL LYMPHOBLASTIC LEUKEMIA

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Background:

PAX5 is an essential transcription factor required for B cell differentiation. It is known that *PAX5* aberrations confer the occurrence of B cell lymphoblastic leukemia (B-ALL) in various forms of abnormality. However, due to the complexity of the structural variation of *PAX5*, comprehensive examination and analysis remain challenging.

Aims:

To decipher the structural aberrations of the *PAX5* gene to investigate their correlation with diagnostic classification and treatment outcome in B-ALL.

Methods:

Optical genome mapping (OGM) and transcriptome sequencing (RNA-seq) were performed on the bone marrow samples of 21 newly diagnosed or relapsed/refractory B-ALL cases to decipher *PAX5* structure variations including the formation of fusion genes, exon deletion, and exon duplication. Other pathological fusion genes and gene mutations in B-ALL were also analyzed, and patients were followed up for treatment outcomes.

Results:

A total of 11 of 21 cases (52.4%) were detected with *PAX5* structural variations, including 5 children (age < 14 years) and 6 adults (2.5 ~ 55 years, median = 20), with a male: female = 4.5:1 (9/2). Of them, 5 cases (45.4%) carried *PAX5* in-frame fusion genes, and the partner genes *RNF38*, *BCL2*, and *NSD1* have not been reported. Four cases (36.3%) carried the concatenation of *PAX5::ZCCHC7* fusion transcript due to 510Kb 9p focal deletion, which functionally resulted in the truncation of *PAX5*. The other 2 cases (18.3%) carried PAX5 focal deletions (exon6, exon6-7, respectively). *IKZF1* alterations were observed in 8 of the 11 (72.7%) cases, with IK10 being the most common (4 cases).

Eight of the 11 cases carried other genetic abnormalities that define B-ALL subtypes, including 2 *BCR::ABL1*, 3 *BCR::ABL1*-like (*NUP214::ABL1*, *EBF1::PDGFRB*, and *RCSD1::ABL2*, respectively), one *E2A::PBX1*, one *ETV6::RUNX1*, and one hyperdiploid case. Two cases were positive for *CRLF2@IGH*, but without genetic abnormalities that define B-ALL subtypes.

Six cases evaluated as high-risk received chimeric antigen receptor T cell (CAR-T) treatment, 5 of which were bridged to allogeneic hematopoietic stem cell transplantation (all0-HSCT), and these 5 cases maintained remission until the last follow-up (21-63m). The patient who was not bridged to allo-HSCT died of relapse 13 months after the disease onset.

Summary/Conclusion:

PAX5 structural aberrations are common and important genetic events in B-ALL with various forms, including in-frame gene fusions, 3′ deletion (*PAX5::ZCCHC7*), and focal exon deletions. OGM combined with RNA-seq helps to decipher pathological *PAX5* structural abnormalities. *PAX5* structural abnormalities mostly occur in *BCR::ABL1*-positive and *BCR::ABL1*-like patients and are often associated with IK10. CART bridging allo-HSCT therapy helps improve these patients' prognosis and survival rates.

G/Ages	PAX5 and other pathological significant SVs	CART	HSCT	OS(m)
M/3	PAX5::NOL4L; IK6	Y	Y	60
M/2.5	PAX5 e6-7 del; E2A::PBX1	N	N	26
M/6	PAX5::ZCCHC7; ETV6::RUNX1; IKZF1::DDC	N	N	32
M/5	PAX5 e6 del; hyperdiploid	N	N	11
M/50	PAX5::ZCCHC7; BCR::ABL1; IK6	N	N	11
F/55	PAX5::ELK3; BCR::ABL1; IKZF1::SPATA48	N	Y	21
F/24	PAX5::ZCCHC7; NUP214::ABL1; IK10	Y	Y	63
M/35	PAX5::RNF38; EBF1::PDGFRB; IK10	Y	Y	31
M/13	PAX5::ZCCHC7; RCSD1::ABL2; IK10	Y	Y	57
M/20	PAX5::BCL2; CRLF2@IGH; IK8	Y	N	13,death
M/23	PAX5::NSD1; CRLF2@IGH; RB1del; IK10	Y	Y	103

Table 1

Keywords: Acute lymphoblastic leukemia, PAX5