Chromosomal Translocations Involving the T-Cell Receptor δ Chain Locus and Two Loci on the Short Arm of Chromosome 11 *

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Chromosomal abnormalities in T-cell acute lymphoblastic leukaemia frequently involve chromosome 14q11, the site of the T-cell receptor (TCR) δ/α chain locus [1–3]. We have previously described the molecular analysis of two such translocations involving the short arm of chromosome 11, t(11; 14)(p15; q11) and t(11; 14)(p13; q11) [4, 5]. Here, we briefly summarise these findings with emphasis on the mechanism by which these translocations arise.

A. The Translocation t(11; 14)(p15; q11) in RPMI 8402

The DNA sequence analysis of chromosomal junction of $11p^+$ and $14q^-$ chromosomes, respectively, indicated that chromosome 11 sequences were joined to a DDJ element of the TCRδ chain gene (chromosome $11p^+$). A typical signal sequence (heptamer/nonamer with 12-bp spacer), presumably derived from the 5′ end of Dδ1, is joined, back to back, to a heptamer-like sequence derived from chromosome 11 at the chromosome $14q^-$ junction. It is noteworthy that there is no nonamer-like sequence on either side of this chromosome 11 derived heptamer. This suggests that the actual translocation involved a break [1] at the 5′ end of a Dδ element, which had previously joined to a DJ segment, and [2] at the heptamer sequence of chromosome 11. It is likely that the recombinase involved in the physiological process of antigen-receptor gene rearrangements attempted to join to a Vδ gene to the DDJ element, but mistakenly utilised the chromosome 11 derived heptamer to cause the translocation.

B. The Translocation t(11; 14)(p13; q11)

The molecular cloning of breakpoints of two tumours carrying the t(11; 14)(p13; q11) translocation [5] showed a DDJ join at one $11p^+$ breakpoint (tumour #8511) and a D-D join at another $11p^+$ junction (tumour LALW-2). The analysis of chromosome 11 germ-line sequences at these respective breakpoints revealed the presence of a heptamer-like sequence in one instance (tumour #8511) but not in the other tumour (LALW-2). In the latter case, the translocation process seemed to have ignored the heptamer used in the #8511 tumour, although both breakpoints in that region occur within only 800 bp [5]. Figure 1A summarises the events leading to the translocation in tumour LALW-2 and indicates that the translocation most likely takes place after a D-D join during an attempt to join a Vδ element. Figure 1B schematically shows the spatial relation-

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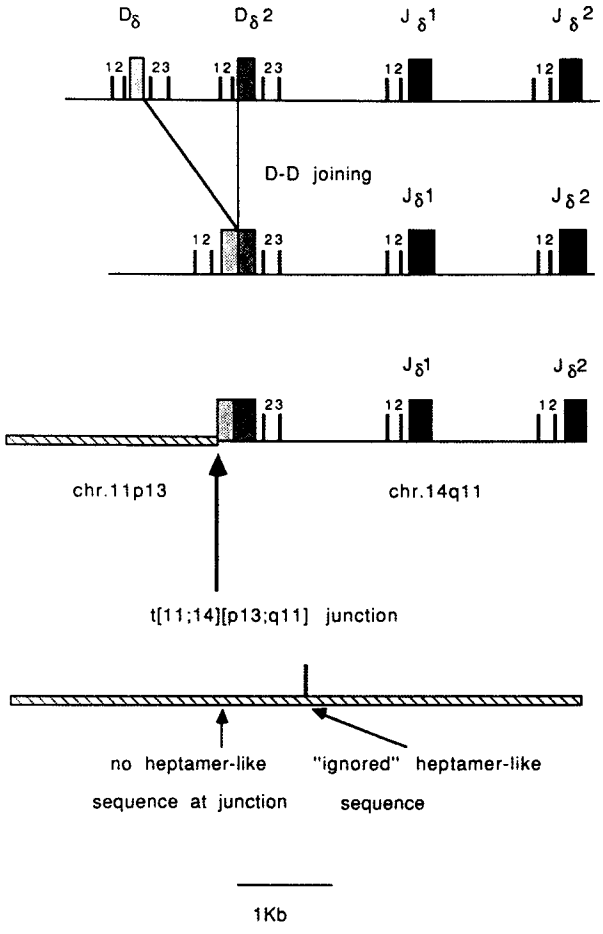

Fig. 1. **A** Schematic illustration of a D-D join at the TCRδ locus and preceding the translocation in tumour LALW-2 [5] and the structure of the $11p^+$ chromosome (*third line*) after translocation. **B** Schematic illustration of the chromosome 11 germ-line breakpoint cluster region, indicating the breakpoint in the LALW-2 tumour about 0.8 kb centromeric to a hepatamer-like sequence

ship of the heptamer to the translocation breakpoint of tumour LALW-2.

C. Conclusion

The contribution of the t(11; 14)(p15; q11) translocation to tumour formation in the RPMI 8402 cell line is as yet unknown. The 11p15 sequences near the breakpoint are transcriptionally active, so the possibility exists that the translocation aberrantly activated this gene in one way or another with pathogenic consequences for the afflicted cell. However, an alternative view would be that the translocation occurred only because of the presence of the heptamer-like sequence near the breakpoint mistakenly utilised by the recombinase while attempting to rearrange a Vδ gene to the DDJ segment. The translocation could thus have been innocuous with respect to tumour formation. As such, the RPMI 8402 provides an excellent example to test the central dogma of cancer cytogenetics about the pathogenic significance of chromosomal abnormalities.

A completely different situation is encountered in the t(11; 14)(p13; q11) translocation. In this case, a breakpoint cluster region can be defined, strongly suggesting that a disrupted 11p13 locus is important for tumour formation. Furthermore, the variable presence of heptamer sequences at the breakpoints within that region suggests that a sequence-specific cut is not necessary on chromosome 11 for the translocation process. This observation distinguishes a two- and a one-site recognition model for sequence-specific recombinase involvement in these translocations [6].

The 11p13 breakpoint may prove to be useful in another respect. Due to its apparent proximity to the WAGR complex, it might help to refine the map of this important region, thought to contain tumour suppressor genes.

References

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