

Leukaemia Section

Mini Review

dup(21q) amplified (RUNX1)

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Identity

Note: This molecular cytogenetic subgroup of ALL is characterised by the presence of multiple copies of the RUNX1 (AML1) gene on a duplicated chromosome 21q (Figure 1). Using metaphase FISH multiple RUNX1 signals are seen along the length of the

duplicated 21q (Figure 2), while in interphase the signals are clustered together (Figure 3). G-banded cytogenetic analysis shows that the morphology of the duplicated chromosome 21q is heterogeneous between cases (Figure 4). Currently, FISH with probes directed to RUNX1 is the only reliable method of detection.

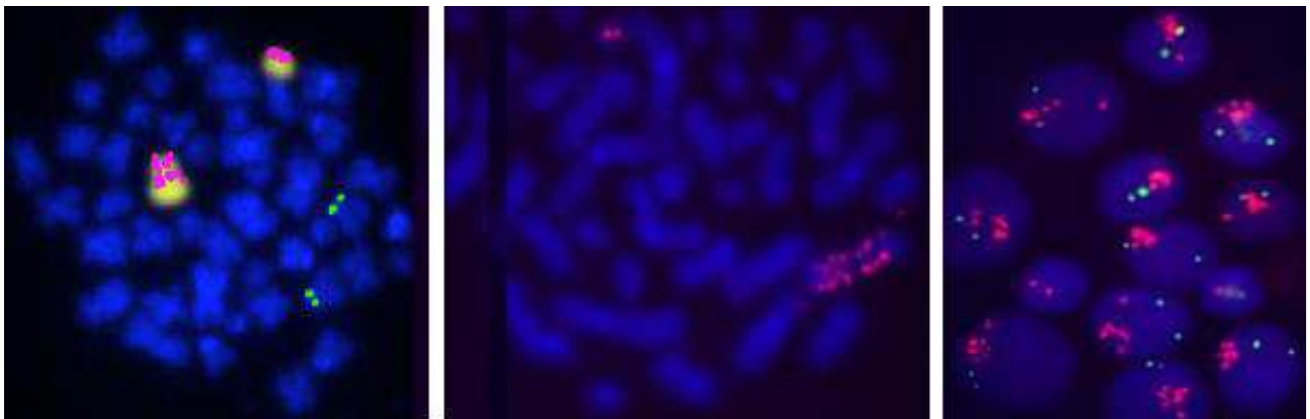


Fig1 : Left: A metaphase showing an abnormal chromosome (whole chromosome paint 21) with multiple RUNX1 (red) and two normal ETV6 (TEL) signals. Middle: A metaphase showing multiple RUNX1 exon signals (red) along the length of an abnormal chromosome 21. Right: Interphase cells showing clustering of the red RUNX1 and the two normal green ETV6 signals, using the LSI TEL-AML1 translocation probe (Vysis).



Partial G-banded karyograms showing heterogeneity in the morphology of the duplicated 21q. The normal chromosome 21 is always on the left.

Clinics and pathology

Disease

Acute lymphoblastic leukaemia: B-lineage immunophenotype (mostly common or Pre-B), FAB L1/L2.

Epidemiology

The estimated incidence in childhood ALL is 1-3%. The majority of patients tend to be older children or adolescents with nearly three-quarters of reported patients aged between 6 and 14 years old. A few young adults have also been reported but too few to estimate its incidence in this age group. No gender bias has been observed.

Clinics

Patients with this abnormality typically present with a low white cell count of $<20 \times 10^9/L$.

Prognosis

The three year event free survival of the 25 patients treated on the UK MRC ALL97 trial was just 51% (95% C.I. 27%-71%) and hence represent a poor risk cytogenetic feature in childhood ALL.

Cytogenetics

Note: Although FISH with a probe to the RUNX1 (AML1) gene is required to accurately identify this abnormality, the duplicated chromosome 21 is easily visible using conventional cytogenetics. The morphology of the abnormal chromosome 21 is highly heterogeneous presenting as a metacentric, acrocentric or ring chromosome (Figure 4). Prior to the identify of this abnormality by FISH many karyotypes were described as -21,+mar.

The duplicated 21q is rarely the sole chromosomal abnormality. The karyotype is frequently complex, although no recurrent secondary abnormality has yet emerged. This abnormality does not occur with other primary chromosomal abnormalities in ALL e.g. t(12;21)(p13;q22) / ETV6-RUNX1, t(9;22)(q34;q11), t(1;19)(q23;p13) etc. However, a few cases of high hyperdiploidy have been reported.

FISH has been instrumental in defining this abnormality and is essential for its accurate detection.

Virtually all cases reported to date have been identified using the LSI TEL-AML1 translocation probe. However, any FISH probe directed to RUNX1 could be used. The identification of metaphases with multiple RUNX1 signals on a single chromosome 21 is the most accurate detection method. However, in the absence of metaphases the presence of multiple clustered RUNX1 signals is also reliable.

The current published definitions of amplification within the context of this abnormality are as follows: only included cases in which the abnormality had been visualised in metaphases and three or more RUNX1 signals were seen on a single abnormal chromosome 21, while others used the same definition when the abnormality was seen in metaphase. Additionally, they included cases which revealed only interphases with five or more RUNX1 signals.

Genes involved and Proteins

RUNX1

Note: By definition the RUNX1 (AML1) gene is amplified in all these patients. Over-expression of RUNX1 or any of the other genes within the amplified region has yet to be established.

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