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Genetic and genomic characterisation of older adults with ALL treated on the UKALL14 and UKALL60+ clinical trials

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INTRODUCTION

- Acute lymphoblastic leukaemia (ALL) is characterised by recurrent chromosomal abnormalities and secondary copy number abnormalities (CNAs) in the leukemic blasts.
- The frequency of individual primary cytogenetic subtypes and secondary CNAs is age-dependent and has a bearing on prognosis.
- B-cell precursor (BCP) ALL patients lacking a cytogenetically-visible recurrent primary abnormality (B-other ALL) have been found to harbour a range of cryptic rearrangements including ABL-class fusions (*ABL1*, *ABL2*, *PDGFRB* and *CSF1R*), JAK-STAT activating lesions (*JAK2* and *CRLF2* rearrangements) or rarer *ZNF384* and *MEF2D* translocations.
- Very few studies have specifically examined the genetic aberrations in older adults with ALL.

METHODS

- All patients recruited into the UKALL14 and UKALL60+ clinical trials and aged ≥60 years at diagnosis were identified.
- Based on karyotype and fluorescence *in situ* hybridisation (FISH) analyses performed in regional cytogenetic centres, each patient was assigned a cytogenetic subgroup of *BCR-ABL1*, *TCF3-PBX1*, *KMT2A* rearranged (*KMT2A*r), low hypodiploidy/near triploidy (HoTr), high hyperdiploidy (HeH), or B-other. T-ALL patients were considered separately.
- B-other ALL cases with suitable material were screened for gene rearrangements using break apart FISH probes for *CRLF2*, *IGH@*, *ABL1*, *ABL2*, *PDGFRB/CSF1R*, *JAK2*, *ZNF384* and *MEF2D.*
- Separately, SNP arrays were performed on all cases with available DNA using Illumina CytoSNP 850K or Affymetrix Cytoscan HD arrays.
- SNP arrays were visualised and interpreted in Nexus Copy Number 10 (Biodiscovery, El Segundo, CA).
- Multiplex ligation-dependent probe amplification (MLPA) using the P335 kit (MRC Holland) was used to validate copy number abnormalities in 9 key genes/loci (*EBF1*, *IKZF1*, *CDKN2A/B*, *JAK2*, *PAX5*, *ETV6*, *BTG1*, *RB1*, and PAR1).

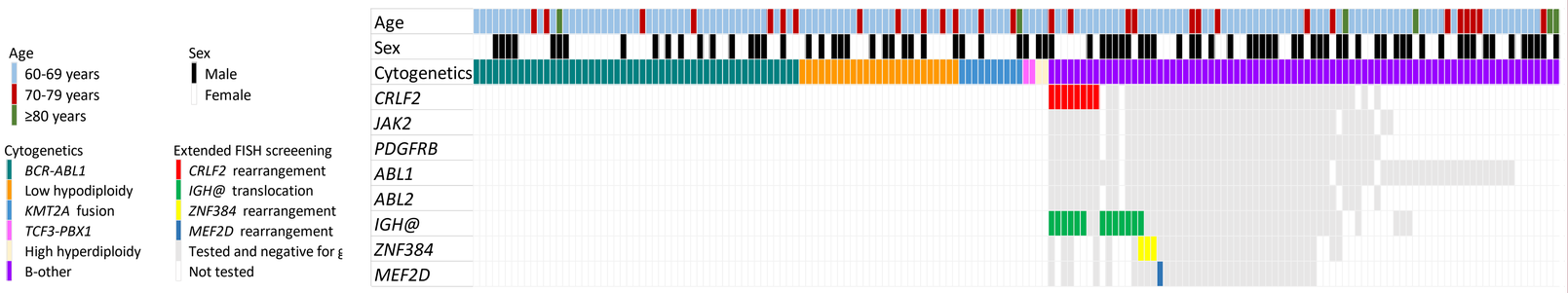
RESULTS

- 207 patients aged ≥60 years at diagnosis were identified: KALL14 (n=91) and UKALL60+ (n=116).
- 178 patients (86%) had cytogenetic data from diagnosis.
- Median age was 64 years (range 60-83).
- Male: Female ratio was 1:1.
- Primary chromosomal abnormalities identified in regional cytogenetic centres (Table 1).
- Extended FISH screening of B-other cases identified *CRLF2* rearrangements in 8/48 cases (17% of B-other, 5% of total). *IGH@* was the translocation partner in 6 cases and *P2RY8* in 1 case.
- Overall *IGH@* translocations were present in 13/50 cases (26% of B-other, 9% of total).
- Complex karyotype was seen in 5/80 (6%) B-others. 4 tested negative for the relevant gene rearrangements on extended FISH screening and one case was not tested due to lack of material.
- Cytogenetic and FISH results of BCP-ALL patients are summarised in figure 1.

Table 1: Primary chromosomal abnormalities' frequencies and patient demographics

Cytogenetics	*BCR-ABL1*	*TCF3-PBX1*	*KMT2A*r	HeH	HoTr	T-ALL	B-other
Number (%)	51 (29%)	2 (1%)	10 (6%)	2 (1%)	25 (14%)	8 (4%)	80 (45%)
Male	37%	50%	30%	100%	48%	50%	59%
Median age (yrs)	64	64.5	63	63.5	64	63	65.5

Figure 1: Cytogenetic and FISH results for BCP-ALL patients (n=170)



- SNP arrays were performed on 83 patient samples using Illumina CytoSNP 850k (n=52) or Affymetrix Cytoscan HD (n=31) arrays.
- Recurrent chromosomal and arm-level copy number events are shown in table 2.

Table 2: Recurrent whole chromosome and whole arm CNAs present in >3 cases

Chromosome/arm abnormality	Number of cases (%)	Details
del(9p)	9 (12%)	5 x BCR-ABL1, 4 x B-other
-7	7 (10%)	5 x BCR-ABL1, 2 x B-other
+21	6 (8%)	3 x BCR-ABL1, 3 x B-other
del(7p)	5 (7%)	3 x BCR-ABL1, 2 x B-other
gain of 1q	5 (7%)	3 x B-other, 2 x BCR-ABL1
del(17p)	4 (5%)	4 x B-other

- Recurrent deletions were identified affecting *IKZF1* in 52% (n=43), *CDKN2A/B* in 45% (n=37), *PAX5* in 39% (n=32), *RB1* in 22% (n=18), *ETV6* in 21% (n=17), *EBF1* in 19% (n=16), *CD200/BTLA* in 16% (n=13), *ATP10A* in 13% (n=11) and *BTG1* in 12% (n=10).
- The frequency of individual deletions varied by genetic subtypes (Figure 2).
- Recurrent novel and less-well described intragenic microdeletions were also seen in *LEMD3* (n=5, 6%), and *KDM6A* (n=4, 5%).

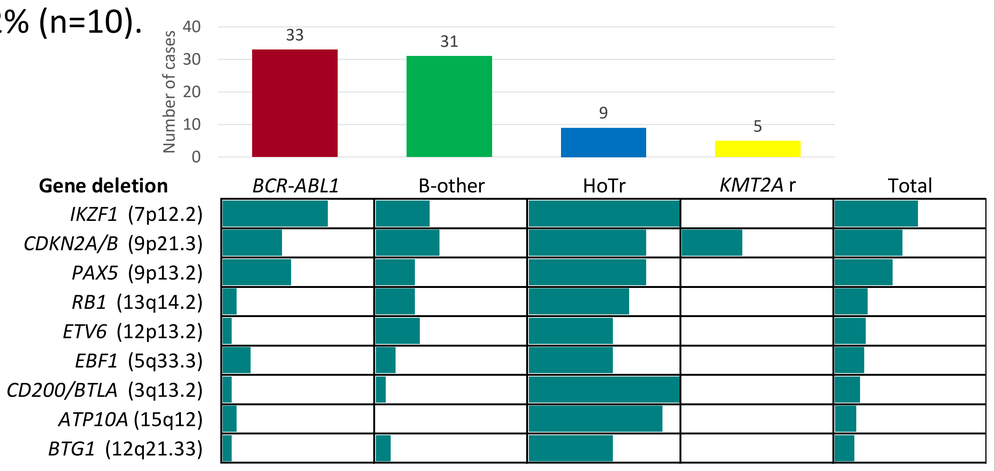


Figure 2: Frequency of deletions by cytogenetic subtype. Length of bars represent proportion of cases. Only cytogenetic subtypes with >4 cases shown.

CONCLUSIONS

- **High risk cytogenetic subtypes were seen in ~50% of the cohort.**
- **Low hypodiploidy is the second most prevalent primary genetic abnormality in older adults.**
- **Primary genetic lesion in most B-other cases remains uncharacterised and ABL-class fusions are notably absent.**
- ***IKZF1* deletions are present in >50% of patients.**

ACKNOWLEDGEMENT

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