Whole Genome Profiling of Adult B-Other Acute Lymphoblastic Leukaemia on the UKALL14 Trial

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Abstract

Background: B-other ALL represents a working definition for patients with B cell precursor (BCP) ALL without a known primary chromosomal abnormality. In this study we use whole genome sequencing (WGS) to characterize adult B-other cases (age ≥ 25yrs) from the UKALL14 trial (NCT01085617). Figure 1 illustrates the recognized clinical entities in adult ALL enrolled in the UKALL 14 trial.

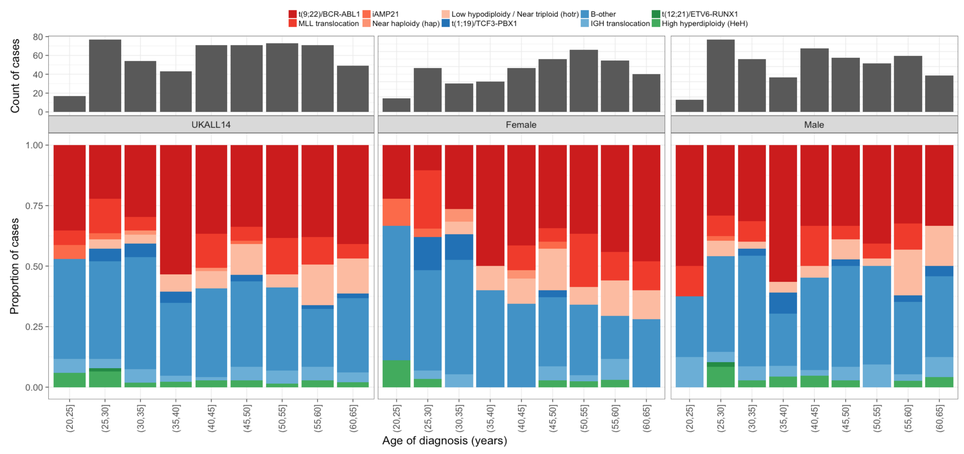

Figure 1: Summary of UKALL14 B-Cell cases demarcated by major subgroups.

Methods: Of 652 patients aged 25-65yrs enrolled onto UKALL14, 333 (51%) had B-other ALL. Sufficient material was available to screen 156/333 B-other cases for recurrent Ph-like fusion events (*CLRF2*, *JAK2*, *ABL1*, *ABL2* & *PDGFRB*) using FISH and MLPA (kit P335). This identified 28 (18%) "Ph-like" fusion events (21 *CRLF2*, 5 *ABL*-class fusions and 2 *JAK2*). Of the remaining 128 B-other cases, 57 had available samples for tumor normal paired WGS (read depth 60x and 30x respectively). Bioinformatic analysis was performed to determine small somatic mutations (SSMs); single nucleotide variants (SNVs) and insertion/deletions (INDELs) as well as copy number aberrations (CNA) and structural variants (SV). We also undertook de novo motif analysis to identify RAG mediated deletions.

Results: We present data for 51/57 cases (6 cases failed sample QC), median age of diagnosis 42, range 25-65. Within this cohort we identified 1,649 SVs, 165,530 SNVs and 8,508 indels, with each case having a median representation of 28 (10-137) SVs, 1,663 (912-77,183) SNVs and 103 (11-2,749) indels. The Median SSM burden was 0.55 per megabase (range 0.31-25), which is in the upper third of previous ALL estimates (median 0.26 range 0.03-2.9) but low compared to most other cancer types (Alexandrov *et al.* 2013).

Disease defining events

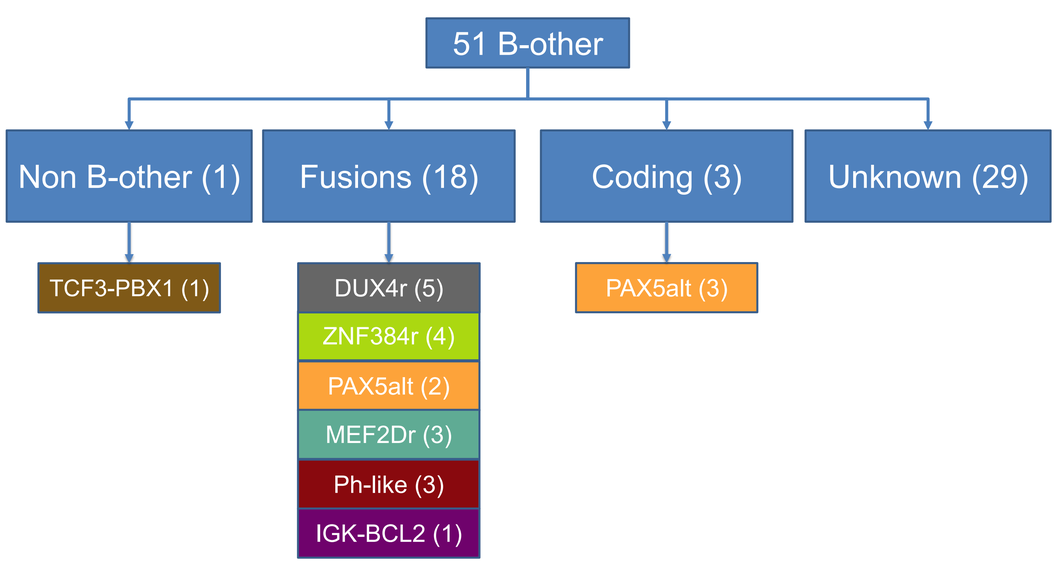

Figure 2: Diagram showing driver discovery in 51 B-other candidate cases; 19 previously described fusions and 3 coding drivers which have been previously described via gene expression (Gu *et al.* 2019)

Molecular characteristics

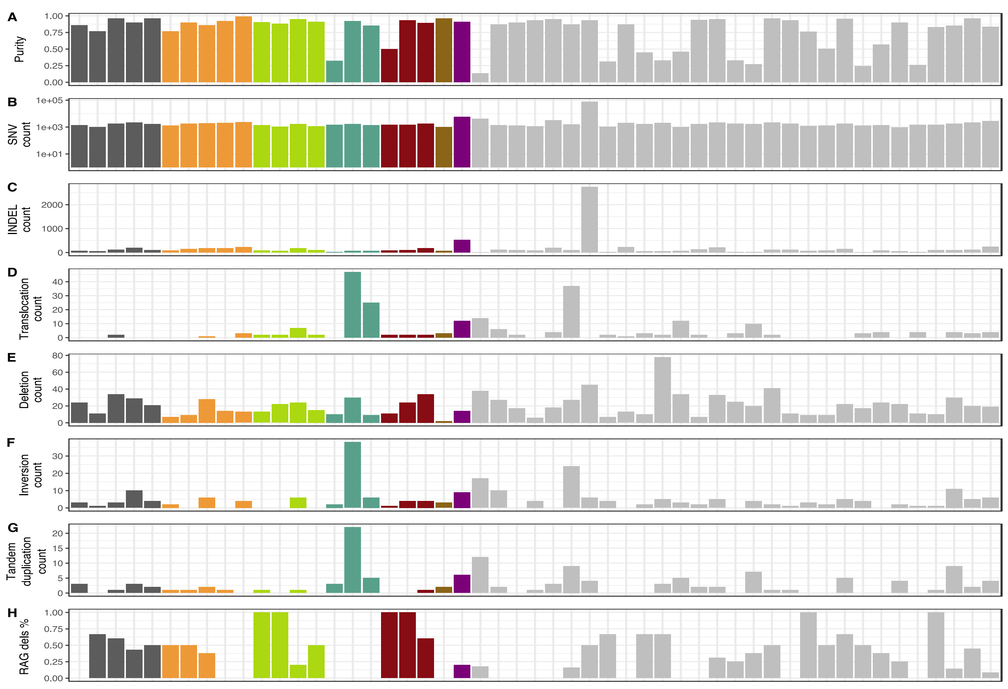

Figure 3: Mutation burden vs Driver type; SNVs and INDELs (B & C) show similar burden within the cohort although INDEL count correlates with purity (A); Translocations, deletions, inversion and tandem-duplications (D, E, F & G) shows MEF2Dr cases to have higher SV burden; RAG deletion % (H) shows MEF2Dr cases are depleted in RAG deletions

Recurrent mutational events

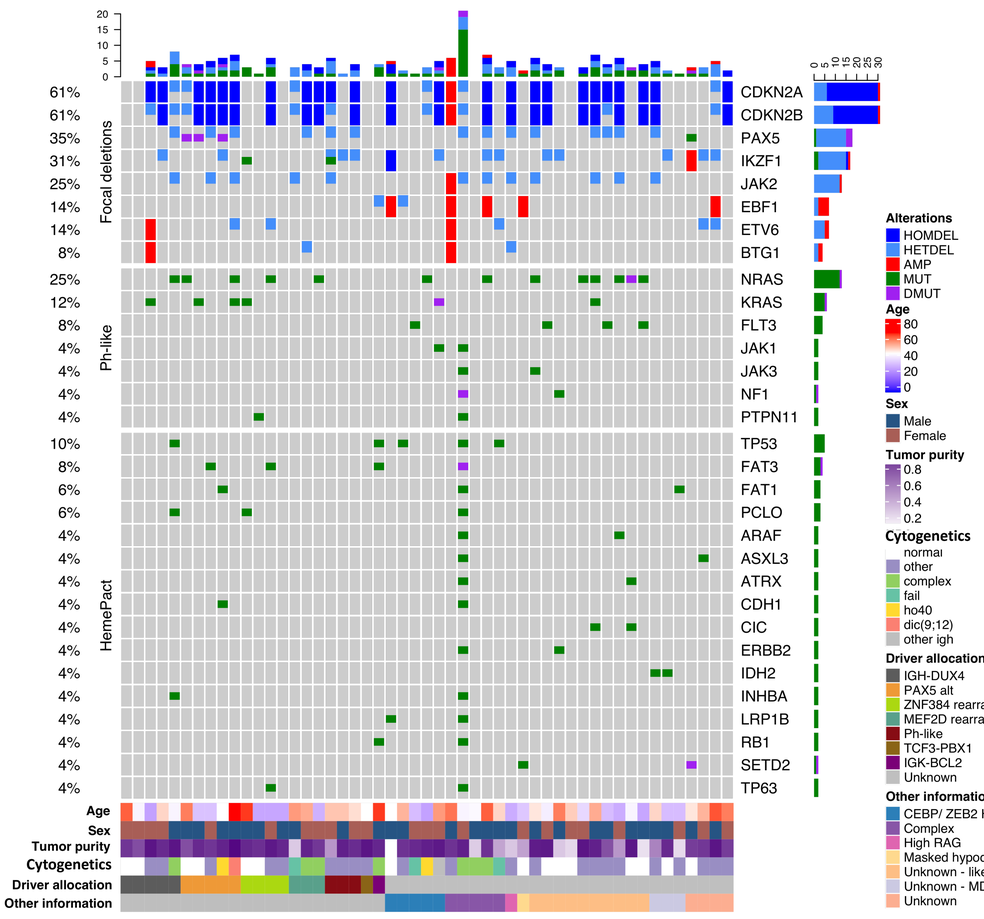

Figure 4: OncoPrint plot showing; recurrent focal deletions, Ph-like and HemePact mutations (seen twice). Tumor purity, Trial cytogenetics, Driver and other information are displayed at the base of the plot.

Normal karyotype sensitivity

30% of cases (15/51) have normal recorded karyotype (46,XX[20]/46,XY[20]);

- 8/15 have large events that should be visible karyotypically
- 3/8 involve multiple chromosomes
- 5/8 have tumour purities < 75%

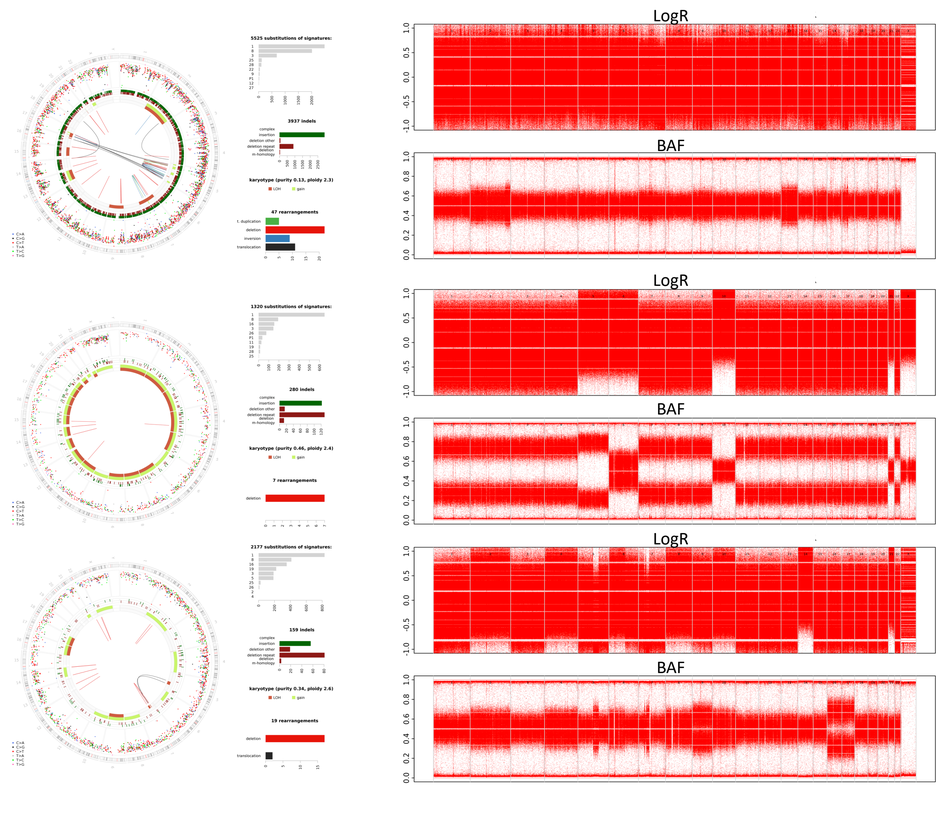

Figure 5: Circos and LogR/BAF plots for 3/8 cases with recorded normal karyotype but with large events detectable by WGS

Unknown candidate groups

We categorised the remaining 29 cases without a recurrent driver into 7 groups

- 5 *CEBP*/ *ZEB* H1038R – likely to be the G12 subtype identified by Li *et al.* 2018
- 5 Complex – cases includes an MMR hypermutator & translocation "chain"
- 1 High RAG burden case
- 1 "masked" hypodiploid previously described by Carroll *et al.* 2009
- 10 "Like" candidates – 9 with Ph-like mutations & a single *ETV6* dominant negative
- 3 MDS mutations – 2x IDH2 R140Q & 1x ASXL1 LOH
- 4 Unknowns – this group we hope to further investigate with RNA-seq

Summary

- Whole genome sequencing enables characterization of disease defining alterations in B-other ALL that are of clinical relevance in 65% of cases.
- 8/51 (15%) of cases with a normal karyotype had large CN events by WGS, suggesting a bias in karyotype detection particular in lower purity samples.
- Distinct classes of genomic instability are identified in B-other ALL this include a RAG mutation phenotype, high SV burden and MMR hypermutator
- This approach sets the premise to design and extended genotype-clinical correlative study on 800 B-ALL cases enrolled in UKALL14 and 60+ trials

References

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Acknowledgments

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