Is The Distribution Of Gene Copy Number Alterations In Ph-positive B-ALL Different From Ph-negative B-ALL?

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INTRODUCTION

- The copy number alterations (CNAs) in B-ALL, particularly IKZF1 deletions have significant implications for disease prognosis and may also lead to resistance to therapy[1].
- Ph-positive B-cell acute lymphoblastic leukemia (B-ALL) is characterised by the presence of BCR::ABL1 and is associated with unfavourable outcome.
- This study explores the difference in the distribution of CNAs in both Ph-positive and Ph-negative B-ALL.

AIM

To establish and compare the prevalence of CNAs in Ph-positive B-ALL and Ph-negative B-ALL.

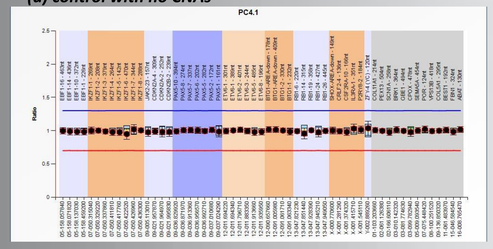
METHOD

- Genomic DNA and total RNA were obtained from the peripheral blood or bone marrow at the time of presentation.
- Multiplex RT-PCR was done for recurrent translocations including BCR::ABL1 fusion.
- CNAs (deletions and amplifications) in B-cell differentiation and cell cycle control genes (EBF1, CDKN2A/B, PAX5, ETV6, BTG1 and RB1) and in the PAR1 region were detected by Multiplex ligation-dependent probe amplification (MLPA) using SALSA P335 kit (MRC, Holland).

RESULTS

- *A total of 201 B-ALL patients enrolled were categorized into Ph-positive (39; 19.4%) and Ph-negative (162; 80.6%).*
- *The median age of the patients was 14 years (8 months–60 years); Ph-positive cases–30.5 years (2–60 years) and Ph-negative–12 years (8 months–61 years).*
- *The CNAs in the overall cohort were detected in 153(76.1%) cases; most commonly altered genes being IKZF1–32.8%, CDKN2A/2B-31.3%, and PAX5-31.3%.*
- *In Ph-positive cohort, CNAs were detected in 36 cases (92%) and in Ph-negative cohort, CNAs were detected in 117 cases (72%).*
- *The commonly altered genes in Ph-positive group were IKZF1–71.8%, PAX5–43.6%, CDKN2B–38.5%, and CDKN2A–35.9%; and in Ph-negative group being CDKN2A–30.2%, CDKN2B–29.6%, PAX5–28.4%, and IKZF1–23.5%.*
- *The patients were grouped into three categories, with CNA in 1 gene-46 cases (22.89%), 2 genes-38(18.91%), and >=3 genes-69(34.33%).*
- *The Ph-positive cohort had 8 cases(20.5%) with CNA in 1 gene, 11(28.2%) with 2 genes and 17(43.6%) >=3 genes; and Ph-negative cohort had 38(23.5%), 27(16.7%), and 52(32.1%) cases with CNAs in 1, 2 and >=3 genes respectively.*

Figure 1: MLPA Ratiocharts showing
(a) control with no CNAs



(b) CNAs in IKZF1, CDKN2A/2B, PAX5 and ETV6 gene

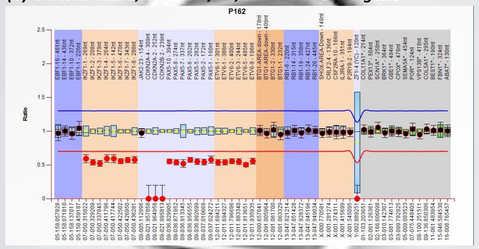


Figure 2: Oncoprint showing CNAs in entire cohort of 201 cases

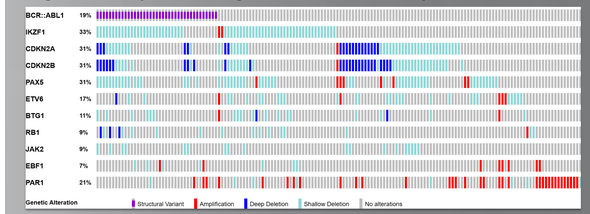


Figure 3: Oncoprint showing CNAs in Ph-positive cases

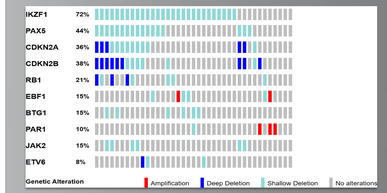
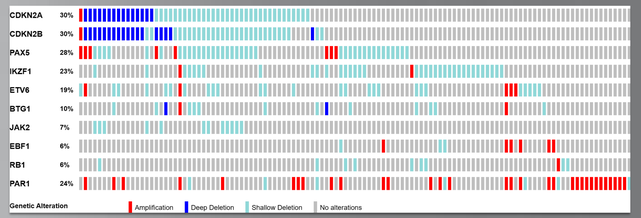


Figure 4: Oncoprint showing CNAs in Ph-negative cases



Genes	Total		Ph-positive		Ph-negative	
	N	%	N	%	N	%
EBF1	15	7.46	6	15.4	9	5.6
IKZF1	66	32.84	28	71.8	38	23.5
JAK2	18	8.96	6	15.4	12	7.4
CDKN2A	63	31.34	14	35.9	49	30.2
CDKN2B	63	31.34	15	38.5	48	29.6
PAX5	63	31.34	17	43.6	46	28.4
ETV6	34	16.92	3	7.7	31	19.1
BTG1	22	10.95	6	15.4	16	9.9
RB1	18	8.96	8	20.5	10	6.2
PAR	43	21.39	4	10.3	39	24.1

CNAs	Total		Ph-positive		Ph-negative	
	N	%	N	%	N	%
1 CNA	46	22.89	8	20.5	38	23.5
2 CNAs	38	18.91	11	28.2	27	16.7
>3 CNAs	69	34.33	17	43.6	52	32.1

CONCLUSIONS

- Our study indicates that the CNAs in Ph-positive B-ALL differ from that of Ph-negative B-ALL.
- The most affected gene in the Ph-positive B-ALL cohort was IKZF1 compared to CDKN2A/B in the Ph-negative cases.
- The Ph-positive cohort overall had CNAs in a higher number of genes (>=3 genes-43.6% cases) than the Ph-negative cohort (32%), possibly indicating a higher genomic susceptibility in Ph-positive B-ALL.
- Overall, the CNAs present were mostly deletions except in PAR1 gene where amplifications were more than deletions.

REFERENCES

1. Gupta SK et al. Gene copy number alteration profile and its clinical correlation in B-cell acute lymphoblastic leukemia. *Leuk Lymphoma. 2017 Feb;58(2):333-342. doi: 10.1080/10428194.2016.1193855.*

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