Identification of Mutations in *RAS* Signalling Associated Genes in Childhood B-Cell Acute Lymphoblastic Leukaemia in Malaysia

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RAS pathway mutations have been linked to paediatric B-cell Precursor Acute Lymphoblastic Leukaemia (BCP-ALL) prognosis, relapse and chemotherapy resistance. Primary chromosomal and gene fusion abnormalities initiate the development of pre-leukaemic clones with subsequent cooperating secondary abnormalities causing leukaemia. Secondary genetic abnormalities involve various gene mutations associated with signalling pathways, such as RAS signalling leading to BCP-ALL development. Among these, genetic alterations of RAS signalling genes are observed in 15% of paediatric BCP-ALL cases. We carried out an identification of mutations using whole-exome sequencing for RAS signalling-associated genes including BRAF, CBL, FLT3, HRAS, KMT2A, KRAS, NF1, NRAS and PTPN11 in 62 paediatric BCP-ALL patients. Scanning for mutations through WES showed that the mutations in the coding region of the KRAS and NRAS genes that resulted in amino acid change in 18 patients. The glycine (G) at position 12 in the GTP binding, active site was replaced with cysteine (C) or aspartic acid (D) in KRAS in four patients possibly disrupting substrate interactions and the GAP arginine finger that are critical for enzymatic activity. The activating point mutations in the tyrosine kinase domain of FLT3 Dore835H have been observed in one patient in the cohort. Furthermore, we detected four mutations in PTPN11, two of them are in the SH2 and two are in the phosphatase domains. Characterisation of the mutations and copy number changes in RAS signalling pathways confirm the occurrence of these modifications in the Malaysian cohort. These findings can be incorporated into current prognostication for comprehensive risk stratification of the BCP-ALL patients

Keywords: B-cell Precursor Acute Lymphoblastic Leukaemia (BCP-ALL)

Acknowledgements
The authors would like to thank the Director General of Health, Malaysia for permission to present this study. This research was funded by the Ministry of Health Malaysia (NMRR-16-1468-32122 (IIR)).

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