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Genomic landscape of childhood acute lymphoblastic leukemia in Malaysia: insights from array-CGH

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Abstract

Background Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, comprising approximately 25% of pediatric malignancies. Notably, chromosomal aberrations and genetic alterations play a central role in the pathogenesis of ALL, serving as critical diagnostic and prognostic markers. In this study, we use array-based comparative genomic hybridization (array-CGH) to explore the landscape of copy number variations (CNVs) and variants of uncertain significance (VUS) in 67 Malaysian childhood ALL patients with normal karyotype.

Results A total of 36 pathogenic CNVs (26 gains, 10 losses) were identified in 19 (28.4%) patients which harbor genes related to the development of ALL. The genes include the *MLLT3* (9p21.3), *ETV6* (12p13.2), *RUNX1* (21q22.12), *ERG* (21q22.2) and *DMD* (Xp21.1). On the other hand, a total of 46 variants of uncertain significance (VUS) was observed in 34 (50.7%) patients.

Conclusions Our study indicates that array-CGH is able to identify and characterize the CNVs responsible for the pathogenesis of childhood ALL. However, further studies are required to determine the pathogenic implications of VUS in the development of childhood ALL.

Keywords Array-based comparative genomic hybridization, Childhood acute lymphoblastic leukemia, Copy number variations, Variants of uncertain significance

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Background

Acute lymphoblastic leukemia (ALL) is the most frequent type of childhood leukemia which accounts for 26% of all childhood cancer [1]. According to the Malaysia National Cancer Registry report: 2012–2016, leukemia is reported to be the 7th most common cancer among the Malaysian population and the most frequent cancer reported among children below 15 years old, with a sex ratio of 1.4:1 in favor of males [2].

In ALL, conventional cytogenetics is routinely used in the initial assessment for the purpose of classification of specific leukemia. Approximately, about 60–80% of patients with ALL have abnormalities in chromosome number or structural rearrangements, whereas the remaining 20–40% have normal karyotype or remain undetected using standard cytogenetic methods [3]. Advances in molecular techniques had revealed and extensively characterized chromosomal rearrangements in ALL [4]. Many studies have demonstrated the ability of array-based comparative genomic hybridization (array-CGH) to detect additional chromosomal rearrangements in childhood ALL [5, 6]. Array-CGH is a technique that allows simultaneous detection of genomic alterations at multiple loci, offers a rapid genome wide analysis in a single experiment.

Over two-third of ALL cases have genetic alterations that disrupt the normal process of lymphoid maturation [7]. Standard molecular methods can detect about 75% genomic variation in lymphoid maturation-associated regions in ALL [8]. Human genetic diversity is primarily driven by DNA copy number variations (CNVs). CNVs can alter gene expression, phenotypes and adaptations by disrupting gene pathways and dosage, thus ultimately leading to a particular disease [9]. The average CNVs in each ALL case is usually low and the region covered are mostly focal; yet defining CNVs nature is a challenging task because of the broad spectrum in its distribution.

The distribution of individual chromosomal alterations in ALL is well documented and their nature and frequency are known to vary according to ethnicity and geographical region of the patients [10–12]. It is interesting to note the prevalence of distinct sub-groups of childhood ALL among the different ethnicities in Asia, although inter-marriages are common between the ethnic communities. Thus, the present study aims to identify and characterize the CNVs associated with childhood ALL in the Malaysian population. We hypothesized that childhood ALL patients with normal karyotype harbor distinct CNVs that contribute to leukemogenesis, with potential ethnic-specific genetic alterations influencing disease susceptibility and progression.

Methods

Patients

A total of archived bone marrow cell suspension samples from 67 patients, aged, between 1 and 14 years old, who were diagnosed with ALL were selected for this study. Patients were selected based on the normal cytogenetic finding and the availability of DNA from the bone marrow samples with leukemic blasts > 20% at diagnosis. The demography of the patients comprised of 53 Malays, 6 Chinese, 5 Indian and 3 of indigenous origin. The study was approved by the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia.

DNA extraction

Genomic DNA was extracted from the archived bone marrow cell suspensions using DNeasy Blood & Tissue Kit (Qiagen) following the manufacturer's protocol. The concentration and quality of the extracted DNA was determined by using NanoDrop ND-1000 UV-VIS spectrophotometer (NanoDrop Technologies) according to manufacturer's instructions. DNA with a 260/280 ratio ranging 1.8 to 2.0 was used in subsequent analysis. DNA was also checked for degradation by gel electrophoresis (FlashGel® DNA Cassettes from Lonza Rockland Inc.).

Array-CGH analysis

Array-CGH was performed using the 8 × 60 k CytoSure Arrays (Oxford Gene Technology Ltd.) according to the manufacturer's protocol. Data analysis was performed using CytoSure Interpret Software v4.2 (Oxford Gene Technology Ltd.), which enabled in-depth, comprehensive analysis, comparison and visualization of the whole genomic data as well as the associated CNVs. Chromosomal aberrations were considered as gains when the log2 ratio was higher than 0.25 and as loss when the ratio was below − 0.25. Further analysis was carried out using the DECIPHER (**D**atabas**E** of **C**hromosomal **I**mbalance and **P**henotype in **H**umans using **E**nsembl **R**esources; http://www.ac.uk/postGen-omics/decipher/) and OMIM (**O**nline **M**endelian **I**nheritance in **M**an; http://www.ncbi.nlm.nih.gov/omim/) databases. The DECIPHER data base was utilized to identify and correlate chromosomal imbalances with observed phenotypic manifestations, aiding in the interpretation of potential genotype-phenotype relationships. DECIPHER's visualization tools and curated data provided insights into structural variants, gene dosage effects, and associated clinical features that were pertinent to this study. Results were analyzed to identify patterns and relationships between chromosomal variations and the phenotypic data of interest. Statistical and bioinformatic tools were employed to assess the frequency and significance of identified variations, ensuring that the findings aligned with established literature. Gene annotations and cross-referencing with OMIM enabled

the identification of candidate genes potentially underlying the observed phenotypes. Additionally, potential implications for clinical diagnosis and therapeutic interventions were explored based on the findings.

Results

Array-CGH

In total, 114 CNVs were observed with an average CNV per patient of 1.7. Among these variants, 36 were identified to be pathogenic CNVs (26 gains, 10 losses) in 19 patients (28.4%), based on the pathogenic implications in the development of ALL with the size ranging between 241.77 kb to 115.17 Mb (Table 1; Fig. 1). CNV gains occurred more frequently than CNV losses with a ratio 2.6:1. The most frequent pathogenic CNV gains involved both the *RUNX1* and *ERG* genes (9 cases) at chromosome 21q22.12 and 21q22.2 respectively. Another common pathogenic CNV was identified at chromosome Xp21.1 with 5 patients showed copy number gains and 1 patient showed copy number loss involving the *DMD* gene. Other common pathogenic CNVs were identified at chromosome 9p21.3, 12p13.2 and 18q11.2, involved the *ETV6*, *MLLT3* and *BCL2* genes respectively. Interestingly, gain of a chromosome was also observed in 5 cases, which include gain of chromosome X (3 cases), gain of chromosome 10 (1 case) and gain of chromosome 18 (1 case).

In addition to pathogenic CNVs, a total of 46 variants of uncertain significance (VUS) was also observed in 34 patients (50.7%), with the size ranging between 262.27 kb – 23.59 Mb, consist of copy number gains and losses at multiple loci (Fig. 2; Supplementary Table 1). Similar to pathogenic CNVs, the total copy number gains are more than losses, with a ratio of 1.3:1. Copy number loss at chromosome 9p21.1 was found to be the most frequent (4 cases), followed by copy number loss at chromosome

Table 1 Pathogenic CNVs identified by array-CGH in 19 childhood ALL patients

No.	Case ID	Chromosome region	Aberration type	Size	Key genes
1	1	21q21.1-q22.3	Gain	48.13 Mb	*RUNX1*, *ERG*
2	4	21q21.1-q22.3	Gain	32.96 Mb	*RUNX1*, *ERG*
3	14	21q21.1-q22.3	Gain	32.20 Mb	*RUNX1*, *ERG*
		Whole chromosome X	Gain	-	-
4	17	12p13.1-p13.2	Loss	3.53 Mb	*ETV6*
5	25	1q23.3-q44	Gain	84.55 Mb	*PBX1*
6	29	9p13.1-p24.3	Loss	71.07 Mb	*MLLT3*, *CDKN2A*, *CDKN2B*
7	33	9p21.3	Loss	1.8 Mb	*MLLT3*
8	34	21q21.1-q22.3	Gain	48.13 Mb	*RUNX1*, *ERG*
		Whole chromosome 10	Gain	-	-
		Whole chromosome 18	Gain	-	-
9	40	6q13-q22.1	Loss	45.38 Mb	*PRDM1*, *FOXO3*
10	45	9p21.2-p21.3	Loss	4.15 Mb	-
		10p11.1-p15.3	Gain	38.75 Mb	-
		12p13.2	Gain	241.77 kb	*ETV6*
		12q21.3-q24.3	Gain	47.15 Mb	-
		13q12.1-q34	Gain	115.17 Mb	-
11	46	12p13.2	Loss	241.77 kb	*ETV6*
		18q11.1-q23	Gain	62.75 Mb	*BCL2*
		21q11.2-q22.3	Gain	36.99 Mb	-
		Xp11.1-p22.3	Gain	61.89 Mb	-
12	50	Xp11.21-p22.2	Gain	48.15 Mb	-
		Xq21.3-q28	Gain	60.87 Mb	-
13	52	21q11.2-q22.3	Gain	36.99 Mb	*RUNX1*, *ERG*
		14q11.2-q32.33	Gain	106.02 Mb	-
		Whole chromosome X	Gain	-	-
14	53	21q21.1-q22.3	Gain	25.45 Mb	*RUNX1*, *ERG*
15	55	14q11.2-q32.33	Gain	85.71 Mb	-
		1q23.3-q44	Gain	84.62 Mb	*PBX1*
16	56	12p11.2-p13.3	Loss	21.46 Mb	*ETV6*
		13q13.1-q34	Loss	81.9 Mb	-
17	59	21q11.2-q22.3	Gain	48.13 Mb	*RUNX1*, *ERG*
18	61	21q11.2-q22.3	Gain	48.13 Mb	*RUNX1*, *ERG*
		12p12.3-p13.31	Loss	6.35 Mb	*ETV6*
		Whole chromosome X	Gain	-	-
19	63	Xp21.1	Loss	2.22 Mb	*DMD*

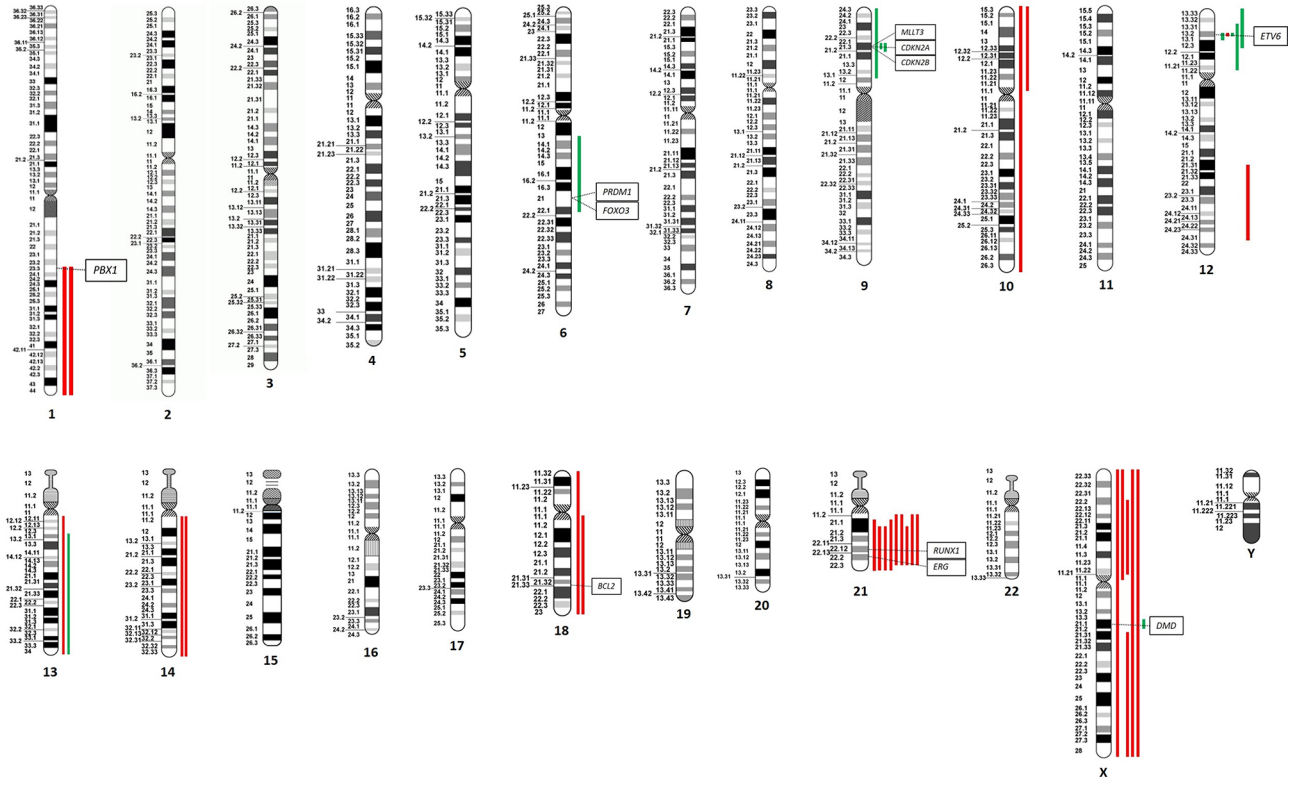

Fig. 1 Ideograms showing pathogenic CNVs identified by array-CGH in 19 childhood ALL patients. The vertical lines on right side of the ideogram indicate losses (green) and gains (red) of the chromosomal region. Key genes are indicated in the box at the specific chromosomal region

5q13.2 (2 cases) and 14q11.2 (2 cases). On the other hand, copy number gains were observed at the 11p15.4, 22q11,23, Xp11.23 and Xp22.31 (2 cases each).

Discussion

CNVs are structurally variant regions, where copy number differences have been observed between two or more genomes that either involve gain or loss of genomic DNA. The characterization of CNVs in childhood ALL would provide insight into genetic lesions that underlie ALL pathogenesis. The application of microarray-based analyses of CNVs in childhood ALL have identified a high frequency of common genetic alterations in both B-progenitor and T-lineage ALL. This method has now become a standard tool in clinical cytogenetics and has improved our understanding of the molecular mechanisms leading to the development of leukemia. In this study, array-CGH was used to characterize CNVs among 67 Malaysian children below 15 years of age diagnosed with ALL.

Many of the pathogenic CNVs detected in this study consist of gains and losses that co-occurred in each patient, consistent with the heterogenous nature of ALL [13]. The pathogenic CNVs were mostly identified at chromosomes 9p21.3, 12p13.2, 18q11.2, 21q22.12, 21q22.2 and Xp21.1, which affect the *MLLT3*, *ETV6*, *BCL2*, *RUNX1*, *ERG* and *DMD* genes. These genes are known to play significant roles in the development of B-ALL [14]. For example, the *ERG* gene is a potent oncogene and encodes for transcription factors which is essential for normal hematopoiesis [15]. Interestingly, gain of *ERG* co-occurred with gain of *RUNX1* in 9 patients at the same chromosomal region 21q22. The *RUNX1* gene, is essential in the development of all hematopoietic cell lineages. Somatic mutations and chromosomal rearrangements involving *RUNX1* are frequently observed in leukemias of myeloid and lymphoid lineages, especially acute myeloid leukemia (AML) and ALL. Intrachromosomal amplification of chromosome 21 (iAMP21) has been reported in a distinct cytogenetic subgroup childhood ALL and associated with poor prognosis [16]; however, it is not known whether extra copies of *RUNX1* contribute to the poor prognosis associated with iAMP21. Moreover, the chromosomal region 21q22.3 contains genes associated with the Down syndrome phenotype, which results from constitutional (germline) trisomy 21. Individuals with Down syndrome have an increased predisposition to leukemia, particularly ALL and acute megakaryoblastic leukemia (AMKL), due to genetic factors that promote abnormal hematopoiesis [17]. Additionally, other inherited disorders, such as Fanconi anemia and ataxia telangiectasia, are known to increase leukemia susceptibility [18]. In this study,

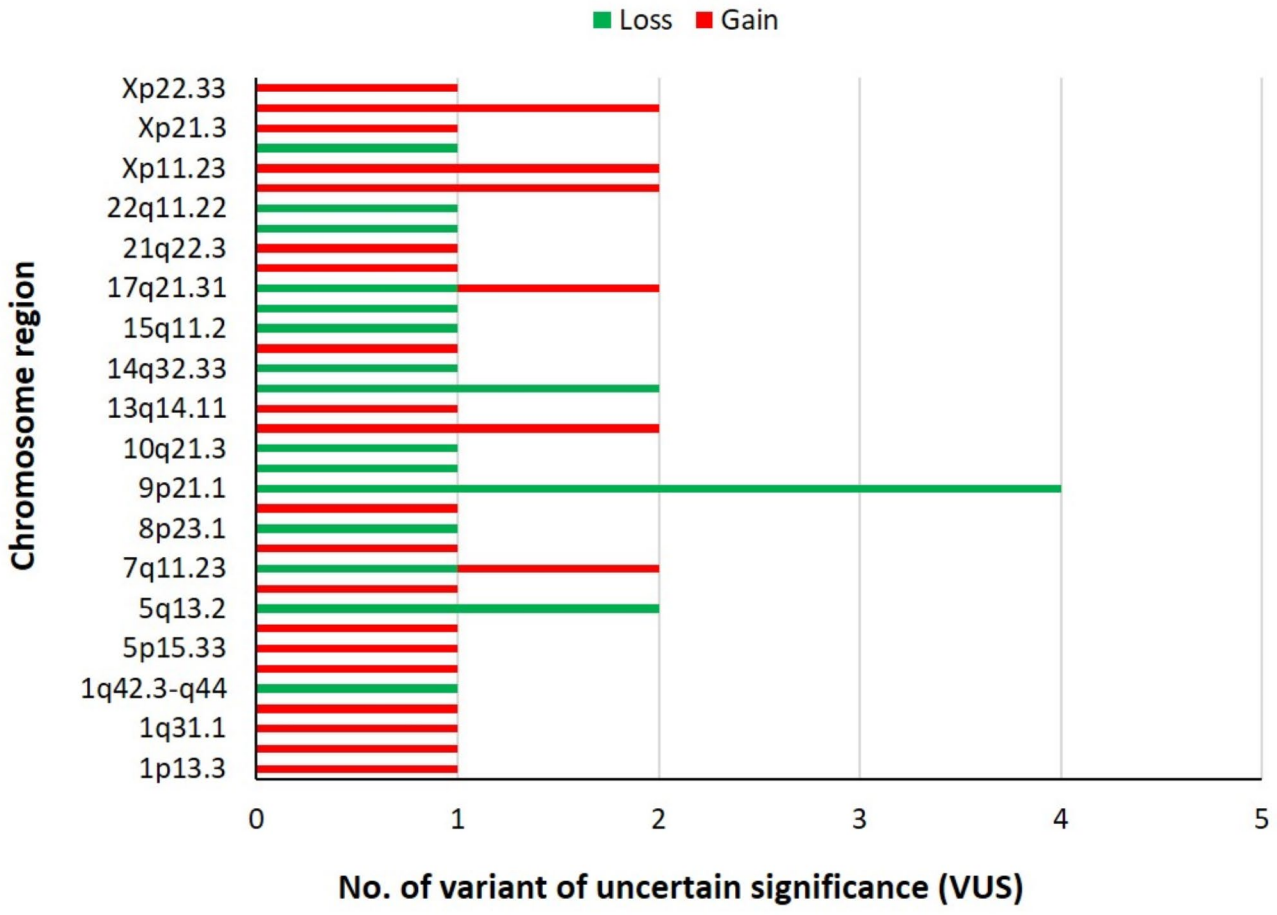

Fig. 2 Variants of uncertain significance (VUS) identified at various chromosomal region by array-CGH in 34 childhood ALL patients

10 patients exhibited somatic CNVs involving 21q22.3. However, only one patient (Case ID: 38) had a constitutional (germline) CNV gain (5.07 Mb) at 21q22.3 and was diagnosed with Down syndrome, with no additional somatic CNVs detected in the leukemic cells. In contrast, the remaining 9 patients exhibited somatic CNVs involving 21q22.3, including gains of *RUNX1* and *ERG*, both of which are frequently altered in leukemia. These somatic duplications of chromosome 21 occur specifically within the leukemic cells and do not imply the presence of Down syndrome in the affected individuals. Instead, such somatic alterations are among the most common genetic abnormalities in ALL and have been implicated in leukemogenesis, regardless of germline trisomy 21 status.

Copy number alterations at 9p21 are also one of the most identified cytogenetic abnormalities recognized in childhood ALL. A patient (Case ID: 30), who was diagnosed with T-ALL, has a copy number loss at the chromosome 9p21.3, consistent with previous findings reporting this alteration as the most frequent occurring deletion in T-ALL [19]. One important gene in this region is the *MLLT3* gene, which is common in hematological diseases and one of the most common fusion partner genes with the *MLL* gene at 11q23, resulting in the t(9;11)(p22;q23) which occurred in about 18% of acute leukemia cases [19]. Deletions of the short arm of chromosome 12, which is associated with tumor suppressor genes, also occur frequently in hematopoietic malignancies. A previous study has showed that 5% of children with ALL had 12p13.12 deletions and detailed examination showed this region contains 2 tumor suppressor genes, *ETV6* and *CDKN1B* [20]. The *ETV6* gene encodes an Ets family transcription factor and is frequently deleted in B-ALL [21] and deletion of *ETV6* gene was observed in all cases involving the 12p13.2 region [22]. *B-cell lymphoma 2* (*BCL2*) gene, located at the chromosome 18q21.33, is a protein coding gene, involved in the regulation of the homeostasis of the hematopoietic stem cell compartment. *BCL2* plays a crucial role in ALL by inhibiting apoptosis and promoting leukemic cell survival [23]. Overexpression of *BCL2* has been associated with chemotherapy resistance, particularly in T-cell ALL and MLL-rearranged ALL, contributing to disease persistence and relapse [24]. Targeting BCL2 with inhibitors like Venetoclax has shown promise in overcoming resistance and improving treatment outcomes in relapsed/

refractory ALL [24]. Additionally, high *BCL2* expression has been linked to poor prognosis, highlighting its potential as a therapeutic target and prognostic biomarker in ALL [25]. Another interesting finding to note is the CNVs at Xp21.1 chromosomal region. Despite located at the sex chromosome, the *DMD* gene at Xp21.1 is known as the fragile site of the chromosome. Recurring deletion of *DMD* has significant roles in the development of leukemia and had been reported to emerge at relapse [26].

This study also revealed several large chromosomal alterations that include copy number gains and losses. One of the most striking is 84.55 Mb copy number gain at chromosomal region 1q23.3-q44 which was found in 2 cases. This alteration is frequently observed in high-risk pediatric ALL and has been associated with poor prognosis and treatment resistance [27]. It has been observed in approximately 10–20% of pediatric B-cell precursor ALL (B-ALL) cases and is associated with inferior event-free survival [27]. Patients with this chromosomal abnormality frequently exhibit a higher likelihood of minimal residual disease (MRD) positivity following induction therapy, increasing their risk of relapse [28]. One of the key genes in this chromosomal region is *PBX1* gene, which is a transcription factor that plays a role in normal B-cell development. This gene particularly involve in t(1;19)(q23;p13.3) translocation, which fuses *PBX1* on chromosome 1q23 with *TCF3* gene on chromosome 19p13, results in the formation of the *TCF3-PBX1* fusion gene, leading to uncontrolled cell proliferation in leukemia [29]. Another interesting finding is a 45.38 Mb copy number loss at chromosomal region 6q13-q22.1. 6q deletions have emerged as recurrent structural abnormalities, particularly in B-ALL, and are associated with high-risk features and poor prognosis (Moorman et al., 2010). Disruption to the *FOXO-PRDM1* axis resulting from deletions of chromosome 6 has been shown to promote cell cycle exit at the pre-B cell stage, contributing to late pre-B cell development [30]. Other large chromosomal alterations affect substantial portion of chromosome 10, 13, 14, 18 and X, which have yet to have significance in ALL.

In addition to CNVs known to cause leukemogenesis in childhood ALL, a large number of variants of uncertain significance (VUS) was also detected in the majority of patients in this study. The size of VUS detected in our patients ranging between 262.27 kb – 84.55 Mb, consist of gains and losses at multiple loci. However, the importance of these VUS remains unknown; therefore, further validation is required to elucidate their biological impact. Functional studies, such as CRISPR/Cas9-mediated gene editing or in vitro assays, could help determine whether these variants contribute to leukemogenesis by assessing changes in gene expression, protein function, or cellular behavior [31]. Additionally, integrating VUS analysis with transcriptomic data from RNA-Seq can provide insight into the functional consequences of these variants, such as aberrant splicing, altered gene expression, or pathway disruptions [32]. Advanced computational approaches, including machine learning-based pathogenicity predictions and protein structural modeling, may further refine the classification of these variants [33]. Furthermore, co-segregation studies in familial leukemia cases and large-scale population analyses could help distinguish benign polymorphisms from potentially deleterious mutations [34]. Given the evolving landscape of precision oncology, comprehensive validation of VUS using multi-omics integration and experimental approaches will be essential to determine their clinical relevance in ALL prognosis and treatment stratification.

The genomic landscape of childhood ALL also varies across different ethnic populations, influenced by genetic ancestry, environmental exposures, and population-specific mutations. In Malaysia, a multiethnic nation comprising Malays, Chinese, Indians, and indigenous groups, genetic heterogeneity may contribute to differences in leukemia susceptibility, progression, and treatment response. Previous studies have reported distinct frequencies of ALL-associated genetic alterations among Asian populations compared to Western cohorts, including lower occurrences of *ETV6-RUNX1* fusion and hyperdiploidy [11]. Ethnicity-specific variations in CNVs and single-nucleotide variants (SNVs) may also affect disease risk and prognosis, as seen in differential frequencies of *IKZF1* deletions and *CRLF2* rearrangements in Southeast Asian children with ALL [35]. Additionally, population genetic studies have highlighted unique germline predispositions, such as *TP53* variants associated with Li-Fraumeni syndrome [36], which may be more prevalent in certain Malaysian subpopulations. The influence of ancestry on leukemia genetics underscores the need for ethnicity-stratified genomic studies to refine risk stratification models and optimize treatment strategies. Future research incorporating whole-genome and transcriptomic profiling across Malaysia's diverse ethnic groups will be essential in identifying novel biomarkers and understanding the role of population-specific genetic drivers in childhood ALL. Such efforts will enhance precision medicine approaches tailored to the Malaysian population and broader Southeast Asian context.

The findings from this study have significant implications for both diagnostic strategies and therapeutic interventions in childhood ALL. The use of array-CGH has proven effective in identifying pathogenic CNVs and VUS, particularly in patients with normal karyotype, highlighting its potential as a complementary diagnostic tool alongside conventional cytogenetics. The detection of recurrent CNVs, such as gains involving *RUNX1* and *ERG* (21q22), underscores their value as genetic

biomarkers for risk stratification and personalized treatment planning. Additionally, the study reinforces the importance of population-specific genetic screening, as ethnic variations in CNV patterns could influence disease prognosis and therapeutic responses. From a clinical perspective, patients with high-risk genetic alterations, including *ETV6* deletions and *iAMP21*, may benefit from intensified treatment regimens, while the identification of oncogenic CNVs, such as those involving *ZNF521* and *DMD*, presents opportunities for targeted therapy development.

While this study provides valuable insights into the genomic landscape of childhood ALL in Malaysia using array-CGH, several limitations should be acknowledged to guide future research. Firstly, the study was conducted on a relatively small cohort of 67 patients, which limits the statistical power and generalizability of the results. A larger sample size is necessary to validate the identified CNVs and VUS, particularly those occurring at lower frequencies. Secondly, the reliance on archived bone marrow cell suspensions may pose challenges related to DNA quality and integrity. Degradation over time could impact the accuracy of CNV detection, leading to potential misinterpretation of results. Moreover, archived samples may not fully represent the disease at different stages, such as progression or relapse, limiting the ability to track genomic changes longitudinally. Thirdly, although the study identified several pathogenic CNVs and VUS, their functional impact on leukemogenesis remains uncertain. The lack of experimental validation, such as gene expression analysis or protein functional studies, prevents definitive conclusions about their role in disease pathogenesis. Future research should incorporate functional assays, including RNA sequencing and proteomic studies, to establish biological relevance. Last but not least, array-CGH unable to detect single nucleotide mutations, balanced chromosomal translocations, or epigenetic modifications, all of which play crucial roles in leukemia pathogenesis. The use of complementary techniques such as whole-genome sequencing (WGS) or whole-exome sequencing (WES) would provide a more comprehensive understanding of the genomic alterations involved in childhood ALL.

Conclusion

In conclusion, the utilization of array-CGH has emerged as a complementary tool in the identification of submicroscopic genomic alterations especially pathogenic CNVs and additional aberrations. The study also highlights the need for further research into the functional significance of VUS, as these unexplored variations may hold the key to novel treatment strategies, especially in the Southeast Asian population. Ultimately, integrating CNV analysis into routine diagnostics could refine leukemia classification, enable earlier detection of high-risk patients, and guide personalized medicine approaches tailored to individual genetic profiles.

Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
Array-CGH	Array-based comparative genomic hybridization
CNV	Copy number variations
iAMP	Intrachromosomal amplification
SNV	Single-nucleotide variant
VUS	Variants of uncertain significance

Supplementary Information

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Supplementary Material 1

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Author contributions

AI and WNM carried out the experimental work, literature research, data acquisition and analysis, statistical analysis, and manuscript preparation. FA and AI were responsible for manuscript editing and review. EE and YMY provided the clinical details of the patients. NRK, ZAS and MAM aid in data acquisition and analysis. EG and ZZ participated in the study design. All authors read and approved the final manuscript.

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Data availability

Data available for sharing upon request.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia. Written informed consent to participate in this study was not applicable for archived diagnostic samples.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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