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Analysis of common cytogenetic abnormalities in New Zealand pediatric ALL shows ethnically diverse carriage of ETV6-RUNX1, without a corresponding difference in survival

Tristan Pettit[1] | Nyree Cole[2] | Wingchi Leung[2] | Kirsten Ballantine[1,3] | Scott Macfarlane[2,3]

[1]Children's Haematology Oncology Centre, Christchurch Hospital, Christchurch, New Zealand

[2]Starship Blood and Cancer Centre, Starship Children's Hospital, Auckland, New Zealand

[3]National Child Cancer Network NZ, Auckland, New Zealand

Correspondence
Tristan Pettit, Children's Haematology Oncology Centre, Christchurch Hospital, Private Bag 4710, Christchurch 8140, New Zealand.
Email: tristan.pettit@cdhb.health.nz

Abstract

Background: The frequency of common cytogenetic abnormalities in pediatric acute lymphoblastic leukemia (ALL) is known to vary by geographic location and ethnic origin. This study aimed to determine the frequency of hypodiploidy, ETV6-RUNX1, BCR-ABL1, and MLL rearrangement within New Zealand's pediatric ALL population and to assess whether the frequency of these ALL prognostic markers varies according to ethnicity.

Procedure: The New Zealand Children's Cancer Registry provided information for all registered pediatric ALL patients that were diagnosed between 2000 and 2009, with medical records available for 246 patients. Each patient's medical record was reviewed to determine the frequency of hypodiploidy, ETV6-RUNX1, BCR-ABL1, MLL rearrangement, and cell lineage. Chi-square tests for independence were undertaken to compare the frequencies of cytogenetic abnormalities according to prioritized ethnicity.

Results: The frequency of cytogenetic ALL abnormalities in the New Zealand pediatric population were consistent with international reference values. A low frequency of ETV6-RUNX1 was evident for Maori pediatric ALL patients (5.4%, $P = 0.018$), when compared to Pacific peoples (21.1%) and non-Maori/non-Pacific peoples (27.4%). This has not impacted on outcome, however, with equivalent 5-year overall survival being observed in Maori (89.4%) compared to Pacific peoples (92.0%) and non-Maori/non-Pacific peoples (90.2%).

Conclusions: A lower frequency of the favorable prognostic marker ETV6-RUNX1 was observed in Maori pediatric ALL patients. This did not translate into poorer survival. Future research into biological and nonbiological prognostic factors in this patient population may assist in explaining this finding.

KEYWORDS

ALL, cytogenetic, ethnicity, ETV6-RUNX1, New Zealand, survival

1 | INTRODUCTION

The presence of recurrent cytogenetic abnormalities are known to be associated with prognosis for pediatric acute lymphoblastic leukemia (ALL).[1,2] These features, in combination with the patient's age, total white cell count at diagnosis, and the use of minimal residual disease analysis to track early response to therapy, are essential for risk stratification and possible intensification of therapy. Prognostic cytogenetic abnormalities include somatic aneuploidy and recurrent chromosomal translocations, which are observed in approximately 75% of pediatric B-cell ALL (B-ALL) cases.[1] At diagnosis, the presence of high hyperdiploidy (>50 chromosomes) or t(12;21)(p13;q22) resulting in ETV6-RUNX1 (TEL-AML1) fusion is known to be associated with a favorable prognosis.[2,3] In contrast, the presence of hypodiploidy (<45 chromosomes), MLL (11q23) rearrangements, intrachromosomal amplification of chromosome 21 (iamp21), t(9;22)(q34;q11.2) resulting in BCR-ABL1 fusion, and BCR-ABL1-like gene rearrangements are

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-cell ALL; NZCCR, New Zealand Children's Cancer Registry; Ph-like ALL, Philadelphia-like ALL; T-ALL, T-cell ALL

associated with a poorer prognosis. Early intensification of therapy can occur as a result, for example with the use of hematopoietic stem cell transplant or the addition of targeted therapy.[1,2]

Within subgroups of the pediatric B-ALL population, variation exists with regard to frequency of cytogenetic abnormalities. For example, the frequency of hyperdiploidy, ETV6-RUNX1 translocations, and MLL rearrangements reduces with age, whereas the frequency of BCR-ABL1- and BCR-ABL1-like rearrangements increases with age.[3–5]

In addition to the findings that genetic abnormalities vary in frequency with age, ethnic variation in the frequency of prognostic biological markers specific to childhood ALL is also well described in the literature. A higher frequency of T-cell ALL (T-ALL) and t(1;19)(q23;p13)/TCF-PBX1 and a lower frequency of hyperdiploidy have previously been reported in African American children.[6] Hispanic American children with ALL have been shown to have a lower frequency of ETV6-RUNX1[7] and a higher frequency of the GATA3 and CRLF2 mutations, which are associated with Philadelphia-like ALL (Ph-like ALL).[8,9] Pediatric ALL patients from the Far East (Japan, Korea, China, Hong Kong, Chinese in Singapore, and Taiwan) have been shown to have lower frequencies of both ETV6-RUNX1 and hyperdiploidy, when compared to patients from the West (Western Europe and the United States).[3] A higher frequency of BCR-ABL1 has previously been identified in both Pakistan and Chinese pediatric ALL populations.[10,11]

New Zealand is an ethnically diverse island nation and has unique patterns of cancer among our population. An example of this is the identification for the first time of germline mutations in the E-cadherin gene (CDH1) that are associated with hereditary gastric cancer syndrome, in kindreds of a small group of Maori families who had high rates of early onset, poorly differentiated gastric cancer.[12]

A 2000–2009 incidence and survival analysis of the New Zealand Children's Cancer Registry (NZCCR) showed that overall New Zealand child cancer incidence was significantly lower for Maori (131 per million) than for non-Maori/non-Pacific peoples (158 per million).[13] There was no evidence of ethnic survival disparities, in stark contrast to what is seen for New Zealand adolescent and young adult and adult oncology patient groups.[14,15] This incidence and survival analysis provided the opportunity to conduct a subanalysis of childhood ALL to assess whether the frequency of common ALL prognostic cytogenetic markers varies according to ethnicity.

2 | METHODS

2.1 | Participants

The NZCCR database was utilized to source reference data for patients under the age of 15 years diagnosed with ALL between January 1, 2000 and December 31, 2009. Patient information that was obtained from the NZCCR included sex, ethnicity, treatment center, and age at diagnosis. Data collection for this national research study was coordinated from New Zealand's two pediatric oncology specialist treatment centers: Starship Blood and Cancer Centre (Auckland) and the Children's Haematology Oncology Centre (Christchurch). Approval to access to NZCCR records and patient medical files was granted by New Zealand's Health and Disability Multi-Region Ethics Committee (MEC/11/EXP/134).

2.2 | Ethnicity classification

Ethnicity information for patients was taken from their admission record at the time of their diagnosis. At this time, demographic information is collected for the patient and this includes a question regarding their ethnicity, which is answered by their parent. Self-identification and cultural affiliation underpin the concept of ethnicity in New Zealand. Each individual may select up to three ethnic groups that they identify with. A prioritized ethnicity classification system, in accordance with the Ministry of Health's ethnicity data protocols,[16] is often used in health data analyses to ensure that ethnic groups of small size or of policy importance are not swamped by the larger New Zealand European group. This is especially relevant in New Zealand, as it is well established that the health status of Maori is lower on average, than that of other ethnic groups.[16] For the purpose of this analysis, each child was assigned to a single ethnic group according to the priority system: Maori, Pacific peoples and non-Maori/non-Pacific peoples. The Maori ethnic group comprises those who indicated Maori as at least one of their ethnic affiliations.[17] The Pacific peoples ethnic group describes the people who make up the Pacific population in New Zealand: both those born in the different Pacific island nations and those born in New Zealand and elsewhere.[16] When prioritized ethnicity is applied to 2006 census data, the New Zealand population under the age of 15 comprises of 23% Maori, 8.7% Pacific peoples, and 68.3% non-Maori/non-Pacific peoples (8.1% Asian, 0.8% other ethnicity, 3.9% "Not elsewhere included", and 55.5% European/New Zealander).[13]

2.3 | Variables

Each participant's electronic medical record was accessed to source diagnostic cytogenetic information that was specific to their ALL. The following genetic aberrations were included: hypodiploidy, and the presence of MLL, BCR-ABL1, and ETV6-RUNX1 rearrangements. Where this information was not readily available, the relevant laboratory department was contacted in a further attempt to source the required data. Children for whom no laboratory results were available were excluded from the study. With regard to ETV6-RUNX1 and BCR-ABL1 translocation, some variability was noted with the use of PCR and FISH diagnostic techniques. This was attributed to geographical variation in practice and changing techniques over time. Each patient's health data were collated and stored on a secure spreadsheet. For this analysis, hypodiploidy was defined as a karyotype with <45 chromosomes.[18] MLL status was recorded as the presence or absence of an MLL rearrangement, detected by FISH. MLL rearrangements included translocations, duplications, deletions, amplifications, and cryptic rearrangements involving the MLL gene breakpoint cluster region. ETV6-RUNX1 and BCR-ABL1 status was recorded as the presence or absence of a mutation identified either by PCR or FISH.

TABLE 1 Demographic characteristics

	New Zealand total 2000–2009		Participants		Nonparticipants	
	n	%	n	%	n	%
Total	353	100.0	246	69.7	107	30.3
Sex						
Male	193	54.7	125	50.8	68	64
Female	160	45.3	121	49.2	39	36
Age (years)						
0–4	180	51.0	120	48.8	60	56
5–9	109	30.9	86	35.0	23	21.4
10–14	64	18.1	40	16.3	24	22.4
Prioritized ethnicity						
Maori	62	17.6	47	19.1	15	14
Pacific peoples	37	10.5	25	10.2	12	11.2
All other	254	72.0	174	70.7	80	74.8

2.4 | Statistical analysis

Ethnicity specific associations were calculated through stratified analysis after grouping subjects as Maori, Pacific peoples, and Non-Maori/non-Pacific peoples.[13] To determine whether there was an association between ethnicity and frequency of cytogenetic mutation or T-cell ALL, the chi-square test for independence was used. The threshold for statistical significance was set at $P \leq 0.05$. Five-year survival was calculated, with all cases followed until death or December 31, 2014, whichever came first. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY).

3 | RESULTS

Between 2000 and 2009, there were 353 new cases of ALL registered on the NZCCR for patients aged between 0 and 14 years at diagnosis. Due to a lack of access to laboratory records for Auckland-based patients who were diagnosed prior to 2004, and a small group of patients who had no cytogenetic information available, 246 cases were included in the final data set. Demographic information for both the ALL patients included, and not included in this study, is presented in Table 1. Final numbers included in the data analysis for each cytogenetic domain varied slightly due to difficulties in sourcing all of the required cytogenetic information for some patients. Twenty-nine cases of T-ALL were excluded from the cytogenetic analysis component of the study that was specific to B-ALL patients.

Table 2 shows that when analyzing the cytogenetic variables for the whole patient population that had existing information available, the frequency of hypodiploidy at 4.6%, MLL rearrangement at 6.1%, ETV6-RUNX1 at 22.5%, and BCR-ABL1 carriage at 1.8% were comparable with international reference data.[19] The analysis showed a T-ALL prevalence of 10.6%, slightly higher than the 9.8% proportion of T-ALL reported in a large childhood ALL review of all patients enrolled on Children's Oncology Group ALL studies between 1990 and 2005.[20]

Using Pearson's chi-square test for independence, investigation of a potential association between ethnicity and carriage of the common B-ALL cytogenetic prognostic markers yielded the following results. Of the four cytogenetic markers analyzed, a statistically significant association exists for ETV6-RUNX1 carriage and ethnicity. Table 3 shows that

TABLE 2 Frequency of cytogenetic abnormalities for the study population

	n		Frequency	%	Reference values (%)[10,11,20]
Hypodiploidy	217	Present	11	4.6	5–6
		Absent	206	94.9	
MLL rearrangement	163	Present	10	6.1	5–8
		Absent	153	93.9	
ETV6-RUNX1	191	Present	43	22.5	20–25
		Absent	148	77.5	
BCR-ABL1	164	Present	3	1.8	2–3
		Absent	161	98.2	
Cell lineage	246	T-ALL	26	10.6	9.8
		B-ALL	217	89.4	

TABLE 3 Subgroup analysis of frequency of cytogenetic abnormalities with corresponding survival

			B-ALL cytogenetic abnormalities									
	T-ALL		Hypodiploidy		MLL		ETV6-RUNX1		BCR-ABL1		5-Year overall survival	
	n	%	n	%	n	%	n	%	n	%	%	95% CI
Sex												
Male	16	12.9	6	5.6	6	7.4	23	24.5	1	1.2	92.8	86.9–96.2
Female	10	8.4	5	4.5	4	4.9	20	20.6	2	2.5	87.6	80.6–92.3
Age (years)												
0–4	4	3.3	2	1.7	8	8.8	20	20.2	0	0.0	92.5	86.4–96.0
5–9	12	14.3	4	5.5	2	3.8	20	31.3	2	2.7	88.4	79.9–93.6
10–14	10	25.6	5	17.2	0	0.0	3	10.7	1	3.8	87.5	73.9–94.5
Prioritized ethnicity												
Maori	4	9.1	3	7.3	1	2.9	2	5.4*	0	0.0	89.4	77.4–95.4
Pacific peoples	3	12.0	0	0.0	1	4.3	4	21.1	0	0.0	92.0	75.0–97.8
Non-Maori/non-Pacific peoples	19	10.9	8	5.2	8	7.2	37	27.4	3	2.6	90.2	84.9–93.8

CI, confidence interval.
*$P < 0.018$.

the Maori patient group have a significantly lower carriage of ETV6-RUNX1 at 5.4% ($P = 0.018$) compared to 21.1% for Pacific peoples and 27.4% for non-Maori/non-Pacific peoples. The striking difference in frequency of carriage of the ETV6-RUNX1 mutation in the three study populations was not observed with the three other cytogenetic abnormalities. In addition, there was no significant difference in the frequency of T-ALL or in 5-year survival when comparing the three ethnic groups.

4 | DISCUSSION

For the New Zealand patient population that had existing cytogenetic information available, the frequency of hypodiploidy, MLL rearrangement, and BCR-ABL1 carriage were comparable with international reference data.[19,20] The frequency of ETV6-RUNX1 among this New Zealand cohort was 22.5%, which sits within the normal range of 20–25%[19] and is comparable with what has been reported in China,[21] Italy,[22] and America.[23] Lower frequencies have been identified in Guatemala,[24] Mexico,[25] Saudi Arabia,[26] Spain,[27] Lebanon,[28] Pakistan,[10] Japan, Korea, and Taiwan[3] and higher frequencies have been identified in England[29] and Australia.[30]

On examination of the New Zealand cohort, the discovery of a low ETV6-RUNX1 frequency for Maori children with ALL (5.4%, $P = 0.018$) when compared to Pacific (21.1%) and Non-Maori/non-Pacific peoples (27.4%) is the most notable finding. This finding contributes to a growing body of literature that demonstrates variation of ETV6-RUNX1 frequency within different ethnic groups in the same country. For example, in a study of pediatric ALL patients in North America, Hispanic patients have been shown to have a significantly lower ETV6-RUNX1 frequency than non-Hispanic White patients (13% c.f. 24%, $P = 0.01$).[7]

The low frequency of ETV6-RUNX1 in Maori children with B-ALL has not contributed to a survival disparity, with the 5-year overall survival rate of Maori children in this cohort of 89.4% comparable to the 92.0% for Pacific peoples and 90.2% for non-Maori/non Pacific peoples.

From a purely biological perspective, this raises the question of whether other protective biological variables exist in the Maori childhood ALL population that are currently unidentified. Future research proposals that investigate this question may include the use of genome-wide association studies to compare the prevalence of ALL susceptibility loci within the ethnic groups of New Zealand's pediatric ALL population. Recently, ethnic variation in the prevalence of these loci, which are associated with both predisposition and outcome, has been identified in childhood ALL populations from other countries. For example, North American studies have shown that the prevalence of specific risk alleles within the ALL susceptibility locus on the ARID5B gene increases in the order of African American, European American, and Hispanic American children with ALL.[31,32] Also, Hispanic children with ALL have been shown to carry higher frequencies of both the GATA3 risk allele and CRLF2 lesions, which are both associated with the high-risk Ph-like ALL.[8,9]

It is acknowledged that nonbiological factors have likely contributed to the equivalent survival seen in Maori children with ALL, despite a lower frequency of ETV6-RUNX1. For example, a single institution study undertaken by Pui et al. identified equal access to modern ALL treatment as the main reason for equal survival outcomes for both African American and White American children with ALL, despite higher risk biological features being observed in the African American patient group.[6] A similar relationship between access to care and outcome likely exists for New Zealand's pediatric ALL population, where equal access to care is facilitated by the universal public health care system.

4.1 | Study limitation

The data analysis in this study was limited by its final sample size, with nearly one-third of patient's data being inaccessible. Nevertheless, as Table 1 shows, the final study population was representative of the entire cohort. The mechanism of ethnicity classification is also a study limitation. For pediatric patients, ethnicity classification was based on self-reporting from the patient's family, whereby cultural identity may be as strong an influence as genetic ancestry. When using prioritized ethnicity classification, the risk of misrepresentation in final ethnicity group allocation is thought to lead to potential bias.[33]

5 | CONCLUSION

This study describes the frequency of a number of cytogenetic prognostic markers in New Zealand's childhood ALL population. ETV6-RUNX1, the childhood ALL marker associated with a good prognosis, has been shown to have a significantly lower frequency in New Zealand's Maori childhood ALL population, with no significant impact on outcome. Future research into biological and nonbiological prognostic factors in this patient population may assist in explaining this finding.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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