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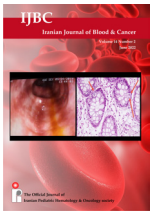

Review

NUDT15 genetic variants and 6-mercaptopurine intolerance in pediatric acute lymphoblastic leukemia: an updated review

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Abstract

Acute lymphoblastic leukemia (ALL) accounts for nearly 30% of pediatric cancers. The maintenance treatment for ALL comprises daily oral 6-mercaptopurine (6-MP) and weekly methotrexate (MTX). 6-MP is a purine analog that can significantly improve the long-term survival of ALL patients. Despite more than 90% of 5-year survival of childhood ALL in developed countries, treatment interruption due to drug toxicities continues to be a grave concern during therapy. Several studies have highlighted the association between some genetic variants and 6-MP toxicities in ALL patients. Some variants of 6-MP metabolizing enzymes received much attention as possible predictors of myelotoxicity following 6-MP therapy. Recently, two landmark genome-wide association studies have highlighted variants in nucleoside diphosphate–linked moiety X-type motif 15 (NUDT15) as promising indicators of 6-MP toxicities. It seems that NUDT15 genotyping can help determine the optimum dose of 6-MP and prevent toxicities, especially fatal myelotoxicity. No association was found between NUDT15 variants and hepatotoxicity or survival rates of ALL patients in previous studies. However, further studies are warranted to shed more light on these issues. The current review updates and evaluates the available scientific data regarding different genetic variants of NUDT15 and their possible roles in 6-MP intolerance in various ethnic groups.

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1. Introduction:

Acute lymphoblastic leukemia (ALL) is a highly heterogeneous hematologic malignancy. It accounts for nearly 30% of all cancers in children under 15 years of age, with a peak incidence between ages 2 to 5 years [1-6]. The 5-year survival rate of ALL has improved dramatically in recent years, and the overall survival rate exceeds 90% for standard-risk pediatric ALL [7-10].

Despite recent improvements, ALL maintenance therapy remains challenging mainly due to toxicities associated with 6-Mercaptopurine (6-MP) and Methotrexate (MTX), which can negatively affect the disease outcome in a subset of patients [11-15]. Fatal myelosuppression is one of the most alarming and relatively frequent side-effects of 6-MP that might lead to increased hospitalization,

suffering, and health care burdens [16-18].

In pediatric ALL, daily exposure to 6-MP is a chief component of maintenance therapy which is vital for long-term survival. However, 6-MP active metabolites can be associated with excessive myelosuppression. Hence, regular monitoring of WBC counts in patients treated with 6-MP can help prevent severe myelosuppression and fatal infections [19-22]. Several studies have demonstrated that genetic polymorphisms in thiopurine metabolizing enzymes may result in 6-MP toxicities [23-27].

Thiopurine s-methyl-transferase (TPMT), a thiopurine metabolizing enzyme, has been associated with myelosuppression. TPMT genotyping is a notable example of pharmacogenomics integration into routine clinical practice. TPMT genotyping is a recommended test before the use of 6-MP in children. Moreover, Clinical Pharmacogenetics Implementation Consortium (CPIC) periodically releases updated guidelines for adjusting the dose of 6-MP based on TPMT genotyping results [28-32]. While low TPMT activity is a reliable indicator of thiopurine-induced leukopenia, a relatively small population of patients with wild-type TPMT still exhibit profound intolerance to 6-MP, highlighting the possible role of additional genetic factors in this process[33, 34]. However, the data regarding the association between Inosine triphosphate pyrophosphatase (ITPA) polymorphisms and 6-MP intolerance were controversial, suggesting that ITPA polymorphisms may not be a robust predictor of 6-MP intolerance. ITPA genotyping is not currently recommended as a routine test before the initiation of thiopurine therapies [35].

More recently, a landmark genome-wide association study (GWAS) in Korean patients with Crohn's disease revealed a nonsynonymous variant in the NUDT15 gene (encoding p.Arg139Cys) that was significantly associated with thiopurine-induced leukopenia. Afterward, another research team working on ALL children also found that NUDT15 polymorphism p.Arg139Cys remarkably contributes to 6-MP dose reduction and intolerance [36, 37]. Simultaneous NUDT15 and TPMT genotyping can help determine the optimum dose of thiopurines and prevent toxicities in susceptible patients [38]. In the present review, we cover and critically discuss available data regarding the importance of NUDT15 germline variants as optimal predictors of 6-MP intolerance in ALL patients from diverse racial/ethnic backgrounds.

2. The NUDT15 enzyme

NUDT15 is a 164-amino-acid enzyme that belongs to the Nudix hydrolase superfamily. This enzyme is a chief component of the thiopurine metabolism pathway[39]. Different studies have evaluated NUDT15 in several respects. Among these, the frequency of different NUDT15 variants, the effects of NUDT15 variants on enzymatic activity, and the clinical impacts of NUDT15 variants in ALL patients received increasing attention.

2.1.NUDT15 in 6-MP metabolism

NUDT15 catalyzes the hydrolysis of nucleoside di- and tri-phosphates, including dGTP (deoxyguanosine triphosphate), dGDP (deoxyguanosine diphosphate), dCTP (deoxycytidine triphosphate), and their oxidized forms, such as 8-oxo-dGTP, thereby reversing the activation of thiopurines and inhibiting their incorporation into DNA. The presence of functional polymorphisms in NUDT15 may lead to the accumulation of deleterious thiopurines' active metabolites in cells. **Fig. 1** illustrates the role of NUDT15 and other enzymes in the metabolism of 6-MP [40, 41].

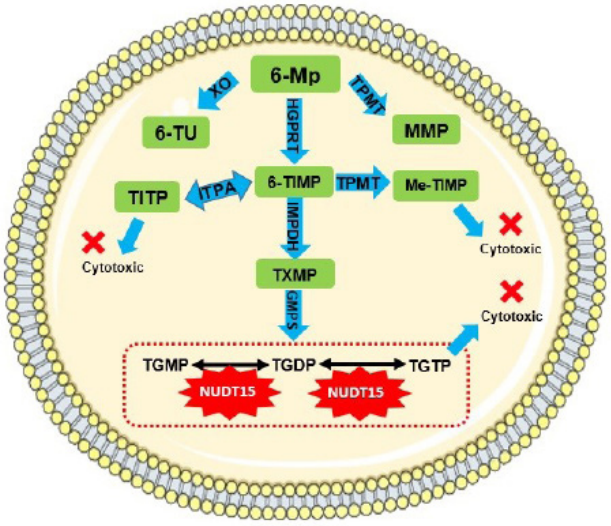

Figure 1: Schematic representation of 6-MP metabolism pathways and role of NUDT15 in these pathways. Abbreviations: MMP, Methylmercaptopurine; XO, Xanthine oxidase; 6-TU, 6-Thiouric acid; HGPRT, Hypoxanthine phosphoribosyl transferase; 6-TIMP, 6-Thioinosine 5-monophosphate; TITP, Thioinosine 5-Tri-phosphate; Me-TIMP, methyl-thioIMP; IMPDH, Inosine-5-monophosphate dehydrogenase; TXMP, thioxanthosine monophosphate; GMPS: GMP-synthase; TGDP, Thioguanine diphosphate; TGMP, Thioguanine monophosphate.

2.2. NUDT15 and thiopurine metabolism in vitro

In a path-breaking study by Moriyama T et al., the NUDT15 gene was knocked down in a human lymphoid cell line. They investigated the effects of NUDT15 gene knockdown on its enzymatic activity, cell apoptosis, and the level of thiopurine active metabolites in both NUDT15-knockdown cells (NUDT15-/-) and control cells treated with different amounts of 6-MP. This study indicated that toxic metabolites or thioguanine nucleotides (TGNs) and DNA-incorporated thioguanine (DNA-TG) were significantly higher in the NUDT15-/- cells. Correspondingly, apoptosis was significantly higher in NUDT15-/- cells. According to the results of this study, the lack of functional NUDT15 enzyme significantly increases both the toxic metabolites of thiopurines and the rate of cell apoptosis. This highlights the importance of NUDT15 role in the inactivation of thiopurine active metabolites. Therefore, this study successfully indicated the probable mechanism of thiopurine toxicities in patients with loss of function NUDT15 variants [42].

2.3. NUDT15 genotypes

NUDT15 gene, also known as MTH2, resides on the long arm of chromosome 13 (13q14.2) and comprises five exons (NBCI, Gene ID: 55270). As shown in **Fig. 2**, there are several functional genetic variants in the NUDT15 gene, mainly in exon1 and exon3. Moriyama T et al. identified 4 coding variants of NUDT15 located in exon 1 and 3, including c.415C >T (p.Arg139Cys), c.416G>A (p.Arg139His), c.52G>A (p.Val18Ile), and c.36_37insGGAGTC (p.Val18_Val19insGlyVal) that decreased NUDT15 stability, melting temperature, and diphosphatase activity (ranging from 74.4%–100% loss of nucleotide diphosphatase activity). Therefore, patients with one or more of these variants may show an increased vulnerability to thiopurine drugs. Based on previous findings, six haplotypes referred to as haplotypes *1-*6 can be inferred from these four mutant variants (See haplotypes and their corresponding frequencies in **Fig. 3**). While haplotype *1 implies wild-type NUDT15, other haplotypes contain at least 1 mutant variant, including NUDT15 *3 (rs116855232, c.415C >T or p.Arg139Cys), NUDT15*4 (rs147390019, c.416G>A or p.Arg139His), NUDT15*5 (rs186364861, c.52G>A or p.Val18Ile), and NUDT15*6 (rs 746071566, c.36_37insGGAGTC or p.Val18_Val19insGlyVal). Since the p.Val18_Val19insGlyVal allele is in high linkage disequilibrium with the p.Arg139Cys. Therefore, the presence of both defines the common haplotype *2 [42-44].

Moreover, some studies classified patients into low, intermediate, and normal metabolizers according to their NUDT15 diplotypes. **Table 1** demonstrates different NUDT15 diplotypes and their related frequencies. Tsujimoto S et al. highlighted that precise determination of NUDT15 diplotypes is crucial because different NUDT15 diplotypes can lead to varying levels of enzymatic activity. As a result, a case with heterozygous c.36_37insGGAGTC and c.415C>T may be described as compound heterozygosity (*3/*6) or mono-allelic variants (*1/*2). As compound heterozygotes are more susceptible to thiopurine-related toxicities, laboratories should be cautious to differentiate them correctly. Furthermore, this study proposed Droplet Digital PCR (ddPCR) as a convenient method for the determination of different NUDT15 diplotypes [44, 45].

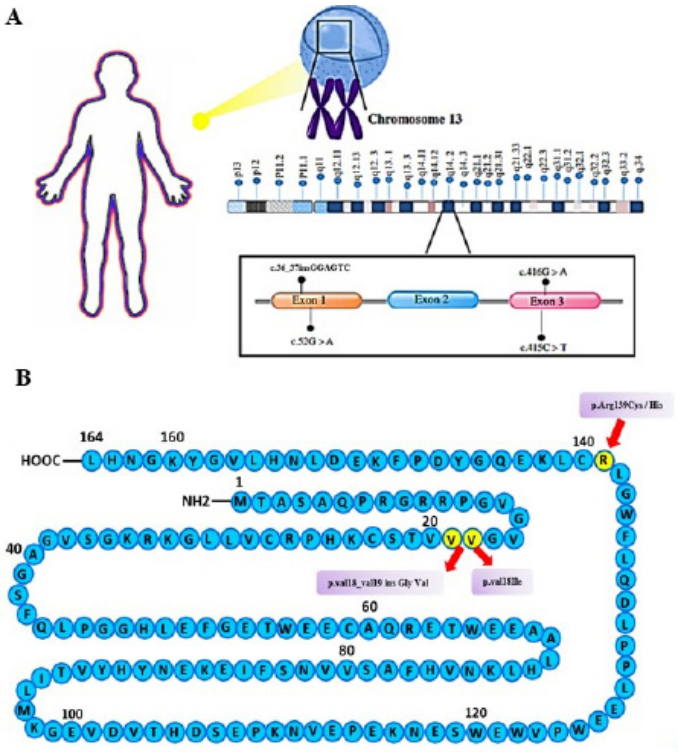

Figure 2: A) Schematic representation of human NUDT15 gene structure and variants, B) NUDT15 protein sequence and variants.

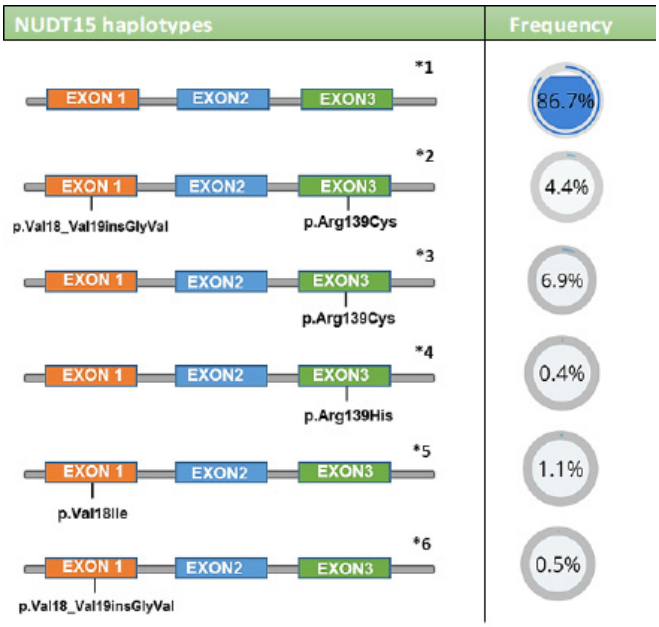

Figure 3: Different NUDT15 haplotypes and frequency of each haplotype is based on a study by Kim HT et al. on 920 Korean patients [55].

2.4. Methods of NUDT15 genotyping

As shown in **Fig. 4**, There are various methods for NUDT15 genotyping. Sequencing is a widely-adopted method for the detection of NUDT15 variants. However, its high cost is a barrier to using it as a screening test, especially in low-income countries [46]. The TaqMan assay is another highly accurate technique for NUDT15 genotyping. However, this method needs specific probes that may hinder employing it in low-income countries [47, 48]. PCR-RFLP is another method that is economical and can identify the most common variant of NUDT15 codon 139 (c.415C> T) using the restriction enzyme TaaI (HpyCH4III). Although PCR-RFLP is cost-effective, it has some flaws, such as a lack of specific enzymes for low-frequent variants and the need for post-PCR procedures, such as gel preparation and enzymatic digestion [6, 49]. In addition, Buaboonnam et al. employed allele-specific polymerase chain reaction (ASP-PCR) as an economical approach for detecting C.415C>T [50]. Furthermore, high-resolution melting (HRM) is a cost-effective method that, unlike TaqMan, does not require expensive probes and, unlike PCR-RFLP, does not require post-PCR procedures. A recent study by Kakuta Y et al. successfully applied HRM for the identification of complex variants in NUDT15 codon 18. It seems that HRM can be a suitable method for the detection of NUDT15 variants [46].

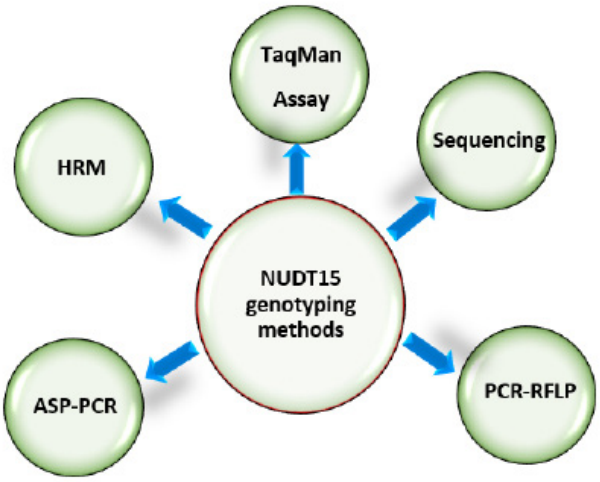

Figure 4: NUDT15 genotyping can be performed by a wide range of techniques including Sequencing, Taqman assay, HRM, ASP-PCR, and PCR-RFLP.

2.5. frequency of NUDT15 variants

NUDT15 variants represent significant differences among various ethnic groups. While East Asians have the highest rates of NUDT15 mutant variants, African, Middle East, and European countries presented remarkably lower prevalence. Despite the low frequency of NUDT15 in some ethnicities, NUDT15 genotyping is still recommended mainly due to the broad range of thiopurines' side effects. NUDT15 genotyping before the initiation of 6-MP may help predict adverse effects and choose safe doses of 6-MP for patients [37, 51-54] In a recent study, Kim HT et al. conducted a comprehensive frequency analysis of NUDT15 variants in 920 Korean individuals. According to their results, wild-type NUDT15 (haplotype *1) comprised 86.7% of the total population, while haplotypes *2,*3,*4,*5, and *6 accounted for 4.4%, 6.9%, 0.4%, 1.1%, and 0.5%, respectively (Figure 3) [55]. Moreover, in a cohort of 124 pediatric ALL patients from Uruguay, almost 8.8% of patients were heterozygote for mutant variants of NUDT15 [56].

Among mutant NUDT15 variants, c.415C >T showed the highest frequency, particularly in East-Asians [57]. Therefore, we specifically focus on this variant from now on. Tanaka Y et al. reported a minor allele frequency (MAF) of 0.16 for this variant in Japanese pediatric patients with ALL. Also, another study from japan by Suzuki H et al. showed a MAF of 0.098 for c.415C >T in children with ALL which was not significantly different from the Japanese general

Table 1: Category and frequency of NUDT15 diplotypes and their impacts on enzymatic activity

			Diplotype frequency(%)						
			Based on 1000Genome project [42]					Based on Yi ES et al. [45]	Tsujimoto S et al. [44]
Type	Diplotype	Enzyme activity	African %(N=655)	American % (N=341)	European % (N=495)	East Asian %(N=504)	South asian %(N=477)	Korean children %(N=258)	Japanese children %(N=138)
Wild	*1/*1	Normal metabolizer	99.5	90	99	77.4	86.4	73.6	72.5
Mono-allelic	*1/*2		0	6.7	0	5.8	0	8.5	10.1
	*1/*3	Intermediate metabolizer	0.2	0.9	0.4	9.7	12.6	12.8	8.7
	*1/*4		0	1.5	0	0.2	0	0	0
	*1/*5		0	0	0	2.6	0.2	1.6	5.1
	*1/*6		0.3	0.3	0.6	2.4	0.4	0.8	0.7
Bi-allelic	*2/*3	Poor metabolizer	0	0.6	0	1	0	1.6	0
	*3/*3		0	0	0	0.6	0.4	0.8	2.2
	*2/*4		-	-	-	-	-	0.4	0
	*2/*5		0	0	0	0.2	0	0	0
	*3/*5		-	-	-	-	-	0	0.7
	*3/*6		0	0	0	0.2	0	0	0

population [53, 58].

In another large-scale study on ALL patients with the estimated numbers of 205 Europeans, 93 Africans, 223 Hispanics, 61 East-Asians, and 82 with other ethnicities, 624 were CC, 31 were TC, and 2 were TT for NUDT15 c.415C >T [37]. Furthermore, a Lebanese team investigated 137 children with ALL and reported a low frequency of 0.72% of CT genotype and no TT genotype in this study from the Middle East [51].

2.6. NUDT15 c.415C> T and leukopenia

A growing body of literature has investigated the association between NUDT15 c.415C> T genotype and the incidence of leukopenia or early-onset leukopenia within the last 5 years. As shown in **Table 2**, most of these studies proposed a significant relationship between c.415C> T and the incidence of leukopenia, neutropenia, or early-onset leukopenia. It has been suggested that individuals carrying the T allele are significantly at greater risk of developing leukopenia [50, 59, 60].

In a cohort of Chinese patients, 6-MP-induced leukopenia was observed in 23 of 105 ALL patients during the first 6 months of maintenance therapy. Leukopenia was more commonly observed in patients with the T allele (CT or TT). Individuals carrying the T allele had a 3.62-fold higher risk of leukopenia than those with wild-type NUDT15 (OR, 3.62; 95%CI, 1.377–9.501; P, 0.009). Also, the T allele was significantly associated with early-onset leukopenia (P, 3.75 × 10−4). According to this study, 18 patients were obliged to discontinue treatment with 6-MP because of severe infection. However, no significant relationship was found between the incidence of severe infection and the T allele (OR, 0.25; 95% CI, 0.054–1.162)[35]. Similarly, in a study on 82 Thai children with ALL, neutropenia was measured at 2, 4, and 6-month intervals following 6-MP therapy. This study demonstrated that the genotype c.415C> T was strongly associated with myeloid suppression and a lowered absolute neutrophil count (ANC). Patients with CT and TT genotypes had a significantly In a study on 92 Japanese ALL children, Tanaka Y et al. investigated the association between 6-MP and induced leukopenia during the maintenance phase of treatment. Based on their findings, 39 of 92 patients developed leukopenia during therapy. They showed that the T allele was associated with a 7-fold increased risk of leukopenia (OR, 7.20; 95% CI, 2.49–20.80; P, 2.7×10-4). They also found that severe leukopenia during the first 60 days of the maintenance treatment phase was associated with the T allele. (OR, 3.25; 95% CI, 1.49–7.07; P, 0.003) [53].

Additionally, in a study on Korean children with ALL, Kim H et al., genotyped patients for c.415C> T. They found 142 CC, 37 CT, and 4 TT patients. 121 patients (65.4%) developed neutropenia following 6-MP therapy. Of which, 15 patients (12.4%) developed early neutropenia within 28 days. However, 106 patients

Table 2: Association between NUDT15c.415C > T and induced leukopenia/neutropenia following initiation of 6-MP therapy in pediatric ALL

Study	Sample size	Age (years)	Ethnicity or country	Definition of Leukopenia or neutropenia	Time of measurment after initiation of 6-MP	Outcome of study
Zhou H china/2018[35]	105	1.1~14	Chinese	Leukopenia (WBC < 2.0 × 109 /L)	During first 6 month During first 60 days	CT/TT were associated with increased risk of leukopenia (during 6month) and early-onset leukopenia (during first 60 days)
Chiengthong K /2016 [61]	82	1~15	Thai	Neutropenia (ANC<500/ul)	2nd month 4th month 6th month	CT/TT were associated with increased risk of neutropenia at all intervals
Tanaka Y/2015 [53]	92	1~17	Japanese	Leukopenia (WBC < 2.0 × 109 /L)	During 6-MP therapy During first 60 days	CT/TT were associated with increased risk of leukoukopenia and early-onset lekuopenia
Buaboonnam J /2019 [50]	102	1.12~14.78	Thai	Neutropenia (ANC<500/ul)	3rd month 6th month 12th month	CT/TT were associated with increased risk of neutropenia in 3rd month
Kim H / 2018 [59]	178	1.1~17.3	Korean	Neutopenia (ANC < 0.5 x 109 L–1)	2-year cumulative incidence	CT/TT were associated with increased risk of neutropenia
Choi R/2019 [60]	139	3.7~ 10.6	Korean	Leukopenia (WBC < 1.5 x 109 L–1) Neutropenia (ANC < 0.5 x 109 L–1)	During 6-MP therapy	CT/TT were associated with increased risk of leukopenia CT/TT were associated with increased risk of neutropenia
Zhou Y et al. /2020[62]	60	2.1 ~ 12.5	Chinese	Leukopenia (Grade3, 1.0 - 2.0 × 109/L, and Grade 4, < 1.0 × 109/L)	During 6-MP therapy	CT/TT were associated with increased risk of leukopenia

(87.6%) experienced neutropenia after day 28. The 2-year cumulative incidence of neutropenia was statistically significant in the presence of the T allele (p <0.01) [59].

2.7. Role of NUDT15 c.415C> T in 6-MP dose adjustment

Dose adjustment of 6-MP based on TPMT genotyping is a successful experience of pharmacogenetics. More recently, several studies have also suggested NUDT15 genotyping alongside TPMT [32, 35, 63, 64]. In a study by Yang JJ et al., ALL patients received an initial dose of 75 mg/m2 daily 6-MP. WBC count <2000 / $mm^3$was defined as the threshold for 6-MP dose reduction in this study. They found a significant relationship between c.415C> T genotype and dose reduction of 6-MP. While patients with CC genotype tolerated 83.5% of the planned daily 6-MP dose, patients with CT and TT tolerated 63% and 8.3% of the standard dose, respectively. According to their findings, patients with the TT genotype experienced a dramatic 91.7% reduction over the standard dose of 6-MP [37]. In a study by Zhou H et al., the initial dose of 6-MP was 50 mg / m2 daily. Patients with CC, CT, and TT genotypes tolerated a dose intensity of 94.24%, 83.83%, and 60.27%, respectively, highlighting the significant effect of the T allele on lowering tolerable doses of 6-MP [35]. Similarly, in a cohort of Taiwanese ALL children, the initial dose was 60 mg / m2, and patients with CC, CT, and TT genotypes tolerated 44.1, 30.7, and 9.4 mg/ m2 of 6-MP, respectively (P <0.0001) [65]. Furthermore, in a study by Suzuki H et al., two groups of patients <7 years of age and ≥7 years of age were analyzed and the association between c.415C> T genotype and 6-MP dose reduction was evaluated. They suggested that patients with CT genotype tolerated significantly lower doses compared to those with CC genotype in the younger age group. The dose reduction was significant for the age group of <7 years old, suggesting that these patients were less able to metabolize thiopurines [58]. In summary, **Table 3** comprehensively illustrates studies that evaluated the effect of c.415C> T genotype on 6-MP dose reduction.

Table 3: 6-MP tolerated dose intensity based on c.415C>T genotype in pediatric ALL

	First author	Patients (n)	Ethnicity or Country	6-MP initial dose for maintenance therapy (mg/m2/day)	Criteria for dose adjustment	Tolerable doses of 6-MP according to c.415C>T genotype
1	Yang JJ et al. [37]	657	Different ethnicities	75	Presence of leukopenia and/or infection	CT and TT genotype tolerated 63% and 8.3% of the planned dose., respectively.
2	Zhou H et al.[35]	105	Chinese	50	WBC <2.0–3.0 × 10^9/L presence of infection ,and/or hepatotoxicity	CT and TT genotype tolerated a dose intesnity of 83.83% and 60.27% of planned dose , respectively.
3	Liang DC et al. [65]	310	Taiwan Chinese	60	WBC <1200/ul ANC <500/ul PLT≤50.000	CC, CT, and TT genotypes tolerated an average doses of 44.1, 30.7, and 9.4 mg/ m2 per day of 6-MP, respectively.
4	Tanaka Y et al.[53]	92	Japanese	40	WBC <2000-3500/ul	CC,CT, and TT genotypes tolerated averaged dosese of 40.7, 29.3,and 8.8 mg/ m2 per day of 6-MP, respectively.
5	Zgheib NK et al.[51]	137	Arab	50(SR), 75(IR-HR)	WBC <1500/ul ANC< 300/ul	Median tolerable dose for CC and CT was 76% and 33.33% of the planned dose.
6	Suzuki H et al. [58]	51	Japanese <7years old	40	WBC < 2000-3500/ul , presence of hepatotoxicity (ALT <750 IU/L)	CT and CC tolerated an averaged dose of 22.3 and 32.7 mg/ m2 per day, respectively.
			Japanese ≥7years old	40		CT and CC tolerated an averaged dose of 37.9 and 28.8 mg/ m2 per day, respectively.
7	Moriyama T et al. [42]	79	Singapore	50 (SR-IR) , 75(HR)	WBC<2.0–4.0 × 10^9/L	Patients with the T allele tolerated significantly lower doses of 6-MP than wild-type patients.
		159	Guatemalans	50–75	WBC< 1.5–3.0 × 10^9/L , presence of Infection	
		32	Japan	50	WBC<2.0–3.0 × 10^9/L	
8	Kim H et al. [59]	178	Korean	50	WBC<2-3.5×10^9/L ANC <500/ul	The average dose for TT,CT, and CC during the final cycle was 5, 17.6, and 26.9 mg/ m2 per day, respectively.
9	Buaboonnam J et al. [50]	102	Thiland	50	ANC <500 cells/ ul PLT <50 000 cells/ ul	The mean dose of 6-MP at 3,6, and 12 months was significantly lower in CT/TT versus CC (p<0.001)

2.8. NUDT15 c.415C> T and hepatotoxicity

The possible association between c.415C> T and the risk of hepatotoxicity in childhood ALL was evaluated in recent years. Zhou H et al. investigated the incidence of hepatotoxicity in a cohort of 105 Chinese patients. They defined hepatotoxicity as alanine aminotransferase/aspartate aminotransferase (AST/ALT)> 500 IU/L and found no significant relationship between the T allele and hepatotoxicity [35]. Similarly, Tanaka Y and colleagues found no significant association between the T allele and hepatotoxicity (defined as ALT > 700 IU/L) in a cohort of Japanese patients [53]. More recently, Zhou Y et al. investigated 60 Chinese children with ALL, they also found no association between NUDT15 c.415C> T and risk of hepatotoxicity (OR, 0.79; 95% CI 0.23-2.73; P 0.71). They defined hepatotoxicity according to guidelines in the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE, version 4.0) [62]. Furthermore, in a study by Zhu Y et al., There was no significant association between the occurrence of hepatotoxicity (an increase in AST and/or ALT by more than five times following 6-MP) and NUDT15 c.415C> T allele (P, 0.56) [66]. Based on the above findings, there is no association between the T allele and hepatotoxicity following 6-MP therapy. However, further research is recommended to clarify this issue.

2.9. NUDT15 c.415C>T and ALL survival

Liang DC et al. evaluated the impact of c.415C> T genotype on 5-year EFS (event-free survival) of ALL patients and found no difference in 5-year EFS between the mutant and wild-type alleles [65]. Similarly, Tanaka Y et al. evaluated the impact of c.415C>T genotype on the survival of 92 Japanese ALL patients. In their study, 13 patients relapsed. Of whom, 3 had CT genotype, and 1 had TT genotype. Their result showed no significant relationship between this genotype and EFS P, 0.279) [53]. Moreover, Buaboonnam J et al. evaluated 102 children with ALL, consisting of 58 boys and 42 girls. They assessed the association between 5-year survival with the genotype c.415C> T and found no statistically significant relationship between 5-year survival with

c.415C> T after risk adjustment (P, 0.181) [50]. Overall, there was no association between c.415C> T genotype and ALL survival. However, there are few publications regarding the association between NUDT15 c.415C> T and childhood ALL survival. Hence, further research on different ethnicities is recommended to confirm the findings of previous studies.

3. Conclusion

Summing up the results, NUDT15 variants, especially c.415C>T can be an optimal predictor of 6-MP-induced leukopenia. Therefore, NUDT15 genotyping before or during 6-MP therapy help determine the optimal dose of 6-MP to avoid life-threatening leukopenia. On the other hand, recent studies show no association between c.415C>T and hepatotoxicity or survival rate of ALL patients. However, further investigations are warranted on these topics.

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Conflicts of Interests

Authors declare no conflicts of interest.

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