

Meta-analysis of the impact of thioprine S-methyltransferase polymorphisms on the tolerable 6-mercaptopurine dose considering initial dose and ethnic difference

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Abstract: A meta-analysis was conducted to decide whether to reduce an initial 6-mercaptopurine (6-MP) dose in *TPMT* heterozygote in the case of an initial 6-MP dose of <75 mg/m²/d and to compare the tolerable 6-MP dose among different ethnic groups. The study was undertaken according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The differences in mean values of the tolerable 6-MP dose were calculated by using Comprehensive Meta-Analysis version 3. The results of the meta-analysis indicated that the tolerable 6-MP dose was significantly lower in the *TPMT* heterozygote group (difference in mean values = 11.729, 95% confidence interval = 7.617–15.842, $P < 0.001$) even when the initial 6-MP dose was <75 mg/m²/d. The *TPMT**3C allele-dominant ethnic group (Asian) needed less reduction in mean 6-MP dose in comparison to the *TPMT**3A allele-dominant ethnic group (Caucasian, Mediterranean, South American) (difference in mean values = 8.884 vs 15.324). In conclusion, the initial 6-MP dose needs to be reduced in *TPMT* heterozygote when compared to the wild-type, and ethnic difference might influence the tolerable 6-MP dose in *TPMT* heterozygotes.

Keywords: 6-mercaptopurine, thiopurine S-methyltransferase, polymorphism, meta-analysis

Introduction

6-Mercaptopurine (6-MP) with methotrexate constitutes the mainstream of the maintenance therapy for acute lymphocytic leukemia (ALL), which is a prevalent hematologic disease seen in those under 20 years of age.¹ To exhibit its cytotoxicity, 6-MP must be converted to its active metabolite, 6-thioguanine nucleotide, by multiple enzymes such as hypoxanthine–guanine phosphoribosyltransferase, inosine-5'-monophosphate dehydrogenase, and guanine monophosphate synthetase. The drug is inactivated into 6-methylmercaptopurine through S-methylation by a polymorphic enzyme named thiopurine S-methyltransferase (TPMT). Thus, TPMT enzyme deficiency results in increased 6-thioguanine nucleotide and hematologic toxicity.

Presently, more than 20 mutant alleles have been reported, and it is known that *TPMT**2, *3A, and *3C account for approximately 90% of the total mutant alleles.² The Clinical Pharmacogenetics Implementation Consortium (CPIC) proposed a dosing recommendation according to *TPMT* genotypes. According to the recommendation, a homozygous wild-type starts 6-MP with a normal dose, the heterozygote starts as 30%–70% of the full dose (50 mg/m²/d), and the homozygous variant starts with an extremely reduced dose.^{3,4} However, in most of Europe and Asia, the initial dose of

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6-MP is 50 mg/m²/d.⁵ Under this condition, it is questionable whether a 6-MP dose should further be reduced.

A reduction in 6-MP dose is recommended for *TPMT* heterozygotes because an increased risk of hematologic toxicity was observed in comparison to those with wild-type *TPMT* in many American and European studies.^{6–12} However, *TPMT* enzyme activity differs between mutant alleles. The *TPMT**3A (460G>A, 719A>G) allele, which is a major mutant allele in Caucasian, Mediterranean, South American, Middle Eastern, and Mexican origins, results in negligible activity, while the *TPMT**3C (719A>G) allele, which is a major allele in Asian and African origins, causes moderate activity compared to the wild-type one.¹³ Furthermore, Asians have another important variant, *NUDT15*, which is strongly associated with tolerable 6-MP dose according to a state-of-the-art genome-wide association study.¹⁴ Thus, 6-MP maintenance therapy according to *TPMT* genotype, which reflects ethnic allele distribution, needs to be evaluated. Although a number of Asian studies have evaluated the relationship between *TPMT* genotypes and tolerable 6-MP dose, the results are still controversial. For example, heterozygotes received less 6-MP dose in comparison to those with wild-type allele (32.1 vs 46.2 mg/m²/d, *P*=0.05). One Indian study concluded that the identification of *TPMT* genotype might be important.¹⁵ On the other hand, the heterozygotes received a similar 6-MP dose (41.5 vs 42.92 mg/m²/d) in another Indian study, and the study concluded that the identification of *TPMT* genotype might not be important.¹⁶

Evidence for individual study was weak because the number of *TPMT* heterozygotes was ≤12, whereas a meta-analysis of these studies could increase the number of *TPMT* heterozygotes and strengthen the evidence.

The primary objective of this study was to decide whether to reduce an initial 6-MP dose in *TPMT* heterozygote when the maintenance regimen included a 6-MP dose of <75 mg/m²/d. The secondary objective was to compare the tolerable 6-MP dose between *TPMT* heterozygotes and those with wild-type allele among different ethnic groups.

Materials and methods

Search strategy

The meta-analysis process was predetermined prior to the study and conducted according to the checklist in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹⁷ For this study, we searched PubMed, Embase, and Cochrane Library Databases for studies that were conducted on childhood ALL patients using 6-MP so as to identify the impact of *TPMT* polymorphism on tolerable

6-MP dose. The latest search was updated on January 20, 2016. The following keywords were employed: (leukemia) AND (*TPMT* OR thiopurine methyltransferase OR thiopurine s methyltransferase OR thiopurine s-methyltransferase) AND (6-MP OR 6-mercaptopurine OR mercaptopurine) AND (polymorphism OR variant OR variation OR mutant OR mutation OR genotype OR haplotype). There were no limitations in the search process. To reduce publication bias, unpublished trials were searched via conference abstracts and trial registries such as the World Health Organization's International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch/) and ClinicalTrials.gov.¹⁸

Study selection

Two authors of this study independently evaluated all papers for eligibility. The criteria for eligibility for this study should 1) involve childhood ALL patients treated with 6-MP as a part of a maintenance therapy, 2) have an initial 6-MP dose of <75 mg/m²/d, 3) analyze *TPMT* genotypes in the patients, and 4) compare tolerable 6-MP dose information according to the status of *TPMT* genotypes.

Articles were excluded if the research 1) was not carried on human subjects, 2) just evaluated the effects of *TPMT* phenotypes, and 3) did not report tolerable doses (pharmacokinetic outcomes or clinical outcomes). Reviews, guidelines, letters, comments, and case reports were also excluded.

EndNote X7.2 (Thomson Reuters, New York, NY, USA; 2014) software was used in the citation process. Cohen's κ coefficient was calculated to confirm that the consensus between the researchers is in the range of excellent agreement.¹⁹ Disagreements were resolved by discussion between two researchers, and a third party was consulted for unresolved disagreements.

Quality assessment and data extraction

A quality assessment was independently performed by two authors according to the Newcastle–Ottawa Scale.²⁰ Reporting, external and internal validities, confounding bias, selection bias, and study power of each study were assessed. A study was regarded as “high quality” if it scored five or more A's out of eight.

Some data were requested by the corresponding author if the included study had no obvious data (eg, only a graph without an exact number). Data were extracted by a standardized data extraction sheet that was prepared in advance. Data included authors, citations, countries or ethnic groups, initial 6-MP dose, 6-MP dose adjustment criteria, *TPMT* genotypes, number of patients according to genotype, and tolerable 6-MP dose information. Statistical measures such

as mean $\pm$ standard deviations (SDs), median with the range of tolerable 6-MP dose, and *P*-values were extracted.

Statistical analysis

The ethnic groups were categorized as *TPMT**3A allele-dominant group or *3C allele-dominant group. Weekly 6-MP doses were converted into daily doses, and dose intensities were converted into exact doses by multiplying the intensity percentage by the 6-MP start dose.

All meta-analyses were carried out by using either the Mantel–Haenszel fixed-effects model²¹ or the DerSimonian–Laird random-effects model,²² which depended on the heterogeneity. The degree of heterogeneity was assessed by *I*² measures (an *I*² > 50% was considered to have substantial heterogeneity).²³ Potential publication bias was detected by reviewing the funnel plot, and a sensitivity analysis was conducted.

An analysis was undertaken by using differences in mean values because tolerable 6-MP dose is continuous data. The mean and SD values from the included studies were used directly, or a substituted median for mean and range/4 for SD in the case that median and range values were presented.¹⁹ The analysis was conducted using Comprehensive Meta-Analysis version 3 (CMA 3; Biostat Inc., Englewood, NJ, USA). All statistical tests were two-sided, and the results are presented as forest plots.

Results

Included studies

A total of 397 potentially relevant articles were obtained and reviewed from a computerized search. Among them, 253 articles were excluded on the basis of publication type.

Another 137 articles were excluded as they did not fulfill the inclusion criteria (Figure 1). A total of seven studies, comprising 3,018 wild-type and 53 mutant allele pediatric ALL patients, were included (Table S1). All studies showed no risk of bias when assessing for quality using the Newcastle–Ottawa Scale. All of the completed trials satisfying our inclusion and exclusion criteria have been published, and there were no unpublished trials. Table 1 describes the basic information of the included studies.

Three studies from Europe (France), South America (Brazil), and the Middle East (Turkey) were categorized as the *TPMT**3A allele-dominant group, and four studies from Asia (India: 2, South Korea: 1, and Taiwan: 1) were categorized as the *TPMT**3C allele-dominant group. In a study, one patient with a homozygous mutant allele was included in the heterozygote group because it could not be separated.²⁴ The *2/*2 mutant allele carrier included in the study by Kim et al²⁵ was excluded from this meta-analysis.

Tolerable 6-MP dose of TPMT heterozygote in the case of an initial 6-MP dose <75 mg/m²/d

Before conducting a pooled meta-analysis, it was observed that three of seven studies showed an insignificant difference in tolerable 6-MP dose between *TPMT* wild-type and heterozygote. The value of the observed *I*² was 30.7%, and the heterogeneity of the included studies might not be important. Thus, the Mantel–Haenszel fixed-effects model was used to estimate the effect of *TPMT* genotype on the tolerable 6-MP dose. The meta-analysis results indicated that the tolerable 6-MP dose was significantly lower in the *TPMT* heterozygote

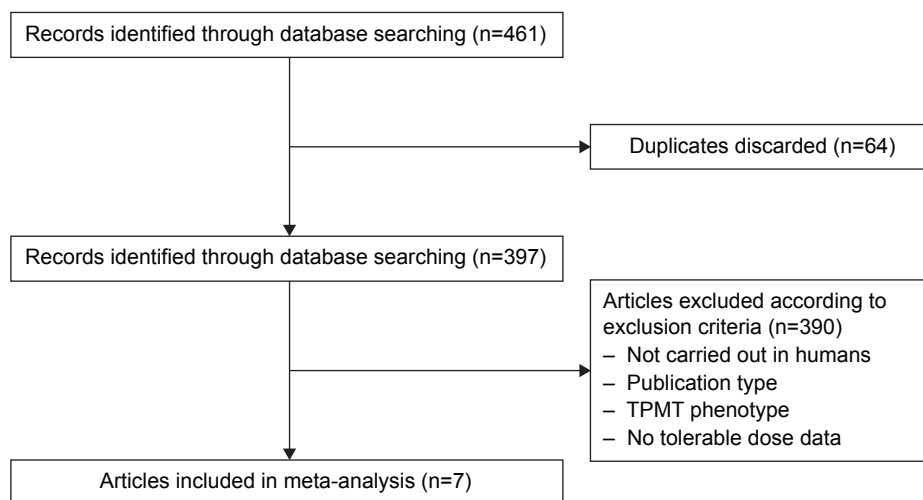


Figure 1 Flowchart for study selection.

Abbreviation: TPMT, thiopurine S-methyltransferase.

Table I Characteristic of included studies

References	Country	TPMT allele	Initial 6-MP dose	Dose adjustment
Dervieux et al ²⁴	France	TPMT*3A dominant	50 mg/m ² /d	Target: WBC 2,000–3,000/μL Adjustment: increase by 25% if two consecutive WBC >4,000/μL, reduce by 25% if WBC <1,500/μL
Silva et al ³⁴	Brazil	TPMT*3A dominant	50 mg/m ² /d	Target: WBC 2,000–3,000/μL, ANC >500/μL or WBC 1,500–3,000/μL, ANC >300/μL according to maintenance regimen
Kapoor et al ¹⁵	India	TPMT*3C dominant	50 mg/m ² /d	Target: WBC 2,500–3,500/μL, ANC 1,000–2,000/μL
Albayrak et al ²⁹	Turkey	TPMT*3A dominant	50 mg/m ² /d	Target: WBC 2,000–3,000/μL Adjustment: reduce by 50% if WBC =1,000–2,000/μL, increase by 150% if WBC >3,000/μL, withdraw if WBC <1,000/μL or AST/ALT ≥5 times the ULN or ≥ grade II neutropenic infection
Kim et al ²⁵	Korea	TPMT*3C dominant	50 mg/m ² /d	Adjustment: hematologic or hepatic toxicity
Linga et al ¹⁶	India	TPMT*3C dominant	56.25 mg/m ² /d (75 mg/m ² /d for 3 weeks and 1 week skip)	Not mentioned
Liang et al ³⁵	Taiwan	TPMT*3C dominant	60 mg/m ² /d	Target: WBC 1,800–3,000/μL, ANC 500–1,200/μL, PLT ≥50,000/μL Adjustment: reduce by 25% if counts are low

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; MP, mercaptopurine; PLT, platelet; TPMT, thiopurine S-methyltransferase; ULN, upper limit of normal; WBC, white blood cell.

group (difference in mean values =11.729, 95% confidence interval [CI] =7.617–15.842, $P<0.001$) (Figure 2A).

Tolerable 6-MP dose among different ethnic groups

Among the four studies conducted in Asia, two showed a significant difference in 6-MP dose. The value of I^2 was 35.2%, and the Mantel–Haenszel fixed-effects model was used. The meta-analysis resulted in a significant difference in 6-MP dose between *TPMT* heterozygote and wild-type (difference in mean values =8.884, 95% CI =2.917–14.850, $P=0.004$) (Figure 2B).

Three studies from the *TPMT**3A allele-dominant countries showed controversial results. The included studies had heterogeneity in their features with an I^2 value of 70.2%. The DerSimonian–Laird random-effects model revealed that the *TPMT* heterozygote received a lower 6-MP dose than the wild-type (difference in mean values =15.324, 95% CI =4.745–25.902, $P=0.005$) (Figure 2C). The *TPMT**3C allele-dominant ethnic groups needed a less reduced mean 6-MP dose (8.884 vs 15.324 mg/m²). However, these results are not a head-to-head comparison.

Discussion

This is the first meta-analysis that compares maximum tolerable 6-MP dose between pediatric ALL patients with *TPMT* wild-type and heterozygous allele when considering ethnicity and receiving an initial 6-MP dose of <75 mg/m²/d. Although the CPIC guidelines gave an example of an initial 6-MP dose

of 75 mg/m²/d for wild-type patients, currently most countries use <75 mg/m²/d because of hematologic toxicity.^{3–5} We found that studies conducted in the USA, the UK, Northern Europe (Denmark, Finland, Iceland, Norway, and Sweden), and Lebanon (only for lower risk patients) used a 6-MP dose of 75 mg/m²/d.^{6,26–28} These particular studies were excluded from the meta-analysis.

The meta-analysis revealed that the 6-MP dose should further be reduced in *TPMT* heterozygote even with an initial 6-MP dose of <75 mg/m²/d. An initial 6-MP dose of 50–60 mg/m²/d still had severe hematologic toxicity and induced intolerance in pediatric ALL patients with the *TPMT* heterozygous allele. Some studies indicated that liver toxicity also partly influenced the dose reduction,^{29,25} although a meta-analysis of inflammatory bowel disease suggested that the *TPMT* polymorphisms were not associated with hepatotoxicity.³⁰ The present meta-analysis supports the CPIC recommendation even in the case of an initial 6-MP dose of 50–60 mg/m²/d.

This meta-analysis showed a difference in tolerable 6-MP dose between *TPMT* heterozygotes and wild-type among different ethnic groups. The *TPMT**3A-dominant ethnic group had a more reduced tolerable 6-MP dose in comparison to the *TPMT**3C-dominant ethnic group when they had a heterozygous allele. In a functional study of 23 allelic variants of the *TPMT* gene, which were *TPMT**2 to *24, the expression levels of *TPMT**2, *3A, *5, *12, *14, and *22 were significantly lower than that of *TPMT**1 ($P<0.005$), while *TPMT**3B and *3C and other variants (except *TPMT**8 and *18) showed a nonsignificant difference with *TPMT**1.³¹ Thus, the *TPMT*

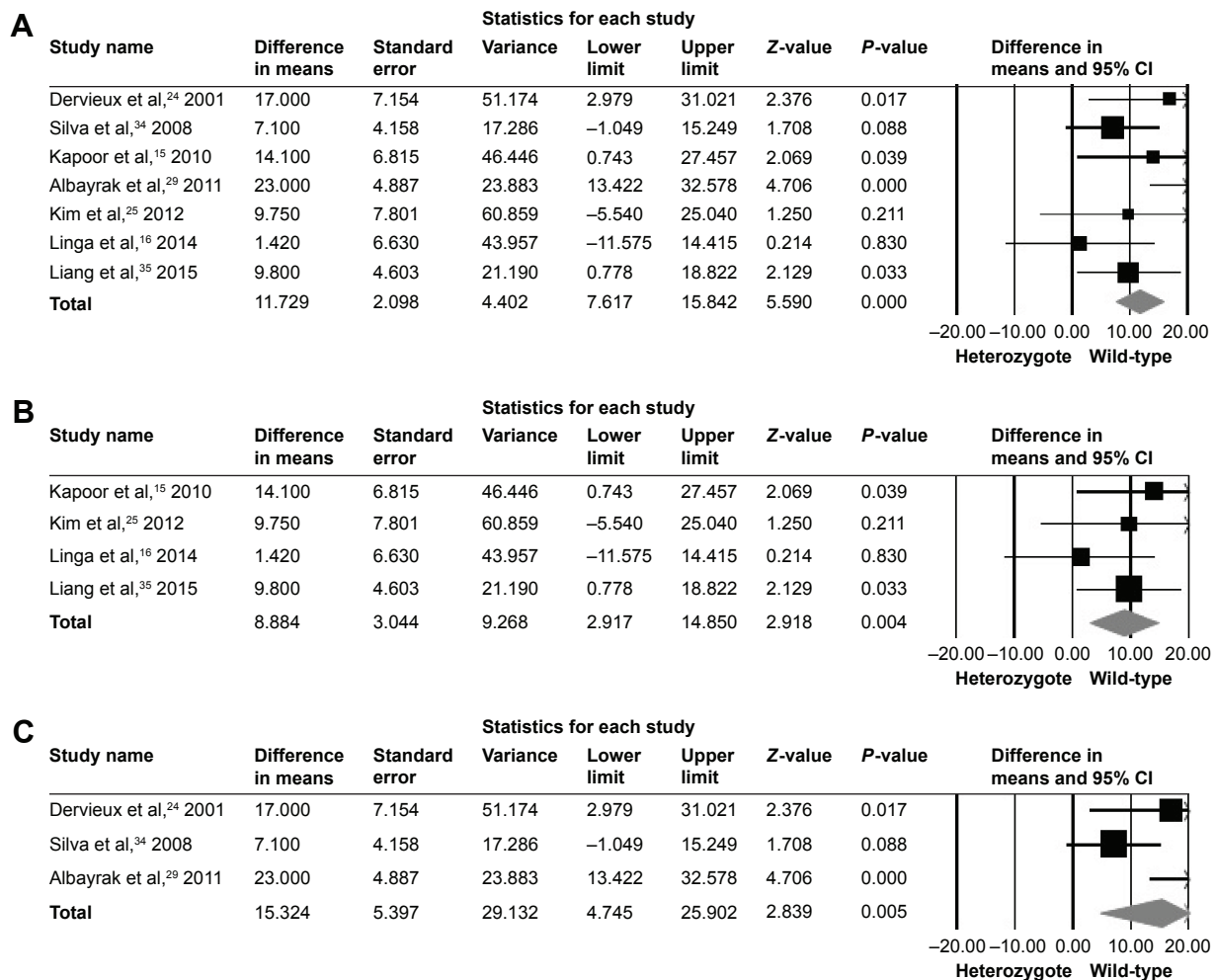


Figure 2 Forest plot of the meta-analysis: the maximum tolerable 6-MP dose of *TPMT* heterozygote and wild-type.

Notes: (A) Total (Mantel–Haenszel fixed-effects model); (B) *TPMT**3C-dominant ethnic group (Mantel–Haenszel fixed-effects model); (C) *TPMT**3A-dominant ethnic group (DerSimonian–Laird random-effects model).

Abbreviations: TPMT, thiopurine S-methyltransferase; 6-MP, 6-mercaptopurine; CI, confidence interval.

enzyme encoded by *TPMT**3A had no activity, whereas the enzyme encoded by *TPMT**3C had similar V_{max} and higher K_m in comparison with the wild-type enzyme, which means decreased enzymatic activity (112 ± 9 vs 111 ± 6 nmol/mg protein/min and 156 ± 12 vs 80 ± 8 μ mol/L, respectively).³¹ Alloenzyme activities of *TPMT**3A and *3C were $1.6\% \pm 0.6\%$ and $17\% \pm 1.3\%$ of the wild-type, respectively.³²

In spite of our efforts to perform a complete and thorough analysis, there are several limitations to this meta-analysis. First, differences in the characteristics of the studies might lead to heterogeneity in the results. Especially, disparate countries in the *TPMT**3A allele-dominant groups (France, Brazil, and Turkey) might increase the I^2 (degree of heterogeneity) over 70%. The DerSimonian–Laird random-effects model was applied to the analysis, which resulted in a decrease in the I^2 value. However, a sensitivity analysis could not be carried out because of the small number of studies. Second, treatment-related advantages, such as

continuous response and event-free survival of the *TPMT* genotype-based dosing in pediatric ALL patients, could not be evaluated because of the limited number of studies. Only one study showed that a reduced 6-MP initial dose for *TPMT* heterozygote might reduce secondary malignancy risk, but increase relapse risk, which is comparable to *TPMT* wild-type.³³ Further studies are warranted to build a consensus on treatment-related advantages of *TPMT* genotype-based dosing. Third, a direct comparison between *TPMT**1/*3A and *1/*3C was not possible because no studies have analyzed these particular TPMT combinations. Despite the limitations, our study can offer inspiration for a subset analysis according to the ethnicity or haplotypes.

Conclusion

The initial 6-MP dose needs to be reduced in *TPMT* heterozygote in comparison to wild-type, and ethnic differences might influence the tolerable 6-MP dose of *TPMT* heterozygote.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Demographics of studied population

References	Sex (male/female)	Age in years	Haplotype distribution (n)
Dervieux et al, ¹ 2001 All patients (n=78)	47/31	5.5±3.1 (mean ± SD)	*1/*1 (70), *1/*2 (2), *1/*3A (4), *1/*3C (1), *3C/*3C (1)
Silva et al, ² 2008 All patients (n=116)	58/58	<1 yr: n=1, 1–9.9 yr: n=95, ≥10 yr: n=20	*1/*1 (104), *1/*2 (1), *1/*3A (9), *1/*3C (2)
Kapoor et al, ³ 2010 Wild-types (n=64) Variants (n=7)	49/15 6/1	≤9 yr: n=43, >9 yr: n=21 ≤9 yr: n=7, >9 yr: n=0	*1/*1 (64) *1/*2 (3), *1/*3A (1), *1/*3C (3)
Albayrak et al, ⁴ 2011 Wild-types (n=47) Variants (n=4)	31/16 2/2	7.2±4.7 (mean ± SD) 8.2±4.6 (mean ± SD)	*1/*1 (47) *1/*3A (3), *1/*3C (1)
Kim et al, ⁵ 2012 All patients (n=100)	57/43	5.2 (1.4–16) (median [range])	*1/*1 (93), *2/*2 (1), *1/*3A (1), *1/*3C (5)
Linga et al, ⁶ 2014 All patients (n=72)	57/15	9 (2–18) (median [range])	*1/*1 (69), *1/*2 (1), *1/*3A (1), *1/*3C (1)
Liang et al, ⁷ 2015 All patients (n=310)	NA	NA	*1/*1 (298), 1/*3A or *3C (12)

Abbreviations: NA, not available; SD, standard deviation; yr, years.

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