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# Genetic variants of m$^1$A modification genes and the risk of neuroblastoma: novel insights from a Chinese case-control study

Jiaming Chang[1†], Lei Lin[1†], Wenli Zhang[1†], Jiliang Yang[1], Mengzhen Zhang[1], Huimin Yin[1], Xinxin Zhang[1], Chunlei Zhou[2], Yan Zou[1*] and Jing He[1*]

## Abstract

**Background** The N$^1$-adenosine methylation (m$^1$A) modification plays a significant role in various cancers. However, the functions of m$^1$A modification genes and their variants in neuroblastoma remain to be elucidated.

**Methods** We conducted a case-control study involving 402 neuroblastoma patients and 473 cancer-free controls from China via the TaqMan genotyping method to evaluate m$^1$A modification gene polymorphisms. Multivariate logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Additionally, expression quantitative trait locus (eQTL) analysis utilizing the Genotype-Tissue Expression database was performed to investigate the impacts of significant polymorphisms on gene expression. The relationships between gene expression and the risk and prognosis of neuroblastoma patients were further examined via publicly available datasets by using the R2 platform.

**Results** We found that *TRMT10C* rs4618204 C > T significantly decreased neuroblastoma risk (CT/TT vs. CC: adjusted OR = 0.74, 95% CI = 0.56–0.97, *P* = 0.030). Moreover, polymorphisms of the *TRMT10C* (rs3762735), *TRMT6* (rs451571 and rs236110), and *ALKBH3* (rs10768993 and rs2292889) genes were associated with neuroblastoma risk in specific subgroups. Complete linkage disequilibrium and eQTL analysis revealed a significant association between rs4618204 C > T and reduced expression of the *TRMT10C* gene. Additionally, higher expression levels of the *TRMT10C* gene were observed to be linked to increased risk, malignancy, and poorer prognosis in neuroblastoma patients.

**Conclusions** *TRMT10C* rs4618204 C > T was demonstrated to be significantly associated with an increased risk of neuroblastoma and may serve as a potential molecular marker for early diagnosis. Further studies are warranted to fully elucidate the specific molecular mechanisms involved in this effect.

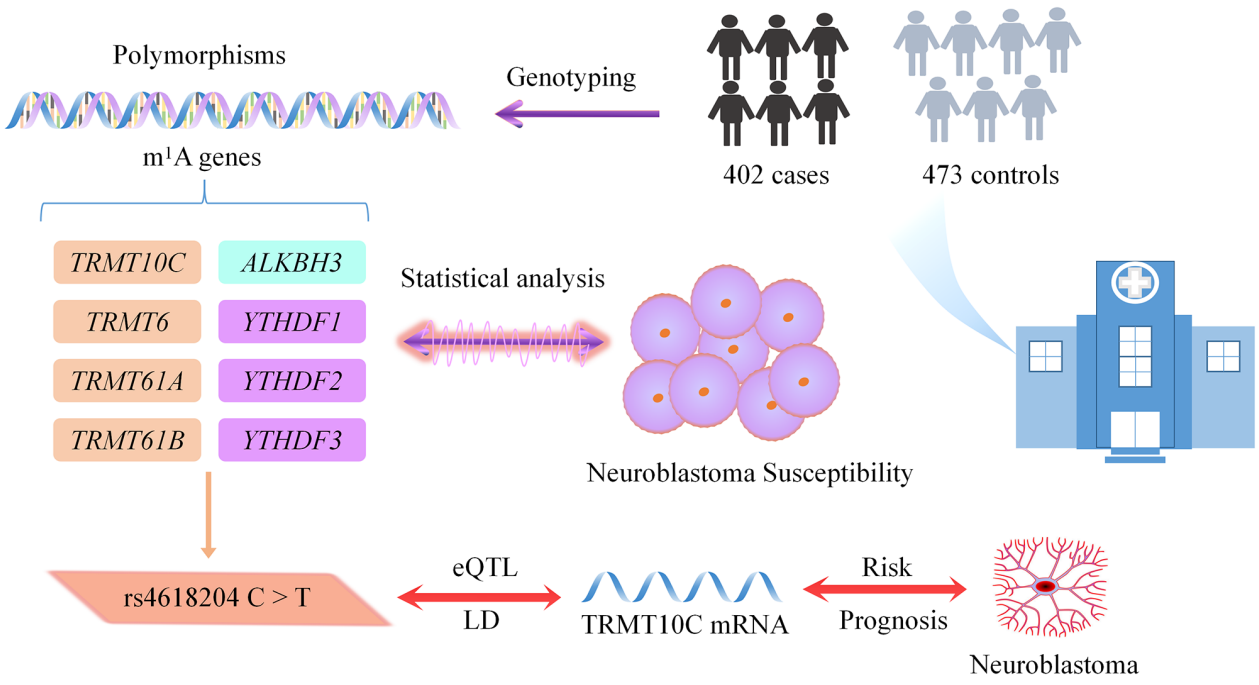
**Clinical trial number** Not applicable.

†Jiaming Chang, Lei Lin and Wenli Zhang contributed equally to this work.

*Correspondence:
Yan Zou
monknut@126.com
Jing He
hejing198374@gmail.com; hejing@gwcmc.org

Full list of author information is available at the end of the article

**Graphical Abstract**




**Keywords** Neuroblastoma, Susceptibility, m¹A modification, Polymorphism

## Introduction

Neuroblastoma is a solid tumor arising within the sympathetic nervous system, and accumulating evidence suggests that it originates from neural crest cells [1]. Neuroblastoma ranks as the second most common extracranial solid tumor in pediatric patients, accounting for approximately 15% of tumor-related mortality [2, 3]. The incidence rate of pediatric neuroblastoma ranges from 7.7 to 8.8 cases per million children in China [4]. In developed regions such as Europe and the United States, the incidence of neuroblastoma in children varies significantly, with the standardized incidence rate ranging from 6.1 to 21.5 cases per million children [5, 6]. Patients with low-risk and moderate-risk neuroblastoma generally have a favorable prognosis, with an overall 5-year survival rate exceeding 90% [7, 8]. However, patients with high-risk neuroblastoma continue to have a poor prognosis despite undergoing intensive multimodal therapies, including surgery, chemotherapy, radiotherapy, and immunotherapy [9]. Neuroblastoma is a highly heterogeneous tumor characterized by diverse clinical and molecular features. For example, *MYCN* amplification is observed in approximately 20–25% of neuroblastoma cases and has been demonstrated to be correlated with an unfavorable prognosis in patients with neuroblastoma [10]. Deletions of chromosomes 1p and 11q have been associated with an increased risk of neuroblastoma [8]. Additionally, mutations in the anaplastic lymphoma kinase (*ALK*) gene have been detected in approximately 8% of neuroblastoma cases, with the *ALK* gene F1174L mutation being associated with *MYCN* amplification [11]. Recent studies have identified *TERT* rearrangements and *ATRX* loss as factors associated with neuroblastoma malignancy [12, 13]. Additionally, mutations in *PTPN14*, *DOCK8*, and *RAS* have been linked to neuroblastoma recurrence [14, 15].

As inherent and stable genetic markers, single nucleotide polymorphisms (SNPs) serve as excellent tools for identifying disease risk factors. Previous large-scale genome-wide association studies (GWASs) have identified several SNPs associated with neuroblastoma susceptibility [16]. For example, Mario et al. identified and validated the significant associations of six SNPs of the *BARD1* gene (rs6435862, rs3768716, rs17487792, rs6712055, rs7587476, and rs6715570) with high-risk neuroblastoma in the discovery cohort and independent validation cohort [17]. Moreover, we validated the associations of the *BARD1* rs6435862 T > G and rs3768716 A > G polymorphisms with increased neuroblastoma susceptibility in southern Chinese children [18]. Another GWAS revealed that *BARD1* rs17489363 and rs1048108 are associated with a high risk of neuroblastoma and that rs17489363 C > T may promote the proliferation of neuroblastoma by reducing *BARD1* expression [19].

Maris et al. reported that a genetic variant (rs110419) of the LIM domain only 1 (*LMO1*) gene was significantly associated with an increased risk of neuroblastoma [16]. A three-center case-control study from eastern China also revealed a significant association between SNPs in the *LMO1* gene (rs110419, rs4758051, rs10840002, and rs2168101) and neuroblastoma risk [20]. The rs2168101 G > T polymorphism reduces the binding of this locus to transcription factors, thereby reducing the expression of the oncogene *LMO1*, which reduces the susceptibility to neuroblastoma [21]. Based on the pleiotropic effects of genetic factors, Formicola et al. identified rs13337397 as being highly associated with neuroblastoma by a meta-analysis of GWAS data for neuroblastoma and coronary artery disease [22]. Additionally, the risk allele at rs13337397 significantly increases *CFDP1* gene expression, and high *CFDP1* gene expression is associated with neuroblastoma cell survival and proliferation. A cross-association analysis combining the GWAS results for melanoma and neuroblastoma revealed a significant association of rs2153977 with neuroblastoma, and the minor allele of rs2153977 was observed to reduce *SLC16A1* gene expression [23]. The *SLC16A1* gene has been observed to be associated with the worst clinical outcome, as well as associated with neuroblastoma cell proliferation and invasion. In a GWAS involving 2817 neuroblastoma patients and 7473 controls, *HACE1* rs4336470 and *LIN28B* rs17065417 were observed to be associated with the risk of neuroblastoma [24]. Specifically, rs17065417 may influence neuroblastoma development by modulating *LIN28B* gene expression. We have identified several SNPs associated with neuroblastoma susceptibility via the use of candidate gene approaches, including polymorphisms in the *ERCC1*, *XPF*, *ALKBH5*, *NSUN2*, and *TET2* genes [25–28]. However, the current findings remain insufficient to fully elucidate the genetic mechanisms underlying all cases of neuroblastoma.

In recent years, a growing body of evidence has demonstrated that RNA methylations play crucial roles in tumorigenesis [29]. $N^1$-adenosine methylation ($m^1A$) is a prevalent RNA modification that occurs in eukaryotes. Initially, the $m^1A$ modification was identified as a conserved modification in tRNA and rRNA, and recent evidence indicates that the $m^1A$ modification is also present in mRNAs [30, 31]. The identified $m^1A$ methyltransferase genes include *TRMT6*, *TRMT61A*, *TRMT61B*, and *TRMT10C*. Additionally, the methyltransferases that primarily recognize $N^1$-methyladenosine in tRNAs regulate tRNA-mediated translation processes [32]. The demethylases of the *ALKBH1* and *ALKBH3* genes recognize tRNAs to facilitate the demethylation of $m^1A$ [33, 34]. Moreover, YTHDF1, YTHDF2, YTHDF3, and YTHDC1 proteins recognize $m^1A$ modifications and regulate RNA stability [35]. Wang et al. reported a significant increase in $m^1A$ modifications in hepatocellular carcinoma (HCC) [36]. In addition, the TRMT6/TRMT61A complex elevates $m^1A$ in tRNAs, thereby increasing PPARδ translation and potentially mediating the growth of cancer. A high expression level of the *TRMT10C* gene is associated with poor prognosis in HCC patients and may contribute to adverse cancer progression via the PI3K-Akt signaling pathway [37]. The ALKBH3 protein promotes the expression of CSF-1 through the demethylation of CSF-1 mRNA, thus contributing to the malignant progression of ovarian and breast cancers [38]. Furthermore, $m^1A$ genes play a significant role in various cancers. However, their role in neuroblastoma remains unclear. Therefore, we hypothesized that SNPs in $m^1A$ modification genes could influence gene expression and mediate neuroblastoma development. To test this hypothesis, we conducted a case-control study to investigate the associations between $m^1A$ gene polymorphisms and neuroblastoma susceptibility in Chinese children.

## Materials and methods

### Study subjects

We recruited 402 children who were diagnosed with neuroblastoma (case group) and 473 children without any tumors (control group) from the Children's Hospital of Nanjing Medical University (Table S1) [27, 39, 40]. The participants in the case group had a confirmed histopathological diagnosis of primary neuroblastoma, had no history of malignancies in other organs, and had not received chemotherapy prior to sample collection. The control group consisted of healthy children aged 0–14 years who had no history of tumors, neurological disorders, congenital genetic diseases, infectious diseases, or other significant medical conditions. Written informed consent was obtained from all of the participants or their legal guardians. This study was approved by the Institutional Review Committee of Children's Hospital of Nanjing Medical University (Approval No: 202112141-1).

### Polymorphism selection and genotyping

We conducted a comprehensive screening of SNPs in the 5' flanking region, 5' untranslated region (UTR), 3' UTR, and intron and exon regions of the $m^1A$ modification genes (*TRMT10C*, *TRMT6*, *TRMT61A*, *TRMT61B*, *ALKBH3*, *YTHDF1*, *YTHDF2*, and *YTHDF3*) via the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP). The potential functions of the selected SNPs were predicted by the online tool SNPinfo (https://snpinfo.niehs.nih.gov/). Single nucleotide polymorphisms located in the coding regions of functional genes that could cause amino acid variations (nonsynonymous SNPs), SNPs located in microRNAs, transcription factor-binding sites, and SNPs

affecting splicing were included in this study. The MAF of the selected SNPs was determined to be greater than 5% in the Chinese Han population. The LDlink tool (https://ldlink.nih.gov/) was employed to assess the linkage disequilibrium (LD) between SNPs, and there was no significant LD observed between the SNPs ($R^2$<0.8). Finally, we successfully included 23 SNPs in the $m^1A$ genes, and their functional annotations are shown in Table S2. Genomic DNA was extracted from the blood or tissue samples of all of the subjects via a TIANamp DNA Kit (TianGen Biotech Co. Ltd., Beijing, China). The DNA concentration and purity were assessed via a UV spectrophotometer (NanoDrop Technologies, Inc., Wilmington, DE). Genotyping was conducted via TaqMan® SNP genotyping assays (Applied Biosystems, CA, USA) [41–43]. To ensure accuracy, 10% of the samples were retested, and the results demonstrated 100% concordance.

### Statistical analysis

Differences in genotype frequency distribution and demographic characteristics between the case group and control group were evaluated via chi-square tests. To assess whether the genotype frequencies adhered to Hardy-Weinberg equilibrium (HWE) in the control group, a goodness-of-fit test was conducted for each SNP. Multivariate logistic regression analyses were employed to estimate the odds ratio (OR) and 95% confidence interval (CI) after adjusting for potential confounding factors (including age and sex). The statistical power was calculated via the PS (Power and Sample Size Calculations) program V.3.1.2. Among 402 neuroblastoma samples and 473 control samples, when the significance level α was 0.05 and the minor allele frequency (MAF) of the SNPs was 0.1–0.5, a power of 80% was determined to detect the minimum effect size ranging from 0.472 to 0.682 and from 1.466 to 1.766. Using the Genotype-Tissue Expression (GTEx) online portal V10 (https://www.gtexportal.org/home/), we conducted an expression quantitative trait loci (eQTL) analysis to preliminarily investigate how SNPs influence gene expression. Log2-transformed gene expression data for neuroblastoma tissues and normal adrenal gland tissues (which were consistent and comparable across the sequencing platforms) were downloaded from the R2 platform (http://r2.amc.nl) (Table S3). Nonparametric statistical tests were employed to analyze differences in gene expression between the different groups. GraphPad Prism (V9.5.1) was used to generate violin plots and bar graphs. Kaplan-Meier analyses were also performed via the R2 platform. All of the tests of statistical significance were two-sided, with a significance level set at 0.05. Raw data management was conducted via STATA V18.0, and statistical analyses were performed via SAS V9.4.

## Results

### Associations of $m^1A$ modification gene polymorphisms with neuroblastoma susceptibility

In this case-control study involving 402 neuroblastoma patients and 473 controls, we successfully conducted genotyping for 23 candidate polymorphisms of $m^1A$ modification genes. In the control group, the genotype frequencies of the candidate SNPs (except for rs6139878 and rs1048928) were in accordance with HWE. Table 1 presents the associations between neuroblastoma susceptibility and the SNPs of the *TRMT10C*, *TRMT6*, *TRMT61A*, *TRMT61B*, *ALKBH3*, *YTHDF1*, *YTHDF2*, and *YTHDF3* genes. The multivariate logistic regression model, which was adjusted for confounding factors (including age and sex), demonstrated that *TRMT10C* rs4618204 was significantly associated with the risk of neuroblastoma. Specifically, the dominant model indicated that individuals with the CT and TT genotypes exhibited a reduced neuroblastoma susceptibility compared with those with the CC genotype (CT/TT vs. CC: adjusted OR = 0.74, 95% CI = 0.56–0.97, *P* = 0.030).

### Stratification analysis of $m^1A$ modification gene polymorphisms

Stratification analysis revealed that the *TRMT10C* rs4618204 CT/TT genotype was significantly associated with a reduced risk of neuroblastoma in some subgroups (age > 18 months: adjusted OR = 0.70, 95% CI = 0.50–0.99, *P* = 0.040; males: adjusted OR = 0.60, 95% CI = 0.41–0.87, *P* = 0.008; retroperitoneal: adjusted OR = 0.68, 95% CI = 0.47–0.98, *P* = 0.037) (Table 2). Compared with the CC genotype, the CG/GG genotypes of *TRMT10C* rs3762735 were associated with an increased risk of neuroblastoma in the male (adjusted OR = 1.62, 95% CI = 1.05–2.49, *P* = 0.028), adrenal gland (adjusted OR = 1.89, 95% CI = 1.18–3.04, *P* = 0.008), and stage I + II + 4s (adjusted OR = 1.51, 95% CI = 1.02–2.22, *P* = 0.037) subgroups. Compared with the 0–2 risk genotype, the 3–5 risk genotype was significantly associated with an increased risk of neuroblastoma across multiple subgroups (age > 18 months: adjusted OR = 1.61, 95% CI = 1.14–2.28, *P* = 0.007; males: adjusted OR = 1.70, 95% CI = 1.14–2.53, *P* = 0.009; retroperitoneal: adjusted OR = 1.64, 95% CI = 1.13–2.39, *P* = 0.010; mediastinum: adjusted OR = 1.54, 95% CI = 1.01–2.35, *P* = 0.048; Stages I + II + 4s: adjusted OR = 1.60, 95% CI = 1.10–2.32, *P* = 0.013; Stages III + IV: adjusted OR = 1.53, 95% CI = 1.05–2.24, *P* = 0.029).

Compared with the TT genotype, the TC/CC genotypes of *TRMT6* rs451571 were associated with a reduced risk of neuroblastoma in the subgroup of tumors originating from the mediastinum (adjusted OR = 0.63, 95% CI = 0.41–0.97, *P* = 0.035) (Table 3). In the retroperitoneal subgroup, the dominant model of *TRMT6* rs236110

**Table 1** Association between m[1]A modification gene polymorphisms and neuroblastoma risk in children from Jiangsu Province

| Gene | SNP | Allele | | Case (*N* = 402) | | | Control (*N* = 473) | | | Adjusted OR [a] | $P^a$ | $P^b$ | Adjusted OR [c] | $P^c$ | $P^b$ | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A | B | AA | AB | BB | AA | AB | BB | (95% CI) | | | (95% CI) | | | |
| *TRMT10C* | rs7641261 | C | T | 226 | 149 | 26 | 273 | 165 | 35 | 1.06 (0.81–1.38) | 0.686 | 1 | 0.87 (0.51–1.47) | 0.600 | 1 | 0.152 |
| *TRMT10C* | rs2303476 | T | C | 254 | 114 | 33 | 295 | 154 | 24 | 0.96 (0.73–1.26) | 0.765 | 1 | 1.68 (0.97–2.89) | 0.062 | 1 | 0.505 |
| *TRMT10C* | rs4618204 | C | T | 166 | 170 | 65 | 162 | 231 | 80 | **0.74 (0.56–0.97)** | **0.030** | 1 | 0.95 (0.66–1.36) | 0.784 | 1 | 0.879 |
| *TRMT10C* | rs4257518 | A | G | 120 | 183 | 98 | 138 | 234 | 101 | 0.96 (0.72–1.29) | 0.807 | 1 | 1.19 (0.87–1.64) | 0.276 | 1 | 0.922 |
| *TRMT10C* | rs3762735 | C | G | 284 | 108 | 9 | 362 | 107 | 4 | 1.34 (0.99–1.82) | 0.056 | 1 | 2.70 (0.83–8.85) | 0.101 | 1 | 0.198 |
| *TRMT6* | rs236170 | A | G | 120 | 185 | 97 | 131 | 229 | 113 | 0.90 (0.67–1.21) | 0.483 | 1 | 1.01 (0.74–1.39) | 0.931 | 1 | 0.510 |
| *TRMT6* | rs451571 | T | C | 252 | 128 | 22 | 273 | 172 | 28 | 0.81 (0.62–1.07) | 0.135 | 1 | 0.92 (0.52–1.64) | 0.777 | 1 | 0.895 |
| *TRMT6* | rs6139878 | G | A | 354 | 45 | 3 | 418 | 49 | 6 | 1.03 (0.68–1.56) | 0.886 | 1 | 0.59 (0.15–2.36) | 0.451 | 1 | 0.002 |
| *TRMT6* | rs236188 | G | A | 331 | 67 | 4 | 376 | 89 | 8 | 0.83 (0.59–1.17) | 0.286 | 1 | 0.58 (0.17–1.95) | 0.381 | 1 | 0.311 |
| *TRMT6* | rs236110 | C | A | 266 | 177 | 19 | 293 | 162 | 18 | 0.83 (0.63–1.10) | 0.195 | 1 | 1.25 (0.65–2.42) | 0.502 | 1 | 0.450 |
| *TRMT61A* | rs2296484 | C | T | 312 | 80 | 8 | 353 | 109 | 11 | 0.83 (0.61–1.14) | 0.246 | 1 | 0.86 (0.34–2.15) | 0.741 | 1 | 0.457 |
| *TRMT61B* | rs4563180 | G | C | 236 | 145 | 21 | 288 | 161 | 24 | 1.10 (0.84–1.44) | 0.511 | 1 | 1.03 (0.57–1.88) | 0.920 | 1 | 0.807 |
| *ALKBH3* | rs11037720 | A | G | 257 | 120 | 23 | 286 | 167 | 20 | 0.85 (0.65–1.12) | 0.251 | 1 | 1.38 (0.75–2.56) | 0.300 | 1 | 0.476 |
| *ALKBH3* | rs1048928 | T | G | 294 | 97 | 9 | 336 | 133 | 4 | 0.88 (0.66–1.19) | 0.419 | 1 | 2.71 (0.83–8.88) | 0.100 | 1 | 0.018 |
| *ALKBH3* | rs10768993 | G | A | 166 | 166 | 68 | 170 | 228 | 75 | 0.79 (0.60–1.04) | 0.093 | 1 | 1.09 (0.76–1.56) | 0.646 | 1 | 0.921 |
| *ALKBH3* | rs2292889 | C | G | 355 | 43 | 2 | 403 | 69 | 1 | 0.73 (0.49–1.09) | 0.123 | 1 | 2.38 (0.22–26.40) | 0.480 | 1 | 0.270 |
| *ALKBH3* | rs2434474 | T | C | 194 | 158 | 48 | 221 | 194 | 58 | 0.93 (0.71–1.22) | 0.605 | 1 | 0.98 (0.65–1.47) | 0.911 | 1 | 0.133 |
| *YTHDF1* | rs6011668 | C | T | 282 | 111 | 9 | 352 | 109 | 12 | 1.24 (0.92–1.67) | 0.159 | 1 | 0.88 (0.37–2.11) | 0.777 | 1 | 0.313 |
| *YTHDF1* | rs6090311 | A | G | 174 | 181 | 47 | 196 | 214 | 63 | 0.93 (0.71–1.21) | 0.581 | 1 | 0.86 (0.58–1.29) | 0.469 | 1 | 0.704 |
| *YTHDF2* | rs3738067 | A | G | 238 | 134 | 30 | 268 | 170 | 35 | 0.90 (0.69–1.18) | 0.448 | 1 | 1.01 (0.61–1.68) | 0.972 | 1 | 0.269 |
| *YTHDF3* | rs2241753 | G | A | 189 | 167 | 46 | 219 | 195 | 59 | 0.97 (0.74–1.27) | 0.834 | 1 | 0.91 (0.60–1.37) | 0.642 | 1 | 0.134 |
| *YTHDF3* | rs2241754 | A | G | 140 | 190 | 72 | 156 | 229 | 88 | 0.92 (0.70–1.22) | 0.565 | 1 | 0.95 (0.68–1.35) | 0.791 | 1 | 0.806 |
| *YTHDF3* | rs7464 | A | G | 205 | 153 | 44 | 264 | 172 | 37 | 1.21 (0.93–1.59) | 0.155 | 1 | 1.45 (0.92–2.29) | 0.113 | 1 | 0.231 |

OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium

[a] Adjusted for age and gender for dominant model

[b] The Bonferroni method was used to correct *P* values for multiple testing

[c] Adjusted for age and gender for recessive model

**Table 2** Stratification analysis for the associations of *TRMT10C* gene polymorphisms with neuroblastoma risk in children from Jiangsu Province

| Variables | rs4618204 (cases/controls) | | AOR (95% CI) [a] | *P*[a] | rs3762735 (cases/controls) | | AOR (95% CI) [a] | *P*[a] | Riks genotypes (cases/controls) | | AOR (95% CI) [a] | *P*[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CC | CT/TT | | | CC | CG/GG | | | 0–2 | 3–5 | | |
| Age, month | | | | | | | | | | | | |
| ≤ 18 | 58/52 | 80/87 | 0.82 (0.51–1.34) | 0.432 | 102/107 | 36/32 | 1.19 (0.68–2.06) | 0.547 | 93/102 | 45/37 | 1.34 (0.80–2.24) | 0.275 |
| > 18 | 108/110 | 155/224 | **0.70 (0.50–0.99)** | **0.040** | 182/255 | 81/79 | 1.44 (1.00-2.07) | 0.051 | 166/245 | 97/89 | **1.61 (1.14–2.28)** | **0.007** |
| Gender | | | | | | | | | | | | |
| Females | 71/80 | 120/145 | 0.93 (0.62–1.39) | 0.730 | 135/164 | 56/61 | 1.12 (0.73–1.71) | 0.617 | 128/164 | 63/61 | 1.32 (0.87–2.02) | 0.192 |
| Males | 95/82 | 115/166 | **0.60 (0.41–0.87)** | **0.008** | 149/198 | 61/50 | **1.62 (1.05–2.49)** | **0.028** | 131/183 | 79/65 | **1.70 (1.14–2.53)** | **0.009** |
| Sites of origin | | | | | | | | | | | | |
| Adrenal gland | 37/162 | 56/311 | 0.79 (0.50–1.25) | 0.317 | 59/362 | 34/111 | **1.89 (1.18–3.04)** | **0.008** | 63/347 | 30/126 | 1.30 (0.81–2.11) | 0.280 |
| Retroperitoneal | 72/162 | 94/311 | **0.68 (0.47–0.98)** | **0.037** | 121/362 | 45/111 | 1.21 (0.81–1.81) | 0.359 | 104/347 | 62/126 | **1.64 (1.13–2.39)** | **0.010** |
| Mediastinum | 49/162 | 71/311 | 0.76 (0.50–1.14) | 0.180 | 89/362 | 31/111 | 1.14 (0.72–1.81) | 0.582 | 77/347 | 43/126 | **1.54 (1.01–2.35)** | **0.048** |
| Others | 6/162 | 12/311 | 1.05 (0.39–2.85) | 0.924 | 12/362 | 6/111 | 1.60 (0.59–4.39) | 0.359 | 13/347 | 5/126 | 1.06 (0.37–3.03) | 0.918 |
| Clinical stages | | | | | | | | | | | | |
| I + II + 4s | 74/162 | 99/311 | 0.70 (0.49-1.00) | 0.053 | 118/362 | 55/111 | **1.51 (1.02–2.22)** | **0.037** | 109/347 | 64/126 | **1.60 (1.10–2.32)** | **0.013** |
| III + IV | 66/162 | 97/311 | 0.76 (0.53–1.10) | 0.141 | 113/362 | 50/111 | 1.47 (0.99–2.18) | 0.058 | 105/347 | 58/126 | **1.53 (1.05–2.24)** | **0.029** |

AOR, adjusted odds ratio; CI, confidence interval

[a] Adjusted for age and gender, omitting the correspondence factor

[b] Risk genotypes were carriers with rs7641261 CC/CT, rs2303476 CC, rs4618204 CC, rs4257518 GG, and rs3762735 CG/GG genotypes

**Table 3** Stratification analysis for the associations of *TRMT6* gene polymorphisms with neuroblastoma risk in children from Jiangsu Province

| Variables | rs451571 (cases/controls) | | AOR (95% CI) [a] | *P*[a] | rs236110 (cases/controls) | | AOR (95% CI) [a] | *P*[a] | Protective genotypes (cases/controls) | | AOR (95% CI) [a] | *P*[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TT | TC/CC | | | CC | CA/AA | | | 0–2 | 3–5 | | |
| Age, month | | | | | | | | | | | | |
| ≤ 18 | 82/82 | 57/57 | 1.00 (0.62–1.61) | 0.997 | 87/88 | 52/51 | 1.03 (0.63–1.68) | 0.902 | 84/83 | 55/56 | 0.97 (0.60–1.57) | 0.900 |
| > 18 | 170/191 | 93/143 | 0.73 (0.52–1.02) | 0.065 | 179/205 | 84/129 | 0.75 (0.53–1.05) | 0.091 | 188/191 | 75/143 | **0.53 (0.38–0.75)** | **0.0003** |
| Gender | | | | | | | | | | | | |
| Females | 121/130 | 70/95 | 0.79 (0.53–1.18) | 0.246 | 128/138 | 63/87 | 0.78 (0.52–1.17) | 0.229 | 124/131 | 67/94 | 0.75 (0.51–1.12) | 0.162 |
| Males | 131/143 | 80/105 | 0.83 (0.57–1.21) | 0.336 | 138/155 | 73/93 | 0.88 (0.60–1.29) | 0.515 | 148/143 | 63/105 | **0.58 (0.39–0.86)** | **0.006** |
| Sites of origin | | | | | | | | | | | | |
| Adrenal gland | 56/273 | 37/200 | 0.90 (0.57–1.42) | 0.664 | 52/293 | 41/180 | 1.28 (0.82–2.01) | 0.277 | 65/274 | 28/199 | **0.60 (0.37–0.96)** | **0.034** |
| Retroperitoneal | 103/273 | 64/200 | 0.85 (0.59–1.22) | 0.372 | 120/293 | 47/180 | **0.64 (0.43–0.94)** | **0.022** | 113/274 | 54/199 | **0.66 (0.45–0.96)** | **0.028** |
| Mediastinum | 82/273 | 38/200 | **0.63 (0.41–0.97)** | **0.035** | 82/293 | 38/180 | 0.75 (0.49–1.16) | 0.196 | 81/274 | 39/199 | 0.66 (0.43–1.01) | 0.057 |
| Others | 10/273 | 8/200 | 1.09 (0.42–2.81) | 0.862 | 10/293 | 8/180 | 1.30 (0.50–3.35) | 0.589 | 11/274 | 7/199 | 0.88 (0.33–2.30) | 0.789 |
| Clinical stages | | | | | | | | | | | | |
| I + II + 4s | 113/273 | 60/200 | 0.73 (0.51–1.05) | 0.094 | 113/293 | 60/180 | 0.87 (0.60–1.25) | 0.447 | 118/274 | 55/199 | **0.64 (0.45–0.93)** | **0.019** |
| III + IV | 95/273 | 68/200 | 0.98 (0.68–1.40) | 0.907 | 106/293 | 57/180 | 0.88 (0.60–1.27) | 0.487 | 110/274 | 53/199 | **0.66 (0.46–0.97)** | **0.032** |

AOR, adjusted odds ratio; CI, confidence interval

[a] Adjusted for age and gender, omitting the correspondence factor

[b] Protective genotypes were carriers with rs236170 AG/GG, rs451571 TC/CC, rs6139878 AA, rs236188 GA/AA, and rs236110 CC/CA genotypes

was significantly associated with reduced susceptibility to neuroblastoma (CA/AA vs. CC: adjusted OR = 0.64, 95% CI = 0.43–0.94, $P = 0.022$). Compared with possessing 0–2 protective genotypes, the possession of 3–5 protective genotypes was significantly associated with a reduced risk of neuroblastoma across multiple subgroups (age > 18 months: adjusted OR = 0.53, 95% CI = 0.38–0.75, $P = 0.0003$; males: adjusted OR = 0.58, 95% CI = 0.39–0.86, $P = 0.006$; adrenal gland: adjusted OR = 0.60, 95% CI = 0.37–0.96, $P = 0.034$; retroperitoneal: adjusted OR = 0.66, 95% CI = 0.45–0.96, $P = 0.028$; stages I + II + 4s: adjusted OR = 0.64, 95% CI = 0.45–0.93, $P = 0.019$; stages III + IV: adjusted OR = 0.66, 95% CI = 0.46–0.97, $P = 0.032$).

The dominant model of *ALKBH3* rs10768993 was significantly associated with a reduced risk of neuroblastoma in the subgroup of tumors originating from the mediastinum (GA/AA vs. GG: adjusted OR = 0.62, 95% CI = 0.41–0.93, $P = 0.021$) (Table 4). Compared with the CC genotype, in children aged ≤ 18 months (adjusted OR = 0.37, 95% CI = 0.17–0.85, $P = 0.018$) and females (adjusted OR = 0.47, 95% CI = 0.26–0.84, $P = 0.012$), the presence of the *ALKBH3* rs2292889 CG/GG genotype was significantly associated with a reduced risk of neuroblastoma. In terms of candidate SNPs of the *ALKBH3* gene, five protective genotypes were significantly associated with a reduced risk of neuroblastoma compared with 0–4 genotypes in the age > 18 months (adjusted OR = 0.64, 95% CI = 0.46–0.89, $P = 0.009$) and mediastinum (adjusted OR = 0.60, 95% CI = 0.39–0.90, $P = 0.014$) subgroups.

No significant associations were identified between the polymorphisms of the *YTHDF1* (rs6011668) and *YTHDF3* (rs7464) genes and neuroblastoma susceptibility within the analyzed subgroups (Table 5).

#### eQTL analysis of significant polymorphisms

Our findings demonstrated that *TRMT10C* rs4618204 C > T significantly influences the risk of neuroblastoma. To investigate the relationship between rs4618204 C > T and gene expression, we conducted eQTL analysis using data from the GTEx database. Given that rs4618204 was not found in the GTEx database, we utilized the LDlink tool to identify SNPs in complete linkage disequilibrium with rs4618204 within the Chinese Han population ($R^2 = 1.00$). We subsequently investigated the impacts of these SNPs on gene expression via GTEx data. We observed that the genotypes of the SNPs in complete linkage disequilibrium with the rs4618204 T allele were associated with reduced *TRMT10C* gene expression (Table S4). Specifically, we focused on rs6809742, which is located near the *TRMT10C* gene, as well as rs13072301, which resides within an intronic region of the *TRMT10C* gene (Fig. 1A). The eQTL analysis revealed that both the rs6809742 T > C and rs13072301 C > G variants were associated with downregulated *TRMT10C* gene expression in skeletal muscle (Fig. 1B, D) and tibial artery tissues (Fig. 1C, E).

#### Association of the *TRMT10C* gene with risk and prognosis in neuroblastomas

The eQTL results revealed that rs4618204 C > T was associated with decreased expression of the *TRMT10C* gene. Compared with that in the normal adrenal gland group, *TRMT10C* gene expression was significantly elevated in the neuroblastoma group (Fig. 2A). In high-risk (Fig. 2B) and advanced-stage (Fig. 2C) neuroblastoma patients, the expression level of the *TRMT10C* gene was significantly elevated. Kaplan-Meier analyses demonstrated that elevated *TRMT10C* gene expression was significantly correlated with adverse outcomes in neuroblastoma patients (Fig. 2D, E).

## Discussion

We conducted a case-control study involving 402 neuroblastoma patients and 473 cancer-free controls from China to investigate the associations between 23 polymorphisms of $m^1A$ modification genes and neuroblastoma susceptibility. Our findings revealed that *TRMT10C* rs4618204 C > T was significantly associated with a reduced risk of neuroblastoma. Additionally, some polymorphisms of the *TRMT10C* (rs3762735), *TRMT6* (rs451571 and rs236110), and *ALKBH3* (rs10768993 and rs2292889) genes were observed to be associated with the risk of neuroblastoma in certain subgroups.

To elucidate the potential mechanism by which *TRMT10C* rs4618204 C > T influences neuroblastoma susceptibility, we conducted a comprehensive linkage analysis and eQTL analysis. Our findings revealed that the rs4618204 T allele was associated with reduced expression of the *TRMT10C* gene in skeletal muscle and tibial artery tissues. Additionally, we observed significantly elevated *TRMT10C* gene expression in neuroblastoma tissues compared with normal adrenal gland tissues. Notably, *TRMT10C* gene expression was also significantly greater in both high-risk and advanced-stage neuroblastoma patients. These results indicate that increased *TRMT10C* gene expression is linked to neuroblastoma risk and invasiveness. Furthermore, Kaplan-Meier analyses demonstrated that high *TRMT10C* gene expression was associated with poorer prognosis in neuroblastoma patients. Collectively, these findings support the significant association between the rs4618204 C > T polymorphism and a reduced risk of neuroblastoma. The rs4618204 C > T variant or linked SNPs may mitigate neuroblastoma risk by downregulating *TRMT10C* gene expression. Taken together, our results suggest that

**Table 4** Stratification analysis for the associations of *ALKBH3* gene polymorphisms with neuroblastoma risk in children from Jiangsu Province

| Variables | rs10768993 (cases/controls) | | AOR (95% CI) [a] | $P^a$ | rs2292889 (cases/controls) | | AOR (95% CI) [a] | $P^a$ | Protective genotypes (cases/controls) | | AOR (95% CI) [a] | $P^a$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GG | GA/AA | | | CC | CG/GG | | | 0–4 | 5 | | |
| Age, month | | | | | | | | | | | | |
| ≤ 18 | 54/46 | 83/93 | 0.76 (0.47–1.24) | 0.275 | 128/117 | 9/22 | **0.37 (0.17–0.85)** | **0.018** | 72/73 | 65/66 | 1.00 (0.62–1.61) | 0.996 |
| > 18 | 112/124 | 151/210 | 0.80 (0.57–1.11) | 0.175 | 227/286 | 36/48 | 0.94 (0.59–1.51) | 0.810 | 163/171 | 100/163 | **0.64 (0.46–0.89)** | **0.009** |
| Gender | | | | | | | | | | | | |
| Females | 80/74 | 111/151 | 0.68 (0.46–1.01) | 0.058 | 173/184 | 18/41 | **0.47 (0.26–0.84)** | **0.012** | 110/113 | 81/112 | 0.74 (0.50–1.09) | 0.131 |
| Males | 86/96 | 123/152 | 0.90 (0.62–1.32) | 0.597 | 182/219 | 27/29 | 1.12 (0.64–1.96) | 0.692 | 125/131 | 84/117 | 0.75 (0.52–1.09) | 0.133 |
| Sites of origin | | | | | | | | | | | | |
| Adrenal gland | 34/170 | 59/303 | 0.98 (0.62–1.56) | 0.936 | 85/403 | 8/70 | 0.55 (0.25–1.18) | 0.124 | 49/244 | 44/229 | 0.96 (0.62–1.50) | 0.863 |
| Retroperitoneal | 68/170 | 97/303 | 0.80 (0.55–1.15) | 0.221 | 147/403 | 18/70 | 0.70 (0.40–1.22) | 0.207 | 94/244 | 71/229 | 0.80 (0.56–1.15) | 0.230 |
| Mediastinum | 57/170 | 63/303 | **0.62 (0.41–0.93)** | **0.021** | 103/403 | 17/70 | 0.95 (0.54–1.69) | 0.870 | 77/244 | 43/229 | **0.60 (0.39–0.90)** | **0.014** |
| Others | 5/170 | 13/303 | 1.43 (0.50–4.09) | 0.506 | 16/403 | 2/70 | 0.71 (0.16–3.15) | 0.647 | 11/244 | 7/229 | 0.68 (0.26–1.77) | 0.426 |
| Clinical stages | | | | | | | | | | | | |
| I + II + 4s | 66/170 | 107/303 | 0.92 (0.64–1.32) | 0.654 | 150/403 | 23/70 | 0.89 (0.53–1.48) | 0.646 | 99/244 | 74/229 | 0.80 (0.56–1.14) | 0.210 |
| III + IV | 70/170 | 93/303 | 0.76 (0.53–1.09) | 0.132 | 148/403 | 15/70 | 0.59 (0.33–1.07) | 0.080 | 95/244 | 68/229 | 0.77 (0.54–1.10) | 0.148 |

AOR, adjusted odds ratio; CI, confidence interval

[a] Adjusted for age and gender, omitting the correspondence factor

[b] Protective genotypes were carriers with rs11037720 AA/AG, rs1048928 TT/TG, rs10768993 GA/AA, rs2292889 CC/CG, and rs2434474 TC/CC genotypes

**Table 5** Stratification analysis for the associations of *YTHDF1* and *YTHDF3* gene polymorphisms with neuroblastoma risk in children from Jiangsu Province

| Variables | *YTHDF1* rs6011668 (cases/controls) | | AOR (95% CI) [a] | *P*[a] | *YTHDF3* rs7464 (cases/controls) | | AOR (95% CI) [a] | *P*[a] |
|---|---|---|---|---|---|---|---|---|
| | CC | CT/TT | | | AA | AG/GG | | |
| Age, month | | | | | | | | |
| ≤ 18 | 96/99 | 43/40 | 1.11 (0.66–1.86) | 0.689 | 77/77 | 62/62 | 1.00 (0.62–1.60) | 0.998 |
| > 18 | 186/253 | 77/81 | 1.29 (0.90–1.86) | 0.167 | 128/187 | 135/147 | 1.34 (0.97–1.86) | 0.075 |
| Gender | | | | | | | | |
| Females | 130/169 | 61/56 | 1.42 (0.92–2.18) | 0.112 | 100/130 | 91/95 | 1.25 (0.85–1.84) | 0.268 |
| Males | 152/183 | 59/65 | 1.09 (0.72–1.65) | 0.677 | 105/134 | 106/114 | 1.19 (0.82–1.71) | 0.365 |
| Sites of origin | | | | | | | | |
| Adrenal gland | 69/352 | 24/121 | 1.01 (0.61–1.68) | 0.963 | 46/264 | 47/209 | 1.28 (0.82-2.00) | 0.274 |
| Retroperitoneal | 113/352 | 54/121 | 1.39 (0.95–2.04) | 0.093 | 91/264 | 76/209 | 1.06 (0.74–1.51) | 0.759 |
| Mediastinum | 87/352 | 33/121 | 1.10 (0.70–1.73) | 0.668 | 55/264 | 65/209 | 1.49 (1.00-2.23) | 0.051 |
| Others | 11/352 | 7/121 | 1.84 (0.70–4.86) | 0.219 | 10/264 | 8/209 | 1.02 (0.40–2.64) | 0.964 |
| Clinical stages | | | | | | | | |
| I + II + 4s | 125/352 | 48/121 | 1.12 (0.76–1.66) | 0.572 | 96/264 | 77/209 | 1.02 (0.71–1.44) | 0.932 |
| III + IV | 109/352 | 54/121 | 1.44 (0.98–2.12) | 0.063 | 79/264 | 84/209 | 1.34 (0.93–1.91) | 0.113 |

AOR, adjusted odds ratio; CI, confidence interval

[a] Adjusted for age and gender, omitting the correspondence factor

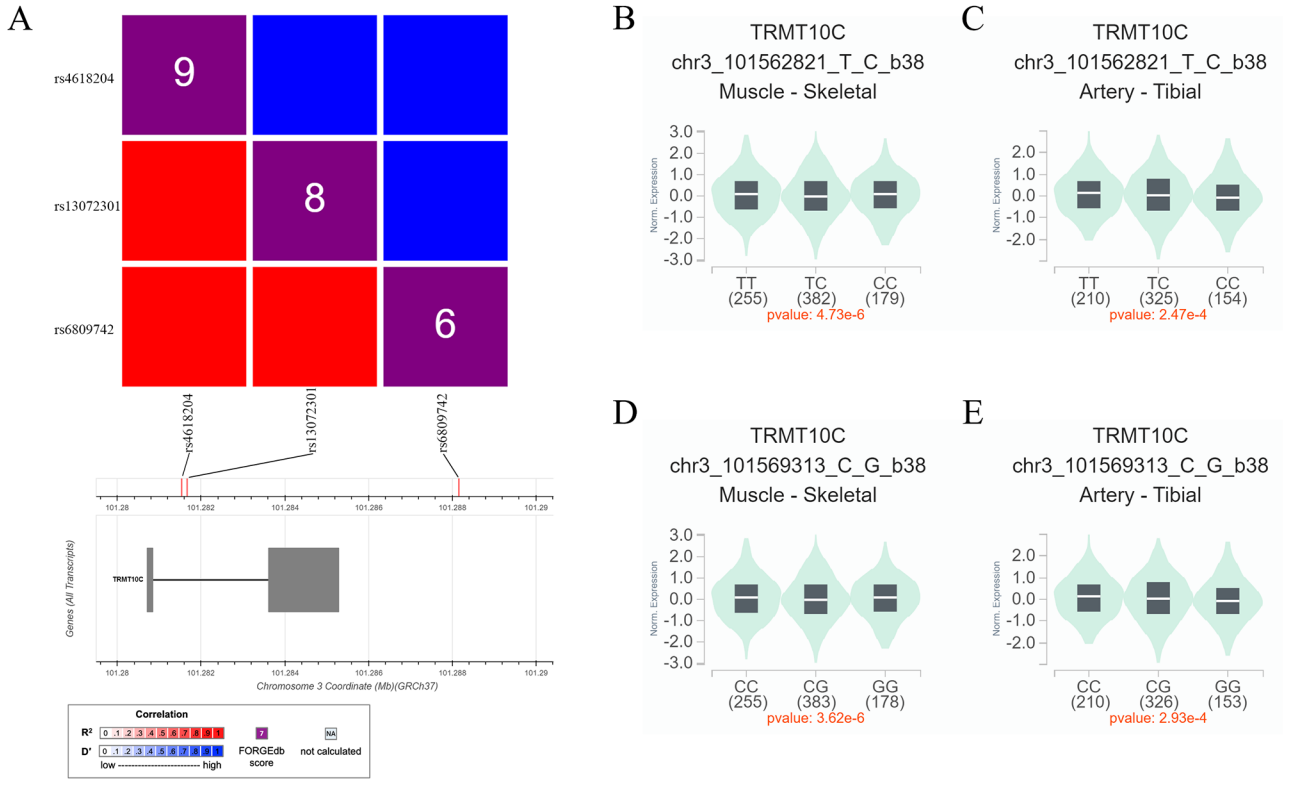



**Fig. 1** Complete linkage analysis and eQTL analysis demonstrated the impact of the *TRMT10C* rs4618204 C > T polymorphism on gene expression. **A**, *TRMT10C* rs4618204 C > T is fully linked to rs13072301 T > C and rs6809742 C > G ($R^2 = 1$). **B**-**C**, rs13072301 T > C is associated with reduced expression of the *TRMT10C* gene in both skeletal muscle ($P = 4.73 \times 10^{-6}$) and tibial artery tissues ($P = 2.47 \times 10^{-4}$). **D**-**E**, rs6809742 C > G significantly decreases *TRMT10C* gene expression in both skeletal muscle ($P = 3.62 \times 10^{-6}$) and tibial artery tissues ($P = 2.93 \times 10^{-4}$)

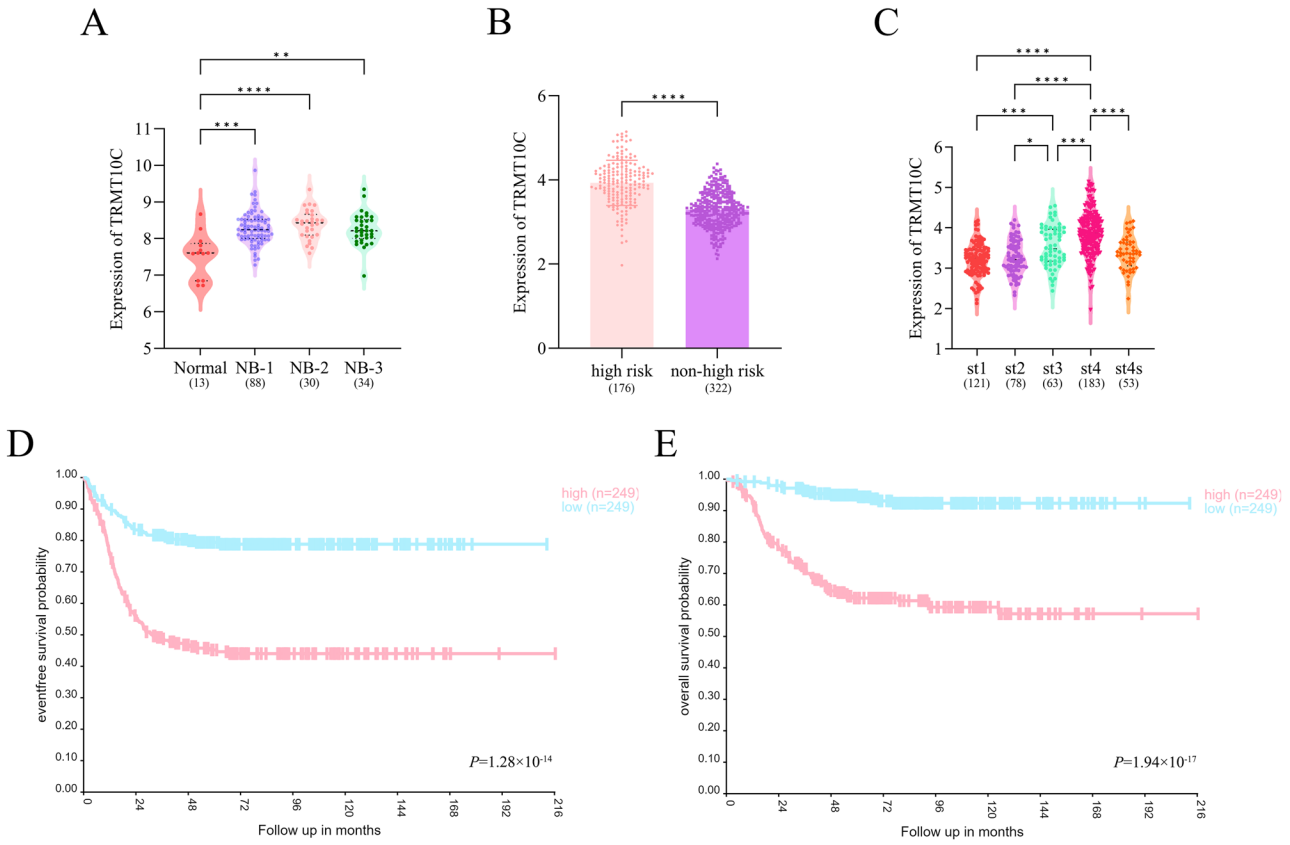



**Fig. 2** The impact of *TRMT10C* gene expression on the risk, invasion, and prognosis of neuroblastoma. **A**, *TRMT10C* gene expression is significantly elevated in neuroblastoma tissues compared with normal adrenal gland tissues. **B**, *TRMT10C* gene expression is significantly elevated in the high-risk neuroblastoma group compared with the non-high-risk group. **C**, *TRMT10C* gene expression is significantly elevated in stage 4 neuroblastoma patients compared with other clinical stage groups. **D**-**E**, Increased expression of the *TRMT10C* gene is significantly associated with reduced event-free survival (EFS) and overall survival (OS) in neuroblastoma patients

rs4618204 C > T is a credible biomarker for neuroblastoma risk.

Our results also suggest that the expression of the *TRMT10C* gene may play an important role in the development and progression of neuroblastoma. The TRMT10C demethylase interacts with SDR5C1 to methylate position 9 of the mitochondrial tRNA [44]. It also catalyzes the formation of $m^1A$ modifications at position 9 of the mitochondrial ND5 mRNA, which play crucial roles in regulating mitochondrial protein translation and function [45]. Metodiev et al. demonstrated that mutations in the *TRMT10C* gene can affect MRPP1 protein stability and mt-tRNA processing, thereby leading to mitochondrial disease [46]. Elevated expression of the *TRMT10C* gene was observed to be associated with poor prognosis in both glioma and HCC patients [47, 48]. The expression level of the *TRMT10C* gene was demonstrated to be positively correlated with the proliferation, colony formation, and migration of both ovarian and cervical cancer cells [49]. Consistent with our findings, previous studies have demonstrated that the *TRMT10C* gene functions as an oncogene. Yu et al. reported via GSEA that the upregulation of the *TRMT10C* gene is associated with cell division and the MYC pathway [37]. Additionally, the downregulation of genes involved in cell division was demonstrated to be the mechanism of cell death induced by *HDAC11* depletion in neuroblastoma cells [50]. As an important member of the MYC family, the *MYCN* gene is frequently amplified in neuroblastoma [51]. Amplification of the *MYCN* oncogene is associated with high-risk neuroblastoma and poor prognosis [52]. Zhu et al. reported that the *MYCN* gene synergizes with the *LMO1* gene to promote the proliferation of adrenal precursor cells, thereby contributing to the development of neuroblastoma [53]. These results suggest that *TRMT10C* may affect the development of neuroblastoma by interacting with cell division and the MYC pathway. The precise molecular mechanisms by which the *TRMT10C* gene influences the onset and progression of neuroblastoma warrant further investigation.

Additionally, stratification analysis revealed that polymorphisms of the *TRMT10C* (rs3762735 C > G), *TRMT6* (rs451571 T > C and rs236110 C > A), and *ALKBH3* (rs10768993 G > A and rs2292889 C > G) genes were

associated with the risk of neuroblastoma in certain subgroups. Liu et al. reported that the rs3762735 C > G polymorphism is associated with increased hepatoblastoma susceptibility [54]. Moreover, Chang et al. reported that the rs236110 C > A polymorphism is associated with an elevated risk of Wilms tumor [55]. In contrast, our findings indicate that this variant may reduce the risk of neuroblastoma in specific subgroups. These observations suggest that the rs236110 C > A polymorphism may exert distinct effects across different types of tumors.

For the first time, we identified a significant association between $m^1A$ modification gene polymorphisms and neuroblastoma susceptibility in Chinese children, along with the underlying involved mechanisms. Our findings provide important molecular markers for the early diagnosis of neuroblastoma and offer insights into its pathogenesis. However, this study has several limitations. First, our study population was derived from Nanjing, China, and further research incorporating samples from a broader geographic distribution is necessary to validate the generalizability of these findings. Second, we did not account for additional environmental factors, which may have resulted in an underestimation of the potential interactions between genetic and environmental factors in the development of neuroblastoma. Third, the use of multiple tests to explore susceptibility loci in neuroblastoma may lead to false-positive results. We adjusted *P* values with the use of the Bonferroni method, which is a more stringent method for adjusting for multiple testing approaches and may lead to nonsignificant associations due to the performance of too many tests. The preliminary positive results require further validation in independent cohorts of neuroblastoma patients and controls. Finally, two SNPs (rs6809742 T > C and rs13072301 C > G) completely linked to rs4618204 C > T were observed to reduce *TRMT10C* gene expression in skeletal muscle and tibial artery tissues via eQTL analysis of the GTEx database. No significant associations were observed between these two SNPs and gene expression in adrenal gland tissues. Further studies are needed to verify the association between rs4618204 C > T and the *TRMT10C* gene in adrenal tissues and explore the specific mechanism affecting neuroblastoma.

## Conclusion

In summary, our findings demonstrate a significant association between the *TRMT10C* gene rs4618204 C > T polymorphism and a reduced risk of neuroblastoma. These results provide an important molecular marker for the early diagnosis of neuroblastoma.

### Abbreviations

| | |
|---|---|
| ALK | Anaplastic lymphoma kinase |
| SNP | Single nucleotide polymorphism |
| GWAS | Genome-wide association study |
| LMO1 | LIM domain only 1 |
| $m^1A$ | $N^1$-methyladenosine |
| HCC | Hepatocellular carcinoma |
| UTR | Untranslated region |
| MAF | Minor allele frequency |
| LD | Linkage disequilibrium |
| HWE | Hardy-Weinberg equilibrium |
| OR | Odds ratio |
| CI | Confidence interval |
| GTEx | Genotype-Tissue Expression |
| eQTL | Expression quantitative trait loci |
| EFS | Event-free survival |
| OS | Overall survival |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-025-00767-0.

Supplementary Material 1

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None.

### Author contributions

All of the involved authors significantly contributed to this research. Jiaming Chang, Lei Lin, Wenli Zhang, Yan Zou, and Jing He: study design; data analysis; table and figure preparation; original article writing; and final approval of the article. Jiaming Chang, Wenli Zhang, Xinxin Zhang, and Jing He: funding acquisition. Chunlei Zhou: sample and data collection; and final approval of the article. Jiliang Yang, Mengzhen Zhang, Huimin Yin, and Xinxin Zhang: DNA extraction; TaqMan genotyping; and final approval of the article.

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### Data availability

All of the data are available upon request.

## Declarations

### Human ethics and consent to participate declarations

The research scheme was approved by the institutional review board of Children's Hospital of Nanjing Medical University (Approval No: 202112141-1). In accordance with the guidelines of the Declaration of Helsinki, each participant provided written informed consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Author details

[1]Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou 510623, Guangdong, China
[2]Department of Pathology, Children's Hospital of Nanjing Medical University, Nanjing 210008, Jiangsu, China

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