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ORIGINAL ARTICLE

Gout in males: a possible role for *COMT* hypomethylation

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Abstract

Objective Gout is a common inflammatory disease, and the prevalence of gout in men is significantly higher than in women. Catechol-O-methyltransferase (COMT) regulates dopamine activity and metabolism, thereby participating in the uric acid metabolism, which in turn affects the occurrence of gout. Our study aimed to investigate the association between *COMT* methylation and gout in men.

Methods This study involved 57 male gout patients and 103 age-matched healthy men. We used quantitative methylation-specific polymerase chain reaction (qMSP) to determine DNA methylation levels in the blood. The *COMT* methylation level was represented by the percentage of methylation reference (PMR).

Results Our results showed that *COMT* methylation levels were significantly lower in gout patients than in the control group (median PMR 9.50 vs 31.34, $p = 3E\text{-}5$). The area under the curve (AUC) was 0.701 (95% CI 0.611–0.790, $p = 2.7E\text{-}5$) with a sensitivity of 68% and a specificity of 68.4%.

Conclusion Our study found that there was a significant correlation between *COMT* hypomethylation and the risk of gout in males, and this provides an epigenetic mechanism of *COMT* in gout. *COMT* hypomethylation might be used as a potential diagnostic biomarker for gout in the future.

Keywords Catechol-O-methyltransferase · DNA methylation · Gout · Male · Promoter

Introduction

Gout is a common inflammatory disease that is featured with chronic deposition of monosodium urate (MSU) crystals [1]. Clinical features of gout include tophi, chronic gouty arthritis, destructive joint disease, and acute recurrence of severe inflammatory arthritis [2]. Gout can develop into a variety of chronic diseases, including hypertension, hyperlipidemia, obesity, kidney disease, and cardiovascular disease, but the direct causal relationship between uric acid and these diseases is unclear [3–5].

Previous studies have shown that there are at least two possible mechanisms for the development of gout. The first mechanism involves the dopaminergic system [6], which plays an important role in regulating blood pressure, sodium balance, and renal function; the second one is associated with dopamine degradation. Dopamine regulates renal function [6], induces glomerular filtration [7], and subsequently reduces uric acid levels and excretion rates [7]. Dopamine degradation may increase the reabsorption of sodium and urate, eventually leading to gout [7–9].

Human *COMT* gene encodes catechol-O-methyltransferase (COMT), which is widely expressed and modulates renal dopamine activity [10]. *COMT* is most expressed in the liver and kidney, and high expression of *COMT* in renal epithelial cells is thought to indirectly regulate the metabolism of dopamine and other catecholamines [11]. Studies have shown that rs4680 (Val158Met) of *COMT* protects from gout and may affect gout by regulating dopamine levels [12]. However, in another study in Taiwan aboriginal Chinese, *COMT* Val158Met was found to be unrelated to gout [13].

COMT methylation has been reported to be associated with coronary heart disease [14] and schizophrenia [15]. *COMT* methylation was found to be inversely correlated with *COMT* mRNA expression in human cell lines [16]. *COMT* hypomethylation predicts an increase in *COMT* expression and decreases the complement level of frontal dopamine in the carriers of *COMT* Met158 allele [16]. The regulation of

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COMT expression is complex and may depend on a variety of factors and interactions, including the *COMT* Val158Met genotype, DNA methylation, and a range of other biological and environmental factors [16]. However, the relationship between *COMT* methylation and gout remains unknown.

The prevalence of gout in men is significantly higher than that in women in many countries, and the ratio of men to women is generally between 3 and 4:1 [17]. The large differences in the risk of men and women may be primarily related to the role of estrogen in promoting uric acid (UA) excretion, as studies have shown that the use of hormone replacement therapy can reduce the risk of gout during menopause [18]. In this study, we selected male individuals and investigated the relationship between *COMT* methylation and gout.

Materials and methods

Subjects

The study included 57 male gout patients and 103 healthy male patients from Ningbo Second Hospital. All gout patients were diagnosed according to the American College of Rheumatology criteria [19]. The blood samples were collected from patients before medical treatment. The age distribution of the cases was 51.52 ± 14.27 years, and the age distribution of the controls was 50.15 ± 11.94 ($p = 0.454$). Plasma levels of various biochemical factors were measured by the method described in the previous study [20, 21], including glutamic-pyruvic transaminase (ALT), glutamic oxalacetic transaminase (AST), creatinine (CRE), UA, blood glucose (Glu), cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG). The research protocol was approved by the Ethics Committee of Ningbo University. All participants signed an informed consent form.

DNA methylation assay

The details of blood DNA separation and subsequent bisulfite conversion were as previously described [22]. The methylation level of *COMT* was measured using a quantitative methylation-specific polymerase chain reaction (qMSP). The primer sequences of *COMT* were 5′-GGTGTAGTTAGTAT AGTAGGATT-3′ (forward primer) and 5′-CCAC ATACGACCTCTTA-3′ (reverse primer), respectively. The forward primer sequence of the reference gene (ACTB) was 5′-TGGTGATGGAGGAGGTTTAGTAAGT-3′, and its reverse primer sequence was 5′-AACCAATAAAACCT ACTCCTCCCTTAA-3′. Details of qMSP can be found in our previous publication [23]. The percentage of methylation reference (PMR) was calculated as: $\mathrm{PMR} = 2^{-(\mathrm{Ct\ sample} - \mathrm{Ct\ internal\ reference})} \times 100\%$ [24].

Bioinformatics data for *COMT* methylation and *COMT* expression

We extracted 413 *COMT* methylation and *COMT* expression data from TCGA database (http://www.cbioportal.org/) to test their correlation. We also downloaded *COMT* expression in LCA and C2C12 cell lines treated with and without demethylation reagents (5′-AZA-deoxycytidine) from the Gene Expression Synthesis (GEO) database (GSE30192) to check whether decreased *COMT* methylation was able to upregulate *COMT* expression.

Statistical analysis

Nonparametric test was used to compare *COMT* methylation between cases and controls. The Spearman rank correlation coefficient was used to quantify the relationship of *COMT* methylation with metabolic characteristics and *COMT* expression. Gene expression in cell lines treated with and without the demethylating agent 5′-AZA-deoxycytidine was compared using a paired sample *T* test. $p < 0.05$ was considered statistically significant.

Results

In this study, we recruited 57 Chinese male gout patients and 103 healthy male controls to investigate the role of *COMT* promoter methylation in gout. Among the 11 clinical phenotypes, ALT, UA, cholesterol, TG, WBC, AST, and Glu were found to be significantly higher in gout cases than in controls (all $p < 0.05$, Table 1).

In the current study, we selected a fragment (hg19: chr22: 19,941,454–19,941,583, Fig. 1) for the methylation assay in the CpG island of the *COMT* promoter. Our results showed that *COMT* methylation levels were significantly lower in gout patients than in the control group (median PMR 9.50 vs 31.34, $p = 3E\text{-}5$, Fig. 2). The area under the curve (AUC) was 0.701 (95% CI 0.611–0.790, $p = 2.7E\text{-}5$, Fig. 3) with a sensitivity of 68% and a specificity of 68.4%.

The relationship between *COMT* methylation and baseline characteristics was tested by Spearman correlation test. In gout patients, our results showed a trend that *COMT* methylation levels were positively correlated with age and glucose levels (age $r = 0.206$; Glu $r = 0.203$), and *COMT* methylation levels were inversely correlated with LDL levels ($r = -0.225$). Aging is closely associated with increased risk of hyperuricemia and gout [25], and several studies have observed that the prevalence of gout or serum uric acid increases with age [26, 27]. Type 2 diabetes has been reported to be associated with an increased risk of gout [28–30]. Both population study and animal model study have shown that hyperuricemia may play a role in insulin and glucose disorders [31]. LDL is

Table 1 Baseline characteristics of all the subjects

Characteristics	Cases ($n = 57$)	Controls ($n = 103$)	p value
Age (years)	52.79 ± 14.56	50.15 ± 11.94	0.217
ALT (U/L)	40.40 (21.00, 44.50)	22.83 (17.00, 26.00)	*< 0.001*[a*]
AST (U/L)	29.79 (20.00, 38.00)	22.70 (18.00, 27.00)	*0.021*[b*]
CRE (μmol/L)	80.16 ± 15.37	77.83 ± 9.77	0.243
UA (μmol/L)	426.51 ± 144.93	344.41 ± 67.15	*< 0.001*[*]
Glu (mmol/L)	5.70 (4.82, 5.79)	5.00 (4.72, 5.25)	*0.005*[a*]
Cholesterol (mmol/L)	5.00 ± 1.34	4.42 ± 0.67	*< 0.001*[*]
HDL (mmol/L)	1.21 ± 0.34	1.51 ± 0.36	0.997
LDL (mmol/L)	2.60 ± 1.05	2.60 ± 0.52	0.553
TG (mmol/L)	2.52 ± 1.46	1.15 ± 0.47	*< 0.001*[b*]
WBC (10^9/L)	9.29 ± 3.31	6.40 ± 1.56	*< 0.001*[*]

*p value less than 0.05 was in italic. [a] Log-transformation was used. [b] Nonparametric rank test was applied. *ALT*, glutamic-pyruvic transaminase; *AST*, glutamic oxalacetic transaminase; *CRE*, creatinine; *UA*, uric acid; *Glu*, blood glucose; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *TG*, triglyceride; *WBC*, white blood cell

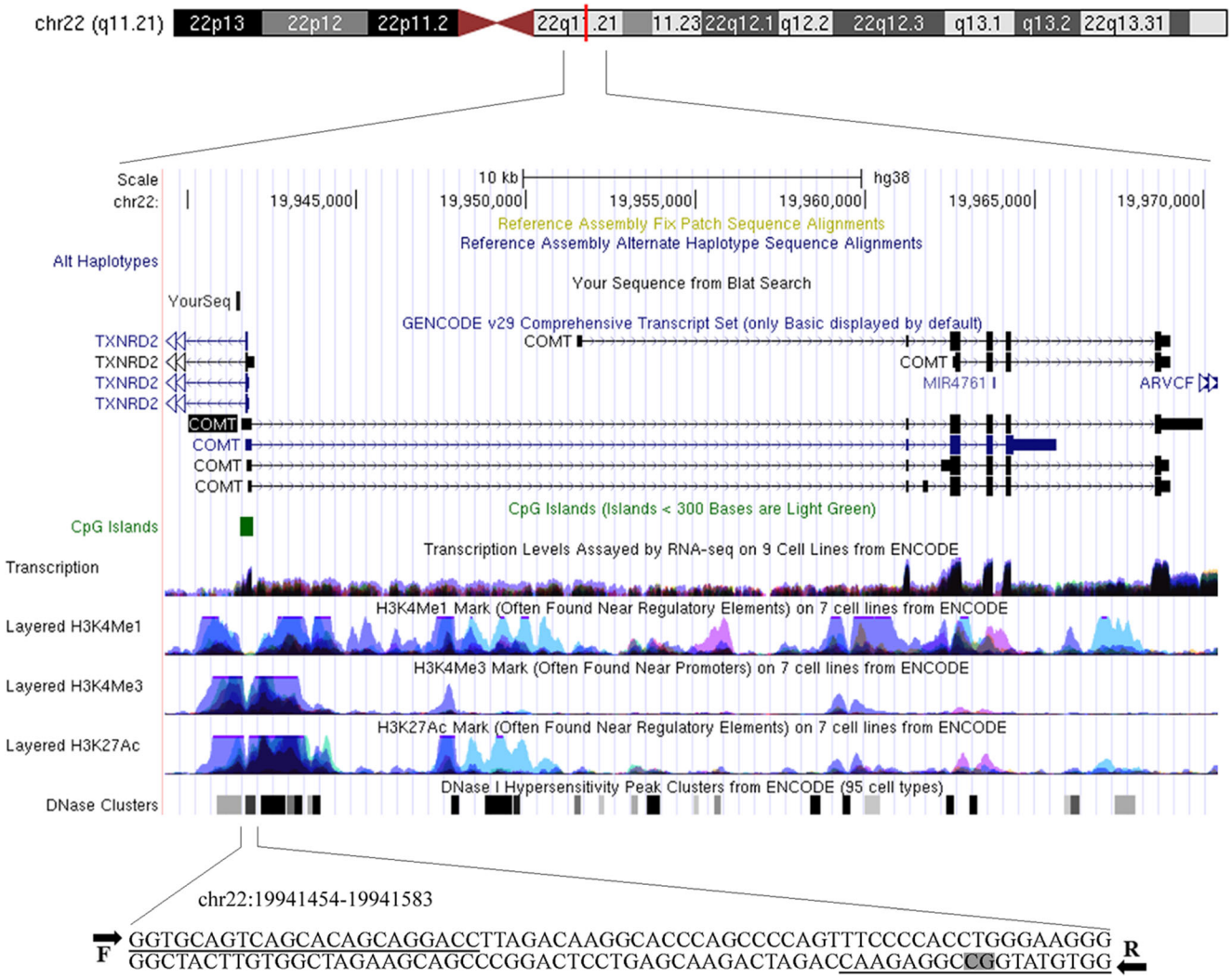

Fig. 1 The selected fragment of *COMT* in the methylation assay. Genomic positions and function annotations were obtained from UCSC genome browser according to human 2009 (GRCh37/hg19) assembly. F and R were forward and reverse primers, respectively. The quantitative methylation-specific polymerase chain reaction (qMSP) primers were underlined, and CpG on the reverse primer was in gray

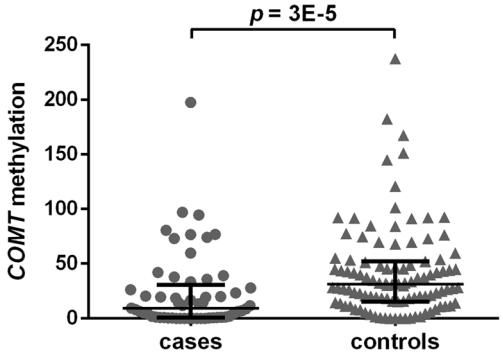

Fig. 2 Comparison of *COMT* methylation levels between gout cases and controls. *COMT* methylation was significantly lower in gout patients than in controls (median PMR 9.50 (0.93, 30.92) vs 31.34 (15.61, 51.92), p = 3E-5, Nonparametric rank test)

often oxidized to ox-LDL in a long-term oxidative environment [32]. Studies have found that ox-LDL levels in gout patients are significantly higher than healthy controls, and the changes in ox-LDL levels may be associated with increased inflammation in gout patients [33]. An increase in LDL levels and a decrease in HDL levels were also found in gout patients [34]. In addition, previous studies have shown that the Val158Met polymorphism of *COMT* is associated with LDL levels in plasma [35, 36]. Our results suggest that the level of *COMT* methylation is inversely correlated with LDL in gout patients, suggesting that LDL is a complex trait, and that both genetic and epigenetic factors are needed to study the relationship between *COMT* and LDL in the future. In the healthy controls, our results showed positive correlations of *COMT* promoter methylation with both age and TG levels (age $r = 0.249$, $p = 0.011$; TG $r = 0.244$, $p = 0.013$). In contrast, an inverse correlation was observed between *COMT* methylation and HDL levels ($r = -0.265$, $p = 0.007$). To note, we did not perform a correction for multiple comparisons, and thus there is a chance of false positive results for the above findings. In addition, *COMT* methylation was not significantly associated with other biochemical indicators (all $p > 0.05$, data not shown).

Our analysis of TCGA data showed a significant inverse correlation between methylation and expression of *COMT* (Spearman rank correlation test, $r = -0.521$, p = 8E-30, Fig. 4). Meanwhile, our analysis of GEO data showed that 5′-AZA-deoxycytidine treatment significantly increased *COMT* expression (mean fold change = 1.41, $p = 0.003$, Fig. 5), suggesting that *COMT* expression can be induced by demethylating agent.

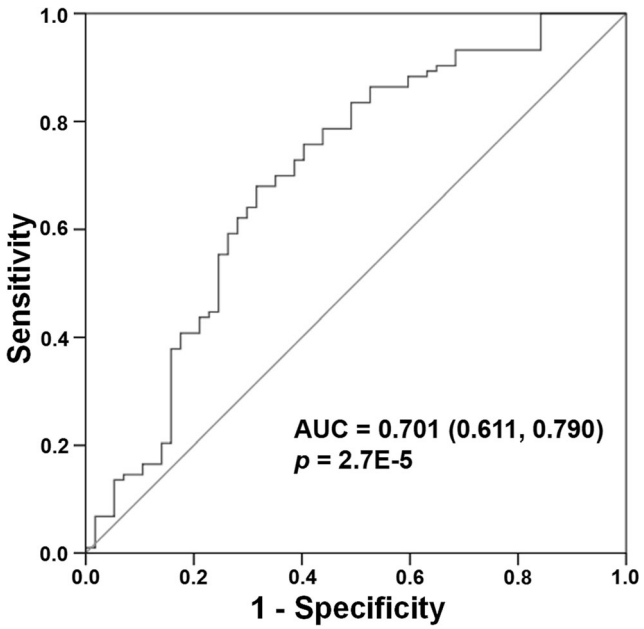

Fig. 3 Receiver operating characteristic (ROC) curve of *COMT* promoter hypomethylation for gout. The area under the curve (AUC) was 0.701 (95% CI 0.611–0.790, p = 2.7E-5) with a sensitivity of 68% and a specificity of 68.4%

Discussion

In this study, we found that *COMT* methylation in gout cases was significantly lower than in the matched controls. The ROC curve suggested that *COMT* hypomethylation was a potential biomarker for gout. In addition, there was a significant correlation between *COMT* methylation and several phenotypes such as HDL levels in controls. All the above findings suggested that *COMT* hypomethylation might be critical for gout development.

COMT is the major enzyme of catecholamine neurotransmitters (including dopamine, norepinephrine, and epinephrine), which degrades catecholamine neurotransmitters by enzymatic O-methylation of a single hydroxyl group in the catecholamine motif [37]. *COMT* is abundantly expressed in the

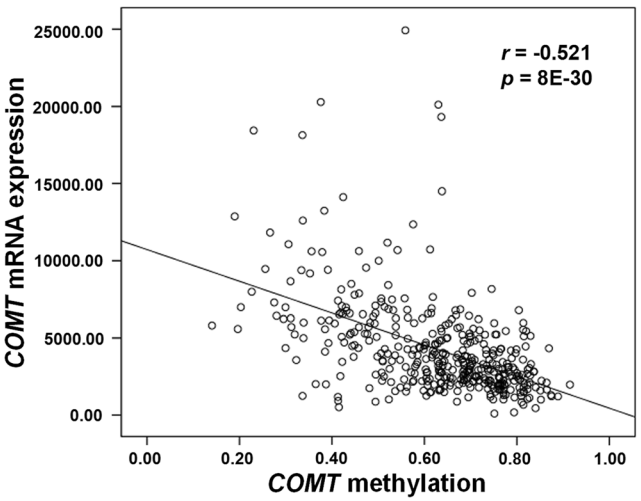

Fig. 4 Inverse correlation between *COMT* methylation and *COMT* expression in 413 individuals from TCGA dataset. The methylation and expression of *COMT* were significantly inversely correlated ($r = -0.521$, p = 8E-30, Spearman rank correlation test)

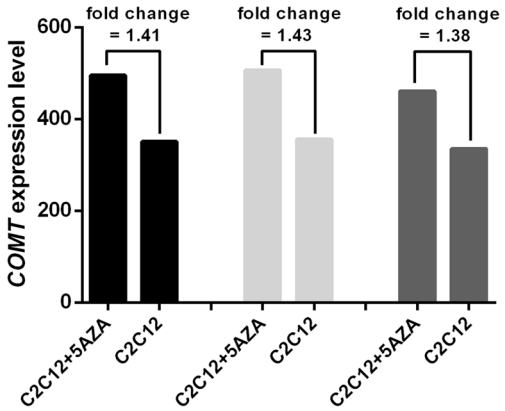

Fig. 5 5′-aza-deoxycytidine treatment increased *COMT* expression. Our results showed C2C12 cell lines with 5′-aza-deoxycytidine treatment had a significantly higher *COMT* expression than those without treatment (average fold change = 1.41, $p = 0.003$, paired-samples t test). The data of *COMT* expression was retrieved from the GEO database (GSE30192)

kidney and plays an important role in dopamine metabolism, especially in the action of the natriuretic peptide of the renal dopamine system [11]. Dopamine-induced glomerular filtration was inversely associated with uric acid concentration and uric acid excretion [7]. Renal uric acid transport plays an important role in the acquisition of factors affecting UA [38]. UA is above the saturation threshold and produces MSU crystals in and around the joints, which is the result of gout after long-term hyperuricemia [39].

Gout patients often have acute inflammatory reactions induced by MSU crystals, and the induced inflammation by gout were mainly mediated by macrophages and neutrophils [40]. In our study, we observed a significant increase in blood leukocytes of gout patients, suggesting a significantly high inflammatory response in our gout patients.

Gout is a complex disease that is often linked to the higher incidence of depression. It is reasonable that some biomarkers of gout might be also linked to other diseases or disorders. Our results showed that *COMT* methylation levels were significantly lower in gout patients than in the control group (median PMR 9.50 vs 31.34, $p = 3E\text{-}5$). The area under the curve (AUC) was 0.701 (95% CI 0.611–0.790, $p = 2.7E\text{-}5$) with a sensitivity of 68% and a specificity of 68.4%.

The moderate specificity of *COMT* methylation in the detection of gout might be due to the potential effect of diverse cellular distribution on gene methylation in whole blood. In acute gout, the natural killer cells emerge as mediator of inflammation [41]. In the blood of gout patients, shorter telomeres were found compared to those in healthy participants, indicating increased cellular senescence in the blood [42]. All the above evidence suggests that the distribution of cellular subsets in blood is likely to be different between gout patients and healthy controls. In the current study, we detected *COMT* methylation in peripheral blood DNA that comes from a variety of cells, such as granulocytes and lymphocytes. Researchers suggested that DNA methylation based-association tests in whole blood should be adjusted by a set of methylation makers to avoid the impact of cellular composition [43]. DNA from a mixture of cells in the blood may affect the specificity of methylation detection to some extent.

Vitamin D levels were reduced in plasma from gout patients [44], and a significant reduction in catechol-o-methyltransferase (COMT) was observed in vitamin D-deficient neonatal rats [45]. There are three VDR binding regions in the *COMT* promoter region, which can be enriched with 1,25-dihydroxyvitamin D, the biologically active form of vitamin D [45]. And this strongly suggests that vitamin D directly regulates the expression of *COMT* [45]. Moreover, recent work has shown that the risk of depression in gout patients increased by 19% [46], especially in elderly gout patients, who had a 42% increased risk of depression [47]. It is known that the main symptoms of depression consist of decreased levels of extracellular dopamine [48]. COMT is an enzyme involved in the degradation of dopamine that affects dopamine levels especially in the prefrontal cortex [49]. The *COMT* Val158Met polymorphism (rs4680) has been reported to be associated with depression [50]. Individuals with the *COMT* Val allele have higher activity of COMT and lower baseline dopamine levels [51] compared to individuals with the *COMT* Met allele. However, the association results between depression and *COMT* Val158Met polymorphism are sometimes contradictory, and this may be due to ethnic differences [52]. *COMT* Val158Met was found to play a protective role in the development of gout In Chinese population [12], and this positive association was not validated in Taiwan's aborigines [13]. No studies have been found between *COMT* methylation and gout. Our study found that there was a significant correlation between *COMT* hypomethylation and the risk of gout in males, and this provides an epigenetic mechanism of COMT in gout. In the future, we need to further study whether there are interactions of the *COMT* promoter methylation with *COMT* Val158Met polymorphism and the regulation of vitamin D.

There are some shortcomings in our research. First of all, previous study showed that *COMT* polymorphisms were associated to gout in Chinese patients [12]. Due to the moderate sample size in our study, future work with more samples is needed to explore whether *COMT* polymorphisms may interact with *COMT* methylation in the contribution of *COMT* to gout. In addition, although TCGA and GEO data analysis confirmed that *COMT* hypomethylation was associated with high expression of *COMT*, future work needs to validate the association of *COMT* hypomethylation with gene expression. Meanwhile, though the CpG site in the current methylation study is likely to represent the CpGs in the surrounding region, it is necessary to further determine the methylation of other

regions of *COMT*. Lastly, but not least, we used peripheral blood in this study to identify molecular markers for in vitro diagnosis of gout risk. Future work on renal epithelial cells is needed to explore the relevant mechanisms of *COMT* methylation.

For the first time our study revealed the relationship between *COMT* hypomethylation and increased risk of gout in men. Our findings might also provide an epigenetic clue of COMT enzyme in gout.

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Compliance with ethical standards

Disclosures None.

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