

Modulatory effect of plasma folate and polymorphisms in one-carbon metabolism on catecholamine methyltransferase (COMT) H108L associated oxidative DNA damage and breast cancer risk

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The present study was aimed to investigate the modulatory role of plasma folate and eight putatively functional polymorphisms of one-carbon metabolism on catecholamine methyltransferase (COMT)-mediated oxidative DNA damage and breast cancer risk. Plasma folate and 8-oxo-2'-deoxyguanosine (8-oxodG) were estimated by commercially available kits, while polymorphisms were screened by PCR-RFLP and PCR-AFLP methods. COMT H108L polymorphism showed independent association with breast cancer (OR: 1.73, 95% CI: 1.31-2.30). No significant interaction was observed between folate status and COMT genotype. Multifactor dimensionality reduction (MDR) analysis gave evidence for the significant epistatic (gene-gene) interactions ($p < 0.0001$) of COMT H108L with reduced folate carrier 1 (RFC1) G80A, thymidylate synthase (TYMS) 5'-UTR 3R2R, TYMS 3'-UTR ins6/del6. Increased plasma 8-oxodG were observed in cases compared to controls (mean \pm SE: 5.59 \pm 0.60 vs. 3.50 \pm 0.40 ng/ml, $p < 0.004$). Plasma folate deficiency alone was not a significant predictor of 8-oxodG elevation. The genotype combinations namely, RFC1 G80A/methionine synthase reductase (MTRR) A66G, RFC1 G80A/SHMT C1420T/TYMS 3R2R and serine hydroxymethyltransferase (SHMT) C1420T/TYMS 3R2R/methionine synthase (MTR) A2756G/COMT H108L were strong predictors of 8-oxodG elevation in the order of risk. To conclude, the current study provides substantial evidence for a cross talk between one-carbon metabolism and COMT catalysis that might influence oxidative DNA damage and breast cancer risk.

Keywords: Catechol-O-methyltransferase (COMT), 8-Oxo-2'-deoxyguanosine (8-oxodG), One-carbon metabolism, Oxidative DNA damage, Breast cancer, Polymorphism, Plasma folate.

The etiology of breast cancer is complex involving genetic, nutritional, environmental and epigenetic factors. Most of the established risk factors, including age at menarche and menopause, age at first full-time pregnancy as well as the number of parturitions indicate association between cumulative estrogen exposure and breast cancer. Estrogens can potentially

induce carcinogenesis i) by stimulating the transcription of genes necessary for cell proliferation via the estrogen receptor, and ii) by causing oxidative DNA damage via their catechol estrogen metabolites^{1,2}. This later pathway popularly known as xenobiotic pathway has two phases i.e. phase I and II that catalyze the generation of electrophiles and their detoxification, respectively (Fig. 1).

Phase I enzymes namely cytochrome P450 (CYP) 1A1 and CYP1B1 catalyze the oxidation of 17 β -estradiol (E2) and estrone (E1) to the 2- and 4-catechol estrogens and 16- α hydroxyestrogen^{3,4}, which on further oxidation generate highly reactive semiquinones and quinones^{5,6}. They interact with DNA to form adducts, leading to oxidative DNA damage, an important event in the molecular pathophysiology of human cancers^{7,8}. On the other hand, phase II enzymes catecholamine methyltransferase (COMT) and glutathione S-transferase (GST) inactivate the toxic effects of phase I

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Abbreviations: AFLP, amplified fragment length polymorphism; COMT, catechol-O-methyltransferase; cSHMT, cytosolic serine hydroxymethyltransferase; GCPII, glutamate carboxypeptidase II; MDR, multifactor dimensionality reduction analysis; MTHF, methylene tetrahydrofolate; MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase; MTRR, methionine synthase reductase; 8-oxodG, 8-Oxo-2'-deoxyguanosine; PCR, polymerase chain reaction; RFC1, reduced folate carrier 1; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; tHcy, total plasma homocysteine; THF, tetrahydrofolate; TYMS, thymidylate synthase.

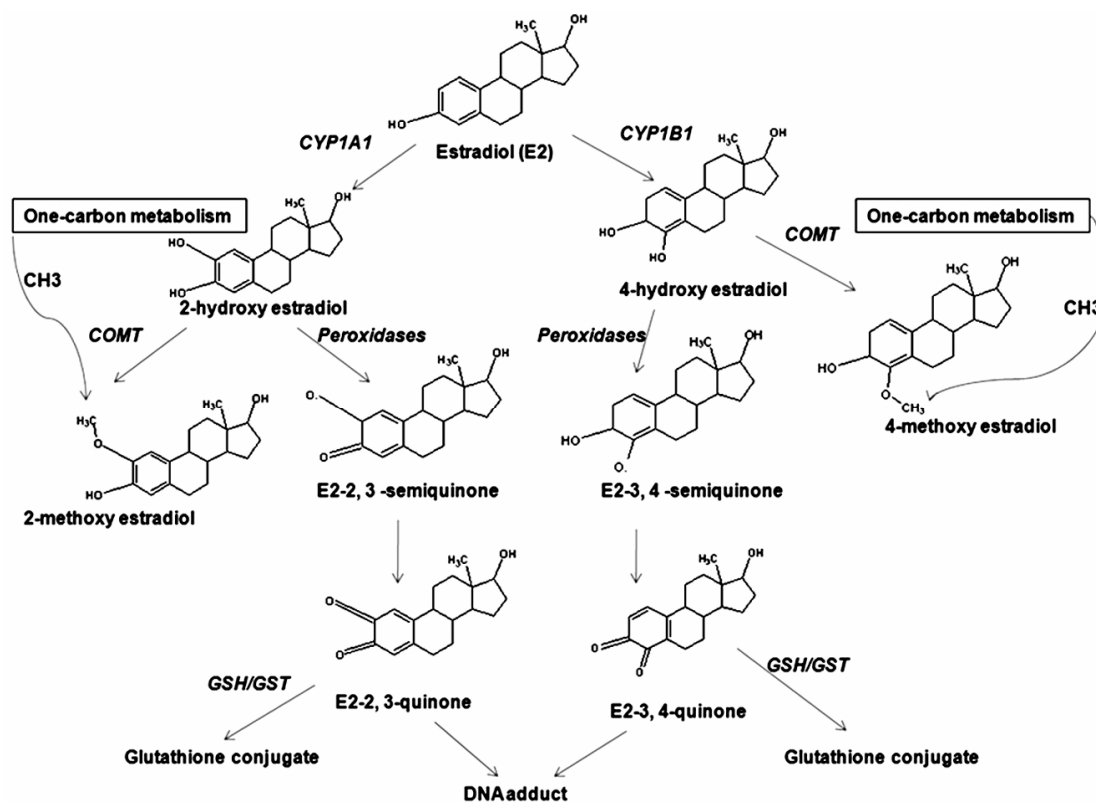


Fig. 1—Xenobiotic metabolic pathway [CYP1A1 and CYP1B1 enzymes catalyze the hydroxylation of estradiol at 2- and 4-positions respectively, thus generating catechol estrogens. Catechol estrogens are converted to semiquinone and quinone in the presence of peroxidases. Semiquinones/quinones form DNA adducts leading to 8-oxodG lesions in DNA and depurination. The catechol estrogens are detoxified at two levels: i) by O-methylation in presence of COMT by accepting methyl group from one-carbon metabolism leading to the formation of methoxy estrogens or ii) by conjugating with glutathione (GSH) in the presence of glutathione S-transferases (GSTs)]

metabolites i) through O-methylation of 2- and 4-catechol estrogens to 2- and 4-methoxyestrogens^{6,9}, ii) through conjugation of semiquinones and quinones with glutathione, respectively. The former reaction depends on the availability of methyl group from S-adenosylmethionine (SAM), a product of one-carbon metabolism. Methoxyestrogens are more lipophilic, have longer half-lives than their corresponding catecholestrogens, have a weak or no binding affinities to the classical estrogen receptor⁶, and inhibit endothelial cell proliferation, migration and angiogenesis¹⁰.

The potential toxicity of catechol estrogens and anti-cancer properties of methoxyestrogens have prompted the researchers to hypothesize that decrease in COMT activity might be detrimental, leading to breast cancer risk. The activity of COMT is found to vary among individuals, and lower activity and low thermal stability was attributed to Val108/158Met single nucleotide polymorphism (SNP) (A to G change at position 1947 rs4680)^{11,12}. The high activity thermostable form (Val) is termed as H, while the low

activity thermolabile form is termed as L (H108L), where 108 and 158 codons represent the same allele in soluble and membrane bound forms of COMT.

Low activity or inhibition of COMT is reported to increase levels of depurinating estrogen-DNA adducts that induce mutations and initiate cancer¹³. L-Allele has shown strong association with ER-positive breast cancer than ER-negative in Japanese population¹⁴. LL-genotype has been found to increase the risk for breast cancer among the post-menopausal Chinese women¹⁵, while no association is observed in a study from USA¹⁶. In a multi-ethnic study, ethnic differences have been observed in the COMT-associated breast cancer risk¹⁷. The factors that contribute to the inconsistencies in association studies could be due to i) variations in the availability of folate or methyl moieties, and ii) variability in CYP1A1 and CYP1B1 polymorphisms, which in turn affect COMT catalysis either by comprising the availability of the substrate or by overproduction of catechol estrogens. Yadav et al¹⁸ have demonstrated modulatory effect of CYP1B1 Leu432Val on COMT

genotype by observing protection against breast cancer among subjects with CYP1B1 wild/COMT heterozygous; and CYP1B1 heterozygous/COMT wild genotype. Goodman *et al.*¹⁹ have observed increased breast cancer risk with the increase in the number of COMT L alleles in women with below median levels of folate or above median levels of homocysteine.

Based on the existing literature, we hypothesized that any perturbation in one-carbon homeostasis may influence the COMT genotypes in modulating the breast cancer risk. To prove this hypothesis, we have tested whether COMT H108L exerts independent effect or it interacts with certain combinations of genetic variations in one-carbon metabolism/co-factors in modulating the breast cancer risk. The primary end point for this risk prediction model being the disease status itself, whereas the secondary end point measured is 8-oxodG to ascertain the initial triggers that drive to mutagenesis.

Materials and Methods

A case-control study was designed comprising of 212 breast cancer cases and 243 controls. The recruitment took place at Nizam's Institute of Medical Sciences, Hyderabad, India during the study period from January 2009 to August 2010. The inclusion criteria for cases were: mammographic and histopathological confirmation of diagnosis of breast cancer and age between 20 to 80 yrs; and for controls no history of benign or malignant breast disease. The exclusion criteria were: history of any other cancer or inflammatory disease. Personal interviews were conducted by trained interviewer to record demographic data, life style risk factors, food frequency questionnaire (FFQ) and reproductive history.

Special emphasis was given on parameters related to cumulative estrogen exposure. These parameters included age, age of menarche, age at first full term pregnancy, parity, use of oral contraceptives, menopause, hormone replacement therapy, etc. The study was approved by the institutional ethical committee of Nizam's Institute of Medical Sciences, Hyderabad, India. Informed consent was obtained from all the subjects of the study group prior to enrollment.

Sample collection

Whole blood samples were collected in EDTA vacutainers and plasma was separated immediately by centrifugation. Genomic DNA was isolated from the buffycoat using the standard protocols.

Biochemical analysis

Plasma samples were used to measure folate and 8-oxo-2-deoxyguanosine (8-oxodG). Commercial kits were used for the estimation of folate (Axsym, Abott Laboratories, USA) and 8-oxodG (Northwest Life Sciences Specialities, USA).

Genetic analysis

COMT H108L polymorphism

A 238-bp band from exon 4 of COMT was amplified using specific primers i.e. 5'-GCC CGC CTG CTG TCA CC-3 and 5'-CTG AGG GGC CTG GTG ATA GTG-3'. Each 25 μ L of PCR mixture was composed of 100 ng genomic DNA, 2.5 μ L 10x PCR buffer [50 mM KCl, 10 mM Tris-HCl (pH: 9.0), 1.5 mM MgCl₂], 0.2 mM of deoxynucleoside triphosphate, 10 pmoles of each primer and 1 unit of Taq DNA polymerase. PCR conditions were: initial denaturation, 95°C for 10 min; denaturation, 95°C for 30 s; annealing, 60°C for 30 s; extension, 72°C for 30 s; number of cycles, 30. To test for the polymorphism, 20 μ L of PCR product was digested with 1 unit of NlaIII restriction enzyme in 1x buffer. Presence of the COMT 108L variant allele created an additional NlaIII restriction site. 114 bp representing uncut allele indicates H variant while its cleavage into 96 bp and 18 bp indicates L variant. 70 bp and 54 bp bands are constant and serve as internal controls of efficiency of NlaIII digestion.

Analysis of functional polymorphisms in one-carbon metabolism

PCR-AFLP approach was used for the analysis of thymidylate synthase (TYMS) 5'-UTR 28 bp tandem repeat polymorphism. PCR-RFLP approaches were used for the analysis of glutamate carboxypeptidase II (GCPII) C1561T, reduced folate carrier 1 (RFC1) G80A, cytosolic serine hydroxymethyltransferase (cSHMT) C1420T, TYMS 3'-UTR ins6/del6, methylene tetrahydrofolate reductase (MTHFR) C677T, methionine synthase (MTR) A2756G and methionine synthase reductase (MTRR) A66G polymorphisms (Table 1).

Statistical analysis

Student's t-test was used for comparing the biochemical parameters between the two groups, while analysis-of-variance (ANOVA) was used for comparing the distribution of biochemical parameters across more than two groups. Fisher's exact test was used to obtain odds ratios (ORs) and confidence

Table 1—Reaction conditions for PCR based genetic analysis

| Polymorphism | Primers (5'-.....-3') | PCR Conditions | Restriction enzyme | Restriction site |
|----------------------------------|------------------------------------------------------------------------------------|-------------------------------------------|--------------------|------------------|
| GCP II C1561T × 35 | CAT TCT GGT AGG AAT TTA GCA AAA CAC CAC CTA TGT TTA ACA | D:95°/30s A:50°/30s E:72°/30s | Acc I | + (T allele) |
| RFC1 G80A × 30 | AGT GTC ACC TTC GTC CCC TC CTC CCG CGT GAA GTT CTT | D:95°/1 min A:59°/1 min E:72°/1 min | Hha I | - (A allele) |
| cSHMT C1420T × 35 | GTG TGG GGT GAC TTC ATT TGT G GGA GCA GCT CAT CCA TCT CTC | D:95°/30s A:56°/30s E:72°/30s | Ear I | + (C allele) |
| TYMS 5'-UTR (AFLP) × 35 | CGT GGC TCC TGC GTT TCC GAG CCG GCC ACA GGC AT | D:95°/30s A:62°/30s E:72°/45s | AFLP | AFLP |
| TYMS 3'-UTR Ins6/del6 × 30 | CAAATCTGAGGGAGCTGAGT CAGATAAGTGGCAGTACAGA | D:95°/30s A:58°/45s E:72°/45s | DraI | - (del6) |
| MTHFR C677T × 30 | TTT GAG GCT GAC CTG AAG CAC TTG AAG GAG GAG TGG TAG CCC TGG ATG GGA AAG ATC CCG | D:95°/1 min A:60°/1 min E:72°/1 min | Hinf I | + (T allele) |
| MTR A2756G × 40 | TGT TCC CAG CTG TTA GAT GAA AAT C GAT CCA AAG CCT TTT ACA CTC CTC | D:95°/30s A:60°/30s E:72°/30s | Hae III | + (G allele) |
| MTRR A66G × 30 | GCA AAG GCC ATC GCA GAA GAC AT GTG AAG ATC TGC AGA AAA TCC ATG TA | D:95°/1 min A:55°/30s E:72°/30s | Nde I | + (A allele) |

D: denaturation, A: annealing, E: extension, ×: number of cycles. +: restriction site created, -: restriction site abolished

intervals (CIs). In order to control for confounding effects such as age, body mass index, age at menarche, age at first full term pregnancy, parity, menopause status and family history of breast cancer etc, unconditional logistic regression analysis was used for obtaining adjusted ORs indicative of independent risk.

Bivariate analysis was performed by considering number of variant alleles as predictors (0, 1, 2, 3 and 4) and with the application of logistic regression. Gene-nutrient interactions were studied by applying trend test across the different tertiles of micronutrients. Multifactor dimensionality reduction (MDR) analysis (version: 2.0, beta 6) was used to ascertain the cross-talk between the polymorphisms of one-carbon metabolism and COMT H108L. For all other statistical analysis, www.statpages.org was used.

Results

The distribution of COMT H108L polymorphism was in accordance with Hardy-Weinberg equilibrium in breast cancer cases ($p = 0.30$) and healthy controls

($p = 0.44$). The frequencies of COMT 108 L-variant allele in cases and controls were 44.3% and 28.5% respectively. The recessive model indicated 1.73-folds (95% CI: 1.31-2.30) risk for breast cancer in subjects carrying COMT 108 L-variant (Table 2).

There was no significant interaction (MDR) observed between the folate status and COMT genotype. In all the tertiles of folate, increase in the number of COMT 108 L-variant alleles showed parallel increase in breast cancer risk as evidenced by statistically significant p_{trend} values (Table 3).

MDR analysis of case-control data on eight putatively functional polymorphisms in one-carbon metabolism and COMT H108L polymorphism gave evidence for the following significant epistatic (gene-gene) interactions: RFC1 G80A/COMT H108L; RFC1 G80A/TYMS 3R2R/COMT H108L; and SHMT C1420T/TYMS 3R2R/TYMS ins6-del6/COMT H108L ($p < 0.0001$). Gene dosage effect was evident based on the observation that there was increase in odds ratio with the increase in variant alleles (Table 4).

Increased plasma 8-oxodG was observed in cases as compared to controls (mean \pm SE: 5.59 ± 0.60 vs.

Table 2—Distribution of COMT H108L polymorphism in breast cancer cases and controls

| COMT genotype | Cases (n = 212) | Controls (n = 243) | Adjusted OR (95% CI) | p value |
|---------------|-----------------|--------------------|----------------------|----------|
| 108 HH | 71 (33.5%) | 115 (47.3%) | 1.00 (Ref) | - |
| 108 HL | 94 (44.3%) | 103 (42.4%) | - | - |
| 108 LL | 47 (22.2%) | 15 (6.2%) | - | - |
| 108 HL+LL | 141 (66.5%) | 153 (48.6%) | 1.73 (1.31-2.30) | <0.0001* |

Adjusted OR: odds ratio adjusted for confounding variables such as age, body mass index, age at menarche, parity, menopause status and family history of breast cancer; CI: confidence interval; Ref: reference, *: statistically significant

Table 3—Modulatory effect of plasma folate on COMT H108L genotype associated breast cancer risk

| COMT genotype | Plasma folate I st tertile (1.51-5.92 ng/ml) | Plasma folate II nd tertile (>5.92-7.55 ng/ml) | Plasma folate III rd tertile (>7.55-11.93 ng/ml) | P _{trend} |
|--------------------|---------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------|--------------------|
| 108 HH | 23/32 | 34/40 | 14/42 | 0.07 |
| 108 HL | 35/33 | 39/25 | 27/40 | 0.20 |
| 108 LL | 15/7 | 16/7 | 22/11 | 0.89 |
| P _{trend} | 0.04* | 0.02* | <0.0001* | |

All the data presented in case/control format; p_{trend}: Statistically significant with increase in folate or increase in number of alleles; *: statistically significant

Table 4—Modulatory effect of polymorphisms in one-carbon metabolism on COMT H108L genotype associated breast cancer risk

| Genotype combination | OR (95% CI) | p value |
|---------------------------------------------------|------------------|----------|
| RFC1 G80A/COMT H108L | 2.67 (1.72-4.14) | <0.0001* |
| RFC1 G80A/TYMS 3R2R/COMT H108L | 3.50 (2.22-5.53) | <0.0001* |
| SHMT C1420T/TYMS 3R2R/ TYMS ins6-del6/ COMT H108L | 5.29 (3.30-8.48) | <0.0001* |

OR: odds ratio, CI: confidence interval, *: p value statistically significant

Table 5—Association of plasma 8-oxo-2'-deoxyguanosine (8-oxodG) with COMT H108L and polymorphisms in one-carbon metabolism

| Variable | OR (95% CI) | p value |
|---------------------------------------------|--------------------|----------|
| Plasma folate deficiency | 2.48 (0.79-7.76) | 0.12 |
| RFC1 G80A/MTRR A66G | 4.67 (1.34-16.24) | 0.01* |
| RFC1 G80A/SHMT C1420T/TYMS 3R2R | 11.81 (3.05-45.81) | <0.0001* |
| SHMT C1420T/TYMS 3R2R/MTR A2756G/COMT H108L | Inf (10.89-Inf) | <0.0001* |

OR: odds ratio calculated based on subjects with 8-oxodG above the median vs. below the median; CI: confidence interval, Inf: infinite risk, *: p value statistically significant

3.50 ± 0.40 ng/ml, p<0.004). The 8-oxodG data was segregated into above median and below median to obtain odd ratios and confidence intervals. Plasma folate deficiency alone was not a significant predictor of 8-oxodG elevation. The genotype combinations namely, RFC1 G80A/MTRRA66G, RFC1 G80A/SHMT C1420T/TYMS 3R2R and SHMT C1420T/TYMS 3R2R/MTR A2756G/COMT H108L were strong predictors of 8-oxodG elevation in the order of risk (Table 5).

Discussion

The results of the current study showed independent association between the COMT H108L polymorphism and breast cancer risk. COMT catalyzes the transfer of methyl group from one-carbon metabolism to the catechol estrogens, thus

facilitating the formation of the methoxy estrogens. Lewis et al²⁰ have demonstrated that 2-methoxyestradiol downregulates cyclin D1 and thereby leading to cell cycle progression by a mechanism involving disruption of ATF-2 binding to cyclin D1 promoter. Any perturbation in one-carbon metabolism affects the formation of methoxy estrogen by inhibiting the bioavailability of methyl group to catechol estrogens as observed in the study by Goodman et al¹⁹, demonstrating increase in breast cancer risk with the increase in COMT 108L-variant alleles in subjects with folate levels below the median and homocysteine levels above the median.

Although our data showed no interaction between the folate and COMT genotypes, COMT H108L was found to interact with certain variants of one-carbon metabolism that are likely to influence homocysteine

levels. Co-segregation of RFC1 G80A, TYMS 5'-UTR 3R2R and TYMS 3'-UTR ins6/del6 polymorphisms with COMT H108L was associated with the inflated risk for breast cancer. SHMT C1420T polymorphism that was observed to confer protection against breast cancer by increasing the plasma folate pool (unpublished data) could not negate the risk associated with combined genotypes of TYMS/COMT. This is the first report demonstrating SNP-SNP interactions between the COMT H108L and polymorphisms in one-carbon metabolism. Till date, only two SNP-SNP interactions i.e. CCND1 A870G/COMT H108L¹⁷ and GSTP1 Ile105Val/COMT H108L²¹ have been reported to influence cell cycle progression and detoxification of catechol estrogens/semiquinones.

We observed an elevated plasma 8-oxodG levels in breast cancer cases as compared to controls. Neither plasma folate nor genetic polymorphisms had the individual effects on plasma 8-oxodG levels. However, certain genotype combinations i.e. RFC1/MTRR, RFC1/SHMT/TYMS, SHMT/TYMS/MTR/COMT were found to be strong predictors of elevated 8-oxodG. This was consistent with the hypothesis that low methyl group availability aggravates the COMT H108L polymorphism-dependent oxidative DNA damage. This was further supported by Lavigne *et al* observation that inhibition of COMT with the specific inhibitor Ro 41-0960 blocks the formation of 2-methoxyestradiol, leading to increased 8-oxodG levels in estradiol-treated MCF-7 cells²². Apart from the genetic variations in COMT, the mechanisms that govern COMT expression such as progesterone half-site response elements in COMT promoter might regulate COMT activity²³. Two progesterone receptor isoforms PR-A and PR-B were found to have opposite effects of the regulation of progesterone on COMT expression; the former upregulates, while the later downregulates COMT²⁴.

The epistatic interactions between the one-carbon metabolism and COMT as observed in the present study might help in understanding the molecular mechanisms underlying the breast carcinogenesis. RFC1, which has shown interaction with COMT, carries folate across the RBC membrane. G80A polymorphism in RFC1 is found to influence RBC folate levels²⁵. Under the conditions of severe folate depletion, RFC1 is downregulated as an adaptive response in the MCF-7 breast cancer cell lines²⁶.

Interestingly, progesterone that regulates COMT expression can also inhibit RFC1²⁷.

Another important interaction of COMT observed in the present study was with TYMS 5'-UTR 3R2R and 3'UTR ins6/del6. The promoter polymorphism is present in transcription enhancer element of TYMS, where 3R allele enhances the transcription while 2R allele suppresses the transcription²⁸. TYMS 3'-UTR ins6/del6 polymorphism affects the post translational mRNA processing²⁹. Treatment of human lung carcinoma cell lines with TYMS inhibitor i.e. N10-propargyl-5, 8-dideazafolic acid has been found to increase intracellular dUTP levels, leading to uracil misincorporation in the DNA³⁰. Uracil misincorporation and 8-oxodG lesion in DNA coupled with RBC folate deficiency might aggravate DNA damage to an extent that is irreparable by DNA repair mechanisms or by increased folate pool (due to SHMT C1420T mediated induction of futile folate cycle)³¹.

Since COMT catalysis is dependent on the availability of methyl group, it is biologically plausible that MTR A2756G and MTRR A66G polymorphisms that impair MTR activity and bioavailability of methylcobalamin might influence the 8-oxodG levels. Ishikawa *et al*³² have demonstrated higher micronuclei frequency in smokers with MTRR 66AA genotype compared to other genotypes. Further, decreased SAM availability impairs the reductive methylation of oxidized cobalamin, thereby decreasing the MTR-mediated catalysis³³. Although this mechanism of feedback inhibition helps in preventing unnecessary accumulation of SAM, it might be detrimental under the conditions of folate deprivation or defective folate transport.

In conclusion, the present study provides the substantial evidence for a cross-talk between one-carbon metabolism and COMT H108L polymorphism. Further investigation into the other genetic variants regulating xenobiotic metabolism is being carried out to have comprehensive vision that can dictate the molecular events starting from folate absorption to initiation of mutagenesis. The gene-gene interactions leading to breast cancer risk and elevated 8-oxodG explain the inconsistencies in various association studies on the role of COMT H108L polymorphism in the pathophysiology of breast cancer. Since certain genotype combinations are associated with high risk for oxidative DNA damage,

further studies on large cohorts might help in identifying high-risk subjects, so that strategies to reduce oxidative DNA damage can be developed.

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