

# CATECHOL O-METHYLTRANSFERASE VAL158/MET AND HYPERTENSION: A META-ANALYSIS

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## ABSTRACT

Hypertension is a preventable risk factor of cardiovascular diseases. It is considered as a major cause for the CVD-morbidity and mortality worldwide. Some risk factors and prevention strategies related to hypertension were studied intensively, however, with growing the burden of this disorder and genetic has become the dominant field of treating diseases, still specific genes involved in increasing blood pressure remain to be identified. This meta-analysis was conducted to assess the relationship of COMT Val158/Met variation to high systolic and diastolic blood pressure. PubMed and Web of Science (WOS) were intensively searched for genetic association on the link of COMT Val158/Met to hypertension. The search was done up to October 15<sup>th</sup> 2020 and updated on November 22<sup>nd</sup> 2020. Two investigators were independently extracting data and evaluating risk of bias using Cochrane risk of bias tool. Q-genie tool was used to assess the quality of all included articles. Met-dominant model (Met/Met + Val/Met vs Val/Val) showed a significant association to systolic and diastolic blood pressure with a pooled standardized mean difference of -0.215 and 95%CI [-0.399 to -0.0300] and -0.205, 95%CI [-0.390 to -0.0197], respectively. Met allele was significantly related to high systolic and diastolic blood pressure. However, high-quality, case-control studies are lacking.

**Keywords:** COMT, rs4680, Val158/Met, catechol O-methyltransferase, hypertension, systolic blood pressure, diastolic blood pressure

## INTRODUCTION

Cardiovascular diseases (CVDs) are listed among the first ten causes of death and result in high mortality rate worldwide<sup>1,2,3</sup>. Preventable risk factors of CVDs have been studied intensively, including hypertension, with the aim of eliminating the prevalence or improving the outcome of CVDs<sup>4</sup>. About half of CVD events were attributed to hypertension. Besides, it is recognized to be the major risk factor for CVD morbidity and mortality worldwide<sup>5</sup>. Alcohol consumption, obesity, high intake of salty-food or fatty-food and some genes were identified to be associated to blood pressure (BP)<sup>6,7,8</sup>. It is a complex polygenic disease, about 120 single nucleotide polymorphism and more than twenty-five mutations were identified to be attributed to hypertension<sup>9</sup>. Despite a favourable modification of unhealthy lifestyle, effectiveness of using some antihypertensive drugs, and genetically determined of some risk factors, still specific genes involved in increasing BP remain to be identified.

Catechol O-methyltransferase (COMT) is an enzyme that has two versions; a membrane-bound form (MB-COMT) which is mainly produced in the brain, and a soluble form (S-COMT) which is produced in the liver, kidney and blood<sup>10</sup>. COMT

has an important role not only in degradation the catecholamine transmitters, but also breaking down the drugs used to treat hypertension<sup>11</sup>.

A single nucleotide polymorphism (SNP) located on the fourth exon, 158 codon of COMT-gene has found to be related to the activity of the gene<sup>10</sup>. Changing in amino acid Methionine (Met) instead of Valine (Val) has been shown to be related in decreasing the catecholamine-degradation activity; and thus leading to increase the availability of dopamine. The enzymatic activity of COMT-gene has found to be three to four-folds decrease among homozygous Met-carriers<sup>12</sup>.

Recently, COMT Val158Met was studied with regards to hypertension variations. Some studies show that Met-homogenous was associated with high systolic and diastolic blood pressure<sup>13,14,15,16</sup>; however, other show a reverse finding<sup>17</sup>. Such contradictions in reporting the association of COMT Val158/Met to hypertension encouraged us to conducting a meta-analysis of these studies.

## METHODS

PubMed and Web of Science (WOS) were intensively searched for genetic association on the link of COMT Val158/Met to Hypertension. The search was done up to October 15<sup>th</sup> 2020 and

updated on November 22<sup>nd</sup> 2020 using these keywords: ‘COMT’, ‘rs4680’, ‘hypertension’, ‘blood pressure’, ‘systolic blood pressure’, and ‘diastolic blood pressure’. References of the selected studies were screened manually to find relevant studies were not indexed by PubMed or WOS. Five out of sixty-two articles were included in this meta study (Figure 1).

Criteria to include studies were set as: (1) rs4680 of COMT- gene should be genotyped for all participants; (2) Means and standard deviations (SD) of systolic (SBP) and diastolic blood pressure (DBP) should be reported separately by genotype; (3) study subjects should not be overlap between studies; if so, the study with highest sample size will be selected; (4) The distribution genotype should follow Hardy-Weinberg Equilibrium (HWE); (5) Blood pressure should be measured at least twice with reporting the mean of the two measurements. Studies were excluded when either reported pulse pressure or not reporting interquartile range (IQR) of the median of SBP and DBP. Data from each single study were extracted as they shown on table 1.

All included articles were assessed for quality using Q-genie tool<sup>18</sup>, while Cochrane risk of bias tool was used to evaluate the risk of bias.

### Statistical Analysis

To assess the relationship of *Met*-dominant model (*Met/Met* + *Val/Met* vs *Val/Val*) of COMT-gene (rs4680) to hypertension, a meta-analysis was used. Mean and standard deviation of SPB and DBP of each study was compared separately to *Met*-dominant model using random effect model with 95% CI. A *t*-test was used to examine the pooled mean difference, and would considered significant when  $p < 0.05$ . Heterogeneity among studies was computed using Q-test, which follows a  $\chi^2$ -distribution with  $df = n - 1$ , where  $n$  is the number of the included studies. To specify the percent of differences across studies due to heterogeneity,  $I^2$  metric was computed ( $I^2 = Q - df / Q$ )<sup>19</sup>. The range of  $I^2$  is from 0 to 100, the highest the  $I^2$ -value means high heterogeneity<sup>20</sup>. A random-effects model was used in this meta-analysis as the heterogeneity existed based on the consideration that a variation is extant within-studies and between-studies<sup>21</sup>. A sensitivity analysis was performed by removing one study at a time to assess whether the significant of pooled mean difference was contributed to a single study. All meta-analyses were performed by MedCalc (v. 19.5.1).

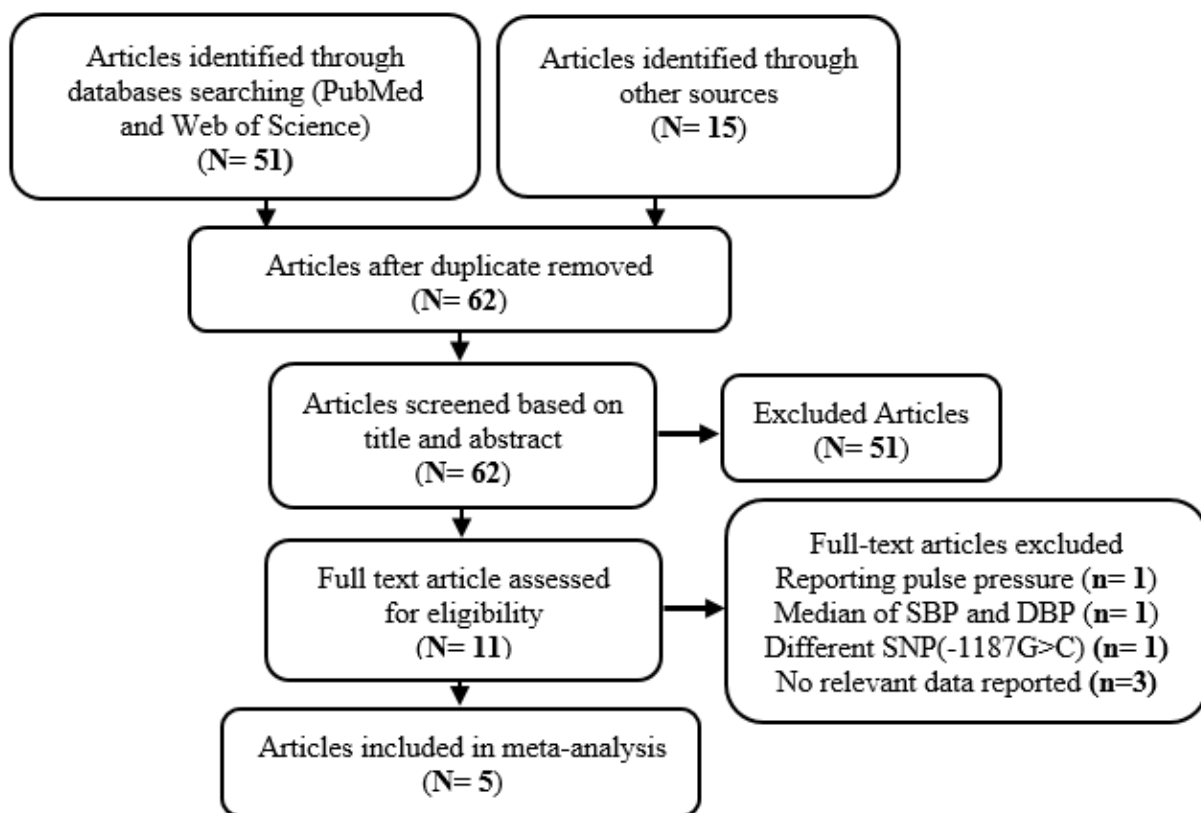


Figure 1: PRISMA flow chart illustrating studies selection process

Table1: Characteristics of studies included in meta-analysis (N=5)

Study	Country	Sample size	Mean age	Mean SBP (mmHg)	Mean DBP (mmHg)	Allele Freq. Met/Val
Yeh, 2010 <sup>13</sup>	Taiwan	558	16.3±0.5	113.9 ± 12.1	71.8 ± 8.3	0.30/0.70
Ge, 2015 <sup>17</sup>	China	3079	55.5±23.6	136.6±25.4	83.8±11.5	0.25/0.75
Htun, 2011 <sup>14</sup>	Japan	735	47.0±8.9	129.9±17.5	79.8±11.8	0.31/0.69
Annerbrink, 2008 <sup>15</sup>	Sweden	204	-	127.1±15.8	82.6±10.0	0.54/0.46
Stewart, 2009 <sup>16</sup>	USA	839	44.2±10.5	134.6±18.1	83.6±11.2	0.46/0.54

RESULTS

A total of 5415 subjects from five studies were included in this meta-analysis with a study sample size 204 to 3079. Accumulatively, 4372 subjects were Asian-ancestry from three different countries, 204 were European- ancestry, while the others were American-ancestry.

In regards to the association of COMT (Val158/Met) with systolic blood pressure, the analysis of the Met-dominant model (Met/Met + Val/Met vs Val/Val) showed a significant

association to SBP with a pooled standardized mean difference of -0.215 and 95%CI [-0.399 to -0.0300] (Figure 2). Likewise, a significant pooled standardized mean difference was found between the Met-dominant model (Met/Met + Val/Met vs Val/Val) of COMT-gene and diastolic blood pressure, SDM=-0.205, 95%CI [-0.390 to -0.0197] (Figure 3).

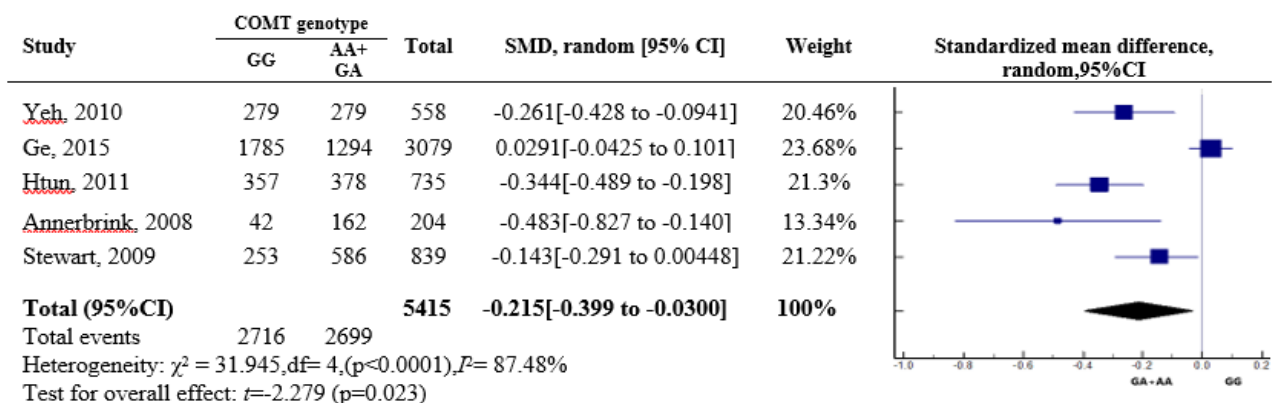


Figure 2: Standardized mean difference of systolic blood pressure with rs4680 (COMT Val158/Met). G, Val; A, Met.

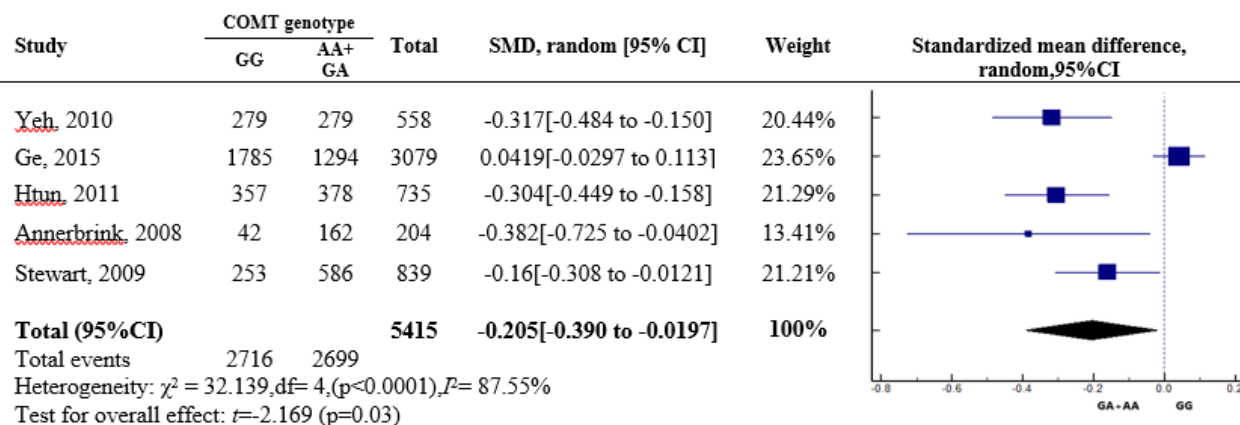


Figure 3: Standardized mean difference of diastolic blood pressure with rs4680 (COMT Val158/Met). G, Val; A, Met.

## DISCUSSION

This analysis was conducted to assess the relationship of *Val/Met* allele variants on hypertension/high blood pressure. The standardized mean difference of SBP and DBP were assessed using *Met*-dominant model of COMT- rs4680. However, *Val*-dominant model was not applied due to the unreported SBP and DBP values for *Val*-homogenous carrier in one of the included studies. A random effect model was used to analyse data since there were high heterogeneity between-included studies. A significant pooled standardized mean difference was found between *Met*-dominant model of COMT *val158/Met* and hypertension (SBP and DBP).

The prevalence of high blood pressure among European population is 60% as compared to United States and Canada<sup>22</sup>. It is contributed to 25% of heart attack in European countries<sup>22</sup>. However, the prevalence of hypertension among East-Asian population were range 7-38% in women and 5-47% in men<sup>23</sup>. This shows a variation in the prevalence of hypertension among different ethnic groups of the population. Likewise, the allelic frequencies were wide-ranging among included studies as they conducted on different ethnic groups, and that might be contributed to the high heterogeneity of this analysis. To emphasize, Asian-descent were having approximately an analogous allele frequency of *Val158/Met* (*Met*= 0.25 - 0.31/ *Val*= 0.69 - 0.75) with high frequency of *Val* allele (Table 1); while, *Met* allele was higher among European-descent (0.54%). From all included studies, the frequency of the minor allele (*Met/A*) is low among Asian and American populations compared to European-descent population, the same reported by others<sup>24,25,26,27,28</sup>. High heterogeneity might be attributed to not only the variation of allelic frequencies, but also to the low number of included reports, sample size of each included studies, and diversity in age of subjects between- and within-studies.

Only one study shows that *Val*-homozygous genotype is linked to the high S/DBP, though it was not significant in this analysis. In contrast, *Met*-dominant model was related significantly to high SBP in three studies (Figure 2), and to high DBP in four studies (Figure 3). This analysis revealed significantly that *Met*-allele is associated with elevating S/DBP. This finding is in a harmony with the fact that low COMT activity is linked to *Met*-allele; as the former leads to increase the concentrations of two important hormones that are control BP (estrogen and dopamine)<sup>13,29,30</sup>. It is worthy knowing that each of the two hormones regulate BP in multifaceted and different pathways; for instance, dopamine plays an important role in regulating BP through regulating blood flow, heart rate, sodium excretion, glomerular filtration rate, and secretion of catecholamine<sup>31</sup>. Indeed, these pathways regulate BP in different ways, some elevate and others

lower BP. Therefore, further studies on understanding the collaborative effects of estrogen and dopamine on BP might pave the way to a better understanding on the effect of COMT genotype.

The inconsistent findings of the included studies might be credited to the fact that *Ge et al.*, study has a wide range of age (55.5±23.6), environmental unmatched subjects (Bama and Pinggue areas with 200km distance, China), and both genders were included; though with highest sample size of the included studies. This study was the only one that linked *Val* allele to high S/DBP. In contrast, other four studies were revealed an opposite finding as *Met*-allele was found to be related to the high S/DBP. Two of them were in accord to *Ge et al.*, as all carried on East-Asian-descent subjects; however, with a narrow range of age and single gender. One study was carried on Japanese-men only with middle age (47.0±8.9)<sup>14</sup>; while the other study was conducted on adult-young-Taiwan-females only with mean age of 16.3 and standard deviation of 0.5<sup>13</sup>. Interestingly, a harmony finding to that of *Htun et al.*, and *Yeh et al.*, was publicised among Swedish middle-age men (51 year)<sup>15</sup>. Likewise, a significant effect of *Met*-allele on BP was found among middle age (44.2±10.5) of both genders of different ethnic group of American subjects<sup>16</sup>. Unfortunately, the latter study<sup>16</sup> has not reported SBP and DBP by ethnic group as 95% of the included subjects were African-American, Hispanic, and non-Hispanic- descent; if so, it would be valuable to analyse data by ethnicity. In sum, variety of the age-group might be the main confounder that leads to unlike findings of the four included studies to the study of *Ge* and co-workers.

## CONCLUSION

Altogether, this analysis revealed a dependent link of *Met*-allele to high S/DBP. Though and due to the low number of published reports on the effect of COMT-rs4680 genotype on BP, further studies need to be conducted to attain a better understanding on the link of COMT genotype to hypertension. Besides, other SNPs of COMT gene should not be neglected (ex: rs4633, rs4818, and rs6269) when assessing its link to any phenotype; in addition, some behaviours would be valuable to be considered as well. For instance, energy intake<sup>14</sup> or alcohol consumption<sup>16</sup> might be allied to the effect of *Met*- allele of COMT-gene on BP.

### Conflict of interest

The authors declare no potential conflict of interest.

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