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Research Article

## Catechol O-Methyltransferase: A Review of the Gene and Enzyme

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### Abstract

Genetic polymorphisms in the Catechol O-Methyltransferase (COMT) gene have been linked to increased pain sensitivity in a number of studies. A literature search was performed to integrate the current knowledge of the gene, its regulation, influences of the polymorphisms upon enzyme function and its population distributions. Assessment also includes the current knowledge of the enzyme structure, isoforms, function and metabolic activities, substrates, and products. Other gene polymorphisms which may influence the components involved within the COMT enzymatic reaction, such as folate metabolism polymorphisms and cofactor availability, were also briefly assessed. A review of enzyme agonists and antagonist and how these may influence the enzymes functions, its substrates and products is undertaken in an attempt to understand the potential interactions between COMT and factors that may influence enzyme activity in the presence or absence of the COMT polymorphic forms.

**Keywords:** Catechol O-Methyltransferase; Monoamine Oxidase; Aldehyde Dehydrogenase; Polymorphism, Genetic; Pain; Temporomandibular disorders; Fatigue Syndrome, Chronic; Antagonists and Inhibitors; Agonists; Catecholamines; Oestrogens; S-Adenosylmethionine; Alcohol Dehydrogenase; Aldosterone; Glucocorticoids

### Introduction

Recent research has provided evidence that polymorphic forms of some genes may be involved in development and/or persistence the pain syndromes, such as temporomandibular joint dysfunction (TMD), fibromyalgia and chronic fatigue syndrome (MECFS). From these data a series of intriguing relationships have been found between the slow reacting polymorphic forms of the enzyme Catechol O-Methyltransferase (EC 2.1.1.6) (COMT) and pain. The slow forms have been reported to have an increased prevalence in subjects who have defined TMD [1-7], MECFS [8,9] and fibromyalgia [10, 11], but other studies have not confirmed these findings for MECFS or fibromyalgia [12-14] or localized pain syndromes as whole groups [15]. However the COMT gene has been found to be associated with a subgroup of MECFS patients, in particular those with increases in depressive symp-

toms [16]. Further studies are warranted to confirm or deny these initial observations.

A series of mutations within the COMT gene sequence and its promoter region have been found to result in low enzyme activity [1, 6, 17, 18]. The crucial event seems to be the alteration in RNA/mRNA conversion or stability, which results in reduction in protein production and hence of total enzyme quantity and activity [17]. A recent study has shown that the instability of these altered COMT proteins is associated with the cellular environment; the higher the level of oxidation products the greater the reduction in COMT enzyme protein and activity [19]. Thus, a combination of genetic susceptibility and environmental factors that increase oxidation by-products or result in higher oxidative damage may significantly alter the normal response to a challenge, particularly in subjects who carry the slow polymorphic forms of COMT.

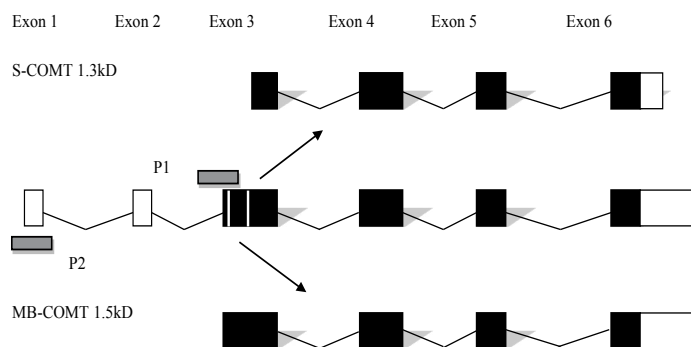
The aim of this review was to assess the known literature about COMT polymorphic alleles and how these polymorphisms and other external/environmental factors (agonists and antagonists) may relate to activity of the gene and its product enzyme. These were undertaken to bring together the often disparate set of literature.

### Catechol O-Methyltransferase (COMT EC.2.1.1.6)

#### The Gene Location and Tissue Distribution

The COMT gene is situated on the long arm of the 22nd chromosome between base pair positions 19,929,262 and 19,957,497 (Cytogenetic Location: 22q11.21-q11.23) [20], which is closer to the centromere than the telomere. (The gene details can be viewed on the website database: <http://www.ebi.ac.uk/>). The COMT gene is composed of 6 exons which produces two different enzyme isoforms, the membrane bound (MB-COMT: 271 amino acids in protein) and soluble cytosolic (S-COMT: 221 amino acids in protein) forms of COMT. Figure 1 shows the proposed structure of the gene. The first two exons are non-coding; the third exon codes two different sets of mRNA: one for each of the two enzyme forms. The sixth exon translated mRNA codon is truncated in the soluble form but complete in the membrane bound form. There are two translation initiation codons, promoter 1 (P1) and promoter 2 (P2) for the different forms of the enzyme, which will be addressed in the section on gene regulation [21-23].

**Figure 1.** COMT Gene Structure, Promoter and S-COMT and MB-COMT transcripts.



The S-COMT 1.3kD mRNA is promoted by Promoter 1 (P1) and the resultant transcript is truncated at exon 3 and exon 6. P1 promoter is located at exon 3 and the transcript starts being read in the middle of Exon 3. The MB-COMT 1.5kD is promoted by Promoter 2 (P2) and the resultant transcript has expression of both exon 3 and exon 6. The P2 promoter is located at exon 1 and the transcript starts being read at the beginning of Exon 3. (Not to scale).

Expression of the COMT gene leads to the formation of two

enzyme isoforms; a) The membrane-bound form (MB-COMT), which is predominately found in nerve cells in the brain and adrenals and has a weight of 28 kDa; and b) the cytoplasmic or soluble form (S-COMT), which is predominately found in the liver, kidneys, and blood and has a weight of 25 kDa. In most human tissues the S-COMT form greatly exceeds the MB-COMT form except in the brain, where the MB-COMT is ~70% of the enzyme present [22,24], and the adrenal glands [25, 26]. Thus, most tissues predominately express the S-COMT form of the enzyme, except the brain and the adrenal glands where the MB-COMT is found to be up to 70% of the expressed enzyme (Reviewed in [27, 28]).

In a series of studies, Tunbridge et al, have found that additional forms of COMT are expressed in certain neurons [29, 30]. These forms have additional protein segments inserted into the enzyme. The action of these additionally expressed forms is not currently known. Thus a complex array of variation of expression of COMT is noted and these vary in a tissue specific way. This makes the data more difficult to interpret.

#### Regulation of the gene.

The COMT gene is associated with 22 regulatory elements such as promoter and transcription binding sites (<http://www.ebi.ac.uk/>). There are both combined and separate promoter elements which may bind to initiate MB-COMT and S-COMT protein expression [21-23]. There are two promoter transcripts, P1 and P2, but there are other regulatory elements in the structure of the gene. Promoter P1 initiates the production of the 1.3kD transcript leading to production of S-COMT and P2 initiates the production of the 1.5kD transcript leading to production of MB-COMT. The positions of these promoters, P1 and P2 are indicated on the gene structure in figure 1. The search for regulatory sequences within the gene has also revealed a complex set of regulatory repeat structures within the intron sections, which together can act as a complete regulatory sequence. The influence of these additional potential regulatory sequences is not currently known.

Table 1 shows the protein promoters and the events known to regulate the COMT gene. A major factor that down regulates the gene is estrogen through both the P1 and P2 promoters. Dietary plant based phytoestrogens, such as SOY proteins, also seem to have similar regulatory effects upon COMT gene expression as that seen with estrogen [31, 32]. CREBP $\alpha$  is an important regulatory factor for COMT and this protein and it related proteins have been found to have altered expression within patients with temporomandibular disorders [33] and chronic fatigue syndrome [34, 35] both of which have been linked to the COMT108/158 allele. It has also been linked to development of hyperalgesia in animal models [36]. Thus the CREBP regulation of COMT expression may be of significance in these pain conditions. An association between COMT

expression and Interleukin 6 (IL6) has not been made in the literature but the fact that Nuclear Factor for IL6 is a regulator of the gene expression suggests this needs to be investigated.

**Table 1.** COMT gene regulation – Proteins and External factors. The highlighted variant is the common slow form COMT108/158.

Factor	Action on COMT/Promoter
<b>Intracellular factors</b>	
Transcription Factor AP2 (TFAP2)	P1 & P2 increased
Specificity Protein 1 (Sp1)	P1 & P2 increased
CEBPB enhancer binding protein alpha (CEBPA)	P1
Nuclear factor for IL6 (NF-IL6 or IL6DBP)	P1
Hepatocyte Nuclear Factor 4 (HNF4)	P1
NFD	P2
Ets1	P2
<b>Host factors</b>	
Oestrogens	Inhibit COMT expression, P1 & P2 mediated
Progesterone	Inhibit COMT expression, P1 & P2 mediated
Testosterone	Increased COMT expression.
<b>Location of Polymorphisms</b>	
Intron 1	rs2097903, rs2020917, rs2075507, rs5746846
Intron 2	rs4646312, rs740603, rs5746849, rs7290221, rs5993883, rs5993882, rs174680, rs174674, rs7287550, rs1544325, rs933271, rs737866
Intron 3	rs6269, rs165722
Exon 3	rs6270
Intron 4	rs2239393
Exon 4	<b>rs4680 (Val/Met)</b> , rs4818
Exon 5	rs165631
Intron 6	rs9332377, rs174699, rs165774.
Exon 6	rs165599
Intron 7	rs165728

Increased production of COMT is associated with increases in a number of other genes. The genes linked to COMT up regulation are:

1. Colorectal mutant cancer protein (MCC). Actual function unknown but may be a tumour suppressor gene located on 5q21. Inhibits DNA binding to  $\beta$ -catenin/TFC/LEF transcription factors [37]. Possibly involved in cell migration.
2. 5'-3' exoribonuclease 2 (XRN2). May promote the termination of transcription by RNA polymerase II by progressive degradation of 3' fragments from mRNA. Thus this gene is involved in regulation of mRNA decay rates [38-40].
3. Lipopolysaccharide-induced tumour necrosis factor-alpha factor (LITAF). Probable role in regulating transcription of specific genes such as tumour necrosis factor alpha (TNF-alpha) gene expression and plays a role in autophagy (controlled removal of cellular components when cells subjected to stress), and development of insulin resistance [41-44]. The gene appears to be up regulated by bacterial lipopolysaccharides (LPS) or the tumour suppressor gene/protein p53/TP53 [43,45-49]. Has been linked to the demyelination disease Charcot-Marie-Tooth syndrome [50, 51] and Paget's

disease [52].

4. Fibronectin (FN1). Fibronectins bind cell surfaces and various compounds including collagen, fibrin, heparin, DNA, and actin and are involved in cell adhesion, cell motility, opsonisation, wound healing, cartilage formation and maintenance of cell shape [53-59].

Thus activation of COMT will be associated with increased activity in other genes, polymorphic variants of which may also influence the outcome of gene expression.

#### *Polymorphic forms.*

The initial study that identified an alteration in COMT activity, as being a recessive trait, was published in Nature in 1974 [60] and in 1991 the sequences were identified for MB-COMT and S-COMT. The sequencing data showed a substitution of methionine for valine at positions 158 (MB-COMT) and 108 (S-COMT) [61, 62]. This initially identified variant is now designated COMT rs4680 or COMT108/158. Since 1991, eleven additional polymorphic forms of the gene have been identified. The major difference between COMT108/158 and the wild gene is a reduction in enzyme protein expression as distinct from an alteration in activity [62]. In an analysis of COMT polymorphic forms in TMD patients, 4 separate polymorphic forms were identified with slow activity [63]. The common feature of all of these polymorphic mutations was the reduction in enzymatic protein levels, as distinct from an alteration in enzymatic activity [17, 18, 63]. The low enzyme protein levels are attributed to a faster decay/deactivation rate of the enzyme [1, 6, 17, 63-65]. One study found that the COMT108/158 valine enzyme (the normal isoform) had a half-life of 4.7 days whilst the methionine isoforms (slow isoform) had a life of 3 days [65]. This is further modified by the cellular environment where an increased oxidative environment results in a greater reduction of enzymatic protein expression [19]. Thus it appears that the slow mutation(s) may be related to a more rapidly degrading enzyme and not an alteration in function.

#### *Paralogue Genes*

COMT has one paralogue gene, a second gene with very similar function which was derived from the same ancestral gene. That paralogue of COMT is a gene Leucine rich transmembrane and O-Methyltransferase domain containing (LRTOMT) (www.ebi.ac.uk). It has been named COMT2 by another research group 66. Its function is the same as COMT and it also has two isoforms, a membrane bound and a cytosolic form, and their distribution appears similar to that of COMT.

LRTOMT is located on the 11th chromosome between base pair 71791382 and 71821828 and has 22 transcripts and 55 exons. It has 547 polymorphic variants and 9 regulatory elements. The protein produced has 291 amino acids and a mo-

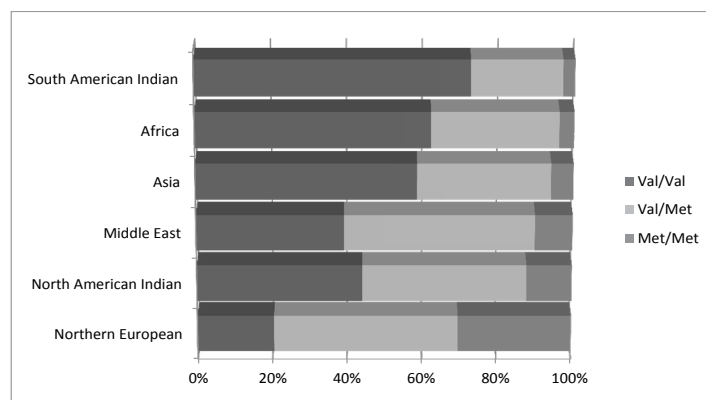
molecular weight of 32kDa (www.genecards.org).

It has the same functions as COMT although an additional function has been described. This additional function is in auditory receptor cell development [67]. Mutations in this gene have been linked to a form of sensorineural hearing loss, as the mutation results in damage to the receptors of the inner ear, its related nerve pathways and the auditory reception area of the brain [68-71]. Interestingly, in addition to the relationship between LRTOMT and sensorineural hearing loss, alterations in COMT have also been linked to sensorineural hearing loss [72] and drug induced hearing loss associated with COMT polymorphic variant (rs9332377) [73].

#### Gene Polymorphism Population Distribution.

There are several polymorphisms noted within the COMT gene. The most common polymorphism is the slow reactive polymorphic allele COMT108/158 and the racial distribution of this has been studied. Palmatier et al [74] assessed the variation in the slow COMT108/158 allele within 1314 individuals from many parts of the planet. Figure 2 shows the proportion of subjects who are homozygous and heterozygous for the COMT108/158 allele. The lowest levels of the COMT108/158 allele frequency were found in the African, Asian and South American populations. Even those populations had significant variations such as in the African group (range +ve 7% - 38%). At the other end of the scale were the northern European population (range +ve 51% - 62%). No Southern European data was available in this study but the Middle-eastern data (range +ve 33% - 38%) was intermediary between the Northern European and the African/Asian grouping. Other studies have found that the Southern European frequency of the COMT108/158 allele to be in the range (45%-47%) [75], which is intermediary between Northern European and Middle-eastern frequencies.

**Figure 2.** Distribution of the COMT108/158 allele in multiple racial groups (Palmatier et al, 1999).



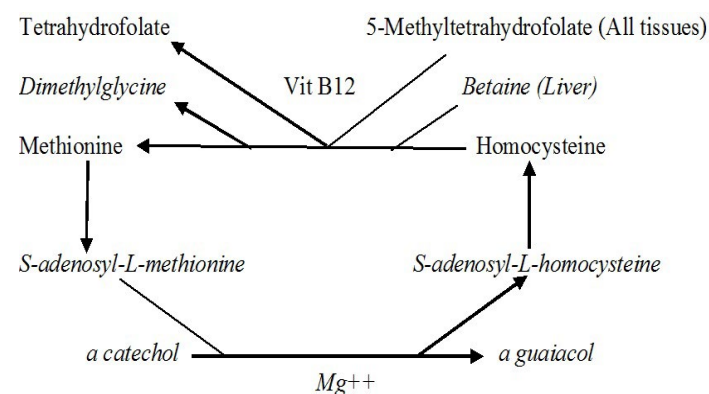
These racial variations in polymorphic forms were also reflect-

ed in the brain data from the Chen et al study [76] where the Met/Val, Met/Met prevalence was 55%, 12% for the African Americans and 82%, 35% for the White Americans. Thus, the epidemiological evidence shows considerable racial and ethnic variation in the COMT slow and fast forms with the highest expression of the slow form in Northern European Germanic/Scandinavian/Celtic racial groups.

#### Physiological activity of COMT.

COMT was first described by Axelrod and Tomchick [77] and is a magnesium dependent enzyme that catalyses the methylation of catechol substrates using S-Adenosylmethionine as the methyl donor as shown in Figure 3. The enzyme activity is dependent not only on the allelic form but also the metabolism of its various cofactors, their transport, activation, degradation, related polymorphic enzyme functions and the metabolite related receptor functions. Some of the metabolites involved in COMT activity shown in figure 3 include: S-Adenosylmethionine (SAME), methionine, S-Adenosylhomocysteine (SAH), homocysteine, Vitamin B12, magnesium and folic acid. What this shows is that COMT activity can be influenced by many other reactions which involve the methylation cycle, vitamin B12 and folic acid.

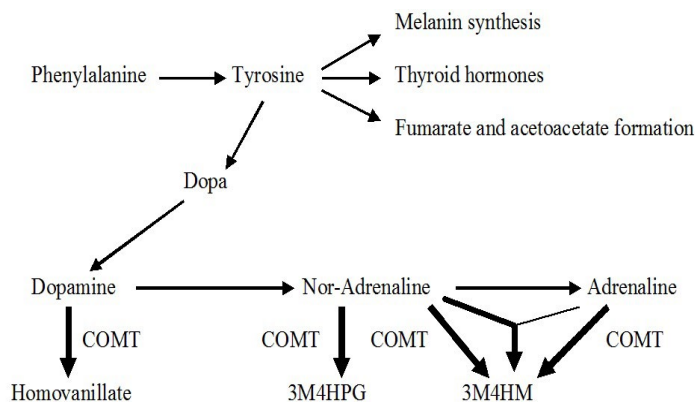
**Figure 3.** Enzyme function for Catechol O-methyltransferase and its interaction with S-Adenosylmethionine, Methionine, Homocysteine and folic acid. The reaction betaine to Dimethylglycine occurs in the liver and the folic acid reaction occurs in all tissues.



The pathway of formation and degradation of catecholamines and the locations in this pathway for COMT are shown in figure 4. The reaction of both forms of the COMT enzyme utilize the conversion of SAME to SAH to transfer methyl groups from molecules involved in the reaction. S-COMT and MB-COMT have an equal affinity for binding SAME, similar magnesium binding capacity, inhibition by calcium, and optimal pH activity [78-80]. However there is a significant difference in the affinities of the two enzyme isoforms for their substrates, with the MB-COMT activity being 10 to 100 fold greater than the S-COMT isoform [62,78, 80-82]. Whether this increase in activity is a result of

the membrane environment or factors associated with the extra N-terminal residues of the MB-COMT form is not currently known. Assessment of the activity of SAH changes revealed alterations in COMT activity in relationship to changes in the availability or structure of the cofactor [83-85]. Analogues of SAH have also been found to modulate COMT activity [86].

**Figure 4.** The pathways for formation and degradation of catecholamines. The COMT containing pathways are marked on bold lines. These involve the degradation of Dopamine, Nor-Adrenaline and Adrenaline. Both Nor-Adrenaline and Adrenaline can be degraded by alternate pathways but both require COMT activity.



Polymorphisms in the genes that are involved in the SAH reaction may influence not only COMT but also all the other methyltransferases which use the same reaction as part of their enzyme activity: these included Histamine-N-Methyltransferase (EC. 2.1.1.8), Glycine N-methyltransferase (EC. 2.1.1.20), Serine Hydroxymethyltransferase (EC. 2.1.2.1) and Adenosylhomocysteine Hydrolase (EC. 3.3.1.1). A mouse study where adenosine and homocysteine were injected revealed a dose dependent reduction in not only COMT but a number of other SAH associated enzymes [87]. In that animal model they injected adenosine and homocysteine and this resulted in increased levels of SAH which in turn inhibited COMT and the other enzymes. Conversely, inhibition of COMT activity is associated with alteration in SAH and SAH levels and high levels of COMT activity were found to produce SAH [88, 89]. Thus polymorphic variants of the multiple SAH/SAH utilizing enzymes are likely to influence COMT activity by alteration in concentrations of SAH. Further research is required into this interesting observation.

Interestingly, viruses have also been found to alter SAH levels via induction of Adenosylhomocysteine Hydrolase which will alter the availability of SAH and its related metabolites, including SAH and adenosine [90, 91]. This activation process is associated with the reactivation of Epstein bar virus (EBV) and may be one of the important underlying events in patients with chronic fatigue syndrome who have recurrent multiple reactivation of EBV [92, 93]. Interestingly the combination of the

normal COMT and herpes simplex 1 antibodies was identified as combined risk factors for the development of Parkinson's disease [94]. This suggests that the COMT108/158 allele is not only protective of Parkinson's disease but also herpes simplex 1 induced host disease. Thus, a number of factors involved directly or indirectly with the COMT reaction have evidence of influencing the metabolism of the SAH /SAH reaction which could also influence the COMT enzymatic activity. In fact increased COMT activity is actually associated with a net production of SAH so it is likely that the COMT108/158 carriers will result in a reduction of SAH and may have compensatory polymorphic variants that are required to normalize the subjects' SAH/SAH metabolism.

One such compensatory enzyme combination may relate to monoamine oxidase activity as it also degrades catecholamines. Monoamine Oxidase (MOX) (E.C. 1.4.3.4.) has two variants, A and B and the catecholamines are preferentially degraded through MOX-A. Combined polymorphisms in COMT and MOX-A are known to be involved in variation of catecholamine degradation within patients [95], with different sex influences, and these in turn influence hormone and behavioural responses [96-99].

Two other potential compensatory enzymes involved in degradation of catecholamines are alcohol dehydrogenase (ADH, EC 1.1.1.1) and aldehyde dehydrogenase (ALDH, EC.1.2.1.3). Considerable ethnic variation also occurs in the polymorphic distribution of fast and slow forms of these two enzymes which may also influence catecholamine degradation rates. The East Asian populations have a high frequency of carriage of a non-functioning mitochondrial Aldehyde dehydrogenase polymorphic form (ALDH2) (Reviewed in [100]). An increase in alcohol consumption in subjects with carriage of the abnormal ALDH2 results in higher catecholamines in serum and urine compared with the normal ALDH subjects [101]. Inhibition of ALDH using the drug, Disulfuram, also results in an increase in blood and urinary catecholamines [102]. Another study revealed that there were increases in dopamine but not noradrenaline in the brain with alcohol exposure [103], which may increase the brains DOPA mediated behaviour rewarding response. Therefore it was not unexpected that a study has linked the combined carriage of ALDH2 and COMT108/158 polymorphisms with increased alcohol consumption and alcohol dependence in East Asian subjects [104]. Only one study has been performed assessing pain thresholds in relationship to ADH and ALDH polymorphic forms and the study revealed significant alterations of the pain thresholds in relationship to the polymorphisms suggesting that COMT may be involved in the reaction [105].

In the brain, COMT is involved in degradation of the catecholamines and is of particular significance in the frontal cortex which influences cognitive behaviour, personality, planning,

and inhibition of behaviours, abstract thinking, emotion, and short term memory. To function efficiently, the prefrontal cortex requires signalling by neurotransmitters such as dopamine and norepinephrine. COMT helps maintain appropriate levels of these neurotransmitters in this part of the brain. In a study of prefrontal cortices of 108 subjects, Chen et al [76] found that both the MB-COMT and S-COMT were expressed, with MB-COMT being in higher levels. Subjects' homozygote for COMT108/158 had 54% less S-COMT immunoreactivity than subjects with the normal COMT allele. The heterozygote COMT108/158 subjects had 21% lower immunoreactivity than the normal COMT subjects. This pattern was also found for enzyme activity where the normal allele had ~38% higher activity than the homozygote COMT108/158 allele subjects. The same alteration in activity was found for the lymphocytes from the various subjects. We also see that higher tissue COMT activity is noted in the brain and the adrenal glands and these two tissues have higher levels of MB-COMT which means the removal rate of the catecholamines is even higher than in other tissues due to the increased affinity characteristics of the MB-COMT over that of S-COMT. The COMT variation was not different between White and African American subjects. However there was a reduction in frontal COMT activity in females compared with the males. Thus there is a significant expression of COMT in the nervous system and it varies with gene polymorphism and sex.

Another area of the brain influenced by COMT activity is the Substantia Nigra which has been linked with the development of Parkinson's disease. The COMT108/158 form which will increase dopamine, appears to be protective of Parkinson disease. As noted earlier an increase in SAH and homocysteine can occur as a result of increased COMT activity and this situation is also noted in patients with Parkinson's disease [106, 107]. COMT is up regulated in the Substantia Nigra after exposure to bacterial lipopolysaccharides [108] and possibly herpes simplex 1 infection and it may be these types of stimuli that could trigger Parkinson's disease through up regulation of COMT and reductions of central Dopamine.

The corpus striatum is also influenced by the COMT108/158 polymorphism. The actual levels of COMT expression in this nucleus are low [109] but the inhibition of COMT activity seems to be related to altered neurotransmitter levels in this nucleus. Studies in animals have shown that diminished prefrontal dopamine neurotransmission leads to up regulation of striatal dopamine activity and this has been confirmed in humans where those with the normal COMT activity have higher tyrosine hydroxylase activity in neurones that project to the Corpus Striatum [110]. This suggested that the COMT108/158 allele will reduce the levels of dopamine within the Corpus striatum and in turn reduce the risk of development of conditions such as schizophrenia and psychosis [111,112]. For a more thorough review of the influence of COMT polymorphic variant on brain function we would direct the reader to several

excellent reviews [113-115].

#### *Substrates, activators and Inhibitors.*

The known substrates for the COMT reaction are shown in Table 2 and the activators and inhibitors of COMT enzymatic activity are listed in Table 3. As can be seen COMT is involved in the metabolism of a number of compounds apart from the catecholamines. One major group of substrates is estrogen and its related metabolites along with Aldosterone [116] and Glucocorticoids [117,118]. It appears that these three hormones actually modulate COMT activity and can also be degraded by the enzyme. It is also involved in the metabolism of Warfarin and caffeine as well as several plant phytoestrogens. Interestingly the levels of folic acid and vitamin B12 have been found to be low in subjects carrying the COMT108/158 allele. This appears to be a result of the potential alteration to the SAME/SAH reaction.

**Table 2.** Substrates and reactions.

Compounds	References
<b>Catecholamines</b>	
Adrenaline, Noradrenaline, Dopa, Dopamine, 3,4-dihydroxymandelic acid, 3,4-dihydroxyephedrine	
<b>Oestrogens</b>	
2-hydroxyestradiol, 17-Beta-hydroxyestradiol, 2-hydroxyestrogen, 4-hydroxyestradiol	134, 135
<b>Drugs</b>	
Warfarin - metabolism is reduced	161, 162
Caffeic acid and caffeine	163, 164
3,4-hydroxyphenylacetic acid	165,167
3,4-dihydroxyamphetamine.	168
3,4-dihydroxybenzoic acid	169
Dobutamine	170-172
Quercetin	145, 173
Folic acid - Low folates associated with slow COMT in breast CA patients.	174
Vit B 12 - slow COMT associated with changed Vitamin B12 levels.	175
Ascorbic acid (Vitamin C)	176, 177

TNF- $\alpha$  and NF-kappa- $\beta$ , markers of inflammation, are inhibitors of COMT activity. But no studies could be identified which assessed polymorphic variation with inflammation. A number of herbs and dietary components are inhibitors of COMT but no studies were found that assessed the influence of these dietary substances on COMT polymorphic variations.

Another important observation is that serotonin is an inhibitor of COMT and it does this through interaction with the SAME binding site [119]. Serotonin levels are elevated in the synovial fluid of patients with arthritis, such as Rheumatoid arthritis; in animal models of Temporomandibular Joint pain [120, 121], and serotonin may also influence myalgia in Temporomandibular disorder patients [122,123] or pain on movement [124]. In support of these possibilities we find the administration of Serotonergic antagonists reduce pain in both myalgia and arthritis in animals and humans [120, 125-127].

**Table 3.** Activators and inhibitors of COMT enzyme activity.

Inhibitors	References
Tumour necrosis factor alpha (TNF-α)	141, 178-180
NF-kappa-β	180,181
Serotonin	119
High ionic strength	182
2-hydroxyoestrogen	183
Methoxyoestradiols	184-187
Dobutamine (β-Adrenoreceptor stimulator drug)	172
6-nitronorepinephrine (nitric oxide produced)	188
Entacapone (COMT inhibitor drug)	166, 189
Calcium	190-192
<b>Herbal and Dietary components</b>	
Soy proteins: Diadzin and Genistein	32,193, 194
Quercetin (Herb extract including Green tea and Hypericin)	31,195-201
6,7-dihydroxycoumarin and Bromelins	202
Ascorbic acid (Vitamin C)	203
Vitamin B6	204
Caffeic acid (plant based antioxidant) found in coffee	205, 206
Coffee	164
Flaxseed	183
β-thujaplicin (Red cedar extract)	207,208
Catechin/Epicatechin (plant flavan-3-ols) found in kola nut, wine, tea.	209-212
Gallic acid. Found in gallnuts, witch hazel, tea, oak bark.	213
<b>Activators</b>	
<b>Herbal and Dietary components</b>	
Vitamin A (deficiency causes inhibition of COMT)	214
Vitamin D (deficiency causes reduction of COMT)	215
Cysteine	216

There are no studies which assess both the serotonin transporter or serotonin receptors in relationship to COMT, but one review has suggested they need to be addressed [128]. However a number of studies have identified interaction between serotonin gene polymorphisms and those of COMT. Hard working, industrious, ambitious subjects had higher scores in these psychological factors if they also had the serotonin transporter promoter region 44p deletion (5htDel) [129]. Those subjects who were homogenous for either Methionine or Valine at COM (108/158) had improved scores in the presence of the deletion whilst the heterogeneous subjects did not show a statistically significant change. Interestingly, from these same gene polymorphic allele sets, COMT and 5htDel, it was the patients with normal COMT (Val/Val) and the 5htDel that had higher levels of psychosis within patients who developed Alzheimer disease [130]. These two polymorphic combinations were not found to be related to Tourette’s syndrome [131] or suicidal ideation [132]. The COMT108/158 allele seems to offer some other significant behavioural responses when combined with serotonin based gene polymorphic variants. The COMT108/158 allele along with tryptophan hydroxylase-2 (TPH2) T allele of G703T, which modulates serotonin neurotransmission, were much better at controlling their emotions and social cognition than the other allele combinations [133]. Thus the COMT108/158 allele appears protective of the serotonin induced change in brain function and in combination with several of the sero-

tonin gene alleles appears to have beneficial outcomes for the carriers.

*COMT and Oestrogens.*

Slow polymorphic forms of COMT seem to have lower activity in females compared with males and this may influence their pain reactivity, making them more prone to pain syndromes. COMT not only metabolizes catecholamines but also metabolizes the oestrogens and in particular 2-hydroxyestradiol, 17-Beta-hydroxyestradiol, 2-hydroxyestrogen, 4-hydroxyestradiol [134, 135]. See table 4 for a summary of estrogenic activity. Oestrogens such as 17-Beta-hydroxyestradiol also activate the P1 and P2 promoter regions of the COMT gene leading to inhibition of COMT production [136-138]. Variation in the estrogen levels seem to modulate COMT activity [139]. Examination of the estrogen levels across the oestrous cycle in rats show that the higher the estrogen and progesterone levels the lower the COMT activity and the higher the catecholamine levels [140]. In support it has been found that increases in oestrogens also inhibited catecholamine degradation rates leading to higher catecholamine levels [136,137,141]. Lower activity of COMT leads to increased levels of several of the estrogen related degradation products [142], which in turn have been linked to increases in breast cancer rates in females. Interestingly the COMT polymorphic form was associated with estrogen related changes in cognitive function [143]. Thus complex interactions occur between oestrogen, its metabolites and COMT activity.

**Table 4.** Oestrogens and COMT activity.

Oestrogen and metabolites		Oestrogenic activity	
		Without COMT inhibition	With COMT inhibition
Oestrogen		Yes	Increased
16-OH-Oest	4-OH-Oest	Yes	Increased
	<b>COMT</b>		
	4-CH3O-Oest	No	No
	2-OH-Oest	Anti-oestrogenic	Increased anti-oestrogenic
	<b>COMT</b>		
2-CH3O-Oest	Anti-oestrogenic	Reduced anti-oestrogenic	
Other		Yes	Increased
Other		Not known	Not known

The hyper-estrogenic effects of the low activity COMT were associated with increased height (mean 5.4cm taller) and a 9.8% increase in cortical bone mineral content in early pubertal development in girls [144]. The slow COMT activity females also had higher serum free estradiol and insulin growth factor levels [144]. Quercetin, an inhibitor of COMT has been found to increase the levels of the COMT metabolized estrogen metabolites [145]. There is also an increased rate of breast cancer in females with lower COMT activity but the breast cancer rate appears to be related to a combined COMT/environment in-

teraction [142,146-148]. The increase in breast cancer rates, in premenopausal women, has been linked to polymorphic variation in estrogen receptor alpha (ER $\alpha$ ) [149]. There has also been found a female specific increase in atherosclerotic plaques in elderly Japanese females who carry the slow COMT isoforms [150]. Similarly, the slow COMT isoforms was also linked to increased odds (OR=2.7) for development of pre-eclampsia [151]. How these COMT associated conditions relate to estrogen is currently not understood.

#### *COMT, Mineralocorticoids and Glucocorticoids.*

Glucocorticoids, the stress hormone, was found to inhibit COMT [117,152] and the levels of serum adrenaline were found to progressively increase with the greater number of COMT108/158 alleles under the same conditions of stimulation [153]. In the control subjects in this study the serum adrenaline levels rose from 0.15, to 0.29, to 0.5 for the COMT Val/Val, Val/Met and Met/Met alleles, respectively. The mean subject stress index also rose from 12.5 to 18 to 21 units across the same alleles. Thus the higher the COMT108/158 allele count the higher the adrenaline level and the higher the patients stress score.

Aldosterone is the major mineralocorticoid which may be influenced by COMT activity and it controls salt and water re-sorption in the kidney. Dopamine has been found to down regulate angiotensin II stimulated Aldosterone production [154] and is known to be protective for the development of hypertension though this mechanism [155] or through regulation of renal prostaglandin homeostasis [156]. However the presence of the COMT108/158 allele within Japanese men was associated with an increase in both diastolic and systolic blood pressures [157] and this may be due to the increase in the other catecholamines not being degraded. Table 3 shows that elevated isotonic solutions will inhibit COMT and this effect is noted in salt loaded rats with salt sensitivity hypertension along with blunting of the alpha-2 adrenoreceptor [158]. The effect is not found in the non-salt sensitive rats. Interestingly the COMT activity within the brain is also inhibited by salt loading of these same salt hypertensive rats [159]. Conversely, the carriage of the COMT108/158 allele was found to reduce the risk of myocardial infarcts within hypertensive subjects [160] and the effect increased with age. This may be due to the COMT108/158 allele reducing the age related fall in dopamine levels which in turn has been linked to increased hypertension. Thus, there is conflicting evidence associating the COMT108/158 allele with hypertension but the conflicting nature appears to relate to external that may influence the dopamine/catecholamine balance, such as salt and other dietary factors.

#### Conclusions

The genetic structure and variation in the COMT activity of cer-

tain of its polymorphic forms, the enzyme structure, isoforms, function and metabolic activities, substrates, and products were evaluated. Significant interactions with availability of co-factors such as SAME, SAH, folate and vitamin B12 do appear to be associated with variation of the enzymes function. A simple overview of enzyme substrates, agonists and antagonist and how these may influence the enzymes functions is undertaken in an attempt to understand the potential interactions between COMT and factors that may influence enzyme activity in the presence or absence of the COMT polymorphic forms.

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