11. GENETICS OF MONOAMINE METABOLIZING ENZYMES:

Psychopharmacogenetics

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1. INTRODUCTION

The monoamine (MA) neurotransmitters, namely the catecholamines dopamine (DA), norepinephrine (NE) and epinephrine (E) and the indolamine serotonin (5-hydroxytryptamine = 5-HT), play important roles in mood, cognition, learning, motor activity, reward, sleep, appetite, and cardiovascular functions.

1.1. Monoamine brain distribution and pathways

Peripheral MA-ergic cells are mainly present in the adrenal medulla (E and NE), sympathetic ganglia (NE) and myenteric plexus (5-HT). In the brain neurons containing DA, NE and 5-HT have a restricted distribution in specific nuclei mainly in the brainstem from where they form pathways that allow regulation of the activity of large regions of the CNS.

1.1.1. Dopamine

Most DA-ergic neurons are located in the *pars compacta* of the substantia nigra (SN) and in the medially adjacent ventral tegmental area (VTA) in the mesencephalon. They project rostrally in three partially overlapping pathways.

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The nigrostriatal projection (or mesostriatal projection) is from the SN to the caudate nucleus and putamen. The mesolimbic and mesocortical pathways travel from the VTA to several forebrain structures such as the nucleus accumbens, septal area, amygdala, and pre-frontal cerebral cortex. Additional DA-ergic neurons are found in the retina, the olfactory bulb, and the hypothalamus and form local contacts.

1.1.2. Norepinephrine

NE-ergic neurons form the locus ceruleus (LC) in the pons and are also found in the medullary reticular formation, in the solitary nucleus and the dorsal motor nucleus of the vagus in the medulla. They project to most of the CNS with ascending fibres reaching the thalamus, hypothalamus, limbic forebrain structures, the somatosensory cerebral cortex and the cerebellar cortex and deep nuclei while descending fibres project to other parts of the brainstem and to all spinal levels.

1.1.3. Serotonin

5-HT-ergic neurons are found in the brainstem where they are concentrated in the raphe nuclei. They innervate virtually all parts of the CNS with projections from the rostral raphe nuclei to the forebrain. The cortical innervation is most dense in sensory and limbic areas. The caudal raphe nuclei provide most of the projections to the brainstem and spinal cord. Moreover, 5-HT is a precursor for melatonin and is therefore synthesized in high amounts in the pineal gland.

1.2. Monoamine pre-synaptic neurotransmission (synthesis, storage, release, uptake and degradation)

Tyrosine Hydroxylase (TH) and Tryptophan Hydroxylase (TPH) are the rate-limiting enzymes involved in the hydroxylation of the amino acids tyrosine and tryptophan, the first step in the synthesis of, respectively, the catecholamines and serotonin. Thereafter, the Aromatic Amino acid Decarboxylase (AAD or Dihydroxyphenylalanine (DOPA) Decarboxylase) decarbo-xylates the DOPA to DA and the 5-hydroxytryptophan to 5-HT. The Dopamine-ß-Hydroxylase (DBH) further converts DA to NE and the Phenylethanolamine-N-Methyl-Transferase (PNMT) NE to E in the adrenal medulla.

After their synthesis, all monoamines are concentrated in vesicles at the nerve terminal by the specific vesicular monoamine transporters VMAT-1, primarily present in endocrine and paracrine cells of peripheral organs, and VMAT-2, the predominant monoamine vesicular transporter in the CNS (Erickson et al., 1996). These transporters favorize the uptake and protect these molecules from leakage and/or intraneuronal metabolism (Masson et al., 1999) and regulate the release of MA from the vesicle pool (Boehm & Kubista, 2002).

Upon their release, the availability of extracellular MA and, thus, the spread and duration of synaptic excitability at their receptors is limited by

presynaptically localized transporters and/or the action of specific catabolyzing enzymes. The transporters NET, DAT and SERT retrieve the released NE, DA and 5-HT, respectively, allowing these neurotransmitters to be repackaged into synaptic vesicles inside the terminal (Gainetdinov & Caron, 2003). The enzymes monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT) carry out the first step in catecholamine catabolism. Two isoforms of MAO (types A and B), which are encoded by separate genes, can be distinguished by substrate specificity and sensitivity to selective inhibitors. MAO-A appears to be the main enzyme for metabolising 5-HT and NE as substrates, and clorgyline is a selective MAO-A inhibitor, whereas MAO-B prefers phenylethylamine as a substrate, and is inactivated by deprenyl as a selective inhibitor. Both MAO-A and MAO-B oxidize DA. MAO-A is preferentially located in dopaminergic and noradrenergic neurons, while MAO-B appears to be the major form present in serotonergic neurons and glia (Shih et al., 1999; Nagatsu, 2004). COMT is bound to membranes and appears to be located principally in postsynaptic neurons. The degradation of catecholamines by the MAO and the COMT enzymes generates aldehyde intermediates that are reduced to 3,4-dihydroxyphenyl-glycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG) by cytosolic aldehyde reductase or oxidized to 3,4-dihydroxy-phenylacetic acid (DOPAC) by mitochondrial aldehyde dehydrogenase. DOPAC may further be catabolized to homovanillic acid (HVA). The MAO and aldehyde reductase enzymes catabolize 5-HT yielding 5-hydroxy indole acetic acid as the end product.

1.2.1. Monoamine functions in the CNS

Each of the MA systems in the brain is consistently associated with distinctive but sometimes overlapping physiological processes whose disturbances are implicated in neuropsychiatric diseases.

The DA systems are important mediators of motor function, mood, reward and cognition (Koob & Nestler, 1997). The loss of the DA neurons in the SN is responsible for Parkinson's disease (Wolters & Calne, 1989). Alterations in DA-ergic neurotransmission are implicated in psychiatric diseases such as bipolar disorder (Schildkraut, 1965), schizophrenia (Carlsson, 1988; Abi-Dargham et al., 1998; Abi-Dargham et al., 2000), attention deficit/hyperactivity disorder (ADHD) (Shastry, 2004), Tourette's syndrome (Segawa, 2003) as well as drug abuse (Koob & Nestler, 1997; Melichar et al., 2001).

The NE system participates in the regulation of arousal, mood, attention and the response to stress suggesting its implication in depression (Schildkraut, 1965; Ressler & Nemeroff, 1999).

The 5-HT system plays a role in mood, aggression, response to alcohol, appetite, sleep, cognition, and sexual and motor activity. 5-HT has been implicated in the etiology of depression mostly based on the pharmacological studies of the mechanism of action on the selective serotonin reuptake inhibitors class of anti-depressant drugs (Vaswani et al., 2003; Gross & Hen, 2004).

2. GENETIC ASPECTS OF MONOAMINE METABOLISM AND NEUROPSYCHIATRIC DISEASES

The role of the MA systems in regulating several biological processes that are disrupted in mental diseases suggests that the imbalance in MA neurotransmission may play a substantial role in the pathophysiology of neuropsychiatric diseases (Grace, 1991; Mallet, 1996; Dreher & Burnod, 2002). The relative abundance and activity of the MA varies in different species and in different cell groups as well as interindividually and between normal and pathological states, albeit it is unclear to what extent any neurobiological findings reflect primary rather than secondary pathology, compensatory mechanisms, or environmental influences. However, the primary source of interindividual differences in MA availability at the synapsis is essentially represented by DNA polymorphisms in the genes encoding the metabolizing machine of the MA systems. Accordingly, the psychiatric genetic studies of the genes encoding these enzymes have highlighted their implication in the genetic predisposition to several neuropsychiatric diseases. The major findings of these studies will be presented focusing on the relevance for behavioral and other complex traits of functional polymorphisms in MA metabolism related genes.

2.1. Tyrosine Hydroxylase

The *TH* gene, encoding the rate limiting enzyme in the synthesis of catecholamines, is a strong candidate gene for neuropsychiatric diseases (Mallet, 1996). A seminal paper showing for the first time a genetic linkage between bipolar disorder in the Amish population and markers at the chromosome 11p15, a region that contains the *TH* locus, strengthened the case for *TH* as a "positional" candidate gene (Egeland et al., 1987). This result was questioned because the lod score method utilized did not take into account genetic heterogeneity that characterizes bipolar disorder and other complex diseases (Hodgkinson et al., 1987). Eventually, further genetic analysis of the Amish or studies of other populations did not confirm this initial result (Detera-Wadleigh et al., 1987; Kelsoe et al., 1989; Ginns et al., 1992; Gerhard et al., 1994; Gershon et al., 1996; Ginns et al., 1996). However, other studies finding significant linkage between markers at the *TH* locus and bipolar disorder, maintained the implication of the *TH* gene in this disease and strengthened the case for genetic heterogeneity (Pakstis et al., 1991; Byerley et al., 1992; Lim et al., 1993; Gurling et al., 1995; Smyth et al., 1996; Malafosse et al., 1997).

In the first of a series of association studies on the *TH* gene, a significant genetic association was found between restriction fragment polymorphism markers at the *TH* locus and bipolar disorder in a French population sample (Leboyer et al., 1990). However, this result has not always been replicated in other studies (Korner et al., 1990; Gill et al., 1991; Inayama et al., 1993; Korner et al., 1994; Kawada et al., 1995).

In order to further investigate the implication of the *TH* gene in the genetic predisposition to bipolar disorder, an association analysis was conducted using the more informative microsatellite HUMTH01 marker. This microsatellite is a

polymorphic polypyrimidine sequence localized in the first intron of the *TH* gene and is characterized by a core (TCAT)n tetranucleotide repeat iterated usually between 6 and 10 times (Polymeropoulos et al., 1991; Brinkmann et al., 1996). The perfect $(TCAT)_{10p}$ repeat is very rare (less than 1%), while an imperfect $(TCAT)_4CAT(TCAT)_5$ repeat allele, named $(TCAT)_{10i}$, is the most common allele in Caucasians (around 30%) (Puers et al., 1993). A significant association has been found between the HUMTH01 7/10i repeat genotype and bipolar disorder in a new sample of French case-controls. Moreover, the patients bearing the risk genotype were clinically characterized by having familial history of bipolar disorder and/or delusive symptoms during manic or depressive episodes (Meloni et al., 1995a). Although the *TH* gene is also a candidate gene for schizophrenia, there was no compelling evidence for linkage of the *TH* locus to schizophrenia (Byerley et al., 1993). However, the rare 10p allele of the HUMTH01 microsatellite was significantly associated with schizophrenia in two different ethnic samples from Normandy (northwestern France) and the Sousse region (eastern Tunisia) (Meloni et al., 1995b).

Several further studies inspired by these results have been inconclusive for association (Cavazzoni et al., 1996; Souery et al., 1996; Turecki et al., 1997; Burgert et al., 1998; Jonsson et al., 1998; Souery et al., 1999) or have replicated the positive association between the HUMTH01 microsatellite and both bipolar disorder (Perez de Castro et al., 1995; Lobos & Todd, 1997; Serretti et al., 1998; Serretti et al., 1998; Furlong et al., 1999; Chiba et al., 2000) and schizophrenia (Wei et al., 1995; Wei et al., 1997; Kurumaji et al., 2001).

The HUMTH01 microsatellite has also been associated with catecholamine neurotransmission by measuring catecholamine metabolite levels in lumbar cerebrospinal fluid (CSF) (Jonsson et al., 1996) or in plasma (Wei et al., 1995; Wei et al., 1997) which are an indirect index of monoamine turnover in the brain. Moreover, in a clinical study in the original Normandy sample, the schizophrenic patients bearing the 10p rare allele presented significantly lower plasma concentrations of the catecholaminergic metabolites HVA and MHPG, which are indices of central DA-ergic and NE-ergic function, respectively, as compared to patients bearing other alleles (Thibaut et al., 1997).

These results suggest a functional link between allelic variations at the HUMTH01 marker and TH activity. Indeed, the (TCAT)n motif of this microsatellite differs by only one nucleotide from the consensus AP1 sequence (TGATTCA) present in the rat and human *TH* gene (Icard Liepkalns et al., 1992), a sequence that is specifically recognized by transcription factors of the Fos and Jun proto-onco-gene families (Sassone-Corsi et al., 1988). Moreover, a less polymorphic HUMTH01 repeated sequence is conserved at its orthologous position in the first intron of the *TH* gene in several non-human primate species (Meyer et al., 1995), hinting that this motif may be an evolutionary conserved regulatory element that has expanded in the human lineage.

Therefore, the functional role of the HUMTH01 microsatellite was assessed in order to investigate the biological significance of the genetic association findings. Indeed both the (TCAT)10i and (TCAT)10p alleles enhanced transcription when placed upstream from a minimal promoter driving the expression of a luciferase reporter gene. Moreover, these repeated sequences

interacted specifically with factors of the fos/jun type and with an even higher affinity with other nuclear proteins (Meloni et al., 1998). Subsequently, ZNF191, a zinc finger protein, and HBP1, a HMG box transcription factor, were identified as the proteins specifically binding the TCAT motif. Interestingly, the specific binding of ZNF191 to the HUMTH01 sequence was correlated in a quantitative fashion to the number of TCAT repeats (Albanese et al., 2001). Moreover, *in vitro* experiments with a *TH*-reporter gene construct established that the HUMTH01 microsatellite regulates the *TH* gene expression by a quantitative silencing effect that correlates with the number of repetitions of the (TCAT) motif (Albanese et al., 2001). Thus, the HUMTH01 sequence may participate in the transcriptional regulation of the *TH* gene by modulating its expression in a quantitative fashion. Since the (TCAT)n polymorphic sequence is widespread in the genome and present in other genes, it may provide a molecular basis for the modulation of gene expression relevant to the genetics of quantitative traits.

2.2. Tryptophan Hydroxylase

Until recently, only this one gene encoding *TPH* had been described (Boularand et al., 1990; Craig et al., 1991). Since TPH catalyzes the rate-limiting step in 5-HT synthesis, this gene has been the target of a series of genetic studies for psychiatric diseases (Herault et al., 1993; Herault et al., 1994; Goldman, 1995; Bellivier et al., 1998; Furlong et al., 1998; Gelernter et al., 1998; Han et al., 1999; Kunugi et al., 1999; McQuillin et al., 1999) with a specific focus on aggressive behavior and suicidality (Nielsen et al., 1994; Abbar et al., 1995; Mann et al., 1997; Nielsen et al., 1998; Manuck et al., 1999; Rotondo et al., 1999; Vincent et al., 1999; Rujescu et al., 2003) as reviewed by Arago (Arango et al., 2003). However, the functional inactivation of the *TPH* gene in mice by two different groups has revealed that 5-HT levels were depleted in the periphery and in the pineal gland but were in the normal range in the brain stem (Cote et al., 2003; Walther et al., 2003). These results led to the detection of a second *TPH* gene, named *TPH2*, which is exclusively expressed in the brain stem of humans (Zill et al., 2004), mice (Cote et al., 2003; Zhang et al., 2004), and rats (Patel et al., 2004). The classical *TPH* gene, now called *TPH1* and whose inactivation results in a pathological cardiovascular phenotype (Cote et al., 2003), is expressed in the myenteric plexus, spleen, thymus and pineal gland. The *TPH1* and *TPH2* genes have non-overlapping expression patterns, different functions and are independently regulated, thus rendering obsolete the finding of genetic studies on *TPH1* and psychiatric diseases. *TPH2* has already been associated with major depression (Zill et al., 2004), but not with bipolar disorder or suicidality (De Luca et al., 2004).

2.3. Aromatic Amino Acid Decarboxylase

The *AAD*, or Dihydroxyphenylalanine (DOPA) Decarboxylase, gene, which encodes the enzyme involved directly in the synthesis of DA and 5-HT, has been mapped to chromosome 7p11-p13. A study for bipolar disorder on Danish

families was negative for linkage in this region (Ewald et al., 1995). Two putative functional polymorphisms have been described for the *AAD* gene: a 1-bp deletion in the promoter and a 4-bp deletion in the untranslated exon 1. Both deletions affect binding sites for known transcription factors and may thus affect *AAD* gene expression (Borglum et al., 1999). A significant association was found between the 1-bp deletion and bipolar disorder in a Danish and a British sample (Borglum et al., 1999) and between both polymorphism and early age of onset in schizophrenia (Borglum et al., 2001). However, other studies failed to reproduce the association between these markers and mood disorders in a German sample (Jahnes et al., 2002) or autism (Lauritsen et al., 2002). *AAD* is located next to the imprinted gene GRB10 which is expressed specifically from the paternal allele in foetal brains. Interestingly, a preferential paternal transmission of alleles at the 4-bp insertion/deletion was observed in family based (trios formed by the proband and both parents) association studies for ADHD (Hawi et al., 2001) and bipolar disorder (Borglum et al., 2003).

2.4. Dopamine ß Hydroxylase

The *DBH* gene is located on chromosome 9q34 (Craig et al., 1988) and encodes the enzyme that catalyses the conversion of DA to NE. Mutations in the *DBH* gene result in lack of sympathetic noradrenergic function and orthostatic hypotension (Garland et al., 2002; Deinum et al., 2004). The DBH enzyme is localised within the soluble and membrane fractions of secretory catecholamine-containing vesicles of noradrenergic and adrenergic cells. These two forms, which originate from a single mRNA with the first ATG is the only effective initiation site, arises from optional cleavage of the signal peptide. The form retaining the signal peptide is completely associated with the membrane, whereas the cleaved form is mostly soluble with only a small portion membrane-bound (Houhou et al., 1995). The soluble form of the enzyme is secreted into the circulation from nerve terminals allowing for assaying its activity in plasma or serum. DBH presents differences in enzymatic activity that are stable and appear to be genetically determined to a great extent (Stolk et al., 1982). Several polymorphisms in the gene have been implicated in these variations. A G/T polymorphism at the nucleotide 910 of the coding sequence results in a change at amino acid residue 304 between Ala (A) and Ser (S) (DBH/A and DBH/S). The resulting proteins have similar kinetic constants, but DBH/S has a homospecific activity that is about one thirteenth lower than that of human DBH/A (Ishii et al., 1991). The DBH/A allele is the most common allele in European, African and several other populations with allele frequencies greater than 0.80 in each sample and significant heterogeneity in allele frequency across population groups (Cubells et al., 1997). These allelic differences cannot alone account for the differences in the activity of DBH in blood since circulating DBH concentrations also vary considerably in the general population. Recently a novel polymorphism (-1021 C/T) in the 5' promoter region of the *DBH* gene was shown to strongly influence plasma DBH-activity, accounting for 35%-52% of its variation in different populations (Zabetian et al., 2001; Kohnke et al., 2002). A further study showed that 10

biallelic markers in a 10 Kb surrounding the -1021C/T polymorphisms were all associated with plasma DBH activity and that this association was strongly correlated with the degree of Linkage Disequilibrium between each marker and the -1021C/T polymorphism (Zabetian et al., 2003). The -1021C/T polymorphism is also associated with variation in the concentration of HVA and 5-HIAA in the CSF (Jönsson et al., 2004). Another association was found between a *DBH* TaqI polymorphism and plasma metabolites of catecholamines (Wei et al., 1998). Other polymorphic variants in the *DBH* gene are represented by a GT dinucleotide microsatellite, a single-base, 444 g/a, substitution at the 3' end of *DBH* exon 2 and a di-allelic variant, DBH5'-ins/del, located approximately 3 kb 5' to the *DBH* transcriptional start site. All these markers, which are in linkage disequilibrium, were also associated with plasma DBH activity. (Wei et al., 1997; Cubells et al., 1998; Cubells et al., 2000; Jönsson et al., 2004). Moreover, the 444 g/a marker was also associated with differences in DBH concentration in the CSF (Cubells et al., 1998; Zabetian et al., 2003).

Psychiatric genetic studies using the polymorphisms at the *DBH* gene have shown a significant association between the *DBH* TaqI polymorphism and ADHD (Daly et al., 1999). Also, albeit it did not reach statistical significance, the *DBH* GT repeat 4 allele, which is associated with high serum levels of DBH, occurred more frequently in the ADHD group than controls, (Müller Smith et al., 2003). However, other groups failed in replicating these results either with the TaqI polymorphism (Wigg et al., 2002) or with other markers (Hawi et al., 2003). A positive association was shown between the *DBH* 5'del-444a haplotype and cocaine-induced paranoia (Cubells et al., 2000) as well as non-response to antipsychotic drug treatment in schizophrenic patients (Yamamoto et al., 2003). Other studies using a *DBH* -1021 C/T variant found no positive association with schizophrenia (Jonsson et al., 2003) or unipolar major depression with psychotic features (Cubells et al., 2002). These results may indicate that the *DBH* gene is indirectly involved in schizophrenia as a modulatory factor of psychotic symptoms, severity of the disorder and therapeutic response to neuroleptic drugs.

2.5. Mono-Amino-Oxydase

MAO-A and *MAO-B* genes are situated on the X chromosome at Xp11. 23–11.4 and result from the duplication of a common ancestral gene. In humans both genes are deleted in patients with Norrie's disease, a rare X-linked recessive neurological disorder characterized by blindness, hearing loss, and mental retardation (Lan et al., 1989). A point deletion in the *MAO-A* gene was discovered in a Dutch family. This mutation resulted in a complete MAO-A inactivation and was linked to abnormally aggressive behavior in the males from this family (Brunner et al., 1993). Conversely *MAO-A* deficient mice show an increased aggressivity in males that is related to increased levels of 5-HT and NE during development and result in brain structural changes (Cases et al., 1995). A functional polymorphism located in the *MAO-A* gene promoter 1.2 kb upstream of the encoding sequence, consists of a 30 bp repeated sequence present in 3, 3.5, 4, or 5 copies. This polymorphism displays significant

variations in allele frequencies across ethnic groups and is able to affect the transcriptional activity of the *MAO-A* gene promoter (Sabol et al., 1998).

Genetic studies with this polymorphism have found that the high-activity *MAO-A* gene promoter alleles were associated with panic disorder (Deckert et al., 1999) and major depressive disorder (Schulze et al., 2000) in females, while the low activity alleles were associated with schizophrenia in males (Jonsson et al., 2003). Other studies have yielded negative results for panic disorders (Hamilton et al., 2000), schizophrenia (Syagailo et al., 2001; Fan et al., 2004) and mood disorders (Kunugi et al., 1999; Jorm et al., 2000; Furlong et al., 1999; Kirov et al., 1999; Syagailo et al., 2001; Huang et al., 2004).

However, more probant results have been found when genetic studies have taken into account an environmental component. A leading study has shown that this functional polymorphism can modulate the association between childhood maltreatment and subsequent antisocial behavior. In males, who have only one copy of the X chromosome, the *MAO-A* functional polymorphism confers either a high or a low activity genotype. The low activity *MAO-A* genotype is associated with antisocial behavior in up to 85% of a cohort of males who had been severely maltreated in their childhood but not in boys who had suffered little or no abuse. In contrast, the high activity *MAO-A* genotype has a protective effect from developing antisocial behavior in maltreated children (Caspi et al., 2002). Women have two X chromosomes and heterozygous low/high *MAO-A* activity cannot be characterized since one of the alleles is randomly inactivated. Therefore, albeit a similar trend for association between *MAO-A* genotype, antisocial behavior and child maltreatment, was present, these results were less straightforward than for males since the whole female sample cannot be analyzed correctly. However, taken together, these results show a clear influence of the *MAO-A* genotype in the behavioral effects of an environmental factor and may help in understanding the marked differences in the frequency of antisocial behavior between sexes (Caspi et al., 2002). Interestingly, in a study of healthy volunteers the functional high activity genotype was correlated with higher cerebrospinal fluid concentrations of HVA and 5-HIAA in women, while an opposite trend was observed in men (Jonsson et al., 2000).

The association between the lower expression *MAO-A* genotype and antisocial behavior consequent to childhood maltreatment has been replicated by another group (Foley et al., 2004). This risk genotype has also been associated with impulsive traits in males that have experienced early abuse (Huang et al., 2004) and with pathological gambling in males (Ibanez et al., 2000).

2.6. Catechol-O-Methyl-Transferase

The *COMT* gene, localized to chromosome 22q11.1-q11.2, encodes a soluble (S-COMT) and a membrane-bound (MB-COMT) form of the enzyme, the latter characterized by an additional 50 amino acids at the *N*-terminal (Bertocci et al., 1991; Grossman et al., 1992). The two length variants of the *COMT* are expressed from two mRNA transcripts: a long mRNA, which is able to transcribe both S-*COMT* and MB-*COMT* from two different initiation sites, and a short mRNA producing S-*COMT* only. The long mRNA and the larger

MB-*COMT* are predominant in the brain while the short mRNA and the S-*COMT* prevail in the other tissues (Tenhunen et al., 1994; Lundstrom et al., 1995).

The COMT enzymatic activity shows high, intermediate and low rates consistent with inheritance of two codominant alleles (Weinshilboum, 1978). This difference in enzyme activity is independent from protein length variations but is caused by an amino acid substitution. A G /A polymorphism in exon 4 at position 472 in the long mRNA, and 322 in the short mRNA, results in a Val to Met amino acid change at codon 158 of MB-*COMT* and codon 108 of S-*COMT*. The G (Val) allele encodes the thermostable, high activity form of the enzyme, while the A (Met) allele encodes the thermolabile, low activity variant that exhibits a 3 to 4 fold decrease in the enzymatic activity level ((Lachman et al., 1996; Lotta et al., 1995). The G (Val) and A (Met) alleles correspond also to the absence or presence, respectively, of a *Nla*III polymorphic restriction site that allows for easily genotyping the functional variations (Karayiorgou et al., 1998).

COMT is an obvious *a priori* candidate gene for neuropsychiatric disorders that involve dopaminergic or noradrenergic systems (for review see Palmatier et al., 1999) but also a strong *positional* candidate gene for schizophrenia because of its chromosomal location in the locus of the velocardiofacial syndrome (VCF). Microdeletions of 22q11 are associated with VCF which is characterized by congenital abnormalities, learning difficulties, and psychosis in up to one third of patients. Conversely, the deletion is also 80-fold more common in patients with psychosis compared to the normal population (Sugama et al., 1999). Both linkage and association studies have implied that chromosome 22q11 is a locus for schizophrenia (Pulver et al., 1994; Pulver et al., 1994; Karayiorgou et al., 1995; Karayiorgou & Gogos, 1997). The case-control association approach has consequently been used to study the role of *COMT* in schizophrenia and other psychiatric diseases, mostly using the Val108/158Met polymorphism. Positive associations have been found between *COMT* and schizophrenia (Ohmori et al., 1998; de Chaldee et al., 1999), violence in schizophrenia (Lachman et al., 1998), bipolar disorder (Li et al., 1997; Mynett-Johnson et al., 1998), unipolar disorder (Ohara et al., 1998), bipolar disorder or ADHD in VCFS patients (Lachman et al., 1996), OCD (Karayiorgou et al., 1997), drug abuse (Vandenbergh et al., 1997) and Parkinson's disease (Kunugi et al., 1997). However, other studies have excluded a major contribution of the *COMT* gene to schizophrenia (Daniels et al., 1996; Chen et al., 1997; Strous et al., 1997; Karayiorgou et al., 1998; Wei & Hemmings, 1999), bipolar disorder (Craddock et al., 1997; Gutierrez et al., 1997; Kunugi et al., 1997; Lachman et al., 1997; Geller & CookJr., 2000), ADHD or bipolar disorder in VCF syndrome patients (Lachman et al., 1996), substance abuse and violence (Lachman et al., 1998; Vandenbergh et al., 1997), as well as Parkinson's disease (Hoda et al., 1996; Syvanen et al., 1997; Xie et al., 1997).

These conflicting results have prompted a meta-analysis indicating that the *COMT* Met allele that characterizes the instable form of the enzyme with low activity phenotype, is not associated with schizophrenia (Lohmueller et al., 2003). However, a new association study conducted in a genetically

homogeneous population yielded a highly significant association between a *COMT* haplotype and schizophrenia (Shifman et al., 2003). This study is the largest case/control analysis in schizophrenia that has been reported with more than 700 patients and 4,000 control subjects. Genotyping was conducted using 12 SNPs, comprising the Val108/158Met polymorphism, across the *COMT* gene, and haplotypes with 7 of these SNPs were established in the large sample of an Israeli Ashkenazi Jewish population. This population has the advantage of presenting a founder effect that allows for reducing genetic heterogeneity thus increasing gene effect, and avoiding false-positive results due to population stratification.

The association between schizophrenia and the Val108/158Met polymorphism was moderate, but extremely high levels of statistical significance were attained when this marker was analyzed as part of a haplotype including two other noncoding SNPs that were more significantly associated with schizophrenia. Moreover, one of these polymorphisms represented a higher risk factor essentially for women than men, hinting at a possible sex-specific genetic component in schizophrenia. These results confirmed a complex association of the *COMT* locus to schizophrenia and suggested that other functional variants besides the Val108/158Met polymorphism are likely to be involved in susceptibility to schizophrenia (Shifman et al., 2003). In the impetus produced by this study a significant association was also found between bipolar disorder and the allele and haplotype in the *COMT* gene found to be associated with schizophrenia. Moreover, the relative risk, as for schizophrenia, was higher in women (Shifman et al., 2004).

In addition to these association studies, the role of *COMT* in schizophrenia and other neuropsychiatric diseases is further supported by functional genetic studies that have essentially focused on the Val108/158Met polymorphism. A large amount of experimental data suggest that heritable abnormalities of prefrontal dopamine function is a prominent feature of schizophrenia (Grace, 1991; Grace, 1993; Moore et al., 1999). *COMT* may constitute a major contributor to these abnormalities by virtue of its unique role in regulating DA-mediated prefrontal information processing, since COMT inhibitors can improve working memory in both rodents and humans (Weinberger et al., 2001). In this perspective, a study combining a genetic and a functional approach has shown that the Val allele of the Val108/158Met polymorphism that characterizes the high activity form of the *COMT* occurs at higher rates in both schizophrenics and their unaffected siblings. Moreover, patients and siblings bearing this allele performed poorly on the Wisconsin card sorting test (a neuropsychological test of frontal lobe function for working memory) and manifested inefficient brain activation as assessed by functional magnetic resonance imaging (fMRI) (Egan et al., 2001). Interestingly, amphetamine, a drug that increases DA-ergic neurotransmission, enhances the efficiency of prefrontal cortex function as assayed with fMRI during a working memory task in subjects with the high activity val/val genotype but not in subjects with the low activity met/met genotype (Mattay et al., 2003). Moreover, this polymorphism is also associated with personality traits, as assessed by the tridimensional personality questionnaire (Benjamin et al., 2000; Benjamin et al., 2000). Also, homozygosity for the

Met allele is associated, particularly in schizophrenic patients, with lower frontal P300 amplitudes which is an index of DA-ergic efficacy in reducing noise during information processing (Gallinat et al., 2003). In agreement with these findings and with the results of the association studies in Ashkenazi Jews (Shifman et al., 2004; Shifman et al., 2003), the analysis of the allele-specific expression using mRNA from human brains indicated that the haplotype implicated in schizophrenia and bipolar disorder is associated with lower expression of *COMT* mRNA (Bray et al., 2003).

These findings suggest that the *COMT* Val allele impairs prefrontal cognition and physiology and, by virtue of this effect, may condition some pathological features of schizophrenia, thus contributing, with other sequence variations at the *COMT* locus, to the increase of the risk for schizophrenia.

3. CONCLUSIONS

The hypothesis driven genetic studies on the implication in neuro-psychiatric diseases of the genes coding for the MA metabolizing enzymes have produced an impressive amount of data. Among contrasting results issued from genetic linkage or association studies using anonymous markers, a common trend has emerged related to the implication of functional polymorphisms in normal and pathological phenotypes. A composite approach that goes beyond mere genetic analysis has permitted to progress from identifying genetic variants in the MA metabolizing genes and their association with disease, to their potential impact on gene function *in vitro* and to gene expression and function in the human brain. Major improvement in this task has been achieved by the utilization of very large patient cohorts, a better definition of the phenotype investigated and the focalization of the recruitment in genetically homogeneous populations. Another fundamental improvement has been introduced by the evaluation of environmental variants in assessing the genetic components of pathological behavior as well as the coupling of genetic studies with neuroimaging techniques. The results obtained to date let us foresee that it will be possible in the near future to clearly identify several endophenotypes as measurable variants linking a genetic polymorphism to a simple biological trait. This, in turn, will help in to dissect more complex behavioral phenotypes and to elucidate the molecular bases underlying the quantitative genetic origin of complex diseases. In this context, molecular genetic studies on the genes of the MA metabolizing system may open new perspectives for understanding brain function in normal and pathological conditions.

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