Genetics in Psychiatry – Up-to-date Review 2011

Radek Ptacek [1], Hana Kuzelova [1,2], George B. Stefano [3]

1 Clinic of Psychiary, 1st Faculty of Medicine, Charles University in Prague, Czech Republic
2 Department of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University in Prague, Czech Republic
3 Neuroscience Research Institute, State University of New York, College at Old Westbury, Old Westbury, NY, U.S.A.

Correspondence to: Radek Ptacek, PhD.
Clinic of Psychiatry, 1st Faculty of Medicine
Ke Karlovu 11, 128 01 Praha 2, Czech Republic.
e-mail: ptacek@neuro.cz

Submitted: 2011-05-16 Accepted: 2011-06-14 Published online: 2011-08-28

Key words: **psychiatric genetics; genes; polymorphism; genetic variants**

Neuroendocrinol Lett 2011; **32**(4):389–399 **PMID:** 21876508 NEL320411R03

Abstract

Psychiatric genetics is a popular and much-discussed topic. Many candidate genes have been investigated in relation to psychiatric disorders and many connections have been found. The utilization of these investigations is currently at a theoretical level. Nevertheless, these findings of candidate genes will be important for further research and subsequent clinical use, for example in pharmacogenetics). Due to the rapidly growing number of empirical studies that provide profound analysis of different genes and their variants in different psychiatrical symptomatology, the field is highly divided, and providing a succinct overview is challenging. This article attempts to provide an up-to-date review of the most important and most discussed genes (mainly transporter and receptor genes) contributing to the etiology of psychiatric disorders.

REVIEW ARTICLE

INTRODUCTION

Knowledge and understanding of the biological and genetic foundations of mental disorders is rapidly growing (Arai 2011; Stefano *et al.* 2010; Croonenberghs *et al.* 2010; Formisano *et al.* 2010; Atmanene *et al.* 2009; Pastucha *et al.* 2009a; Pastucha *et al.* 2009b), but the field still remains on a more or less theoretical level (Vithoulkas & Carlino 2010; Prasko *et al.* 2009; Raszka *et al.* 2009). Rapid progress in biological (Sokolowska *et al.* 2010; Hernando 2010; Galinska *et al.* 2009) and genetic (Dogan *et al.* 2009; Smolarek *et al.* 2010; Pietras *et al.* 2010; Sokolowska 2010; Pietras *et al.* 2010) research, especially in psychiatry and in prenatal diagnostics (Vlkova *et al.* 2010) has significantly aided assessment of a few developmental disorders; but this progress has only been in monogenic disorders. In reality, the majority of psychiatric disorders are complex; therefore application of these recent research findings is limited. Many disorders are multifactorial (with interaction of environment and genetics) and polygenic, where multiple genes play roles, or oligogenic, with epistasis. These genes are usually responsible for vulnerability to a specific disorder. This fact complicates genetic tests because these genes currently represent only a risk factor for development of disorders, as is the case with psychiatric genetics.

Results from recent studies indicate that genetics plays a substantial role in most major mental illnesses, including schizophrenia, affective disorders, autism, neurotism, anxiety disorders, ADHD (attention deficit hyperactivity disorder), learning disabilities, OCD (obsessive compulsive disorder), alcoholism and drug dependence. Family studies

confirm the genetic basis of many disorders; bipolar disorder, major depression and other common psychiatric conditions are more frequent among close relatives.

Genome-wide association studies cannot test every gene in the genome for each gene's relationship to illness. Genetic analysis investigates whether there is a significant difference in the frequency of a given genetic variant (alleles of a polymorphism) between case and control groups. The polygenicity of a disorder means that very large samples are needed to detect relationships.

The genetic background is usually examined through three primary types of investigation: family studies, twin studies, and candidate gene association studies. Association studies help to find candidate genes for specific psychiatric disorders (Kovacs-Nagy 2009). The identification of candidate genes should be performed by specialized collaborative groups such as the International Molecular Genetic Study of Autism Consortium (IMGSAC), the Autism Genome Project Consortium, and the Autism Genetic Resource Exchange (AGRE).

CANDIDATE GENES

Gene-gene and gene-environment interactions make searching for candidate genes in psychiatric conditions very complicated. In psychiatric genetics, candidate genes are tested for associations with neurobiological and clinical signs of a disorder (Lobo *et al.* 2009). Genes active in the dopaminergic, serotonergic and noradrenergic systems are thought to participate in development of psychiatric disorders via their central role in neurotransmitter pathways. These systems are also important in self-regulation and management of stress (Esch & Stefano 2010), and genes determine how certain neurotransmitters are produced, transmitted and metabolized. The most-used markers are single nucleotide polymorphisms (SNP) and copy number variations (CNV), important in receptor and transporter genes.

Many specific candidate genes have been associated with bipolar disorder: dopamine transporter SLC6A3, brain-derived neurotrophic factor (BDNF), the NMDA glutamate receptor, subunit 2B GRIN2B, D-amino-acid oxidase activator (DAOA), peroxisome proliferator-activated receptor delta (PPARD), neuregulin1 (NRG1), the 5-HT transporter SLC6A4, tryptophan hydroxylase-2 (TPH2) and catechol-o-methyl transferase (COMT) (McQueen *et al.* 2005a). The situation is much more complicated in disorders with clinical and etiological heterogeneity, such as OCD (Samuels 2009). Heritability of alcoholism is thought to range from 50% to 60%, indicating the importance of both genetic and environmental factors in its etiology (Stacey *et al.* 2009). Genetic factors explain between 35% and 54% of the risk of developing any particular symptom of pathological gambling, with each gene accounting for less than 2%, and about 54% of environmental factors (Lobo *et al.* 2009). No specific genes have been found to determine development of nicotine addiction, but several have been found to cause susceptibility to it (Davies *et al.* 2009).

This paper presents a review of only the most studied genetic variants, primarily those that are associated with more than one psychiatric disorder.

DOPAMINERGIC SYSTEM

DRD1

Dopamine D1 receptor, 5q35.1

The DRD1 gene encodes the D1 subtype of the dopamine receptor, the most abundant dopamine receptor in the central nervous system, which regulates neuronal growth and development and mediates behavioral responses.

Single-nucleotide polymorphisms (SNPs) in DRD1 have been investigated in connection with psychiatric disorders such as *A-48G DdeI*. SNPs in the promoter region may play a role in the neurobiology of addictions and may affect vulnerability to addictions (Novak *et al.* 2010) and disorder-associated decreased impulse control such as attention deficit hyperactivity disorder (ADHD) (Oades *et al.* 2008; Bobb *et al.* 2005), nicotine and alcohol dependence (Novak *et al.* 2010; Batel *et al.* 2008; Huang *et al.* 2008) and pathological gambling (da Silva Lobo *et al.* 2007). According to Hoenicka *et al.* (2010), the SNPs *rs11746641* and *rs11749676* are associated with schizophrenia.

DRD2

Dopamine D2 receptor, 11q23

DRD2 encodes the D2 subtype of the dopamine receptor – G-protein coupled receptor inhibits adenylyl cyclase activity.

Variants in this gene (*TaqIA, ANKK1*) have been published in association with dependences (Kasiakogia-Worlley *et al.* 2011) or ADHD (Paclt *et al.* 2010) and some symptoms of schizophrenia (Zahari *et al.* 2011).

Initial studies reported associations of pathological gambling with allele T of the dopamine 2DRD2 *TaqIA* polymorphism (Comings *et al.* 2001; Lobo *et al.* 2010). Some studies have found associations with neighboring polymorphisms on *ANKK1* (Dick *et al.* 2007; Huang *et al.* 2009). According to Zhang *et al.* (2010), DRD2 genetic variation is associated with clinical response to antipsychotic drug treatment and can explain variation in the timing of clinical response to antipsychotics in patients with first-episode schizophrenia (Lencz *et al.* 2009; Zahari *et al.* 2011). A highly positive correlation was described between the combined type of ADHD without co-morbidity and *ANKKl* polymorphism (Paclt *et al.* 2010). An association of the DRD2 genetic variants with impulsive self-injurious behaviors was also demonstrated (Namoda *et al.* 2010).

DRD3

Dopamine D3 receptor, 3q13.3

The DRD3 gene encodes the D3 subtype of the dopamine receptor – G-protein coupled receptor, which inhibits adenylyl cyclase.

Few variants in this gene have been shown to be involved in psychiatric disorders. However, DRD3 variant (Ser9Gly) has been studied together with other DRD genes, mainly in pharmacogenetics (Leggiou *et al.* 2011; deKrom *et al.* 2009), genetics of ADHD (Kopeckova *et al.* 2008; Davis *et al.* 2009), and bipolar disorder (Lee *et al.* 2010), and associations with schizophrenia have been recently published (Pawel *et al.* 2010; Zai *et al.* 2010; Aguilar-Pulido *et al.* 2010).

DRD4

Dopamine D4 receptor, 11p15.5

DRD4 gene encodes the D4 subtype of the dopamine receptor – G-protein coupled receptor, which inhibits adenylyl cyclase.

A length polymorphism in *exon III* (7-repeat allele) has been reported to encode a receptor with lower affinity for dopamine (Jovanovic *et al.* 1999) and associated with various psychiatric disorders (Nemoda *et al.* 2010) including ADHD (Becker *et al.* 2010; Smith 2010), dependences, pathological gambling (Comings *et al.* 1999), alcoholism (Du *et al.* 2010) and drug dependence (Chien *et al.* 2010). Levitan *et al.* (2010) found an association between DRD4 variants and bulimia nervosa, and Emanuele *et al.* (2010) described associations with autism, where the understanding of biological mechanisms becomes more and more important (Boso *et al.* 2010; Emanuele *et al.* 2010a; b; Martirosian *et al.* 2009; Hrdlicka 2008a; b). DRD4 length polymorphism has been described in connection with specific behavioral phenotypes including externalizing behavior problems (Hohman *et al.* 2009), the personality trait of novelty seeking, impulsive personality traits (Misterska *et al.* 2010; Strobel *et al.* 1999), anger (Kang *et al.* 2008), short temper and thrill seeking in males (Dmitrieva *et al.* 2010), and aggressive and delinquent behavior, as compared to other genotypes (Hohmann *et al.* 2009). Khang *et al.* (2008) found that the short allele had significantly lower anger in tendency to anger and higher forgiveness traits. DRD4 variants also play an important role in pharmacogenetics (Kranzler *et al.* 2010).

DRD5

Dopamine D5 receptor, 4p16.1

The DRD5 gene encodes the D5 subtype of the dopamine receptor – G-protein coupled receptor, which stimulates adenylyl cyclase. This receptor is expressed in neurons in the limbic regions of the brain.

DRD5 gene variants were described in association with ADHD (Husarova *et al.* 2010; Ptacek *et al.* 2009), dependences and schizophrenia. Several studies have investigated the association between a dinucleotide *(CA)(n) repeat* polymorphism and ADHD (Banschewski *et al.* 2010; Coghill *et al.* 2009; Gizer *et al.* 2009; Kebir *et al.* 2009). Despite the fact that several studies have suggested that DRD5 repeat polymorphism confers significant risk for ADHD (Squassina *et al.* 2008; Langley *et al.* 2009), results are inconsistent and insignificant (Manor *et al.* 2004). An association of schizophrenia with DRD5 SNP variant was found (Pal *et al.* 2009; Golimbet *et al.* 2008), and associations with drug addiction (Le Foll *et al.* 2009) and alcohol dependence (Hack *et al.* 2011) have been published.

DAT

Dopamine transporter (DAT, DAT1), SLC6A3

DAT gene encodes dopamine transporter, a membrane-spanning protein, which pumps the neurotransmitter dopamine out of the synapse back into cytosol.

Length variants in the DAT gene (*40-bp VNTR)* have been investigated in association with several disorders (Guo *et al.* 2007); variants with 10 repetitions (10R) are associated with depression (Felicio *et al.* 2010), ADHD (Sharp *et al.* 2009) and delinquency (Guo *et al.* 2007; 2010). According to Reese *et al.* (2010), DAT polymorphism is also associated with antisocial personality disorder in alcoholics. Variants with 9 repetitions (9R) exert a general protective effect against a spectrum of risky behaviors (Guo *et al.* 2010).

The 10-repeat variant is also thought to be associated with left-sided inattention in ADHD (Bellgrove *et al.* 2005) and has been linked to an enhanced response to methylphenidate (Bellgrove *et al.* 2005); however, results from these studies are very contradictory (Contini *et al.* 2010).

DBH

Dopamine-beta-hydroxylase, 9q34

DBH gene provides instructions for producing the enzyme dopamine beta (β)-hydroxylase, which converts dopamine to norepinephrine.

The DBH gene and its variants (SNP) are one of the candidate genes studied for anxiety disorders (Itoi *et al.* 2010). *DBH-1021C/T* gene polymorphism and lower DBH activity was studied in correspondence to post-traumatic stress disorder (Mustapic *et al.* 2007) and in ADHD (Paclt *et al.* 2009). According to Hesset *et al.* (2009), DBH-1021T/T genotype is significantly associated with increased neuroticism scores and impulsive and aggressive behavior in ADHD. DBH variants were also examined in association with addictions (Fernàndez-Castillo *et al.* 2010). *SNP rs3025343G* is significantly associated with smoking cessation (Tobacco and Genetics Consortium 2010); however, other results contradict this (Breitling *et al.* 2010).

SEROTONERGIC SYSTEM

5HTT

Serotonin transporter (SLC6A4), 17q11.1–q12

The 5HTT gene encodes serotonin transporter, which transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons and plays a major role in serotonin transmission.

The most extensively studied variant in genetic studies is a length polymorphism (variable number of repeats) in the promoter region of the serotonin transporter gene (*5HTTLPR*). The short (S) allele is associated with lower transporter activity and mental illness, high trait anxiety, mood and anxiety disorders (Blom *et al.* 2011), predispositions to fear-related behaviors, negative emotionality, both unipolar and bipolar forms of depression and neuroticism (Ohaeri *et al.* 2010; Hariri & Holmes 2003), pathological gambling (Perez de Castro *et al.* 1999), sui-

cidal behavior, alcohol dependence and treatment of alcohol dependence (Kenna 2010), eating disorders, post-traumatic stress disorders and other disorders (Kuzelova *et al.* 2010; Anguelova *et al.* 2003a; 2003b). It may have a role in human aggression (Craig *et al.* 2009). Long allele (L) is associated with ADHD and binge eating (Kuzelova *et al.* 2010).

HT1A

Serotonin receptor 5-HT1A

The 5-HT1A receptor is a subtype of the 5-HT receptor, which binds the endogenous serotonin.

The receptors associated with serotonergic neurons, together with the serotonin transporter, appear to be key players in the control of aggression (Olivier & van Oorschot 2005). Altered transcription of the 5-HT1A receptor caused by genetic variants (C(-1019)G polymorphism) can lead to increased predisposition to depression (Benedetti *et al.* 2011; Albert *et al.* 2004; Gleason *et al.* 2010; Liu *et al.* 2011; Idova *et al.* 2010), psychosis (Kishi *et al.* 2010), panic, phobic and anxiety disorders (Lanzenberger *et al.* 2007; Gleason *et al.* 2010) and eating disorders (Lim *et al.* 2010).

HTR2A

Serotonin receptor 5-HT2A

The 5-HT2A receptor is a subtype of the 5-HT2 receptor, which is the main excitatory receptor subtype.

Several polymorphisms have been identified for HTR2A (A-1438G [rs6311], C102T [rs6313] and His452Tyr [rs6314]). HTR2A is thought to play a role in impulsiveness (Salo *et al.* 2010). Several studies have seen links between the -1438G/A polymorphism and mood disorders such as bipolar disorder and major depressive disorder (Chee *et al.* 2001). An association with schizophrenia has also been suggested (Tsunoka *et al.* 2010; Kim *et al.* 2011). Mutation in intron 2 is connected with changes in treatment response and therapeutic effect of several clinically effective and potential atypical antipsychotics, as well as several antidepressants (Kishi *et al.* 2010; Hruby *et al.* 2010).

HTR2C

Serotonin receptor 5-HT2C

The 5-HT2C receptor is a subtype of the 5-HT receptor, which binds the endogenous neurotransmitter serotonin. It modulates serotonergic neurotransmission in the central nervous system.

Studies in humans have reported abnormalities in patterns of HTR2C (functional polymorphism 68G>C [Cys23Ser] and in promoter polymorphism-995G>A) editing in depressed suicide victims (Videtic *et al.* 2009; Serreti *et al.* 2009). Several studies suggest associations with specific symptoms in schizophrenia (Bai *et al.* 2011). Yasseen *et al.* (2010) found possible association with alcohol use disorder comorbidity. Polymorphisms in HTR2C (rs498207, C-759T, G-697C and Ser23Cys) can be associated with weight gain after using psychiatric medication (Sicard *et al.* 2010).

ENZYME GENES

MAO-A

Monoamine oxidase A, Xp11.3

MAO-A and MAO-B are two related enzymes that play an important role in the metabolism of biogenic amines in the central nervous system and in the periphery.

The most investigated is of these is MAO-A. The MAO-A gene is located on the X chromosome, thus sex differences in its expression may occur. Most research in this area has centered on detecting behavioral associations with SNPs, microsatellites and/or promoter VNTR variants in MAO-A (Craig *et al.* 2009). A functional promoter-region polymorphism of this gene has been described in connection to mental illnesses. MAO-A promoter-region polymorphism is also thought to influence risk for ADHD development (Coccini *et al.* 2009; Nedic *et al.* 2010; Gizer *et al.* 2009) and plays an important role in effectiveness of pharmacotherapy (Fisar *et al.* 2010; Dell´osso *et al.* 2010). Subsequent investigations revealed an association of the more severe forms of pathological gambling and polymorphisms in MAO-A (3 repeat in promoter region) (Perez de Castro *et al.* 2002).

COMT

Catechol-O-methyl transferase, 22q11.2

COMT is the enzyme that degrades catecholamines such as dopamine, epinephrine and norepinephrine.

COMT variants (Val158Met, rs737865 and rs165599) were studied for association with personality traits. COMT (Val158Met) plays a role in determining interindividual variability in the proclivity for violent behavior in subjects without major mental disorder (Vevera *et al.* 2009). This variant also is connected with schizophrenia (Hoenicka *et al.* 2010; Costas *et al.* 2010; Kong *et al.* 2011), novelty seeking (Hosak *et al.* 2006) and some symptoms of ADHD (Kebir *et al.* 2011) including bulimia nervosa in ADHD patients (Yilmaz *et al.* 2011). COMT variants are also important for pharmacogenetics (Kereszturi *et al.* 2008; Hamidovic *et al.* 2010).

TPH

Tryptophan hydroxylases 1 and 2 (TPH1 and TPH2)

Tryptophan hydroxylase enzyme (TPH1) catalyses the rate-limiting step in the synthesis of serotonin.

TPH1 has two well-characterized *SNPs (A218C and A779C)* in intron 7. An association between the A218C polymorphism with the disorders on the schizophrenia spectrum was demonstrated (Efimov *et al.* 2009; Watanabe *et al.* 2007). Connection of TPH expression with anxiety (Charoenphandhu *et al.* 2011) and endogenous psychoses (Efimov *et al.* 2009) was described, and Kim *et al.* (2010) found an association with drinking behavior.

OTHER TRANSPORTER GENES

NET

Noradrenaline transporter, monoamine transporter, SLC6A2, 16q12.2

This gene encodes a member of the sodium: neurotransmitter symporter family.

Several studies revealed a positive association of the *NET-T182C* polymorphism with susceptibility to and severity of depression (Min *et al.* 2009) and response to antidepressants with homologous monoamine transporter targets (Kim *et al.* 2006). The variant *NET G1287A* GG genotype (56% of the population) was associated with better response to the NRI than to SSRI. Inconclusive results were published on an association with ADHD (Cho *et al.* 2008; Kollins *et al.* 2008).

VMAT1

Vesicular monoamine transporter, member 1, SLC18A1, 8p21

VMAT2

Vesicular monoamine transporter, member 2, SLC18A2, 10q25

VMATs act to accumulate cytosolic monoamines into synaptic vesicles. Their function is essential to the correct functioning of the monoaminergic systems, which has been implicated in several human neuropsychiatric disorders.

VMATs are an important target for biological research in neuropsychiatric disorders. Linkage studies found associations with schizophrenia, bipolar disorder and anxiety-related phenotypes (Lohoff 2010).

VMAT2 was investigated mainly in connection to schizophrenia (Talkowski *et al.* 2008; Iritani *et al.* 2010).

OTHER CANDIDATE GENES

Many other gene variants have been investigated in relation to psychiatric disorders (Galecki *et al.* 2010), mainly in connection to autism and schizophrenia (Melkersson 2011; Kałuzna-Czaplinska *et al.* 2010a; b). For example, ***GABA*** (gamma-amino butyric acid) receptor genes are associated with autism (e.g. Fasemi *et al.* 2010), ***Sry*** locus (Sex-determining region Y) on ***Y*** chromosome has been investigated in connection with aggressive behavior (Miczek *et al.* 2007; Gatewood *et al.* 2006), and a missense polymorphism in ***GPR55*** (G protein-coupled receptor 55) receptor gene is associated with anorexia nervosa (Ishiguro *et al.* 2010). Rajender *et al.* (2008) found a highly significant association between violent criminal activity and the shorter CAG repeats in the gene for androgen receptor ***AR***.

Table 1 summarizes findings on association of genes and psychiatric disorders.

MORPHINERGIC PROCESSES

After many years of investigation by various groups' it has now been demonstrated that morphine can be synthesized in human and other animal tissues (Mantione *et al.* 2010d; Kream & Stefano 2006a, b; Stefano *et al.* 2008; Zhu *et al.* 2005a, b). This complements other studies demonstrating novel

Tab. 1. The main candidate genes in psychiatric genetics.

	Attention-deficit and disruptive behavior disorders	Substance-related disorders	Schizophrenia	Mood disorders	Anxiety disorders	Eating disorders	Treatment response
DRD1	x	x	x				
DRD2	x	x	x				
DRD3	x		x				
DRD4	x	x					x
DRD5	x						
DBH					x		
DAT	x			x			x
5HTT	x	x		x	x	x	x
5-HT1A				x		x	
5-HTR2A							
5-HRT2C		x		x			
MAO A	x	x					
COMT			x				x
TPH			x	x			
NET					x		x
VMAT1,2			x		x		

opiate receptors that are opiate alkaloid selective and opioid peptide insensitive in human and other animal tissues, including neural (see Fricchione *et al.* 2005; Kream & Stefano 2005a). Both the mu3 (mu3 opiate receptor subtype) and 4 receptors have been cloned (see Kream & Stefano 2005a) and found to be 6 transmembrane in nature (Kream & Stefano 2005a). Furthermore, these opiate receptors are coupled to constitutive nitric oxide release (Kream & Stefano 2009; Mantione *et al.* 2008; Stefano *et al.* 2008a, b; Stefan & Kream 2007; 2010). In addition, the enzymes associated with endogenous morphine biosynthesis have been determined and shown to be regulated by end product inhibition and/or nitric oxide generated via mu3-4 occupancy (Kream & Stefano 2006a; Mantione *et al.* 2008, 2010a, b, c; Stefano 2007; Zhu 2005a, b). The enzymes/genes include among others CYP2D6 (Cytochrome P450 2D6), COMT (Catechol-O-methyltransferase), TH (tyrosine hydroxylase), PNMT (phenylethanolamine N-methyltransferase), DDC (DOPA decarboxylase 5) (Kream & Stefano 2006a; Mantione 2008, 2010a, b, c; Stefano 2007; Zhu 2005a, b). Not surprisingly some are linked to dopamine synthesis, which is an important feature of this pathway since dopamine serves as a morphine precursor (see Kream & Stefano 2006a). Thus, in previous reports it has been surmised that morphine has functions that transcend analgesia (Esch & Stefano 2011; Kream & Stefano 2008; Mantione *et al.* 2010c; Salamon *et al.* 2005; Stefano *et al.* 2005, 2007, 2008b). Given the anatomical localization of endogenous morphine, the presence of its novel receptors and its coupling to nitric oxide release and linkages to the catecholamine pathway authors have also speculated on its role in psychiatry (Kream *et al.* 2010). Here too, as documented by these reports polymorphisms and splice variations will play a critical role in mental health.

DISCUSSION AND CONCLUSION

Many psychiatric disorders are highly heritable; however, psychiatric disorders are not monogenic and many interactions participate in the development of a disorder. The utility of a candidate gene is limited because most disorders are determined by a combination of genetic and environmental factors (Norrholm *et al.* 2009; Latalova *et al.* 2010). Moreover, the situation could be complicated by the presence of many other comorbid disorders (Ohaeri *et al.* 2010). The mechanism of heritability has not yet been adequately elucidated, and limitations also exist in the validation of the interactions (Bill *et al.* 2009).

Candidate genes have been intensively studied through modern methods, but the methods of these studies are very heterogeneous and in many cases incorrect. Many studies investigated only one gene polymorphism in connection to psychiatric disorders, and on the basis of their results formed questionable conclusions. In reality, psychiatric disorders are mainly polygenic, and multiple genes and interactions take part in their development. For example, Hohmnn *et al.* (2009) suggested that there could be an epistasis between DRD4 and 5-HTTLPR.

Many polymorphisms have been so widely studied that they have been associated with an implausibly large number of psychiatric and non-psychiatric phenotypes, many of which are likely to be false positives. In this regard, the study of gene pattern expression, i.e., microarray (Casares *et al.* 2009), promises to be a valuable technique since it relies on observing many expressions at once. Clearly this approach is more realistic since so many chemical messengers are involved in both normal and abnormal activity.

As more studies are conducted it is possible to understand more clearly the biological mechanisms of psychiatric disorders. The aim of psychiatric genetics is to better understand the etiology of psychiatric disorders and improve treatment methods. The basic assumption of studies investigating genetic relations of psychiatric disorders is that correct diagnostic methods were used.

REFERENCES

1 Aguiar-Pulido V, Seoane JA, Rabuñal JR, Dorado J, Pazos A, Munteanu CR (2010) Machine learning techniques for single nucleotide polymorphism--disease classification models in schizophrenia. Molecules. **12**: 15(7): 4875–89.

2 Albert PR, Lemonde S (2004) 5-HT1A receptors, gene repression, and depression: guilt by association. Neuroscientist. **10**(6): 575–93.

3 Arai M (2011) Increased plasma arginine vasopressin levels in dopamine agonist-treated Parkinson's disease patiens. Neuroendocrinol Lett. **32**(1): 39–43.

4 Atmanene C, Laux A, Glattard E, Muller A, Schoentgen F, Metz-Boutigue MH, Aunis D, Van Dorsselaer A, Stefano G, Sanglier-Cianferani S, Goumon (2009) Characterization of human and bovine phosphatidylethanolamine-binding protein (PEBP/RKIP) interactions with morphine and morphine-glucuronides determined by noncovalent mass spectrometry. Med Sci Monit. **15**(7): BR178–187.

5 Bai YM, Chen TT, Liou YJ, Hong CJ, Tsai SJ (2011) Association between HTR2C polymorphisms and metabolic syndrome in patients with schizophrenia treated with atypical antipsychotics. Schizophr Res. **125**(2–3): 179–86.

6 Banaschewski T, Becker K, Scherag S, Franke B, Coghill D (2010) Molecular genetics of attention-deficit/hyperactivity disorder: an overview. Eur Child Adolesc Psychiatry. **19**(3): 237–57.

7 Batel P. , Houchi H. , Daoust M. , Ramoz N. , Naassila M. , Gorwood P (2008) A haplotype of the DRD1 gene is associated with alcohol dependence. Alcohol Clin Exp Res. **32**: 567–72.

8 Becker K, Blomeyer D, El-Faddagh M, Esser G, Schmidt MH, Banaschewski T, Laucht M (2010) From Regulatory Problems in Infancy to Attention-Deficit/Hyperactivity Disorder in Childhood: A Moderating Role for the Dopamine D4 Receptor Gene? J Pediatr. [Epub ahead of print]

9 Bellgrove MA, Hawi Z, Kirley A, Fitzgerald M, Gill M, Robertson IH (2005) Association between dopamine transporter (DAT1) genotype, left-sided inattention, and an enhanced response to methylphenidate in attention-deficit hyperactivity disorder. Neuropsychopharmacology. **30**(12): 2290–7.

10 Benedetti F, Radaelli D, Poletti S, Locatelli C, Dallaspezia S, Lorenzi C, Pirovano A, Colombo C, Smeraldi E (2011) Association of the C(-1019)G 5-HT1A promoter polymorphism with exposure to stressors preceding hospitalization for bipolar depression. J Affect Disord. [Epub ahead of print]

11 Blom RM, Samuels JF, Riddle MA, Joseph Bienvenu O, Grados MA, Reti IM, Eaton WW, Liang KY, Nestadt G (2011) Association between a serotonin transporter promoter polymorphism (5HTTLPR) and personality disorder traits in a community sample. J Psychiatr Res. [Epub ahead of print]

12 Bobb AJ, Addington AM, Sidransky E, Gornick MC, Lerch JP, Greenstein DK *et al* (2005) Support for association between ADHD and two candidate genes: NET1 and DRD1. Am J Med Genet B Neuropsychiatr Genet. **5**: 67–72.
13 Boso M, Comelli M, Emanuele E, Podavini F, Marini M, Mancini L, Ucelli di Nemi S, Barale F, Politi P (2010) Seasonal fluctuations in problem behaviors among young adults with autism and intellectual disability. Med Sci Monit. **16**(5): CR213–6.
14 Breitling LP, Twardella D, Hoffmann MM, Witt SH, Treutlein J, Brenner H (2010) Prospective association of dopamine-related polymorphisms with smoking cessation in general care. Pharmacogenomics. **11**(4): 527–36.
15 Casares FM, Mantione KJ, Kream RM, *et al* (2009) Neurotransmitter Gene Microarray Analysis in Human White Blood Cells and Human Stem Cells Following Morphine Exposure. Act Nerv Super Rediviva **51**: 127–132.
16 Charoenphandhu J, Teerapornpuntakit J, Nuntapornsak A, Krishnamra N, Charoenphandhu N (2011) Anxiety-like behaviors and expression of SERT and TPH in the dorsal raphé of estrogen- and fluoxetine-treated ovariectomized rats. Pharmacol Biochem Behav. **5**. 98(4): 503–510. [Epub ahead of print].
17 Chee IS, Lee SW, Kim JL, Wang SK, Shin YO, Shin SC, Lee YH, Hwang HM, Lim M (2001) 5-HT2A receptor gene promoter polymorphism -1438A/G and bipolar disorder. Psychiatr Genet. **11**(3): 111–4.
18 Cheon KA, Ryu YH, Kim JW, Cho DY (2005) The homozygosity for 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. Eur Neuropsychopharmacol. **15**(1): 95–101.
19 Chien CC, Lin CH, Chang YY, Lung FW (2010) Association of VNTR polymorphisms in the MAOA promoter and DRD4 exon 3 with heroin dependence in male Chinese addicts. World J Biol Psychiatry. **11**(2 Pt 2): 409–16.
20 Cho SC, Kim JW, Kim BN, Hwang JW, Park M, Kim SA, Cho DY, Yoo HJ, Chung US, Son JW, Park TW (2008) No evidence of an association between norepinephrine transporter gene polymorphisms and attention deficit hyperactivity disorder: a family-based and case-control association study in a Korean sample. Neuropsychobiology. **57**(3): 131–8. Epub 2008 Jun 13.
21 Coccini T, Crevani A, Rossi G, Assandri F, Balottin U, Nardo RD, Manzo L (2009) Reduced platelet monoamine oxidase type B activity and lymphocyte muscarinic receptor binding in unmedicated children with attention deficit hyperactivity disorder. Biomarkers. **14**(7): 513–22.
22 Coghill D, Banaschewski T (2009) The genetics of attention-deficit/hyperactivity disorder. Expert Rev Neurother. **9**(10): 1547–65.
23 Comings DE, Gade R, Wu S, Chiu C, Dietz G, Muhleman D *et al* (1997) Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. Mol Psychiatry. **2**: 44–56.
24 Comings DE, Gade-Andavolu R, Gonzalez N, Wu S, Muhleman D, Chen C *et al* (2001) The additive effect of neurotransmitter genes in pathological gambling. Clin Genet. **60**: 107–16.
25 Contini V, Victor MM, Marques FZ, Bertuzzi GP, Salgado CA, Silva KL, Sousa NO, Grevet EH, Belmonte–de–Abreu P, Bau CH (2010) Response to methylphenidate is not influenced by DAT1 polymorphisms in a sample of Brazilian adult patients with ADHD. J Neural Transm. **117**(2): 269–76.
26 Costas J, Sanjuán J, Ramos-Ríos R, Paz E, Agra S, Ivorra JL, Páramo M, Brenlla J, Arrojo M (2010) Heterozygosity at catechol-O-methyltransferase Val158Met and schizophrenia: New data and meta-analysis. J Psychiatr Res. [Epub ahead of print]
27 Craig IW, Halon KE (2009) Genetics of human aggressive behavior Hum Genet. **126**: 101–113.
28 Croonenberghs J, Grieken S, Wauters A, West D, Brouw L, Maes M (2010) Serum testosterone concentration in male autistic youngsters. Neuroendocrinol Lett. **31**(4): 483–488.
29 da Silva Lobo DS, Vallada HP, Knight J, Martins SS, Tavares H, Gentil V *et al* (2007) Dopamine genes and pathological gambling in discordant sib-pairs. J Gambl Stud. **23**: 421–33.
30 Davies GE, Soundy TJ (2009) The genetics of smoking and nicotine addiction. S D Med. Spec No: 43–9.
31 Davis C, Patte K, Levitan RD, Carter J, Kaplan AS, Zai C, Reid C, Curtis C, Kennedy JL (2009) A psycho-genetic study of associations between the symptoms of binge eating disorder and those of attention deficit (hyperactivity) disorder. J Psychiatr Res. **43**(7): 687–96.
32 de Krom M, Staal WG, Ophoff RA, Hendriks J, Buitelaar J, Franke B, de Jonge MV, Bolton P, Collier D, Curran S, van Engeland H, van Ree JM (2009) A common variant in DRD3 receptor is associated with autism spectrum disorder. Biol Psychiatry. **65**(7): 625–30.
33 Dell'osso B, Palazzo MC, Oldani L, Altamura AC (2010) The Noradrenergic Action in Antidepressant Treatments: Pharmacological and Clinical Aspects. CNS Neurosci Ther. [Epub ahead of print]
34 Dick DM, Wang JC, Plunkett J, Aliev F, Hinrichs A, Bertelsen S *et al* (2007) Family-based association analyses of alcohol dependence phenotypes across DRD2 and neighboring gene ANKK1. Alcohol Clin Exp Res. **31**: 1645–53.
35 Dmitrieva J, Chen C, Greenberger E, Ogunseitan O, Ding YC (2010) Gender-specific expression of the DRD4 gene on adolescent delinquency, anger and thrill seeking. Soc Cogn Affect Neurosci. [Epub ahead of print].
36 Dogan I, Onen H, Yurdakul A, Konac E, OzturkE, Varol E, Ekmekci A (2009) Polymorphisms in the vitamin D receptor gene and risk of lung cancer. Med Sci Monit. **15**(8): BR232–242.
37 Dominguez E, Loza MI, Padin F, Gesteira A, Paz E, Paramo M, Brenlla J, Pumar E, Iglesias F, Cibeira A *et al.* (2007) Extensive linkage disequilibrium mapping at HTR2A and DRD3 for schizophrenia susceptibility genes in the Galician population. Schizophr Res. **90**: 123–129.
38 Du Y, Yang M, Yeh HW, Wan YJ (2010) The association of exon 3 VNTR polymorphism of the dopamine receptor D4 (DRD4) gene with alcoholism in Mexican Americans. Psychiatry Res. **177**(3): 358–360.
39 Efimov RV, Mavlyudova AS, Golimbet VE (2009) [Association between the tryptophan hydroxylase (TPH) gene polymorphic markers and endogenous psychoses] Genetika. **45**(12): 1668–73 (In Russian).
40 Emanuele E, Boso M, Cassola F, Broglia D, Bonoldi I, Mancini L, Marini M, Politi P. (2010b). Increased dopamine DRD4 receptor mRNA expression in lymphocytes of musicians and autistic individuals: bridging the music-autism connection. Neuroendocrinol Lett. **31**(1): 122–125.
41 Emanuele E, Colombo R, Martinelli V, Brondino N, Marini M, Boso M, Barale F, Politi P. (2010a). Elevated urine levels of bufotenine in patients with autistic spectrum disorders and schizophrenia. Neuroendocrinol Lett. **31**(1): 117–121.
42 Esch T, Stefano GB (2010) The neurobiology of stress management. Neuroendocrinol Lett. **31**(1): 19–39.
43 Esch T, Stefano GB (2011) The neurobiological link between compassion and love. Med Sci Monit. **17**: RA65–RA75.
44 Fatemi SH, Reutiman TJ, Folsom TD, Rooney RJ, Patel DH, Thuras P (2010) mRNA and protein levels for GABAAalpha4, alpha5, beta1 and GABABR1 receptors are altered in brains from subjects with autism. J Autism Dev Disord. **40**(6): 743–50.
45 Felicio AC, Moriyama TS, Godeiro-Junior C, Shih MC, Hoexter MQ, Borges V, Silva SM, Amaro-Junior E, Andrade LA, Ferraz HB, Bressan RA (2010) Higher dopamine transporter density in Parkinson's disease patients with depression. Psychopharmacology (Berl). [Epub ahead of print].
46 Fernàndez-Castillo N, Ribasés M, Roncero C, Casas M, Gonzalvo B, Cormand B (2010) Association study between the DAT1, DBH and DRD2 genes and cocaine dependence in a Spanish sample. Psychiatr Genet. [Epub ahead of print].
47 Fisar Z, Hroudová J, Raboch J (2010) Inhibition of monoamine oxidase activity by antidepressants and mood stabilizers. Neuroendocrinol Lett. **31**(5): 645–56.
48 Formisano R, Cicinelli P, Buzzi MG, Brunelli S, Zafonte R, Vinicola V, Gabrielli A, Sabatini U (2009) Blink reflex changes in parkinsonism following severe traumatic brain injury correlates with diffuse axonal Indry. Med Sci Monit. **15**(3): CR101–106.

49 Fricchione G, Zhu W, Cadet P, *et al* (2008) Identification of endogenous morphine and a mu3-like opiate alkaloid receptor in human brain tissue taken from a patient with intractable complex partial epilepsy. Med Sci Mon. **14**: CS45–CS49.
50 Galecki P, Szemraj J, Florkowski A, Talarowska M, Bienkiewicz M, Galecka E, Lewinski (2010) Single nucleotide polymorphism of the KIBRA gene in recurrent depressive disorders. Neuroendocrinol Lett. **31**(1): 97–102.
51 Galinska B, Szulc A, Tarasow E, Kubas B, Dzienis W, Czernikiewicz A, Walecki J (2009) Duration of untreated psychosis and proton magnetic resonance spectroscopy (1H-MRS) findings in first-episode schizophrenia. Med Sci Monit. **15**(2): CR82–CR88.
52 Gatewood JD, Wills A, Shetty S, Xu J, Arnold AP, Burgoyne PS, Rissman EF (2006) Sex chromosome complement and gonadal sex influence aggressive and parental behaviors in mice. J Neurosci. **26**: 2335–2342.
53 Gizer IR, Ficks C, Waldman ID (2009) Candidate gene studies of ADHD: a meta-analytic review. Hum Genet. **126**(1): 51–90.
54 Gleason G, Liu B, Bruening S, Zupan B, Auerbach A, Mark W, Oh JE, Gal-Toth J, Lee F, Toth M (2010) The serotonin1A receptor gene as a genetic and prenatal maternal environmental factor in anxiety. Proc Natl Acad Sci U S A. **107**(16): 7592–7.
55 Golimbet VE, Alfimova MV, Gritsenko IK, Lezheiko TV, Ebstein R (2008) Association of dopamine receptor D5 gene polymorphism with peculiarities of voluntary attention in schizophrenic patients and their relatives. Bull Exp Biol Med. **145**(1): 65–7.
56 Guo G, Cai T, Guo R, Wang H, Harris KM (2010) The dopamine transporter gene, a spectrum of most common risky behaviors, and the legal status of the behaviors. PLoS One. **5**(2): e9352.
57 Guo G, Roettger ME, Shih JC (2007) Contributions of the DAT1 and DRD2 genes to serious and violent delinquency among adolescents and young adults. Hum Genet. **121**(1): 125–36.
58 Hack LM, Kalsi G, Aliev F, Kuo PH, Prescott CA, Patterson DG, Walsh D, Dick DM, Riley BP, Kendler KS (2011) Limited associations of dopamine system genes with alcohol dependence and related traits in the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD). Alcohol Clin Exp Res. **35**(2): 376–85.
59 Hamidovic A, Dlugos A, Palmer AA, de Wit H (2010) Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. Psychiatr Genet. **20**(3): 85–92.
60 Hernando R (2010) Cerebral atherosclerosis causes neurodegenerative diseasesMed Sci Monit. **16**(1): LE1–2.
61 Hess C, Reif A, Strobel A, Boreatti-Hummer A, Heine M, Lesch KP, Jacob CP (2009) A functional dopamine-beta-hydroxylase gene promoter polymorphism is associated with impulsive personality styles, but not with aVective disorders. J Neural Transm. **116**: 121–130.
62 Hoenicka J, Garrido E, Ponce G, Rodríguez-Jiménez R, Martínez I, Rubio G, Jiménez-Arriero MA, Palomo T (2010) Sexually dimorphic interaction between the DRD1 and COMT genes in schizophrenia. Am J Med Genet B Neuropsychiatr Genet. [Epub ahead of print].
63 Hohmann S, Becker K, Fellinger J, Banaschewski T, Schmidt MH, Esser G, Laucht M (2009) Evidence for epistasis between the 5-HTTLPR and the dopamine D4 receptor polymorphisms in externalizing behavior among 15-year-olds. J Neural Transm. **116**(12): 1621–9.
64 Hosák L, Libiger J, Cizek J, Beránek M, Cermáková E (2006) The COMT Val158Met polymorphism is associated with novelty seeking in Czech methamphetamine abusers: preliminary results. Neuroendocrinol Lett. **27**(6): 799–802.
65 Hrdlicka M. (2008a). Structural neuroimaging in autism. Neuroendocrinol Lett. **29**(3): 281–6.
66 Hrdlicka M. (2008b). EEG abnormalities, epilepsy and regression in autism: a review. Neuroendocrinol Lett. **29**(4): 405–9.
67 Hruby R, Nosalova G, Hruba S (2010) Predictive significance of TCI-R for antidepressant treatment. Med Sci Monit. **16**(8): CR383–8.
68 Huang W, Ma JZ, Payne TJ, Beuten J, Dupont RT, Li MD (2008) Significant association of DRD1 with nicotine dependence. Hum Genet. **123**(2): 133–40.
69 Huang W, Payne TJ, Ma JZ, Beuten J, Dupont RT, Inohara N *et al* (2009) Significant association of ANKK1 and detection of a functional polymorphism with nicotine dependence in an African-American sample. Neuropsychopharmacology. **34**: 319–30.
70 Husarova V, Ondrejka I, Tonhajzerova I (2010) Potential pathomechanisms of ADHD based on neurometabolite changes. Neuroendocrinol Lett. **31**(4): 438–445.
71 Idova GV, Iur'ev DV, Kuznetsova SM. (2010) [Immune response under activation of pre- and postsynaptic serotonin 5-HT1A-receptors in mice with depressive-like behavior]. [Article in Russian] Ross Fiziol Zh Im I M Sechenova. **96**(11): 1097–102.
72 Iritani S, Sekiguchi H, Habuchi C, Hikita T, Taya S, Kaibuchi K, Ozaki N (2010) Immunohistochemical study of vesicle monoamine transporter 2 in the hippocampal region of genetic animal model of schizophrenia. Synapse. **64**(12): 948–53.
73 Ishiguro H, Onaivi ES, Horiuchi Y, Imai K, Komaki G, Ishikawa T, Suzuki M, Watanabe Y, Ando T, Higuchi S, Arinami T (2010) Functional polymorphism in the GPR55 gene is associated with Anorexia Nervosa. Synapse. [Epub ahead of print].
74 Itoi K, Sugimoto N (2010) The brainstem noradrenergic systems in stress, anxiety and depression. J Neuroendocrinol. **22**(5): 355–61.
75 Jovanovic V, Guan HC, Van Tol HH (1999) Comparative pharmacological and functional analysis of the human dopamine D4. 2 and D4. 10 receptor variants. Pharmacogenetics. **9**: 561–8.
76 Kałuzna-Czaplinska J, Michalska M, Rynkowski J (2010a) Determination of tryptophan in urine of autistic and healthy children by gas chromatography/mass spectrometry. Med Sci Monit. **16**(10): CR488–92.
77 Kałuzna-Czaplińska J, Socha E, Rynkowski J (2010b) Determination of homovanillic acid and vanillylmandelic acid in urine of autistic children by gas chromatography/mass spectrometry. Med Sci Monit. **16**(9): CR445–50.
78 Kang JI, Namkoong K, Kim SJ (2008) Association of DRD4 and COMT polymorphisms with anger and forgiveness traits in healthy volunteers. Neurosci Lett. **430**(3): 252–7.
79 Kasiakogia-Worlley K, McQuillin A, Lydall GJ, Patel S, Kottalgi G, Gunwardena P, Cherian R, Rao H, Hillman A, Gobikrishnan N, Douglas E, Qureshi SY, Jauhar S, Ball D, O'Kane A, Owens L, Dedman A, Sharp SI, Kandaswamy R, Guerrini I, Thomson AD, Smith I, Dar K, Morgan MY, Gurling HM (2011) Lack of allelic association between markers at the DRD2 and ANKK1 gene loci with the alcohol-dependence syndrome and criminal activity. Psychiatr Genet. [Epub ahead of print].
80 Kebir O, Joober R (2011) Neuropsychological endophenotypes in attention-deficit/hyperactivity disorder: a review of genetic association studies. Eur Arch Psychiatry Clin Neurosci. [Epub ahead of print].
81 Kebir O, Tabbane K, Sengupta S, Joober R (2009) Candidate genes and neuropsychological phenotypes in children with ADHD: review of association studies. J Psychiatry Neurosci. **34**(2): 88–101.
82 Kenna GA (2010) Medications Acting on the Serotonergic System for the Treatment of Alcohol Dependent Patients. Curr Pharm Des. [Epub ahead of print].
83 Kereszturi E, Tarnok Z, Bognar E, Lakatos K, Farkas L, Gadoros J, Sasvari-Szekely M, Nemoda Z (2008) Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. Am J Med Genet B Neuropsychiatr Genet. **147B**(8): 1431–5.
84 Kim H, Lim SW, Kim S, Kim JW, Chang YH, Carroll BJ, Kim DK (2006) Monoamine transporter gene polymorphisms and antidepressant response in koreans with late-life depression. JAMA. **296**(13): 1609–18.
85 Kim SK, Lee SI, Shin CJ, Son JW, Ju G (2010) The genetic factors affecting drinking behaviors of korean young adults with variant aldehyde dehydrogenase 2 genotype. Psychiatry Investig. **7**(4): 270–7.
86 Kim YK, Yoon HK (2011) Effect of Serotonin-Related Gene Polymorphisms on Pathogenesis and Treatment Response in Korean Schizophrenic Patients. Behav Genet. [Epub ahead of print].

87 Kishi T, Tsunoka T, Ikeda M, Kitajima T, Kawashima K, Okochi T, Okumura T, Yamanouchi Y, Kinoshita Y, Ujike H, Inada T, Yamada M, Uchimura N, Sora I, Iyo M, Ozaki N, Iwata N (2010) Serotonin 1A receptor gene is associated with Japanese methamphetamine-induced psychosis patients. Neuropharmacology. **58**(2): 452–6.

88 Kishi T, Yoshimura R, Kitajima T, Okochi T, Okumura T, Tsunoka T, Yamanouchi Y, Kinoshita Y, Kawashima K, Naitoh H, Nakamura J, Ozaki N, Iwata N (2010) HTR2A is associated with SSRI response in major depressive disorder in a Japanese cohort. Neuromolecular Med. **12**(3): 237–42.

89 Kollins SH, Anastopoulos AD, Lachiewicz AM, FitzGerald D, Morrissey-Kane E, Garrett ME, Keatts SL, Ashley-Koch AE (2008) SNPs in dopamine D2 receptor gene (DRD2) and norepinephrine transporter gene (NET) are associated with continuous performance task (CPT) phenotypes in ADHD children and their families. Am J Med Genet B Neuropsychiatr Genet. **147B**(8): 1580–8.

90 Kong F, Peng Z, Jiang T, Hong X (2011) [An association study of COMT gene polymorphisms with schizophrenia.] [Article in Chinese] Zhonghua Yi Xue Yi Chuan Xue Za Zhi. **28**(2): 208–211.

91 Kopecková M, Paclt I, Petrásek J, Pacltová D, Malíková M, Zagatová V (2008) Some ADHD polymorphisms (in genes DAT1, DRD2, DRD3, DBH, 5-HTT) in case-control study of 100 subjects 6–10 age. Neuroendocrinol Lett. **29**(2): 246–51.

92 Kovács-Nagy R, Hu J, Rónai Z, Sasvári-Székely M (2009) SNAP-25: a novel candidate gene in psychiatric genetics. Neuropsychopharmacol Hung. **11**(2): 89–94.

93 Kranzler HR, Edenberg HJ (2010) Pharmacogenetics of Alcohol and Alcohol Dependence Treatment. Curr Pharm Des. [Epub ahead of print].

94 Kream RM, Mantione KJ, Sheehan M, *et al* (2009) Morphine's chemical messenger status in animals. Activitas Nervosa Superior Rediviva. **51**: 153–161.

95 Kream RM, Stefano GB, Ptacek R (2010) Psychiatric Implications of Endogenous Morphine: Up-To-Date Review. Folia Biologica: Journal of Cellular and Molecular Biology. **56**: 231–241.

96 Kream RM, Stefano GB. (2006a). De novo biosynthesis of morphine in animal cells: An evidence-based model. Med Sci Monit. **12**: RA207–RA219.

97 Kream RM, Stefano GB. (2006b). Morphine synthesis in animals (Editorial). Med Sci Monit. **12**: ED1–ED2.

98 Kream RM, Stefano GB (2009) Endogenous morphine and nitric oxide coupled regulation of mitochondrial processes. Med Sci Monit. **15**: RA263–RA268.

99 Kuzelova H, Ptacek R, Macek M (2010) The serotonin transporter gene (5-HTT) variant and psychiatric disorders: review of current literature. Neuroendocrinol Lett. **31**(1): 4–10.

100 Langley K, Fowler TA, Grady DL, Moyzis RK, Holmans PA, van den Bree MB, Owen MJ, O'Donovan MC, Thapar A (2009) Molecular genetic contribution to the developmental course of attention-deficit hyperactivity disorder. Eur Child Adolesc Psychiatry. **18**(1): 26–32.

101 Lanzenberger RR, Mitterhauser M, Spindelegger C *et al* (2007) Reduced serotonin-1A receptor binding in social anxiety disorder. Biol Psychiatry. **61**: 1081–1089.

102 Latalova K, Prasko J, Diveky T, Grambal A, Kamaradova D, Velartova H, Salinger J, Opavsky J (2010) Autonomic nervous system in euthymic patients with bipolar affective disorder. Neuroendocrinol Lett. **31**(6): 829–36.

103 Le Foll B, Gallo A, Le Strat Y, Lu L, Gorwood P (2009) Genetics of dopamine receptors and drug addiction: a comprehensive review. Behav Pharmacol. **20**(1): 1–17.

104 Lee SY, Chen SL, Chen SH, Huang SY, Tzeng NS, Chang YH, Wang CL, Lee IH, Yeh TL, Yang YK, Lu RB (2010) The COMT and DRD3 genes interacted in bipolar I but not bipolar II disorder. World J Biol Psychiatry. [Epub ahead of print].

105 Leggio GM, Micale V, Le Foll B, Mazzola C, Nobrega JN, Drago F (2011) Dopamine D(3) receptor knock-out mice exhibit increased behavioral sensitivity to the anxiolytic drug diazepam. Eur Neuropsychopharmacol. **21**(4): 325–32.

106 Lencz T, Robinson DG, Xu K, Ekholm J, Sevy S, Gunduz-Bruce H, Woerner MG, Kane JM, Goldman D, Malhotra AK (2006) DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. Am J Psychiatry. **163**(3): 529–31.

107 Levitan RD, Kaplan AS, Davis C, Lam RW, Kennedy JL (2010) A Season-of-Birth/DRD4 Interaction Predicts Maximal Body Mass Index in Women with Bulimia Nervosa. Neuropsychopharmacology. [Epub ahead of print].

108 Lim SW, Ha J, Shin DW, Woo HY, Kim KH (2010) Associations between the serotonin-1A receptor C(-1019)G polymorphism and disordered eating symptoms in female adolescents. J Neural Transm. [Epub ahead of print].

109 Liu H, Wang HT, Han F, Shi YX (2011) Activity of 5-HT1A receptor is involved in neuronal apoptosis of the amygdala in a rat model of post-traumatic stress disorder. Mol Med Report. **4**(2): 291–5.

110 Lohoff FW, Bloch PJ, Hodge R, Nall AH, Ferraro TN, Kampman KM, Dackis CA, O'Brien CP, Pettinati HM, Oslin DW (2010) Association analysis between polymorphisms in the dopamine D2 receptor (DRD2) and dopamine transporter (DAT1) genes with cocaine dependence. Neurosci Lett. [Epub ahead of print].

111 Lohoff FW (2010) Genetic variants in the vesicular monoamine transporter 1 (VMAT1/SLC18A1) and neuropsychiatric disorders. Methods Mol Biol. **637**: 165–80.

112 Mantione K, Angert R, Cadet P, Kream R, Stefano G. (2010d). Identification of a micro opiate receptor signaling mechanism in human placenta. Med Sci Monit. **16**(11): BR347–352.

113 Mantione KJ, Cadet P, Zhu W *et al* (2008) Endogenous morphine signaling via nitric oxide regulates the expression of CYP2D6 and COMT: autocrine/paracrine feedback inhibition. Addict Biol. **13**: 118–123.

114 Mantione KJ, Goumon Y, Esch T *et al* (2005) Morphine 6b glucuronide: Fortuitous morphine metabolite or preferred peripheral regulatory opiate? Med Sci Monit. **11**: MS43–MS46.

115 Mantione KJ, Kream RM, Stefano GB (2010a). Catechol-O-methyltransferase: Potential Relationship to Idiopathic Hypertension. Archives of Medical Science. **6**: 291–295.

116 Mantione KJ, Kream RM, Stefano GB (2010b). Variations in critical morphine biosynthesis genes and their potential to influence human health. Neuroendocrinol Lett. **31**: 11–18.

117 Mantione KJ, Zhu W, Kream RM *et al.* (2010c). Regulation of the Transcription of the Catechol-O-Methyltransferase Gene by Morphine and Epinephrine. Act Nerv Super Rediviva. **52**: 51–56.

118 Martirosian G, Ekiel A, Aptekorz M, Kazek B, Marszał E, Jankowska-Steifer E, Moskalewski S (2009) Intestinal anaerobic bacteria and autistic mind: is there some relations? Comment to: the autistic mind: a case study - Med Sci Monit. **15**(1): CS5–13. Med Sci Monit. **15**(3): LE2–3.

119 Markiewicz K, MacQueen (2009) The autistic mind: A case study. Med Sci Monit. **15**(1): CS5–13.

120 McQueen MB, Devlin B, Faraone SV, Nimgaonkar VL, Sklar P, Smoller JW, Abou Jamra R, Albus M, Bacanu SA, Baron M, Barrett TB, Berrettini W, Blacker D, Byerley W, Cichon S, Coryell W, Craddock N, Daly MJ, Depaulo JR, Edenberg HJ, Foroud T, Gill M, Gilliam TC, Hamshere M, Jones I, Jones L, Juo SH, Kelsoe JR, Lambert D, Lange C, Lerer B, Liu J, Maier W, Mackinnon JD, McInnis MG, McMahon FJ, Murphy DL, Nothen MM, Nurnberger JI, Pato CN, Pato MT, Potash JB, Propping P, Pulver AE, Rice JP, Rietschel M, Scheftner W, Schumacher J, Segurado R, Van Steen K, Xie W, Zandi PP, Laird NM. (2005a). Combined analysis from eleven linkage studies of bipolar disorder provides strong evidence of susceptibility loci on chromosomes 6q and 8q. Am J Hum Genet. **77**: 582–595.

121 Melkersson K (2011) The insulin receptor substrate-4 (IRS-4) gene and schizophrenia: no evidence for a main genetic factor, however one report of a single schizophrenia patient with a mutation. Neuroendocrinol Lett. **32**(1). [Epub ahead of print]

122 Miczek KA, de Almeida RM, Kravitz EA, Rissman EF, de Boer SF, Raine A (2007) Neurobiology of escalated aggression and violence. J Neurosci. **27**(44): 11803–6.

123 Min W, Li T, Ma X, Li Z, Yu T, Gao D, Zhang B, Yun Y, Sun X (2009) Monoamine transporter gene polymorphisms affect susceptibility to depression and predict antidepressant response. Psychopharmacology (Berl). **205**(3): 409–17.
124 Misterska E, Glowacki M, Harasymczuk J (2010) Personality characteristics of females with adolescent idiopathic scoliosis after brace or surgical treatment compared to healthy controls. Med Sci Monit. **16**(12): CR606–15.
125 Mustapić M, Pivac N, Kozarić-Kovacić D, Dezeljin M, Cubells JF, Mück-Seler D (2007) Dopamine beta-hydroxylase (DBH) activity and -1021C/T polymorphism of DBH gene in combat-related post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet. **144B**(8): 1087–9.
126 Nedic G, Pivac N, Hercigonja DK, Jovancevic M, Curkovic KD, Muck-Seler D (2010) Platelet monoamine oxidase activity in children with attention-deficit/hyperactivity disorder. Psychiatry Res. **175**(3): 252–5.
127 Nemoda Z, Lyons-Ruth K, Szekely A, Bertha E, Faludi G, Sasvari-Szekely M. (2010) Association between dopaminergic polymorphisms and borderline personality traits among at-risk young adults and psychiatric inpatients. Behav Brain Funct. **6**: 4.
128 Norrholm SD, Ressler KJ (2009) Genetics of anxienty and trauma-related disorders. Neuroscience. **164**: 272–287.
129 Novak G, Leblanc M, Zai C, Shaikh S, Renou J, Deluca V, Bulgin N, Kennedy JL, Le Foll B (2010) Association of polymorphisms in the BDNF, DRD1 and DRD3 genes with tobacco smoking in schizophrenia. Ann Hum Genet. [Epub ahead of print].
130 Novak G, LeBlanc M, Zai C, Shaikh S, Renou J, DeLuca V, Bulgin N, Kennedy JL, Le Foll B (2010) Association of polymorphisms in the BDNF, DRD1 and DRD3 genes with tobacco smoking in schizophrenia. Ann Hum Genet. **74**(4): 291–8.
131 Oades RD, Lasky-Su J, Christiansen H, Faraone SV, Sonuga-Barke EJ, Banaschewski T, Chen W, Anney RJ, Buitelaar JK, Ebstein RP, Franke B, Gill M, Miranda A, Roeyers H, Rothenberger A, Sergeant JA, Steinhausen HC, Taylor EA, Thompson M, Asherson P (2008) The influence of serotonin- and other genes on impulsive behavioral aggression and cognitive impulsivity in children with attention-deficit/hyperactivity disorder (ADHD): Findings from a family-based association test (FBAT) analysis. Behav Brain Funct. **4**: 48.
132 Ohaeri JU, Awadalla AW, Gado OM (2010) Relationship between symptoms of major depressive and generalized anxiety disorders in an Arab population using diagnostic criteria-based instruments. Med Sci Monit. **16**(12): PH103–15.
133 Paclt I, Drtilkova I, Kopeckova M, Theiner P, Serý O, Cermakova N (2010) The association between TaqI A polymorphism of ANKK1 (DRD2) gene and ADHD in the Czech boys aged between 6 and 13 years. NeuroendocrinolLett. **31**(1): 20. [Epub ahead of print].
134 Paclt I, Koudelová J, Pacltova D, Kopeckova M (2009) Dopamine beta hydroxylase (DBH) plasma activity in childhood mental disorders. Neuroendocrinol Lett. **30**(5): 604–9.
135 Pal P, Mihanović M, Molnar S, Xi H, Sun G, Guha S, Jeran N, Tomljenović A, Malnar A, Missoni S, Deka R, Rudan P (2009) Association of tagging single nucleotide polymorphisms on 8 candidate genes in dopaminergic pathway with schizophrenia in Croatian population. Croat Med J. **50**(4): 361–9.
136 Pastucha P, Prasko J, Grambal A, Latalova K, Sigmundova Z, Sykorova T, Tichackova A. (2009b). Panic disorder and dissociation – comparison with healthy controls. Neuroendocrinol Lett. **30**(6): 774–8.
137 Pastucha P, Prasko J, Grambal A, Latalova K, Sigmundova Z, Tichackova A. (2009a). Dissociative disorder and dissociation – comparison with healthy controls. Neuroendocrinol Lett. **30**(6): 769–73.
138 Paweł K, Hauser J, Skibińska M, Szczepankiewicz A, Dmitrzak-Weglarz M, Gorzkowska K, Pawlak J, Czerski PM (2010) [Family based association study of DRD1, DRD2, DRD3, DRD4, DAT, COMT gene polymorphism in schizophrenia]. [Article in Polish] Psychiatr Pol. **44**(3): 405–13.
139 Perez de Castro I, Ibanez A, Saiz-Ruiz J, Fernandez-Piqueras J (1999) Genetic contribution to pathological gambling: possible association between a functional DNA polymorphism at the serotonin transporter gene (5-HTT) and affected men. Pharmacogenetics. **9**: 397–400.
140 Perez de Castro I, Ibanez A, Saiz-Ruiz J, Fernandez- Piqueras J (2002) Concurrent positive association between pathological gambling and functional DNA polymorphisms at the MAO-A and the 5-HT transporter genes. Mol Psychiatry. **7**: 927–8.
141 Pietras T, PanekM, Kuprys-Lipinska I, Oszajca K, Wujcik R, Kuna P, Gorski P, Szemraj J (2010) Frequencies of Bcl I, E22E, and N363S of h-GR/NR3C1 restriction fragment length polymorphisms of glucocorticoid receptor gene in Polish adult population. Med Sci Monit. **16**(10): CR475–479.
142 Pietras T, Szemraj J, Witusik A, Hołub M, Panek M, Górski P, Wujcik R (2010) The sequence polymorphism of MnSOD gene in subjects with respiratory insufficiency in COPD. Med Sci Monit. **16**(9): CR427–432.
143 Prasko J, Raszka M, Adamcova K, Grambal A, Koprivova J, Kudrnovská H, Latalova K, Vyskocilová J (2009) Predicting the therapeutic response to cognitive behavioural therapy in patients with pharmacoresistant obsessive-compulsive disorder. Neuroendocrinol Lett. **30**(5): 615–23.
144 Ptacek R, Kuzelova H, Paclt I, Zukov I, Fischer S (2009) ADHD and growth: anthropometric changes in medicated and non-medicated ADHD boys. Med Sci Monit. **15**(12): CR595–9.
145 Rajender S, Pandu G, Sharma JD, Gandhi KPC, Singh L, Thangaraj K (2008) Reduced CAG repeats length in androgen receptor gene is associated with violent criminal behavior. Int J Legal Med. **122**: 367–372.
146 Raszka M, Prasko J, Koprivová J, Novák T, Adamcová K (2009) Psychological dissociation in obsessive-compulsive disorder is associated with anxiety level but not with severity of obsessive-compulsive symptoms. Neuroendocrinol Lett. **30**(5): 624–8.
147 Reese J, Kraschewski A, Anghelescu I, Winterer G, Schmidt LG, Gallinat J, Rüschendorf F, Rommelspacher H, Wernicke C (2010) Haplotypes of dopamine and serotonin transporter genes are associated with antisocial personality disorder in alcoholics. Psychiatr Genet. [Epub ahead of print]
148 Salamon E, Esch T, Stefano GB (2005) The role of the amygdala in mediating sexual and emotional behavior via coupled nitric oxide release. Acta Pharmacologica Sinica. **26**: 389–395.
149 Salo J, Pulkki-Råback L, Hintsanen M, Lehtimäki T, Keltikangas-Järvinen L (2010) The interaction between serotonin receptor 2A and catechol-O-methyltransferase gene polymorphisms is associated with the novelty-seeking subscale impulsiveness. Psychiatr Genet. [Epub ahead of print].
150 Samuels JF (2009) Recent advances in the genetics of obsessive-compulsive disorder. Curr Psychiatry Rep. **11**(4): 277–82.
151 Serretti A, Calati R, Giegling I, Hartmann AM, Möller HJ, Rujescu D (2009) Serotonin receptor HTR1A and HTR2C variants and personality traits in suicide attempters and controls. J Psychiatr Res. **43**(5): 519–25.
152 Sharp SI, McQuillin A, Gurling HM (2009) Genetics of attention-deficit hyperactivity disorder (ADHD). Neuropharmacology. **57**(7–8): 590–600.
153 Sicard MN, Zai CC, Tiwari AK, Souza RP, Meltzer HY, Lieberman JA, Kennedy JL, Müller DJ (2010) Polymorphisms of the HTR2C gene and antipsychotic-induced weight gain: an update and meta-analysis. Pharmacogenomics. **11**(11): 1561–71.
154 Smith TF (2010) Meta-analysis of the heterogeneity in association of DRD4 7-repeat allele and AD/HD: Stronger association with AD/HD combined type. Am J Med Genet B Neuropsychiatr Genet. [Epub ahead of print].
155 Smolarek I, Wyszko E, Barciszewska A, Nowak S, Gawronska I, Jablecka A, Barciszewska M (2010) Global DNA methylation changes in blood of patients with essential hypertension. Med Sci Monit. **16**(3): CR149–155.
156 Smoller JW, Sheidley BR, Tsuang MT (2008) Psychiatric Genetics: Applications in Clinical Practice, American Psychiatric Publishing, 337.
157 Sokolowska M, Stefanska J, Wodz-Naskiewicz K, Pawliczak R. Cytosolic phospholipase A2 group IVA influence on GM-CSF expression in human lung cells: A pilot study. Med Sci Monit 2010. **16**(9): BR300–306.
158 Sonetti D, Peruzzi E, Stefano GB (2005) Endogenous morphine and ACTH association in neural tissues. Med Sci Monit. 11: MS22–MS30.

159 Squassina A, Lanktree M, De Luca V, Jain U, Krinsky M, Kennedy JL, Muglia P (2008) Investigation of the dopamine D5 receptor gene (DRD5) in adult attention deficit hyperactivity disorder. Neurosci Lett. **432**(1): 50–3.
160 Stacey D, Clarke TK, Schumann G (2009) The genetics of alcoholism. Curr Psychiatry Rep. **11**(5): 364–9.
161 Stefano G, Esch T, Bilfinger T, Kream R (2010) Proinflammation and preconditioning protection are part of a common nitric oxide mediated process. Med Sci Monit. **16**(6): RA125–130
162 Stefano GB, Bianchi E, Guarna M, *et al* (2007) Nicotine, alcohol and cocaine coupling to reward processes via endogenous morphine signaling: The dopamine-morphine hypothesis. Med Sci Monit. **13**: RA91–102.
163 Stefano GB, Burrill JD, Labur S, *et al* (2005) Regulation of various genes in human leukocytes acutely exposed to morphine: Expression microarray analysis. Med Sci Monit. **11**: MS35–MS42.
164 Stefano GB, Cadet P, Kream RM, *et al.* (2008a). The presence of endogenous morphine signaling in animals. Neurochemical Research. **33**: 1933–1939.
165 Stefano GB, Esch T, Kream RM (2009) Xenobiotic perturbation of endogenous morphine signaling: paradoxical opiate hyperalgesia. Med Sci Monit. **15**: RA107–RA110.
166 Stefano GB, Fricchione GL, Goumon Y *et al* (2005) Pain, immunity, opiate and opioid compounds and health. Med Sci Monit. **11**: MS47–MS53.
167 Stefano GB, Kream RM, Esch T (2009) Revisiting tolerance from the endogenous morphine perspective. Med Sci Monit. **15**: RA189–RA198.
168 Stefano GB, Kream RM, Mantione KJ *et al.* (2008b). Endogenous morphine/nitric oxide-coupled regulation of cellular physiology and gene expression: implications for cancer biology. Semin Cancer Biol. **18**: 199–210.
169 Stefano GB, Kream RM, Mantione KJ, Ptacek R (2011) Endogenous morphine, stress and psychiatric disorders – review of actual findings. Journal of Czech Psychology. In Press.
170 Stefano GB, Kream RM (2007) Endogenous morphine synthetic pathway preceded and gave rise to catecholamine synthesis in evolution (Review). Int J Mol Med. **20**: 837–841.
171 Stefano GB, Kream RM (2010) Dopamine, Morphine, and Nitric Oxide: An Evolutionary Signaling Triad. CNS Neurosci Ther. **16**: e124–e137.
172 Stefano GB, Scharrer B (1994) Endogenous morphine and related opiates, a new class of chemical messengers. Adv Neuroimmunol. **4**: 57–68.
173 Stefano GB, Stefano JM, Esch T (2008) Anticipatory Stress Response: A significant commonality in stress, relaxation, pleasure and love responses. Med Sci Monit. **14**: RA17–RA21.
174 Strobel A, Wehr A, Michel A, Brocke B (1999) Association between the dopamine D4 receptor (DRD4) exon III polymorphism and measures of novelty seeking in a German population. Mol Psychiatry. **4**: 378–84.
175 Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, Liu XQ, Vincent JB, Skaug JL, Thompson AP, Senman L *et al* (2007) Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet. **39**: 319–328.
176 Talkowski ME, Kirov G, Bamne M, Georgieva L, Torres G, Mansour H, Chowdari KV, Milanova V, Wood J, McClain L, Prasad K, Shirts B, Zhang J, O'Donovan MC, Owen MJ, Devlin B, Nimgaonkar VL (2008) A network of dopaminergic gene variations implicated as risk factors for schizophrenia. Hum Mol Genet. **17**(5): 747–58.
177 Talkowski ME, Mansour H, Chowdari KV, Wood J, Butler A, Varma PG, Prasad S, Semwal P, Bhatia T, Deshpande S *et al* (2006) Novel, Replicated Associations Between Dopamine D3 Receptor Gene Polymorphisms and Schizophrenia in Two Independent Samples. Biol Psychiatry. **60**: 570–577.
178 Tobacco and Genetics Consortium (2010) Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet. **42**(5): 441–7.
179 Tsunoka T, Kishi T, Kitajima T, Okochi T, Okumura T, Yamanouchi Y, Kinoshita Y, Kawashima K, Naitoh H, Inada T, Ujike H, Yamada M, Uchimura N, Sora I, Iyo M, Ozaki N, Iwata N (2010) Association analysis of GRM2 and HTR2A with methamphetamine-induced psychosis and schizophrenia in the Japanese population. Prog Neuropsychopharmacol Biol Psychiatry. **34**(4): 639–44.
180 Unschuld PG, Ising M, Erhardt A, Lucae S, Kloiber S, Kohli M, Salyakina D, Welt T, Kern N, Lieb R, Uhr M, Binder EB, Muller-Myhsok B, Holsboer F, Keck ME (2007) Polymorphisms in the Serotonin Receptor Gene HTR2A Are Associated With Quantitative Traits in Panic Disorder American. Journal of Medical Genetics Part B (Neuropsychiatric Genetics). **144B**: 424–429.
181 Vaiman M, Olevson Y, Habler L, Kessler A, Zehavi S, Sandbank J (2010) Diagnostic value of estrogen receptors in thyroid lesions Med Sci Monit. **16**(7): BR203–207.
182 van Oorschot OB (2005) 5-HT1B receptors and aggression: a review. Eur J Pharmacol **526**: 207–217.
183 Vevera J, Stopkova R, Bes M, Albrecht T, Papezova H, Zukov I, Raboch J, Stopka P (2009) COMT polymorphisms in impulsively violent offenders with antisocial personality disorder. Neuroendocrinol Lett. **30**(6): 753–6.
184 Videtic A, Peternelj TT, Zupanc T, Balazic J, Komel R (2009) Promoter and functional polymorphisms of HTR2C and suicide victims. Genes Brain Behav. **8**(5): 541–5.
185 Vithoulkas G, Carlino S (2010) The "continuum" of a unified theory of diseases. Med Sci Monit. **16**(2): SR7–15.
186 Vlkova B, Szemes T, Minarik G, Turna J, Celec P (2010) Advances in the research of fetal DNA in maternal plasma for noninvasive prenatal diagnostics. Med Sci Monit. **16**(4): RA85–91.
187 Watanabe Y, Nunokawa A, Kaneko N, Someya T (2007) The tryptophan hydroxylase 1 (TPH1) gene and risk of schizophrenia: a moderate-scale case-control study and meta-analysis. Neurosci Res. **59**(3): 322–6.
188 Yasseen B, Kennedy JL, Zawertailo LA, Busto UE (2010) Comorbidity between bipolar disorder and alcohol use disorder: Association of dopamine and serotonin gene polymorphisms. Psychiatry Res. **176**(1): 30–33.
189 Yilmaz Z, Kaplan AS, Zai CC, Levitan RD, Kennedy JL (2011) COMT Val158Met variant and functional haplotypes associated with childhood ADHD history in women with bulimia nervosa. Prog Neuropsychopharmacol Biol Psychiatry. [Epub ahead of print]
190 Zahari Z, Teh LK, Ismail R, Razali SM (2011) Influence of DRD2 polymorphisms on the clinical outcomesofpatients with schizophrenia. Psychiatr Genet. [Epub ahead of print]
191 Zai CC, Manchia M, De Luca V, Tiwari AK, Squassina A, Zai GC, Strauss J, Shaikh SA, Freeman N, Meltzer HY, Lieberman J, Le Foll B, Kennedy JL (2010) Association study of BDNF and DRD3 genes in schizophrenia diagnosis using matched case-control and family based study designs. Prog Neuropsychopharmacol Biol Psychiatry. **34**(8): 1412–8.
192 Zhang JP, Lencz T, Malhotra AK (2010) D2 Receptor Genetic Variation and Clinical Response to Antipsychotic Drug Treatment: A Meta-Analysis. Am J Psychiatry. [Epub ahead of print]
193 Zhu W, Cadet P, Baggerman G *et al.* (2005a). Human white blood cells synthesize morphine: CYP2D6 modulation. J Immunol. **175**: 7357–7362.
194 Zhu W, Esch T, Kream RM, *et al* (2008) Converging cellular processes for substances of abuse: endogenous morphine. Neuroendocrinol Lett. **29**: 63–66.
195 Zhu W, Mantione K, Kream RM *et al* (2006) Alcohol-, Nicotine-, and Cocaine-Evoked Release of Morphine from Human White Blood Cells: Substances of Abuse Actions Converge on Endogenous Morphine Release. Med Sci Monit. **12**: BR350–BR354.
196 Zhu W, Mantione KJ, Shen L, *et al.* (2005b). Tyrosine and tyramine increase endogenous ganglionic morphine and dopamine levels in vitro and in vivo: CYP2D6 and tyrosine hydroxylase modulation demonstrates a dopamine coupling. Med Sci Monit. **11**: BR397–BR404.