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Genetic Variation and Shared Biological Susceptibility Underlying Comorbidity in Neuropsychiatry

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Genetic factors underlying alcoholism, substance abuse, antisocial and violent behaviour, psychosis, schizophrenia and psychopathy are emerging to implicate dopaminergic and cannabinoid, but also monoaminergic and glutamatergic systems through the maze of promoter genes and polymorphisms. Candidate gene association studies suggest the involvement of a range of genes in different disorders of CNS structure and function. Indices of comorbidity both complicate the array of gene-involvement and provide a substrate of hazardous interactivity. The putative role of the serotonin transporter gene in affective-dissociative spectrum disorders presents both plausible genetic variation and complication of comorbidity. The position of genetic variation is further complicated through ethnic, contextual and social factors that provide geometric progressions in the comordity already underlying diagnostic obstacles. The concept of shared biological susceptibilty to two or more disorder conditions of comorbidity seems a recurring observation, *e.g.*, bipolar disorder with alcoholism or schizophrenia with alcohol/substance abuse or diabetes with schizopsychotic disorder. Several lines of evidence seem to suggest that the factors influencing variation in one set of symptoms and those affecting one or more disorders are observed to a marked extent which ought to facilitate the search for susceptibility genes in comorbid brain disorders. Identification of regional genetic factors is awaited for a more compelling outline that ought eventually to lead to greater efficacy of symptom-disorder arrangements and an augmentation of current pharmacological treatment therapies.

Keywords: Genes; *DRD1; DRD2; DRD3; DRD4; DRD5; CNR1; MAOA; GRIK4; FAAH; ANKKI*; Alcoholism; Antisocial personality; Schizophrenia; Affective disorder; Serotonin transporter gene - reward deficiency syndrome; Treatment strategy

INTRODUCTION

The genetics of psychiatric disorders has made considerable progress in recent years but conflicting results continue to dog researchers. The classificatory systems for most psychiatric disorders have been built upon observations of symptom clusters and most disorders do not have a definitive biological marker detectable in a diagnostic test. This

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historical reality, while providing psychiatric practitioners with guidelines for making decisions about pharmacotherapies, probably at the same time provides genetics researchers with heterogeneous patient groups that add variability to their measurements. One approach by genetics researchers has been to identify endophenotypes that may narrow the range of heterogeneity in their groups. The goal is eventually to get to a point where psychiatric diagnoses are based on definitive diagnostic tests; such tests might involve brain scans and/or genotyping perhaps in tandem with historical data and test performance results from individuals.

Comorbidity of symptom clusters only exacerbates the problem of diagnosis and treatment. Yet even with the inherent uncertainties of co-existing diagnoses, genetics researchers have begun to identify gene candidates for comorbid disorders. The genetics of comorbid psychiatric disorders was one of the topics of a meeting sponsored by the *Fundation Cerebro y Mente* of Madrid entitled, "Implications of comorbidity for etiology and treatment of neuropsychiatric disorders", held in Mazagon (Huelva), Spain, 19-23 Oct. 2005. A number of speakers wrote reviews of their topics that have appeared in this journal. This paper provides an overview of those papers within the context of a broader consideration of the genetics of comorbid psychiatric disorders.

GENE-ENVIRONMENT INTERACTIONS

Polymorphisms of various genes are associated with various psychiatric disorders but genes do work in isolation. Environmental factors modulate the expression and functional consequences of many genes. This challenges researchers to try to identify gene-environment interactions associated with complex psychiatric conditions. This challenge is even greater in the case of comorbidly existing psychiatric disorders. Two examples are the comorbid presence of epilepsy and depression and of internalizing disorders and neuroticism.

Current notions of comorbid etiology focus beyond immediate circumstance, such as, for example, the psychosocial burdens of the epileptic patient's depression, emphasizing instead shared etiological features in the genesis of depression and epilepsy (Bremner *et al.*, 2000; Hesdorffer *et al.*, 2000; 2006; Gilliam *et al.*, 2004; Johnson *et al.*, 2004; Gilliam, 2005); an example of such a shared etiological feature is in the hippocampal and limbic circuits (Bromfield *et al.*, 1992; Quiske *et al.*, 2000; Van Bogaert *et al.*, 2001; Toczek *et al.*, 2003; Savic *et al.*, 2004), suggesting that epilepsy and depression share common biological pathways (*cf.*, Bolwig, 2007). Recently Koh *et al.* (2007) examined whether seizure-induced downregulation of the serotonin receptor 5-HT_{5B} gene expression correlated with behavioral changes in tests thought to model depression. They found decreased mobility (*i.e.*, an increase in the depression-like state) in the forced swim test. Depressive responses following KA-induced status epilepticus in juvenile rats were correlated with selective downregulation of the 5-HT receptor in the hippocampus. Isolated rearing conditions aggravated seizure-induced alterations in behaviour and gene expression whereas enriched rearing conditions ameliorated these effects (see also Faverjon *et al.*, 2002; Young *et al.*, 2002; Koh *et al.*, 2005). The implications of these observations are manifold; children and adolescents with epilepsy have an elevated risk of comorbidity that will be modulated by social engagement and support (Boylan *et al.*, 2004; Pellock, 2004).

High rates of comorbidity exist too among the so-called 'internalizing' disorders, *i.e.*, anxiety and depressive states, with high levels of neuroticism in these conditions (Andrews *et al.*, 1990; Bienvenu *et al.*, 2001). In a population-based twin study, Hettema *et al.* (2006) examined the comorbidity of neurotocism and internalizing disorders in over 9,000 twins from male-male, female-female, and opposite sex pairs. They found that genetic factors shared with neuroticism accounted for one-third to one-half of the genetic risk across the internalizing disorders. Genetic correlations between neuroticism and each disorder were high whereas individual-specific correlations were much lower. A neuroticism-independent genetic factor that markedly increased risk for major depression, generalised anxiety disorder and panic disorder was identified. The overlap between those factors modulating individual variation in neuroticism and those affecting internalizing disorder-liability appeared substantial. Results encourage the search for susceptibility genes in comorbid conditions.

GENETIC VARIATIONS UNDERLYING COMORBIDITIES WITH PSYCHOSIS

Genetic factors common to substance abuse disorders and disease states involving personality and conduct disorders have been found (Bohman *et al.*, 1984; Cloninger *et al.*, 1988; Helzer and Pryzbeck, 1988); such findings provide a remarkable avenue for improved understanding of neuropsychiatric disorders (Zubenko *et al.*, 2003; Harrison and Weinberger, 2005; Pickard *et al.*, 2005). For example, the dopamine (DA) D_2 receptor gene (*DRD2*) and its phenotypes has been implicated in a range of comorbid neuropsychiatric and neurologic disorders (Cook *et al.*, 1995; Ueno *et al.*, 1999; Noble, 2003; Ponce *et al.*, 2003a). Hoenicka *et al.* (2007a,b) described in detail the strategy of utilizing allelic, association and linkage analysis methodologies; one example was the use of single nucleotide polymorphisms (SNPs). They have developed new technologies for studying dopaminergic and cannabinoid pathways involved in neuropathology, including alcoholism, schizophrenia and antisocial personality disorder. There are about 20,000 different genes of which about 10,000 are expressed in the brain with candidate genes for schizophrenia at different loci in chromosomes 1q (*DISC1*, disrupted in schizophrenia), 6q (*RGS4*), 7q (*DTNBP1*), 8p (*NRG1*, *neureglin*), 13q, 11q22 (*GRIK4*; glutamate receptor, ionotropic, kainate, type 4) and 22q. Additional candidates include the SNP *Taq*I-A located nearby the *DRD2* gene, the 10-repeat allele of a variable number tandem repeats (VNTR) of the *SLC6A3* gene, the C385A *FAAH* SNP and the 3'-UTR microsatellite of the *CNR1* gene. Hoenicka *et al.* (2007a) described findings from a sample of Spanish patients with alcoholism, of whom 38.5% presented with comorbid antisocial personality disorder. They demonstrated a relationship with specific genes related to the dopaminergic and cannabinoid systems. Thus, there was a significant association between antisocial personality disorder and the endocannabinoid genes *FAAH* and *CNRI*, as well as with the *Taq*I-A polymorphism previously associated with alcoholism (Noble, 2003; see also findings by Martinez-Gras *et al.*, 2006). Hoenicka *et al.* (2006) examined the genotypic distribution of this SNP in a set of clinically ascertained schizophrenic patients (n=131) and age-matched control subjects (n=364). Individuals were genotyped using automated analysis of fluorescently labeled PCR products. The distribution of grouped genotypes for the C957T *DRD2* SNP (CC *vs* CT, TT) showed that the C homozygote genotype was overrepresented in their patient sample when compared with control subjects. Their findings have provided additional evidence that genetic variation at the *DRD2* gene plays an important role in the vulnerability to schizophrenia. Taken together, these results both confirm several other studies indicating the high degree of heritability of psychopathological traits and abuse disorders (Regier *et al.*, 1990; Livesey *et al.*, 1993; Smith *et al.*, 1993; McDermott *et al.*, 2000).

The DA receptor D_3 gene, *DRD3*, has been implicated in neuropsychiatric disorders, including substance abuse (Duaux *et al.*, 1998; Comings *et al.*, 1999b; Thome *et al.*, 1999) and in disorder comorbidities (Limosin *et al.*, 2003a). In a recent study of 108 French alcohol-dependent patients, Limosin *et al.* (2005) observed that homozygosity for the *DRD3* gene BalI polymorphism was significantly increased in alcohol-dependent patients with low cognitive impulsiveness when several other factors, e.g., antisocial personality disorders, were taken into account. They hypothesized that alcohol may be considered to augment impulsiveness, potentially through increases in DA neurotransmission, in a subgroup of patients homozygous for the gene coding for *DRD3*. This suggestion is not unreasonable; alcohol may induce dependence through some 'normalisation' of abnormalities of affective/emotional states including irritability, dysphoria or impulsiveness (see Palomo *et al.*, 2007).

Blackwood *et al.* (2007) approached comorbidity from another perspective; they outlined and described the issue of whether or not there were genetic risk factors common to schizophrenia, bipolar disorder and depression, examining the likelihood that incumbent phenotypes presented under the categories of affective and non-affective psychoses share certain genetic risk factors (Detera-Wadleigh *et al.*, 1999; Blackwood *et al.*, 2001; Fallin *et al.*, 2005). From family linkage studies, several chromosomal regions likely to contain risk genes for affective disorder (bipolar) and schizophrenia are identified, suggesting shared common susceptibilities. Other studies have indicated that

certain genes, *DISC1* and *NRG1*, contributed to affective and non-affective psychoses (Stefansson *et al.*, 2003; Li *et al.*, 2004; Hamshere *et al.*, 2005; Petryshen *et al.*, 2005). Other candidate genes in the disorders included *NRG1* mapped to chromosome 11q23 (Shibata *et al.*, 2006), and *NPAS3* (Neuronal PAS domain protein 3), a transcription factor mapped to chromosome 14q. Blackwood and co-workers implicated *GRK4* in both affective conditions and schizophrenia, observing that it was disrupted by a translocation breakpoint in a schizophrenic patient. Case control studies demonstrated significant association of *GRIK* with both schizophrenia and bipolar disorder, further reinforcing the comorbid component (Wildenauer *et al.*, 1999; Park *et al.*, 2004; Thomson *et al.*, 2005).

The shared biological susceptibility to two or more disorders that underlie comorbid relations, often observed from family studies, can be exemplified from the comorbidity between schizophrenia and Type 2 diabetes where linkage analyses have identified common loci, chromosomes 2p22.1-p13.2 and 6q21-q24.1, as well as the DA D_5 receptor gene (*DRD5*) on chromosome 5 and the tyrosine hydroxylase gene on chromosome 11 (*cf.*, Bellivier, 2005). Genetic influences on major depression, with or without comorbid disorders, are observed too from family studies (Weissman *et al.*, 1993) and twin studies (McGuffin *et al.*, 1996; Bierut *et al.*, 1999). Linkage and association of the D2S2944 tetranucleotide repeat region with major depression is reported (Philibert *et al.*, 2003). Langbehn *et al.* (2006) studied the association of this microsatellite, D2S2944 allele, with major depression together with substance abuse/antisocial personality disorder in 247 participants from the Iowa Adoption Studies covering lifetime affective, alcohol, drug, and antisocial personality disorder information. They found that the 124-bp allele at D2S2944 had a strong association with major depression specific to individuals with histories of alcohol abuse/dependence and/or antisocial personality disorder, not gender-specific and not limited to alcohol-related depressive episodes. It may be suggested that the 124-bp allele endows additional comorbid liabilities, supporting the notion of depressive spectrum illness (Winokur, 1974). The extent of genetic influence in neuropsychiatric comorbidity in affective and alcohol disorders covers a wide range of neurotransmitters. For instance, an association between CCK gene-promoter regions (-45C/T and -196G/A) and suicidality in Japanese men but not women has been reported (Shindo and Yoshioka, 2005), as well as between this region and alcohol withdrawal symptoms (Okubo *et al.*, 1999).

In conclusion, genetic studies have linked variation with comorbid psychoses and other psychiatric disorders. Genes encoding for proteins involved in glutamatergic, cannabinoid or dopaminergic neurotransmission have been implicated in comorbid schizophrenia and substance abuse. Some of the same and other genes have been implicated in comorbid schizophrenia and affective disorders and still others with cormorbid affective disorders and substance abuse. Results continue to reveal the complexities of genetic variations underlying comorbidity with psychosis.

GENETIC VARIATION IN AFFECTIVE-DISSOCIATIVE SPECTRUM DISORDERS

Genetic analyses reveal polymorphisms that increase the risk of comorbid vulnerability for several overlapping diagnoses within an affective-dissociative disorders spectrum including bipolar disorder, alcoholism, post-traumatic stress disorder (PTSD), anxiety, sensation-seeking and impulsivity, novelty-seeking, and obsessive-compulsive disorder. Polymorphisms have been found for DA receptor genes (Lawford *et al.*, 1995; Li *et al.*, 1999; Thome *et al.*, 1999; Garner *et al.*, 2001; Ronai *et al.*, 2001; Shink *et al.*, 2002; Limosin *et al.*, 2003b; 2005; Severino *et al.*, 2005; Dmitrzak-Weglarz *et al.*, 2006) and for serotonin receptor genes (Lesch *et al.*, 1996; McDougle *et al.*, 1998; Bengel *et al.*, 1999; Frisch *et al.*, 2000; Cavallini *et al.*, 2002; Di Bella *et al.*, 2002; Rotondo *et al.*, 2002; Walitza *et al.*, 2002; Grados *et al.*, 2003). For example, Lawford *et al.* (2006) analysed clusters of PTSD patients (57 untreated Caucasian Vietnam veterans) according to symptom profiles and examined the association of the A1 allele of the *DRD2 Taq*I-A polymorphism with these clusters. PTSD patients carrying the A1 allele presented significantly higher scores on anxiety/insomnia, social dysfunction and depression, compared to those without the A1 allele. Two primary groups were identified: a "high psychopathology" cluster with high comorbid lev-

els of somatic concerns, anxiety/insomnia, social dysfunction and depression, and a "low psychopathology" cluster that manifested the reverse pattern. It was concluded that *DRD2* variants are linked with severe comorbid psychopathology in PTSD patients.

There is a high level of comorbid bipolar disorder and alcoholism comorbidity that may or may not result from common genetic factors arising from each; polymorphisms in DA pathway candidate genes have been implicated. Szczepankiewicz *et al.* (2006) analysed possible relationships between polymorphisms in one SNP for each DA receptor gene (*DRD1* to *DRD4*) and comorbid alcohol abuse in bipolar disorder patients (42 with comorbidity). Analyses of polymorphisms in the four genes revealed neither any association of the analysed polymorphisms in comorbid bipolar patient group nor any differences compared to the healthy control group. Nevertheless, to really determine whether or not an association exists, studies involving more polymorphisms and haplotypes must be carried out.

Much evidence implicates significant involvement of the serotonin transporter gene polymorphism in anxiety states. Katsuragi *et al.* (1999) showed that individuals with the two short allele genotype presented higher 'harm avoidance' scores (Cloninger's TCI scales, see Palomo *et al.*, 2007) than individuals with other genotypes among a Japanese sample looking at anxiety-related traits. Cloninger's harm avoidance factor contributes to temperament. Taking into account the notion of temperament-external locus of control versus character-internal locus of control as relating to negative affect and positive affect, respectively, direct links between the two short allele genotypes and the symptom-profile triad, temperament-extrenal locus of control-negative affect, ought to be observed. Lesch *et al.* (1996) found that the Cattell's 'anxiety factor' (16PF Personality Inventory) was associated with the serotonin transporter genotype, whereby individuals with one or two shorter alleles presented higher anxiety scores than individuals with two long alleles. Mazzanti *et al.* (1998) obtained the result that an alcoholic group, with higher frequencies of the short variant of the serotonin transporter gene, also scored higher harm avoidance points (high temperament) than the control group. Ohara *et al.* (1998) showed that patients presenting anxiety disorders also had higher frequencies of the short allele of the serotonin transporter gene in comparison with healthy controls. Perez *et al.* (2006) compared obsessive-compulsive disorder individuals with non-disordered controls and showed that the former had higher frequencies of the homozygous short allele genotype *5-HTT* gene. Furthermore, it has been proposed that a polymorphism in the promoter of the 5-HT_{2A} receptor gene may be related to impulsive behavior. Nomura and Nomura (2007) examined whether the polymorphism in the 5-HT_{2A} receptor gene promoter is involved in impulsive aggression by evaluating a behavioral Go/No-go task in normal volunteers. The polymorphism of the 5-HT_{2A} receptor gene promoter in lymphocytes from 71 volunteers was analyzed by using PCR. Subjects that carried the 1438A allele for the 5-HT_{2A} receptor gene made more commission errors (*i.e.*, showed more impulsivity) under the punishment-reward condition in the Go/No-go task than those in the 1438G group, suggesting the possible involvement of the G1438A polymorphism of the $5HT_{2A}$ receptor gene promoter in impulsive behaviour (see also Nomura *et al.*, 2006; Preuss *et al.*, 2006). As reviewed and discussed recently, the influence of impulsive behaviour appears to be a central tenet of comorbidity in neuropsychiatry (Palomo *et al.*, 2007).

Associations between variations in the serotonin transporter gene and anxiety levels are not universal: Matsushita *et al.* (1997) observing a Japanese sample did not obtain any difference between panic disorder patients and controls on the polymorphisms of the serotonin transporter gene (see also, Schmidt *et al.*, 2000; Rotondo *et al.*, 2002; Denys *et al.*, 2006). It is possible that the different outcomes may be due to differential contributions of genetic and environmental factors. A second possibility is that diagnostic classification of the endophenotypes may vary from study to study (see Palomo *et al.*, 2004c). A third possibility pertains to the essence of comorbidity, as exemplified by Cavallini *et al.* (2002); controlling for tic disorders comorbid with obsessive-compulsive disorder, they found that only the obsessive-compulsive-tic comorbid group showed higher frequencies of the long genotype. Results emphasize the need for careful phenotyping.

Linkage studies have been applied to uncover both gene involvement in susceptibility to comorbid disorders, e.g., through evidence that chromosome 22q12-13 may contain one or more shared susceptibility genes for bipolar affective disorder and schizophrenia. Recently, Severinsen *et al.* (2006) reported an association analysis across five genes (including 14 SNPs and 2 microsatellite polymorphisms) in this interval from a case-control sample consisting of 162 bipolar affective disorder patients, 103 schizophrenic patients and 200 healthy controls. The Bromodomain-containing 1 gene (*BRD1*) showed an association with both disorders. Similarly, brain-derived neurotrophic-factor (BDNF), involved in neural survival, differentiation and plasticity may be involved in gene susceptibility for brain disorders. Qian *et al.* (2007) genotyped one $(GT)_n$ dinucleotide repeat and three SNPs (rs6265, rs2030324, and rs2883187) in a Chinese sample consisting of 617 cases of schizophrenia spectrum disorder and 672 healthy controls. They carried out too a meta-analysis based on 16 population-based case-control studies that examined associations between rs6265 and the disorder in Asian and Caucasian subjects. The single-locus analysis did not show any significant association between schizophrenia and *BDNF* polymorphisms nor did the meta-analysis provide any positive result that rs6265 is linked to the disorder. Nevertheless, a haplotype analysis showed that there existed a common four SNPs haplotype protective against schizophrenia, which was interpreted as evidence that *BDNF* is a susceptibility gene for schizophrenia spectrum disorders in Chinese subjects.

PSYCHOPATHOLOGICAL COMORDITY OVER GENE-REGULATED SIGNALLING PATHWAYS

Gene-environment interactions (Palomo *et al.*, 2004a,b,c,d) and multiple phenotypes even within a psychiatric disorder classification contribute to challenge the goal of identifying genes and their products that contribute to comorbid disorder (Moffitt, 2005; Viding *et al.*, 2005; Rutter *et al.*, 2006). Comings and Blum (2007), in their treatise on the reward deficiency syndrome, explored and presented the hypothesis that dysregulation of prefrontal glutamate outputs to the ventral tegmental area (VTA) and nucleus accumbens (NAc) underlie progressive sensitisation and relapse in addiction and schizophrenia. The neurotransmitters DA, norepinephrine (NE), 5-HT, GABA, glutamate, acetylcholine and endogenous opioids may interact at mesolimbic sites including the NAc to produce reward. Genetic variants underlie dysfunctions of reward, a condition termed hypodopaminergic trait, that may lead to multiple drug-seeking behaviours, most abused drugs activating forebrain DA neurotransmission. Compromised DA-D_2 receptors in carriers of *DRD2* A1 allele of the *Taq*I-A polymorphism located nearby the *DRD2* gene may underlie susceptibility to drug abuse (Comings *et al.*, 1991). *Taq*I-A is located within the ankyrin repeat and kinase domain containing the gene *ANKKI* (Neville *et al.*, 2004). Although residing outside the *DRD2* gene, the *Taq*I-A polymorphism could be in linkage disequilibrium with other functional polymorphisms within the *DRD2* gene that could contribute towards substance abuse and other self-gratifying behaviour (Noble *et al.*, 1991; Comings *et al.*, 1996; Cook and Gurling, 1996; Kranzler and Rosenthal, 2003).

The particular profile described by the reward deficiency syndrome is influenced by genes that could contribute to comorbidity involving Tourette's syndrome (Comings and Comings, 1993; Comings *et al.*, 1999a), pathological gambling (Koepp *et al.*, 1998), smoking (Spitz *et al.*, 1998), personality disorders including antisocial behaviour (Comings *et al.*, 1997; Noble *et al.*, 1998; Koenen *et al.*, 2006; Thapar *et al.*, 2006), antisocial behaviour comorbid with heroin addiction (Gerra *et al.*, 2005) or ADHD (LaHoste *et al.*, 1996; Daly *et al.*, 1999; Comings *et al.*, 2000; Johann *et al.*, 2003). The cannabinoid receptor may similarly contribute to comorbidities with alcoholism (Schmidt *et al.*, 2002; Ponce *et al.*, 2003b). Recent findings confirmed the linkage of the *Taq*I-A polymorphism to the *DRD2* gene associated with alcoholism (*cf.*, Parsian *et al.*, 2000; Amadeo *et al.*, 1993; Chen *et al.*, 1999; Bau *et al.*, 2000). Rodriguez-Jimenez *et al.* (2006) investigated attention and inhibitory control in an alcoholic sample using the continuous performance test (Thompson and Nichols, 1992), and the association of the *Taq*I-A polymorphism with alcoholism. It was found that the alcoholic patients with the A1 allele showed lower sustained attention and less

inhibitory control than those patients that were not carriers of this allele. Studies on the comorbidity of drug dependence and alcohol dependence that focus on the *ADH* gene cluster in European Americans and African Americans demonstrated the involvement of the *ADH* genotypes in both types of abuse, suggesting one reason for high comorbidity in this case (Lou *et al.*, 2006). Results continue to implicate genes in comorbid disorders and make a strong case for the application of genostatic variables, the development of multi-gene risk assessment and the continued use of case-control association studies (Blum *et al.*, 1996; Comings and Blum, 2000; Hiroi and Agatsuma, 2005; Xu *et al.*, 2007).

The complexity of genetic risk and related comorbidity associated with alcoholism (Merikangas, 1990; Goldman, 1993; Reich *et al.*, 1999) has been exemplified by family, twin and adoption studies in establishing genetic susceptibility (Ferguson and Goldberg, 1997; Schork and Schork, 1998). In particular, genes have been identified that associate with the comorbidity of antisocial personality disorder and alcoholism (Van den Bree *et al.*, 1998). Other investigations either link the monoamine oxidase A (*MAOA*) gene with antisocial personality disorder or do not (*e.g.*, Parsian, 1999; Samochowiec *et al.*, 1999; Parsian and Cloninger, 2001; Saito *et al.*, 2002; Lu *et al.*, 2003). Thus, both the *DRD2/ANKKI* and *MAOA* genes are putative candidate genes for antisocial behaviour with alcoholism comorbidity. Recently, Wang *et al.* (2007) examined whether or not antisocial behaviour with alcoholism may be associated with the possible interactions of the *Taq*I-A polymorphism with *MAOA* gene in 231 Han Chinese subjects, of whom 73 participants were diagnosed antisocial behaviour *with* alcoholism, and 158 participants were diagnosed antisocial behaviour *without* alcoholism. They found that the *Taq*I-A polymorphism and *MAOA*-uVNTR (variable number of tandem repeat located upstream) polymorphisms were not linked to antisocial behaviour with alcoholism. An association between *Taq*I-A polymorphisms and antisocial behaviour with alcoholism was obtained after stratification for the *MAOA*-uVNTR 4-repeat polymorphism. Following multiple regression, it was seen that under stratification of *MAOA*-uVNTR 4-repeat polymorphism and in comparison with the *DRD2* A1 homozygous genotype as reference group, the *DRD2* A1/A1 had a possible protective effect against alcoholism in individuals with antisocial personality disorder. Studies continue to point to possible genes that contribute to comorbid disorders.

ADVERSE CHILDHOOD INDUCED COMORBIDITY

Childhood maltreatment (physical, sexual, emotional, as well as neglect) appears to promote aberrations in brain systems and elevated neurotransmitter levels persisting through childhood (De Bellis, 2001; Glaser, 2001; Teicher *et al.*, 2002), with lasting consequences for adult behavioural neurobiology. For example, among individuals with the less efficient serotonin transporter gene (*5-HTT*, by functional polymorphism in the promoter region - short allele), childhood maltreatment predicted adult depression, with 63% risk of a major depressive episode (Caspi *et al.*, 2003). The gene *MAOA*, together with catechol-*O*-methyltransferase (COMT), which maintains neurotransmitter homeostasis, is linked to impulsive, aggressive and violence-related behavioural disturbances. Against the background of functional polymorphism in the *MAOA* gene promoter (Sabol *et al.*, 1998; Shih *et al.*, 1999), it has been proposed (Caspi *et al.*, 2002) that differences in the *MAOA* genotype may moderate between childhood mistreatment and later violent and antisocial behaviour (Foley *et al.*, 2004; Newman *et al.*, 2005), although this is far from established (Haberstick *et al.*, 2005; Young *et al.*, 2006). Recently, Huizinga *et al.* (2006) used regression-based analyses to test for the genotype-environment interaction by applying self-reported abuse and *MAOA*-genotype to predict antisocial behaviour and/or arrests for violence in the National Youth Survey Family Study (USA). They found that maltreatment by parents during adolescence was a risk factor for adult and adolescent violent and antisocial behaviour although the main effect *MAOA* and *MAOA*-maltreatment interactions were non-significant. An upbringing under conditions of disorganised and socially-disruptive conditions and/or poor parenting (Farrington, 1998; Scott, 1998; Salter *et al.*, 2003), or violent childhood victimization (Widom, 1989; Widom *et al.*, 1999; Ertem *et al.*, 2000), seems also to increase risk for later antisocial behaviour, and may implicate spe-

cific genotypes (Rhee and Waldman, 2002; Nilsson *et al.*, 2005). Nilsson *et al.* (2005) performed a cross-sectional study (randomized sample of 81 16-19 year-olds) of groups representing different degrees of deviant risk behaviour. They found that the 3-repeat allele of the *MAOA* gene promoter increased the risk of male adolescent criminal behaviour when in interaction with psychosocial factors, but no effects of the *MAOA* genotype on adolescent criminal activity arose when the *MAOA* genotype was taken alone.

The 'cycle of violence' and its interacting components of maltreatment, MAOA, *MAOA* genotype and risk for later violence and criminality (Maxfield and Widom, 1996) have been examined (McGloin and Widom, 2001). Widom and Brzustowicz (2006) studied whether or not high levels of MAOA could protect against the impact of childhood maltreatment and adversity upon future development of antisocial behaviour and conduct disorder. Court-substantiated cases of child abuse and neglect together with a comparison group (N=802) were followed into adulthood and interviewed; 82% provided DNA. A composite index of violent and antisocial behaviour was developed from arrest, self-report and diagnostic information. The authors found no main effect for the relationship between *MAOA* genotype and violent and antisocial behaviour. Genotypes associated with high levels of MAOA activity buffered Whites, but not non-whites, from increased risk of violence and/or antisocial behaviour in later life. The authors suggested that contextual factors (environmental stressors) may have underlaid the differences between the races. Serious negative consequences are linked to child abuse and neglect and the genetic 'make-up' of individuals may or may not contribute significantly to their eventual outcome and fate; veritably, *MAOA* genotype role ought to offer only a small 'peeping-hole' at a more complete scenario.

CONCLUSIONS

In conclusion, a number of genes and neurotransmitter systems have been linked to symptom clusters found in individuals with comorbid neuropsychiatric disorders. For example, genes associated with substance abuse (alcoholism) were also associated with antisocial personality disorder, conditions found to co-occur in about one third of alcoholics. Genes common to substance abuse and schizophrenia also have been identified. Genes have been associated with impulsive behaviour that may link a number of neuropsychiatric disorders. Some studies have failed to find the linkage reported by others possibly because of heterogeneity of samples emphasizing the need for careful phenotyping. Environmental factors interact with the effects of genes on behaviour providing a further variable that needs to be controlled in these studies. As the role of various factors influencing the effects of genes on behaviour and the refinement of behavioural phenotyping progresses, the contribution of genetic variation and biological susceptibility to comorbid psychiatric disorders will continue to come into focus.

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