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Genetic Association Studies of Antioxidant Pathway Genes and Schizophrenia

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Abstract

The endogenous production of highly reactive oxidation species is an inherent by-product of cellular energy metabolism. Cellular antioxidant defense systems (AODS) comprising various antioxidants counter these damaging effects. Several lines of evidence, including postmortem studies, suggest increased oxidative stress in patients with schizophrenia. Some genetic association studies and gene-expression studies suggest that patients also may have altered ability to mount antioxidative mechanisms. As the genetic associations may provide etiologic evidence in support of the oxidative-stress hypothesis of schizophrenia, a focused review has been conducted. We also suggest avenues for further research. *Antioxid. Redox Signal.* 15, 2037—2045.

Introduction

THE GENESIS OF SCHIZOPHRENIA (SZ) is obscure. Several promising leads are being pursued. Here we focus on processes related to oxidative stress. We initially surveyed the clinical feature of SZ, followed by a review of gene-expression and gene-mapping studies in relation to antioxidant pathways. Finally, we synthesize available data and suggest further lines of enquiry.

Clinical Features

Schizophrenia typically has its onset in adolescence or early adulthood. It is characterized by psychotic phenomena such as delusions, hallucinations, and thought disorder, along with impairment in emotions and social function (6). Schizophrenia has been documented in all ethnic groups investigated to date (22). *Schizoaffective disorder* (SZA) is a related, common disorder that lies on a continuum between SZ and bipolar I disorder (BP1) with regard to its clinical features and possibly also in relation to etiology (7, 32).

Treatment for SZ is largely empiric, symptomatic, and palliative. A significant proportion of patients do not respond satisfactorily. Many reasons exist for the unsatisfactory response, including lack of compliance (65). Given this unsatisfactory state of affairs, it is important to understand the etiology and pathogenesis of SZ. Although imaging and postmortem studies, as well as studies of cognitive variables, point to abnormalities in brain function, the precise biologic basis for SZ is obscure (19).

Epidemiology

SZ has a lifetime morbid risk of 1%, although geographic variations in the prevalence are likely (41). The incidence of SZ is 0.53 per 1,000 population approximately (23). Several environmental risk factors such as perinatal viral infections, obstetric trauma, and maternal malnutrition have been identified as risk factors, as well as familial clustering for both SZ and SZA (24, 71).

Genetic Epidemiology

Based on family, twin, and adoption studies, the heritability for SZ has been estimated at 60–80% (37). The recurrence risk ratio to first-degree relatives compared with the population prevalence has been estimated at 8.6 to 10 (55). Complex segregation analyses have consistently rejected monogenic models in favor of polygenic inheritance (37). Several novel models have recently been suggested, including rare variants such as copy-number variants (CNVs) (74), and possibly, methylation in specific chromosomal regions (48).

The Concept of Gene-mapping Studies

At its heart, any gene mapping effort attempts to find genetic variant/s that explain all or a portion of the variance in a trait in a population (2, 3). This can typically be attained in a family-study setting ("linkage"), or through unrelated individuals ("association"). Linkage studies evaluate the cosegregation of the trait of interest and a set of genetic polymorphisms in families. With the availability of polymorphisms

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across the genome, it is possible to interrogate the entire genome. Demonstration of statistically significant co-segregation between marker(s) and the trait in the selected families is called linkage. It indicates that the linked polymorphism confers variation for the trait. Because large chromosomal regions can be "linked," it is necessary to follow up linkage with further "fine mapping" studies. This is achieved through association studies, in which the trait is typically evaluated in a set of unrelated individuals. Statistically significant correlation between the trait and a genetic variant (or a significant case–control difference, the frequency of a marker, for a disease association study) denotes association. Because associations are typically present over much smaller genomic regions than linkage, association studies have been conventionally conducted after demonstration of significant linkage as part of the fine-mapping effort. With the availability of densely spaced sets of polymorphisms, sufficiently large samples, and ease of genotyping assays, it is now feasible to conduct association studies across the genome without resorting to initial linkage analysis.

Progress in Gene-mapping Studies for SZ

Like other genetically complex disorders, linkage studies have been relatively unsuccessful for BP1/SZ, although some meta-analyses suggest significant linkage after genome-wide corrections for multiple comparisons (28, 38). Association studies have also been pursued. Initial association studies focused on "biologic" candidates (*i.e.*, genes thought to be related to SZ pathogenesis based on pharmacologic or pathologic studies). Such studies yielded inconsistent results (61). Later studies investigated "positional candidates" (*i.e.*, genes localized to linked regions that are expressed in the brain and plausibly play a role in pathogenesis). Several positional candidate genes have been suggested. Examples include *Dysbindin* (*DTNBP1*), *Neuregulin 1*(*NRG1*), *D-amino-acid oxidase* (*DAO*), and *G72* (also named d-amino acid oxidase activator, *DAOA*) (45, 61). However, many of the results have also been inconsistent (40, 42).

In view of the emerging success in other diseases, several genome-wide association studies (GWASs) have been completed, whereas others are in progress (66). A locus in the HLA region has been reported to be associated at genome-wide significant levels (59), and two other studies have provided supportive evidence (51, 64). Other studies support a role for *ZNF804A* (43). To date, identified genetic risk factors have modest effects individually [odds ratios (ORs) $\sim$1.1–1.8)] (27, 31). Other risk factors, such as CNVs, confer greater risk, but are rare, and replications are awaited (74). Thus, it is very difficult to confirm associations with genetic risk factors by using currently available samples (40). Meta-analyses of these data are planned (8).

Key Issues Related to Gene-mapping Studies of SZ

The variants identified to date through linkage, candidate-gene association, and GWASs explain only a fraction of the heritability of SZ. This "missing heritability" problem has also been noted for other genetically complex disorders (33). The missing heritability problem not only highlights inherent difficulties in identifying primary genetic risk factors for genetically complex disorders, but also points to certain deficiencies in earlier SZ association studies. The main difficulties arise from the diversity and number of polymorphisms in the human genome. It is fairly routine to evaluate 500,000 to 1,000,000 SNPs during GWASs. The sheer number of comparisons involved in investigating such polymorphisms raises the prior probability of detecting false-positive associations if conventional levels of significance are adopted (*e.g.*, $p = 0.05$) (3). Therefore, more-stringent levels of significance, such as $p = 10^{-7}$ to 10^{-8} have been recommended. If the recommended levels of significance are adopted, thousands of individuals must be investigated to detect relatively small risks (ORs $\sim$1.2) (8). Conversely, analysis of relatively small samples increases the probability of false-negative associations. By this metric alone, most SZ genetic-association studies to date are underpowered. In the same vein, many studies have not evaluated a sufficient number of representative polymorphisms at many loci (67). It is difficult to derive meaningful conclusions from association studies in which sufficient numbers of polymorphisms have not been analyzed. Certain artifacts of association studies can be overcome by analyzing associations within families (62). Nevertheless, gene-mapping studies may not discriminate between sets of correlated polymorphisms that commonly occur within the genome because of a phenomenon called linkage disequilibrium (LD). For this reason, it is helpful to evaluate plausible biologic functions for associated polymorphisms.

Results

Reported association studies with antioxidant gene polymorphisms

Some published studies investigating candidate proteins suggest dysregulated AODS-related abnormalities in SZ (53). The damage could be due to sustained oxidative stress induced by exogenous factors like infection, which may overwhelm the cellular antioxidative stress machinery. Conversely, it is possible that a dysfunction occurs in oxidative stress–response mechanisms. Numerous genes encode antioxidant factors (10). Genetic-association studies have been conducted with polymorphisms in some of these genes. These studies, as well as gene-expression studies, are described later. They are discussed in relation to relevant demographic and statistical information for each study provided in Table 1.

Glutathione synthesis genes (*GSS*, *GCLC*, and *GCLM*). Glutathione (GSH) plays a crucial role as a key element of antioxidation defense mechanism in the brain (58). The synthesis of GSH is regulated by glutathione synthetase [(*GSS*, chromosome (Chr) 20q11.2], *g*lutamate cysteine ligase catalytic subunit (*GCLC*, Chr 6p12), and glutamate cysteine ligase modifier subunit (*GCLM*, Chr 1p21). Tosic *et al.* (70) investigated a Danish and a Swiss sample, but did not observe significant association between *GSS* and SZ. However, they observed an association with two *GCLM* polymorphisms (*i.e.*, rs2301022 and rs3170633). This group later studied a trinucleotide repeat (TNR) polymorphism in the *GCLC* gene (16). They also conducted *in vitro* functional assays, suggesting a role of *GCLC* and the TNR polymorphism in SZ. Ma *et al.* (30) also observed association between a *GCLM* gene polymorphism and SZ in a Han Chinese sample. After sequencing exons and the promoter region of *GLCM*, Butticaz *et al.* (5) also genotyped two key polymorphisms reported to be associated in prior studies. They suggested that the risk for SZ, if present

Table 1. Reported Association Studies with Antioxidant Gene Polymorphisms

Gene/study	*Marker/s*	N *(cases/controls)*	*Ethnicity*	*Results*
GCLC (16)	Trinucleotide repeat (TNR) polymorphism	66/48	Caucasian	$p = 0.002$
GCLM (70)	Eight polymorphisms	389/379	Caucasian	rs2301022, $p = 0.0005$ (OR = 2.72); rs3170633 $p = 0.002$ (OR = 1.77)
GCLM (30)	rs2301022, rs3170633, and ss60197536	427/415	Chinese Han	rs2301022, $p = 0.026$ (OR = 1.29) rs3170633 $p = 0.012$ (OR = 1.37)
GCLM (25)	rs2301022, rs3170633, rs718875, and ss60197536	742/819	Japanese	NS
GCLM (5)	rs2301022 and rs3170633	72/83	Caucasian	NS
GSS (70)	Nine markers	389/379	Caucasian	NS
GSTM1 (17)	CNV[a]	87/117	Japanese	$p = 0.0075$ (OR = 1.79), null allele[b]
GSTM1 (46)	CNV[a]	111/130	Korean	$p = 0.014$ (OR = 1.93), null allele[b]
GSTM1/GSTT2 (56)	CNV[a]	654/604	Spanish	$p = 0.0008$ (OR = 1.92), positive genotype[c]
GSTT1 (57)	CNV[a]	292/292	Iranian	$p < 0.001$ (OR = 2.37), positive genotype[c]
GSTM1/GSTP1/GSTO1/ GSTT1/GSTT2/GPX1/ GCLM (36)	CNV[a] -GSTT1 & GSTM1; < BR/ > GPX1(Pro198Leu- rs1050450); GSTP1 (Ile105Val- rs1695); GSTO1 (Ala140Asp- rs4925); GSTT2 (Met139Ile- rs1622002). ss60197536 & rs2301022-GCLM	214/220	Japanese	Residual SZ, GSTM1 genotype $p = 0.0367$, OR = 1.79
MnSOD (21)	Ala–9Val exonic SNP	192/141	Japanese	NS for SZ, association with tardive dyskinesia
MnSOD (1)	Ala–9Val exonic SNP	153/196	Turkish	$p = 0.0001$
MnSOD (47)	Ala–9Val exonic SNP	262/263	Korean	NS
MnSOD (72)	Ala–9Val exonic SNP	212/257	Caucasian	NS
MSRA (75)	Multiple markers; tetra nucleotide deletion	125 families 321 families	Latin-American	$p = 0.0292$ $p = 0.0367$
MT-ND5 (4)	Sequencing ND5 gene-219 variants		Caucasian	NS
MT-ND4 (34)	m.12027T>C (mitochondrial DNA variant)	181/184	Caucasian	$p < 0.0001$
NOS1 (60)	rs2682826	215/182	Japanese	$p = 0.000007$
NOS1 (29)	CA-Repeat_exon29	198/274	Chinese Han	$p = 0.372$,
NOS1 (68)	12 markers	262/480	Chinese Han	rs3782206, $p = 0.014$, OR = 0.77; haplotypes (rs3837437 + rs3782206) $p = 0.0026$
NOS1 (44)	rs41279104, rs3782221, rs3782219, rs561712, rs3782206, rs2682826, and rs6490121	1154/1260	Japanese	NS
NOS1 (54)	Exon sequencing, promoter VNTR, 4 SNPs- rs41279104, rs2293054, rs1047735, rs2133681	195/284	Caucasian	$p = 0.020$ for rs41279104(G-84A), $\chi^2 = 5.42$
NOS1 (39)	Multiple markers, GWAS	479/2938	Caucasian	$p < 0.00005$
NOS1 (12)	Nine markers	274 trios	Ashkenazi Jew	rs3782219, $p = 0.0003$ (OR = 2.05); rs3782221, $p = 0.001$ (OR = 2.70)
NQO2 (18)	12 markers; promoter + exons; 29 bp insertion/deletion	102/234	Japanese	$p = 0.0109$ ($p = 0.0016$ for episodic SZ)
PON1 (35)	Gln192Arg	244/177	Japanese	NS
PON1 (26)	Gln192Arg(Q/R192) Leu55Met(M/L55PON1)	267/292	Turkish	$p = 0.001$

GCLC, glutamate cysteine ligase catalytic subunit; GPX1, glutathione peroxidase 1; GSS, glutathione synthetase; GSTT1, glutathione *S*-transferase theta-1; GSTT2, glutathione *S*-transferase theta 2; GSTM1, glutathione *S*-transferase mu 1; GSTO1,glutathione *S*-transferase omega-1; GSTP1, glutathione *S*-transferase pi; GWAS, genome-wide association studies; MnSOD, manganese superoxide dismutase; MSRA, peptide methionine sulfoxide reductase; MT-ND5, mitochondrial NADH dehydrogenase 5; MT-ND4, mitochondrial NADH dehydrogenase 4; NOS1, nitric oxide synthase 1; NQO2, NADPH dehydrogenase, quinone 2; NS, Not significant (p value >0.05); PON1, paraoxonase1.

[a]CNVs, copy number variations, deletion/nondeletion of entire gene.

[b]Null allele, deletion of the gene.

[c]Positive genotype, no deletion of the gene.

at *GCLM,* is unlikely to be due to exonic mutations. In contrast, another group did not find a significant association between *GCLM* polymorphisms and SZ (25). This study analyzed more polymorphisms and was almost twice the size of any of the other published studies. The nonsignificant results thus raise concerns about the earlier published associations.

GSH-related genes (*GSTM1*, *GSTP1*, *GSTO1*, *GSTT1*, *GSTT2*) and *GPX1*. Glutathione *S*-transferases (GSTs) represent a family of detoxifying enzymes coded by genes on different chromosomes [*glutathione S-transferase mu 1(GSTM1),* Chr 1p13.3; *glutathione S-transferase theta-1* and *theta-2 (GSTT1* and *T2),* Chr 22q11.2; *glutathione S-transferase pi* (*GSTP1),* Chr 11q13, and *glutathione S-transferase omega-1* (*GSTO1),* Chr 10q24.3]. They play a crucial role in the detoxification of charged compounds, products of oxidative stress, and other electrophilic components, such as environmental toxins (20). GSTM1 and GSTT1 are known to be deleted in some individuals because of gross structural variations, leading to CNVs (*i.e.*, null genotypes/null alleles) (63). Homozygous deletions of these genes results in loss of biochemical activity of these gene products (15). Thus, evaluation of such CNVs should be a priority for testing the oxidative stress model for SZ.

Glutathione peroxidase 1(GPX1), located on Chr 3p21.3, codes for a crucial antioxidation enzyme involved in the detoxification of hydrogen peroxide. Reduced levels of GPX1 have been observed in SZ patients (52, 79). Several investigators have detected associations with polymorphisms at *GSTT1, GSTT2,* and *GSTM1* (17) (Table 1). Recently, Matsuzawa *et al*. (36) investigated GSH-related genes, as well as polymorphisms of *GCLM* in a Japanese sample. They did not find any persuasive evidence supporting associations with these polymorphisms, apart from *GSTM1*. They observed that the *GSTM1*-null genotype was overrepresented in SZ patients with "residual schizophrenia," compared with controls. This important result must be evaluated independently, preferably in a well-powered Japanese sample.

Manganese superoxide dismutase. Manganese superoxide dismutase (*MnSOD*) gene, localized to Chr 6q25.3, codes for a critical enzyme involved in protecting mitochondrial components from highly charged free radicals produced during mitochondrial metabolism (13). It converts (dismutates) the superoxide anion into water and hydrogen peroxide. Because increased mitochondrial activity occurs in metabolically active cells such as neurons, MnSOD acts as a primary defense against charged species released by complexes I and III of mitochondrial electron transport. Comparative proteomic analysis in postmortem human hippocampal tissues indicated a significant association of *MnSOD* with SZ (11). Other studies, summarized in Table 1, have investigated associations with a coding polymorphism rs4880 (denoted Ala–9Val), with mixed results. This nonsynonymous SNP results in the loss of a signal moiety that guides/translocates MnSOD to mitochondria after its translation. Akyol *et al.* (1) found a significant association with this SNP in a Turkish sample (1). Initial work suggested an association with tardive dyskinesia, but not with schizophrenia, in a Japanese sample (21). Other studies also did not find any significant association between the *MnSOD* marker and SZ (47, 72). Thus, the only published association with the functionally important Ala–9Val polymorphism was reported in a Turkish sample, with negative reports from Korean, Japanese, and Caucasian samples. To test the possibility that the association is restricted to individuals of Turkish ethnicity, replicate studies are appropriate in this ethnic group.

Peptide methionine sulfoxide reductase (*MSRA*). *MSRA* is located on Chr 8p23.1 and plays a protective role against oxidative stress by reducing methionine moieties of proteins oxidized by charged oxidative species (14). Based on two independent studies in Latin-American samples, Walss-Bass *et al.* (75) suggested that *MSRA* polymorphism(s) could be associated with SZ (75). They also conducted *in vitro* assays by using lymphoblastoid cell lines derived from the subjects with selected genotypes. In sum, they suggested *under*-transmission of the shorter S allele (tetra nucleotide deletion: c.-1796 to −1793delATGA) to SZ patients, consistent with a protective role for this allele. To our knowledge, the promising functional assays have not been independently investigated.

Mitochondrial genes. Mitochondria are the seat of cellular energy production and also produce highly charged species as a by-product. Defense systems scavenge these charged molecules, and any alteration in their levels could cause imbalance. By using parallel transcriptomics, proteomics, metabolomics, and hierarchic clustering, Prabhakaran *et al.* (49) identified 59 genes with significantly altered expressions. These genes were related mainly to mitochondria and energy metabolism, allowing substantial separation of schizophrenia from control samples across the 92 assays (48 schizophrenia and 44 control brain samples). Earlier, Whatley and colleagues (77) reported reduced expression of ubiquinone reductase and cytochrome *b5* reductase in patients receiving neuroleptic flupenthixol treatment. Taurines and colleagues (69) also reported elevated levels of mitochondrial complex I 75-kDa subunit mRNA in early-onset schizophrenia. Complex 1 of mitochondria plays critical role in mitochondrial energy metabolism. Any alteration in complex 1 activity due to mutations in its subunit [mitochondrial DNA NADH dehydrogenase, subunits 2, 4, and 5 (*MTND2, MTND4 and MTND5*] genes could trigger oxidative stress–related damage (9). The *MTND5* gene encoding the mitochondrial complex 1 subunit and localized to the mitochondrial genome was investigated by our group for association with SZ (4). We did not observe any significant association with MTND5 variants and SZ. We did observe an increase in the frequency of synonymous as well as overall mitochondrial genomic variations among SZ cases compared with controls ($p = 0.014$ and $p = 0.02$, respectively) (4). Marchbanks *et al.* (34) investigated *MTND4* gene variations in SZ subjects. They observed that a *MTND4* gene variant, m.12027T >C, was associated with SZ. Their *in vitro* assays also complemented their genetic associations, strengthening a potential role of this variation to oxidative stress in SZ. The MTND4 protein is part of complex 1 of the mitochondrial electron-transport chain, and *MTND4* gene mutations may increase production of reactive oxygen species within mitochondria. These suggestive studies must be extended to larger samples, after accounting for possible population stratification.

Nitric oxide synthase 1. Nitric oxide (NO) is a free radical with diverse biologic functions, including host immune re-

sponse and neurotransmission (73). Nitric oxide synthase 1 (*NOS1*) is located on chromosome 12q24 and encodes a protein catalyzing the synthesis of NO. Shinkai *et al*. (60) were the first to report a nominally significant genetic association between a *NOS1* polymorphism and SZ. They observed that a C→T polymorphism in exon 29 (rs2682826) may cause increased risk for SZ in the Japanese population. However, Tang *et al*. (68) did not detect these associations in a Han Chinese sample. Instead, they observed an association with SZ (OR, 0.77) when they investigated the 5′ flanking region (including SNPs rs499776–rs561712–rs3837437–rs3782206, encompassing the promoter region), as well as with the initial three exons. In another study, a dinucleotide repeat polymorphism 166 base pairs downstream from rs2682826 in exon 29 did not show a significant association with SZ in a Han Chinese sample (29). After an extensive genotyping effort, Fallin *et al*. (12) observed significant association of two other SNPs, rs3782219 and rs3782221 ($p = 0.0003$; OR, 2.05 and 2.70, respectively). They did not find a significant association with rs2682826, the exon 29 SNP reported to be associated among the Japanese (60). Another group suggested an association with a promoter polymorphism (rs41279104) (54). Although recent investigations in other Japanese samples do not suggest significant associations with seven previously associated SNPs (44), a recent GWAS indicated association of an intronic SNP rs6490121, albeit not at the level of genome-wide significance (39). Meta-analyses for *NOS1* gene variations would be desirable, in the light of the variable associations.

NADPH quinone oxidoreductase2. NADPH quinone oxidoreductase2 (*NQO2*) is located on Chr 6pter-q12 and codes for protein involved in oxidation of NADH and NADPH by quinones. The promoter of *NQO2* gene harbors a 29-base-pair insertion/deletion polymorphism assumed to interact with the SP1 binding site. This interference with a transcription factor binding site can affect NQO2 transcript levels. Harada *et al*. (18) investigated this 29-base-pair insertion/deletion polymorphism along with other polymorphisms in the promoter and exonic regions of the *NQO2* gene. They observed a significant association with this marker with SZ in their subjects. This association was even stronger in a subset of SZ subjects (episodic SZ). Apart from genetic association studies, they also observed alteration in the NQO2 transcript in relation to this marker. This highly promising result merits replicative studies, as the functional polymorphism would not be encountered in GWASs using conventional SNP arrays.

Paraoxonase1. Paraoxonase1 (*PON1*) is located on Chr 7q21.3 and reported to serve antioxidative functions against low-density lipoproteins (35). Matsumoto *et al*. (36) did not observe a significant association between SZ and one nonsynonymous polymorphism (Gln192Arg). In another study by Kucukali *et al*. (26), they observed overrepresentation of nonsynonymous polymorphism (Gln192Arg), also known as Q/R192 in schizophrenia subjects. With *in vitro* assays, they also showed that *PON1* variations are associated with variation in PON1 activity.

Corticoid receptors. Mineralocorticoid and glucocorticoid receptors are important in the control of stress-related and circadian hypothalamic–pituitary–adrenal activity. Mineralocorticoid receptor mRNA levels have been reported to be decreased in schizophrenia and may be negatively correlated with the duration of psychiatric illnesses (78). Glucocorticoid-receptor mRNA levels may be reduced in the hippocampal region in schizophrenia patients (76). In these studies, no significant differences were found in gene-expression patterns because of a history of suicide, substance abuse or dependence, or exposure to antidepressants or neuroleptics at the time of death.

Discussion

Synthesis of published studies and avenues for additional research

The studies discussed earlier and summarized in Table 1 suggest several promising candidate genes and suggestive genetic associations. For example, the associations with *NOS1*, *MnSOD,* and *MSRA*, in conjunction with the reported cellular studies and the published clinical studies of SZ, suggest a pathogenic role for the related protein products. Suggestive associations observed with a *GSTM1*-null genotype, as well as the potentially functional polymorphism of the *NQO2 gene* deserve further investigation, preferably in adequately powered Japanese samples (18, 36). In contrast, other studies have not detected significant associations. The lack of significance may be related to insufficient power, so evaluation in larger samples is clearly indicated.

The published GWASs provide a rich resource for such analyses. Thus far, no published GWASs have provided convincing evidence for associations at any of the genes reviewed earlier. In view of the missing heritability problem, it would be unwise to shelve further genetic-association studies for a number of reasons. First, the GWASs have not adequately tested key functional polymorphisms, such as the *GSTM1* and the *NQO2* variants. It should be noted that the GWASs have provided persuasive evidence for associations with only a handful of polymorphisms, suggesting that additional GWASs with larger samples may be necessary (51). Such studies may provide more convincing evidence (or the lack thereof) for the genes of interest. In addition to the genes reviewed here, such studies may highlight additional candidate genes for analyses by using gene-expression studies. Because several products of the antioxidant genes have complementary functional roles, it is legitimate to enquire whether genetic risk could be conferred by two or more polymorphisms (epistasis). The potentially enormous analytic space entailed in investigating epistatic interactions would require substantially larger samples than those currently available (50). Therefore, analysis of networks of functionally related genes, although a tantalizing possibility, may not yield statistically convincing evidence for genetic associations at present.

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Abbreviations Used

BP1 = bipolar I disorder
Chr = chromosome
CNVs = copy-number variations
C→T = cytosine to thymine
Del = deletion
GCLC = glutamate cysteine ligase catalytic subunit
GCLM = glutamate cysteine ligase modifier subunit
GPX1 = glutathione peroxidase 1
GSH = glutathione
GSS = glutathione synthetase
GSTs = glutathione *S*-transferases
GSTM1 = glutathione *S*-transferase mu 1
GSTO1 = glutathione *S*-transferase omega-1
GSTP1 = glutathione *S*-transferase pi
GSTT1 = glutathione *S*-transferase theta-1
GSTT2 = glutathione *S*-transferase theta-2
GWASs = genome-wide association studies
HLA = human leukocyte antigen
kDa = Kilodalton
MnSOD = manganese superoxide dismutase
mRNA = messenger ribonucleic acid
MSRA = peptide methionine sulfoxide reductase
MT-ND2 = mitochondrial NADH dehydrogenase subunit 2
MT-ND4 = mitochondrial NADH dehydrogenase subunit 4
MT-ND5 = mitochondrial NADH dehydrogenase subunit 5
N = *number of subjects*
NO = nitric oxide
NOS1 = nitric oxide synthase
NQO2 = NADPH quinone oxidoreductase 2
NS = not significant
OR = odds ratio
PON1 = paraoxonase1
SNP = single-nucleotide polymorphism
SP1 = SP1 transcription factor
SZ = schizophrenia
SZA = schizoaffective disorder
TNR = trinucleotide repeat
ZNF804A = zinc-finger protein 804A

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