The dopamine hypothesis of schizophrenia (SZ) has motivated a large number of genetic association studies but few if any dopaminergic (DA) polymorphisms are accepted as credible risk factors at present. To evaluate whether dopamine-related genes have been investigated adequately, we surveyed public genetic databases and published SZ association studies with regard to 14 conventional DA genes and 7 selected dopamine-interacting proteins. We estimate that 325 polymorphisms would be required to evaluate the impact of common variation on SZ risk among Caucasian samples. To date, 98 polymorphisms have been analyzed in published association studies. We estimate that only 19 of these variations have been evaluated in samples with at least 50% power to detect an association of the effect size commonly found in genetically complex disorders. While it is possible that DA genes do not harbor genetic risk factors for SZ, our review suggests that satisfactory conclusions for most genes cannot be drawn at present. Whole-genome association studies have begun to fill this void, but additional analyses are likely to be needed. Recommendations for future association studies include analysis of adequately powered samples, judiciously selected polymorphisms, multiple ethnic groups, and concurrent evaluation of function at associated single-nucleotide polymorphisms.

**Key words:** genetic association/schizophrenia/dopamine/ meta-analysis

**Introduction**

Over the past 2 decades, schizophrenia (SZ)-mapping studies have grappled with several difficulties inherent to all studies of common, genetically complex disorders. Heritability estimates for the disorder vary from 60% to 70%, but complex segregation analyses have consistently rejected monogenic models of inheritance in favor of polygenic/multifactorial threshold models. A genetic model including multiple interacting loci of small effect may provide the best fit for the available data, making it difficult to identify individual genetic risk factors. Some analyses suggest that common genetic variants confer risk (also called the “common variant common disease” [CDCV] hypothesis), but others have argued in favor of rare variants. Aided by technological and statistical advances, genetic association studies have grown in size and sophistication. Thanks to these advances, some promising associations have been detected. For example, studies utilizing extended panels of single-nucleotide polymorphisms (SNPs) have identified associations with polymorphisms of dysbindin (*DTNBP1*), neuregulin 1 (*NRG1*), disrupted in SZ (*DISC1*), regulator of G protein signaling (*RGS4*), G72 and D-amino acid oxidase. Consistent with the polygenic model, the risk conferred by the associated alleles is modest (odds ratios [OR] ~1.2).

A sizable fraction of other association studies have focused on dopaminergic (DA) genes, but few credible genetic risk factors have emerged. Two broad conclusions are thus possible: either there are no significant associations between SZ and DA polymorphisms or sufficient evidence is not currently available. In this review, we evaluate the possible impact of DA gene polymorphisms on SZ risk. We summarize the motivation for, and details of, prior genetic association studies involving DA genes. We also survey public database information to determine the proportion of representative common variants that have actually been evaluated at these genes and the number of SNPs analyzed with adequate power to detect an association of the modest effect sizes expected. We conclude with suggested designs for future studies and discuss the relevance of such studies in the context of whole-genome association (WGA) studies.

**The Dopamine Hypothesis**

The DA hypothesis suggests hyperactivity of DA brain function in SZ pathogenesis. It originated from correlations between the clinical potency of antipsychotic drugs and their affinity for dopamine D2 receptors (*DRD2*). Two lines of enquiry have yielded relatively
consistent results regarding the DA hypothesis of SZ. First, patients with SZ display increased sensitivity to the psychotogenic effects of agents that increase synaptic DA release.20–24 Second, acute amphetamine challenge to patients leads to increased DA transmission in vivo, as measured by radioligand binding to DRD2 during positron emission tomography (PET) scans.25–27 However, the DA hypothesis has not been supported consistently using measures such as postmortem DA receptor density or DA metabolite concentrations, in vivo measures of DA receptor density using PET scans, or DA metabolite concentrations in the cerebrospinal fluid.28–35 The discrepancies could be due to medication effects and sampling variation.36,37

Refining the DA Hypothesis
Subtle DA dysregulation could occur in SZ, rather than overall DA hyperactivity; eg, regional variation, selected receptor types, temporal sensitization, or variations during different phases of illness.23,37–39 Hypofunction in prefrontal neuronal circuits has been documented repeatedly in postmortem brain studies of SZ; this may also lead to disinhibition of the prefrontal drive to the limbic striatum with a resultant hyperdopaminergic state in the limbic striatum.36,40 These subtle changes likely reflect a chain of events, so a number of susceptibility factors may be present. This is consistent with the polygenic model of SZ.

Genetic Association Studies Using DA Polymorphisms
The extensive interest in the DA hypothesis has also motivated numerous association studies of DA genes under the rationale that credible genetic associations would motivate further studies of pathogenesis. However, most early association studies were hampered by significant deficiencies in technology and relatively modest sample sizes available. Despite these limitations, the gamut of genes involved in DA neurotransmission was investigated. We conducted PubMed searches using the following combinations of terms: (1) “(individual gene name)” and “schizophrenia”; (2) “(gene symbol)” and “schizophrenia”; (3) “dopamine” and “schizophrenia.” Genetic association studies were then extracted from these sets. As discussed below, most studies followed a similar pattern. An initial study reported on one or a few putatively functional polymorphisms, and subsequent studies analyzed only those variants. Some study designs, such as mutation detection followed by association tests in relatively small samples, are better suited to identify susceptibility loci harboring a substantial impact on risk. Thus, no consistent associations have been detected for a number of key DA genes, potentially leading to the conclusion that susceptibility variants are not present in the DA network.

The DA genes investigated in multiple independent samples include tyrosine hydroxylase,41–43 dopamine decarboxylase,44,45 dopamine beta hydroxylase,46–49 catechol-O-methyltransferase (COMT) (see below), MAOA,50–55 and 1 of the 2 isoforms of the vesicular monoamine transporter (SLC18A1 alias VMAT1).56–58 The dopamine receptors DRD1, DRD2, DRD3, DRD4, and DRD5 have also been investigated.59–64 The vesicular monoamine transporter, member 2 (VMAT2, SLC18A2), has only been investigated in one study to date.65

Other investigators have reported on dopamine-interacting proteins, with similarly inconsistent results. They include orphan nuclear receptor Subunit 4 (NURR, NR4A21); D1 receptor–interacting protein (CALCYON, DRD1IP); protein phosphatase 1, regulatory (inhibitory) subunit 1B (DARPP-32, PPP1R1B); syntaxin 1A (STX1A); protein interacting with PRKCA 1 (PICK1); synaptosomal-associated protein, 25 kDa (SNAP25); and beta adrenergic receptor kinase 2 (GRK3, ADRBK2).66–75

Because space restrictions preclude detailed discussion of each gene, we have reviewed 4 of the most extensively analyzed DA genes. While early association studies have been inconsistent for all of them, recently published studies have provided intriguing new facets. Each gene thus provides precepts for future association studies.

Dopamine D2 Receptor
The DRD2 was a logical early target for association studies because of the effects of therapeutic agents reviewed above. Two genetic variants have been the target of most studies. One is a cysteine to serine substitution at codon 311 (Cys311Ser) and the other an insertion/deletion of 141 bases in the 5’ region of the gene (—141C ins/del). Two independent meta-analyses identified a significant association between the rare Cys311 allele and SZ.76,77 A result that has since been confirmed by a more comprehensive meta-analysis including data from 3707 cases and 5363 controls.60 In contrast, a meta-analysis did not support an association with the insertion/deletion polymorphism. Other polymorphisms have been investigated more recently with significant results from 4 different studies,78–81 but significant associations were not detected when 5 SNPs were analyzed among a family cohort of Ashkenazi Jewish families.82 It would be instructive if the same set of polymorphisms could be analyzed in all these samples, followed by meta-analysis.

Dopamine D3 Receptor
A large number of studies have sought associations at DRD3, but most have focused exclusively on rs6280 (Ser9Gly), a nonsynonymous SNP in the first exon with possible functional effects.83 Repeated meta-analyses have suggested a modest association, but all meta-analyses have not been consistent.61,84,85 Recent studies
have evaluated other variations with somewhat more consistent results. Four studies focused on associations with SNPs upstream to exon 1.86–89 Three of these studies detected significant associations, suggesting that inconsistencies at rs6280 could represent associations with other, correlated SNPs. However, one large case-control study and analysis of a family-based sample did not reveal any significant associations.82,89 Two recent studies evaluated a larger proportion of representative variation; both detected significant haplotype-based associations. We found significant associations with SNPs and haplotypes spanning the gene in 2 independent samples.90 Another group reported significant haplotype-based associations in the 3' region of DRD3 in a Galician population.91 In sum, the numerous association studies conducted at rs6280 appear to be equivocal with respect to SZ susceptibility; however, more recent results considering a greater proportion of common variation within the gene have been more encouraging. These recent findings may represent other liability loci at this gene and might highlight the value of comparative analyses of varied ethnic groups. Such studies lend themselves to evolutionary analyses that may identify ancient mutations.92–94

**Catechol-O-methyltransferase**

COMT is localized to chromosome 22q11, a region implicated in several linkage studies.95 Deletions in this region also lead to the velocardiofacial syndrome, with an increased risk of psychoses.96 Most association studies have investigated an exonic Met158Val polymorphism, which appears to influence COMT activity in vitro. Two different meta-analyses suggest that an association between this variant and SZ, if present, is complex and may be influenced by population substructure.97,98 Interest in the Met158Val polymorphism has continued because it may be correlated with working memory, a trait known to be impaired in SZ.50,99,100

Recent association studies have investigated a larger set of SNPs. Li examined 8 markers in a Chinese sample and detected a significant association with an extended haplotype including Met158Val.101 Another large study of Ashkenazi Jewish patients revealed a highly significant association with 2 COMT SNPs, as well as a haplotype comprising 3 SNPs spanning the 5' to 3' region of the gene (rs737865–rs4680–rs165599).102 However, a study among unrelated cases and controls did not replicate this finding,103 nor did a study of 274 Ashkenazi families investigating 7 COMT SNPs.104 Intriguingly, The Met158Val polymorphism was part of this haplotype and the association was more prominent among women. Gender-specific associations have been detected with a variant within this haplotype (rs737865) in Alzheimer disease as well.104 Notably, rs737865 is in proximity to an estrogen response element.104 These associations highlight the need to evaluate valid subgroups of SZ and the need to consider functional impacts of associated alleles.

**Dopamine Transporter (DAT, DAT1, SLC6A3)**

Most association studies have focused on a putatively functional variable number tandem repeat, 3’ to the stop codon in exon 15, but meta-analyses suggest no significant association.62,105–108 An association has been reported with an exonic SNP among Koreans (1389 C>T; rs2270912).109 A case-control study among Iranians identified a significant association with a putative promoter variant (−67A/T; rs2975226; P = .0003; OR = 2.25).110 The association is particularly intriguing because cis-acting variation in the 5' region of this locus may contribute to differential SLC6A3 expression in vitro and in vivo.111,112 The Korean and Iranian studies need to be evaluated in additional samples. Additional studies using common polymorphisms spanning the gene are also required.

**A Synthesis of Published DA Association Studies**

We examined 14 DA genes and 7 dopamine-interacting proteins that have been used for prior association studies. Our goal was to identify a representative set of common SNPs that should be evaluated to enable a reasonable test of the CDCV hypothesis for each gene. The samples utilized were 60 unrelated Caucasians from the International HapMap project (CEPH; Utah residents with ancestry from northern and western Europe)113 or 90 unrelated individuals representative of the US population from the NIH Polymorphism Discovery Resource 90 individual subset (http://egp.gs.washington.edu/). Data were obtained using the Genome Variation Server resource (http://gvs.gs.washington.edu/GVS/).114 All SNPs with minor allele frequencies over 5% were identified because currently available samples may lack power to detect associations with less frequent polymorphisms. Because genotypes at many of these SNPs may be correlated due to linkage disequilibrium (LD), we selected representative “tag” SNPs using a conventional cutoff (r² < 0.8 between loci). Based on these analyses, we found that 325 tag SNPs would be needed to tag all available common variations from these populations (table 1).

These estimates were next compared with the published association studies. At each gene, we listed the number of variations evaluated in previous association studies (SNPs and other polymorphisms), as well as the largest individual association study for each gene (defined in terms of the number of cases, see table 1). If possible, LD between the polymorphisms was analyzed. We also estimated the number of studies that had 50% power to detect associations of modest effect size for each of the polymorphisms tested (alpha = .05). We assumed an additive risk model with a genotype relative
### Table 1. Published Dopaminergic Association Studies and Estimates of Their Comprehensiveness

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Gene Name (alias)</th>
<th>Size (kb)a</th>
<th>Common SNPs</th>
<th>Tag SNPs</th>
<th>No. of Markers Studiedg</th>
<th>Power &gt; 50%h</th>
<th>Cases/Controlsi</th>
<th>Reference</th>
<th>SNPs</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine Pathway Genes</strong></td>
<td></td>
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<tr>
<td>TH</td>
<td>11p15.5</td>
<td>Tyrosine hydroxylase</td>
<td>17.9</td>
<td>14</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>334/391</td>
<td>Pae et al139</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>DBH</td>
<td>9q34</td>
<td>Dopamine beta hydroxylase</td>
<td>33.0</td>
<td>68</td>
<td>39</td>
<td>2</td>
<td>0</td>
<td>178/178</td>
<td>Williams et al140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDC</td>
<td>7p11</td>
<td>Dopamine decarboxylase</td>
<td>112.6</td>
<td>204</td>
<td>36</td>
<td>2</td>
<td>0</td>
<td>173/204</td>
<td>Borglum et al145</td>
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<td></td>
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<tr>
<td>DRD1</td>
<td>5q35.1</td>
<td>Dopamine D1 receptor</td>
<td>13.1</td>
<td>12</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>407/399</td>
<td>Dmitrzak-Weglarz et al141</td>
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<tr>
<td>DRD2</td>
<td>11q23</td>
<td>Dopamine D2 receptor</td>
<td>75.6</td>
<td>78</td>
<td>19</td>
<td>7</td>
<td>2</td>
<td>188/384</td>
<td>Hanninen et al140</td>
<td>2</td>
<td>+/-</td>
</tr>
<tr>
<td>DRD3</td>
<td>3q13.3</td>
<td>Dopamine D3 receptor</td>
<td>60.2</td>
<td>69</td>
<td>18</td>
<td>17</td>
<td>4</td>
<td>331/274, (292)k</td>
<td>Talkowski et al140</td>
<td>1</td>
<td>+/-</td>
</tr>
<tr>
<td>DRD4</td>
<td>11p15.5</td>
<td>Dopamine D4 receptor</td>
<td>13.4</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>570/570</td>
<td>Nakajima et al142</td>
<td>2</td>
<td>–</td>
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<tr>
<td>DRD5</td>
<td>4p16.1</td>
<td>Dopamine D5 receptor</td>
<td>12.1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>158/437</td>
<td>Muir et al144</td>
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<tr>
<td>SLC18A1</td>
<td>8p21.3</td>
<td>Vesicular monoamine transporter, 1 (VMAT1)</td>
<td>48.4</td>
<td>60</td>
<td>20</td>
<td>4</td>
<td>0</td>
<td>354/365</td>
<td>Richards et al157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC18A2</td>
<td>10q25</td>
<td>Vesicular monoamine transporter, 2 (VMAT2)</td>
<td>45.9</td>
<td>43</td>
<td>15</td>
<td>6</td>
<td>0</td>
<td>(50)</td>
<td>Kunugi et al165</td>
<td></td>
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</tr>
<tr>
<td>SLC6A3</td>
<td>5p15.3</td>
<td>Neurotransmitter transporter, dopamine (DAT, DAT1)</td>
<td>62.6</td>
<td>120</td>
<td>49</td>
<td>7</td>
<td>1</td>
<td>252/271</td>
<td>Jeong et al109</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>COMT</td>
<td>22q11.2</td>
<td>Catechol-O-methyltransferase</td>
<td>37.2</td>
<td>50</td>
<td>30</td>
<td>11</td>
<td>3</td>
<td>1643/3980</td>
<td>Shifman et al102</td>
<td>1</td>
<td>+/-</td>
</tr>
<tr>
<td>MAOA</td>
<td>Xp11.3</td>
<td>Monoamine oxidase A</td>
<td>100.7</td>
<td>38</td>
<td>8</td>
<td>3</td>
<td></td>
<td>346/334</td>
<td>Norton et al154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAOB</td>
<td>Xp11.3</td>
<td>Monoamine oxidase B</td>
<td>125.8</td>
<td>16</td>
<td>12</td>
<td>0</td>
<td></td>
<td>87/100</td>
<td>Tachikawa et al173</td>
<td></td>
<td></td>
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<tr>
<td><strong>Dopamine-Interacting Genes</strong></td>
<td></td>
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</tr>
<tr>
<td>NR4A2</td>
<td>2q24.1</td>
<td>Orphan nuclear receptor subunit 4 (NURRI)</td>
<td>18.3</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>180/180</td>
<td>Iwayama-Shigeno et al166</td>
<td></td>
<td></td>
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<tr>
<td>DRD1IP</td>
<td>10q26.3</td>
<td>D1 receptor–interacting protein (CALCYON)</td>
<td>21.5</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>276/253</td>
<td>Luo et al168</td>
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<td></td>
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<tr>
<td>PPP1R1B</td>
<td>17q21.2</td>
<td>Protein phosphatase 1, regulatory (inhibitory) subunit 1B (DARPP-32)</td>
<td>19.7</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>249/273</td>
<td>Li et al169</td>
<td></td>
<td></td>
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<tr>
<td>STX1A</td>
<td>7q11.23</td>
<td>Syntaxin 1A</td>
<td>30.4</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td></td>
<td>192/192, (238)</td>
<td>Wong et al175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PICK1</td>
<td>22q13.1</td>
<td>Protein interacting with PRKCA 1</td>
<td>28.4</td>
<td>17</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1765/1851</td>
<td>Ishiguro et al172</td>
<td></td>
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</tr>
<tr>
<td>SNAP25</td>
<td>20p12-p11.2</td>
<td>Synaptosomal-associated protein, 25 kDa</td>
<td>98.5</td>
<td>97</td>
<td>32</td>
<td>1</td>
<td>0</td>
<td>87/100</td>
<td>Tachikawa et al173</td>
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</table>
Given the diffculties outlined above, it is worthwhile to weigh the utility of further gene-mapping studies for SZ. We believe such studies are needed primarily because DA function is already an area of intensive research, including drug development efforts. However, genetic association studies that have been published have not adequately addressed such disorders, particularly the substantial methodological issues that have been identified in previous studies. Our review of the literature suggests that there is a need for both better methodology and more comprehensive analysis of the data. In particular, we recommend that genetic association studies be designed to investigate epistatic interactions, which may play a role in the genetic etiology of SZ. We also believe that further research is needed to elucidate the functional implications of genetic variants associated with SZ, as well as to identify potential therapeutic targets. By focusing on these areas, we hope to make progress in understanding the genetic factors underlying SZ.
in pathogenesis of many multifactorial disorders. Carefully designed genetic studies might enable the identification of such networks, including key nodes to which novel therapeutics can be targeted. Second, such analyses might help identify novel genes related functionally to “conventional” DA genes.

Which Genes Should Be targeted?
Apart from the genes involved in DA metabolism or those encoding DA receptors, a definition of “DA” genes is difficult because of the known cross talk between neurotransmitter systems. Any list of “DA genes” is also unlikely to remain static in the face of advances in neuroscience research. We recommend starting with genes for which prior association evidence is available. If further studies provide credible, consistent associations, additional functional interactants of the associated genes can be targeted.

Which Polymorphisms Should Be Investigated?
Different types of polymorphisms are known in the human genome, ranging from SNPs to large copy number variations. SNPs are obvious starting points because they have been characterized extensively and because they can be assayed cheaply and accurately. A secondary question is the choice of SNPs. While it is relatively easy to select representative tag SNPs, the allele frequency of the selected SNPs is a more difficult choice. The feasibility of detecting associations for common diseases using “common” SNPs has been questioned on the grounds that they may not mirror the primary associations accurately and/or because risk may be due to relatively rare alleles. While the possibility of rare variants predisposing to SZ cannot be discounted, currently available samples may not enable detection of statistical associations if such variants are examined directly. One practical solution may be to select common tag SNPs and follow up suggestive associations with more dense sets of SNPs, including rare variants. Such intensive analyses may enable us to detect causal variants.

Sample Configurations
The possibility of spurious associations due to ethnic admixture has motivated much debate and the espousal of family-based association studies. While family-based samples detect association only in the presence of linkage and are thus particularly valuable, it is now feasible to correct for population substructure. Though the choice of controls may be dictated by convenience, biased selection of controls has obvious implication for detecting associations. Hence, it is important to plan for follow up of initial associations in other independent samples.

Sample Size
The power analyses reviewed above suggest the need for relatively large samples. Given the possibility of false-positive associations, replicate analyses are also recommended. While sample size limitations remain significant hurdles for association studies, the availability of public repositories (http://www.nimh.nih.gov/) and the feasibility of staged analyses may make this issue more tractable.

Which Ethnic Group(s)?
The overwhelming majority of genetic association studies are being conducted among individuals of Caucasian ancestry. Our review suggests ethnic variation in the magnitude of some of the associations. Such variation is known in other disorders, eg, the association between ApoE alleles and Alzheimer disease. Evaluation of multiple ethnic groups may also enable us to identify primary associations based on ancestral recombinations.

Functional Analyses
The majority of genetic associations for SZ have been reported with noncoding polymorphisms, making it difficult to attribute function to the associated alleles. Nevertheless, such analyses are critical for understanding pathogenesis and may also be helpful in determining primary associations. An interactive design, with genetic associations informing functional analyses, and vice versa, is desirable.

Should WGA Studies Supplant Candidate Gene Studies?
Recently, WGA have come to the fore, thanks to the availability of a comprehensive trove of common polymorphisms, rapid and accurate genotyping platforms, and sophisticated analytic techniques. By analyzing a representative set of SNPs among cases and controls, WGA studies seek to evaluate the relative impact of common polymorphisms. Judicious analyses may also provide insights into epistatic interactions. Remarkable consistencies have recently been attained for a diverse set of common diseases, including age-related macular degeneration, prostate cancer, Crohn disease, and type I diabetes mellitus. WGA studies have already been reported for SZ, and other independent studies are in progress. These studies are likely to yield important new insights, so it is reasonable to question the need for focused candidate gene studies.

It is important to note that WGA represent the beginning of a new effort, rather than an end point in the gene-mapping effort. For example, WGA studies will undoubtedly require replicate studies, followed by more detailed analysis of prioritized genes using more dense sets of polymorphisms. Thus, “candidate gene analyses” will still be needed. Indeed, common polymorphisms are
not tagged uniformly across the genome in some arrays used for WGA. Thus, key associations may remain undetected, even with WGA. In other diseases, candidate gene analyses have also identified associations with SNPs that were not sufficiently large for detection using WGA; eg, associations between late-onset Alzheimer disease and SORL1 SNPs.\textsuperscript{138}

Conclusions

Our review of published association studies involving DA genes highlights the lack of adequate analyses of variation at these genes. Our findings suggest that more comprehensive analyses are required in sufficiently powered samples, particularly in view of some promising recent results. Replicate analyses, as well as analyses of multiple ethnic groups, in conjunction with functional evaluation of associated SNPs would be preferable.

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