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G72/G30 Genes and Schizophrenia: A Systematic Meta-analysis of Association Studies

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ABSTRACT

Schizophrenia may result from a neurotransmission hypofunction of glutamatergic and *N*-methyl-D-aspartate (NMDA) receptors. Linkage disequilibrium mapping has identified several promising and novel positional candidates, including the *G72/G30* and D-amino-acid oxidase (*DAAO*) genes. Since the first positive association report, many subsequent studies have attempted to replicate the association but the results have been mixed. To try to resolve this inconsistency and to elucidate the relationship between the important glutamate-related genes and schizophrenia, the current meta-analysis has combined samples involving 16 polymorphisms covering all published case-control and family-based association studies up to October 2005. The results suggest that there is weak evidence of association between the *G72/G30* genes and schizophrenia.

SCHIZOPHRENIA is a serious psychiatric disease that affects up to 1% of the population worldwide (Cannon *et al.* 1998; Jablensky 2000). Studies have suggested that schizophrenia might result from a neurotransmission hypofunction of glutamatergic and *N*-methyl-D-aspartate (NMDA) receptors (Tsai and Coyle 2002; Harrison and Owen 2003; Hall *et al.* 2004; Owen *et al.* 2004; Rapoport *et al.* 2005). A number of studies have provided evidence of linkage scans and mapping to chromosome 13q22–q34 (Lin *et al.* 1997; Blouin *et al.* 1998; Shaw *et al.* 1998; Brzustowicz *et al.* 1999; Levinson *et al.* 2000). Chumakov *et al.* (2002) found robust evidence of genetic association within the 13q linkage region for schizophrenia. Two overlapping genes, *G72* and *G30*, located at 13q34 and spanning a 65-kb segment, have been shown to be significantly associated with schizophrenia using both individual single nucleotide polymorphism (SNP) and haplotype analysis (Chumakov *et al.* 2002).

G72 has been hypothesized to produce protein PLG72, which is an agonist for the glycine-binding site of the NMDA glutamate receptors (Mothet *et al.* 2000). The postmortem analysis of schizophrenic patients has revealed overproduced G72 together with a lower NMDA glutamate receptor activity, which could result in glutamate-signaling hypofunction (Chumakov *et al.* 2002). Further expression and functional studies have also supported the role of *G72* in the etiology of schizophrenia (Mothet *et al.* 2000; Chumakov *et al.* 2002; Tsai and Coyle 2002; O'Donovan *et al.* 2003; Shirts and Nimgaonkar 2004). G72 protein interacts with the gene for D-amino-acid oxidase (DAAO) on 12q24 to regulate glutaminergic signaling through the NMDA receptors pathway (Tsai and Coyle 2002), and variation within G72 could affect NMDA signaling through the functional pathway (Chumakov *et al.* 2002). The synergic effect on the risk for schizophrenia was higher than the effect of each individual gene due to the interaction between the proteins of *G72* and *DAAO* (Chumakov *et al.* 2002). The story of G72/G30 is quite complex, as set out in an article by Detera-Wadleigh and McMahon (2006). *G72/G30* is also believed to be associated with other psychiatric disorders, such as bipolar disorder (Hattori *et al.* 2003; Chen *et al.* 2004; Schumacher *et al.* 2004).

Chumakov *et al.* (2002) initially reported strong associations between schizophrenia and dozens of SNPs in the *G72/G30* and *DAAO* genes. The associations have been replicated independently in several, but not in all, studies. The available evidence shows inconsistency with regard to which alleles show association with the disease. In an attempt to clarify this inconsistency and to measure the magnitude of the effect of the putative risk alleles, the current meta-analysis has combined all available case-control and family-based association studies dealing with the *G72/G30* and *DAAO* genes and schizophrenia.

MATERIALS AND METHODS

Literature search: The literature included in the analysis was selected using PubMed and focusing on the keywords "schizophrenia," "*G72*," "*G30*," "D-amino-acid oxidase," and

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"*DAAO*." All references cited in these studies and published reviews were examined to identify additional work not indexed by MEDLINE. The analyzed data cover work from all English-language publications up to October 2005.

Inclusion criteria: Eligible studies had to meet all of the following criteria: (1) the studies were published in peer-reviewed journals and were independent studies using original data; (2) the studies provided sufficient data to calculate the odds ratio (OR) with confidence interval and *P*-value; (3) the studies investigated one or more of the 16 polymorphisms using either case-control or family-based approaches; (4) the studies described the genotyping primers, equipment, and protocols used or provided reference to them; (5) the studies diagnosed schizophrenia patients according to the International Classification of Diseases, *Diagnostic and Statistical Manual*, or *Chinese Classification of Mental Disorders* systems; and (6) the studies used healthy individuals as controls. Authors were contacted in cases where there were questions regarding their studies.

Quality assessments: For association studies with inconsistent results based on the same polymorphisms, the methodological quality needed to be assessed using appropriate criteria to limit the risk of introducing bias into meta-analyses or systematic reviews. The classification method known as the "extended-quality score" (Li *et al.* 2006; Li and He 2006) was used to assess the quality of association studies. The extended-quality score categorizes studies as "high," "medium," or "poor" quality.

Statistical analyses: Any study that contained data from different ethnic populations (or genders) was considered effectively as several individual studies. Data from the case-control studies were summarized in two-by-two tables and transmission disequilibrium test (TDT) studies were summarized in two-by-one tables. From each table, a log-OR and its sampling variance were calculated (Cho *et al.* 2005). Cochran's chi-square-based *Q*-statistic test was used to assess possible heterogeneity among the individual studies. Heterogeneity *Q*-tests were also performed to test for differences in OR between design types (case control *vs.* family based). A test for funnel plot asymmetry, described by Egger *et al.* (1997), was used to assess evidence for publication bias. ORs were pooled using the method of DerSimonian and Laird (1986), and 95% C.I.'s were constructed using Woolf's method. The significance of the overall OR was determined by the *Z*-test. For the sensitivity analysis, each study in turn was removed from the total, and the remaining were reanalyzed. This procedure was used to ensure that no individual study was entirely responsible for a finding. The type I error rate was set at 0.05. *P*-values are two tailed. An R-project program was used to depict the degree of differences and trend of association of risk allele frequency from controls to patients. If the vector had the same direction, this indicated the same kind of association, and vice versa.

Haplotype construction, counting, and linkage disequilibrium (LD) block defining were performed on 30 Centre d'Etude du Polymorphisme Humain trios (Utah residents) using Haploview software (http://www.hapmap.org). The multiallelic D' was computed by performing a series of pairwise D' calculations using each haplotype in turn as an allele, with all other haplotypes at the locus serving as the other allele. This was then repeated for each haplotype at each locus and averaged by haplotype frequency. Maximum-likelihood haplotype blocks were calculated using an EM algorithm.

Electronic database information: Accession numbers and URLs for data in this article are as follows: for *G72/G30* and *DAAO*, Online Mendelian Inheritance in Man at http://www.ncbi.nlm.nih.gov/Omim; genotype data for *G72/G30* and *DAAO*, http://www.hapmap.org/; and genome data for *G72/G30* and *DAAO*, http://genome.ucsc.edu/.

RESULTS

The combined search yielded 49 references. After discarding overlapping references and those that clearly did not meet the criteria, 14 studies were retained. These studies were then filtered to ensure conformity with the inclusion criteria. For the *G72/G30* genes, two studies (Hattori *et al.* 2003; Chen *et al.* 2004) were excluded because they were concerned with bipolar affective disorders rather than schizophrenia; for the *DAAO* gene, one study (Chumakov *et al.* 2002) was excluded on the grounds of insufficient data. Finally, 11 studies, consisting of 6 case-control (1292 cases and 1392 controls) (Chumakov *et al.* 2002; Korostishevsky *et al.* 2004; Schumacher *et al.* 2004; Wang *et al.* 2004) and 3 TDT studies (Addington *et al.* 2004; Mulle *et al.* 2005; Zou *et al.* 2005) for the *G72/G30* genes, and 2 case-control studies (846 cases and 836 controls) (Liu *et al.* 2004; Schumacher *et al.* 2004) for the *DAAO* gene, met our criteria for inclusion. The 11 studies included 2138 cases, 2228 controls, and 463 parent–offspring trios. They all fell into the category of medium-to-high quality, with no study falling into the "poor" category.

For M12 of the *G72/G30* genes, all studies showed a pooled *P*-value of 0.02 [overall OR = 1.12 (1.02, 1.24)] with evidence of heterogeneity between studies ($P = 0.003$) (Table 1). There was no evidence of heterogeneity between design types (case control *vs.* TDT) ($P > 0.05$) (supplemental Table 1 at http://www.genetics.org/supplemental/).

For M15, all studies showed a significant *P*-value of 0.0086 [overall OR = 1.15 (1.04, 1.27)] with evidence of heterogeneity ($P = 0.003$) (Table 1). There was no evidence of heterogeneity between design types (supplemental Table 1 at http://www.genetics.org/supplemental/). For M23, all studies showed a pooled *P*-value of 0.01 [overall OR = 0.88 (0.79, 0.97)] also with evidence of heterogeneity ($P = 0.0004$) (Table 1). For M24, all studies showed a significant *P*-value of 0.001 [overall OR = 0.8 (0.69, 0.91)], and there was no evidence of heterogeneity ($P = 0.64$) (Table 1). The forest plots for the four SNPs are shown in Figure 1.

No statistically significant association was found in nine other SNPs (Table 1), and we found no significant association in the genotypic analyses for these SNPs whether the genotypes were combined with risk alleles or nonrisk alleles (Table 2).

As for the *DAAO* gene, there was no evidence of association in the allelic analysis for any of the three polymorphisms MDAAO-4, -5, or -6 ($P > 0.05$) (not shown) although positive evidence of haplotypes for the three SNPs was reported ($P < 0.00001$) (Liu *et al.* 2004). However, when the genotype data of the three SNPs were combined, the pooled *P*-value was 0.0003 [overall OR = 1.42 (1.17, 1.71)] (Table 2). No publication bias was found for allelic and genotypic analyses with regard to any polymorphism [no $P(T) < 0.05$].

TABLE 1

The overall results of all polymorphisms of the *G72/G30* genes

Markers	OR (95% C.I.)	*P*(*Z*)	*P*(*Q*)
M12 (A/G)[a] (8)[b]	1.12 (1.02, 1.24)	*0.0225*	*0.0031*
M13 (A/C) (4)	1.06 (0.9, 1.24)	0.4794	0.3857
M14 (A/G) (8)	0.99 (0.89, 1.1)	0.8909	0.1388
M15 (A/G) (8)	1.15 (1.04, 1.27)	*0.0086*	0.0030
M16 (A/G) (3)	1.12 (0.92, 1.35)	0.2521	0.7874
M18 (A/C) (3)	0.95 (0.79, 1.13)	0.5571	0.5008
M19 (A/G) (4)	0.98 (0.83, 1.16)	0.8451	0.2428
M20 (A/G) (3)	1.03 (0.86, 1.23)	0.7663	0.7641
M21 (C/T) (4)	1.14 (0.97, 1.34)	0.1090	0.7115
M22 (A/G) (7)	1.04 (0.93, 1.17)	0.5096	0.0151
M23 (C/T) (7)	0.88 (0.79, 0.97)	*0.0136*	0.0004
M24 (A/T) (4)	0.8 (0.69, 0.91)	*0.0010*	0.6421
rs1935062 (A/C) (4)	0.91 (0.79, 1.04)	0.1611	0.3605

P(*Z*), *Z*-test used to determine the significance of the overall OR. *P*-values < 0.05 are in italics. *P*(*Q*), the Cochran's χ^2-based *Q*-statistic test was used to assess the heterogeneity. *P*(*T*), *T*-test was used to evaluate the significance of publication bias. No *P*(*T*) < 0.05 (not shown). The NCBI rs ID for the M-SNPs (Chumakov *et al.* 2002) are the following: M12 (rs3916965), M13 (rs3916966), M14 (rs3916967), M15 (rs2391191), M16 (rs3918341), M18 (rs947267), M19 (rs778294), M20 (rs3916970), M21 (rs3916971), M22 (rs778293), M23 (rs3918342), and M24 (rs1421292).

[a] The first allele is the risk allele.

[b] The number of studies included are indicated in parentheses.

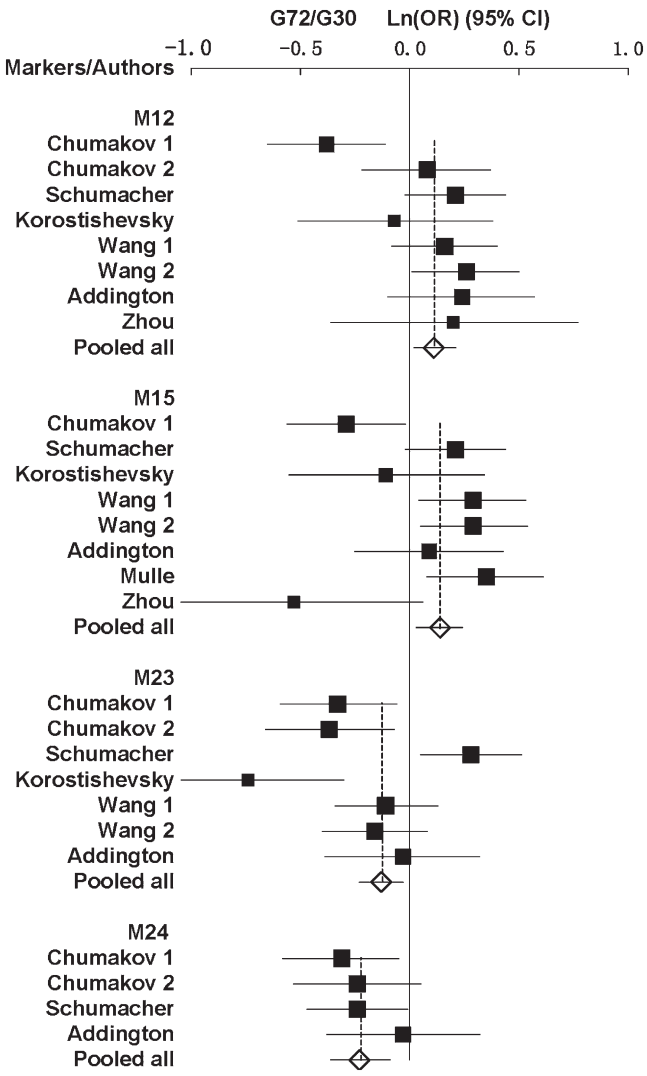

Figure 1.—Forest plots of ln(OR) with 95% C.I. for the associated polymorphisms of the *G72/G30* genes. Solid squares indicate the ln(OR), with the size of the square inversely proportional to its variance, and horizontal lines represent the 95% C.I.'s. The pooled results are indicated by the open diamond.

For M24, the results showed consistency, with the largest *P*-value being 0.015. However, for M12, M15, and M23, evidence of sensitivity was found, with the largest *P*-value > 0.05 (supplemental Table 2 at http://www.genetics.org/supplemental/). The retrospective asymptote lines of the analysis based on the publication year showed that a cumulative synthesis of M12 and M15 tended to be stable after 2004, in line with the meta-analysis. However, more replications are suggested for M23 and M24 due to instability of asymptotic slopes (Figure 2).

The funnel plots and trend of allele frequency by R project are shown for *G72/G30* as supplemental Figures 1 and 2 at http://www.genetics.org/supplemental/. Lack of space precluded the inclusion of the results of individual studies but these are available on request.

DISCUSSION

As for the LD and haplotype structure for the *G72/G30* genes, the 13 polymorphisms, covering four blocks, were in two strong LD structures (Figure 3). Furthermore, the M12 and M15 polymorphisms were located in one block, while M23 and M24 were in another strong block, which was consistent with results of the retrospective analysis. For the *DAAO* gene, the three SNPs were in a strong LD block, as we have described elsewhere (Liu *et al.* 2004).

Although previous individual studies have reported strong associations in the allelic, genotypic, or haplotypic analyses using either family-based or case-control methods, the current meta-analysis confirmed only weak overall association with *G72/G30*, and there was considerable heterogeneity among the associated alleles. First, for most SNPs with heterogeneity, different alleles, genotypes, or haplotypes seemed to be associated in different studies. Heterogeneity is partly due to possible sampling bias, including population stratification due to ethnicities and diagnostic variations or considerable differences in allele frequencies. Second, the *G72/G30* genes may be under a complex expression control. It is likely that different regulatory elements respond to different cell types and developmental stages and that different SNP combinations affect the

TABLE 2

The overall results of genotypic analysis

Markers	Combinations	OR (95% C.I.)	*P*(*Z*)	*P*(*Q*)
M12 (A/G)	(11+12)/22	1.19 (0.89, 1.61)	0.2406	0.1207
	11/(12+22)	1.38 (0.91, 2.08)	0.1260	0.7559
M15 (A/G)	(11+12)/22	0.98 (0.48, 2)	0.9577	0.0436
	11/(12+22)	1.35 (0.89, 2.04)	0.1586	0.7418
M19 (A/G)	(11+12)/22	0.79 (0.59, 1.05)	0.0985	0.5385
	11/(12+22)	0.95 (0.55, 1.65)	0.8614	0.4701
M23 (C/T)	(11+12)/22	0.61 (0.12, 3.08)	0.5527	0.00003
	11/(12+22)	1.16 (0.84, 1.61)	0.3702	0.0524
MDAAO-4-5-6	(11+12)/22	1.48 (1.09, 2.00)	0.012	0.7617
	11/(12+22)	1.42 (1.17, 1.71)	0.0003	0.7621

1 represents the first allele, and 2 represents the second allele. The NCBI rs ID for the MDAAO-SNPs are the following: MDAAO-4 (rs2111902), MDAAO-5 (rs3918346), and MDAAO-6 (rs3741775).

regulation of expression. Third, environmental factors, such as the season of birth, may contribute to several psychiatric and neurological disorders, including schizophrenia.(Chotai *et al.* 2003) Schizophrenia may be characterized by genetic heterogeneity, and the genetic architecture in different populations can differ. Heterogeneity may also be a factor in explaining the results of the sensitivity analysis.

Only one meta-analysis on G72 has previously been performed (Detera-Wadleigh and McMahon 2006), and it combined data from different studies at the level of *P*-values. Compared with that study, this meta-analysis uses more extensive statistical methods, which can systematically incorporate information on specific alleles and genotypes. This study, therefore, is a valuable addition to the literature on G72. However, it has a number of limitations, principal among which is that no real genotypes were available, which prevented comparison of haplotype frequencies. Other limitations include the possible effects of variables such as age, ethnicity, and gender, which can be dealt with only by using a greater range of studies. For subsequent meta-analyses, the sample size needed may depend on the degree of association, linkage disequilibrium, accuracy of phenotypic data, and heterogeneity of allelic frequencies. More accurate phenotype definition, strict selection of samples, and uniformity of diagnosis and classification as well as use of standard demographic statistical methods would reduce the discrepancies and simplify collaboration and comparisons between studies.

Recent meta-analyses covering international populations have pointed to glutamate-related genes such as the *NRG1* (Li *et al.* 2006) and *DTNBP1* (our unpublished results) as promising candidates for schizophrenia. It

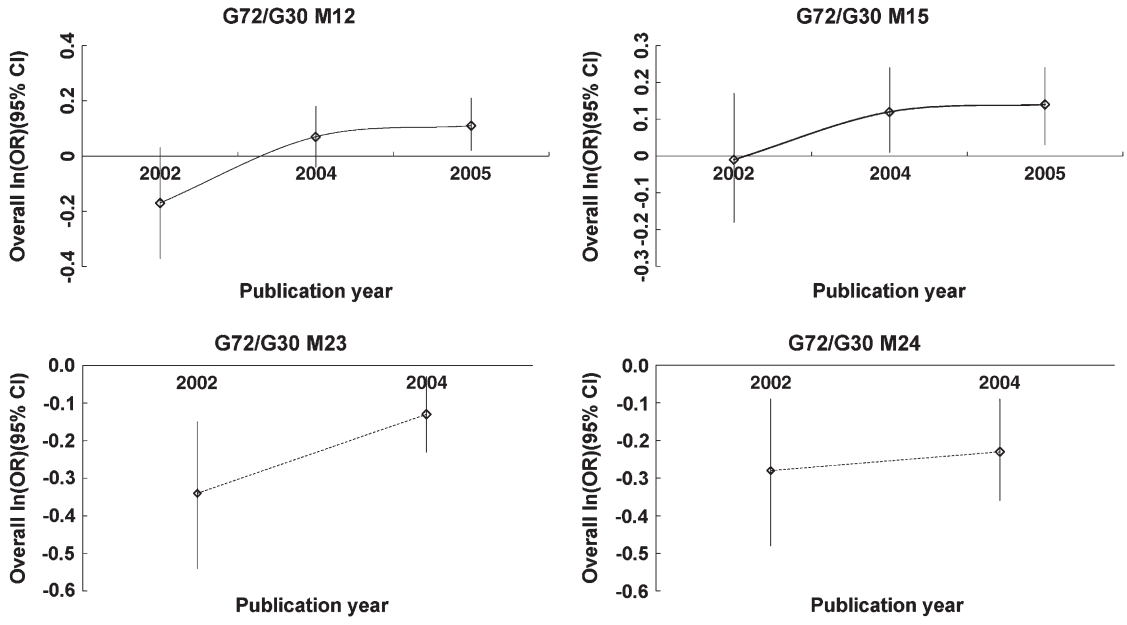

Figure 2.—Retrospective analysis of associated polymorphisms was based on publication years since 2002.

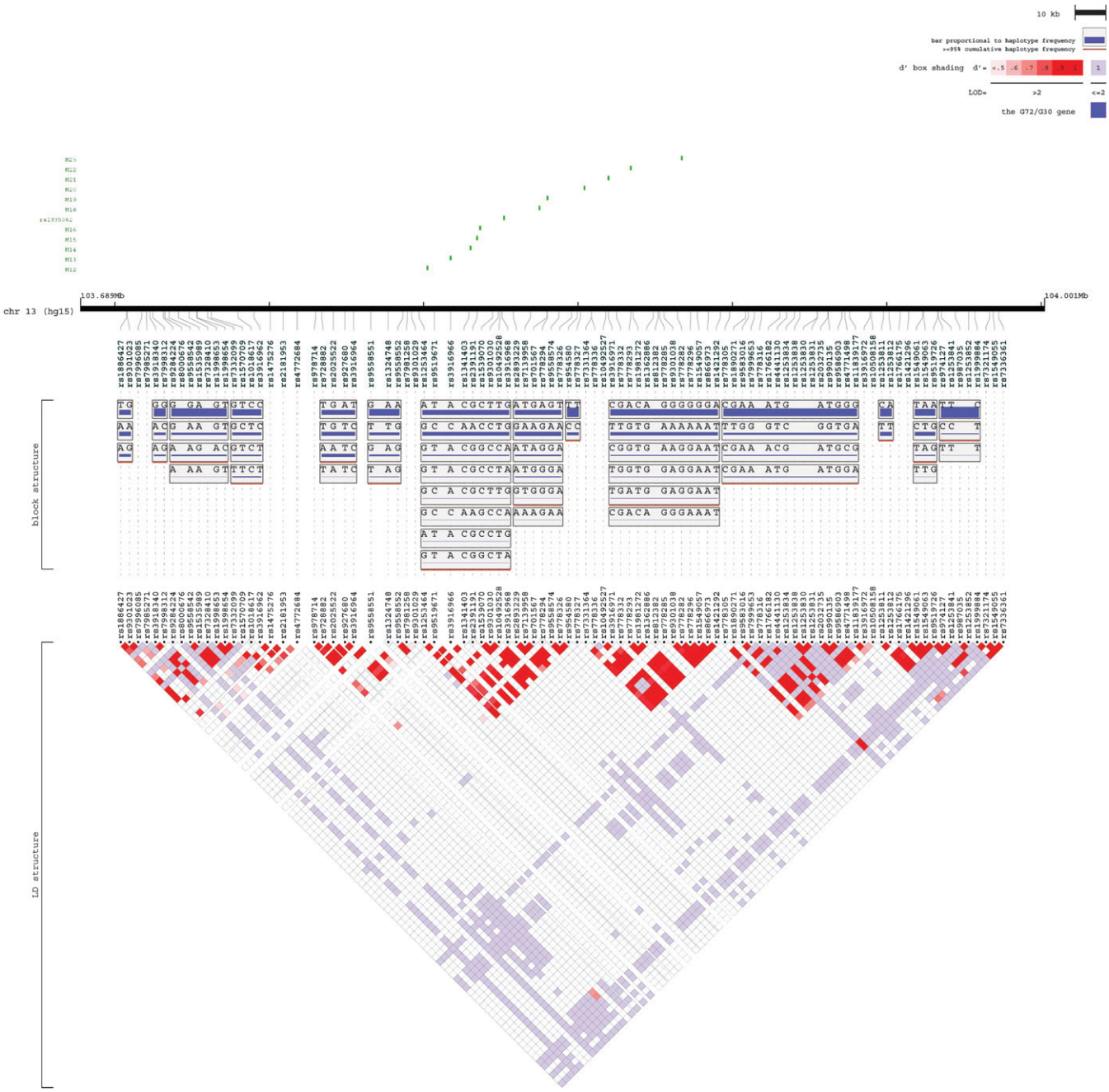

FIGURE 3.—Representation of the LD structure. The LD structure for the *G72/G30* genes, spanning 282 kb, was constructed using genotype data from 108 SNPs. The 12 polymorphisms are shown in green. Vertical tick marks above the name indicate the relative genomic position of each SNP. The LD structure represents the pairwise calculation of D' for each possible combination of SNPs. $D' < 0.5$ is shown in white, $D' = 1.0$ in dark red, with increasing shades of red representing increasing D' among the SNPs. It was produced by Locusview software (T. PETRYSHEN, A. KIRBY and M. AINSCOW, unpublished results).

may be that these genes confer susceptibility to schizophrenia in interaction with one another in either an epistatic or a polygenic manner. Further investigations are required to identify if other at-risk polymorphisms within *G72/G30* and *DAAO* confer a risk of schizophrenia and to clarify the role of the *G72/G30* genes.

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