thought to be unlinked to this region, supporting the hypothesis that a true susceptibility locus exists on chromosome 13q32.

JG Mulle[1,4], JA McDonough[2,4], KV Chowdari[3], V Nimgaonkar[3] and A Chakravarti[1]

[1]*McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA;* [2]*Oak Clinic for MS Research, Kent State University, Kent, OH, USA;* [3]*Western Psychiatric Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA*

Correspondence should be addressed to Dr A Chakravarti, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, 733 North Broadway, Broadway Research Building 579, Baltimore, MD 21205, USA.
E-mail: aravinda@jhmi.edu
[4]These two authors contributed equally to this work.

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No evidence for association to the G72/G30 locus in an independent sample of schizophrenia families

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SIR – Mapping efforts to characterize the genetic basis of schizophrenia have indicated chromosome 13q32 as a potential susceptibility locus. In 2002, Chumakov *et al* reported an association (since replicated) for schizophrenia with single-nucleotide polymorphisms (SNPs) on chromosome 13q32 at the G72/G30 locus.[1–3] Evidence for linkage at this locus in our sample (NPL = 2.95, $P = 0.001$ at D13s174 (Mulle *et al*, 2005[4])) encouraged us to investigate this association. We obtained 159 trios from the NIMH Genetics Initiative (66 trios) and the Western Psychiatric Institute and Clinic at University of Pittsburgh (93 trios), and genotyped 11 associated SNP markers as reported by Chumakov *et al*. Despite evidence for linkage to this region, we fail to find evidence for association at the G72/G30 locus.

Ascertainment of schizophrenia trios has been previously described, for both the NIMH sample[5] and the Pittsburgh sample.[6] We selected pedigrees for our study if the pedigree had a case and DNAs from both parents were available. We obtained 66 trios from the NIMH resource, and 93 trios from the Pittsburgh sample. A total of 11 SNPs were selected for genotyping based on evidence for statistically significant association with schizophrenia as published in Chumakov *et al*. SNPs were genotyped using Taqman genotyping technology (ABI), in a 384-well format with 10 ng of DNA per reaction. For data quality purposes, at least 15% of the sample was genotyped in duplicate for each SNP assayed. Out of >750 replicates, zero discrepancies existed (average rate of missing data = 3%). The TDT statistic, which accounts for transmission of alleles from heterozygous parents, was computed according to Spielman and Ewens.[7] Parental genotypes were not imputed.

The results of TDT analysis for individual SNPs are shown in Table 1, which shows the results of Chumakov *et al*'s case–control association study side by side with the results for the TDT from our sample (where the putative associated allele was reported, results are shown for that allele). No SNP shows evidence for association with schizophrenia. We have evidence for linkage in a subset ($n = 33$) of these families, and TDT analysis in the linkage sample, a separate set of 100 trios, and the entire sample combined, revealed almost no evidence for association (see Table 2 for stratified analysis). Results for SNP M4 approach statistical significance ($P = 0.04$ in whole sample, $P = 0.01$ in linkage sample, uncorrected for multiple tests).

An *a priori* analysis of power revealed that in our sample of 159 trios, at minor allele frequencies indicated by Chumakov (0.3–0.5), we have greater than 90% power to detect a distortion in transmission from the expected 50 : 50 ratio, for genotype relative risks as low as 1.7. Previous reports imply that the effect at the G72 locus may be slightly smaller (odds ratios estimates are 1.3–1.45[1,8]). This study may therefore be underpowered to detect the small effects reported by the previous two studies. However, the evidence for association in Tables 1 and 2 fail to reveal even a small trend toward overtransmission, particularly at SNPs M12-24, where both prior studies achieved the most significant evidence for association. In our sample, the allele previously reported as associated is frequently untransmitted exactly as often as it is transmitted. Furthermore, our linkage findings imply that a subset of our families are 'loaded' for a schizophrenia susceptibility locus on chromosome 13q32; therefore, our prior probability of finding evidence for association from linkage disequilibrium is increased.

Several explanations exist to explain the discrepancy between our results, and those of prior studies. Chumakov *et al* tested SNPs in a French Canadian

Table 1 Comparison of case–control and TDT results

		Chumakov et al				*This study*		
SNP	*Allele*	*Cases*	*Controls*	*P-value*		*T*	*U*	*P-value*
M-1	nr	nr	nr	$P<0.05$				
M-2	nr	nr	nr	$P<0.05$	(A)	48	57	0.44
M-3	nr	nr	nr	$P<0.05$	(A)	49	53	0.77
M-4	nr	nr	nr	$P<0.05$	(C)	59	85	0.04
M-5	nr	nr	nr	$P<0.05$				
M-11	T	0.44	0.37	0.062		60	76	0.19
M-12	G	0.64	0.55	0.007		68	68	1.0
M-13	A	0.63	0.57	0.071		70	70	1.0
M-14	A	0.64	0.58	0.038		62	66	0.79
M-15	G	0.65	0.58	0.032		63	69	0.66
M-16	A	0.61	0.57	nr		69	68	1.0
M-21	C	0.63	0.58	0.069		65	63	0.92
M-22	A	0.69	0.60	0.003		59	74	0.22
M-23	T	0.57	0.49	0.019		62	60	0.93
M-24	T	0.55	0.47	0.019		65	63	0.93

*nr; not reported in original study.
T: Transmitted; U: Untransmitted.
M1 and M5: SNPs resided in repeats and an assay could not be designed.

Table 2 TDT Results stratified by sample

		Linkage sample (59 trios)			*Supplemental sample (100 trios)*		
SNP	*Allele*	*T*	*U*	*P-value*	*T*	*U*	*P-value*
M-2	A	10	17	0.24	37	39	0.91
M-3	A	17	14	0.72	31	38	0.47
M-4	C	17	36	0.01	40	47	0.52
M-11	T	17	24	0.34	41	52	0.29
M-12	G	26	25	1.0	41	43	0.91
M-13	A	29	27	0.89	40	43	0.83
M-14	A	22	24	0.88	39	42	0.82
M-15	G	22	24	0.88	40	45	0.66
M-16	A	27	24	0.78	41	44	0.83
M-21	C	14	19	0.49	51	44	0.54
M-22	A	20	23	0.76	39	50	0.29
M-23	T	16	19	0.74	46	41	0.67
M-24	T	20	15	0.50	45	48	0.84

T: Transmitted, U: Untransmitted.

sample, and Schumacher *et al* used a German population. It is possible that these populations have causative alleles for schizophrenia that are distinct from the alleles that cause schizophrenia in the population in our study. Our sample population is 84% Caucasian, 9% African American, and the remainder of the study population is comprised of a mix of different races. In order to minimize the effects of this heterogeneity, we used the TDT; by design, the TDT is robust to issues of population substructure.[7] However, it is possible that residual effects of heterogeneity have masked an association in the current analysis. It is worthwhile to note that for SNPs M12, M15, M19, and M23, the SNP reported as more frequent in cases in the Chumakov study is actually reported as *less frequent* in cases by Schumacher *et al*.[1,8] Barring an error in labeling of alleles or samples, this implies that these populations are truly different, and the results from each case–control analysis may not be generalizable to other populations. Chumakov *et al* tested a total of 191 SNPs and report 11 statistically significant associa-

tions. In total, 10 *P*-values less than 0.05 are expected under the null hypothesis; it is therefore possible that their results are false positives. It is also possible that the differences in allele frequencies seen by Chumakov *et al* and Schumacher *et al* are confounded by subtle differences in population structure between cases and controls, unrelated to the phenotype of schizophrenia.

Evidence is strong that a schizophrenia susceptibility locus exists on chromosome 13q32.[9–11] The exact nature of this susceptibility locus remains to be identified. Detailed association studies with a very dense map of SNPs in well-phenotyped populations are an appropriate way to investigate the genetic basis of schizophrenia.

JG Mulle[1], KV Chowdari[2], V Nimgaonkar[2] and A Chakravarti[1]

[1]*McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA;* [2]*Western Psychiatric Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA*

Correspondence should be addressed to A Chakravarti, PhD, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University of Medicine, 733 North Broadway, Broadway Research Building 579, Baltimore, MD 21205, USA.

E-mail: aravinda@jhmi.edu

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