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Alcoholism and Related Traits: A Summary of Group 13 Contributions

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Ten groups set out to study the genetics of alcoholism, using various measures of alcohol dependence such as Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, and related endophenotypes such as the electrophysiological evaluation of event-related potentials. The groups used both genome-wide microsatellite and single-nucleotide polymorphism (SNP) genotyping data in families selected from the Collaborative Study on the Genetics of Alcoholism. The majority of investigators studied alcohol-related phenotypes and chose linkage rather than association analysis. The analysis of SNP data presented several challenges, including marker linkage disequilibrium issues and computational limitations. Many groups pursued novel techniques, both in dealing with the SNP data and the definition of phenotypes. While there was a limited amount of concordance among linkage findings, it was very instructive to see so many new strategies at work. Generally the SNP genotype data seemed to yield more information for multipoint linkage analysis than the microsatellite data, a finding that will benefit the genetic analysis of complex disease in the future. A novel linkage peak was detected using the SNP markers. *Genet. Epidemiol.* 29(Suppl. 1):S96–S102, 2005. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

The Collaborative Study on the Genetics of Alcoholism (COGA) provided a wealth of data for Genetic Analysis Workshop 14 (GAW14). COGA was described by Edenberg et al. [2005], and was also the source of data for GAW11 [Begleiter et al., 1999]. In addition to the microsatellite genetic markers provided by COGA, the Center for Inherited Disease Research (CIDR), in conjunction with Affymetrix and Illumina, provided single-nucleotide polymorphism (SNP) genotyping of the COGA sample [Edenberg et al., 2005].

We summarize 10 GAW14 contributions that analyzed these data. As noted below, there were a variety of phenotypes, both qualitative ones such as the diagnosis of alcoholism, and quantitative ones such as electrophysiology measures and the maximum number of drinks consumed in a 24-hr period. Groups used various combinations of the approximately 400 microsatellites, the 10,000 SNPs from the Affymetrix chip, and the 6,000 SNPs from the Illumina screening set. Many scientific groups are starting to use SNP-based technologies for linkage studies, and this was the first time that many of the genetic analysts at GAW had the opportunity to analyze such genome-screen data. Indeed, a common theme at the GAW meeting was the difficulty presented by having an order of magnitude more SNP markers than microsatellite markers. This difficulty reflects limitations in the number of markers that can be analyzed simultaneously by some linkage software, the difficulty in constructing a genetic map, and the computational resources and time needed for these analyses. Moreover, most available linkage software requires the assumption that the markers are in linkage equilibrium, an assumption that may not hold with dense SNP data. Accordingly, although some of the analyses summarized seem straightforward, they often were not. An overview of the phenotypes, marker sets, methods, and samples used is given in Table I.

TABLE I. Samples, markers and phenotypes used in Group 13 contributions

First author	Sample	Marker data	Chromosome	Phenotypes	Program(s)
Apprey	All	Afftmetrix	Genome screen	ALDX1	GEMs
Arya	All	Microsatellite	Genome screen	MAXDRINKS	SOLAR, LOKI
Barlett	All	Microsatellite	4	ecb21, ALDX1	SOLAR
Dunn	Caucasian	All	7	ALDX1, ttth1	GENEHUNTER, SOLAR
Martin	All	Microsatellite	7	EEG, ALDX1	SOLAR
Saccone	All	All	Genome screen	MAXDRINKS	MERLIN, QTDPHASE
Wiener	All	Microsatellite, Affymetrix	Genome screen	ALDX1, ALDX2, EEG, latent variables	SAGE/SIBPAL
Yuan	All	Affymetrix	4	EEG, ntth1–4	GEMs
Zhao	All	Microsatellite	4, 7	ALDX1	R package, KINSHIP
Zhu	Caucasian	Microsatellite, Affymetrix	Genome screen	ALDX1	ALLEGRO, FBAT

RESULTS

We briefly describe each individual contribution, grouped by the phenotype of primary interest.

LINKAGE ANALYSIS OF ALCOHOL DEPENDENCE

Apprey et al. [2005] used the COGA definition of alcoholism (ALDX1) and first tested for association with age-of-onset and each Affymetrix SNP at the 0.01 level. They found significant association on chromosomes 1, 2, 3, 5, and 10. They next performed linkage analysis on the six SNPs found to be associated from the first step. They used the log-normal age-of-onset model in their software genetic epidemiology models (GEMs) under three models (age-of-onset; age-of-onset and sex effects; and age-of-onset, sex, and smoking), and found signals on chromosomes 2 and 3, as noted in Table II.

Dunn et al. [2005] used the COGA definition of alcoholism in the 112 Caucasian pedigrees. They restricted their analysis to chromosome 7, and found LOD scores of 3.09, 3.69, and 4.08 for the microsatellite, Affymetrix, and Illumina markers, respectively. They also used a sparser version of the Illumina marker set to remove any effects of marker linkage disequilibrium (LD) in their GENEHUNTER analysis, and obtained a LOD of 4.11.

Zhao [2005] used a mixed-effects Cox model and limited his analysis to the microsatellite markers on chromosomes 4 and 7. This method incorporates kinship and identity-by-descent (IBD) matrices into the standard Cox model, and is available as part of S-PLUS, as referenced in his paper. He found D4S1645 to be the most promising signal, and D7S509 to be the largest contributor to the likelihood on chromosome 7. His method did not yield a LOD-score equivalent.

Zhu et al. [2005] analyzed the COGA definition of alcohol dependence, using the microsatellite markers and the linkage program ALLEGRO. Using single-point analysis, they found a single marker on chromosomes 1 and 2, six markers on chromosome 7, and two markers each on chromosomes 12 and 21, with LOD scores above 1. We display the highest multipoint LOD score above 1 for each chromosome in Table II. As a second step, they examined 188 SNPs between markers D7S1870–D7S1817, and found the highest multipoint LOD score of 2.12 at the marker tsc0039708 (113.922 cM).

Bartlett and Vieland [2005] applied the posterior probability of linkage (PPL) method on all chromosome 4 microsatellites. They found considerable support for linkage for the electroencephalogram (EEG) phenotype (described below), but weaker evidence for alcohol dependence alone using ALDX1.

All of the linkage analyses of alcohol dependence in Table II used the same phenotype, but found different regions of interest. This mostly reflects different analytic strategies: Apprey et al. [2005] required significant association before testing for linkage, Dunn et al. [2005] only analyzed chromosome 7, and Zhao [2005] only considered chromosomes 4 and 7. Moreover, as noted by Dunn et al. [2005], the microsatellite markers yielded a LOD score of 3.09 (compared to 4.08) on

TABLE II. Linkage results

First author	Chromosome	Marker	Location	LOD	Single vs. multipoint
Alcohol dependence					
Apprey	2	tsc0041591	200.911 cM	3.25	SP
	3	tsc0894042	120.770 cM	1.94	SP
Dunn	7		101 MB	4.08	MP
Zhao	4	D4S1645	62.4 cM		
	7	D7S509	164 cM		
Zhu	2	D2S1329	4.9 cM	1.26	MP
	7	D7S1870	94.2 cM	1.77	MP
	12	D12S392	177.3 cM	1.41	MP
	21	D21S1446	62.7 cM	1.71	MP
	7	tsc0039708	113.922 cM	2.12	MP
Maximum number of drinks in 24-hr period					
Arya	4	D4S1651	126.0 cM	1.50	MP
	15	D15S205	100.0 cM	2.04	MP
Saccone	2	rs1525351	212.9 cM	2.68	SP
	7	rs322812	131.3 cM	2.77	SP
Electrophysiology					
Barlett	4	GABRBI	51.0 cM	2.21	MP
Dunn	7		130 Mb	3.22	MP
Martin	7		158 cM	3.80	MP
Wiener	2		245 cM	1.80	MP
Yuan	4	tsc0045058	53.3 cM	3.40	MP
	4	tsc0055068	89.3 cM	3.00	MP

chromosome 7. This may reflect lower information content or greater genotyping error in the microsatellite markers.

ASSOCIATION ANALYSIS OF ALCOHOL DEPENDENCE

In addition to the above linkage analyses, several groups used the SNP data to test for association. As noted above under Linkage Analysis of Alcohol Dependence, Apprey et al. [2005] found association between age-of-onset of COGA alcoholism and six SNPs at the 0.01 significance level. These are given in Table III.

Zhu et al. [2005] used family-based association testing (FBAT) with the Affymetrix SNPs and found 670, 167, and 19 SNPs significant at levels of 0.05, 0.01, and 0.001, respectively. None of the 19 significant SNPs at the 0.001 level agreed with the SNPs identified by Apprey et al. [2005]. In Table III, we list the two SNPs significant at the 0.0001 level.

Both of these studies used the same phenotype (ALDX1), but found different association signals. None of the six SNPs identified by Apprey et al. [2005] were in the top 24 in the full table of Zhu et al. [2005]. This may be due to the different methods used, or to the fact that Zhu et al. [2005] analyzed the subsample of Caucasians.

TABLE III. Association results

First author	Chromosome	Marker	Location	*P*-value
Alcohol dependence				
Apprey	1	tsc0056724	139.838 cM	<0.01
	2	tsc0041591	200.911 cM	<0.01
	2	tsc0512083	200.914 cM	<0.01
	3	tsc0894042	120.770 cM	<0.01
	5	tsc1640504	96.473 cM	<0.01
	10	tsc9597716	120.955 cM	<0.01
Zhu	3	tsc0515272	164.236 cM	<0.0001
	20	tsc0060446	35.4473 cM	<0.0001
Maximum number of drinks in 24-hr period				
Saccone	7	rs766420	130.600 cM	<0.017

LINKAGE ANALYSIS OF MAXIMUM NUMBER OF DRINKS IN A 24-HR PERIOD

Linkage to the maximum number of drinks phenotype (MAXDRINKS) was first discovered by Saccone et al. [2000]. The Haseman-Elston regression method showed linkage to chromosome 4 at marker D4S2047, located at roughly 105 cM. Build 34.3 of the National Center for Biotechnology Information (NCBI) physical map puts this marker at approximately 100 Mb.

Two papers in this group studied MAXDRINKS. Arya et al. [2005] analyzed several quantitative phenotypes for genotype $\times$ alcoholism (G $\times$ A)

interaction. Significant interaction was detected for the natural logarithm of MAXDRINKS (LNMAXDR), and this was followed up by a variance-component linkage analysis using SOLAR. Both a customized model incorporating G × A interaction and one without G × A interaction was used to determine the trait. The former method uses the alcoholism diagnosis variables ALDX1 and ALDX2, in contrast to Saccone et al. [2005]. These models were used to perform variance-components linkage analysis using microsatellite marker data. For LNMAXDR, the highest LODs were reported on chromosomes 13 (2.2 at 64 cM), 4 (1.1 at 126 cM), and 1 (1.1 at 282 cM) without incorporation of G × A interaction. Interaction analysis yielded four suggestive linkage regions on chromosomes 1 (max LOD = 1.3, corrected LOD (LOD_c) = 0.9 at 238 cM), 4 (max LOD = 1.5, LOD_c = 1.1 at 126 cM), 13 (max LOD = 1.2, LOD_c = 0.8 at 59 cM), and a new region on chromosome 15 (max LOD = 2.04, LOD_c = 1.6 at 100 cM). On chromosome 4, a max LOD of 1.5 at the same location as the initial analysis was obtained after incorporating G × A interaction effects. However, after correcting for extra parameters, the LOD score was reduced to a corrected LOD of 1.1, which is similar to the LOD observed in the noninteraction analysis. Despite the fact that only small differences in LOD scores were observed, some linkage regions showed large differences in the magnitudes of estimated quantitative trait locus (QTL) heritabilities between the alcoholic and nonalcoholic groups. These potential hints of differences in genetic effect may influence future analyses of variants under these linkage peaks. Furthermore, drinking behavior appears to be influenced by environment-specific genes in both alcoholics and nonalcoholics. The implicated regions on chromosomes 1, 4, and 15 are consistent with previously reported linkage findings. These results indicate that further analyses may benefit from considering the possibility of differing genetic effects in alcoholics and nonalcoholics, e.g., by stratifying analysis on alcoholism diagnoses.

Saccone et al. [2005] used a linear regression to correct the natural logarithm of MAXDRINKS for sex. Two methods were used for the purpose of comparing microsatellite and SNP data. Nonparametric multipoint linkage analysis was performed, using MERLIN on the microsatellite data across the genome. For the Illumina SNP data, two-point linkage analysis was done using MERLIN across the genome; for those markers showing linkage, SNPs from the combined Affymetrix and Illumina set were selected in regions centered at the marker and were tested for association using Quantitative Pedigree Disequilibrium Test (QPDT) as implemented in the program QPDTPHASE, part of the UNPHASED package. No significant findings were found with multipoint analysis using the microsatellite data. The most significant finding was on chromosome 7, where a two-point LOD score of 2.8 was detected at 127.3 Mb. In stage 2, QPDT produced a *P*-value of 0.017 at 125.7 Mb. In addition, a LOD of 2.7 was found on chromosome 2 at 216.5 Mb, and the Pedigree Disequilibrium Test (PDT) found a *P*-value of 0.031 at 212.9 Mb.

ELECTROPHYSIOLOGY PHENOTYPES

The Stage II COGA families underwent an electrophysiologic evaluation of event-related potentials (ERP), event-related oscillations (EROs), and resting EEG [Edenberg et al., 2005]. These were shown to be associated with alcohol dependence by Porjesz et al. [2002].

Two primary tests were conducted, the ''Visual Oddball Experiment'' and the ''Eyes-Closed Resting EEG Experiment.'' In the former, the subject is presented with various geometric figures on a computer screen and asked to identify them in a certain time period. Meanwhile, data are collected by four electrodes placed on his or her head. In the latter experiment, the subject is instructed to keep his or her eyes closed and remain relaxed, but not to fall asleep. During this time, EEG data are collected and then processed, using wavelet technology.

Fourteen variables pertaining to these experiments were provided. The measurements ttth1–ttth4 come from the Visual Oddball Experiment for the four electrode placements: the far frontal left side, frontal midline, central midline, and parietal midline. The extracted measures correspond to the ''late'' time window, which is set at 300–700 msec following stimulus presentation, and theta band power (3–7 Hz). Similarly, the measurements ttdt1–ttdt4 are from the Visual Oddball Experiment for the ''late'' time window and delta band power (1–2.5 Hz), and ntth1–ntth4 are for the ''early'' time window (100–300 msec), using the theta band. The variable ecb21 is from the Eyes-Closed Resting EEG Experiment, and corresponds to the first component of a trilinear singular value decomposition (SVD) of the beta 2 band (16.5–20 Hz) bipolar electrode. The age of

the subject when electrophysiological data were collected (ERP age) was also recorded.

Six papers from this group analyzed these electrophysiological data. Arya et al. [2005] screened all ERP data, along with other traits, for significant G × A interaction. However, only MAXDRINKS was found to be significant (this analysis is described in Linkage Analysis of Maximum Number of Drinks in a 24-Hr Period, above).

Martin et al. [2005] also studied G × A interaction. Using a variance-components linkage model, they analyzed tth1 in the microsatellite marker data on chromosome 7, using SOLAR. An initial analysis revealed a LOD score of 3.8 at 158 cM. Although the authors did not identify a covariate effect for alcoholism, in order to examine the effects of alcoholism on ttth1, subgroups were defined according to the ALDX1 classification, and linkage analysis was performed on the subgroups. In each subgroup, the result was a shift in the linkage peak by 50 cM, with substantial evidence for linkage in alcoholics. Furthermore, significant evidence for G × A interaction was detected at both loci, with the strongest linkage signal coming from nonalcoholic individuals. This apparent contraction could be due to a lack of power in the unaffected subgroup.

Bartlett and Vieland [2005] defined a quantitative trait posterior probability of linkage (QT-PPL) to analyze ecb21 on chromosome 4, using the microsatellite data. At GABRB1 (51 cM), a multipoint variance-components analysis produced a LOD score of 2.2, while the QT-PPL method yielded a posterior probability of 96%. To study the effects of alcoholism, ALDX1 diagnosis and ecb21 were incorporated in a joint analysis that assumed ALDX1 to be mediated by ecb21, with ALDX1 being beyond an unknown threshold. The unknown threshold was treated as a nuisance parameter and integrated out of the final quantitative trait/threshold PPL (QTT-PPL). This joint analysis yielded a posterior probability of only 4%, which suggests that linkage to GABRB1 cannot be explained in terms of alcoholism phenotypes.

Wiener et al. [2005] used a combination of discriminant analysis and principal-components analysis to derive phenotypes from the EEG variables and latent variables (e.g., persistent desire to stop drinking). Using the microsatellite data, a genome screen was performed on the resulting phenotypes, using the Haseman-Elston regression as implemented in the program SIBPAL, part of the SAGE package. Significant linkage was detected on chromosome 2 in the region from 200–250 cM. A follow-up analysis using the Affymetrix SNP data in this region concurred with the microsatellite findings, and a combination of microsatellite and Affymetrix SNP data narrowed the region of significance.

Yuan et al. [2005] applied a principal-components analysis to ntth1–ntth4, and used their GEMs package to analyze the first principal component, as well as ntth1 itself, which had a factor loading of 0.93 on the second principal component. Regressive models were used to test for association and linkage. To reduce the computational workload, a two-stage analysis was performed: an association analysis of the Affymetrix SNPs on chromosome 4, followed by linkage analysis on the SNPs found to be significant in the first stage. While significant linkage was not detected for the first principal component, ntth1 produced a LOD score of 3.3 at 53 cM, and a LOD score of 3.0 at 89 cM.

Dunn et al. [2005] studied tth1 in the Caucasian sample, using all available SNP and microsatellite data for chromosome 7. Multipoint IBD matrices were computed using LOKI, and linkage analysis was carried out using SOLAR. A subset of the Illumina markers (named the ''sparse map'') was defined by removing markers in high LD. The largest LOD score of 3.2 occurred at roughly 130 Mb for the full Illumina map, and when Dunn et al. [2005] shifted to the sparse map, the LOD dropped to 2.7. The peak for microsatellite data was in the same location, with a LOD of 2.7. The results suggest that SNP genotype data contain a comparable, if not superior, amount of information for linkage as microsatellite markers.

Aside from Wiener et al. [2005], none of the investigators attempted a genome-wide screen; only chromosomes 2, 4, and 7 were targeted. Furthermore, only Yuan et al. [2005] used association analysis, and this was mainly done as a measure to screen SNPs for use in a linkage analysis. This reverses the conventional approach of starting with linkage regions and then using association analysis. The authors noted that linkage analysis using so many SNPs required considerable computing power and this limited their analyses. The only concordance among findings seems to be in the results of Bartlett and Vieland [2005] and Yuan et al. [2005] near 51 cM on chromosome 4. This is interesting, because they did two different experiments: Bartlett and Vieland [2005] looked at the Eyes-Closed Resting EEG Experiment (ecb21), and

Yuan et al. [2005] the Visual Oddball Experiment for the "late" time window, with delta band power on the far frontal left side (ttth1). Of the two, only Bartlett and Vieland [2005] attempted to connect their results directly to alcoholism phenotypes, but their efforts were not successful. The lack of overlap for linkage regions in Dunn et al. [2005] and Martin et al. [2005] is interesting, given that the analyses applied the same method (variance components) to the same phenotype (tth1). This could be due to the fact that Dunn et al. [2005] used only Caucasians in their analysis.

DISCUSSION

It should be noted that the COGA families were ascertained starting with a proband with alcohol dependence identified through a treatment facility. If two additional first-degree relatives were also alcoholic, then a blood sample was obtained, as well as data from an extensive electrophysiology battery. The families were genotyped in two waves, and descriptions were published separately [Reich et al., 1998; Foroud et al., 2000]. GAW14 was given the subset of families from the combined waves that were densely affected, and with the most members genotyped. Thus, a direct comparison with the published results can only be approximate. Moreover, there would be no easy way to incorporate an ascertainment correction into analyses. Finally, the sample was ethnically heterogeneous, although mostly Caucasian. The analyses of Reich et al. [1998] analyzed all the families in the first wave, but used nuclear families in which both parents were genotyped to avoid problems associated with different marker allele frequencies in the various ethnic groups.

Although several groups used the SNP data for association analysis, one could argue there would be inadequate power due to the limited number of SNPs available. The average spacing between SNPs for the Affymetrix and Illumina sets would be approximately 330 kb and 550 kb, respectively. Accordingly, the results in Table III may reflect false positives due to multiple testing.

Overall, it would seem that either SNP set performed better than the microsatellites for multipoint linkage analysis. This may reflect the greater information content and a lower genotyping error rate for the SNP sets. Examination of the chromosome 7 LOD curves by Dunn et al. [2005] indicates that the localization using the SNP set was much better. They also used a trimmed set of SNPs to ensure that the increase in LOD scores was not an artifact of the LD in the full set. This was not the case. Having LD between markers may be more problematic if parents are not genotyped. Some contributors avoided the potential problem of intermarker LD by performing single-point analysis with the SNPs. Dunn et al. [2005] also calculated the single-point LOD scores from the Illumina set (1.65) and the microsatellite set (2.32). This may suggest that single-point analysis is not a good solution, because the maximum heterozygosity is 50% for a SNP.

Concordance among linkage results was limited, although several signals occurred on chromosomes 2, 4, and 7. Essentially none of the signals on chromosome 2 were at the same locations. On chromosome 4, Bartlett and Vieland [2005] and Yuan et al. [2005], using significantly different novel approaches, found linkage to an ERP phenotype at 51.0 cM and 53.3 cM, respectively. Another interesting finding was that the maximum LOD score in the genome screen for maximum number of drinks by Saccone et al. [2005] occurred near the same location on chromosome 7 (131.3 cM) as the linkage signal for ttth1 found by Dunn et al. [2005] (130 Mb, roughly 137 cM), who restricted their analysis to chromosome 7. This result was accompanied by a signal from the association analysis by Saccone et al. [2005] at rs766420 (130.6 cM).

The extent of concordance is affected by considerable heterogeneity in the phenotypes and methods utilized in analyses. We note that only two analyses were limited to just Caucasians. Given the potential differences in marker allele frequencies, both for microsatellites and SNPs, and the potential impact on linkage and association analyses, it is of interest that standard approaches, such as computing within ethnic group frequencies, were not applied. The majority of papers used SNP data, but a minority of papers used markers from multiple sources. Several analyses were limited to a few chromosomes previously implicated in published reports. This no doubt reflects the computational burden required for a whole-genome analysis using these data. Even when it appears that the same phenotype was used, many choices are made in any analysis that will affect the results and their interpretation, e.g., the definition of unaffected individuals, the procedures for trimming large pedigrees, or the elimination of SNPs not in Hardy-Weinberg equilibrium. In addition to choices made during data preparation, different

methods require different assumptions to hold, and the results using a multistep plan depend on the sequence and statistical cutoffs used at each stage. Given all of these choices, it is perhaps not surprising that there is considerable variability in the conclusions reached from these analyses.

An interesting observation from Figure 2 in Dunn et al. [2005] is that the SNP markers covered an additional 10-Mb region on chromosome 7 p–ter of the last microsatellite marker. There was in fact a LOD score of 3.5 for alcohol dependence in this region not covered in the original genome screen. This is an interesting finding that will be followed up by the COGA investigators. In general, an average spacing of 10 cM in a genome screen may include rather large gaps that may miss a linkage signal. Another advantage of the comparatively dense SNP markers is that there are no gaps.

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