Gene-based and pathway-based genome-wide association study of alcohol dependence

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characterized but the functions of whole genes and particular gene pathways are more clearly characterized; many functional studies (e.g., gene expression studies) have been conducted at the gene or pathway level making it possible to assess the association of biological functions with specific genes and pathways. Second, locus heterogeneity (i.e., alleles at different loci cause diseases in different populations) make it difficult to replicate association findings for a single marker, but replication at the gene or pathway level might still be possible when locus heterogeneity exists because a gene or pathway can harbor multiple alleles of the heterogeneous risk markers. Finally, because the numbers of genes and pathways across the genome are much less than the number of single markers, gene-based and pathway-based analyses can substantially reduce the number of comparisons considered and, thus, lead to better statistical power.

In the present study, we aimed to identify the risk genes for alcohol dependence and the pathways that are enriched in alcohol dependence-related genes. In view of the fact that the effects of an entire gene that integrates many SNPs would be different from those of a single SNP, and the effects of an entire pathway that integrates many genes would be different from those of a single gene, it is anticipated that the results from gene-based analyses might not be completely consistent with those from pathway-based analyses that use the same dataset, and, similarly, the results from gene- and pathway-based analyses might not be completely consistent with those from SNP-based analyses in previous GWASs on the same datasets. In other words, gene- and pathway-based analysis may lead to novel findings.

2. Materials and Methods
2.1 Subjects
The identification of the GWAS data used in this analysis is shown in Figure 1. Data from 1409 European-American (EA) cases with alcohol dependence (based on DSM-IV criteria),1518 EA healthy controls,681 African-American (AA) cases, and 508 AA healthy controls were included in this analysis. Detailed demographic data on these subjects were presented in previous GWASs.[11,12] These data came from the merged SAGE (Study of Addiction: Genetics and Environment) and COGA (Collaborative Study On The Genetics of Alcoholism) datasets, which are available on the database of Genotypes and Phenotypes (dbGaP) [https://www.ncbi.nlm.nih.gov/gap]. The SAGE dataset (dbGaP access number: phs000092.v1.p1) included COGA, COGEND (Collaborative Genetic Study of Nicotine Dependence), and FSCD (Family Study of Cocaine Dependence) subsets. This COGA subset included in the SAGE dataset was a subset of the main dbGaP COGA dataset (access number: phs000125.v1.p1), so when we merged the SAGE and COGA datasets, one copy of 1477 overlapping subjects were excluded.[11] The projects that collected these data were all approved by the respective institutional review boards, all subjects participating in the projects provided written informed consent, and the current analysis was approved by the institutional review board of Yale University.

2.2 Genotyping
All subjects were genotyped on the Illumina Human 1M beadchip. Phenotype and genotype data were rigorously cleaned before association analysis. Subjects with poor genotypic data, allele discordance, problematic sample identification (relatedness, misidentification, misspecification), duplicated identifiers, gender or chromosomal anomalies, ethnicity issues (including missing information, non-EA or AA, mismatch between self- and genetically-inferred ethnicity), or with a missing genotype call rate ≥2% across all SNPs were excluded. Furthermore, SNPs with allele discordance, chromosomal anomalies or batch effect, SNPs with an overall missing genotype call rate ≥2%, monomorphic SNPs, SNPs with minor allele frequencies <0.01 in either EAs or AAs, and SNPs that deviated from Hardy-Weinberg equilibrium ($p<10^{-4}$) within EA or AA controls were also excluded. This selection process yielded 805,814 SNPs in EAs and 895,714 SNPs in AAs.[11,12]

2.3 Statistical methods
The genotyping data on autosomes were extracted from an Oracle database and stored efficiently in flat files for gene- and pathway-based analysis.

2.3.1 Gene-based GWAS analysis
The genotype was configured into a genotype score of 1, 2, or 3: 1 represented a minor allele homozygote, 2
represented a heterozygote, and 3 represented a major allele homozygote. SNPs were mapped to known genes/exons/introns boundaries obtained from the National Center for Biotechnology Information (NCBI). Principal component analysis was applied to the SNPs within the defined gene boundary and then the components which explained at least 85% of the variation were used as explanatory variables in the regression to explain disease status. The disease status was defined as 2 for alcohol dependence and 1 for healthy control. The gene level score was defined as the p-value for the gene-based association from this multiple regression.

Gene flanking is defined as increasing the SNPs associated with a gene by extending the gene region by a number of bases in the 5’ and 3’ directions. By doing this, SNPs that may be involved in the transcription process are considered in the analysis. In the discovery analysis in EAs, 50Kb flanking regions were chosen. The 10Kb flanking regions were also explored for top-ranked genes. The top-ranked risk genes identified in EAs were also replicated in AAs (with 50Kb flanking regions).

2.3.2 Pathway-based GWAS analysis
Pathway annotation was obtained from the collection of pathways curated by the Molecular Signatures database (MSigDB) using seven public databases: BioCarta, Gene arrays, BioSciences Corp, KEGG, REACTOME, Sigma-Aldrich pathways, Signal transcription knowledge environment, and Signaling gateway (http://www.broadinstitute.org/gsea/msigdb/collection_details.jsp #CP). The gene set enrichment method was used to determine the pathway enrichment.[13] The test statistic was calculated as the negative sum of the log p-values for each gene assigned to the pathway. The enrichment was determined by randomly permuting the gene scores (5000 times) and recalculating the test statistic for each pathway. The p-value of each pathway was calculated as the percentage of the permuted test statistics larger than the observed p-value. The top-ranked pathways identified in EAs were replicated in AAs (with 50Kb flanking regions).

2.3.3 Correction for multiple testing in gene- and pathway-based GWAS analyses
A total of 26307 genes and 221 pathways were analyzed. The significance levels (α) for gene- and pathway-based GWAS tests were corrected by the Bonferroni correction and, thus, set at 1.9E-6 and 2.3E-4, respectively. P-values larger than α but less than 0.05 were labelled as ‘nominally significant’.

3. Results
A total of 2464 genes were nominally associated with alcohol dependence in EAs (p<0.05). The 20 top-ranked risk genes (based on the level of statistical significance) are listed in Table 1. After correction for multiple testing (α=1.9E-6), the paxillin gene (PXN) (±50kb) was significantly associated with alcohol dependence (p=3.9E-7). If flanking regions were reduced to ±10kb, PXN (±10kb) remained significantly associated with alcohol dependence in EAs (p<0.05), and the other 19 top-ranked risk genes remained nominally significant (p<0.05).

<p>| Table 1. Top-ranked and replicable genes for alcohol dependence |
|---------------------------------|-----------------|--------------------|</p>
<table>
<thead>
<tr>
<th>gene number of SNPs p-valueα number of SNPs p-valueα</th>
<th>risk genes in European-Americans (using ±50kb flanking regions)</th>
<th>replicable risk genes in European-Americans (using ±50kb flanking regions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PXN 40 3.9E-7 4 &lt;E-8</td>
<td>OR5T3 23 1.4E-5 5 6.3E-3</td>
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<td>ZNF800 42 2.6E-5 13 1.6E-5</td>
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</tr>
<tr>
<td>DCC1 41 3.2E-5 19 2.2E-2</td>
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</tr>
<tr>
<td>SAMHD1 43 3.9E-5 25 8.5E-3</td>
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<tr>
<td>DOLPP1 26 5.6E-5 8 4.6E-4</td>
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<tr>
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<tr>
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<tr>
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<td>ZNF256 36 2.9E-4 9 9.9E-3</td>
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</tr>
<tr>
<td>IQSEC3 60 3.1E-2 67 4.7E-2</td>
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</tr>
</tbody>
</table>

* based on the Bonferroni correction for multiple testing, the statistical significance threshold is set at p-value <1.9E-6
Among the 2464 nominally associated genes in EA, 129 were nominally replicable in AAs (p<0.05) (data not shown). As shown in Table 1, six of these genes (ZNF236, CPLX2, LOC646820, SLC38A1, PGBD3, and AP3S2) were associated with alcohol dependence at the p<0.01 level in both EAs and AAs. Only one of these six genes, SLC38A1, is a component of a nominally significant pathway (the ‘amino acid transport across the plasma membrane’ pathway, pathway #18 in Table 2). Among the other 123 nominally replicable genes, only two genes are components of top-ranked pathways: BAD belongs to the ‘VEGF signaling’ pathway (pathway #4 in Table 2) and IQSEC3 belongs to the ‘endocytosis’ pathway (pathway #6 in Table 2).

Twenty pathways enriched in alcohol dependence-related genes in EAs are listed in Table 2, including the 17 top-ranked pathways (based on the level of statistical significance) and 3 other important pathways; pathway #18 (the ‘amino acid transport across the plasma membrane’ pathway) is the only nominally significant pathway that contains one of the six replicable genes with p-values <0.01 shown in Table 1 (SLC38A1), pathway #19 was previously reported to be related to addiction, and pathway #20 was nominally replicable in both EA and AA. Using 50kb flanking regions in the analysis of EAs, the top-ranked (1) risk pathway was the ‘cell-extracellular matrix interactions’ pathway (RSU1, LIMS1, LIMS2, ARHGEF6, FERMT2, ACTN1, BLIM1, FLNC, ITGB1, PXN, FNLA, VASP, ILK, TESK1, PARVB, and PARVA) (p=2.0E-4). Two other pathways of particular interest were the ‘VEGF signaling’ pathway (pathway #4) (PXN, BAD, HRAS, NRAS, et al.) (p=1.4E-3) because it contains the nominally replicable BAD gene and the ‘endocytosis’ pathway (pathway #6) (IQSEC3, HRAS, et al.) (p=7.4E-3) because it contains the nominally replicable IQSEC3 gene.

After correction for multiple testing, the only pathway that remained significantly associated with alcohol dependence (p<2.3E-4) was pathway #1. If 10kb flanking regions were set, the association of all of the listed pathways with alcohol dependence in EAs remained nominally significant (p<0.05), but none of them were statistically significant after correction for multiple testing. The two pathways most strongly associated with alcohol dependence when using 10kb flanking regions were the ‘Na+/Cl- dependent neurotransmitter transporters’ pathway (pathway #15) (SLC6A1, SLC6A2, SLC6A3, SLC6A5, SLC6A6, SLC6A7, SLC6A9, SLC6A11, SLC6A12, SLC6A13, SLC6A14, SLC6A15, SLC6A18, SLC6A19, SLC6A20, SLC18A1, SLC18A2, and SLC22A2) and the ‘amino acid transport across the plasma membrane’ pathway (pathway #18) (SLC1A4, SLC1A5, SLC3A1, SLC3A2, SLC6A6, SLC6A12, SLC6A14, SLC6A15, SLC6A18, SLC6A19, SLC6A20, SLC17A1, SLC17A2, SLC7A3, SLC7A5, SLC7A6, SLC7A7, SLC7A8, SLC7A9, SLC7A10, SLC7A11, SLC16A10, SLC36A1, SLC36A2, SLC38A1, SLC38A2, SLC38A3, SLC38A4, SLC38A5, SLC43A1, and SLC43A2) (both p=1.8E-3).

As shown in Table 2, there were 2 nominally replicable pathways (based on 50kb flanking) enriched in alcohol dependence-related genes in both EAs (0.015≤p<0.035) and AAs (0.025≤p<0.050): the ‘Na+/Cl- dependent neurotransmitter transporters’ pathway (pathway #15) (specified above), and the ‘other glycan degradation’ pathway (pathway #20) (AGA, HEXA, HEXB, ENGASE, FUCA2, FUCA1, MANBA, GLB1, MAN2C1, MAN2B2, NEU1, NEU3, MAN2B1, NEU2, GBA, and NEU4).

4. Discussion

4.1 Main findings

In the present study, we found significant genome-wide replicable risk genes and risk pathways that were associated with alcohol dependence. Incorporating the biological, bioinformatic, statistical, and association evidence with previous reports of these genes and pathways, the ‘cell-extracellular matrix interactions’ pathway (#1) and the PXN gene (which encodes paxillin) were the most promising risk factors for alcohol dependence; their association with alcohol dependence remained statistically significant after adjusting for multiple testing using the Bonferroni correction.

The ‘cell-extracellular matrix (ECM) interactions’ pathway plays a critical role in regulating a variety of cellular processes in multi-cellular organisms including motility, shape change, survival, proliferation, and differentiation. Cell-ECM contact is mediated by transmembrane cell adhesion receptors (integrins) that interact with extracellular matrix proteins and cytoplasmic adaptor proteins. Many of these adaptor proteins physically interact with the actin cytoskeleton or function in signal transduction. Paxillin is an important component of this pathway that binds directly to α-integrins.

The PXN gene was significantly associated with alcohol dependence in the present study, suggesting the possible role of paxillin in alcoholism. Paxillin is expressed in multiple tissues (including the brain) where it acts as a multidomain scaffolding protein for bringing together signaling molecules, structural components, and regulatory proteins that control the adhesion and organization of the internal cytoskeleton for processes such as cell migration (reviewed in [15]).

Paxillin is also a component of the ‘VEGF signaling’ pathway (pathway #4). This pathway is enriched in alcohol dependence-related genes in EAs, though the association (p=1.4E-3) does not reach our criteria for statistical significance. This pathway has been implicated in stress reactivity and in the symptoms of mood disorders [16] potential contributors to the risk for alcohol dependence. [17] It has also been associated with drug addiction (including alcoholism) (p=3.2E-3) in a previous report. [18] Interestingly, the BAD (BCL2-associated agonist of cell death) gene also belongs to this pathway; we found a strong, but not statistically significant, association of BAD to alcohol dependence both in EAs and AAs, supporting the possible role of the ‘VEGF signaling’ pathway in alcohol dependence.
Pathways comprehensively integrate information from multiple genes. The complexity of pathway structure makes the replicability of pathway-wise associations very difficult. Replications between homogeneous samples may be relatively common, but replications between genetically heterogeneous samples, such as that between EAs and AAs, would be relatively uncommon. Therefore, replications of pathway-disease associations between EAs and AAs may indicate a functional relationship between the specific pathways and the disease of interest. We identified two replicable pathways for associations with alcohol dependence across EAs and AAs: the 'Na+/Cl- dependent neurotransmitter transporters' pathway (pathway #15 in Table 2) and the ‘other glycan degradation’ pathway (pathway #20 in Table 2). Among all pathways we studied, pathway #15 had the strongest association with alcohol dependence when 10Kb flanking regions were set ($p=1.8E-3$). All the genes within this pathway are neurotransmitter transporter genes, encoding proteins that mediate neurotransmitter uptake and, thus, terminate a synaptic signal. These transporters are mainly present in the central and peripheral nervous systems (19) where they mediate transport of GABA (gamma-aminobutyric acid), norepinephrine, dopamine, serotonin, glycine, taurine, L-proline, creatine, and betaine. These genes have been associated with several neuropsychiatric conditions; for example, SLC6A3 (the dopamine transporter gene, DAT1) and SLC18A2 (the monoamine transporter gene) have been associated with alcohol dependence (20-28) and smoking (27-31).

Another pathway of interest is pathway #18 (the ‘amino acid transport across the plasma membrane’ pathway) that had a non-significant enrichment of alcohol dependence-related genes in EAs. This pathway was not replicable in AAs, but it contained an important gene, SLC38A1, that was replicable in both the EA population ($p=5.7E-3$) and the AA population ($p=9.9E-3$). All genes within this pathway belong to the solute carrier (SLC) family, including amino acid transporter genes which encode proteins that transport amino acid across plasma membranes. These proteins are critical to the uptake of amino acids from the gut, from the renal proximal tubules, and in cells throughout the body where amino acids are required for neurotransmission and for the synthesis of proteins and metabolic intermediates. (32) This pathway is a component of the 18 systems identified in physiological studies that mediate amino acid transport, each characterized by its amino acid substrates, its pH sensitivity, and its association (or not) with ion transport. (33) The SLC38A1 (amino acid transporter A1) gene within pathway #18 plays an essential role in the uptake of nutrients, production of energy, chemical metabolism, detoxification, and neurotransmitter cycling. It is an important transporter of glutamine – an intermediate in the detoxification of ammonia and in the production of urea. Glutamine serves as a precursor for the synaptic transmitters glutamate and GABA, both of which have been implicated in the neurobiology of alcohol intoxication and withdrawal. (34) Moreover, glutamate and GABA signaling pathways have been associated with alcohol
dependence in a recent pathway-based association study.[35]

Several other top-ranked pathways identified in EAs in our study have also been identified as potential risk factors for drug addiction and alcoholism in previous reports.[18] These include the ‘long term depression (LTD)’ pathway (#12) \( (p=2.2E-2 \text{ in our study, and } p=2.1E-7 \text{ in a previous study})^{[18]} \); the ‘Fc epsilon RI signaling’ pathway (#13) \( (p=2.3E-2 \text{ in our study, and } p=6.9E-3 \text{ in a previous study})^{[18]} \); and the ‘amyotrophic lateral sclerosis’ pathway (#19) \( (p=5.8E-3 \text{ in our study, and } p=3.9E-5 \text{ in a previous study})^{[18]} \). Cerebellar LTD is thought to be a molecular and cellular basis for cerebellar learning which promotes the type of neuroplasticity that underlies development and recovery from addiction; a hypothesis that is supported by the finding that many molecular substrates of addiction are shared with other forms of learning.[36, 37] Moreover, the LTD pathway has also been found to be enriched in genes associated with smoking cessation, a close phenotype to alcohol dependence.[38]

The ‘Fc epsilon RI signaling’ pathway (#13) in mast cells is initiated by the interaction of an antigen (Ag) with IgE which is bound to the extracellular component of the alpha chain of Fc epsilon RI; the activated pathway is regulated both positively and negatively by the interactions of numerous signaling molecules. Activated mast cells release preformed granules containing biogenic amines, especially histamines—the chemicals that regulate alcohol-related behaviors in the brain.[39, 40] The ‘amyotrophic lateral sclerosis (ALS)’ pathway (#19) may be involved in glutamate dysregulation, oxidative stress, and mitochondrial damage which may, in turn, be associated with the development of alcohol dependence[34] and alcohol-related neurotoxicity.[41]

4.2 Limitations

With the exception of a significant association of the PXN gene and the ‘cell-extracellular matrix interactions’ pathway in EAs, none of the other top-ranked risk genes or risk pathways identified in the present study remained significantly associated with alcohol dependence after the results were adjusted for multiple testing using the Bonferroni correction. Further replication studies with even larger samples will be needed to confirm or disprove their relevance to alcohol dependence.

4.3 Implications

In summary, a gene- and pathway-based reanalysis of prior GWAS data provides new evidence highlighting several genes and biological signaling processes that may be related to the risk for alcohol dependence. These pathways converge on glutamate neurotransmission, a process previously implicated in both the neurobiology and treatment of alcoholism. These findings may be helpful in linking genes implicated in the heritable risk for alcohol dependence to this underlying neurobiology.

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Conflict of interest

None of the authors report any conflict of interest related to this manuscript.

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Ethics approval

The protocols described in the paper were all approved by the relevant institutional review boards. All subjects were de-identified in this study and the study was approved by the institutional review board at Yale University.

Informed consent

All subjects provided written informed consent to participate in the projects at each of the participating institutions.
酒精依赖的基于基因和基于通路的全基因组关联研究


背景：信号通路中风险基因的构成可能可以解释酒精依赖风险基因协同的神经生物学作用。

目的：我们采用基因富集（gene-set-rich）分析方法对酒精依赖进行了基于通路的全基因组关联分析（GWAS）。在包括1409名欧裔美国人（European-American, EA）酒精依赖者和1518名EA健康对照者的探索性样本人群中检测了近一百万个基因标志物。此外，将681名非裔美国人（African-American, AA）病例和508名AA健康受试者作为重测样本。

方法：我们发现了几个与酒精依赖显著相关的可重复的全基因组风险基因和风险通路。在多重比较Bonferroni校正后，“细胞 - 细胞外基质相互作用”通路（EA样本中p<2.0E-4）和该通路中PXN基因（编码粘蛋白paxillin）(EA样本中p=3.9E-7)是最有可能的酒精依赖的危险因素。在EA样本（0.015s0.035）和AA样本（0.025s0.050）中还有两条富含酒精依赖相关基因的可重复的通路：“Na+/Cl-依赖性神经递质转运体”通路和“其他聚糖降解”通路。

结论：一些基因和生物信号传导过程可能与酒精依赖的风险相关，本研究的发现为此提供了新的证据。

关键词：基于基因的全基因组关联分析；基于通路的全基因组关联分析；细胞 - 细胞外基质相互作用的通路；PXN；粘蛋白；酒精依赖

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References


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