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Progress toward identification of alcoholism susceptibility genes on chromosome 7 in the COGA dataset

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Progress Toward Identification of Alcoholism Susceptibility Genes on Chromosome 7 in the COGA dataset

Alison M. Goate, Ph.D.

This research is supported by NIH Grant (U10AA08403) from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). There are no interests to disclose.
Genetics of alcoholism

1) To what extent do genetic influences impact the trait of interest?

2) Can we identify these genetic influences?

3) How do these genes act and interact with other genetic/environmental influences?
The heritability of alcoholism

- Twin & adoption studies
  - Denmark, Sweden, Finland, Australia, USA

- Across birth cohorts
  - late 1800s to early 1970s

- Across methods of assessment
  - In-patient hospitalizations, gov’t records, diagnostics interview

- Across diagnostic criteria
  - Feighner, DSMIII-R, DSMIV, ICD

- Heritability estimates
  - 51-65% in females
  - 48-73% in males
“The long-term objective of this multi-dimensional interdisciplinary research project is to characterize the genetic factors involved in the determination of predisposition to alcoholism. This substantial undertaking involves the expertise of biochemists, clinicians, geneticists, neuropsychologists, neurophysiologists, and statisticians.”

--original COGA grant application, 1989
COGA strategy

1. Ascertain alcoholic families
2. Linkage analyses to identify chromosomal regions
3. Association analyses to identify specific genes

Polydiagnostic interview
Electrophysiological data

↑ allele-sharing among affecteds within a family
Patients identified through inpatient/outpatient treatment programs at 6 sites

- **General sample**: 1,227 families (n=9265)
  - Semi-structured Assessment for the Genetics of Alcoholism Interview (SSAGA)

- **Genetic sample**: 262 families (n=2282)
  - Blood draw, EEG/ERP, neuropsychological assessments
  - 2 waves of data collection
Phenotypes used in the genetic analyses

◆ Alcohol dependence
  → COGA= DSMIIIR plus Feighner criteria
  → DSMIV
  → ICD10

◆ Other substance abuse
  → Cocaine dependence
  → Marijuana dependence
  → Habitual smoking (2 packs/day for at least 6 months)

◆ Comorbid disorders
  → depression

◆ Endophenotypes
  → Electroencephalogram (EEG)
  → Event related potential (ERP)
Neurophysiological Endophenotypes

- S-transform of evoked activity to target in VP3
  - yields time-frequency characteristics of signal

- Endophenotypes: Theta band (3-7 Hz) + delta band (1-2 Hz) between 300-700 ms (when P3 component is maximum) in brain regions (frontal, central, parietal)
  - Time-frequency distribution mean value

- SOLAR linkage analysis
  - Using 1340 individuals in 253 families

Jones et al.
Theta + Delta Oscillations Underlying GO NO-GO P3 Are Reduced In Alcoholics

Kamarajan et al., 2003
SOLAR Linkage Analysis: Theta + Delta Oscillations
VP3 Target (S-Transform)

ERP
TARGET

TIME by
FREQ

THETA

DELTA

N=1340/253
Difficulties with Complex Disorders

- Many genes of small effect
- Genetic heterogeneity
- Gene-gene interaction
- Gene-environment interaction
- Phenotype definition
EEG Summary

- Imbalance in excitation/inhibition (CNS disinhibition) in alcoholics and individuals at risk

- **Hypothesis:** CNS disinhibition involved in genetic predisposition for development of alcohol dependence

- EEG as an endophenotype for alcohol dependence
## EEG Heritabilities

<table>
<thead>
<tr>
<th>Frequency band</th>
<th>Mean $h^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta (1.5-3.5 Hz)</td>
<td>76%</td>
</tr>
<tr>
<td>Theta (4-7.5 Hz)</td>
<td>89%</td>
</tr>
<tr>
<td>Alpha (8-12.5 Hz)</td>
<td>89%</td>
</tr>
<tr>
<td>Beta (13-25 Hz)</td>
<td>86%</td>
</tr>
</tbody>
</table>

Van Beijsterveldt et al., 1996
Linkage Results in COGA
Results of the initial genome screen for COGA alcohol dependence

- 3 chromosomal regions showed evidence for a susceptibility locus
  - Chromosome 1 near D1S1588
  - Chromosome 2 near D2S1790
  - Chromosome 7 near D7S1793

- 1 chromosomal region showed evidence for a protective locus
  - Chromosome 4 near ADH3
Evidence for a susceptibility gene for alcohol dependence on chromosome 7
Evidence for a susceptibility gene for depression on chromosome 7
Linkage to chromosome 7
Linkage Analysis Of Theta ERO: Chromosome 7

Frontal theta LOD = 6.28 at 171 cM

Figure 1. Linkage analysis of evoked theta on Chromosome 7
COGA association strategy

◆ Multiple analytic methods: family-based
  ➔ Extended families (PDT; trios & discordant sibs)
  ➔ Classic TDT trios (TRANSMIT; SAGE)

◆ Multiple SNPs in each gene

◆ LD across the region

◆ Consistency!
Family-based association methods

TDT – Transmission Disequilibrium Test

![Family tree diagram showing genotypes: 1/2, 3/3, 2/3]
Family-based association methods

TDT – Transmission Disequilibrium Test

PDT – Pedigree Disequilibrium Test

All possible trios
Affected vs unaffected siblings
Location of SNPs within and flanking the *CHRM2* gene on chromosome 7

CHRM2

rs2061174
rs2350786
rs1824024
rs2350786
rs324640
rs8191992
rs8191992
rs8191993
rs1424548
rs324650
rs1378650
rs324656
rs324656
rs324656

Intron = 22.6 kb
Table 2. Pedigree disequilibrium test (PDT) of 9 SNPs within and flanking the CHRM2 gene and Major Depressive Disorder.

<table>
<thead>
<tr>
<th>SNP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2350786</td>
<td>0.034</td>
</tr>
<tr>
<td>rs324640</td>
<td>0.064</td>
</tr>
<tr>
<td>rs324650</td>
<td>0.047</td>
</tr>
<tr>
<td>rs324651</td>
<td>0.649</td>
</tr>
<tr>
<td>M164040.078</td>
<td></td>
</tr>
<tr>
<td>M256</td>
<td>0.056</td>
</tr>
<tr>
<td>rs1378650</td>
<td>0.122</td>
</tr>
<tr>
<td>rs1424548</td>
<td>0.710</td>
</tr>
<tr>
<td>rs324656</td>
<td>0.486</td>
</tr>
</tbody>
</table>
Transmit disequilibrium test (TDT) of 9 SNPs within and flanking the CHRM2 gene and alcohol dependence.

<table>
<thead>
<tr>
<th>Diagnosis SNP</th>
<th>COGA_M1 (N=888)</th>
<th>DSM4_M1 (N=756)</th>
<th>ICD10_M1 (N=575)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi</td>
<td>p-val</td>
<td>Chi</td>
</tr>
<tr>
<td>rs2350786</td>
<td>0.02</td>
<td>0.888</td>
<td>0.00</td>
</tr>
<tr>
<td>rs324640</td>
<td>1.01</td>
<td>0.315</td>
<td>0.53</td>
</tr>
<tr>
<td>rs324650</td>
<td>0.98</td>
<td>0.321</td>
<td>0.73</td>
</tr>
<tr>
<td>rs324651</td>
<td>1.44</td>
<td>0.231</td>
<td>2.13</td>
</tr>
<tr>
<td>M16404</td>
<td>0.27</td>
<td>0.603</td>
<td>0.17</td>
</tr>
<tr>
<td>M256</td>
<td>0.01</td>
<td>0.928</td>
<td>0.01</td>
</tr>
<tr>
<td>rs1378650</td>
<td>0.20</td>
<td>0.653</td>
<td>0.29</td>
</tr>
<tr>
<td>rs1424548</td>
<td>0.65</td>
<td>0.421</td>
<td>0.00</td>
</tr>
<tr>
<td>rs324656</td>
<td>0.02</td>
<td>0.896</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Model 1: Unaffected subjects are defined as individuals who drink but do not endorse any symptoms of alcohol dependence.
Pair-wise disequilibrium between SNPs in the CHRM2 gene

<table>
<thead>
<tr>
<th>SNP</th>
<th>D'</th>
<th>rs2350786</th>
<th>rs324651</th>
<th>M16404</th>
<th>rs1378650</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2350786 (A:0.29/G:0.81)</td>
<td></td>
<td>0.67</td>
<td>0.44</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>rs324651 (G:0.87/T:0.13)</td>
<td>0.03</td>
<td></td>
<td>0.97</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>M16404 (A:0.41/T:0.59)</td>
<td>0.13</td>
<td>0.09</td>
<td></td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>rs1378650 (C:0.58/T:0.42)</td>
<td>0.23</td>
<td>0.07</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pedigree disequilibrium test (PDT) of 4 SNPs within and flanking the CHRM2 gene and alcohol dependence

<table>
<thead>
<tr>
<th>Disease Model</th>
<th>SNP (P-values)</th>
<th>rs2350786</th>
<th>rs324651</th>
<th>M16404</th>
<th>rs1378650</th>
</tr>
</thead>
<tbody>
<tr>
<td>COGA M1</td>
<td></td>
<td>0.733</td>
<td>0.195</td>
<td>0.036</td>
<td>0.032</td>
</tr>
<tr>
<td>COGA M2</td>
<td></td>
<td>0.682</td>
<td>0.264</td>
<td>0.050</td>
<td>0.051</td>
</tr>
<tr>
<td>DSM4 M1</td>
<td></td>
<td>0.811</td>
<td>0.025</td>
<td>0.008</td>
<td>0.022</td>
</tr>
<tr>
<td>DSM4 M2</td>
<td></td>
<td>0.707</td>
<td>0.107</td>
<td>0.023</td>
<td>0.043</td>
</tr>
<tr>
<td>ICD10 M1</td>
<td></td>
<td>0.704</td>
<td>0.061</td>
<td>0.079</td>
<td>0.196</td>
</tr>
<tr>
<td>ICD10 M2</td>
<td></td>
<td>0.677</td>
<td>0.289</td>
<td>0.167</td>
<td>0.203</td>
</tr>
</tbody>
</table>

Model 1: Unaffected subjects are defined as individuals who drink but do not endorse any symptoms of alcohol dependence.
Model 2: Unaffected subjects are defined as individuals who drink but do not meet diagnostic criteria for alcohol dependence.
Haplotype analysis three SNPs within the CHRM2 gene using SIMWALK with DSM IV diagnosis Model 1.

<table>
<thead>
<tr>
<th>rs324651</th>
<th>M16404</th>
<th>rs1378650</th>
<th>Haplotype frequencies in founders (N)</th>
<th>Parental Contribution Discordant Sibs</th>
</tr>
</thead>
<tbody>
<tr>
<td>G A C</td>
<td>0.072</td>
<td>(87)</td>
<td>44ZZZZZ3ZZZZZZZ9ZZZZZZ 14ZZZZZZZZ 0.654ZZZ</td>
<td></td>
</tr>
<tr>
<td>G A T</td>
<td>0.393</td>
<td>(479)</td>
<td>298ZZZZ308ZZZZ48ZZZZ   105ZZZZZ -1.431ZZZ</td>
<td></td>
</tr>
<tr>
<td>G T C</td>
<td>0.326</td>
<td>(396)</td>
<td>274ZZZZ251ZZZZ40ZZZZ   102ZZZZZZ 2.642ZZZ</td>
<td></td>
</tr>
<tr>
<td>G T T</td>
<td>0.081</td>
<td>(98)</td>
<td>34ZZZZZZ1ZZZZZZZZZZZZZZ 20ZZZZZZZZ 0.208ZZZ</td>
<td></td>
</tr>
<tr>
<td>T A C</td>
<td>0.008</td>
<td>(10)</td>
<td>1ZZZZZZZZZZZZZZZZZZZZZZ 0ZZZZZZZ -1.000ZZZ</td>
<td></td>
</tr>
<tr>
<td>T A T</td>
<td>0.101</td>
<td>(123)</td>
<td>70ZZZZZZ3ZZZZZZZZ9ZZZZZZ 31ZZZZZZZ -1.956ZZZ</td>
<td></td>
</tr>
<tr>
<td>T T C</td>
<td>0.010</td>
<td>(12)</td>
<td>2ZZZZZZZZZZZZZZZZZZZZZZ 0ZZZZZZZZ 0.000ZZZ</td>
<td></td>
</tr>
<tr>
<td>T T T</td>
<td>0.009</td>
<td>(11)</td>
<td>3ZZZZZZZZZZZZZZZZZZZZZZ 0ZZZZZZZ -1.069ZZZ</td>
<td></td>
</tr>
</tbody>
</table>

Global PDT test of SNP haplotypes (excluding the 3 rare haplotypes) with DSM IV_m1 = \( \chi^2 = 10.43 \) p=0.034, 4 d.f.
<table>
<thead>
<tr>
<th>CHRM2 SNPs LD SOLAR MEASURED GENOTYPE</th>
<th>DELTA TARGET</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2350786 Frontal 0.66</td>
<td>rs8191992</td>
</tr>
<tr>
<td>Central 0.09</td>
<td>Frontal 0.21</td>
</tr>
<tr>
<td>Parietal 0.08</td>
<td>Central 0.0046</td>
</tr>
<tr>
<td>rs324640 Frontal 0.99</td>
<td>rs8191993</td>
</tr>
<tr>
<td>Central 0.02</td>
<td>Frontal 0.69</td>
</tr>
<tr>
<td>Parietal 0.08</td>
<td>Central 0.39</td>
</tr>
<tr>
<td>rs324650 Frontal 0.82</td>
<td>rs1378650</td>
</tr>
<tr>
<td>Central 0.048</td>
<td>Frontal 0.21</td>
</tr>
<tr>
<td>Parietal 0.01</td>
<td>Central 0.008</td>
</tr>
<tr>
<td>rs324651 Frontal 0.36</td>
<td>rs1424548</td>
</tr>
<tr>
<td>Central 0.12</td>
<td>Frontal 0.95</td>
</tr>
<tr>
<td>Parietal 0.2</td>
<td>Central 0.66</td>
</tr>
<tr>
<td>rs324656 Frontal 0.24</td>
<td></td>
</tr>
<tr>
<td>Central 0.033</td>
<td></td>
</tr>
<tr>
<td>Parietal 0.065</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions I – Association Studies

◆ COGA strategy for testing candidate genes
  ➔ Within family tests
  ➔ Multiple SNPs in each gene
  ➔ Consistency between association results and patterns of LD

◆ Evidence for association
  ➔ GABRA2 on chromosome 4
  ➔ GABRG3 on chromosome 15
Why association with some GABA-A receptors and not others?

→ Chromosome 4:
  ◆ GABRA2 (not GABRG1, GABRA4, GABRB1)

→ Chromosome 15:
  ◆ GABRG3 (not GABRB3, GABRA5)

What about these genetic variants alters risk?

→ Sequencing, no amino acid substitutions
→ Regulatory differences
What next?

- Demonstrated genetic influence on alcoholism
- Identified specific genes
- Characterizing the risk associated with these genes
Conclusions

➔ From identifying genetic influence

➔ To identifying specific genes

➔ To characterizing the risk associated with those genes

• Gene-gene & gene-environment interaction
• Developmental trajectories associated with genetic risk factors
Acknowledgments - COGA

H. Begleiter, SUNY HSC @ Brooklyn, Principal Investigator
H. Edenberg, Indiana University, Co-Principal Investigator

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Lisa Neuhold, NIAAA Staff Collaborator

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