Genetic and Environmental Influences on Disordered Gambling in Men and Women

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Context: Women now represent nearly half of all individuals in treatment for pathological gambling (PG), but relatively little is known about the causes of PG among women or potential sex differences in the causes of PG.

Objectives: To (1) investigate the role of genetic and environmental risk factors in the development of disordered gambling (DG) among women and (2) determine the extent to which the genetic and environmental risk of DG among women differs quantitatively or qualitatively from the risk of DG among men. (Disordered gambling refers to the full continuum of gambling-related problems that includes PG disorder.)

Design: Twin study.

Setting: The national community-based Australian Twin Registry.

Participants: Four thousand seven hundred sixty-four individuals from 2889 twin pairs; twins were aged 32 to 43 years and 57% were women.

Main Outcome Measure: Disordered gambling was defined based on lifetime DSM-IV PG symptom counts.

Results: The estimate of the proportion of variation in liability for DG due to genetic influences was 49.2% (95% confidence interval, 26.7-60.9). There was no evidence for shared environmental influences contributing to variation in DG liability. There was no evidence for quantitative or qualitative sex differences in the causes of variation in DG liability.

Conclusions: This study establishes for the first time that genes are as important in the etiology of DG in women as they are in men and that the susceptibility genes contributing to variation in liability for DG are likely to overlap considerably in men and women.

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PATHOLOGICAL GAMBLING (PG) runs in families. In a recent family study, 8% of the first-degree relatives of PG-affected probands, compared with 2% of the first-degree relatives of unaffected controls, had a lifetime history of PG. The results of such family studies raise the question of the extent to which the familial transmission of PG can be explained by shared genes or shared environments. To date, only a single study has addressed this question. In the Vietnam Era Twin Registry, 23% of the monozygotic (MZ) and 10% of the dizygotic (DZ) co-twins of men with PG, compared with 1.4% of the full sample, had a lifetime history of PG. Biometric modeling revealed that the familial aggregation of PG was mainly attributable to shared genetic rather than shared environmental factors. Whether the results from the all-male Vietnam Era Twin Registry study can be generalized to women has still not been established.

Although women are outnumbered by men approximately 2-fold in their probability of being affected with PG, they now represent nearly half of all individuals in treatment for the disorder. Despite this, women are still underrepresented in most etiologic research, and the familial transmission of PG among women and potential sex differences in the familial transmission of PG are largely uncharted territory. Given how poorly represented women have been in gambling research, there are only a few modest pieces of evidence to point to: (1) a review of 17 family studies suggested that the familial transmission of PG was weaker for women than for men (although the more recent study cited earlier did not detect such a sex difference) and that having a mother affected with PG did not increase the risk of PG in the offspring; (2) a small twin study of 155 twin pairs (63 female pairs) that concluded that gambling involvement was significantly heritable among men but not among women; and (3) a
genetic association study of 68 individuals with PG (21 women) reported 3 associations that were significant in men but not in women\(^3\) (appropriate tests of sex differences\(^10-12\) were not always conducted in these early studies). Some have speculated that PG among women may not have genetic underpinnings.

In the present study, we investigated the role of genetic and environmental risk factors in the development of disordered gambling (disordered gambling [DG]) refers to the full continuum of gambling-related problems that includes PG as well as subclinical problems\(^13\) in a large community-based sample of male, female, and opposite-sex twin pairs. Based on previous twin research on related disorders, we did not expect there to be significant sex differences in the role of genetic and environmental influences in the risk of DG. Meta-analyses of population-based twin studies of alcohol dependence\(^10,11\) and major depression\(^13\) have yielded very similar estimates of the contribution of genetic and environmental factors for men vs women. Based on these more developed literatures, we hypothesized that the same would also be observed for DG, and the main goal was to establish for the first time that DG has genetic underpinnings in women as well as men. The extent to which the genetic and environmental risk factors differ in men vs women was also explored by comparing twins from same- and opposite-sex twin pairs.

### METHODS

#### PARTICIPANTS

Participants for this study were 4764 members of the Australian Twin Registry Cohort II (details about the study participants and the zygosity determination have been published previously\(^13\)). In 2004-2007, a telephone interview containing a thorough assessment of gambling behaviors was conducted in the Australian Twin Registry Cohort II members (individual response rate of 80.4%).\(^12\) The mean age was 37.7 years (range, 32-43 years), and 57.2% of the sample was female. There were 1875 complete twin pairs (867 MZ pairs [520 female and 347 male] and 1008 DZ pairs [367 female/female, 227 male/male, and 414 female/male]), and 1014 individual twins from incomplete pairs (304 MZ individuals [151 female and 153 male] and 710 DZ individuals [181 women from female/female pairs, 216 men from male/male pairs, and 207 women and 106 men from female/male pairs]).

#### PROCEDURE

Twins were assessed through a structured telephone interview. Interviews were administered by trained lay interviewers who were blind to the status of the co-twin. Interviewers were supervised by a project coordinator, a clinical psychologist with more than 10 years of experience. All interview protocols were reviewed either by the project coordinator or by research editors (veteran, skilled interviewers from previous studies who had maintained consistently low error rates in coding). All interviews were tape-recorded and a random sample of 5% of the interview tapes was reviewed for quality control and coding inconsistencies. A small subsample of the participants (n=160) were reinterviewed several months after their initial interview (mean interval, 3.4 months [SD, 1.4 months]; range, 1.2-9.5 months) to establish the test-retest reliability of the interview measures. Individuals with a history of PG symptoms were oversampled for the test-retest reliability study. The institutional review boards at the University of Missouri-Columbia and the Queensland Institute of Medical Research approved this study. All of the participants provided informed consent.

### MEASURES

#### Disordered Gambling

The National Opinion Research Center DSM-IV Screen for Gambling Problems (NODS)\(^23\) was used to assess DG. The NODS DSM-IV diagnostic criteria were assessed for all participants who reported that they had ever gambled at least 5 times within a single 12-month period; most participants (77.5%) surpassed this gambling threshold.

The NODS is a structured interview that was developed for a national United States gambling prevalence survey conducted in 1999.\(^24\) The NODS assesses the 10 DSM-IV diagnostic criteria for PG. The test-retest reliability of the lifetime diagnosis of PG from the NODS was high (kappa = 0.67; Yule Y = 0.79). Exploratory factor analyses provided strong and convincing evidence consistent with a single-factor model of PG for the DSM-IV symptom set: there was only a single large eigenvalue greater than 1, and the root mean square error of approximation and root mean square residual were 0.021 and 0.03, respectively. Typically, a single eigenvalue greater than 1, a root mean square error of approximation of less than 0.05, and all of the indicators having high loadings on a single factor support the hypothesis that a single factor is sufficient for explaining the interitem correlations. The exploratory factor analyses support the proposition that all of the DSM-IV symptoms are measuring the same underlying dimension and that endorsing even a single item is informative about an individual’s DG liability.

Because the DSM-IV diagnostic criteria for PG also include an exclusion criterion that the “gambling behavior is not better accounted for by a manic episode,” a manic screen was also included in the interview. Participants who endorsed having a period of unusually elevated mood accompanied by behaviors noticeable to others (rapid speech and impulsive behaviors) and treatment (hospitalization or medication) were considered to have probable mania. 1.2% of the sample met these criteria. This included 6 individuals with DSM-IV PG. Only 2 of the 6 individuals with DSM-IV PG who were classified with probable mania reported that there was an increase in the frequency and quantity of gambling expenditures during the manic episode. Because there were so few individuals who met this criterion for exclusion, and to maintain consistency with previous research (this exclusion was a new addition to the DSM-IV), we retained these individuals in the sample.

#### Environmental Similarity

Data obtained from a previous structured telephone interview\(^25\) conducted in 1996-2000 (on average 7.8 years prior to the present study when the participants were aged 24-36 years) were used to evaluate the validity of the equal environmental similarity assumption of twin studies for DG. Childhood environmental similarity was assessed with 4 questions. Each twin was asked how often they (1) shared the same friends when they were aged 6 to 13 years, (2) dressed alike when they were aged 6 to 13 years, (3) had the same friends at school or (4) high school. The responses from twins within pairs were combined for each item, and the 4 items were combined into a composite indicator of childhood similarity. Adult en-
Ever gambled at least once a month (Month) as a measure of disordered gambling. The symptoms making up the scale are all indicators of the same unidimensional construct, as indicated by the exploratory factor analyses and previous research. The cutoff for the threshold in the liability-threshold model does not necessarily have to correspond to the cutoff used for a clinical diagnosis. The liability-threshold model assumes that the causes of variation in risk will be the same at any point along the liability distribution and for any threshold imposed. Therefore, to maximize the statistical power, we dichotomized the DSM-IV liability distribution and for any threshold imposed. The decision to use this model was based on the following 2 considerations: (1) maintaining consistency with the previous twin study of DG,2,3,30 and (2) the use of a continuous symptom count measure was intractable because the distribution was highly skewed even after a data transformation.

RESULTS

Many of the participants were frequent gamblers. Nearly all of the participants had ever gambled, about one-half had gambled at least once a month, and about one-third had gambled at least once a week (Table 1). The overall lifetime prevalence of PG according to the DSM-IV was 2.2% (3.4% among men and 1.2% among women). The overall lifetime prevalence of ever experiencing 1 or more DSM-IV PG symptoms was 12.5% (18.2% among men and 8.3% among women).

TESTS OF MEASUREMENT INVARIANCE

Of the 10 DSM-IV PG symptoms, 1 had to be excluded from the cross-sex measurement invariance analyses owing to low rates of endorsement in both sexes (committing illegal acts to finance gambling). The remaining...
**Tests of Sex Differences**

Prior to fitting biometric models, tests of the differences between the twin correlations for the different zygosity groups were conducted using Mx (Table 2). In these and all subsequent biometric models, thresholds (prevalences) for men and women were allowed to vary because they could not be constrained to be equal (Δχ² = 92.4, P < .001, n = 4758). The twin correlations from both the 2 MZ groups (male and female) and the 2 same-sex DZ groups (male/male and female/female) could be constrained to be equal (Δχ² = 0.07, P = .97, n = 4759), and the 3 correlations from the 2 same-sex DZ groups and the opposite-sex DZ group (male/male, female/female, and male/female) could also be constrained to be equal (Δχ² = 0.00, P = .95, n = 4760).

These results indicate that there is no evidence of quantitative sex differences or qualitative sex differences. Based on these findings, it would be appropriate to proceed with biometric modeling without allowing for sex differences in parameter estimates; but because there are so few data on the etiology of DG among women, we present results of fitting models to the pooled data from men and women.

**Biometric Model Fitting**

The best fitting model was one that included additive genetic and nonshared environmental sources of variation. Shared environmental or nonadditive genetic factors did not account for significant portions of variation in liability. The results of fitting a full univariate biometric model that included additive genetic, shared environmental, and nonshared environmental sources of variation are presented in Table 3 for the purpose of delineating the confidence bounds around the parameter estimates (of the nonsignificant as well as the significant parameters). For example, shared environmental factors were estimated at 0, but the narrow confidence interval (CI) around this estimate suggests that shared environmental factors could have accounted for only 4% of the variation in liability at best. Parameter estimates for men and women did not significantly differ from each other (Δχ² = 0.1, P = .97, n = 4760).

As a check on the validity of the underlying assumption of the liability-threshold model, we compared the heritability estimates obtained from fitting full univariate biometric models to the data from the full sample when the diagnostic cutoffs were set at 1 or more, 3 or more, or 5 or more symptoms (the latter cutoff corresponds to a diagnosis of DSM-IV PG). This yielded heritability estimates of 49% (95% CI, 28%-61%; Table 3), 38% (95% CI, 35%-78%), and 40% (95% CI, 9%-74%), respectively. These results are consistent with the hypothesis that the causes of variation in risk are similar at any point along the DG liability distribution and for any diagnostic cutoff imposed.

**Tests of the Equal Environmental Similarity Assumption**

As a check on the underlying equal environment assumption of the twin method, we conducted logistic regressions predicting twin pair concordance for DG from childhood similarity of experiences (sharing the same friends, dressing alike, being in the same classes in primary school, and being in the same classes in high school) or frequency of contact as adults. After controlling for sex, age, and zygosity, neither childhood environmental similarity nor adult frequency of contact significantly predicted twin pair concordance for DG. This suggests that the equal environment assumption holds for DG in this study. The greater similarity of MZ than DZ.

### Table 2. Twin Correlations in Liability for Disordered Gambling

<table>
<thead>
<tr>
<th>Zygosity Group</th>
<th>Twin Correlation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male MZ</td>
<td>0.49 (0.30-0.65)</td>
</tr>
<tr>
<td>Male/male DZ</td>
<td>0.21 (0.00-0.45)</td>
</tr>
<tr>
<td>Female MZ</td>
<td>0.55 (0.34-0.72)</td>
</tr>
<tr>
<td>Female/female DZ</td>
<td>0.21 (0.00-0.51)</td>
</tr>
<tr>
<td>Male/female DZ</td>
<td>0.22 (0.01-0.41)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DZ, dizygotic; MZ, monozygotic.

### Table 3. Parameter Estimates From Biometric Model-Fitting of Sources of Variation in Liability for Disordered Gambling

<table>
<thead>
<tr>
<th>Group</th>
<th>Additive Genetic</th>
<th>Shared Environment</th>
<th>Nonshared Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full sample</td>
<td>49.2 (26.7-69.9)</td>
<td>0.00 (0.0-4.1)</td>
<td>50.7 (39.0-64.3)</td>
</tr>
<tr>
<td>Men</td>
<td>46.5 (10.3-61.4)</td>
<td>0.01 (0.0-46.1)</td>
<td>51.4 (35.8-70.8)</td>
</tr>
<tr>
<td>Women</td>
<td>51.8 (26.4-69.0)</td>
<td>0.00 (0.0-9.0)</td>
<td>48.2 (30.8-69.6)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
tions of phenotypic variation for most traits.34 Personality, and cognition have consistently found that shared quantitative genetic research on psychopathology, per- pendence20,21 and major depression.22 In fact, decades of analyses of population-based twin studies of alcohol de- tal influences contributing to variation in DG liability. This is similar to the results obtained from meta-

The present study obtained evidence of shared environmen-
tal influences were 48%, 0%, and 52%, respectively, which is nearly identical to the estimates for men in the present study (Table 3).

Neither the Vietnam Era Twin Registry study nor the present study obtained evidence of shared environmental influences contributing to variation in DG liability. This is similar to the results obtained from meta-

An exemplar genotype × shared environment correla-
tion for DG arises when a child is raised by a biological parent with a gambling problem. In this scenario, the child is potentially exposed to a problem gambling role model and inherits problem gambling susceptibility genes.

Women have been the focus of very little etiologic re-

The contribution of geneti-
c, shared, and nonshared environmental factors to variation in DG liability did not significantly differ be-
tween men and women, and the estimated parameters of these effects were very similar. The genetic risk fac-
tors implicated in the liability to DG also did not signifi-
cantly differ between men and women. The results of this study suggest that much of the existing literature on DG that has been based upon research with men might also be generalized to women.

There have been only 11 published molecular ge-
etic studies of DG to date,17 and the studies were based on only 4 independent samples. Altogether, only 318 in-
dividuals with DG (mostly men) have been included in molecular genetic investigations of DG. All of the stud-
ies have been candidate gene association studies; there has not yet been a genome-wide linkage or association study of DG. The focus of most of the association studies has been 1 or more of the dopamine receptor genes (including DRD1, DRD2, DRD3, DRD4, and DRD5) and the dopamine transporter gene (DAT), with at least 1 posi-
tive finding reported for DRD1, DRD2, and DRD4.39-41

Although it is difficult to draw firm conclusions from so few association studies38 of dopamine genes and DG, there are at least 2 other lines of evidence that suggest that the dopamine genes are related to susceptibility for DG. First, meta-analyses of association studies of the DRD2 gene and alcohol dependence40 and the DRD4 C521T polymorphism and novelty seeking41 suggest that there are small but significant associations with these correlated traits. Second, there have been a series of reports on the incidence of DG among individuals with Parkinson dis-

In searching for susceptibility genes, it will be im-
portant to acknowledge the stage-sequential nature of DG.49 Like other addictive disorders, DG requires that one pass through a series of stages, including the participation in gambling activities and progression to regular involve-
ment, prior to the eventual development of DG symp-
toms. Thus, genetic susceptibility for DG will also in-
clude genes related to individual differences in these earlier stages. In a previous article from this sample, we pre-

This study has a number of limitations. It is unclear how the results of this Australian twin study will gener-

Australia was specifically chosen as the site for this study because it has a heavy gambling culture43 and higher prevalences of PG. For example, the lifetime prevalences of DSM-IV PG in this Australian na-
tional survey were 3.4% and 1.2% among men and women, respectively, compared with 0.64% and 0.23% among men and women in a recent national US sur-

The univariate model-fitting results for men were simi-
lar to the results obtained from the all-male Viet-
nam Era Twin Registry study, but there are no similar twin studies among women with which to compare our results. Furthermore, like the Vietnam Era Twin Registry study, the age range of the sample was relatively narrow (32-43 years). The extent to which these results can be generalized to other age groups such as adolescents and older individuals remains an unanswered question.

Despite the higher prevalence of PG in this Australian twin sample, it was still necessary to broaden the DG phenotype to have adequate numbers of affected twins to fit sex-limitation models. Supplementary analyses using a diagnostic cutoff of 5 or more symptoms, corresponding to a diagnosis of PG, yielded a heritability estimate that was similar to the results obtained when using the lower DG cutoff of 1 or more symptoms. This supports the assumption of the liability-threshold model and suggests that the results apply to PG disorder as well as the broader DG phenotype that was used throughout this article.

Despite limitations, this study represents a major step forward in that it establishes for the first time that genes are as important in the etiology of DG in women as they are in men. In addition to similar relative contributions of genetic vs environmental factors to variation in liability for DG, the results suggest that the susceptibility genes contributing to variation in liability for DG may also overlap considerably in men and women. Twin studies can only indicate the importance of latent sources of genetic and environmental influence, but are mute concerning the specific genes or environments involved. The discovery of the specific genes and environments involved in the development of DG remains an important direction for future research.

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