A Direct, Controlled, Blind Family Study of *DSM-IV* Pathological Gambling

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ABSTRACT

Objective: Pathological gambling is a major public health problem. We sought to examine the familiality of pathological gambling and determine patterns of familial aggregation of disorders.

Method: We assessed probands with *DSM-IV* pathological gambling, controls, and their first-degree relatives. Detailed family history information was collected on relatives who were deceased or unavailable.

Results: Ninety-five pathological gambling probands, 91 controls, and their 1,075 first-degree relatives over age 18 (537 relatives of pathological gambling probands, 538 relatives of controls) were evaluated between February 2005 and June 2010. Relatives were assessed blind to proband status. Best estimate diagnoses were assigned. Rates of lifetime pathological gambling (definite/probable) was significantly greater among the first-degree relatives of probands with pathological gambling than among comparison relatives (11% vs 1%, OR = 8.19, $P < .001$). The prevalence of pathological gambling and subclinical pathological gambling combined was 16% and 3% in case and control relatives, respectively (OR = 6.57, $P < .001$). Pathological gambling relatives had higher rates of major depression (OR = 1.49, $P < .05$), bipolar disorder (OR = 3.82, $P < .05$), any mood disorder (OR = 1.59, $P < .05$), social anxiety disorder (OR = 4.76, $P < .01$), any substance use disorder (OR = 1.47, $P < .05$), posttraumatic stress disorder (OR = 2.59, $P < .05$), and antisocial personality disorder (OR = 3.72, $P < .001$). Antisocial personality disorder (OR = 3.12, $P < .01$), social anxiety disorder (OR = 4.15, $P < .01$), and posttraumatic stress disorder (OR = 2.85, $P < .05$) were more frequent in case relatives independent of the presence of pathological gambling. Age at onset of pathological gambling in case probands (< 40 years/≥ 40 years) was not related to familiality in their first-degree relatives (OR = 1.03, $P = .927$).

Conclusions: Pathological gambling is familial. Mood and substance use disorders may emerge as a consequence of the pathological gambling or as a more complex syndrome. In contrast, antisocial personality disorder, social anxiety disorder, and posttraumatic stress disorder may share a common familial etiology with pathological gambling. The phenotype may extend beyond pathological gambling to include subclinical forms of the disorder.

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Pathological gambling is a major public health problem characterized by poorly controlled and maladaptive gambling behavior. The disorder has a lifetime prevalence of 0.5%–1.5% in the general adult population and is costly to society in direct and indirect terms.[1–6] First included in the psychiatric nomenclature in *DSM-III*,[7] pathological gambling has been renamed "gambling disorder" in *DSM-5*[8] and classified as a non–substance-related disorder.

Pathological gambling has long been thought to have a hereditary basis. Several family studies, including our own, have reported elevated rates of disordered gambling in first-degree relatives of probands with pathological gambling, along with elevated rates of mood and anxiety disorders, substance use disorders, and antisocial personality disorder.[9–14] Twin data are congruent with family studies in suggesting that pathological gambling is not only familial but heritable.[15–19] Eisen et al[15] calculated that heredity explained 35%–54% of the liability for the 5 symptoms of pathological gambling in a study of 3,359 male twin pairs. Using the same data, Slutske et al[16,17] concluded that pathological gambling, substance use disorders, and antisocial personality disorder were genetically-linked, while Potenza et al[18] drew similar conclusions with regard to pathological gambling and major depression. In summary, converging data suggest that pathological gambling is familial, coaggregates with several psychiatric disorders, and is probably genetically transmitted to some extent.

We now report the results of the world's largest family study of pathological gambling. The study was developed to replicate and extend our pilot studies[12,13] and improve upon earlier family studies. Pathological gambling probands were recruited from the community, and controls were recruited through random digit dialing procedures. Comprehensive evaluations of probands and first-degree relatives were conducted by trained raters. Detailed family history information was collected on relatives who were deceased or were unavailable, usually from multiple sources. The best estimate method was used to assign psychiatric diagnoses to all subjects.

The primary goals of the study were to definitively determine whether pathological gambling is familial, examine patterns of familial aggregation of disorders, and investigate demographic and clinical characteristics that might contribute to the familial aggregation of pathological gambling. On the basis of earlier studies, we hypothesized that pathological gambling would occur significantly more often among the first-degree relatives of pathological gambling probands than among comparison relatives and that certain patterns of coaggregation of disorders would occur among pathological gambling first-degree relatives, including higher rates of mood and anxiety disorders, antisocial personality disorder, and substance use disorders. We believe the results will lead to a better understanding of the etiology and pathophysiology of pathological gambling, its classification, and both treatment and preventive strategies.

METHOD

Study Sample

Pathological gambling probands were recruited through a study registry (n = 19), psychiatric treatment facilities (n = 15), gambling treatment programs (n = 19), advertisements (n = 19), Gamblers Anonymous meetings (n = 15), and word-of-mouth (n = 7). Controls were recruited via random digit dialing by the Center of Social and Behavioral Research (University of Northern Iowa, Cedar Falls) and were group matched to pathological gambling subjects for age, sex, and educational level.

Pathological gambling probands were required to meet lifetime *DSM-IV*[1] pathological gambling criteria, have a South Oaks Gambling Score (SOGS)[20,21] ≥ 5, and have a lifetime National Opinion Research Center (NORC) *DSM* Screen for Gambling Problems (NODS)[5,22] score ≥ 5. Control probands were required to have a SOGS score ≤ 2 and a NODS score of 0. Probands were also required to be ≥ 18 years old; speak English; and not have schizophrenia, schizoaffective disorder, a psychotic mood disorder, a cognitive disorder, or a chronic neurologic disorder.

Study Procedures

Trained raters interviewed subjects between February 2005 and June 2010. A roster of first-degree relatives was obtained from probands and permission was sought to contact relatives ≥ 18 years old. Participating relatives were interviewed in person or by telephone by raters blind to the status of the proband (pathological gambling or control). To preserve the blindness of study objectives, relatives were told that they would be participating in a family study of "emotions and behavior." Subjects gave written informed consent through procedures approved by the University of Iowa Institutional Review Board. Random interviews (~ 10%) were videotaped for training, quality control, and reliability assessment purposes.

Diagnostic information was collected on relatives who were deceased, chose not to participate, or could not be located or for whom the proband would not allow contact. "Proxy interviews" were conducted with the proband and ≥ 1 relative in 84% of cases. Children < 18 years old were evaluated by using similar procedures along with the Child Behavior Checklist,[23] completed by the proband.

Diagnostic and Other Assessments

Interviews included the Structured Clinical Interview for *DSM-IV*,[24] the Structured Interview for *DSM-IV* Personality Disorders,[25] and the Family History Research Diagnostic Criteria, adapted to include criteria for pathological gambling.[26,27] The NORC gambling self-administered questionnaire was used to assess gambling attitudes and behaviors.[5] The Family Assessment Device[28] was used to classify dimensions of family life as "healthy" or "unhealthy" (eg, problem solving, communication roles, behavioral control). Questions on childhood adversity were taken from the Revised Childhood Experiences Questionnaire.[29] Other study results have been published.[30,31]

Clinical Points

- Pathological gambling is highly familial, with rates of lifetime pathological gambling and subclinical pathological gambling significantly greater among the relatives of probands with pathological gambling (11% and 6%, respectively) than among comparison relatives (1% and 1%, respectively).
- Pathological gambling relatives had higher rates than control relatives of major depression, bipolar disorder, any mood disorder, social anxiety disorder, any substance use disorder, posttraumatic stress disorder, and antisocial personality disorder.
- Antisocial personality disorder, social anxiety disorder, and posttraumatic stress disorder were more frequent in case relatives independent of the presence of pathological gambling. This familial association suggests that pathological gambling may share an underlying genetic diathesis with these disorders.

Best Estimate Diagnostic Procedure

The best estimate method was used to assign *DSM-IV* diagnoses in all subjects.[32,33] Raw interview materials and a brief narrative were independently reviewed by 2 of 3 diagnosticians (W.H.C., R.R.C., D.W.B.) after removing identifying data. A "definite" diagnosis was assigned if all required criteria were met. If any necessary criterion was unmet, a diagnosis was considered "probable." If it appeared likely that the subject had the diagnosis, but the diagnosticians could not be certain of a given criterion, then the diagnosis was considered "possible." The diagnosis was recorded as "unknown" if diagnosticians were unsure of the presence or absence of a given diagnosis. Antisocial personality disorder was the only personality disorder included. Interrater reliability of the best estimate procedure was examined in a subsample of 30 probands and first-degree relatives. There was excellent diagnostic agreement for pathological gambling ($\kappa = 1.0$), major depression ($\kappa = 0.7$), and antisocial personality disorder ($\kappa = 1.0$).

Subjects were rated for the presence of pathological gambling, subclinical pathological gambling, recreational gambling, and no gambling. Only definite and probable cases of pathological gambling and subclinical pathological gambling were included in the analyses.

Statistical Analysis

Social and clinical characteristics of probands and their first-degree relatives were compared using the χ^2 test (or Fisher exact test) for categorical variables and the Mann-Whitney test for dimensional variables. Statistical tests were 2-tailed, with $\alpha = .05$.

Pathological gambling and control probands were compared on lifetime psychiatric disorders. The χ^2 test (or Fisher exact test) was used to test for significant group differences. Comparisons were also made for first-degree relatives. These comparisons did not account for within-family correlation or other covariates.

Logistic regression was used to compare pathological gambling and control first-degree relatives for probable/definite pathological gambling, definite pathological gambling, probable pathological gambling, probable/definite subclinical pathological gambling, definite subclinical pathological gambling, probable subclinical pathological gambling, and any gambling disorder. Generalized estimating equation (GEE) models were used to account for within-family correlation in outcomes.[34,35] The same GEE model was used to compare pathological gambling and control relatives for lifetime psychiatric disorders. For gambling and psychiatric outcomes, the relative's relationship to the proband, the proband's years of education, racial/ethnic minority status, and interview status and type were used as covariates. Relatives with unknown status for the phenotype of interest (pathological gambling, subclinical pathological gambling) were excluded from both a numerator and denominator. Half siblings (n = 81) were excluded because they are considered second-degree relatives.

The familial relationship between pathological gambling and comorbid psychiatric disorders was examined using logistic regression with GEE for correlated data.[36] First, we established which disorders occurred more frequently among the first-degree relatives of pathological gambling probands, indicating a common familial etiology. To determine possible independent transmission, the additional diagnosis of interest in the proband (eg, major depression) was included in the model. Comorbid disorders were examined independently and sequentially. Lastly, the presence of pathological gambling in first-degree relatives was included in the models to determine whether the comorbid disorder is transmitted independently of pathological gambling. Thus, for each comorbid disorder, 3 GEE models were run sequentially with the following predictors: (1) proband race/ethnicity and years of education, interview status, and relationship to the proband (the base model); (2) the base model and the proband's diagnosis for additional diagnosis of interest; and (3) the base model, the proband's diagnosis for the additional diagnosis of interest, and the relative's pathological gambling status (diagnosis of definite/probable pathological gambling).

The logistic regression GEE model was also used to test whether pathological gambling proband characteristics were associated with pathological gambling in relatives. We examined the following proband characteristics: age at pathological gambling onset (dimensional and categorical [< 40/≥ 40 years]), gambling severity (based on the SOGS and NODS), sex, race/ethnicity, years of education, childhood abuse, and "unhealthy" family functioning.[28]

RESULTS

The total sample included 1,261 individuals: 186 probands (95 pathological gambling probands, 91 control probands), 318 directly interviewed first-degree relatives (148 relatives of pathological gambling probands, 173 relatives of control probands), and 757 indirectly assessed

Table 1. Demographic Characteristics of Pathological Gambling and Control Probands and Their First-Degree Relatives

Characteristic	Pathological Gambling	Control	χ^2	*df*	*P* Value
Probands					
n	95	91			
Female, %	58	63	0.44	1	.509
Age, mean (SD), y	45.6 (12.8)	49.4 (16.0)	2.33[a]	1	.127
European-Caucasian, %	85	95	4.33	1	.038
Marital status, %					
Married	35	80	Fisher		< .001
Divorced/separated	36	8	exact		
Widowed	3	5	test		
Single	26	7			
Years of school, mean (SD)	14.1 (1.9)	15.2 (2.4)	7.37[a]	1	.007
First-degree relatives					
n	537	538			
Interview status, n (%)					
Interviewed	148 (28)	173 (32)	5.01	2	.082
Refused, not located	292 (54)	256 (48)			
Deceased	97 (18)	109 (20)			
Interview type, n (%)					
In-person	38 (26)	25 (14)	6.37	1	.012
Telephone	110 (74)	148 (86)			
Relationship to proband, n (%)					
Parent	180 (34)	172 (32)	3.97	2	.137
Sibling	254 (47)	236 (44)			
Offspring	103 (19)	130 (24)			
Female, n (%)	266 (50)	264 (49)	0.02	1	.879
Age, mean (SD), y[b]	49.4 (18.7)	48.0 (16.7)	0.29[a]	1	.593
European-Caucasian, n/n (%)	135/148 (91)	161/173 (93)	2.83	1	.093
Years of school, mean (SD)[c]	13.6 (2.2)	14.6 (2.6)	9.79[a]	1	.002

[a]Mann-Whitney test.
[b]Interviewed pathological gambling relatives, n = 148; interviewed control relatives, n = 168.
[c]Interviewed pathological gambling relatives, n = 147; interviewed control relatives, n = 167.

Table 2. Lifetime Prevalence of *DSM-IV* Disorders in Probands

Disorder	Proband Diagnosis: Pathological Gambling (n = 95), n (%)	Proband Diagnosis: Control (n = 91), n (%)	χ^2	*df*	*P* Value
Mood disorders					
Major depression	58 (61)	26 (29)	19.80	1	< .001
Dysthymia	3 (3)	0 (0)	FET		.246
Bipolar disorder	9 (9)	0 (0)	FET		.003
Other mood disorder	0 (0)	1 (1)	FET		.489
Any mood disorder	68 (72)	27 (30)	32.67	1	< .001
Substance use disorders					
Alcohol use disorders	57 (60)	23 (25)	22.87	1	< .001
Drug use disorders	31 (33)	11 (12)	11.22	1	.001
Any substance use disorder	65 (68)	25 (27)	31.21	1	< .001
Anxiety disorders					
Panic disorder	17 (18)	2 (2)	12.49	1	< .001
Agoraphobia	11 (12)	2 (2)	6.29	1	.012
Social anxiety disorder	11 (12)	3 (3)	4.58	1	.032
Specific phobia	6 (6)	7 (8)	0.14	1	.713
PTSD	10 (11)	5 (5)	1.59	1	.208
GAD	13 (14)	4 (4)	4.83	1	.028
OCD	12 (13)	3 (3)	5.46	1	.019
Any anxiety disorder	48 (51)	21 (23)	15.01	1	< .001
Eating disorders	13 (14)	0 (0)	13.39	1	< .001
Somatoform disorders	5 (5)	1 (1)	FET		.212
Antisocial PD	14 (15)	0 (0)	11.66	1	< .001

Abbreviations: FET = Fisher exact test, GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PD = personality disorder, PTSD = posttraumatic stress disorder.

Table 3. Lifetime Prevalence of Gambling Disorders in First-Degree Relatives

Disorder	Proband Diagnosis: Pathological Gambling (n = 537), n (%)	Proband Diagnosis: Control (n = 538), n (%)	OR (95% CI)[a]	*P* Value[a]
Pathological gambling (definite/probable)	58 (11.0)	7 (1.0)	8.19 (3.37–19.91)	< .001
Pathological gambling (definite)	43 (8.0)	5 (1.0)	8.91 (3.03–26.21)	< .001
Pathological gambling (probable)	15 (3.0)	2 (0.4)	6.73 (1.36–33.29)	.019
Subclinical pathological gambling (definite/probable)	30 (6.0)	7 (1.0)	4.55 (1.97–10.54)	< .001
Subclinical pathological gambling (definite)	24 (4.0)	6 (1.0)	4.24 (1.68–10.73)	.002
Subclinical pathological gambling (probable)	6 (1.0)	1 (0.2)	5.74 (0.77–42.77)	.088
Any gambling disorder	88 (16.0)	14 (3.0)	6.57 (3.34–12.93)	< .001

[a]Based on generalized estimating equations (GEE) model.

relatives (389 relatives of pathological gambling probands, 365 relatives of control probands).

Table 1 presents a comparison of pathological gambling and control probands and their respective first-degree relatives. Proband age at pathological gambling onset ranged from 8 to 67 years, with a mean (SD) of 34.1 (13.1) years. Fifty-six percent of the probands had an onset by age 39 years, and 85% by age 49 years. Mean and median age at pathological gambling onset was earlier in men (mean = 28.0, median = 25) than in women (mean = 38.9, median = 40) ($P < .001$). Among pathological gambling relatives diagnosed with some form of pathological gambling, age at onset was positively correlated with proband age at onset ($r = 0.29$, $P < .05$).

Distribution of type of relative (parent, sibling, offspring) was similar for the 2 groups (Table 1). Siblings comprised the largest share of relatives, followed by parents and offspring. The groups were similar in terms of sex, age, marital status, and having more than 1 child. Both pathological gambling and control relatives were evenly split by gender, and most relatives were of European-Caucasian ancestry. Pathological gambling relatives were less likely to be employed in the last year, but more likely to be retired or disabled. Control relatives had more years of education than pathological gambling relatives. The groups were similar in terms of interview status, but interviewed pathological gambling relatives were more likely to have an in-person interview.

Pathological gambling probands were more likely than control probands to have a co-occurring psychiatric disorder (Table 2). Mood disorders, substance use disorders, and anxiety disorders were more frequent in pathological gambling probands. Significant differences were also observed for eating disorders and antisocial personality disorder.

Prevalence of Gambling Disorders Among First-Degree Relatives

First-degree relatives of pathological gambling probands met criteria for pathological gambling–related phenotypes significantly more often than control relatives (Table 3). In general, using more stringent criteria for affected status (ie, definite) resulted in larger ORs. The prevalence of definite pathological gambling was substantially higher in pathological gambling than in control relatives, and the odds were more than 8 times greater. The prevalence of definite/probable pathological gambling was also higher in pathological gambling relatives. In addition, significant ORs were found for other definitions of the affected phenotype, including probable pathological gambling, definite/probable subclinical pathological gambling, definite subclinical pathological gambling, and any form of disordered gambling (definite/probable pathological gambling or subclinical pathological gambling).

Table 4. Lifetime Prevalence of *DSM-IV* Disorders in First-Degree Relatives

Disorder	Proband Diagnosis: Pathological Gambling (n = 537), n (%)	Proband Diagnosis: Control (n = 538), n (%)	χ^2	*df*	*P* Value
Mood disorders					
Major depression	133 (25)	95 (18)	8.13	1	.004
Dysthymia	1 (0)	2 (0)	FET		1.000
Bipolar disorder	14 (3)	4 (1)	5.67	1	.017
Other mood disorder	7 (1)	8 (1)	0.07	1	.798
Any mood disorder	154 (29)	107 (20)	11.29	1	.001
Substance use disorders					
Alcohol disorder	159 (30)	123 (23)	6.32	1	.012
Drug disorder	70 (13)	41 (8)	8.51	1	.004
Any substance use disorder	188 (35)	135 (25)	12.57	1	< .001
Psychotic disorders	2 (0)	2 (0)	FET		1.000
Anxiety disorders					
Panic disorder	38 (7)	26 (5)	2.42	1	.120
Agoraphobia	9 (2)	9 (2)	0.00	1	.997
Social anxiety disorder	17 (3)	5 (1)	6.71	1	.010
Specific phobia	29 (5)	26 (5)	0.18	1	.673
PTSD	23 (4)	12 (2)	3.59	1	.058
GAD	21 (4)	15 (3)	1.05	1	.306
OCD	27 (5)	21 (4)	0.80	1	.372
Any anxiety disorder	104 (19)	83 (15)	2.90	1	.088
Eating disorders	12 (2)	11 (2)	0.05	1	.830
Somatoform disorders	4 (1)	0 (0)	FET		.062
Antisocial PD	33 (6)	8 (1)	15.90	1	< .001

Abbreviations: FET = Fisher exact test, GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PD = personality disorder, PTSD = posttraumatic stress disorder.

Prevalence of Co-Occurring Psychiatric Disorders in First-Degree Relatives

Pathological gambling relatives had significantly higher rates than control relatives for major depression, bipolar disorder, alcohol use disorders, drug use disorders, social anxiety disorder, and antisocial personality disorder (Table 4). Table 5 shows the ORs with 95% CIs for comorbid disorders that

Table 5. Odds Ratios and 95% CIs[a] of Lifetime *DSM-IV* Disorders in First-Degree Relatives of Pathological Gambling Probands Compared With Control Probands

Disorder	Base Model	Adjusted for Proband Diagnosis	Adjusted for Proband Diagnosis and Pathological Gambling
Major depression	1.49 (1.03–2.17)*	1.25 (0.88–1.79)	1.23 (0.85–1.77)
Bipolar disorder	3.82 (1.18–12.40)*	3.67 (1.11–12.17)*	3.16 (0.97–10.30)
Any mood disorder	1.59 (1.11–2.27)*	1.24 (0.88–1.76)	1.19 (0.82–1.72)
Alcohol disorder	1.32 (0.91–1.91)	1.17 (0.78–1.75)	1.05 (0.70–1.55)
Drug disorder	1.64 (0.93–2.88)	1.47 (0.83–2.60)	1.42 (0.81–2.51)
Any substance use disorder	1.47 (1.02–2.10)*	1.25 (0.83–1.88)	1.12 (0.75–1.66)
Social anxiety disorder	4.76 (1.79–12.64)**	4.67 (1. 71–12.71)**	4.15 (1.52–11.32)**
Posttraumatic stress disorder	2.59 (1.11–6.03)*	2.77 (1.20–6.37)*	2.85 (1.21–6.72)*
Antisocial personality disorder	3.72 (1.64–8.42)***	3.50 (1.53–8.02)**	3.12 (1.35–7.21)**

[a]Based on generalized estimating equations (GEE) model.
*P < .05. **P < .01. ***P < .001.

occurred more frequently in pathological gambling than control relatives. Results are presented sequentially to show how proband diagnosis for each disorder and pathological gambling affect the group comparison (pathological gambling vs control relatives). With the base model, ORs are significant for all conditions except alcohol and drug use disorders. The second series of models adjusts for the presence of the comorbid disorder of interest in the proband to control for the potential that disorders are transmitted independently from pathological gambling. In this model, bipolar disorder, social anxiety disorder, PTSD, and antisocial personality disorder are significantly more frequent in pathological gambling relatives. The third series of models also controls for the presence of pathological gambling in relatives to determine whether the disorders cosegregate with pathological gambling. Social anxiety disorder, PTSD, and antisocial personality disorder are significantly more frequent in pathological gambling relatives *independent* of the presence of pathological gambling.

Prevalence of Pathological Gambling in Case Relatives by Proband Characteristics

We examined whether proband characteristics predicted definite/probable pathological gambling in first-degree relatives of pathological gambling probands. Age at onset in pathological gambling probands (< 40 years/≥ 40 years) was not associated with definite/probable pathological gambling in their first-degree relatives (OR = 1.03, P = .927). Similarly, per-year increase in proband age at onset was not associated to risk for definite/probably pathological gambling in their first-degree relatives (OR = 1.00 per 1-year increase, P = .975). Relatives of male probands with pathological gambling were *less* likely to develop pathological gambling (OR = 0.38, P < .01) than relatives of female probands. Gambling severity in pathological gambling probands was predictive of pathological gambling in relatives when the NODS was used (OR = 1.08 per 1 point score increase, P < .05), but not when the SOGS was used (P = .063). Childhood emotional abuse (OR = 2.16) and neglect (OR = 2.22) in pathological gambling probands were significantly associated with pathological gambling in relatives. "Unhealthy" behavior control was associated with pathological gambling in relatives (OR = 1.97, P < .05).

DISCUSSION

The study confirms our hypothesis that pathological gambling is familial. Along with published twin data,[15–17] the data suggest that pathological gambling may have a hereditary basis. Pathological gambling relatives had greater than an 8-fold higher lifetime prevalence of definite/probable pathological gambling than control relatives. This finding is more robust for a definite (ie, meeting all *DSM-IV* criteria) than a probable pathological gambling diagnosis, but it is also significant for those with subclinical pathological gambling. The rate of pathological gambling in control relatives approximates the rate reported in the general population and provides perspective by comparing differences in rates between pathological gambling and control relatives.[2,3] All forms of disordered gambling are more frequent among pathological gambling than control relatives, a finding that suggests the phenotype extends beyond pathological gambling and includes subclinical forms.[16,37]

The pathological gambling probands had high divorce rates, a variable that may serve as a proxy for family dysfunction.[28,38] Comorbid psychiatric disorders were frequent as well, occurring in patterns consistent with the literature showing an excess of mood, anxiety, substance use, and personality disorders.[2–4,39–41] The men had a younger age at pathological gambling onset, a finding consistent with earlier work showing women to have a truncated course.[4,42] Despite these differences, familiality was *unrelated* to age at onset, a finding contrary to expectation because younger age at onset is often associated with familial loading (eg, schizophrenia, bipolar disorder, obsessive-compulsive disorder).[43–45] Nonetheless, we found a positive association between age at onset for pathological gambling in probands and pathological gambling in their first-degree relatives, suggesting that *within* families, disordered gambling develops at a similar time in life, perhaps because either it is under genetic control or it reflects an offspring's interest in gambling behavior modeled by a parent.

Major depression, bipolar disorder, any mood disorder, any substance use disorder, PTSD, social anxiety disorder, and antisocial personality disorder occurred more frequently

in the pathological gambling relatives. In contrast, PTSD, social anxiety disorder, and antisocial personality disorder occurred among pathological gambling relatives regardless of the presence of pathological gambling. These data suggest that mood and substance use disorders may develop as a *consequence* of pathological gambling (eg, gambling losses inducing depression), but PTSD, social anxiety disorder, and antisocial personality disorder may share a common familial etiology with pathological gambling. This underlying diathesis could be genetic and biologically based (eg, shared neurocircuitry),[46,47] but nongenetic causes cannot be ruled out (eg, childhood adversity).

For many years, pathological gambling was considered by some experts to fall within an obsessive-compulsive spectrum.[48,49] We found little evidence supporting a familial link with obsessive-compulsive disorder. On the other hand, the results partially support the notion that pathological gambling is related to substance use disorders, an idea that gained support during discussions on the *DSM-5* revision.[50]

Pathological gambling familiality appears related to female gender in this study. Some investigators have suggested that pathological gambling in women may not be genetically transmitted,[12,19] but Slutske et al[37] showed that the genetic influences for "disordered gambling" in women are just as important as for men. Further, environmental factors associated with familiality included childhood adversity and "unhealthy" behavioral control reported by the proband and occurring within the family context. Both childhood adversity and disturbed family dynamics have been linked to the development of several psychiatric disorders, including major depression, PTSD, antisocial personality disorder, and borderline personality disorder.[51–53] Similar processes may be at play in the development of pathological gambling in vulnerable persons.

The results argue for molecular studies that aim to identify a genetic etiology for pathological gambling. Early candidate gene association studies have focused on dopamine receptor and transporter genes thought to be involved in the brain's reward mechanisms, with at least 1 positive finding reported for *DRD1*, *DRD2*, and *DRD4*.[54] Genome-wide studies are needed to target genes implicated in pathological gambling and to investigate gene-gene and gene-environment interactions.

Limitations

First, pathological gambling probands were recruited because they had received psychiatric or gambling-related treatment services, responded to an ad, were on a study registry, or learned of the study through word-of-mouth. A community sample would have been preferred, but was not feasible. Second, probands were adults, and older age may have reduced the estimate of familial risk, given that research suggests rates of pathological gambling may be *higher* in youth.[55,56] Third, the low participation rate of minority subjects may reduce the generalizability of our findings to these populations. Fourth, control probands may have agreed to participate based on personal concerns about emotional illness. To minimize potential bias, control probands were identified through a stringent sampling method using random digit dialing within the community in which the pathological gambling probands resided (eastern Iowa), matching on important characteristics. Fifth, not all interviews were direct and in person. While probands were assessed in person, most relatives (80%) were interviewed by telephone, and it is possible that some disorders were missed, although research shows that telephone and in-person interviews are comparable.[57,58] Sixth, we made every effort to keep raters blind to a subject's family status (pathological gambling vs control) and subjects blind to study objectives. If the blind was broken by the rater regarding study objectives or by the subject with regard to family status, this unblinding did not occur in a systematic fashion. Last, some relatives could not be directly interviewed due to death or other reasons. In these cases, assessment was based on information provided by the proband and ≥ 1 relative in 84% of cases.

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