Shared Genetic Contributions to Pathological Gambling and Major Depression in Men

Marc N. Potenza, MD, PhD; Hong Xian, PhD; Kamini Shah, MHS; Jeffrey F. Scherrer, PhD; Seth A. Eisen, MD

Context: Although pathological gambling (PG) and major depression (MD) frequently co-occur, little is known regarding the relative contributions of environmental and genetic factors to the codevelopment of the disorders.

Objectives: To estimate environmental and genetic contributions to PG and MD as defined in DSM-III-R and the lifetime co-occurrence of PG and MD.

Design: Survey data from the Vietnam Era Twin Registry were examined in biometric models.

Setting: Telephone interview.

Participants: Of 10,253 eligible participants, 7,869 were successfully interviewed.

Main Outcome Measures: Estimated genetic, shared environmental, and unique environmental contributions to PG and MD and their lifetime co-occurrence in bivariate models.

Results: Elevated odds ratios for MD were associated with those of PG (4.06; 95% confidence interval, 2.68-6.13), and the association remained significant following adjustment for sociodemographic and other psychiatric variables (odds ratio = 1.98; 95% confidence interval, 1.14-3.45). The best-fitting bivariate model indicated that 66% of the variance in PG and 41% of the variance in MD were owing to genetic factors, and 34% of the variance in PG and 59% of the variance in MD were owing to unique environmental factors. There was a substantial correlation between the genetic components of PG and MD (r = 0.58), with 34% of the genetic variance for each disorder also contributing to that of the other. The best-fitting model estimated that 100% of the total overlap between PG and MD was genetic.

Conclusions: The correlation between PG and MD in middle-aged men appears to be largely influenced by overlapping genetic factors. Future research is needed to determine the extent to which these findings extend to other groups (eg, women), identify specific genes, and generate improved prevention and treatment strategies.

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A recent examination investigating environmental and genetic contributions to common mental health disorders categorized 7 psychiatric syndromes into 3 internalizing and 4 externalizing disorders. Within this model, 1 genetic factor loading strongly onto externalizing disorders was weakly associated with MD, and a second genetic factor strongly associated with MD and other internalizing disorders was weakly associated with externalizing disorders. Similarly, a unique environmental factor contributing most strongly to MD also contributed less strongly to externalizing disorders, particularly to alcohol dependence. No shared environmental factor loaded onto MD in the same model. Given the close relationship between alcohol dependence and MD, as well as between alcohol dependence and PG, the question was raised whether a similar pattern of genetic and environmental contributions exists between MD and PG as between MD and externalizing disorders.

We used data from the VET Registry to investigate the following hypotheses. First, lifetime PG and MD frequently co-occur. Second, PG and MD correlate more substantially within monozygotic twins as compared with dizygotic twins. Third, genetic and unique environmental factors, but not shared environmental factors, contribute to the risk for PG and MD. Fourth, the factors contributing to the risk for PG correlate with those contributing to the risk for MD.

METHODS

PARTICIPANTS

All of the participants were members of the VET Registry, a national sample of male twins, both of whom served during the Vietnam era (1965-1975) and were born between 1939 and 1957, inclusively. A detailed description of the VET Registry development and participants has been described. Of 10,253 eligible participants, 7,869 (76.7%) of known zygosity (1,125 single twins and 3,372 twin pairs) were successfully interviewed in 1992 for the present study. Of the twin pairs, 1,874 were monozygotic and 1,498 were dizygotic as determined by responses and supplemental blood typing. Of the subjects, and lifetime criteria for MD were met by 755 (9.6%) of the subjects. High rates of lifetime co-occurrence were observed between PG and MD. In individuals with PG as compared with those without PG, the unadjusted OR for MD was 4.06 (95% CI, 2.68-6.13). In a logistic regression model adjusting for sociodemographic measures, the OR for MD was 4.13 (95% CI, 2.63-6.50). After adjusting for sociodemographic and externalizing variables (alcohol

HYPOTHESIS TESTING: ANALYSES EXAMINING THE RELATIONSHIP BETWEEN PG AND MD

To examine the hypothesis that lifetime PG and MD frequently co-occur, odds ratios (ORs) for MD in subjects with PG were determined. Because twin pair data are not statistically independent observations, Stata software (Stata Corp, College Station, Tex) was used to compute Huber-White robust variance estimates to obtain 95% confidence intervals (CIs) for parameter estimates. Unadjusted ORs and ORs adjusted for sociodemographics (age, income, and education) and non-PG, non-MD psychiatric disorders (DSM-III-R externalizing disorders [alcohol abuse/dependence, nicotine dependence, drug abuse/dependence, and antisocial personality disorder] and internalizing disorders [posttraumatic stress disorder, panic disorder, and generalized anxiety disorder] were examined by logistic regression analysis. A similar approach was used to determine the ORs for PG in subjects with MD.

To examine the hypothesis that PG and MD correlate more substantially within monozygotic twins than in dizygotic twins, tetrachoric correlations were examined using PRELIS, as described previously.

To examine the hypotheses that genetic and unique environmental factors, but not shared environmental factors, contribute to the lifetime co-occurrence of PG and MD and that these factors correlate across disorders, bivariate models fitting the association between PG and MD were examined as described elsewhere. The variation in liability for each of the 2 diagnoses (PG and MD) was decomposed into that caused by additive genetic influences (A), shared environmental influences (C), and unique environmental influences plus measurement error (E) (Figure). The correlation between the 2 diagnoses was similarly partitioned into components resulting from additive genetic influences, shared environmental influences, and unique environmental influences plus measurement error (Figure). Using Mx software (Virginia Commonwealth University, Richmond), models were fit by the method of maximum likelihood. A series of nested submodels were each tested for their goodness of fit against a saturated model that placed no constraints on the elements of the estimated monozygotic and dizygotic twin correlation matrices. The most parsimonious model was selected as best fitting. The 95% CIs around parameter estimates for this model were examined to evaluate whether the genetic, shared environmental, or unique environmental contributions to PG and MD differed significantly from 0 and 1.

RESULTS

Lifetime criteria for PG were met by 112 (1.4%) of the subjects, and lifetime criteria for MD were met by 755 (9.6%) of the subjects. High rates of lifetime co-occurrence were observed between PG and MD. In individuals with PG as compared with those without PG, the unadjusted OR for MD was 4.06 (95% CI, 2.68-6.13). In a logistic regression model adjusting for sociodemographic measures, the OR for MD was 4.13 (95% CI, 2.63-6.50). After adjusting for sociodemographic and externalizing variables (alcohol

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tributions to PG and MD. Genotypic twins (Table 2), suggesting overlapping genetic con-
gneral environmental contributions to the individual disorders suggest that there are significant
genetic and unique environmental contributions to each disorder (Figure). Unique environmental factors
to PG, approximately one third (22%; 95% CI, 8%-47%) was shared with MD and two thirds (44%; 95% CI, 19%-67%) was not. Of the 41% genetic variance contributing to MD, approximately one third (14%; 95% CI, 5%-30%) was shared with PG and two thirds (27%; 95% CI, 12%-43%) was not. In other words, 34% of the genetic variance for each disorder also contributed to that for the other. All of the overlap between PG and MD was accounted for by genetic factors.

CO-OCCURRENCE OF PG AND MD

Our hypothesis regarding the observation of high rates of lifetime co-occurrence between PG and MD was supported. The ORs for MD in association with PG when adjusting for sociodemographic measures alone (OR=4.13) or in conjunction with externalizing and internalizing psychiatric disorders (OR=1.98) remained significantly elevated. These ORs are comparable to that of 3.3 observed for MD in association with problem gambling in data from the St Louis site of the Epidemiologic Catchment Area (ECA) study.20 These similarities are observed despite differences between the 2 studies, including varying thresholds of gambling severity (problem gambling vs PG), eras of data acquisition (ECA data were collected in 1981 and VET data in 1992), and subject characteristics. Using a problem gambling threshold similar to that used in the ECA study reduced the unadjusted OR for MD from 4.06 to 2.49, indicating a weaker association between MD and subsyndromal gambling. The VET sample largely comprises white, highly educated, middle-aged, male twins with military service whereas ECA participants were oversampled for African Americans and included approximately equal numbers of men and women from the St Louis community. Together, these data suggest that the high rates of lifetime co-occurrence for PG and 59% (95% CI, 49%-69%) of the variance for MD. Genetic factors accounted for 66% (95% CI, 47%-80%) of the variance for PG and 41% (95% CI, 30%-51%) of that for MD. Of the 66% genetic variance contributing to PG, approximately one third (22%; 95% CI, 8%-47%) was shared with MD and two thirds (44%; 95% CI, 19%-67%) was not. The ORs for MD in association with PG when adjusting for multiple externalizing and internalizing disorders (Table 1). The unadjusted OR for PG in subjects with MD was elevated (OR=4.12; 95% CI, 2.62-6.49) and remained elevated following adjustment for sociodemographic measures alone (OR=4.12; 95% CI, 2.62-6.49) or with the psychiatric variables listed in Table 1 (OR=2.03; 95% CI, 1.19-3.47).

Tetrachoric correlations (Table 2) demonstrated greater within-diagnosis concordance for both PG and MD in monozygotic twins as compared with that in dizygotic twins. Within-twin, cross-diagnosis correlations were comparable for monozygotic and dizygotic twins, and cross-twin, cross-diagnosis correlations were more substantial in monozygotic twins than in dizygotic twins (Table 2), suggesting overlapping genetic contributions to PG and MD.

The best-fitting bivariate model (Table 3) for the relationship between PG and MD had the correlations for shared and unique environmental factors (r_c and r_e, respectively) set to 0 and estimated the correlation for additive genetic factors (r_a) at 0.38 (95% CI, 0.40-0.77). Parameter estimates for the additive genetic, shared environmental, and unique environmental contributions to the individual disorders suggest that there are significant genetic and unique environmental contributions to each disorder (Figure). Unique environmental factors accounted for 34% (95% CI, 20%-53%) of the variance for PG and 59% (95% CI, 49%-69%) of the variance for MD. Genetic factors accounted for 66% (95% CI, 47%-80%) of the variance for PG and 41% (95% CI, 30%-51%) of that for MD. Of the 66% genetic variance contributing to PG, approximately one third (22%; 95% CI, 8%-47%) was shared with MD and two thirds (44%; 95% CI, 19%-67%) was not. Of the 41% genetic variance contributing to MD, approximately one third (14%; 95% CI, 5%-30%) was shared with PG and two thirds (27%; 95% CI, 12%-43%) was not. In other words, 34% of the genetic variance for each disorder also contributed to that for the other. All of the overlap between PG and MD was accounted for by genetic factors.

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Table 1. Logistic Regression Model Examining the Risk for Major Depression Associated With Pathological Gambling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>SE*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.36 (0.87-2.14)</td>
<td>0.31</td>
<td>.18</td>
</tr>
<tr>
<td>Income</td>
<td>0.76 (0.49-1.19)</td>
<td>0.17</td>
<td>.23</td>
</tr>
<tr>
<td>High school education</td>
<td>0.83 (0.36-1.89)</td>
<td>0.35</td>
<td>.66</td>
</tr>
<tr>
<td>College education</td>
<td>0.66 (0.29-1.48)</td>
<td>0.27</td>
<td>.32</td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>2.66 (1.52-4.66)</td>
<td>0.76</td>
<td>.001</td>
</tr>
<tr>
<td>Nicotine dependence</td>
<td>1.15 (0.69-1.92)</td>
<td>0.30</td>
<td>.58</td>
</tr>
<tr>
<td>Drug abuse/dependence</td>
<td>1.86 (1.04-3.31)</td>
<td>0.55</td>
<td>.04</td>
</tr>
<tr>
<td>Antisocial personality</td>
<td>2.50 (1.13-5.53)</td>
<td>1.01</td>
<td>.02</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>0.73 (0.39-1.39)</td>
<td>0.24</td>
<td>.34</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>1.23 (0.47-3.21)</td>
<td>0.60</td>
<td>.68</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>2.97 (1.34-6.55)</td>
<td>1.20</td>
<td>.007</td>
</tr>
<tr>
<td>Major depression</td>
<td>1.98 (1.14-3.45)</td>
<td>0.56</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*The standard errors are adjusted for clustering on case.
occurrence observed in the present study generalize beyond the cohort of VET participants. Unfortunately, other ECA sites and large national surveys of psychiatric disorders6 have generally not included gambling measures, contributing to a relative deficiency in our understanding of the relationship between PG and other psychiatric disorders.

The finding that, when controlling for other psychiatric disorders, the OR for MD in PG is reduced from 4.13 to 1.98 suggests that some of the risk for MD in individuals with PG is attributable to psychiatric disorders that frequently co-occur with PG. Among the disorders showing increased ORs in subjects with PG were alcohol abuse/dependence, drug abuse/dependence, antisocial personality disorder, panic disorder, and generalized anxiety disorder, findings largely consistent with those from population-based and clinical samples.1,20 Surprisingly, an elevated OR for nicotine dependence in association with PG was not observed, seemingly contrasting with findings from the St Louis ECA study20 and clinical samples.21 Specific features of the VET sample, such as those listed earlier or the sample's high prevalence of nicotine dependence,22 might contribute to this finding. The association in men between MD and externalizing disorders such as alcohol abuse/dependence appears to be mediated by influences of antisocial personality disorder,10 and internalizing disorders like MD and anxiety disorders cluster together in models of psychiatric disorders.7 Thus, it is not surprising that modeling measures of externalizing and internalizing disorders reduces the OR between MD and PG. The finding that the OR remains significantly elevated following adjustment for sociodemographic and other psychiatric measures suggests that a considerable portion of the risk for MD in association with PG is not accounted for by sociodemographics and commonly co-occurring psychiatric disorders.

**PG AND MD IN MONOZYGOTIC AND DIZYGOTIC TWINS**

Our hypothesis regarding higher rates of lifetime co-occurrence of PG and MD in monozygotic twins as compared with the rates in dizygotic twins appears to be partially supported. Higher rates of within-diagnosis concordance for both PG and MD within monozygotic vs dizygotic twins are consistent with prior reports from the VET data and heritable contributions to each disorder.3,4 The observations of largely similar within-twin, cross-disorder correlations for monozygotic and dizygotic twins and substantially larger cross-twin, cross-

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### Table 2. Tetrachoric Correlations Between Pathological Gambling and Major Depression in Monozygotic and Dizygotic Twins

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>PG Within-Diagnosis (SE)</th>
<th>MD Within-Diagnosis (SE)</th>
<th>PG MD Cross-Diagnosis (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MZ</strong></td>
<td>0.62 (0.10)</td>
<td>0.42 (0.06)</td>
<td>0.29 (0.10)</td>
</tr>
<tr>
<td><strong>DZ</strong></td>
<td>0.49 (0.16)</td>
<td>0.13 (0.07)</td>
<td>0.33 (0.10)</td>
</tr>
</tbody>
</table>

*Abbreviations: DZ, dizygotic; MD, major depression as defined in DSM-III-R; MZ, monozygotic; PG, pathological gambling disorder as defined in DSM-III-R.*

### Table 3. Bivariate Model-Fitting Results for Pathological Gambling and Major Depression

| Bivariate Model | Correlation | Genetic Shared Unique Fit of Model |
|-----------------|-------------|-----------------------------------|----------------------------------|
|                 | PG MD       | Correlation, $\rho_2$ | Environmental | Environmental | $-2 \log$ Likelihood | $-2 \log$ Likelihood | $\Delta$df | AIC |
| ACE ACE         | 0.46        | 0.05                  | 0.20          | 6 026.28       | NA                   | NA                  |
| ACE ACE         | 0.46        | 0.05                  | 0.20          | 6 026.28       | 10.95                | 1                   | 9.95 |
| ACE ACE         | 0.46        | 0.05                  | 0.20          | 6 026.28       | 0.00                 | 1                   | -2.00 |
| ACE ACE         | 0.46        | 0.05                  | 0.20          | 6 026.28       | 0.00                 | 1                   | -2.00 |
| ACE ACE         | 0.46        | 0.05                  | 0.20          | 6 026.28       | 1.63                 | 1                   | -0.37 |
| ACE ACE         | 0.46        | 0.05                  | 0.20          | 6 026.28       | 0.00                 | 3                   | -6.00 |
| ACE AE          | 0.46        | *                    | 0.20          | 6 026.28       | 0.00                 | 4                   | 2.95 |
| ACE AE          | 0.46        | *                    | 0.20          | 6 026.28       | 0.00                 | 4                   | 7.55 |
| ACE AE          | 0.46        | *                    | 0.20          | 6 026.28       | 0.00                 | 4                   | -6.37 |
| AE AE           | 0.46        | *                    | 0.20          | 6 026.28       | 0.00                 | 4                   | -2.00 |
| AE AE           | 0.46        | *                    | 0.20          | 6 026.28       | 0.00                 | 4                   | -2.00 |
| AE AE           | 0.46        | *                    | 0.20          | 6 026.28       | 1.63                 | 1                   | -0.37 |
| AE AE           | 0.46        | *                    | 0.20          | 6 026.28       | 0.00                 | 3                   | -6.00 |

*Abbreviations: A, additive genetic factors; C, shared environmental factors; E, unique environmental factors plus error; MD, major depression as defined in DSM-III-R; NA, not applicable; PG, pathological gambling as defined in DSM-III-R.*

*Correlation fixed to 0.
†Correlation fixed to 1.
‡Best-fitting model.
disorder correlations in monozygotic twins as compared with those in dizygotic twins are consistent with the possibility of significant genetic contributions to the lifetime co-occurrence of PG and MD.

**SHARED GENETIC CONTRIBUTIONS TO PG AND MD**

The most significant finding from the present study was the identification of substantial genetic overlap between PG and MD. The findings from the best-fitting bivariate model for PG and MD were consistent with our hypothesis that PG and MD would exhibit overlapping genetic influences but not shared environmental influences. Our hypothesis that the unique environmental factors for PG and MD would correlate was not supported by the best-fitting model. These findings suggest that the environmental factors influencing PG and MD differ.

A surprising finding was the magnitude of the genetic overlap between PG and MD. The genetic correlation between PG and MD ($r_g = 0.58$) is comparable to or larger than that observed between PG and AD ($r_g = 0.35$) and those between a multiple-threshold formulation of gambling and antisocial behaviors (correlation range, 0.40-0.47). Thus, the correlation between genetic factors for PG and MD is as substantial as or more substantial than any such correlation previously reported for PG and any other psychiatric disorder. The genetic correlation between PG and MD is as great as or greater than those reported for other disorders grouped together within the DSM-IV-TR, eg, those between different substance use disorders (correlation range, 0.26-0.54). Nonetheless, the finding that 34% of the genetic variance for each disorder also contributed to the other suggests that a substantial portion of the genetic liability for PG is not shared with MD and vice versa.

Our hypothesis regarding the relationship between environmental and genetic contributions to PG and MD were based on recent studies of internalizing and externalizing disorders and considerations regarding the categorization of PG within these groups. Internalizing disorders, associated with negative emotionality and including depressive and anxiety disorders, and externalizing disorders, associated with negative emotionality and a lack of constraint and including substance use disorders and antisocial behaviors, have clustered separately in factor analyses. Although PG has not formally been included in these models, PG shares a lack of constraint and features of impulsivity with externalizing disorders. Prior analyses of the VET data have identified genetic and environmental overlaps between PG and alcohol dependence as well as PG and antisocial behaviors, which is consistent with a categorization of PG as an externalizing disorder. Genetic and unique environmental contributions have previously been described to load relatively strongly within groups of externalizing and internalizing disorders and relatively weakly across the groups. As such, the genetic overlap presently observed between PG and MD is more substantial than hypothesized and raises questions regarding the nature of the relationship of PG to other internalizing disorders. Investigation of the structure of mental disorders has suggested reconsideration of classifications of other psychiatric disorders, eg, that posttraumatic stress disorder might be best considered a mood disorder rather than an anxiety disorder. Similar studies of PG are needed to guide its most appropriate categorization.

**IMPLICATIONS**

The finding of substantial genetic overlap between PG and MD has multiple research and clinical implications. First, more research is needed to identify specific genes involved in the pathophysiology of both MD and PG. Although candidate genes implicated in PG overlap with those implicated in MD, large-scale, genome-wide genetic investigations in PG have not yet been published to our knowledge and are needed. Gambling assessments should be included in genetic studies of MD and vice versa. Although many widely used diagnostic assessments, including the Structured Clinical Interview for DSM-IV, have not included PG measures, the recent availability of a Structured Clinical Interview for DSM-IV-compatible module for PG should minimize this concern.

Second, the existence of genetic overlap suggests that PG and MD share biological mechanisms that could include abnormalities in stress-response pathways, biogenic amine systems, or impulse control networks identified in preliminary studies of PG and implicated in MD. Third, the findings suggest that treatments effective for MD might be helpful for individuals with PG. As pharmacological trials involving subjects with PG have generally excluded individuals with co-occurring MD, it will be important to evaluate the clinical utility of specific treatments, both pharmacological and behavioral, in individuals with co-occurring MD. Fourth, overlapping genetic features between PG and MD suggest that identification of specific allelic variants might help to target treatments. For example, variants of the µ-opioid receptor gene predict naltrexone treatment outcome for alcohol dependence. Similar approaches might guide treatment selection in co-occurring PG and MD. Fifth, the findings raise questions regarding the categorization of PG. It is currently classified in DSM-IV-TR as an impulse control disorder, although categorizations as an addiction without the drug or a disorder lying along an obsessive-compulsive spectrum or mood continuum have also been described. Inclusion of PG measures in studies of the structure of mental health disorders could guide the most appropriate categorization of PG.

**LIMITATIONS**

The current study has multiple limitations. First, the VET Registry sample comprises middle-aged, male twins who are largely well educated and white. Thus, the findings might not generalize to other populations including adolescents, women, and other racial/ethnic groups. As the average age of the subjects was 42 years, late-life onset of PG or MD may be poorly represented. The absence of women seems particularly salient given their high rates of MD and sex-related differences in etiologies for depression and types/patterns of PG. Some observations suggest that the present findings might extend to
women. Specifically, the presence of multiple psychiatric disorders appears to increase the risk for MD largely similarly in women and men, and genetic and environmental contributions to externalizing and internalizing disorders are largely similar across sexes. However, these studies did not include gambling measures, and direct investigation is needed to assess the generalizability of the present findings. Sex-related differences in mood disorders and gambling disorders (eg, higher rates of the former in women and the latter in men) and the observation of sex-related differences in heritability of certain forms of gambling suggest a sex specificity and emphasize the need for additional investigation. Second, the sole availability of lifetime diagnoses precludes investigation of temporal co-occurrence of MD and PG. Third, as previously described, co-occurrence of multiple psychiatric disorders with PG confounds interpretation of the results. Fourth, the data were collected in 1992. The availability and social acceptance of legalized gambling have been increasing, thus limiting generalizability to the current gambling environment. Fifth, only subjects acknowledging having gambled 25 or more times within a year were queried regarding PG. Subjects with less frequent gambling might have met criteria for PG and been incorrectly classified, potentially altering the results. Sixth, DSM-III-R criteria were used to assess PG. Multiple changes have occurred in the diagnostic criteria, including the number of inclusionary criteria needed to fulfill PG (4 of 9 in DSM-III-R and 5 of 10 in DSM-IV-TR), and the specific criteria used. Perhaps most relevant to the present study, the current criterion of gambling “as a way of escaping from problems or of relieving a dysphoric mood (eg, feelings of helplessness, guilt, anxiety, depression)” was absent in the DSM-III-R criteria. This criterion is frequently endorsed among those with PG behavior, and further investigation is needed to determine the extent to which its inclusion might influence the current findings. Seventh, the bivariate models are based on assumptions (eg, the equal environment assumption) that might overestimate genetic contributions. Consequently, environmental contributions to PG and MD might be underestimated.

CONCLUSIONS

The finding of genetic overlap between PG and MD highlights the need for closer examination of PG in individuals with MD and vice versa. Future investigation is needed not only to identify specific genetic factors that PG and MD have in common, but also to translate these findings into advances in prevention and treatment of the disorders. The identification of specific genes could facilitate the development of improved treatments, such as those targeting specific gene products.

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Correspondence: Marc N. Potenza, MD, PhD, Connecticut Mental Health Center, 34 Park St, Room S-104, New Haven, CT 06519 (marc.potenza@yale.edu).

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