Clin Genet 2001: 60: 107–116
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CLINICAL GENETICS
ISSN 0009-9163

Original Article

The additive effect of neurotransmitter genes in pathological gambling

Comings DE, Gade-Andavolu R, Gonzalez N, Wu S, Muhleman D, Chen C, Koh P, Farwell K, Blake H, Dietz G, MacMurray JP, Lesieur HR, Rugle LJ, Rosenthal RJ. The additive effect of neurotransmitter genes in pathological gambling.
Clin Genet 2001: 60: 107–116. © Munksgaard, 2001

As access to gambling increases there is a corresponding increase in the frequency of addiction to gambling, known as pathological gambling. Studies have shown that a number of different neurotransmitters are affected in pathological gamblers and that genetic factors play a role. Polymorphisms at 31 different genes involved in dopamine, serotonin, norepinephrine, GABA and neurotransmitters were genotyped in 139 pathological gamblers and 139 age, race, and sex-matched controls. Multivariate regression analysis was used with the presence or absence of pathological gambling as the dependent variable, and the 31 coded genes as the independent variables. Fifteen genes were included in the regression equation. The most significant were the *DRD2*, *DRD4*, *DAT1*, *TPH*, *ADRA2C*, *NMDA1*, and *PS1* genes. The r^2 or fraction of the variance was less than 0.02 for most genes. Dopamine, serotonin, and norepinephrine genes contributed approximately equally to the risk for pathological gambling. These results indicate that genes influencing a range of brain functions play an additive role as risk factors for pathological gambling. Multi-gene profiles in specific individuals may be of assistance in choosing the appropriate treatment.

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Key words: behavior – dopamine – gambling – multifactorial – norepinephrine – polygenic – psychiatric – serotonin

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Received 22 March 2001, revised and accepted for publication 24 April 2001

Some form of gambling is now legal in all but two of the United States, and gambling on the Internet is available to anyone with a computer regardless of the local laws. Unfortunately, not everyone who participates in gambling can take it or leave it. Some become addicted. As access to gambling by adolescents and adults increases, the number that will become addicted will also increase. Such an addiction is termed pathological gambling. There are many similarities between alcohol and drug addiction and pathological gambling, including the development of a euphoric state (a 'high'), cravings (a need for more), tolerance (increasingly larger bets or greater risks needed to produce a desired level of excitement), and withdrawal-like symptoms (1–9). There is a typical course or progression through four stages (winning, losing, desperation, and hopelessness) (7). The DSM-IV criteria for pathological gambling draw heavily upon the substance abuse model and includes a preoccupation with gambling, needing to gamble increasing amounts of money, inability to cut back, withdrawal symptoms, and a significant effect on one's life through loss of occupation, personal relationships and resorting to illegal acts to obtain money for gambling (10).

Pathological gambling is estimated to be present in 0.1–2.7% of the adult population (11). It has increased in frequency in recent years (12). Associated disorders include depression, cyclothymia, and bipolar disorder (13–16), alcohol, tobacco, and other drug abuse/dependence (17, 3, 18, 19); attention deficit hyperactivity (20–22), obsessive-compulsive (23), antisocial (24) and narcissistic,

borderline personality (25, 26) disorders. In an epidemiologic study using a structured psychiatric interview, Chunningham-Williams et al. (27) found that the strongest association was with antisocial personality disorder and substance abuse disorder.

Twin studies (28, 29) indicate that genetic factors play a role in pathological gambling. Several specific genes have been implicated as risk factors including the dopamine D_2 (*DRD2*) (30), dopamine D_1 (*DRD1*) (31) and dopamine D_4 (*DRD4*) receptor genes (32, 33), tryptophan 2,3-dioxygenase (34), and the monoamine oxidase A gene (35). In addition, defects in a number of neurotransmitters have been implicated including dopamine (36), norepinephrine (36), serotonin (37), and endorphins (38). These findings suggest that as with most other behavioral disorders, pathological gambling is a multifactorial, polygenic disorder.

The identification of the genes involved in pathological gambling could demonstrate that pathological gambling has biological underpinnings, help to identify those individuals who were are at greatest risk for this disorder, identify new modes of treatment, and identify those treatments that would be most effective for a given individual. To identify some of the genes involved we have utilized a procedure called the multivariate analysis of associations (MAA) technique (39–41). This approach is based on the assumption that the best way to identify the genes involved in disorders that are due to the additive effect of multiple genes is to examine the additive effect of multiple candidate genes.

Methods

Patients

The pathological gamblers were identified and entered into the study by Drs Richard Rosenthal, Henry Lesieur, and Loreen Rugle. All subjects fulfilled the DSM-IV (1994) criteria for pathological gambling and all were non-Hispanic Caucasians. They came from inpatient and outpatient gambling treatment programs, from Gamblers Anonymous, and from attendees at national conferences on compulsive gambling. Drs Rosenthal, Lesieur or Rugle have personally interviewed each of them to ensure the correct diagnosis. Those who agreed to participate were asked to: a) sign an informed consent form; b) fill out the Gambling Questionnaire developed by Lesieur and Rosenthal in their field testing of the DSM-IV criteria for pathological gambling; c) fill out a questionnaire based on the Diagnostic Interview Schedule (DIS) (42, 43) that covered each of the DSM-III-R criteria for pathological gambling; d) contribute a sample of blood for genetic studies. The blood was sent to the Department of Medical Genetics at the City of Hope National Medical Center for genetic analysis. The study was approved by the City of Hope IRB. The details concerning the subjects and the questionnaires are covered elsewhere (30).

Controls

The non-Hispanic Caucasian controls of Western European ancestry came from several sources including unrelated (adopting, step or foster parents) of children with disorders such as ADHD or Tourette syndrome, older college students from the California State University at San Bernardino and staff members from Loma Linda University. All completed one or more of the above instruments to assess the presence of substance abuse or gambling problems and only those without any of these behaviors were utilized. All signed the informed consent form.

Multivariate analysis of associations

This technique involves a series of nine steps. First, a phenotype to be studied is chosen, in this case pathological gambling.

Second, DNA samples and clinical data are obtained from a series of subjects with the phenotype and a series of controls without the phenotype.

Third, the severity of the phenotype is assessed either by a linear or a dichotomous score. In the present case a dichotomous score was used, where controls = 0 and pathological gamblers = 1.

Fourth, a series of candidate genes each associated with single nucleotide polymorphism (SNP) or a short tandem repeat polymorphism (STRP) is chosen. The genotypes are divided into three groups. For SNPs they are simply the 11, 12, and 22 genotypes. For STRPs the alleles are arbitrarily divided into two maximally equal groups by length, short (S) and long (L) to form the three genotypes SS, SL, and LL. Prior studies on many STRPs have shown the utility of this approach, based on evidence that the varying lengths of repeats play a role in causing changes in gene function (44, 45). This approach is also statistically robust since even if there are dozens of alleles, the degrees of freedom remain at 1. The selection of the candidate genes to be studied is based on hypotheses concerning the causes of the phenotype. In this case we chose 31 genes associated with dopamine, serotonin, norepinephrine, GABA, and other types of metabolism, and related factors were the candidate genes.

Fifth, in each individual, each gene is assigned an optimized gene code, 0, 1, or 2 (39). These gene codes identify the type of inheritance as dominant, codominant, recessive, or heterotic. They are based on results of analysis to determine which of the three genotypes are associated with the highest, intermediate, or lowest phenotype score. These are termed optimized scores since the coding is performed on the same set of subjects as the multivariate analysis.

Sixth, the phenotype score (controls = 0, pathological gamblers = 1) is used as the dependent variable and the gene scores as the independent variables in a multivariate or logistic regression analysis using backward elimination of the independent variables. p_{in} is set at 0.1 and p_{out} at 0.2. This is based on prior experience with the MAA technique (39–41). If the p_{out} is set at higher values the contributions of the included genes become smaller and smaller to the point that virtually all the genes are included. If the p_{in} is set too low, only a few of the most significant genes are included and the intermediate genes that still contribute to the summed variance are excluded. For each of the included genes, this produces r, or the correlation coefficient between the individual gene and the phenotype variable, and r^2, the fraction of the variance that the gene contributes to the phenotype. The use of optimized gene scores allows the comparison of the relative effect of the r^2 for each included gene on the phenotype.

Seventh, the individual r^2 values are added for each functionally related group of genes. Polygenic disorders are characterized by considerable genetic heterogeneity (different sets of genes utilized in different individuals or different studies) and by a small effect size (r^2) for each gene. Thus, one of the characteristics of polygenic disorders when individual genes are examined one at a time is that the results may be positive in one study and negative in another. Since different genes within a functional set of genes, such as dopamine genes or serotonin genes, may tend to have a similar effect on the phenotype, the relative total r^2 per functional group may be more reproducible than studies of individual genes (39–41).

Eighth, the results for the individual genes are plotted with the genes on the abscissa and r^2 the ordinate (Fig. 1).

Ninth, the results of the total r^2 for functionally related groups of genes are also plotted with the gene groups on the abscissa and summed r^2 the ordinate (Fig. 2).

The advantages of this approach to the study of polygenic disorders have been discussed in detail elsewhere (39–41). The SPSS statistical package was used (SPSS, Inc., Chicago, IL, USA).

Candidate genes

The gene symbol, name of the gene, type of polymorphism used, references to the techniques for detecting and naming the polymorphisms, and references to prior assessments of the method of genotype scoring have been presented elsewhere (39, 40). The genes we examined, arranged by functional group, were as follows.

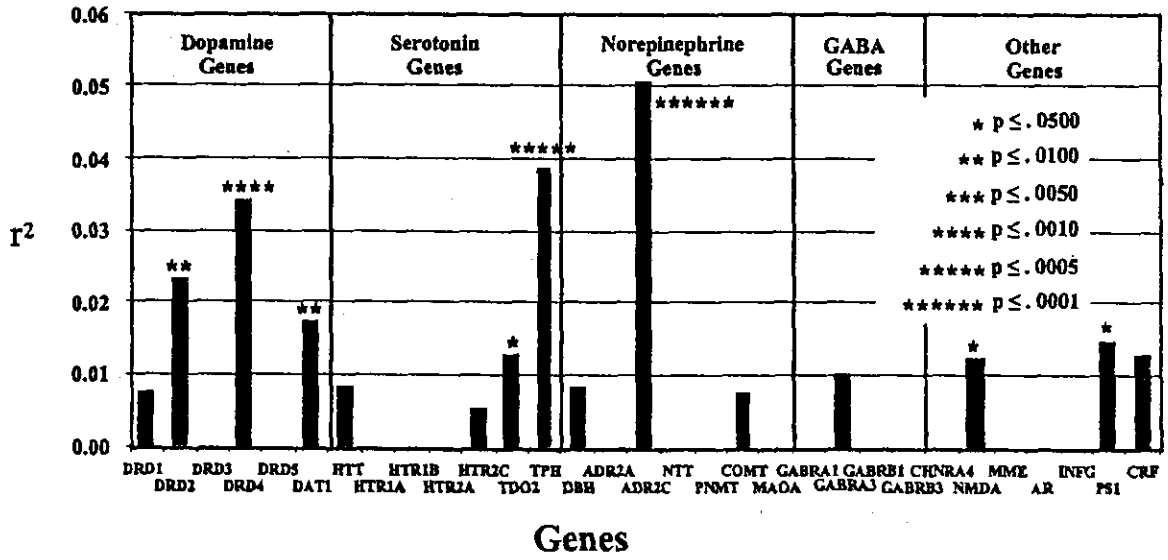

Fig. 1. Diagram showing which of the 31 genes were included in the regression equation, the r^2 or fraction of the variance of pathological gambling attributed to each gene, and significance level of each gene. The names of the genes are given on the abscissa. The genes are divided into groups of six dopamine, seven serotonin, seven norepinephrine, four GABA, and seven other genes.

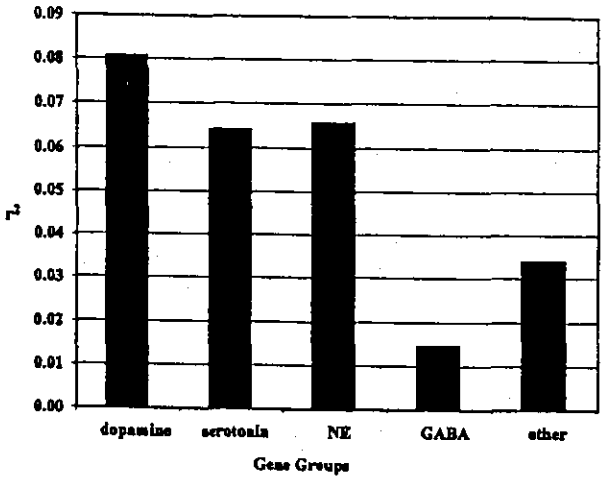

Fig. 2. This diagram shows the total r^2 for genes of each of the five gene groups. This value is highest for the dopamine genes, next highest for the serotonin and norepinephrine genes, lower for the other genes and lowest for the GABA genes.

Dopamine genes. The six dopamine genes examined were the dopamine D_{1-5} receptors (*DRD1, DRD2, DRD3, DRD4, DRD5*) and the dopamine transporter (*DAT1*).

Serotonin genes. The seven serotonin genes examined were the serotonin transporter *HTT* (SLC6A4), 5-HTR1A, 1Dβ, 2A and 2C receptors (*HTR1A, HTR1DB, HTR2A, HTR2C*), tryptophan 2,3-dioxygenase (*TDO2*), and tryptophan hydroxylase (*TPH*).

Norepinephrine genes. The seven norepinephrine genes were dopamine β-hydroxylase (*DBH*), adrenergic $\alpha 2_A$ and $\alpha 2_C$ receptors (*ADRA2A, ADRA2C*), the norepinephrine transporter (*NET, SLC6A2*), phenylethanolamine N-methyltransferase (*PNMT*), catechol-o-methyltransferase (*COMT*), and monoamine oxidase A (*MAOA*). To avoid a group containing only two genes, the *COMT* and *MAOA* genes were placed in the norepinephrine group even though is it recognized they metabolize other neurotransmitters as well.

GABA genes. The four GABA genes were for the GABA A1, A3, B1, and B3 receptors (*GABRA1, GABRA3, GABRB1, GABRB3*). A final group of seven other genes included those for the NMDA receptor (*NMDAR1*), the acetylcholine nicotinic α_4 receptor (*CHRNA4*), the androgen receptor (*AR*), interferon gamma (*INFG*), and PS-1 (*PS1*) and the corticosterone-releasing hormone (*CRH*).

Our experience with many other gene association studies has shown that because of the role of molecular heterosis (46), heterozygotes may contribute disproportionately to the effect of a given gene on a given phenotype. As a result, erroneous results may be obtained if the number of females to males is different in the control versus the subject group. Since in this study the number of males and females was equal in both the PG and control groups, we were able to include X-linked genes. The X-linked genes were the *HTR2C, GABA3, AR*, and *MAOA*. The polymorphism for *HTR2C* was a SNP utilizing the *Hin*f restriction endonuclease (47). The polymorphism for the *GABRA3* gene was a dinucleotide repeat (48). The genotype groups were $< 168/< 168 = 1$, het = 2, $\geq 168/\geq 168 = 3$. The polymorphism for the *AR* gene was a trinucleotide GGC repeat. The genotype groups have been described previously (49). The *MAOA* polymorphism was a SNP utilizing the *Fnu*I restriction endonuclease (50).

Substance abuse

To allow an evaluation of the potential role of substance abuse as a factor in the genetic susceptibility to pathological gambling, the questionnaires included many items concerning both alcohol and drug abuse/dependence. This allowed the pathological gamblers to be divided into two groups, those with and without substance abuse/dependence. Pathological gamblers who answered 'yes' to any of the following questions were considered to have problems with substance use: Do you consider yourself an alcoholic? Have you ever joined AA? Have you ever been unable to stop drinking? Have you ever been hospitalized for drinking? Have you ever had liver disease, such as cirrhosis, from drinking? Have you ever drunk in the morning? Has drinking ever caused family problems? Do you binge drink? Have you ever neglected responsibilities because of drinking? Do you consider yourself a drug addict? Have you ever used illicit drugs for more than 2 weeks? Have you even been dependent upon drugs? Have you ever tried to cut down on your use of drugs and been unable to? Have you ever needed to take more and more drugs? Have you ever had problems with withdrawal from drugs? Have you ever overdosed on drugs?

Results

The pathological gamblers consisted of a group of 106 males and 33 females for a total of 139 subjects. This was matched by an equal group of 139 controls also consisting of 106 males and 33 females. The mean age of the pathological gamblers was 43.5 years, SD 11.4, and of the controls was 36.9 years, SD 11.6. The relevant outcome results

consisted of the genes that were included in the regression equation, the gene code, r^2 and p value for the included genes, and the sum of the r^2 values for each of the functional groups of genes in the presence of all the other genes. The first three are shown in Fig. 1, the latter is shown in Fig. 2.

Dopamine genes

The dopamine genes that were included in the regression equation were *DRD1*, *DRD2*, *DRD4*, and *DAT1*. The first three have previously been reported to be significantly associated with PG in this set of gamblers, using a different set of controls (30–32). The *DRD2* and *DRD4* genes were significant at $p < 0.01$ and the *DAT1* was significant at $p < 0.05$. When only the dopamine genes (without the presence of the other genes) were examined by regression analysis, $r = 0.281$, $r^2 = 0.079$, $F = 7.84$ and $p \leq 0.0001$.

Serotonin genes

The included serotonin genes were *HTT*, *HTR2C*, *TDO2* and *TPH*. The *TDO2* gene was previously reported to be associated with PG in this set of gamblers, using a different set of controls (34). The *TPH* gene was significant at $p < 0.0005$, and the *TDO2* gene was significant at $p < 0.05$. When only the serotonin genes were examined by regression analysis, $r = 0.264$, $r^2 = 0.069$, $F = 6.81$, and $p \leq 0.0002$.

Norepinephrine genes

The included norepinephrine genes were *DBH*, *ADRA2C*, and *COMT*. The *ADRA2C* gene was significant at $p \leq 0.0001$. When only the serotonin genes were examined by regression analysis, $r = 0.28$, $r^2 = 0.079$, $F = 4.71$, $p \leq 0.0004$.

GABA genes

The only included $GABA_A$ gene was the *GABRA3* gene. When only the GABA genes were examined by regression analysis, $r = 0.087$, $r^2 = 0.0076$, $F = 2.13$, and $p \leq 0.15$.

Other genes

The included other genes were *NMDR1*, *PS1* and *CRF*. The *NMDR1* and *PS1* genes were significant at $p < 0.05$. When only the other genes were examined by regression analysis, $r = 0.173$, $r^2 = 0.030$, $F = 4.27$, $p = 0.015$.

All genes

Optimizing the gene scores on the same sample as used for the analysis is suitable when comparing the relative effect of different genes and groups of genes. While this provides only a maximized estimate of the total variance attributable to all the genes examined, this value is of some interest. For the total set, $r = 0.50$, $r^2 = 0.25$, corrected $r^2 = 0.21$, $F = 5.54$, $p < 0.0001$. The corrected r^2 adjusts for the tendency of the multivariate regression analysis to inflate estimates of r. These results suggest that the 16 included genes account for somewhere between 15 and 21% of the variance of pathological gambling.

Contribution of substance abuse

Of the 139 pathological gamblers, 81 completed the substance abuse questions. Of these, 43 (53%) were substance abusers (SA +) and 38 (47%) were not (SA −). Any controls who answered 'yes' to any of the substance abuse questions were excluded. Since the controls were prescreened to have had 'no problems with drug or alcohol abuse', very few were excluded. To ensure that any differences in the genetic profiles were due to differences in the SA + versus the SA − groups rather than differences in the controls, the same set of 139 controls was used for both. The results are shown in Fig. 3. There were five genes that were common to the pathological gamblers with and without SA. These were *DRD2*, *DRD4*, *TPH*, *COMT* and *PS1*. Seven genes, *DAT1*, *HTT*, *HTR1C*, *ADRA2A*, *PNMT*, *CHNRA4*, and *MME*, were included in the regression equation for subjects with in with PG + SA. Five genes, *TDO2*, *ADR2C*, *NMDA*, *AR*, and *CRF* were included in subjects with PG − SA. Finally, 14 genes were not included in either the PG + SA or the PB − SA groups. Since the number of cases in these two groups was relatively small, and since there is great genetic heterogeneity in polygenic disorders, some of these differences may be chance variations while some may represent real differences. A major question was whether much of the genetic variance of pathological gambling was due to the presence of comorbid SA. The total r (0.48 vs 0.42), r^2 (0.23 vs 0.18) and corrected r^2 (0.18 vs 0.13), F (4.26 vs 3.77), and p (≤ 0.0001 vs ≤ 0.0002) were similar for the two groups, with the values for those with SA being only modestly greater. The considerable similarity for the two groups is shown in more detail in Fig. 4. This shows the total variance for each group of genes/the total variance for all genes in percent for the SA + versus the SA − groups. This shows that

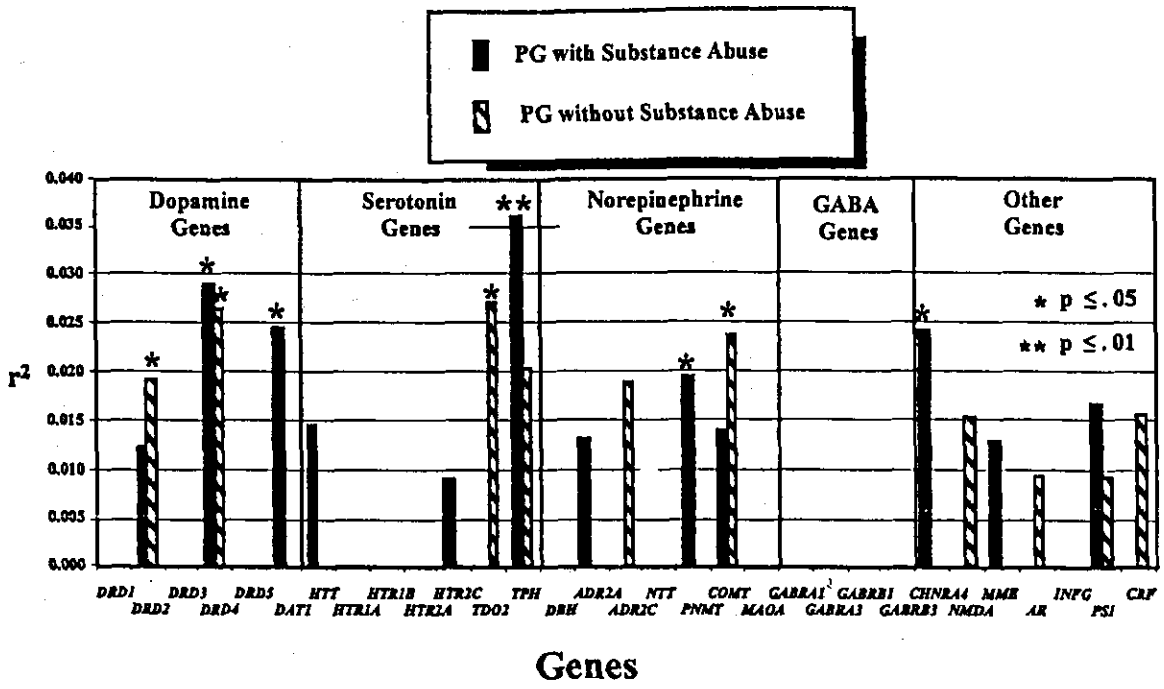

Fig. 3. This diagram compares the r^2 and p values for the 31 genes for those pathological gamblers with substance abuse versus those without substance abuse. See text for the details.

whether SA was present or absent, there was approximately equal contribution of the total dopamine, serotonin, norepinephrine, and other genes.

Discussion

The multivariate analysis of associations technique is based on the assumption that the most logical method of identifying the genes involved in complex polygenic disorders that are due to the additive effect of multiple gene, each with a small effect, is to examine the additive effect of multiple candidate genes. In the present results, examining the role of 31 genes, divided into four major groups of dopamine, serotonin, norepinephrine, GABA, and other genes, 15 of the 31 genes were included in the regression equation.

There are several aspects of the present approach that deserve discussion. The first aspect is that the gene codes are derived from the same data set used for the regression analysis. As discussed in more detail elsewhere (39) if the purpose of the study was to examine the total variance of pathological gambling explained by the genes examined, this would clearly produce a figure biased to produce an optimal result. However, the purpose instead is to examine the relative involvement of different genes and especially, groups of genes. In addition, since the MAA technique is designed to examine the effect of multiple genes, it can easily accommodate new genes that have never previously been tested for a given phenotype and for which there is no prior evidence about a likely gene code. Finally, one of the ultimate goals of these studies is to reverse the process, i.e. study a single individual and estimate either their risk for a given phenotype or, if the diagnosis is clear, estimate which genes or groups of genes are most involved for treatment optimization. A second aspect of this approach is the potential for variations in the racial or ethnic makeup of the control versus the

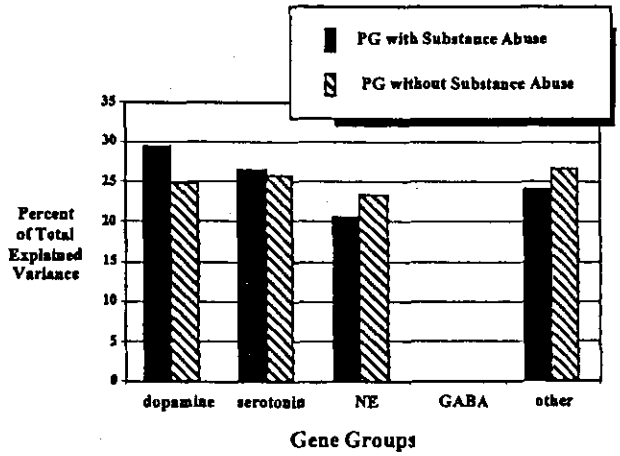

Fig. 4. Diagram comparing the total r^2 for each for the individual groups of genes/total variance for all genes in percent, for the pathological gamblers with and without comorbid substance abuse. See text for details.

pathological gambling sample to influence results. While this is minimized by restricting both samples to Caucasians of Western European ancestry it is not possible to completely eliminate this as a confounding factor. While the use of parent–child sets can help to control this confound, such sets are difficult to obtain when the subjects are adults. The use of affected sib pairs is also less than satisfactory given the low power of sib pair analysis compared with association studies (51) and the small number of pathological gamblers with available affected sibs. We have suggested elsewhere (52, 53) that when studies are restricted to a single racial group, the low percent of the variance attributable to each gene and the considerable genetic heterogeneity typical of polygenic disorders is more likely to account for variations between studies than hidden ethnic stratification. This is supported by the finding that the ratio of positive versus negative results is comparable for population-based compared with family-based association studies (54).

Of the six dopamine genes examined, the *DRD1*, *DRD2*, *DRD4*, and *DAT1* were included in the equation, with the greatest contribution from the 5 to 7 repeat alleles of the *DRD4* gene ($p \leq 0.001$), followed by the *DRD2* and the *DAT1* genes ($p \leq 0.01$), then the *DRD1* gene. The 5 to 7 repeat alleles of the *DRD4* gene have been reported to be associated with novelty seeking behaviors (55) and ADHD (56). These results are consistent with the role of dopamine in reward pathways (57–59), the striatial release of dopamine during gambling (60), the increased level of dopamine metabolites in the CSF of pathological gamblers (36), and with the reward deficiency hypothesis (61), which suggests that defects in one or more dopamine genes play a role in susceptibility to a range of addictive, compulsive, impulsive behaviors. They also agree with prior genetic studies of individual genes showing a significant contribution of the *DRD1*, *DRD2*, *DRD4* genes to pathological gambling (30–33). Finally, these results are consistent with the PET studies of Grover and Semple (personal communication, 1998) showing a significant decrease in frontal lobe blood flow and dopamine D_2 receptor density in the striatial nuclei of pathological gamblers. This is consistent with the present study showing an increase in the frequency of the D_2A1 allele in pathological gamblers and the studies by Noble et al. (62) and others showing an association between the presence of the D_2A1 allele and decreased dopamine D_2 receptor density in the striatum (62–64) and a decrease in frontal lobe blood flow by PET scan (65).

Of the seven serotonin genes, four were included in the equation. The most significant was tryptophan hydroxylase gene (*TPH*) ($p \leq 0.0005$). The *TDO2* gene was significant ($p \leq 0.05$), and the *HTT* and *HTR2C* genes were also included. Serotonin abnormalities have been reported in pathological gamblers (37), and in depression, obsessive-compulsive disorder, and anxiety, all of which are comorbid with PG (27). The role of the tryptophan 2,3-dioxygenase (*TDO2*) gene, in those with pathological gambling only, but not with pathological gambling associated with substance abuse (Fig. 3), is consistent with our prior studies showing a positive association of this gene with pathological gambling but not with alcoholism (34). The *TPH* gene has been reported to be associated with suicidality and alcoholism (66–68), both of which are increased in frequency in PG (3, 13, 14, 16, 17, 27). The association of the *TPH* gene with some types of alcoholism is consistent with the greater association of the *TPH* gene with PG + SA than with PG – SA (Fig. 3).

Of the seven norepinephrine genes, three were included in the equation with *ADRA2C* being the most significant gene ($p \leq 0.0001$). This is consistent with our prior studies showing a significant association of this gene with attention deficit disorder and conduct disorder (39, 40), both of which are frequently associated with PG (20, 22, 27). It is also consistent with studies of others showing an increase in norepinephrine metabolites in the CSF of pathological gamblers (69) and especially a significant correlation between increased CSF norepinephrine metabolites and the extraversion scale of the Eysenck personality questionnaire in pathological gamblers (69). The *COMT* gene was associated with both PG + SA and PG – SA, consistent with independent studies showing an association of this with both alcoholism and ADHD (70–73).

Of the four GABA genes only the *GABRA3* gene was included in the equation for the total set of controls and pathological gamblers, but was not significant at $p \leq 0.05$. When the smaller sets of PG + SA and PG – SA were examined, no GABA genes were included for either group. This is consistent with the studies of Roy et al. (74) showing no significant differences in CSF GABA levels in controls versus pathological gamblers. Of the seven other genes, three were included in the equation, *NMDA1*, *PS1*, and *CRF*. On these only the first two were significant at $p \leq 0.05$.

These studies indicate genes for dopamine, serotonin and norepinephrine metabolism play a

significant role in the risk for pathological gambling. These genes, however, are not unique to this disorder. Many of them were also found to play a role in ADHD, oppositional defiant disorder, conduct disorder, alcoholism and tobacco dependence (39) and other disorders. This is consistent with the concept that individuals who inherit a threshold number of these genes are at a significantly increased risk of developing one of a number of impulsive, compulsive, and addictive behaviors (61). Which specific disorder an individual develops is likely to be influenced by environmental factors or by other genes yet to be examined for their role in pathological gambling.

One of the potential advantages of the MAA technique is that non-genetic (i.e. environmental factors) can also be included in the regression equation. However, to be included they have to be measured. Such factors were not included in the present study. If such factors were identified, measured, and included, they may or may not alter the relative effect of the total variance for different groups of genes. Because of the relatively small number of females in the study, we did not attempt an examination of males versus females. However, when a larger number of female gamblers become available, this would be of considerable interest.

These studies are also consistent with the reported effectiveness of selective serotonin reuptake inhibitiors in the treatment of pathological gambling (75, 76). The heavy involvement of dopamine and norepinephrine genes as well suggest that treatment with dopamine and norepinephrine re-uptake inhibitors might also be effective. We suggest that multi-gene genetic profiling of the type used here, especially when additional genes are added, will be of benefit in understanding the role of genetic risk factors in PG. Since standard behavioral or cognitive behavioral approaches often show only modest success rates (77), we also anticipate that reversing the process and examining the risk genes that are present in a single individual may aid in the identification of those pathological gamblers most likely to respond to medical treatment and the determination which medications might be most effective.

As alluded to above, we believe that reversing the above process, to examine the relative contribution of specific genes and groups of genes in a given individual, may have great promise in identifying those individuals most likely to respond to medical treatment and to a specific type of medication.

Acknowledgements

This study was supported by the Gaming Entertainment Research and Education Foundation and National Center for Responsible Gaming.

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