Genetics of Pathological Gambling

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Pathological gambling (PG) is an impulse control disorder and a model 'behavioral' addiction. Familial factors have been observed in clinical studies of pathological gamblers, and twin studies have demonstrated a genetic influence contributing to the development of PG. Serotonergic, noradrenergic, and dopaminergic dysfunction have been reported as biological factors contributing to the pathophysiology of PG. Molecular genetic techniques have been used to investigate the role of genetic factors in PG. Molecular genetic research has identified specific allele variants of candidate genes corresponding to these neurotransmitter systems to be associated with PG. Associations have been reported between pathological gamblers and allele variants of polymorphisms at dopamine receptor genes, the serotonin transporter gene, and the mono-amine-oxidase A gene. Although preliminary data suggest that some of these differences are gender-specific, more research needs to be performed to substantiate gender-specific genetic contributions to the development of pathological gambling.

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The review of the current findings on genetics of PG suggests that liability to PG is in part mediated by genetic factors. Additional studies are needed to replicate and extend these findings, as well as to better understand the influence of specific allelic variants to differences in biological and behavioral functioning.

INTRODUCTION

Pathological gambling (PG) is a "persistent and recurrent maladaptive gambling behavior that disrupts personal, family or vocational pursuits" as defined by the Fourth Edition (Text Revision) of the Diagnostic and Statistical Manual of Psychiatric Disorder (DSM-IV-TR). It is a disabling and prevalent disorder that is increasingly becoming the focus of public and professional interest (Potenza et al., 2001). PG was first included as a disorder in 1980 in the Third Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and classified as an impulse control disorder. Based on that classification, several lines of research have been undertaken to identify factors associated with the pathophysiology of PG. Concurrently, there has been an increased interest in the application of modern genetic methods to the study of mental health disorders in general. Consequently, genetic epidemiology and molecular genetic techniques have been used to investigate for genetic factors contributing to PG. This manuscript reviews the published literature on the genetics of PG.

EPIDEMIOLOGICAL GENETIC STUDIES
IN PATHOLOGICAL GAMBLING

Initial evidence for the genetic influence on the etiology of PG came from family studies. Studies with clinical samples of pathological gamblers suggest an incidence of about 20% of PG in first degree relatives (Lesieur, 1988; Ibáñez & Saiz, 2000), and led to the consideration of the possible role of a genetic component in the development of PG. Gambino et al. (1993) found that patients at a Veterans Administration hospital in Boston who perceived that their parents had gambling problems were three times more likely to score as probable pathological gamblers on the South Oaks Gambling Screen (Lesieur

and Blume, 1987) than those who did not perceive that their parents had gambling problems. The same study reported that those individuals who also perceived that their grandparents had gambling problems had a 12-fold increased risk compared to patients who did not perceive gambling problems in their parents and their grandparents. Nonetheless, "familial" and "genetic" contributions are not synonymous. Family studies determine the extent to which a disorder clusters in families. Disorders can run in families for many reasons, including common genetic factors, cultural transmission, and shared environments (Faraone et al., 1999).

The relative contributions of genetic, common environmental and unique environmental influences can be elucidated more accurately in twin and adoption studies. Similarities and differences between twins could be explained by genetic factors, shared environmental factors and non-shared environmental factors such as exposure to peer groups or birth complications. Monozygotic twins share 100 percent of their genes with each other. Dizygotic twins share only 50 percent of their genes. Shared environmental factors are common in monozygotic and dizygotic twins raised in the same setting. If genes predispose to a disorder, then it should co-occur more among monozygotic twins than among dizygotic twins. Heritability measures the degree to which the vulnerability to develop a disorder is influenced by genes. This measure can be elucidated by comparing the concordance rate of a disorder (how often the second member of a twin pair has the disorder when the first member has it) for monozygotic twins and dizygotic twins.

At present, the main source of evidence for the genetic influence in the etiology of PG derives from analyses performed on 3359 male twin pairs of the Vietnam Era Twin Registry cohort (Eisen et al., 1998; Slutske et al., 2000; Slutske et al., 2001; Eisen et al., 2001). The study was conducted via phone interview and used DSM-III-R diagnostic criteria. The results showed that shared factors explained 56% of the report of three or more symptoms of PG and 62% of the variance in the diagnosis of PG disorder (Eisen et al., 1998). Analyses of the Vietnam Era Twin Registry cohort suggest that gambling problems of increasing severity represent a single continuum of vulnerability rather than distinct entities (Eisen et al., 2001). Initial analyses of the data suggested a genetic susceptibility model in the pathogenesis of PG (Eisen et al., 1998). Further analysis of this sample supported this in-

terpretation and indicated a common genetic vulnerability for PG and alcohol dependence in men (Slutske et al., 2000).

In a smaller twin study, Winters and Rich (1999) found a significant heritability explaining "high action" gambling such as casinos and gambling slot machines among 92 monozygotic and dizygotic male twin pairs. In contrast, no significant differences in heritability were found among males for "low action" games and among 63 female monozygotic and dizygotic twin pairs for either "high action" or "low action" gambling.

NEUROBIOLOGICAL RESEARCH
IN PATHOLOGICAL GAMBLING

Research into the neurobiology of PG has suggested the involvement of multiple neurotransmitter systems in the pathophysiology of PG (Blanco et al., 2000; Potenza, 2001; Ibáñez et al., 2002a). Research based on the nosological affinities of PG with other impulse control disorders suggests the involvement of serotonergic mechanisms. Theories postulating arousal and sensation seeking as central to PG often implicate the noradrenergic system. Hypotheses emphasizing the relationship of PG with addictive disorders often propose the involvement of the dopaminergic pathways.

Preliminary evidence of serotonergic dysfunction in PG is derived from results of two pharmacological challenge studies suggesting decreased serotonin synaptic activity in PG (Moreno et al., 1991) and 5-HT postsynaptic receptor hypersensitivity which may be related to decreased serotonin availability (DeCaria et al., 1996). A second line of evidence of the involvement of serotonergic mechanisms in the pathophysiology of PG is the finding of decreased platelet monoamine oxidase B (MAO-B) activity in pathological gamblers as compared to healthy volunteers, an observation suggesting a primary serotonergic deficit (Blanco et al., 1996; Carrasco et al., 1994).

Based on the hypothesis of noradrenaline involvement in PG, Roy et al. (1988) investigated the levels of norepinephrine and its metabolites in the urine, blood and cerebrospinal fluid (CSF) of males with PG. He found that pathological gamblers had higher urinary noradrenergic output, higher CSF noradrenaline and higher CSF 3-methoxy-4-hydroxyphenylglicol (CSF MHPG) compared to controls. In a

separate study, an elevated growth hormone response to 0.15 mg. of the alpha adrenergic receptor agonist clonidine was found in five male pathological gamblers as compared to eight healthy male volunteers (DeCaria et al., 1997), further suggesting noradrenergic dysfunction in males with PG.

Two studies have investigated levels of dopamine in the CSF (CSF DA) and yielded different results. Roy et al. (1988) did not find differences between male pathological gamblers and healthy volunteers in levels of plasma, urinary or CSF DA. A more recent study by Bergh et al. (1997) found decreased CSF levels of DA and increased CSF levels of DA metabolites in 10 male pathological gamblers as compared with 7 male controls, a finding suggestive of an increased rate of DA neurotransmission or turnover in male pathological gamblers.

In summary, these results suggest the existence of serotonergic, noradrenergic and dopaminergic dysfunction in PG. Each neurotransmitter system has been proposed to play a unique role in the mechanisms that underlie arousal, behavioral initiation, behavioral disinhibition and reward, each of which has been implicated in the pathophysiology of PG and other impulse control disorders. Thus, abnormal regulation of serotonergic, noradrenergic and dopaminergic functions may facilitate or underlie specific components of impulsive and addictive behaviors. Since abnormal regulation of any neurotransmitter system could be mediated by genetic factors, genetic research could be a promising instrument to investigate into the etiology and the pathophysiology of PG.

MOLECULAR GENETIC RESEARCH
IN PATHOLOGICAL GAMBLING

There is a growing literature suggesting the involvement of genetic factors in disorders related to PG such as alcoholism, abuse of illicit drugs, and smoking (Blum et al., 1995). Nonetheless, studies of the molecular genetics of PG are in their beginning stages. Serotonergic, noradrenergic and dopaminergic genes have been the most investigated due to the putative role of these neurotransmitters in PG, and a number of molecular genetic studies performed to date have reported findings consistent with the involvement of these neurotransmitter systems in PG. However, some of studies performed to date

have not been adequately controlled for potential differences in racial and ethnic compositions, factors that in and of themselves could account for differences in allelic variant distributions. As such, findings from the following studies, although appearing promising, should be regarded as preliminary.

There are several ways to probe the molecular genetic bases of a disorder, with linkage and association studies representing the two main lines of investigation. Linkage analysis relies upon the ability to detect co-segregation of marker alleles with those of the disease gene in families with several members affected by a specific disease. This approach tries to find marker alleles that tend to be shared among affected relatives and not among unaffected individuals of the same pedigree. If one specific allele is linked with the disease it will be present in affected but not in unaffected members of a particular family more often than would be expected by chance. Association studies are performed by comparing the frequency of a polymorphic allele in a patient group with a specific disease to that in a control group without the disease drawn from the same population. If a particular allele predisposes individuals to the disease in question, that allele should occur statistically more frequently in the disease group as compared with controls. Linkage analysis studies have been successful for diseases with well-defined modes of inheritance. In complex illnesses, such as mental health disorders including PG, association studies using specific polymorphic DNA markers in candidate genes represent one way of detecting genetic factors which may be contributing to the development of the disorder. Candidate genes are those that *a priori* are hypothesized to be involved in the pathogenesis of a specific disease, taking into account the postulated neurobiological bases of the disease. Consequently, genes relevant to the function of serotonergic, dopaminergic and noradrenergic systems could be considered as candidate genes in PG.

No linkage studies in PG have been reported in the literature to date. Association studies in PG are summarized in Table I. Our group performed an association study to investigate whether there were significant differences in the allelic and genotypic frequencies of specific DNA polymorphisms in a group of 68 pathological gamblers (47 male and 21 female) admitted to our Pathological Gambling Unit as compared with a group of 68 healthy volunteers with similar age, sex, racial and ethnic composition. The South Oaks Gambling Screen by Le-

Table 1
Summary of Association Studies in Pathological Gambling

Sample size PG[a]	Controls	Ethnicity	Gene (Polymorphism)	Functional Relevance	Results
222	714	Non-Hispanic Caucasian (across USA)	DRD2[b] (*Taq I* A)	NO	A1 allele significantly more frequently in PG (Comings et al., 1996)
68	68	Caucasian (Central Spain, racial and ethnic composition controlled)	DRD4[c] (exon III)	YES	Less functional 7 repeat allele significantly more frequent in female PG (Pérez de Castro et al., 1997)
			5HTT[d] (LPR-promoter)	YES	Less functional short allele significantly more frequent in male PG (Pérez de Castro et al., 1999)
			TH[e] (intron I)	NO	No association (Ibáñez et al., 1999)
			MAOB[f] (intron II)	NO	No association (Ibáñez et al., 2000)
			MAOA[g] (intron I)	NO	4 repeat allele significantly more frequent in male PG (Ibáñez et al., 2000)
			MAOA (promoter)	YES	Less functional 3 repeat alelle significantly more frequent in male PG (Ibáñez et al., 2000; Pérez de Castro et al., 2002)

[a]PG: Pathological Gamblers.
[b]DRD2: Dopamine receptor D2 gene.
[c]DRD4: Dopamine receptor D4 gene.
[d]5HTT: Serotonin transporter gene.
[e]TH: Tyrosine hydroxylase gene.
[f]MAOB: Monoamine oxidase B gene.
[g]MAOA: Monoamine oxidase A gene.

sieur and Blume (1987) was used to assess the severity of PG. We found no differences in the frequencies of allelic distribution of a polymorphism in the MAO-B gene in the groups of pathological gamblers and healthy volunteers. In contrast, our study found an association between an allele variant of a polymorphism in the MAO-A gene and more severe cases of male pathological gamblers in the sample, suggesting there may be gender differences in the etiology of PG (Ibáñez et al., 2000a). Moreover, the low-activity 3-repeat allele of the 30-bp MAO-A promoter polymorphism that is associated with lower transcriptional and lower enzymatic activity was found to be significantly increased in male pathological gamblers compared to male controls (Ibáñez et al., 2000b; Pérez de Castro et al., 2002). Interestingly, although serotonin is a preferential substrate for MAO-A, MAO-A is expressed in the brain mainly in dopaminergic neurons (Westlund et al., 1993), raising the question of whether those allele variants are more likely to result in changes in serotonergic or dopaminergic transmission.

We also found that the less functional short variant of a polymorphism at the serotonin transporter gene (5-HTTLPR), a variant which is associated with decreased promoter activity, was found significantly more frequently in male pathological gamblers than in male controls (Pérez de Castro et al., 1999). This finding was not observed in females, further suggesting the existence of sex-related differences in the genetic compositions of individuals with PG (Pérez de Castro et al., 1999).

Other studies have investigated the role of genes related to the dopaminergic system in the genesis of PG. A study by Comings et al. (1996) found a statistically significant association between the Taq-A1 allele of the D2 dopamine receptor gene in pathological gamblers compared to controls. The Taq-A1 allele has also been found to be associated with other impulsive-addictive-compulsive behaviors, leading some researchers to propose a *Reward Deficiency Syndrome* as an underlying genetic foundation for these disorders (Blum et al., 1995). Our group analyzed another polymorphism within the D2 dopamine receptor gene and found significant differences in allele distribution in pathological gamblers with as compared with those without comorbid psychiatric disorders, a finding supporting the role of this gene as a liability factor for psychiatric disorders (Ibáñez et al., 2001). Variants of the dopamine D1 receptor gene have also been associated

with impulsive-addictive-compulsive behaviors, including PG (Comings et al., 1997).

A polymorphism located in the exon III of the dopamine D4 receptor (DRD4) gene (encoding a functionally different protein) has been found to be associated with PG (Perez de Castro et al., 1997). Specifically, the DRD4 7-repeat allele, coding for a "less efficient" version of the DRD4 receptor, was found significantly more frequently in female pathological gamblers as compared to female controls (Perez de Castro et al., 1997). This association was not observed in males. These results suggest that dopaminergic pathways through the involvement of DRD4 may play a role in the etiology of PG in females (Perez de Castro et al., 1997).

It should be emphasized that interpretation of findings from case-control association studies in neuropsychiatry is complicated, and findings from the described investigations should be considered preliminary. Several major criticisms of association studies include their potential to generate false-positive results due to: a) chance (type I error), which is increased with an increased number of independent markers analyzed; b) inappropriate prior probability (given the vast size of the human genome, the prior probability that a selected gene will be associated with a neuropsychiatric disorder is small); and c) poorly characterized or matched control groups on population stratification (Sullivan et al., 2001). That is, in a sample composed of two or more subgroups with different genetic backgrounds, a disorder could be more prevalent in one racial or ethnic group or the frequency of the genetic marker could differ by race or ethnicity (Sullivan et al., 2001). Furthermore, the results of the association studies summarized above should be cautiously analyzed since they have low power due to the relatively small sample sizes (particularly when analyzing males and females separately) and there is a high risk of identifying false positive associations. Thus, the validity of the results of case-control association studies could be improved in part through their replication in larger sample sizes and the performance of meta-analyses. More importantly, controlling for such variables as racial/ethnic composition will be necessary in interpreting results from future association studies. Finally, an understanding of the functional significance of differences in allelic distribution patterns will be important in determining their relevance to the disorders in question. For example, it is unclear whether the Taq-A1 allelic variant of the D2 dopamine recep-

tor is associated with any change in receptor expression, structure or function. As such, the Taq-A1 allelic variant could hold little or no functional consequences for D2 dopamine receptor systems. Further research is needed to define more precisely the interpretation of association studies in PG in order to advance our understanding of the neurobiology of the disorder.

CONCLUSIONS

Overall, our review of the genetics of PG suggests the need for additional research. Multiple genetic factors are likely to contribute to the pathophysiology of PG. Preliminary data suggest the possibility of differences in the genetic contributions to PG for males and females and could perhaps contribute to gender differences in the clinical manifestations of PG (Ibáñez et al., 1998; Ibáñez et al., 2002b). Although tantalizing to hypothesize, additional studies including replication in other samples and determination of the relationship between genetic allelic variants and biological and behavioral functions are needed to confirm and extend these findings and determine their relevance to the pathophysiology of PG. It is important to note that for many polymorphic allelic variants, identifiable differential functional correlates are not known or relatively incompletely understood, making the proposed involvement of the corresponding candidate genes speculative in nature. Future research should address the relationship between genetic substrates, biological function and specific clinical manifestations of PG, delineate further possible gender-related differences in genetics as they relate to pathophysiology, and help advance the development of more effective therapies for this disorder (Blanco et al., 2001). Additional studies in larger and diverse samples are needed to confirm and extend the current findings, identify specific genetic influences and elucidate the complex interactions between the environmental and the genetic contributions to the onset and progression of PG.

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