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VIEWPOINT



Genetics of gambling disorder and related phenotypes: The potential uses of polygenic and multifactorial risk models to enable early detection and improve clinical outcomes

VARUN WARRIER¹ , SAMUEL R CHAMBERLAIN² ,
SHANE A. THOMAS³ and
HENRIETTA BOWDEN-JONES^{1,4,5*}

¹ Department of Psychiatry, University of Cambridge, UK

² Department of Psychiatry, Faculty of Medicine, University of Southampton, Southern Health NHS Foundation Trust, Southampton, UK

³ Vice Chancellor's Office and Institute of Health and Wellbeing, Federation University, Australia

⁴ National Problem Gambling Clinic & National Centre for Gaming Disorders, London, UK

⁵ Department of Brain Sciences, University College London, London, UK

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ABSTRACT

Gambling Disorder (GD) is an impactful behavioural addiction for which there appear to be underpinning genetic contributors. Twin studies show significant GD heritability results and intergenerational transmission show high rates of transmission. Recent developments in polygenic and multifactorial risk prediction modelling provide promising opportunities to enable early identification and intervention for at risk individuals. People with GD often have significant delays in diagnosis and subsequent help-seeking that can compromise their recovery. In this paper we advocate for more research into the utility of polygenic and multifactorial risk modelling in GD research and treatment programs and rigorous evaluation of its costs and benefits.

KEYWORDS

polygenic risk scores, multifactorial risk scores, problem gambling, early diagnosis, early intervention

Gambling Disorder (GD) is the only formally recognised behavioural addiction in the Diagnostic and Statistical Manual Version 5 (DSM-5) (American Psychiatric Association, 2013) and is currently listed in the category of 'Substance Related and Addictive Disorder' having entered DSM-3 in 1980. It is characterised by persistent patterns of pathological gambling over an extended period of time, resulting in distress and impaired personal, interpersonal, educational, occupational functioning. GD is also likely to co-occur with other psychiatric disorders, especially mood disorders, anxiety disorders, substance and alcohol use disorders, and impulsive/compulsive disorders; as well as potential co-occurrence with some physical health conditions.

Individuals who do not meet all the criteria for GD but have subthreshold problem gambling (i.e. meet some criteria) experience marked functional impairment and high rates of comorbidities, in many cases to a similar degree as those with the full disorder. Here, we refer to this continuum which includes GD, subthreshold problem gambling, and normative gambling behaviour as GD and related phenotypes. We also refer to clinical diagnosis across the different versions of the DSM and ICD manuals as GD, although the diagnostic criteria have evolved over time.

Several lines of evidence indicate a genetic component for GD and related phenotypes. The earliest study of familiarity of gambling, in the 1980s suggested that over a third of the individuals with 'pathological gambling' are children of parents with 'pathological gambling'

*Corresponding author.
E-mail: Hb584@cam.ac.uk

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(Lesieur, Blume, & Zoppa, 1986). Gyollai et al. (2014) conducted an early systematic review of the genetics of GD in which they identified 21 studies with data from eight unique samples. Empirical research utilizing twin data accounted for eight of the studies. The studies included gene association data and one genome wide-association study [GWAS] study. They concluded that there was strong evidence for genetic influences in GD. Subsequent studies confirmed familial recurrence. This intergenerational transmission may reflect shared genetics, shared familial environment, or both (Dowling et al., 2017; Kotyuk et al., 2019).

It is also important to note that GD has long established high rates of comorbidities with other psychological and addictive disorders. Such comorbidities provide obvious candidates for the foundation of multi-attribute multi factorial risk prediction (Dowling et al., 2015; Dowling et al., 2017; Lorains, Cowlishaw, & Thomas, 2011).

Twin studies can quantify both the genetic and shared environmental components of GD and related phenotypes. To date, there have been two large twin studies of GD and related phenotypes and a handful of smaller studies (Lobo & Kennedy, 2009). The largest of these, was conducted in an all-male sample from the Vietnam Era Twin Registry. Depending on how GD was defined, the heritability ranged from 40 to 54%. The second large study included data from both males and females from the Australian Twin Registry. Heritability estimates were similar (40–58%), and additionally, this study did not identify any sex differences in heritability estimates. A recent study (Davis, Slutske, Martin, Agrawal, & Lynskey, 2019) replicated the findings from the Australian Twin Registry in a non-overlapping sample of twins from Australia: the twin heritability was 60% and yet again, there was no evidence for sex-differences in heritability of GD. Neither of the two recent twin studies found evidence for a significant shared environment in GD.

Twin studies have also helped demonstrate the shared genetics between GD and the extended subclinical phenotypes and other psychiatric disorders. One study (Slutske et al., 2000) has demonstrated that rates of GD are elevated among both monozygotic and dizygotic cotwins of individuals with subthreshold gambling problems compared to those without. The rate of elevation was higher among monozygotic co-twins compared to dizygotic co-twins, indicative of shared genetics along the continuum. Furthermore, consistent with high familial aggregation and co-occurrence in diagnoses, there appears to be high genetic correlation between GD related phenotypes and substance use disorders (e.g., genetic correlation ~ 0.7 for alcohol disorder; Lorains et al., 2011), antisocial behaviour disorders, and mood disorders. This profile of shared genetics with antisocial behaviour and mood disorders is similar to that observed for substance use disorders. Shared genetics is in itself insufficient to ascribe causality. Methods that use molecular genetics such as Mendelian Randomization can help delineate causal relationships between GD and other psychiatric disorders.

A few molecular genetic studies have sought to identify specific genes linked to GD and related phenotypes. These

include several candidate gene association studies in small sample sizes, predominantly testing the role of dopamine related genes (Davis et al., 2019). However, in other psychiatric conditions, genome-wide association studies using much larger sample sizes have often failed to replicate findings from candidate gene association studies, suggesting that these findings must be interpreted cautiously. To date, there are two genome-wide association studies (Lind et al., 2013; Lang et al., 2016) of GD related phenotypes, both with relatively small sample sizes ($n < 2000$) compared to current standards for psychiatric conditions. Neither identified significant loci, although the genetic signal was enriched for pathways relating to dopamine and Huntington's Disease. However, the sample sizes of the currently available studies are too small to draw robust conclusions. Studies have identified that increased polygenic scores for schizophrenia and neuroticism and decreased polygenic scores for agreeableness are associated with higher likelihood for GD related phenotypes (Piasecki, Gizer, & Slutske, 2019; Sychala et al., 2022). Taken together with twin genetic correlation, this suggests substantial shared genetics between GD related phenotypes and other psychiatric disorders and trait factors. The significance of high rates of identified multifactorial polygenic traits is that this may enable the development of highly predictive risk scores that will permit the early identification of those at risk of subsequently developing GD and related disorders. In physical conditions such as hypertension the non-genetic phenotypical terms used in risk prediction models used in general practice settings can be quite mundane. For example, Echouffo-Tcheugui, Batty, Kivimäki, and Kengne (2013) reviewed hypertension risk and found that the most common predictive risk factors included in the models were age, sex, BMI and diabetes status. In one key study, Jiménez-Murcia et al. (2019) of gambling disorder studied phenotypic factors such as cultural background, sex, educational attainment, marital status, employment status, use of tobacco, alcohol, drugs, age, DSCL 90-R sub scales and TCI-R sub-scales. Obviously gambling behaviors and family history would also be obvious candidates.

As with many conditions there is good evidence to suggest across many addiction disorders that outcomes for those who are detected early in their illness trajectory and treated early are typically much better than for those who have engrained long term disorders with significant diagnosis and treatment delays (Ducci & Goldman, 2012; Škařupová, Vlach, & Mravčík, 2020). Early detection is a potentially very important benefit of effective polygenic multifactorial risk prediction tools if it is followed by early intervention. Coloizzi, Lasalvia & Ruggeri (2020) provided a comprehensive review including 139 studies of research evidence for better outcomes achieved with earlier intervention for a range of mental health disorders. They advocated for the use of integrated and multidisciplinary services to limit the risk of poor outcomes. Skinner, Occhipinti, Song, and Hickie (2023) proposed a model that suggests that targeted risk prediction for adolescents and adults with a range of mental disorders provides a more effective and



efficient approach than population level universal interventions. Çirakman, Karslıoğlu, Bal, and Çayköylü (2023) demonstrated substantial positive associations between early initiation of long-acting antipsychotic medications in people with schizophrenia, and relatively better quality of life, lower depression, and lower anxiety; as compared to later initiation of such medication. Relative positive associations were also observed in caregivers of those patients. For mental health disorders, this delay in presentation and intervention can be particularly long, adding to the burden of disease.

Other large scale systematic reviews and epidemiological studies have shown lengthy delays in initial treatment contact after the onset of mental health disorders (McLaughlin, 2004; Wang, Berglund, Olfson, & Kessler, 2004). For example, obsessive-compulsive disorder (OCD) is one of the top ten leading causes of disability in the developed world and has a typical duration of untreated illness of around 10 years (Fineberg et al., 2019). While less well studied, a similar typical duration of untreated illness has been reported for gambling disorder – around 10 years in affected individuals presenting for treatment. Unfortunately, the prevalence of mental health disorders is increasing amongst children as are the associated costs (Tkacz & Brady, 2021).

Genetic testing has been shown to be relevant for a range of mental health disorders. For example, one study has shown that development of anxiety disorders, has a heritability of 30–50% (Shimada-Sugimoto, Otowa, and Hettema, 2015). Maternal depression and anxiety and child genomic polygenic risk have been found to predict later psychiatric symptoms in childhood and up to mid adolescence (Chen et al., 2023). Therefore, the situation regarding gambling disorder polygenic and multifactorial risk modelling is not unique in comparison to other mental health conditions and disorders, except that we currently have a smaller evidence base. At the same time, of course much more work is needed to establish the clinical utility of such testing in particular mental health contexts and for specific purposes (e.g. early detection or prediction of symptom occurrence).

A further consideration is the mechanism(s) by which GD and other mental health disorders are linked. The genetic basis for impulsivity has been studied (and verified to be robust) for a significant period of time (Bevilacqua & Goldman, 2013; Sanchez-Roige et al., 2019). It is possible that the linkages between GD and other mental disorders may be through the impulsivity traits underpinning these disorders. Yau and Potenza (2015) reviewed the epidemiological co-occurrence of gambling disorder and other behavioural addictions and suggest that this may be due to shared genetic risks for impulsivity and reward seeking.

Thus the time is ripe for larger-scale molecular genetic investigation of GD related phenotypes (Vereczkei et al., 2022). Such studies should benefit from lessons learned from other psychiatric genetics studies. The hoped-for benefits of early diagnosis and intervention that may accrue from polygenic and multifactorial risk modelling for gambling disorder need to be subjected to rigorous economic modelling. Rigorous evaluation of the impact of these approaches in combination and their efficacy across varied

populations and chronic diseases and disorders is required. The systematic reviews that have been done of the cost-effectiveness of programs to address chronic diseases show significant advantages but many studies do not include adequate economic analysis (Thomas & Browning, 2016).

CONCLUSIONS AND RECOMMENDATIONS

First, large sample sizes and representative samples will be critical to obtain robust genetic findings for gambling disorder related phenotypes. As an example of the sample sizes available in some studies, the largest GWAS of problematic alcohol use has identified 29 significant loci when combining data from $N = 435,563$ individuals (Zhou et al., 2020). However, strategically targeted sampling strategies are likely to reduce the required sample sizes by several orders of magnitude.

Second, genetic results are likely to vary based on phenotype. For instance, alcohol consumption, problematic alcohol use, and clinically defined alcohol dependence are all only moderately genetically correlated with each other. Whilst balancing sample size with phenotyping is difficult, the availability of large-scale biobanks and electronic data records, and improved statistical methods to model the underlying phenotypes can help surmount this. For instance, the GWAS of problematic alcohol use combined both self-report data and electronic-health records to identify 29 significant loci. In behavioural addictions, it is important to note that gambling behavior is complex. This includes consideration of modalities used, frequency and history of use and severity of the addiction re important factors. A binary diagnosis of gambling addiction on one modality may not be an adequate representation of the phenotypic variability. One of our team's next priorities is to define a standard minimum data set of measures to be included in the conduct and analysis of such studies that are ready for use in genetic risk prediction studies.

Third, genetic loci need not be shared across ancestrally heterogeneous groups. For instance, the genetic correlation between East Asians and Europeans is low (~ 0.4) for major depressive disorder and moderate (~ 0.6) for alcohol use disorder. If these inconsistencies are adequately measured and addressed in models, molecular genetics holds the promise of identifying potential molecular mechanisms underlying gambling disorders, opening up one avenue for therapeutics. Precision medicine may in future be a real possibility for the treatment of gambling and other addiction disorders (National Human Genome Research Institute (National Institutes of Health); Centers for Disease Control and Prevention 2023).

Fourth, if the promise of risk prediction provided by genetic testing and its use in polygenic and multifactorial risk modelling is realised, this unlocks important capacity to intervene early and achieve better clinical outcomes because of earlier intervention. There are many studies of mental health disorders that show significant benefits from early diagnosis and early intervention. We must also



not underestimate the predictive power of (non-genetic) models that can be derived from existing large scale epidemiological studies of co-morbidity and multimorbidity in problem gambling and other behavioural addictions. It is an important priority to validate and check the performance of such models from existing data sets and sit them alongside risk prediction models that incorporate polygenic risk score components. The additional predictive power that is to be obtained from the incorporation of polygenic terms in risk prediction models is promising, but nevertheless, a matter yet to be fully empirically determined. We consider it is a priority to conduct the necessary studies to address this issue.

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