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**Article**

# Contributions of Nicholas Martin to Gambling Disorder Research

Wendy S. Slutske[1] and Penelope A. Lind[2]

[1]Department of Psychological Sciences, University of Missouri, Columbia, MO, USA and [2]Psychiatric Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia

**Abstract**

Professor Nicholas G. Martin, from QIMR Berghofer Medical Research Institute in Brisbane, Australia, is a world leader in the effort to understand the genetic architecture underlying disordered gambling. This article pays tribute to Nick and his almost two decades of gambling research, highlighting his many strengths, ranging from the use of ingenious recruitment approaches, twin study methods, genomewide association studies, to facilitating international collaborations.

**Keywords:** Disordered gambling; genetics; genomewide association study; GWAS; twin studies

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Nick Martin is the least likely person to set foot in a casino or purchase a lottery ticket. He is too sensible and is eager to remark that 'the lottery is a tax on the foolish'. Yet, it was mostly good luck that led to his becoming one of the world leaders in the effort to discover the genetic underpinnings of disordered gambling.

Nick and his colleagues have been conducting ground-breaking investigations of the genetics of alcohol use disorder based in his Genetic Epidemiology Unit at QIMR Berghofer Medical Research Institute for nearly four decades, and we were fortunate to be a part of these efforts. When one of us (WSS) learned that the highest per-capita spending on gambling in the world was in Australia, she felt virtually obligated (!) to study disordered gambling in the Australian Twin Registry (ATR). When Nick was approached with the idea, he was all in. We were able to obtain funding from the National Institute of Mental Health (NIMH; one of the few funded projects that focused on gambling disorder before NIMH decided that gambling disorder was a low priority) to conduct a survey of gambling behaviors and disorder in the ATR. Data from the Australian Twin Study of Gambling (OZ-GAM) have been a goldmine for new discoveries about gambling and gambling disorder — there are no other data like these in the world. To date, 17 gambling-related publications have been based on these data.

This represented only the second large-scale twin study of disordered gambling ever conducted, and the only one that had included women (Slutske, Zhu et al., 2010). As expected, we were able to demonstrate that disordered gambling was heritable, that it was equally heritable in men and women (Davis et al., 2019; Slutske, Zhu et al., 2010), and that the association between disordered gambling and alcohol use disorder was largely due to genetic factors (Slutske et al., 2013). These data also allowed us to confirm or refute established wisdom from the social sciences about the role of the environment in disordered gambling. For example, among discordant twin pairs (i.e., after controlling for genetic and shared environmental factors), the twin who spent more time gambling with her parents was no more likely to frequently gamble or to develop gambling problems than the twin who spent less time gambling with her parents (Slutske, Piasecki et al., 2010). And among discordant pairs, the twin who began to gamble at a younger age was no more likely to go on to develop gambling problems than the twin who started to gamble at an older age (Slutske et al., 2014). On the other hand, among discordant pairs, the twin who lived in a more disadvantaged neighborhood was more likely to develop gambling problems than the twin who lived in a more advantaged neighborhood (Slutske et al., 2019). Relatively few genetic association studies of disordered gambling have been conducted; all but two have been candidate gene studies and the majority of those have focused on genes in the dopaminergic system. It was not until 2013 that we published the first ever gambling-related genomewide association study (GWAS) with Nick in *Addiction Biology*. The power of the study was limited by the small number of genotyped OZ-GAM participants ($N = 1{,}312$), and there were no genomewide significant single-nucleotide polymorphisms (SNPs) identified (Lind et al., 2013). However, we reported three novel loci for disordered gambling with highly suggestive evidence of association and enriched biological pathways that were previously associated with substance addiction. We then contributed data to the only other published gambling disorder GWAS, which was also underpowered to identify genomewide significant loci (Lang et al., 2016).

While WSS was visiting QIMR, Nick drew to our attention a report from the Australian Adverse Drug Reactions Bulletin for the drug cabergoline, a potent dopamine $D_2$ receptor agonist (Australian Therapeutic Goods Administration, 2005). There were reports of four patients taking long-term levodopa for the treatment of Parkinson's disease who began to gamble excessively a few months after cabergoline was added, and whose gambling problems abated when the cabergoline was discontinued. Similar

**Author for correspondence:** Penelope Lind, Email: Penelope.Lind@qimrberghofer.edu.au

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adverse drug effects were reported in North America with the dopamine receptor agonist pramipexole. These pharmacologic findings provided a compelling clue to a potential neurobiological pathway to disordered gambling that might prove to be useful in gene identification. To explore this further, we conducted a gene-enrichment analysis within the OZ-GAM study using a gene set derived from the literature on dopamine-induced disordered gambling and candidate gene studies of gambling disorder; we observed enrichment of association with disordered gambling at both the level of the SNP and the gene (Lind et al., 2013).

Lack of federal funding for gambling disorder research has slowed down but has not blocked efforts to move forward. In the ensuing years, Nick, PAL and colleagues have continued to deliberately include measures of disordered gambling (and of course, GWAS genotyping) in new data collection projects at QIMR Berghofer Medical Research Institute, including two new twin samples (e.g., Davis et al., 2019) and large national efforts to recruit individuals with histories of depression or bipolar disorder. In two of these samples, polygenic risk scores for Parkinson's disease and bipolar disorder were created as predictors of disordered gambling; there was a significant association between the genetic risk for Parkinson's disease, but not between the genetic risk for bipolar disorder, and disordered gambling, (Lind et al., 2019). This was the first study to demonstrate a genetic link between Parkinson's disease and disordered gambling and is especially intriguing in light of the pharmacologic findings described above. There is now converging evidence from two distinct lines of inquiry suggesting that the pathophysiology underlying Parkinson's disease may play an important role in the etiology of disordered gambling.

Genetic risk variants for disordered gambling have not yet been robustly identified due in part to the limited availability, at an international level, of existing community and clinically ascertained cohorts with DNA samples. Mostly due to Nick's foresight, we are now moving in the direction of having an adequately sized GWAS meta-analysis of disordered gambling by including our QIMR-based Australian studies and cohorts from the UK, Germany, and the USA — what we are optimistically calling 'GD1', with the expectation that it will be the first in a series of gambling disorder GWAS meta-analyses. Establishment of this international consortium was important as it is only through large collaborative GWAS meta-analyses that we will get a clearer picture of genetic mechanisms contributing to disordered gambling. For the first time, we will be able to examine whether genetic risk for disordered gambling overlaps with genetic contributions to psychiatric and medical comorbidities, as well as educational attainment, cognitive functioning, brain structure, and personality traits.

From a genetic perspective, gambling disorder has been an 'orphan disorder'. It has been the subject of very few twin or genomic studies and is one of the few major mental disorders that has not been included in the Psychiatric Genomics Consortium. Looking to the future, we are optimistic that many of the great insights about the etiology of disordered gambling will come from our fledgling international GWAS consortium, which would not exist without the intellectual curiosity and generosity of Nick Martin.

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