NAME OF PRESENTING AUTHOR: Penelope A. Lind

EMAIL ADDRESS OF PRESENTING AUTHOR:
Penelope.Lind@qimrberghofer.edu.au

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TITLE: Exploring the genetic architecture of disordered gambling and the influence of genetics risk of gambling on substance use

FULL AUTHOR LIST: Penelope A Lind[1], Ian R Gizer[2], Thomas M Piasecki[2], Wendy S Slutske[2], Nicholas G Martin[3]

AFFILIATIONS: [1] Psychiatric Genetics Group, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; [2] Department of Psychological Sciences, University of Missouri, Columbia, MO, USA; [3] Genetic Epidemiology Group, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

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ABSTRACT:
Disordered gambling (DG) refers to the full continuum of problems related to excessive gambling that include pathological gambling symptomatology and versatility of gambling involvement. DG also has a high level of comorbidity with substance use. The underlying genetic basis is largely unknown; few candidate gene studies and only two genome-wide association studies (GWAS) of gambling-related traits have been published. Using self-report data from the Australian Twin Study of Gambling and Australian Genetics of Depression Study, we performed the largest GWAS to date (n_{max} = 14,646), for three measures of gambling behaviour: ever gambled (EVRGAM), versatility of gambling involvement (VERS), and a DG factor score (DGF). We identified two independent genome-wide significant loci for VERS and one for DGF ($p<5E-8$). GCTA SNP-based heritability estimates were 1.7% (EVRGAM), 13.4% (VERS) and 11.2% (DGF). Next, we calculated polygenic risk scores (PRS) from the GWAS summary for a range of p-value thresholds. Using LMM, we then examined the extent to which the PRS could predict gambling be-

haviour and substance use (alcohol and tobacco use, and total number of substances ever used [subVERS]) in the Australian 25UP Study (n_{max} = 2,155). PRS_{VERS} was most predictive of gambling behaviours (explaining 0.8% and 0.45% of variance in VERS in DGF) and frequency of alcohol use (p=0.0071, R^2=0.40%). The best predictive value of the PRS_{DGF} was observed for cigarettes per day (p=0.0079, R^2=1.65%) and subVERS (p=0.0098, R^2=0.37%). Finally, PRS_{EVRGAM} only predicted DGF (p=0.0029, R^2=0.54%).

