Shared genetic etiology between alcohol dependence and major depressive disorder

Jerome C. Foo[a,*], Fabian Streit[a,*], Jens Treutlein[a], Stephan Ripke[x,q,y], Stephanie H. Witt[a], Jana Strohmaier[a], Franziska Degenhardt[c,d], Andreas J. Forstner[c,d,r,s], Per Hoffmann[c,d,r,v], Michael Soyka[f,g], Norbert Dahmen[j], Norbert Scherbaum[k], Norbert Wodarz[l], Stefanie Heilmann-Heimbach[c,d], Stefan Herms[c,d,r], Sven Cichon[c,t,u], Ulrich Preuss[m,n], Wolfgang Gaebel[p], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Monika Ridinger[w], Sabine Hoffmann[b], Thomas G. Schulze[a,t,o,z,h], Wolfgang Maier[e], Peter Zill[g], Bertram Müller-Myhsok[i], Marcus Ising[i], Susanne Lucae[i], Markus M. Nöthen[c,d], Karl Mann[b], Falk Kiefer[b], Marcella Rietschel[a] and Josef Frank[a]

The clinical comorbidity of alcohol dependence (AD) and major depressive disorder (MDD) is well established, whereas genetic factors influencing co-occurrence remain unclear. A recent study using polygenic risk scores (PRS) calculated based on the first-wave Psychiatric Genomics Consortium MDD meta-analysis (PGC-MDD1) suggests a modest shared genetic contribution to MDD and AD. Using a (∼10 fold) larger discovery sample, we calculated PRS based on the second wave (PGC-MDD2) of results, in a severe AD case–control target sample. We found significant associations between AD disease status and MDD-PRS derived from both PGC-MDD2 (most informative *P*-threshold = 1.0, $P = 0.00063$, $R^2 = 0.533\%$) and PGC-MDD1 (*P*-threshold = 0.2, $P = 0.00014$, $R^2 = 0.663\%$) meta-analyses; the larger discovery sample did not yield additional predictive power. In contrast, calculating PRS in a MDD target sample yielded increased power when using PGC-MDD2 (*P*-threshold = 1.0, $P = 0.000038$, $R^2 = 1.34\%$) versus PGC-MDD1 (*P*-threshold = 1.0, $P = 0.0013$, $R^2 = 0.81\%$). Furthermore, when calculating PGC-MDD2 PRS in a subsample of patients with AD recruited explicitly excluding comorbid MDD, significant associations were still found ($n = 331$; *P*-threshold = 1.0, $P = 0.042$, $R^2 = 0.398\%$). Meanwhile, in the subset of patients in which MDD was not the explicit exclusion criteria, PRS predicted more variance ($n = 999$; *P*-threshold = 1.0, $P = 0.0003$, $R^2 = 0.693\%$). Our findings replicate the reported genetic overlap between AD and MDD and also suggest the need for improved, rigorous phenotyping to identify true shared cross-disorder genetic factors. Larger target samples are needed to reduce noise and take advantage of increasing discovery sample size. *Psychiatr Genet* **28:66–70 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Departments of [a]Genetic Epidemiology in Psychiatry, [b]Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, [c]Institute of Human Genetics, [d]Department of Genomics, Life and Brain Center, [e]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, [f]Medical Park Chiemseeblick in Bernau-Felden, Bernau-Felden, [g]Psychiatric Hospital, Ludwig-Maximilians University, [h]Institute of Psychiatric Phenomics and Genomics (IPPG), Campus Innenstadt, Medical Center of the University of Munich, [i]Max Planck Institute of Psychiatry Munich, Munich, [j]Department of Psychiatry, University of Mainz, Mainz, [k]LVR-Hospital Essen, Department of Psychiatry and Psychotherapy, Medical Faculty, University of Duisburg-Essen, Duisburg and Essen, [l]Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, [m]Department of Psychiatry and Psychotherapy, Vitos Hospital Herborn, Herborn, [n]Department of Psychiatry, Psychotherapy and Psychosomatics, Martin-Luther University, Halle-Wittenberg, [o]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, [p]Department of Psychiatry and Psychotherapy, University of Düsseldorf, Düsseldorf, [q]Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, Germany, [r]Human Genomics Research Group, Department of Biomedicine, Departments of [s]Psychiatry (UPK), [t]Biomedicine, [u]Division of Medical Genetics, University of Basel, [v]Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, [w]Psychiatric Health Care Aargau, Brugg, Switzerland, [x]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, [y]Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, [z]Human Genetics Branch, NIMH Division of Intramural Research Programs, Bethesda and [†]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, Maryland, USA

Correspondence to Jerome C. Foo, PhD, Central Institute of Mental Health, Department of Genetic Epidemiology in Psychiatry, Medical Faculty Mannheim, University of Heidelberg, J5, 68159 Mannheim, Germany
Tel: +49 621 1703 6093; fax: +49 621 1703 6055;
e-mail: jerome.foo@zi-mannheim.de

*Jerome C. Foo and Fabian Streit contributed equally to the writing of this article.

Members of Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium are listed in Supplementary Material (Supplemental digital content 1, *http://links.lww.com/PG/A204*)

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Introduction

The co-occurrence of alcohol dependence (AD) and major depressive disorder (MDD) has been well established, and epidemiological assessments of AD and MDD have linked AD to higher risk of depression and vice versa (Woodruff *et al.*, 1973; Kessler *et al.*, 1996; Swendsen and Merikangas, 2000; Crum *et al.*, 2008; Foulds *et al.*, 2015). Formal genetic studies indicate that AD and MDD share common genetic factors (Winokur and Coryell, 1991; Maier *et al.*, 1994; Kendler *et al.*, 1995; Prescott *et al.*, 2000; Nurnberger *et al.*, 2002; Lyons *et al.*, 2006). Genome-wide association studies (GWAS) have the ability to identify genetic loci associated with complex disorders [e.g. AD (Treutlein *et al.*, 2009; Kapoor *et al.*, 2014; Zuo *et al.*, 2014; Gelernter *et al.*, 2014) and MDD (Ripke *et al.*, 2013; Wray and Sullivan, 2017)] and allow the study of genetic risk shared between complex genetic disorders (Wray *et al.*, 2014). So far, however, only limited support for specific genes contributing to the two illnesses on the level of individual genetic variation has been found (Edwards *et al.*, 2012).

The polygenic risk score (PRS) approach is a statistical method that enables the assessment of additive effects of multiple common genome-wide genetic variations on risk for a disorder, and is well suited to characterize shared genetic etiology of complex disorders (Purcell *et al.*, 2009). A recent study (Andersen *et al.*, 2017) used this approach to examine the genetic overlap between AD and MDD. They calculated MDD-PRS based on the results of the first-wave meta-analysis of the MDD Working Group of the Psychiatric Genomics Consortium (PGC) (PGC-MDD1: cases, $n = 9240$; controls, $n = 9519$) GWAS (Ripke *et al.*, 2013), finding associations with increased risk for AD in four independent AD-GWAS data sets (cases ranged from 317 to 2135), explaining from 0.18 to 2.6% of the variance in AD (Nagelkerke's R^2). Mentioned as a limitation was the small size of the MDD discovery sample used, proposing that increased sample sizes would improve MDD-PRS predictive ability.

Here, we sought to substantiate the findings of Andersen *et al.* (2017) in an independent sample of patients having severe AD while calculating MDD-PRS based on the much larger PGC-MDD2 discovery sample ($n = 59\,265$ cases, $n = 112\,092$ controls; Wray and Sullivan, 2017). For context, we also calculated PRS using an MDD target sample. Furthermore, we examined whether any association would be observed using a subset of this AD sample whose patients had been recruited explicitly excluding comorbid MDD.

Materials and methods

Target samples

The target sample comprised 1333 male patients with German ancestry having severe AD requiring hospitalization and 1307 population-based controls, previously described in Treutlein *et al.* (2009) and Frank *et al.* (2012) [i.e. the German Study on the Genetics of Addiction (Alcoholism), *GESGA*]. Controls overlapping between the *GESGA* sample and PGC-MDD discovery samples were removed before analysis. In summary, all patients fulfilled the AD DSM-IV criteria and were recruited from consecutive admissions to psychiatry and addiction medicine departments of psychiatric hospitals participating in the German addiction research network.

A subset of the cases (*PREDICT* subsample; Mann *et al.*, 2009) comprising 332 patients with AD was recruited explicitly excluding comorbid MDD.

The MDD target sample comprised cases ($n = 597$) from the Bonn/Mannheim (BoMa) MDD study and German population-based controls ($n = 1292$), described previously (Rietschel *et al.*, 2010; Ripke *et al.*, 2013).

All participants provided written informed consent, and procedures used were approved by the respective local ethics committees and in accordance with the Declaration of Helsinki.

Discovery samples

The PGC-MDD2 discovery sample comprised 59 265 cases and 112 092 controls (leave-one-out meta-analysis omitting the BoMa-MDD sample included in the original PGC-MDD2 (Wray and Sullivan, 2017) meta-analysis).

The PGC-MDD1 discovery sample comprised 8148 cases and 7955 controls (leave-one-out meta-analysis omitting the BoMa-MDD and RADIANT-German samples included in the original PGC-MDD1 (Ripke *et al.*, 2013) meta-analysis which had overlapping controls with the *GESGA* sample). The PGC-MDD1 data set is a subset of the PGC-MDD2 data set.

Genotyping and quality control

Detailed information on genotyping and QC is available in Frank *et al.* (2012). In summary, filtering for uncommon SNPs (minor allele frequency < 0.1), individual missingness (>0.01), low-quality genotyping (missingness > 0.02), and Hardy–Weinberg equilibrium (1.0×10^{-6}) was performed. After QC and excluding overlapping samples, the final GESGA sample comprised 1330 cases and 1051 controls ($n = 382001$ SNPs). Of these cases, 331 were from the PREDICT study and 999 were not. Additional minor allele frequency filtering was performed for each subsample (PREDICT: $n = 381453$ SNPs; non-PREDICT: $n = 381914$ SNPs). After QC and removing overlap, the BoMa-MDD sample comprised 586 cases and 1062 controls ($n = 3523389$ SNPs).

Polygenic risk score calculation

PRSs were calculated using PRSice v1.25 (Euesden *et al.*, 2015). We calculated MDD-PRS in the *GESGA* sample using the PGC-MDD2 results following previously published methods (Ripke *et al.*, 2014).

In summary, linkage disequilibrium (LD) clumping was carried out, retaining the variant with the smallest *P* value from each LD block and discarding all variants with r^2 greater than or equal to 0.1 located within 500 kb around that variant. The major histocompatibility complex of chromosome 6 was excluded, as frequently done when calculating PRS owing to long-range LD, making linkage equilibrium difficult to contain (Euesden *et al.*, 2015). PRS were calculated at a range of *P* value thresholds ($P = 5 \times 10^{-8}$, 1×10^{-6}, 1×10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0).

Regression analyses were performed on AD case–control status with the first 10 principal components as covariates. The proportion of variance in case–control status explained by MDD-PRS was assessed by Nagelkerke's pseudo R^2 derived from the difference between the full regression model (PRS + covariates) and the null model (only covariates) (Purcell *et al.*, 2009; Power *et al.*, 2015). For comparison, we calculated MDD-PRS in the *GESGA* sample using the PGC-MDD1 discovery sample.

For context, we further analyzed the association of the MDD-PRS with MDD phenotype using the same parameters in the BoMa-MDD target sample, using both PGC-MDD1 and PGC-MDD2 results, serving as a positive control.

To examine whether existing AD/MDD comorbidity might be driving association, we conducted several additional analyses. Using the PGC-MDD2 results as the discovery sample, we analyzed PRS separately in *PREDICT* subsample cases ($n = 331$) and non-*PREDICT* cases ($n = 999$).

Results

Tables S1-3 show *P* value thresholds, significance (*P* values), R^2, and number of informative SNPs, which were included at each *P* value threshold for each PRS analysis.

We found significant associations between AD disease status and MDD-PRS derived from both PGC-MDD2 (most informative *P*-threshold = 1.0, $P = 0.00063$, $R^2 = 0.533\%$; Fig. 1a) and PGC-MDD1 (*P*-threshold = 0.2, $P = 0.00014$, $R^2 = 0.663\%$; Fig. 1b) meta-analyses; the larger discovery sample did not yield additional predictive power.

In contrast, calculating PRS in a MDD target sample yielded increased power when using PGC-MDD2 (*P*-threshold = 1.0, $P = 0.000038$, $R^2 = 1.34\%$; Fig. 1c) versus PGC-MDD1 (*P*-threshold = 1.0, $P = 0.0013$, $R^2 = 0.81\%$; Fig. 1d).

When calculating PGC-MDD2 PRS in the *PREDICT* subsample (excluding comorbid MDD), significant associations were still found (*P*-threshold = 1.0, $P = 0.042$, $R^2 = 0.398\%$). Meanwhile, PRS in non-*PREDICT* cases (i.e. not explicitly excluding MDD comorbidity) predicted more variance (*P*-threshold = 1.0, $P = 0.0003$, $R^2 = 0.693\%$; Fig. 1e, inset).

Discussion

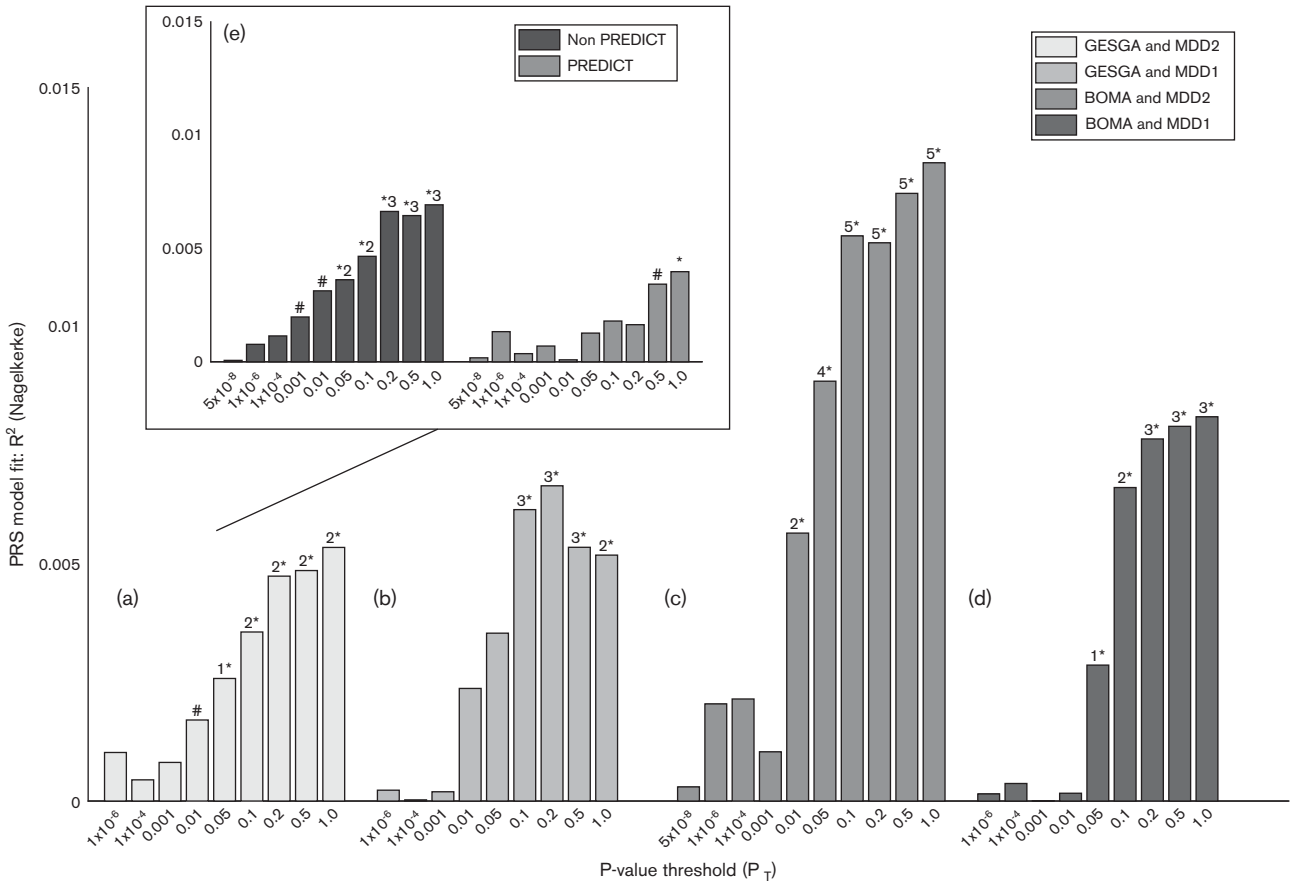
Our analysis confirms the contribution of shared genetic risk for AD and MDD long suggested by formal genetics studies that was only recently detected using a molecular approach in Andersen *et al.* (2017).

Determining shared genetic etiology in comorbid disorders is necessarily faced with the problem of 'enrichment' of the comorbid disorders in both discovery and target samples. Our analysis of the *PREDICT* sample alone revealed that even in AD cases expressly excluding comorbid MDD, genetic overlap is observed; a higher proportion of explained variance was observed using only non-*PREDICT* cases. These findings are consistent with those of Andersen *et al.* (2017), who showed that significant genetic overlap remained when calculating PRS in the AD-GWAS data sets after adjusting for MDD status, and also when using a MDD GWAS data set without comorbid MDD-AD cases (Andersen *et al.*, 2017). These results suggest that although PGC-MDD-GWAS samples are likely to contain individuals with AD, these are not fully responsible for the associations observed. For our current analysis, comorbidity information with AD in the PGC-MDD2 discovery sample was not available, nor was MDD status in the full GESGA sample; it should be noted that the possibility of enrichment nevertheless remains. Moreover, these findings underscore the need for rigorous phenotyping and improved characterization of samples, and in particular detailed assessment of disease comorbidity, symptomatology, and severity, all of which will be vital in the effort to understand shared genetic risk of complex diseases.

Interestingly, our use of a substantially larger discovery sample did not demonstrate increased predictive power in the AD sample. One reason for this is that the effect itself is modest in size and less robust against noise. In contrast, the larger discovery sample did yield increased predictive power in the MDD sample; the effects were much stronger. One consideration with respect to our findings is that patients in our AD sample were all males, whereas the discovery sample in addition contained females, potentially affecting predictability. Meanwhile, the MDD target sample contained both males and female patients. However, additional analysis using male-only MDD-PRS, and statistically controlling for sex in the MDD-BoMa samples, did not indicate a substantial influence of sex on our results (see Supplementary Material, Supplemental digital content 1, *http://links.lww.com/PG/A204*).

Another recent study using a polygenic approach has shown that the level and risk of AD and MDD comorbidity may be linked to neuropsychiatric traits and brain volumes (Zhou *et al.*, 2017). Further research is needed to decipher this pleiotropy and to assess causality. Although not possible here owing to the relatively small size of the target sample, the application of techniques to dissect

Fig. 1



Polygenic risk score model fit. (a) GESGA target sample based on PGC-MDD2 ($n = 59\,265$ cases; $n = 112\,092$ controls); (b) PGC-MDD1 ($n = 8148$ cases; $n = 7955$ controls) discovery samples; (c) BoMa-MDD target sample based on PGC-MDD2 and (d) PGC-MDD1; and inset (e) non-*PREDICT* (left) and *PREDICT* (right) *GESGA* target subsamples based on PGC-MDD2. MDD, major depressive disorder; PGC, Psychiatric Genomics Consortium. $^{\#}P < 0.10$; $^{1*}P < 0.05$; $^{2*}P < 0.01$; $^{3*}P < 0.001$; $^{4*}P < 0.0001$; $^{5*}P < 0.00001$.

pleiotropy, such as BUHMBOX (Han *et al.*, 2016) or Mendelian randomization (Davey Smith and Hemani, 2014), will lead to better understanding of this disease comorbidity. Another approach which can be utilized with larger target samples is LD score regression to estimate genetic correlation across diseases and subgroups (Bulik-Sullivan *et al.*, 2015).

Ongoing increases in discovery sample size will lead to continued increases in the ability to explain variance in mental disorders, augmenting the ability to further dissect the shared pathophysiology reflected in the genetic overlap between comorbid diseases. Larger target samples are needed to reduce noise and take advantage of increasing discovery sample size.

Our findings replicate the genetic overlap between AD and MDD and suggest the need for improved, rigorous phenotyping to identify true shared cross-disorder genetic factors. Once assessed, future efforts in the field will be able to take advantage of symptomatology and precise comorbidity information to inform analyses. Importantly, this will also lead to both improved patient stratification and corresponding personalization of care in clinical settings.

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Conflicts of interest

There are no conflicts of interest.

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