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A recessive genetic model and runs of homozygosity in major depressive disorder

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Abstract

Genome-wide association studies (GWASs) of major depressive disorder (MDD) have yet to identify variants that surpass the threshold for genome-wide significance. A recent study reported that runs of homozygosity (ROH) are associated with schizophrenia, reflecting a novel genetic risk factor resulting from increased parental relatedness and recessive genetic effects. Here we undertake an analysis of ROH for MDD using the 9,238 MDD cases and 9,521 controls reported in a recent mega-analysis of 9 GWAS. Since evidence for association with ROH could reflect a recessive mode of action at loci, we also conducted a genome-wide association analyses under a recessive model.

The genome-wide association analysis using a recessive model found no significant associations. Our analysis of ROH suggested that there was significant heterogeneity of effect across studies in effect (p=0.001), and it was associated with genotyping platform and country of origin. The results of the ROH analysis show that differences across studies can lead to conflicting systematic genome-wide differences between cases and controls that are unaccounted for by traditional covariates. They highlight the sensitivity of the ROH method to spurious associations, and the

need to carefully control for potential confounds in such analyses. We found no strong evidence for a recessive model underlying MDD.

Introduction

Major depressive disorder (MDD) is one of the leading burdens of disease in the world, with a lifetime prevalence of ~15% (Hasin and others 2005; Kessler and others 2003). It has been found to be moderately heritable, from 31 to 42% (Sullivan and others 2000), though with greater heritability in severe, recurrent forms of the disorder (Levinson 2006; McGuffin and others 1996). A recent mega-analysis of nine genome-wide association studies found no significant associations with individual genetic variants (Psychiatric Genomics Consortium MDD Working Group 2012), compared to ~5 genome-wide significant associations in similar sized studies of other psychiatric disorders (Ripke and others 2011; Sklar and others 2011). These association studies are conducted under an additive model, but some risk variants may be recessive, for which individuals with two copies of an allele are at greater risk than would be predicted from twice a single allele's effect. In a fully recessive model only those with 2 copies of the risk allele are at risk, though there is also the possibility of partial recessive effects. As selection acts to remove deleterious alleles with respect to overall fitness from the population, genetic risk variants that are recessive can escape selection longer. Inbreeding within families (e.g. consanguineous marriages) often exposes such recessive alleles due to an increased likelihood of alleles at each locus being identical by descent. Until recently studies of inbreeding were focused on families or communities in which inbreeding is expressed relative to the founder generation, which is assumed to be unrelated and where inbreeding information was determined from self-reports or knowledge of pedigrees (pedigree inbreeding). For example, Rudan et al. (2003) found a higher incidence of six complex genetic diseases/disorders including MDD among Croatian villages with higher levels of pedigree inbreeding (Rudan and others 2003). However, by using genome-wide genotype data it is possible to estimate an individual's inbreeding from more distant common ancestors to provide evidence for whether a recessive genetic model is more appropriate for a disorder.

One method to analyse the effect of inbreeding from genome-wide genotype data is to identify segments of continuous homozygous SNPs, reflecting blocks of the genome that are identical by descent from a common ancestor. Runs of homozygosity (ROH) capture inbreeding effects that are due to common or rare causal variants better than a simple measure of excess number of homozygous SNPs across the genome, which tends to only capture the recessive effects of common variants (Keller and others 2011). An association between percentage of genome covered by ROH (F_{ROH}) and schizophrenia has been reported (Keller and others 2012). Due to the possibility of genetic overlap between MDD and schizophrenia (Schulze and others 2012), a similar association between F_{ROH} and MDD might be expected. However, MDD has a lower heritability (h^2 ~ .37, Sullivan and others 2000) than schizophrenia (h2 ~ .81, Sullivan and others 2003), which should attenuate genetic relationships. Moreover, some authors have suggested that MDD may not be under negative selection and the casual genetic variants may be beneficial in some circumstances (Belsky and Pluess 2009; Nesse 1999; Power and others 2012; Watson and Andrews 2002).

Here we look at the association between MDD and SNPs in 9,238 cases and 9,521 controls across 9 studies (Table 1) (Consortium 2012) under a recessive genetic model. We also use genome-wide estimates of inbreeding to look for a consistent difference between cases and controls across 9 studies of MDD, in order to support a recessive model of the disorder.

Material and Methods

Sample

In this report, we analyzed individual data from the nine discovery samples (Ising and others 2009; Lewis and others 2010; Muglia and others 2010; Rietschel and others 2010; Shi and others 2011; Shyn and others 2011; Sullivan and others 2009; Wray and others 2012) of the PGC-MDD that together comprise 9,238 cases and 9,521 controls. Full sample details are given in the supplementary materials of the original analysis (Psychiatric Genomics Consortium MDD Working Group 2012), and are outlined in Table 1. All subjects were of European ancestry (as determined from genome-wide genotypes). Cases were required to have diagnoses of DSM-IV lifetime MDD established using structured diagnostic instruments from direct interviews by trained interviewers (two studies required recurrent MDD and one recurrent, early-onset MDD) or clinician-administered DSM-IV checklists. Studies ascertained cases mostly from clinical sources, and controls were largely randomly selected from the population and screened for lifetime history of MDD.

Method of ROH calling and analysis

Genotyping was described in the supplementary materials in the original analysis (Psychiatric Genomics Consortium MDD Working Group 2012). All samples were genotyped with single nucleotide polymorphism (SNP) arrays of greater than 200K genome-wide SNPs, with analysis restricted to polymorphic SNP probes. In the original analysis, imputation to the CEU HapMap3 reference sample (Altshuler and others 2010), 1,235,109 autosomal SNPs, was performed using Beagle 3.0.4 (Browning and Browning 2009). In order to perform an association analysis under a recessive model or call runs of homozygosity (ROH), imputed SNP dosage data was converted to discrete genotype calls, keeping those SNPs with a probability of at least 0.95. The use of imputed SNPs helped to increase similarity of genomic coverage across studies. SNPs with a missingness of >2% or minor allele frequency (MAF) <5% were removed, as were then individuals with missingness over 2%. Prior to analysis SNPs were pruned for LD within PLINK, removing any SNPs with an R^2 0.90 with any other SNP in a 50 SNP window. The use of imputed data in ROH has previously been shown to give similar results to those restricting to only genotyped SNPs (Keller and others 2012). The calling of ROH and percentage of genome covered by ROH per individual (F_{ROH}) were derived within PLINK (Purcell and others 2007) following the same method found to optimally detect effects of autozygosity, as described in Howrigan et al (2011). In particular, we used a series of sliding windows across the genome to call ROH within each individual separately. The size of the windows was set to 65 consecutive SNPs, so any single SNP would be found in 65 different windows. If at least 4 (>5%) of these windows contained entirely homozygous SNPs, then the SNP in question could be included within a ROH. Within windows, one missing SNP was allowed. To avoid false positives, only ROH with a minimum of 65 consecutive SNPs covering

2.3Mb were used when calculating F_{ROH}. In addition, the required minimum density in a ROH was set at 200 kb per SNP and the maximum gap between two consecutive homozygous SNPs was set at 500 kb. The estimate of the total genome captured was 2.77×10^9 bp. The analysis was performed by study, using F_{ROH} as a predictor of case-control status in a logistic regression. Percentage of SNPs missing, a SNP-by-SNP measure of homozygosity determined by PLINK's --het command, and the first 5 ancestry-informative principal components were used as covariates. The SNP-by-SNP measure of homozygosity was included to correct for differences in genomic-homozygosity levels unrelated to inbreeding, such as DNA quality or population ancestry. A mixed model was also examined combining all samples, using study as a random effect. This analysis was performed in STATA (StataCorp. 2011).

Genome-wide recessive model

The genome-wide recessive model analysis used the autosomal dosage data converted to genotype calls as described above in the analysis of ROH. Analyses was performed in PLINK (Purcell and others 2007), using the --recessive command. The first 5 ancestry-informative principal components were included as covariates. Analysis was restricted to autosomes. Each study was analysed separately and then a meta-analysis was performed for each SNP across studies (using fixed effect p value in PLINK). As the risk allele is set as the minor allele by default, and this may differ by study for alleles at frequencies near 0.5, we used the minor allele in the analysis of imputed data from the whole sample as a reference. A p-value $<5\times10^{-8}$ was considered as genome-wide significant. For this significance cut-off, we had 90% power to detect a relative risk of 1.47 for the rare recessive genotype for SNPs with a MAF from 0.3–0.5. However power decreased rapidly for those alleles with lower MAF, with 90% power to detect those with a relative risk of 1.81 and MAF of 0.2, or with a relative risk of 2.21 and MAF of 0.15. For those SNPs with lower MAF, power reduced rapidly for a recessive model. Calculations were performed using CaTS Power Calculator (Skol and others 2006).

Results

Across all samples the average percentage of the genome covered by ROH (F_{ROH}) was 0.11% (95% CI 0.102–0.112; Table 1), similar albeit slightly lower than average F_{ROH} (0.15%) reported in an earlier report using the same parameters (Keller and others 2012). In our mixed model analysis across all samples with study as a random effect, we found no significant effect of F_{ROH} on MDD status. However, there was substantial heterogeneity in direction of effect across studies (p=0.001, Figure 1). Overall, 4 studies showed increased F_{ROH} in cases (one significantly, p=0.007), while 5 studies showed increased F_{ROH} in controls (one where p=0.005). Including further principal components (up to 20) and increasing ROH size (up to 170 SNPs) made no difference to the results.

To explore this apparent heterogeneity we examined two features of the included studies that might provide insight into the results. The first issue was potential poor matching of cases and controls which we tested within the combined RADIANT German and Bonn-Mannheim sample. Here cases were recruited from both of these two studies, whereas the controls were

collected and genotyped only as part of the Bonn-Mannheim study. However, excluding the
RADIANT cases and restricting to only the matched Bonn-Mannheim study's cases and
controls still resulted in a significant association with ROH (p=0.03), as both sets of cases
were found to have similar mean F_{ROH}. This tentatively suggested that the heterogeneity
apparent across studies was not replicated within studies. Secondly, we were interested in
the effects of genomic coverage on ROH. Cases and controls from the Queensland Institute
of Medical Research (QIMR) were recruited as one sample but included as two independent
cohorts, based on their genotyping platform (Illumina 317k and 610k chips). When we
restricted the analysis to only those SNPs directly genotyped on both platforms (202,062
SNPs), we found that the mean F_{ROH} for the QIMR-610k sample reduced from .086% to .
077%, compared to .078% for the QIMR-317k sample. This implies, as expected, that
genotyping platform and genome coverage were influencing estimates of mean F_{ROH}.

To better understand potential sources of heterogeneity in our findings, we used a linear
meta-regression with a study's effect size as the outcome and features of the studies
individually analysed as predictors. We tested percentage of cases with recurrent MDD,
mean F_{ROH} and genome-wide homozygosity, country of recruitment, presence of copy
number variant probes on the platform, and genotyping platform as potential predictors of
direction of effect (see Supplementary Table 1). Genotyping platform was nominally
associated with effect size (p=0.05), and the direction of effect of F_{ROH} differed when
studies on non-Illumina platforms were analysed separately. Within the 3 non-Illumina
genotyped studies, increased inbreeding was protective against MDD (p=0.007) while
within the 6 Illumina genotyped studies inbreeding was a significant risk factor for MDD
(p=0.02). We noted that when more than one study was recruited from a country, the
direction of effect for ROH was consistent across all studies recruited from the same country
(see Figure 1). However, this was only a significant predictor in the meta-regression when
distinguishing between German and non-German studies (p=0.02). This level of
confounding from genotyping and country likely reduced our power to detect a true effect of
ROH and MDD.

In the meta-analysis of a recessive model of association, 929,138 SNPs were analysed,
though not all appeared in all 9 studies due to differences in genotyping coverage. The most
significant recessive association was for rs13261582 on chromosome 8 in an intergenic
region between *SNTB1* and *HAS2* (odds ratio of 2.0 for the minor A allele, MAF 0.22,
p=2.58×10⁻⁶). However this SNP was only present in two studies (GenRED and STAR*D),
and so is only supported by a subset of the sample. It did not appear among the reported top
SNPs from the primary analysis of this dataset under an additive genetic model in the full
sample (p=0.12). The results of the meta-analysis also showed a lower median p-value than
expected by chance (λ_{GC} 0.97, see Supplementary Figures 1 and 2 for Manhattan and QQ
plots). The λ_{GC} was 1.03 for SNPs with MAF > 0.2 and 0.90 for SNPs with MAF < 0.2,
implying smaller differences of genotype frequencies between cases and controls than
expected by chance for SNPS with low MAF. This is possibly the result of the less accurate
imputation of rare alleles.

Discussion

Our analyses show systematic differences in F_{ROH} between cases and controls that differ in direction across studies. There are several explanations for these results, mostly highlighting limitations of this analysis. Firstly, we found systematic differences in mean F_{ROH} between studies. This is not unexpected and likely reflects the density of the genomic coverage and the accuracy of imputation, since SNPs were restricted to those with high quality imputation. A similar level of variation in F_{ROH} was observed in the Psychiatric GWAS Consortium's analysis of F_{ROH} across 17 studies of schizophrenia (Keller and others 2012), though they did not report any heterogeneity of effect as a function of genotyping platform or country of recruitment. It seems unlikely that the heterogeneity of effect in the present study could be the result of differing SNP inclusion on the platforms, because such an explanation would imply systematic differences between cases and controls in the probability of homozygosity across SNPs as a function of platform. More likely in our opinion is the possibility that factors related to ascertainment of cases and controls differed across studies and influenced overall homozygosity. Such factors could include changes in homozygosity levels due to length and quality of DNA storage, or differences in ascertainment of cases and controls across populations. It is noteworthy that the two out of nine studies that genotyped controls independently of cases (GenRED and STAR*D) both showed higher F_{ROH} in controls than cases. Further, studies appear to cluster by country of origin and direction of the effect of F_{ROH}. All three German studies had increased F_{ROH} in cases for example, while the two Australian and two US studies all showed increased F_{ROH} in controls. This may reflect confounding demographic factors specific to each country. These unknown confounders, such as urban/rural status or religion, that influence both distant inbreeding (F_{ROH}) and MDD could explain the differences in effects between studies. A recent analysis of ROH and MDD in a partially overlapping sample of the GAIN study analysis here found exactly that, with religion confounding of the association because of reduced levels of depression but increased inbreeding in within the religious population of the Netherlands (Abdellaoui and others 2013). Certainly the initial hypothesis of this study, that an association with inbreeding would reflect negative selection on MDD and an excess of recessive causal mutations, seems an implausible explanation for the observed heterogeneity as the evolutionary cost of MDD status seems unlikely to have differed greatly among the ancestors of those included in the present study. Any of these explanations for the results of the F_{ROH} analysis may give some insight into why the mega-analysis of the 9 studies did not lead to any replicable genome-wide significant findings.

Our results from the genome-wide association analysis of MDD under a recessive model also produced no evidence for a recessive model, failing to produce any genome-wide significant associations. It is possible that our underlying model of recessive effect is unsuitable for an outbred population. Here we looked at a recessive effect for the minor allele, but two alternate models may also have been viable: compound heterozygote and overdominance. Compound heterozygosity is an additional risk in individuals carrying two recessive but non-identical alleles within a genetic locus, while overdominance is the increased risk of homozygosity of any allele compared to being heterozygous. However, our analysis of both would have been restricted by low power and the use of biallelic markers,

and were, therefore, not performed. Both the GWAS and ROH analyses suggest though that there is no underlying recessive model of MDD, at least not of large effect. Such an association was previously reported for schizophrenia in a similarly sized sample (Keller and others 2012), showing an increase of risk for schizophrenia by 17% for every additional percentage of the genome covered by ROH and was taken as evidence for historical selection against schizophrenia risk variants. The lack of a similar association here adds molecular evidence to that from epidemiological studies suggesting MDD has little impact on reproductive fitness compared to other psychiatric disorders, and so is under substantially less negative selection (e.g. Power and others 2012).

These results also highlight that analysis of F_{ROH} appears to be sensitive to systematic differences between studies that are ostensibly unrelated to MDD status, potentially give rise to either false positive or false negative results. This suggests there are genome-wide differences in homozygosity and/or inbreeding between populations that are not corrected for by methods such as ancestry-informative principal components. We recommend the use of large combined samples in the analysis of F_{ROH} as a predictor of traits and disorders, due to the high risk of spurious associations within one study. Preferably such analyses should be done in datasets with access to data on potential social and demographic confounders. One possible further improvement might be the development of novel methods for analysing ROH, particularly in imputed genotype data where probability for homozygosity across a region is available. As similar heterogeneity across studies was not seen in other analyses of ROH within consortia (Keller and others 2012; McQuillan and others 2012), the significant heterogeneity in our results suggest that MDD is particularly sensitive to differing demographics in the ascertainment of cases and controls and this may present a problem to genome-wide polygenic approaches such as ROH. Certainly no strong evidence for a recessive model was apparent, supporting the view of MDD being under weaker negative selection than other psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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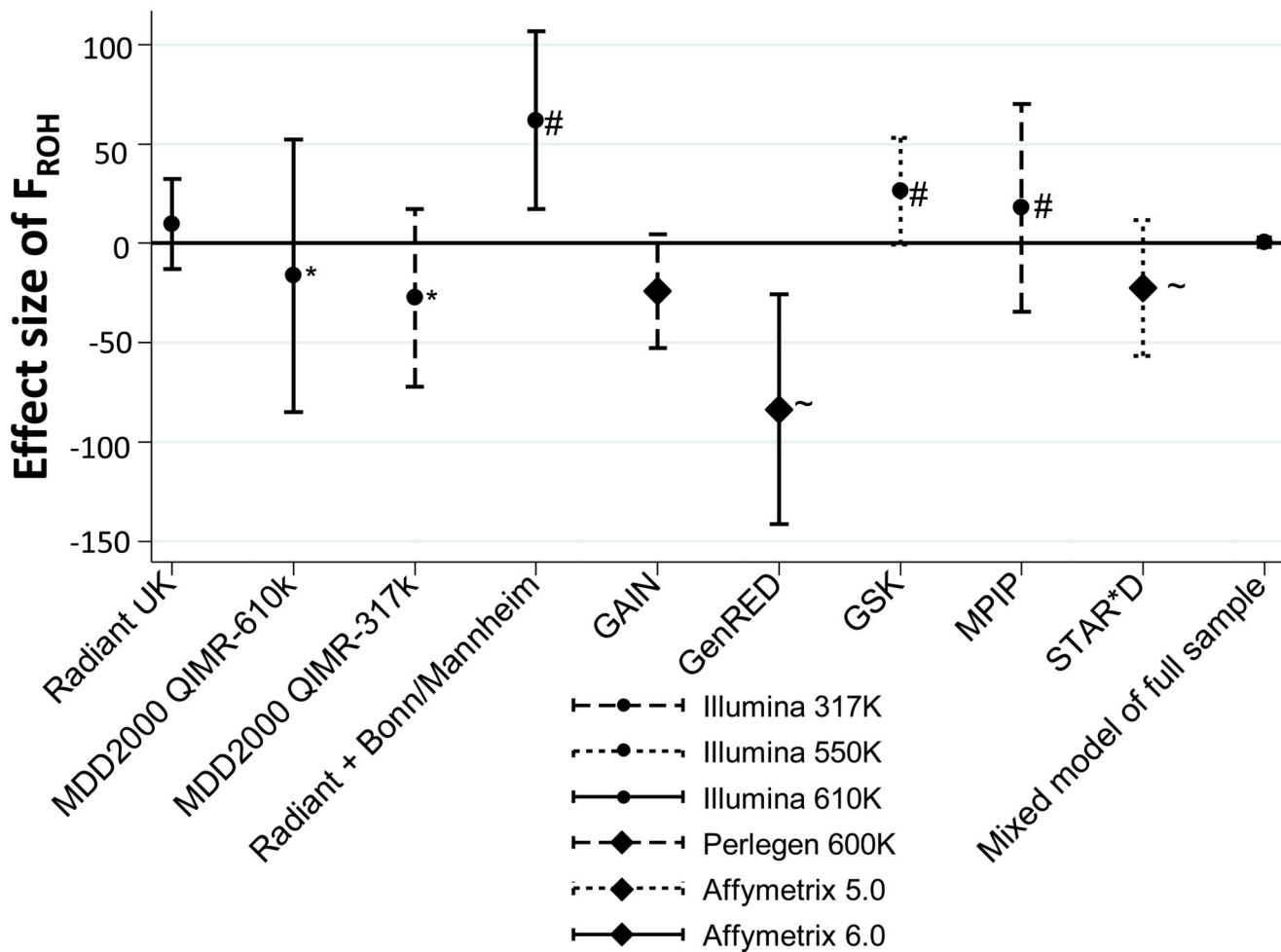
Figure 1.
Beta coefficient from logistic regression of F_{ROH} predicting MDD per study (with 95% CI, accounting for covariates). Positive effects suggest that ROHs are a risk factor for MDD. Note that though no combined effect in the mixed model of the full sample, in Illumina studies increased F_{ROH} was a risk factor (p=0.02) and in non-Illumina studies it was protective (p=0.007). Note also the consistency in studies from the same country: *Australian studies; ~American studies; # German studies.

Table 1

Summary statistics of each of the nine studies and results of runs of homozygosity analysis

Study	N cases	N controls	Platform	Recurrence (%)	Ascertainment	Country	Number of SNPs[b]	Mean F_{ROH} (%)[c]	SD of Mean F_{ROH} (%)[c]	Traditional F estimate (%)[d]	Mean size of ROH (kb)	SD for Mean size of kb	Ref
RADIANT UK	1,625	1,588	Illumina 610K	97.1	Clinical	UK	263,728	0.10	0.41	0.1	3294	1373	(Lewis and others 2010)
MDD2000 QIMR-610k	433	751	Illumina 610K	57.6	Population	Australia	275,259	0.09	0.19	–0.01	3376	1049	(Wray and others 2012)
MDD2000 QIMR-317k	1,017	960	Illumina 317K[a]	51.4	Population	Australia	210,075	0.09	0.24	0.06	3330	937	(Wray and others 2012)
Radiant + Bonn/Mannheim	935	1,290	Illumina 610K	74.2	Clinical	Germany	260,561	0.10	0.30	0.06	3580	1565	(Rietschel and others 2010)
GAIN	1,694	1,767	Perlegen 600K	50.7	Clinical /population	The Netherlands	199,749	0.12	0.36	0.15	3780	1840	(Sullivan and others 2009)
GenRED	1,030	1,253	Affymetrix 6.0	100	Volunteers	USA	253,826	0.08	0.18	0.09	3238	763	(Shi and others 2011)
GSK	887	864	Illumina 550K	100	Clinical	Germany	281,029	0.16	0.67	0.14	3732	1711	(Muglia and others 2010)
MPIP	376	537	Illumina 317K	36.7	Clinical	Germany	215,393	0.11	0.30	0.04	3533	1424	(Ising and others 2009)
STAR*D	1,241	511	Affymetrix 5.0	74.3	Clinical	USA	155,428	0.10	0.40	0.17	3362	783	(Shyn and others 2011)

[a] Genotyping was on either Illumina 317K or Illumina 370K SNPs, but only SNPs from Illumina 317K were used for imputation.

[b] After QC and pruning on linkage disequilibrium

[c] F_{ROH} is the percentage of the genome covered by runs of homozygosity.

[d] This measure of F reflects an individual's observed number of homozygous loci compared to that expected under Hardy–Weinberg equilibrium.