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No evidence that runs of homozygosity are associated with schizophrenia in an Irish genome-wide association dataset

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ABSTRACT

Runs of homozygosity (ROH), regions of the genome containing many consecutive homozygous SNPs, may represent two copies of a haplotype inherited from a common ancestor. A rare variant on this haplotype could thus be present in a homozygous and potentially recessive state. To detect rare risk variants for schizophrenia, we performed an ROH analysis in a homogeneous Irish genome wide association study (GWAS) dataset consisting of 1606 cases and 1794 controls. There was no genome-wide excess of ROH in cases compared to controls ($p = 0.7986$). No consensus ROH at individual loci showed association with schizophrenia after genome-wide correction.

1. Introduction

Schizophrenia is a complex psychiatric disorder of substantial heritability ($h^2 \sim 0.8$) characterized by hallucinations, delusions, disordered thinking and cognitive deficits (Cardno and Gottesman, 2000). The disorder poses a significant public health problem as it affects approximately 0.8% of the population, causes considerable morbidity and reduces average life expectancy by 20–25 years (Tiihonen et al., 2009). The onset of illness is typically in early adulthood, but despite current treatments, the evolution of symptoms, severity and course of the disorder are variable.

Understanding the genetic component of schizophrenia has been a major focus in the field, with the hope that this will aid development of more effective diagnostics and therapeutics. Recently a number of genome wide association studies (GWAS) have made encouraging progress in identifying a spectrum of common and rare genetic risk variants that contribute to schizophrenia susceptibility (Purcell et al., 2009; O'Donovan et al., 2008; Stefansson et al., 2008; Shi et al., 2009; International Schizophrenia Consortium, 2008; Ripke et al., 2011; Shi et al., 2011; Yue et al., 2011; Bergen et al., 2012; Irish Schizophrenia Genomics Consortium and the Wellcome Trust Case Control Consortium 2, 2012; Ripke et al., 2013). They have found evidence for a number of susceptibility loci including the major histocompatibility complex (MHC) region on chromosome 6p21–6p22.

Rare variant studies have primarily been studies of copy number variation. More recently, next-generation sequencing has extended the search for rare genetic risk factors to smaller structural and sequence variants using trio-based studies of *de novo* variation (Girard et al., 2011; Xu et al., 2011, 2012). An additional method of identifying genomic regions that harbor rare recessive risk mutations is to study runs of homozygosity (ROHs). These are regions of the genome that have many consecutive homozygous single nucleotide polymorphisms (SNPs). Unrelated individuals would be expected to possess several different homozygous regions of varying lengths across their genomes. If these regions are identical-by-descent, then both haplotypes have been inherited from a common ancestor. If a rare variant is carried on this haplotype, it will now be present in a homozygous and potentially recessive state. If a greater proportion of affected individuals share overlapping ROHs in a chromosomal region compared to controls, then this would present evidence that the region harbors a disease locus.

A number of studies have investigated the association between ROHs and schizophrenia (Lencz et al., 2007; Kurotaki et al., 2011; Keller et al., 2012) and also in bipolar disorder (Vine et al., 2009). Lencz et al. (2007) identified an excess burden of ROHs in individuals with schizophrenia compared to controls and went on to identify a number of

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regions that contained ROHs that were present in a higher proportion of the cases than in the controls. The design of Kurotaki et al. (2011) study was not a case–control study but instead examined nine individuals with schizophrenia whose parents were first cousins. The genome-wide SNP analysis of these individuals enabled the identification of a number of autozygous segments that were present in at least three of the individuals but the authors have not yet reported the fine mapping of a disease gene in these regions.

Keller et al. (2012) used ROHs to estimate the proportion of the autosome that exists in autozygous tracts. Autozygous tracts occur when the two chromosomal segments that are identical, coming from a common ancestor, are inherited from each parent. Keller et al. (2012) went on to estimate that the odds of schizophrenia increase by approximately 17% for every 1% increase in genome-wide autozygosity. They concluded that both distant and close inbreeding are risk factors for schizophrenia but their analysis of a very large multi-site sample ($n = 21{,}844$ from 17 sites in 11 countries) that contained data from various genotyping platforms did not identify any specific individual genomic regions as sites of rare risk variants.

We have undertaken a study of ROHs in a large all-Ireland schizophrenia case–control sample ($n = 3400$). Although obviously smaller than the Keller et al. (2012) study, this sample is three-fold larger than all but one of the individual-site samples in that study, and has the advantage of being drawn from a single relatively homogeneous population and has been genotyped on a single GWAS platform. The Keller et al. (2012) study contained 1130 Irish samples (264 cases and 866 controls). These samples are included in the study detailed in this paper with the addition of 1342 cases and 928 controls.

2. Materials and methods

2.1. Data and quality control (QC)

The data analyzed in this study consist of an Irish cohort of 1606 schizophrenia samples and 1794 unaffected population controls that were analyzed as part of the Wellcome Trust Case Control Consortium 2 (WTCCC2). The Keller et al. (2012) study included 1130 Irish samples which are also included in this study. A GWAS analysis of these data has previously been carried out and describes the sample, genotyping method (Affymetrix 6.0) and QC in full (Irish Schizophrenia Genomics Consortium and the Wellcome Trust Case Control Consortium 2, 2012). Following Howrigan et al. (2011), we also carried out additional QC before embarking on the ROH analysis, details of which are contained in the Supplementary material. After this QC, 252,688 SNPs remain for analysis. A CNV analysis was previously carried out on a subset of these data, but it was deemed that the effect of CNVs on the analyses presented here would be believed to be minimal; further details are provided in the Supplementary material.

2.2. Identification of ROHs and CROHs

Identification of ROHs was carried out using the PLINK (Purcell et al., 2007) software. Following Howrigan et al. (2011), ROHs were identified in each individual when 65 or more consecutive SNPs that belonged to homozygous regions were determined. Further details of how this was carried out are provided in Supplementary material. After identifying ROHs in individual samples the next step was to identify pools of overlapping and potentially matching ROHs across the samples. From these pools of overlapping ROHs we identified consensus ROHs (CROHs) — segments of ROHs that had a minimum number of SNPs (3), were of a minimum size (100 kb) and were shared by a minimum number of samples (2). CROHs were categorized according to their frequency into both common (observed in >1% of individuals (≥34 individuals in these data)) and rare CROHs (observed in ≤1% of individuals (<34 individuals in these data)).

The reason for examining ROHs was to detect evidence of identity-by-descent and hence that both haplotypes had been inherited from a common ancestor. In this scenario, if a rare variant is carried on this haplotype, then it is in a homozygous state and potentially a recessive variant. The reason for examining CROHs was to detect example loci where multiple cases and/or controls have ROH in the same region. But within a CROH, it is not the case that the same homozygous haplotypes are present in each individual. It may be the case that a number of different haplotypes are present in the homozygous state. This can indicate allelic heterogeneity, multiple different rare variants in the homozygous state, each originating from a different common ancestor. It is the two alleles or haplotypes that have the common ancestor and not necessarily the individual cases or controls.

3. Results

3.1. Burden analysis

In total 38,732 ROHs were identified (18,353 in cases, 20,379 in controls) with the mean number of ROHs per individual being very similar for both the cases (11.43) and the controls (11.36). The mean amount of ROH (kb) is also similar for both the cases and the controls (12,820.54 kb in cases and 12,757.93 in controls). See Table 1 and Supplementary material for further details. A logistic regression analysis was also carried out to investigate whether the amount of ROH per individual could be used to predict case–control status. There is no evidence in the data to suggest this (OR = 1.000001, $p = 0.7986$).

3.2. CROH common and rare analysis

For each of the CROHs an analysis was carried out to determine if the proportion of individuals with the CROH was the same in cases and in controls. This was carried out using either a chi-square test or Fisher's exact test if the expected cell counts in the corresponding 2×2 tables were low. In total, 89 common CROHs were detected (mean size = 209.67 kb, SD = 136.36 kb) and 3 of these reached nominal significance when tested in cases versus controls (Table 2). A total of 1501 rare CROHs were detected (mean size = 189.68 kb, SD = 109.27 kb) and 58 of these reached nominal significance ($p \leq 0.05$) when tested for

Table 1
Summary statistics for ROHs.

	Pruned VIF = 10 (252688 autosomal SNPs)	
	Cases ($n = 1606$)	Controls ($n = 1794$)
Number of ROHs		
Total no. of ROHs	18,353	20,379
Mean (SD) no. of ROHs per individual	11.43 (3.91)	11.36 (4.03)
Median no. of ROHs per individual	11	11
Min no. of ROHs per individual	2	1
Max no. of ROHs per individual	37	40
Amount of ROH per individual		
Mean (SD) amount of ROH (kb) per individual	12,820.54 (7270.4)	12,757.93 (7032.22)
Median amount of ROH (kb) per individual	11,596.86	11,632.85
Min amount of ROH (kb) per individual	1195.43	942.32
Max amount of ROH (kb) per individual	105,605.35	78,611.3
Proportions with ROHs		
Proportion of individuals with >2 ROH	1	1
Proportion of individuals with >5 ROH	0.96	0.95
Proportion of individuals with >10 ROH	0.56	0.56
Proportion of individuals with >15 ROH	0	0

Data pruning was carried out using the variance inflation factor (VIF) LD option in PLINK v1.07 (Purcell et al., 2007). SNPs with a VIF > 10 ($R^2 > 0.9$) with other SNPs in a 50 SNP window were removed. Standard deviation is abbreviated as SD.

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Table 2
Analysis of common CROHs.

Common CROHS										
Chr	SNP1	SNP2	BP1	BP2	KB	NSNP	Cases *n*	Controls *n*	*p*	EMP *p*
3	rs4263329	rs17717909	167022304	167254993	232.689	11	9	27	0.0072	0.4549
5	rs9313871	rs1382334	160480641	160584945	104.304	6	14	32	0.0216	0.862
12	rs2081817	rs17312079	85620974	85824142	203.168	9	11	25	0.0439	0.9257

BP1: base pair location for start of CROH (consensus run of homozygosity), BP2: base pair location for end of CROH. NSNP: number of SNPs in the CROH. EMP *p*: empirical global *p* based on 500,000 permutations, carried out using PLINK (Purcell et al., 2007).

association (Table 3 shows significance less than 0.01; all nominally significant rare CROHs are shown in Table S1). Tables 2 and 3 also display genome-wide corrected empirical global *p*s for each of the nominally significant CROHs based on 500,000 permutations (carried out using PLINK (Purcell et al., 2007)). None of the CROHs remain significant after this correction.

4. Discussion

We have used GWAS data from the relatively homogeneous Irish population to perform an ROH analysis in a schizophrenia case–control sample in order to detect potential sites of risk variation for this disorder. In populations where consanguineous marriages occur and in isolated populations where limited random mating can take place, an increase in the level of homozygosity is expected. But there is evidence that in outbred populations a high frequency of ROHs exists (Gibson et al., 2006; Li et al., 2006; Simon-Sanchez et al., 2007). It is this evidence that has led a number of authors to explore the possibility that ROHs may harbor rare genetic variants that might offer an explanation for part of the heritability of a number of complex disorders.

It is not the case that the Irish population can be considered a population isolate; rather it is an outbred population that is relatively homogeneous with limited admixture (Hill et al., 2000). Evidence has previously been presented, showing slightly elevated levels of linkage disequilibrium and genome-wide homozygosity in Ireland when compared with neighboring British and European populations (O'Dushlaine et al., 2010). This suggests that the Irish population can be considered a suitable population for the study of recessive genetic effects such as those likely to be identified through CROHs.

Current evidence provided mainly through large sample GWASs (for example, Ripke et al., 2011, 2013), shows that there is a substantially large number of variants that are contributing to the risk of schizophrenia. Each of these individual variants is of small effect, but this evidence lends support for the polygenic model of schizophrenia. Although many of these variants may be common, there is also evidence suggesting that many rare variants are also playing a role and contributing to risk (Moens et al., 2011; Lee et al., 2012). As argued by Keller et al., 2012, rare risk variants of large effect will have been selected against and are more likely to appear in a recessive state. This lends support for pursuing ROHs as a potential means of identifying rare recessive variants that may be contributing to the heritability of schizophrenia.

Overall, we did not find any major differences between cases and controls in terms of the number of ROHs per individual or the amount of genomic sequence within ROHs per individual. We did identify specific genomic regions where the number of CROHs mapping to these regions was significantly different between cases and controls. These totaled 3 regions for common CROHs and 58 regions for rare CROHs but none remained significant after we performed empirical genome-wide corrections. We cross-referenced these 61 regions with regions of interest in schizophrenia genetics. Specifically, we checked for overlap with sites of known CNVs for schizophrenia and other neurodevelopmental disorders (Cooper et al., 2011 and Malhotra and Sebat, 2012) and with sites where common variants have been associated with schizophrenia at a genome-wide level (Purcell et al., 2009; O'Donovan et al., 2008; Stefansson et al., 2008; Shi et al., 2009; Ripke et al., 2011; Shi et al., 2011; Yue et al., 2011). No schizophrenia region of interest based on either CNV or SNP data was hit by a nominally associated CROH from this study.

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Contributors

DWM and APC proposed the study. PC, GD, FAON, KSK, BPR, WTCCC2, MG, APC, and DWM carried out sample collection and data preparation. EAH and DWM carried out the statistical analyses and writing of the manuscript.

Table 3
Analysis of rare CROHs.

Rare CROHS										
Chr	SNP1	SNP2	BP1	BP2	KB	NSNP	Cases *n*	Controls *n*	*p*	EMP *p*
10	rs808411	rs6585323	116774628	117029683	255.055	4	3	18	0.0024	0.0984
5	rs10051972	rs16873292	75280670	75603935	323.265	46	8	0	0.0025	0.151
1	rs6428453	rs2038926	196592080	196867820	275.74	16	6	24	0.0027	0.1701
1	rs3819033	rs11247932	26380880	26562246	181.366	14	2	15	0.0033	0.2276
4	rs13139421	rs1960679	173233931	173351703	117.772	9	10	1	0.0037	0.2339
6	rs2504433	rs1598866	77437260	77556894	119.634	20	10	1	0.0037	0.2037
1	rs1011338	rs2146483	196958987	197162234	203.247	15	7	25	0.0039	0.2843
3	rs6794860	rs2625288	102892355	103028009	135.654	5	18	6	0.0063	0.382
3	rs17066802	rs11711506	62637893	62823366	185.473	32	11	2	0.0068	0.4303
4	rs17628268	rs6831071	113550221	113671486	121.265	13	1	11	0.0068	0.4711
17	rs516434	rs2091317	8811740	8953426	141.686	22	1	11	0.0068	0.1843
18	rs9949320	rs11660574	25199079	25326068	126.989	6	11	2	0.0068	0.1907
17	rs3785579	rs9894480	62472963	62720260	247.297	9	0	8	0.0084	0.1988
7	rs7783102	rs7805021	127302906	127447587	144.681	5	3	15	0.0092	0.4359

BP1: base pair location for start of CROH (consensus run of homozygosity), BP2: base pair location for end of CROH. NSNP: number of SNPs in the CROH. EMP *p*: empirical global *p* based on 500,000 permutations, carried out using PLINK (Purcell et al., 2007).

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Conflict of interest

All authors disclose that they have no conflict of interest in relation to the publication of this manuscript and its contents.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.01.038.

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