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Genetic liability for schizophrenia predicts risk of immune disorders

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ABSTRACT

Background: Schizophrenia patients and their parents have an increased risk of immune disorders compared to population controls and their parents. This may be explained by genetic overlap in the pathogenesis of both types of disorders. The purpose of this study was to investigate the genetic overlap between schizophrenia and three immune disorders and to compare with the overlap between schizophrenia and two disorders not primarily characterized by immune dysregulation: bipolar disorder and type 2 diabetes.
Methods: We performed a polygenic risk score analysis using results from the schizophrenia Psychiatric GWAS consortium (PGC) (8922 cases and 9528 controls) and five Wellcome Trust Case Control Consortium (WTCCC) case samples as target cases: bipolar disorder (n = 1998), type 1 diabetes (n = 2000), Crohn's diseases (n = 2005), rheumatoid arthritis (n = 1999), and type 2 diabetes (n = 1999). The WTCCC British Birth Cohort and National Blood Service samples (n = 3004) were used as target controls. Additionally, we tested whether schizophrenia polygenic risk scores significantly differed between patients with immune disorder, bipolar disorder, and type 2 diabetes respectively.
Results: Polygenic risk scores for schizophrenia significantly predicted disease status in all three immune disorder samples (Nagelkerke-R^2 1.1%–1.3%; $p < 0.05$). The polygenic risk of schizophrenia in patients with immune disorders was significantly lower than in patients with bipolar disorder (Nagelkerke-R^2 6.0%; $p < 0.05$), but higher than in type 2 diabetes patients (Nagelkerke-R^2 0.5%; $p < 0.05$).
Conclusions: Our results suggest that genetic factors are shared between schizophrenia and immune disorders. This contributes to an accumulating body of evidence that immune processes may play a role in the etiology of schizophrenia.

1. Introduction

Schizophrenia is to a large extent influenced by genetic factors (Sullivan et al., 2003). The genetic architecture is complex: between 23% and 50% of the variance is explained by thousands of independent common genetic variants (Lee et al., 2012; Ripke et al., 2013), suggesting a polygenic model in which a large number of genetic variants contribute to disease risk (Purcell et al., 2009; Lee et al., 2012). Epidemiological studies have shown increased incidence of immune disorders in patients with schizophrenia and their relatives. A large epidemiological study performed in Denmark, including 7704 patients with schizophrenia and 192,590 matched controls without a psychiatric record, showed that schizophrenia patients have a 45% higher lifetime incidence of one or more immune disorders which were present prior to the onset of schizophrenia compared to matched controls (Eaton et al., 2006). This increased risk is not merely a consequence of the psychiatric disorder since the diagnosis of immune disorder was made before the onset of schizophrenia. Furthermore, the incidence rate ratio (IRR) was also higher in parents of schizophrenia patients than among parents of comparison subjects. The risk for 12 out of 29 reported immune disorders in parents of schizophrenia patients was significantly increased, whereas no significant decrease in risk was reported for any of the disorders (Eaton et al., 2006).

The increased incidence of immune disorders in schizophrenia patients and their parents is generally consistent with other epidemiological findings (Leucht et al., 2007; Eaton et al., 2010; Chen et al., 2012). A notable exception is the risk of rheumatoid arthritis, which has been found to be increased in parents of schizophrenia patients compared to parents of controls (Gilvarry et al., 1996; Eaton et al., 2006), whereas other epidemiological studies comparing patients with controls have reported schizophrenia to be a protective factor for rheumatoid arthritis (Leucht et al., 2007; Chen et al., 2012). This discrepancy suggests that although environmental and disease-related factors may protect schizophrenia patients from rheumatoid arthritis, genetic or other family-related factors may increase the risk of rheumatoid arthritis.

One of the hypotheses for the increased incidence of immune disorders in schizophrenia patients and their relatives is that common molecular pathways are involved in the pathogenesis of both types of

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disorders. Genetic alterations in these pathways may therefore contribute to a higher incidence of both schizophrenia and immune diseases. Obvious candidates for such shared genetic risk factors include the variants in the human leukocyte antigen (HLA) region which contribute to the risk of schizophrenia (Purcell et al., 2009; Stefansson et al., 2009). In addition, a recent study showed that a relatively large segment at chromosome 5 is enriched for single nucleotide polymorphisms (SNPs) which are significantly associated with schizophrenia (Gladwin et al., 2012). This region contains genes previously found to be related with schizophrenia (e.g., ACSL6, NEUROG1) and many immune-related genes, such as interleukin (IL)-4, IL-5, IL-13, and transforming growth factor (TGF) β-1. Interestingly, linkage studies had already implicated chromosome 5q31 in both schizophrenia and Crohn's disease (Schwab et al., 2000; Rioux et al., 2001).

Thus far, the genetic overlap between schizophrenia and autoimmune disorders has been investigated by targeted approaches which focus on the role of specific candidate genes or regions which may contribute to the risk of both types of disorders. However, like schizophrenia, immune disorders have a complex genetic architecture (Goris and Liston, 2012; Parkes et al., 2013). Therefore, a more systematic approach would be to study the genetic overlap between schizophrenia and immune disorders based on genome-wide association data using polygenic risk score analysis (Purcell et al., 2009). Polygenic risk scores are a measure of disease liability and can be used to investigate the genetic overlap between disorders at a genome-wide level.

The aim of this study is to investigate the genome-wide genetic overlap between schizophrenia and three disorders primarily characterized by immune dysregulation: type 1 diabetes, rheumatoid arthritis, and Crohn's disease. We compare the genetic overlap between schizophrenia and immune disorder patients with the overlap between schizophrenia and bipolar and type 2 diabetes patients, a psychiatric disease and a somatic disease which is not primarily characterized by immune dysfunction.

2. Methods

2.1. Data

We used results from the schizophrenia Psychiatric GWAS Consortium (PGC) data, a large collection of 17 case–control GWAS samples of European descent (9394 cases and 12,462 controls in total) (Ripke et al., 2011), to compute polygenic risk scores in five case–control samples from the Wellcome Trust Case Control Consortium (WTCCC) (Burton et al., 2007). The case samples included type 1 diabetes (T1D) (n = 2000), rheumatoid arthritis (RA) (n = 1999), Crohn's disease (CD) (n = 2005), bipolar disorder (BD) (n = 1998), and type 2 diabetes (BD) (n = 1999) (Burton et al., 2007). These case samples were chosen to compare the three immune disorders (i.e., rheumatoid arthritis, Crohn's disease, and type 1 diabetes) with a psychiatric disease (bipolar disorder) and a somatic disorder which is not primarily characterized by immune dysfunction (type 2 diabetes). For all disorders the same WTCCC control subjects from the National Blood Service (NBS) (n = 1500) and 1958 Birth Cohort (1958BC) (n = 1504) were used (Burton et al., 2007).

2.2. Quality control

We first removed subjects and SNPs that the WTCCC recommended to exclude (Burton et al., 2007). See Fig. S1 in the Supplemental information for a detailed flow chart of the subsequent pre-imputation Filter 1 to 5. Before merging the WTCCC case and control samples, we applied the following filtering steps to the seven WTCCC subsamples using PLINK (Purcell et al., 2007): minor allele frequency (<0.01), genotype missingness (>0.05), individual missingness (>0.02), genotype missingness once again (>0.02) (Filter 1), Hardy–Weinberg equilibrium in controls ($p < 0.001$) (Filter 2), and minor allele frequency difference with a HapMap reference panel (>0.1) (Filter 3). The reference panel consisted of HapMap III founders from the CEPH Utah residents with Northern and Western European ancestry sample (CEU) and Tuscans in Italy (TSI) sample (n = 200) (Altshuler et al., 2010).

After combining the NBS and 1958BC control samples, we removed SNPs significantly ($p < 10^{-8}$) associated with control sample membership (Filter 4). Subsequently, we combined case and control samples for each disorder, applied Filter 1 again to the resulting case–control samples, and removed any SNPs which were extremely significantly ($p < 10^{-50}$) associated with disease status (Filter 5).

2.3. Principal component analysis

To correct for population stratification, we then calculated ten principal components for each WTCCC case–control sample. Each case–control sample was pruned to ensure relative independence between SNPs (PLINK command –indep-pairwise 50 5 0.2) for principal component analysis. The remaining SNPs were used to calculate ten principal components with EIGENSTRAT (Price et al., 2006). We similarly computed ten principal components for all cases combined to allow for correction of population stratification in a direct comparison of diseases (see section).

2.4. Imputation

After principal component analysis, all WTCCC subsamples were imputed with Beagle (Browning and Browning, 2007) using the HapMap Phase III CEU + TSI founders (version 2, build 36) as a reference panel (Altshuler et al., 2010). SNPs with a quality threshold of $r^2 < 0.6$ were excluded. The 113,664 independent SNPs remaining after the schizophrenia PGC clumping analysis were considered for upstream analysis (Ripke et al., 2011). Further post-imputation QC consisted of removing SNPs with MAF < 0.01. Additionally, subjects identified as outliers (s.d. > 6) during principal component analysis were removed from the case–control samples. One of the members of a pair of relatives (pi-hat > 0.2 in PLINK) was removed as well. Table S1 in the Supplemental information shows the number of subjects and SNPs retained per case–control sample after these preprocessing steps.

2.5. Meta-analysis of PGC schizophrenia effect sizes

We meta-analyzed the effect sizes of the PGC schizophrenia samples (Ripke et al., 2011) using a fixed effects model in METAL (Willer et al., 2010), excluding the Cardiff UK sample to prevent overlap with the WTCCC controls (resulting in 8922 cases and 9528 controls).

2.6. Polygenic risk score analysis

Based on the meta-analyzed log(odds ratios) we computed additive schizophrenia polygenic risk scores for individuals in all five preprocessed WTCCC case–control samples using PLINK (Purcell et al., 2007). Based on different p-value thresholds for association with schizophrenia ($p < 0.1$ to $p < 1$ with steps of 0.1), we created different subsets of SNPs to compute the polygenic risk scores. These threshold-dependent polygenic risk scores were then standardized and used as a predictor in logistic regression to predict disease status in each respective case–control sample. Standardization limits the range of the coefficients, but does not affect the Nagelkerke-R^2 and p-values. To account for differences in population structure, we first included only 10 PCA components as covariates in the logistic regression and then added the polygenic risk score in a second model. We used the difference in Nagelkerke's pseudo-R^2 between the two nested models to represent the effect of polygenic risk score above and beyond the effect of population stratification. The Nagelkerke R^2 is analogous, but

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