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Interaction between compound genetic risk for schizophrenia and high birth weight contributes to social anhedonia and schizophrenia in women

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ABSTRACT

Schizophrenia is a highly heritable disease, but despite extensive study, its genetic background remains unresolved. The lack of environmental measures in genetic studies may offer some explanation. In recent Finnish studies, high birth weight was found to increase the risk for familial schizophrenia. We examined the interaction between a polygenic risk score for schizophrenia and high birth weight on social anhedonia and schizophrenia in a general population birth cohort. The study sample included 4223 participants from the 1966 Northern Finland Birth Cohort. As a replication sample we used 256 participants from a systematically collected sample of Finnish schizophrenia families. The polygenic risk score comprised of variants published in the large genome-wide meta-analysis for schizophrenia. We found the association between the polygenic risk score and social anhedonia stronger among those with high birth weight, and the same phenomenon was seen for schizophrenia among women, suggesting a gene-environment interaction. Similar results were found within the replication sample. Our results suggest a role for gene-environment interactions in assessing the risk of schizophrenia. Failure to take environmental effects into account may be one of the reasons why identifying significant SNPs for schizophrenia in genome-wide studies has been challenging.

1. Introduction

Schizophrenia is a highly heritable mental disorder - its heritability estimate is up to 80% (Sullivan et al., 2003) - and its genetic background has been studied intensively. Nonetheless, the genetic architecture behind schizophrenia is not well understood, as a substantial proportion of its genetic background remains unresolved. It has been shown that thousands of common single nucleotide variants, each with a minor effect, might cumulatively explain one-third of the variance in the disease risk (International Schizophrenia Consortium et al., 2009).

Several hypotheses have been proposed to explain the unexplained portion of the heritability estimate. One such hypothesis is gene-environment interactions (G x E) (van Dongen and Boomsma, 2013). Environment clearly plays a role in the development of schizophrenia (Tandon et al., 2008), and, like genetic effects, environmental effects have shown wide heterogeneity across individuals as well. Genes do not operate in isolation of the environment and it is highly plausible that we will not fully understand the genetics of schizophrenia if the environment is not also taken into consideration. A proof of principle for gene-environment interactions in schizophrenia has been provided by candidate gene studies (Modinos et al., 2013), and in studies where familial background has been used as a measure of genetic liability (e.g.

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Clarke et al., 2009). To our knowledge there is one published genome-wide gene-environment interaction study (GEWIS) on schizophrenia (Børglum et al., 2014). In that study Borglum and colleagues (2014) found a significant interaction between a SNP on *CTNNA3* and maternal cytomegalovirus infection on schizophrenia. To date, G x E studies have not yet fully exploited the genetic knowledge gained from large genome-wide meta-analyses. To our knowledge there is one published study that studied G x E with polygenic risk scores on schizophrenia (Trotta et al., 2016).

The prenatal environment is one of the environments most consistently related to schizophrenia. One of the most widely used markers of prenatal environment is birth weight. Both low and high birth weight have been related to the risk of schizophrenia (Moilanen et al., 2010). While the effect of low birth weight seems to be consistent across cohorts (Abel et al., 2010a), high birth weight tends to be a risk factor in older cohorts when, for example, gestational diabetes was neither systematically screened nor treated, induction of delivery was more rare and based on less accurate estimation of fetal weight, and high-quality obstetric care was not always available if a large birth weight caused problems during delivery (Moilanen et al., 2010; Wegelius et al., 2011). The variable associations with *high* birth weight suggest that it is particularly relevant with respect to gene-environment interactions. Accordingly, in two recent Finnish studies, *high* birth weight was found to considerably increase the risk for schizophrenia in already high-risk families (Keskinen et al., 2013; Wegelius et al., 2011). Keskinen and coauthors (2013) observed that high birth weight, not low, increased the risk for schizophrenia if the participant's parents had a history of psychosis. This suggests that genetic liability for schizophrenia, as indicated by parental psychosis, might interact with *high* birth weight in the development of schizophrenia.

Our aim was to examine the interaction between a polygenic risk score for schizophrenia and high birth weight on social anhedonia, an intermediate phenotype reflecting schizophrenia liability (Cohen et al., 2011; Miettunen et al., 2011; Kwapil, 1998), and schizophrenia diagnosis in a general population birth cohort. We hypothesized that having higher genetic risk score together with high birth weight would be associated with higher scores on social anhedonia and with higher risk for schizophrenia.

2. Methods

2.1. Study sample

The study sample (n = 4223) was derived from the Northern Finland Birth Cohort 1966 (NFBC1966), which is an unselected birth cohort consisting of 12 058 live-born children in Northern Finland (Rantakallio, 1969). The cohort represents the general population by covering 96,3% of all births during year 1966 in the provinces of Lapland and Oulu. The cohort has been prospectively followed from the perinatal period to adulthood, and the study sample consists of those participants of the 31-year follow-up study who had DNA and other data used in the study available. Attrition analysis of the 31-year follow-up has been described elsewhere (Haapea et al., 2008). The study has been approved by The Ethics Committee of the Northern Ostrobothnia Hospital District, and all participants gave written consent.

2.2. Replication sample

The replication sample (n = 256) was derived from a systematically collected sample of Finnish schizophrenia families, the Schizophrenia family sample (FSZ). Families were identified through a search of nationwide health care and population registries. All individuals born in Finland between 1940 and 1976 were screened for hospitalization during the period from 1969 to 1998 (Hospital Discharge Register), for use of free outpatient antipsychotic medication (Medication Reimbursement Register), or disability pension (Pension Register) due to schizophrenia, schizoaffective disorder, or schizophreniform disorder. Pedigrees were constructed by linking the personal identification numbers of the affected individuals to their parents and siblings, derived from the Population Register Centre. Two samples of subjects were contacted: 1) the first sample (All Finland) consisted of families with at least two siblings with schizophrenia and their first-degree relatives from the whole geographical area of Finland; and 2) the second sample (Internal Isolate) comprised patients and their relatives from families with at least one member with schizophrenia from Kuusamo, a historically isolated region in the north-eastern part of the country with an exceptionally high lifetime risk of schizophrenia (Hovatta et al., 1999; Arajärvi et al., 2005). The study has been approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa, and all participants gave written consent.

The total sample consists of 3335 individuals with DNA samples, but availability of birth weight and social anhedonia data limits the number of participants used for the replication; we had 256 and 133 individuals for the schizophrenia and social anhedonia analysis, respectively.

2.3. Measures

2.3.1. Social anhedonia

Social anhedonia was self-rated using the revised Social Anhedonia Scale (Chapman et al., 1976). The scale includes 40 true/false questions assessing one's interest in social interaction. Sample items of the scale are: “Having close friends is not as important as many people say.” and “People sometimes think I am shy when I really just want to be left alone.” The distribution of the social anhedonia scale was positively skewed in both samples and we performed a square-root transformation for the scale. *Study Sample*. Social anhedonia was measured as a part of the cohort's 31-year follow-up in 1997. The psychometric properties of the scale in this cohort have been described elsewhere (Miettunen et al., 2010). *Replication Sample*. Social anhedonia was only measured in a subsample derived from the *All Finland Sample* during the data collection in 1999–2001. The reliability of the scale in this sample has been reported earlier (Kuha et al., 2011).

2.3.2. Schizophrenia spectrum diagnosis

Schizophrenia spectrum diagnosis in the *Study Sample* was assessed using several national registers (the Finnish Hospital Discharge Register and national registers of the Finnish Social Insurance Institute) and clinical interviews. The diagnoses were made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, revised 3rd edition (DSM-III-R). In order to increase the power of our population-based study, we included as cases all participants who had either schizophrenia diagnosis or a diagnosis belonging to the schizophrenia spectrum (schizoaffective, schizophreniform, delusional disorder). *Replication Sample*. Schizophrenia diagnoses were made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). All available inpatient and outpatient records were collected from participants and their relatives, if they had any psychiatric diagnosis according to the registers (Hospital Discharge Register, Medication Reimbursement Register, and Pension Register). Some of the participants were also interviewed with the Structured Clinical Interview for DSM-IV diagnosis. Two psychiatrists blind to the family structure estimated independently the best-estimate lifetime diagnosis according to the criteria of the DSM-IV. In case of any disagreement, a third reviewer was used. Consensus diagnoses were made based on these independent estimates.

2.3.3. Birth weight

Study Sample. Information on birth weight was collected from child welfare clinic registries and with questionnaires filled in by the mothers during the years 1965–1967. We dichotomized birth weight as “more than 4 kg” and “4 kg or less” based on earlier Finnish findings on the