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Effects of season of birth and a common MTHFR gene variant on the risk of schizophrenia

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Abstract
Season of birth – in particular winter birth – has been persistently related to increased schizophrenia risk. Variation in folate intake is among the explanations for this seasonal effect. Methylenetetrahydrofolate reductase (MTHFR) is an essential enzyme in the folate mediated methylation transfer reactions. Interestingly, the MTHFR gene has been related to schizophrenia risk in various studies. We investigated a possible interaction between MTHFR 677 C>T polymorphism and winter birth in the development of schizophrenia in a group of 742 schizophrenia patients and 884 control subjects. All subjects were of Dutch ancestry. Winter birth (December up to and including February) was associated with a 20% increase in schizophrenia risk (odds ratio (OR) of 1.20 and 95% confidence interval (CI), 0.96–1.5; $P=0.113$). The MTHFR 677TT genotype was associated with an overall schizophrenia risk of 1.13 (95% CI, 0.82–1.57; $P=0.454$) compared with the MTHFR 677CC genotype. In the winter period the MTHFR 677TT genotype associated schizophrenia risk was 0.90 (95% CI, 0.47–1.70; $P=0.744$). In conclusion, neither winter birth nor MTHFR genotype were significantly associated with increased schizophrenia risk. There was no evidence for interaction between MTHFR 677TT genotype and winter birth in the development of schizophrenia.

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1. Introduction

Schizophrenia is thought to be a complex and chronic brain disorder caused by multiple interacting genes influenced by environmental factors (Tandon et al., 2008) possibly starting in utero (Weinberger, 1987). An environmental factor that has persistently been related to schizophrenia risk is the season of birth. Since the first report in 1929 (Tramer, 1929), numerous studies have been published providing evidence for a correlation between schizophrenia and season of birth (Davies et al., 2003; Torrey et al., 1997). For individuals born in the Northern Hemisphere in particular birth during late winter or early spring has been associated with a 5–10% greater likelihood of developing schizophrenia (Bembenek and Kociuba, 2005; Davies et al., 2003; Mino and Oshima, 2006; Selten et al., 2000; Torrey et al., 1997). A winter birth effect has been associated also with several other diseases of the central nervous system, such as Multiple Sclerosis, Alzheimer's disease, Parkinson's disease (Mattson and Shea, 2003), and neural tube defects (NTD) (Blom et al., 2006). Remarkably, schizophrenia and NTD show similarities in a number of other epidemiological findings such as post famine peaks and urban place of birth (Zammit et al., 2007). These overlapping patterns of risk for schizophrenia and NTD may indicate one or more shared etiological risk factors.

In neural tube defects the findings that periconceptual folate administration was followed by a reduction in occurrence (Czeizel and Dudás, 1992) and recurrence (MRC Vitamin Study Research Group, 1991) of NTD initiated research in the role genes involved in the folate-related pathways. The first and nowadays most consistently replicated folate-sensitive genetic factor of NTD is the MTHFR 677 C>T polymorphism (Blom et al., 2006; Van der Put et al., 1995). The 677 C>T polymorphism results in a thermolabile enzyme with decreased activity. MTHFR specific activity in homozygous 677TT genotype individuals is 30–50% of that of 677CC wild-type genotype individuals (Chango et al., 2000; Frosst et al., 1995). The MTHFR specific activity in 677CT heterozygotes shows a intermediate value. The 677TT genotype may cause elevated plasma homocysteine concentrations and aberrant methylation especially when folate concentrations are in the low-to-normal range (Jacques et al., 1996; Tanaka et al., 2009). MTHFR is a key enzyme in homocysteine metabolism which provides methyl groups for the formation of DNA, RNA, lipids, or neurotransmitters and plays a role in the composition of purines and pyrimidines (Mason, 2003). These methylation processes are vital for normal cell functioning, especially during periods of rapid growth. In vitro and animal studies support the view of direct adverse effects of homocysteine on neuronal cells showing that the nervous system is sensitive to folate deprivation and raised homocysteine levels (Mattson and Shea, 2003). Meta-analyses also support the association of the MTHFR 677 C>T polymorphism and risk of schizophrenia (Allen et al., 2008; Muntjewerff et al., 2006; Yoshimi et al., 2010).

We propose that folate as seasonally varying environmental factor acting in utero might influence the risk of schizophrenia in concert with the MTHFR gene. Folate requirements during gestation are 5 to 10 fold those in nonpregnant women (Bailey, 2000; Chitambar and Antony, 2005) a demand that must be met by adequate maternal dietary intake. Seasonal variation of maternal nutrient intake in pregnancy has been determined, showing that folate intake was lowest in winter months (Watson and McDonald, 2007), which may affect fetal development.

We hypothesized an interaction between MTHFR 677 C>T polymorphism and winter birth in the development of schizophrenia. In this context low folate especially during the last gestational trimester may act as a potential environmental risk factor interacting with the MTHFR gene. We investigated the frequency and its variation of this polymorphism according to seasonality of birth in a group of schizophrenia patients and control subjects.

2. Experimental procedures

2.1. Subjects

We included 742 unrelated schizophrenia patients (75% male), mean age of 39 years (SD=14). The patients were recruited from different psychiatric hospitals and institutions throughout the Netherlands, coordinated via academic hospitals in Amsterdam, Groningen, Maastricht and Utrecht. Detailed medical and psychiatric histories were collected, including the Comprehensive Assessment of Symptoms and History (CASH), an instrument for assessing diagnosis and psychopathology. All patients met the diagnostic DSM-IV criteria for schizophrenia. All patients were of Dutch descent, with at least three out of four grandparents of Dutch ancestry. The control group consisted of 884 participants recruited from the UMC Utrecht (46% male), mean age of 52 years (SD=20). The control sample consisted of volunteers and were screened with questionnaires in order to rule out manifest psychiatric disorders. All control subjects were free of any psychiatric history.

All subjects born in the Southern Hemisphere or having an unknown place of birth were excluded to ensure similar seasonal patterns. DNA samples were available of all 742 schizophrenia patients, and 884 control subjects. To exclude related patients and controls, all subjects were fingerprinted (Illumina DNA panel, 400 SNPs). Written informed consent was obtained from all participants. This study was approved by the Ethical Committee of the University Medical Centre Utrecht, Utrecht, The Netherlands.

2.2. Genotype analysis

Genomic DNA was extracted from peripheral lymphocytes. Samples were genotyped at the University of California, Los Angeles, on HumanHap550v3 BeadArrayTM (Illumina, San Diego, USA). The presence of a minor allele (A1) or major allele (A2) of SNP rs1801133 was determined.

2.3. Statistical analysis

We calculated odds ratio's (ORs) and corresponding 95% confidence intervals (CIs) as estimates of relative risk for schizophrenia in relation each month of birth relative to January and plotted these estimates together with a curve based on periodic regression. To assess seasonality of schizophrenia the month of birth was categorized into four climatic quarters: December–February (winter), March–May (spring), June–August (summer), September–November (autumn). Subsequently, the OR was used as the estimate of association between season of birth and risk of schizophrenia in those who are born in spring, summer and autumn compared to those born in winter.

To assess a possible interaction with MTHFR 677TT genotype we calculated odds ratio's as estimates of relative risk for schizophrenia for those with MTHFR 677TT compared to those with MTHFR 677CC genotype stratified for season. Again, we made a figure of the odds ratio's for each month of birth with a curve based on periodic