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Research report

Glutamate cysteine ligase (GCL) and self reported depression: An association study from the HUNT

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ABSTRACT

Background: There is increasing evidence suggesting oxidative stress may play a role in the aetiology of depression. Glutathione is the brain's predominant free radical scavenger, and associated polymorphisms of the glutamate cysteine ligase (GCL) gene have been reported for related psychiatric disorders. The aim of the study was to investigate candidate polymorphisms of GCL validated in schizophrenia and their association with current state depression, as measured by the Hospital Anxiety and Depression Scale (HADS).

Methods: Polymorphisms were genotyped on 983 cases and 967 controls selected from a population sample of adults participating in the Nord-Trøndelag Health Study. Cases were the top scoring individuals (98.5th percentile) on the HADS depression subscale while the controls were randomly selected from below this cut-off. The polymorphisms comprised three SNPs from GCLM, the gene encoding the GCL modifier and 9 SNPs plus a trinucleotide repeat (TNTR) from intron 1 and the 5′UTR of GCLC, the gene encoding the GCL catalytic subunit. Using the linkage disequilibrium between the GCLC markers we also tested whether SNPs could represent the variation of the TNTR.

Results: The candidate polymorphisms showed no evidence for association with depression. The C allele of SNP rs9474592 is coupled with the 9 GAG repeats allele of the TNTR, $r^2 = 0.81$. None of the other SNPs either individually or as two or three-SNP haplotypes was associated with the TNTR alleles.

Limitations: Depression was self-reported and measured at one time point.

Conclusions: This study provides no evidence to suggest that polymorphisms of GCL are associated with self-reported depression.

1. Introduction

Depression is a syndrome of complex and heterogeneous aetiology, with multiple interacting biopsychosocial factors,

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and the pathophysiology of depression remains incompletely understood (Malhi et al., 2005). In this context, there is growing evidence for the role of redox biology in a number of psychiatric disorders and their pathogenesis, including schizophrenia (Prabakaran et al., 2004), affective disorders (Ozcan et al., 2004), obsessive–compulsive disorder (Kuloglu et al., 2002a,b), panic disorder (Kuloglu et al., 2002b) and autism (Mostafa et al., 2010).

Oxidative stress refers to the accrual of oxidative products that ultimately leads to cellular dysfunction. The process of oxidative energy generation produces free radicals including reactive oxygen species (ROS) and reactive nitrogen species (RNS). In excess, or if buffering defences fail, these reactive species constitute oxidative stress, in turn oxidising proteins, lipids and deoxyribonucleic acid (DNA), resulting in cellular damage and dysfunction. Neurones may be particularly susceptible to oxidative damage, as the brain is among the most metabolically active tissues and generates particularly high levels of free radicals. Oxidative stress has been linked to mitochondrial dysfunction (Shao et al., 2008) and immune and inflammatory changes (Berk et al., 1997).

There is a range of data linking depression and oxidative stress. Individuals with depression have significantly elevated markers of oxidative damage, including the oxidised DNA marker 8-hydroxy-2′-deoxyguanosine (Forlenza and Miller, 2006), lipid peroxidation products (Ng et al., 2008), F_2-isoprostanes (*iso*-$PGF_{2\alpha}$) being biomarkers of oxidative damage and lipid peroxidation (Dimopoulos et al., 2008), and depleted omega-3 fatty acids indicative of oxidative damage of erythrocytic membranes (Peet et al., 1998). Reduced levels of antioxidants have been found in depression, including serum vitamins C and E and albumin (Khanzode et al., 2003; Maes et al., 2000; Van Hunsel et al., 1996). Additionally, alterations in key antioxidative enzymes superoxide dismustase (SOD) (Bilici et al., 2001; Khanzode et al., 2003; Sarandol et al., 2007), glutathione peroxidase (GSH-Px) and glutathione reductase (GR) (Bilici et al., 2001) have been described. Glutathione (GSH) is a key component of the defence system (Meister, 1988). N-acetyl cysteine (NAC), a precursor of glutathione, improved the core symptoms of schizophrenia (Berk et al., 2008a,b) and significantly reduced depressive symptoms in bipolar disorder with large effect sizes (Berk et al., 2008a,b).

The emerging oxidative stress hypothesis implies that genetic variants within genes of the oxidative pathways have a role in depression. Only a small group of studies have examined genetic markers of the glutathione system in psychiatric disorders. Tosic et al. (2006) compared the activity of glutamate cysteine ligase (GCL), the rate-limiting enzyme for glutathione synthesis, between schizophrenia cases and controls. They measured mRNA levels of the two GCL subunits, GCL modifier (GCLM) and GCL catalytic (GCLC) subunit. Both GCL subunits showed a trend for decreased mRNA levels in cases, which was significant for the modifier subunit. Furthermore, they investigated the associations of genetic polymorphisms of the gene encoding GCLM (GCLM), and reported evidence for dominant association of the G alleles of both rs2301022 (odds ratio (OR) 2.72, $P=.0005$) and rs3170633 (OR = 1.77, $P=.002$). Fullerton et al. (2010) have found an equivocal association between the G allele of rs2301022 and bipolar disorder. Gysin et al. (2007) showed that people with schizophrenia have a 26% decreased activity of GCL compared with controls in skin fibroblasts cultured under condition which increase the expression of genes involved in GSH synthesis. They complemented this functional study with a genetic association study using the trinucleotide GAG repeat located 10 bp 5′ to the start codon of the gene encoding GCLC (*GCLC*). This trinucleotide repeat (TNTR) is included in each of the four major transcripts of *GCLC*, and allelic variation at this polymorphism is strongly associated with GSH expression (Walsh et al., 2001); repeat sequences within promoter regions of genes are associated with transcriptional divergence (Vinces et al., 2009). Gysin et al. (2007) also reported an increased frequency of the rare 8/8 genotype in schizophrenia cases (6.8% vs. 2.4% in controls, OR = 2.96, p = 0.004) and a decreased frequency of the common 7/7 genotype in schizophrenia cases (27.8% vs. 37.8% in controls, OR = 0.61, p = 0.003). Kishi et al. (2008) examined the association between the GCLM gene and both methamphetamine use disorder and schizophrenia in a case control study. In this analysis, four SNPs were examined; one SNP showed an association with both methamphetamine use disorder and methamphetamine induced psychosis, but this was not significant after correction for multiple testing, and there was no significant association with schizophrenia (Kishi et al., 2008). Hashimoto and colleagues found a significant difference in the genotype frequency of GSTT1 between patients with methamphetamine psychosis and controls, as well as a higher frequency of the GSTT1 null genotype among individuals with a prolonged methamphetamine induced psychosis and spontaneous relapse (Hashimoto et al., 2008). In a report by Matsuzawa (2009), association studies examining the link between GSH-related genes (GSTM1, GSTP1, GSTO1, GSTT1, GSTT2, GPX1, and GCLM) and schizophrenia were performed in a Japanese population. This failed to find differences between schizophrenic patients and controls. However in those with residual-type schizophrenia, there was a suggestion of a different distribution of the GSTM1 genotype and in the combination analysis of GSTs, GPX1, and GCLM genotypes (Matsuzawa et al., 2009). Lastly, Butticaz et al. (2009) failed to replicate the association between polymorphisms of GCL and risk for schizophrenia. The relationship between this polymorphism and risk of psychiatric disorder therefore remains unclear.

Based on the evidence for a role of the glutathione system in depression, and in particular of GCLM and GCLC in schizophrenia, acknowledging both overlaps and differences in neurobiology between the two disorders, we investigated the association between the candidate polymorphisms identified by Gysin et al. (2007) and Tosic et al. (2006) and self reported depression, as measured by the Hospital Anxiety and Depression Scale (HADS) in a sample selected from a large Norwegian population study.

2. Methods

2.1. Study setting and subjects

This study uses data collected from both men and women participating in the second Nord-Trøndelag Health