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Glucocorticoid receptor gene haplotype predicts increased risk of hospital admission for depressive disorders in the Helsinki birth cohort study

Jari Lahti [a], Katri Räikkönen [a,*], Sara Bruce [b], Kati Heinonen [a], Anu-Katariina Pesonen [a,c], Anna Rautanen [d], Kristian Wahlbeck [e], Juha Kere [b,f], Eero Kajantie [c,e], Johan G. Eriksson [e,f,g]

[a] Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland
[b] Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden
[c] Hospital for Children and Adolescents, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland
[d] Wellcome Trust Centre for Human Genetics, University of Oxford, United Kingdom
[e] National Institute for Health and Welfare, Helsinki, Finland
[f] Folkhälsan Institute of Genetics, Helsinki, and Department of Medical Genetics, University of Helsinki, Finland
[g] Department of General Practice and Primary Health Care, University of Helsinki, Finland

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ABSTRACT

Background: Although glucocorticoid receptors (GR) are involved in mediating hypothalamic-pituitary-adrenal-axis functioning, which is altered in acute depression, data on associations between GR gene (*NR3C1*) polymorphisms and depression are scarce. We examined if single nucleotide polymorphisms (SNPs) and their haplotypes spanning the entire *NR3C1* are associated with depressive disorders and with self-reported depressive symptoms in adulthood.

Methods: We successfully genotyped 10 SNPs spanning the *NR3C1*, and performed SNP and haplotype analyses in 1075 women and 928 men participating in the Helsinki birth cohort study. Diagnoses of depressive disorders were extracted from the Finnish Hospital Discharge Register covering a 35-year period from early to late adulthood. In addition, depressive symptoms were self-reported with standardized questionnaire in late adulthood.

Results: In comparison to the most common haplotype, one haplotype in the regulatory region of the *NR3C1* was associated with increased risk of hospital admission (OR: 3.35; 95% confidence interval 1.5 to 7.3) for depressive disorders after adjusting for sex, birth year, and education. The association was statistically significant after Bonferroni correction for multiple testing. There were no other significant associations.

Conclusions: Haplotypic variation in the regulatory region of the *NR3C1* may increase vulnerability to depressive disorders requiring hospital admission, but is not associated with self-reported symptoms.

1. Introduction

Major depressive disorder (MDD) is a common and complex disorder with a moderate to strong genetic component (Belmaker and Agam, 2008; Sullivan et al., 2000). Altered function of the hypothalamic-pituitary-adrenal (HPA) axis is among the most consistent biological findings in the pathophysiology of depression. Several lines of evidence point to a hyperactive HPA axis (Gillespie and Nemeroff, 2005) and attenuated function or expression of the type II glucocorticoid receptor (GR) (Pariante, 2006) in individuals with depression. Thus, there is a strong rationale for exploring associations between depression and HPA axis-related genes, and particularly the GR gene (*NR3C1*; located at the 5q31.3).

Most previous studies relating the *NR3C1* to MDD have focused on a set of a few single nucleotide polymorphisms (SNPs) including *ER22/23EK* (rs6189, rs6190) and *BclI* (rs41423247) located at or near exon 2 (Brouwer et al., 2006; van Rossum et al., 2006; van West et al., 2006) and *NR3C1-1* (rs10482605) located in the regulatory region (Mill et al., 2008; van West et al., 2006). One study used *NR3C1* haplotypes based in part on these SNPs (Otte et al., 2009). Although not all results are consistent, the results point to an association between MDD or antidepressant medication efficacy and variation near exon 2 and/or the regulatory regions. This was also supported by a recent comprehensive family-based study that encompassed most of the common variation within the *NR3C1* and showed that this variation influenced the risk of mood disorders in children (Mill et al., 2008).

* Corresponding author. Institute of Behavioural Sciences, University of Helsinki, PO Box 9, FI 00014 University of Helsinki, Finland. Tel.: +358 9 191 29 501; fax: +358 9 191 29 521.
E-mail address: katri.raikkonen@helsinki.fi (K. Räikkönen).

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We extended these findings by testing in a large birth cohort whether SNPs and derived haplotypes encompassing most of the common variation spanning the whole *NR3C1* are associated with (a) risk of hospital admission for depressive disorders over early to late adulthood and with (b) variation in depressive symptoms as assessed by a standardized self-report questionnaire in late adulthood.

2. Materials and methods

2.1. Participants

The source cohort comprised 4130 women and 4630 men born as singletons at Helsinki University Central Hospital during 1934–44, who had birth and child welfare records and who were living in Finland in 1971. To approach an intended sample size of $n = 2000$, we invited a random subsample of 2902 subjects to ask for participation in the clinical study; 2003 of them (1075 women and 928 men) were finally included. Their average age was 61.5 years (SD = 2.9, range: 56.7–69.8) (Barker et al., 2005; Yliharsila et al., 2008).

The study was carried out in accordance with the Declaration of Helsinki, the study protocol was approved by the Institutional Review Board of the National Public Health Institute, and informed consent was obtained from all participants.

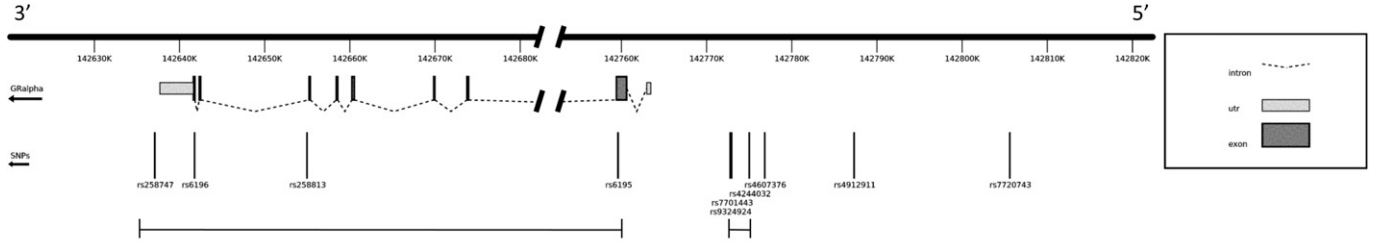
2.2. Hospital-treated depressive disorders and self-reported depressive symptoms

Diagnoses on hospital admission for depressive disorders were extracted from the hospital discharge register (HDR) carrying diagnoses of all hospitalizations in Finland between 1969 and 2004. For diagnoses, International Classification of Diseases, 8th revision (ICD-8) was used during 1969–1986, ICD-9 with criteria from the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-IIIR) during 1987–1995, and ICD-10 from 1996 onwards. Forty-seven participants (59.6% females) had been hospitalized due to depressive disorders with the following diagnostic codes: 298.00 and 300.4 from the ICD-8, 2968A, 2961, and 3004 from the ICD-9, and F32, F33, and F34.1 from the ICD-10. Among those hospitalized for depression, mean number of hospitalizations due to depression was 1.6 (SD: 0.85, range: 1–4) and mean age of first hospitalization was 49.9 years (SD: 8.7, range 26.3–63.3). Cases with other mood disorder, unspecified mood disorder, or bipolar disorder were excluded (codes 301.1 and 296 from the ICD-8, 301.1 and 2962–67 from the ICD-9, and F30, F31, F34.0, F34.8, F34.9, F38, F39 from the ICD-10; $n = 7$). The HDR is a valid and reliable tool for research (Keskimäki and Aro, 1991). Although we are not aware of studies formally evaluating sensitivity and specificity of diagnoses of depressive disorders in the HDR, these diagnoses have been used in several studies (e.g. Hakkarainen et al., 2004). In conjunction with the clinical examination in 2001–2004, the participants completed the Beck Depression Inventory (BDI) (Beck et al., 1961) assessing depressive symptoms.

2.3. SNP selection and genotyping

Twelve SNPs located in the *NR3C1* were selected to cover most of the common variation in the locus. In the SNP selection we used HapMap CEU as a reference data and aimed at identifying all haplotypes in the *NR3C1* locus with the frequency of more than five percent. However, SNP rs12656106 failed at assay validation stage and rs17100236 failed at genotyping, leaving us 10 genotyped SNPs (Fig. 1). Genotyping was conducted with Sequenom's Mass-Array® MALDI-TOF assay according to manufacturer's recommendations. Genotyping success rate was >95% in all SNPs and on average 3.6% and 3.3% of alleles were missing in those with the diagnosis of depression and those without, respectively. The multiplexed assays were designed using the SpectoDesigner software (Sequenom, San Diego, CA, USA). Primer sequences are available upon request. Observed genotype frequencies did not deviate from the Hardy–Weinberg equilibrium in participants without diagnoses of depressive disorders ($p > 0.05$).

In order to confirm the initial haplotypic structure and results with genotypes providing coverage of the complete GR gene, we repeated the haplotype analyses after including additional 14 SNPS derived from a Genome-Wide Association (GWA) scan with a modified Illumina 610 k chip providing a good coverage of the CEU HapMap population (Spencer et al., 2009). Genotyping was conducted in the Wellcome Trust Sanger Institute, Cambridge, UK. The new SNPs were rs10482682, rs10482672, rs10482655, rs33383,



	rs258747	rs6196	rs258813	rs6195	Cases# (n=44)	Controls (n=1871)	Overall (n=1915)*
HapB	T	A	G	A	45.5%	46.7%	46.7%
Hap1	C	A	G	A	21.6%	22.2%	22.2%
Hap2	C	G	A	A	17.2%	19.6%	19.6%
Hap3	C	A	A	A	12.3%	9.4%	9.5%

	rs9324924	rs7701443	rs4244032	Cases# (n=42)	Controls (n=1882)	Overall (n=1924)*
HapB	T	A	A	18.5%	31.7%	31.4%
Hap1	G	G	A	10.4%	25.9%	25.6%
Hap2	G	A	A	38.4%	19.0%	19.4%
Hap3	G	A	G	3.8%	11.8%	11.6%
Hap4	T	G	A	16.0%	10.9%	11.0%

Fig. 1. Overview of glucocorticoid receptor gene structure, polymorphisms genotyped in this study, and inferred haplotype frequencies (figure drawn with FancyGene accessed 8.10.2009 [http://host13.bioinfo3.ifom-ieo-campus.it/fancygene/] by using UCSC Genome Browser locations on Human Mar. 2006 Assembly (hg18)). *: 81 and 72 participants excluded due to missing data in SNPs located in Block I and Block II, respectively. #: Cases refer to individuals with hospital admission for depressive disorders.