

Observational Studies

Ann-Christin Sannes*, Jan Olav Christensen, Morten Birkeland Nielsen and Johannes Gjerstad

Stress-induced headache in the general working population is moderated by the NRCAM rs2300043 genotype

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Abstract

Objectives: Earlier findings suggest that social stress such as abusive supervision may promote pain. In the present study we examine the possible moderating role of genetic variability in the *NRCAM* gene in this process.

Methods: The data were collected through a national survey drawn from the National Central Employee Register by Statistics Norway. A total of 1,205 individuals returned both the questionnaire and the saliva kit. Abusive supervision was scored by a 5-item version of the Tepper's 2,000 scale. Headache was measured on a four-category scale; 'not bothered,' 'a little bothered,' 'considerably bothered,' 'seriously bothered'. Genotyping with regards to NRCAM rs2300043 was carried out using Taqman assay. Ordinal logistic regression was used to analyse the data.

Results: For males exposed to abusive supervision, those carrying the rs2300043 CC genotype reported the highest levels of headache. Women showed a trend towards the opposite pattern. Women with the rs2300043 CC genotype seem to have a weaker effect of abusive supervision regarding reported headache than their male counterparts with the CC genotype when exposed to abusive supervision.

Conclusions: The present results indicated that the association between abusive supervision and headache in men with the NRCAM rs2300043 C allele was stronger than in other men. This suggests that the NRCAM genotype

in men is important for the tolerance of social stress e.g., repeated negative acts from a superior. In contrast, a trend, though non-significant, towards the opposite pattern was observed in women. Our result suggests that the NRCAM genotype in men manifestly affects stress-induced pain such as headache.

Keywords: abusive supervision; headache; NRCAM genotype; psychosocial stress.

Background

Previous findings show that work related psychosocial stressors increase the risk of psychological distress [1–3] and a variety of health complaints [4–9]. Pain complaints such as headache has previously been associated with psychosocial stressors [10–12]. Despite no previous studies on its relationship with headache, abusive supervision has been established as a highly detrimental psychosocial stressor. The term abusive supervision is defined as the employees' perceptions of the supervisor's hostile verbal and nonverbal behaviours, not including physical contact [1, 13], with prevalence rates ranging from 10 to 16% [14].

Earlier data suggest that between 50 and 90% of adults have experienced headache within the last year [15, 16]. Moreover, headache is third largest reason for years lived with disability, globally [17]. The most common primary headaches are tension-type headache (60%) and migraine (15%) [15, 18, 19], which often co-occur [20]. In addition, cervicogenic headache (17–50%) [21, 22] and other types of headache such as chronic-, medication over-use-and cluster headache are frequently reported (4%, 1–2%, and 0.2–0.3%, respectively) [15].

Many parts of the brain may be involved in the mechanisms underlying stress-induced health complaints. For example, social stress activates the hypothalamic-pituitary-adrenal (HPA) axis [23, 24], which in turn

*Corresponding author: Ann-Christin Sannes, National Institute of Occupational Health, Norway, Pb 5330 Majorstuen, 0304 Oslo, Norway, E-mail: ac.sannes@gmail.com

Jan Olav Christensen, Morten Birkeland Nielsen and Johannes Gjerstad, National Institute of Occupational Health, Norway, Oslo, Norway

regulates circulating glucocorticoid levels [25]. Evidence exists that stress-induced anger and anxiety may be associated with activation of the amygdala, the limbic system [24], the periaqueductal gray (PAG) and the hypothalamus [26], which are all involved in behavioural responses to threatening stimuli and pain [27]. The same brain regions are also important for the influence of past emotional experience and cognitive-emotional pain modulation [26], and thereby also perceptions of aversive event such as abusive supervision.

Stress-induced processes may differ by both gender [5] and genetic factors [6]. One genetic factor, which might also affect the pituitary gland [28], could be the Neuronal Cell Adhesion Molecule (NRCAM) gene. Located at 7q31, the *NRCAM* encodes a protein expressed in neurons and glial cells in many brain regions. Interestingly, previous data show that the rs2300043 C allele of the *NRCAM* gene is overrepresented in subjects with autism [29]. Encoding a member of the immunoglobulin superfamily protein, *NRCAM* might be involved in organising the neural network during neural development [30, 31]. Further, the *NRCAM* and its protein is proposed to have a role in neuronal plasticity [32], myelination of Schwann cells and the Na⁺ channels of the nodes of Ranvier [33].

Recent data suggest that *NRCAM* also may be linked to emotional aspects such as negative affect [34] and somatic complaints e.g., neuropathic pain [29]. However, studies addressing the association between individual stress exposure, the *NRCAM* genotype and common pain states such as headache, are lacking. Hence, based on the possible link between social stress, *NRCAM* and central or peripheral neuronal processes, we hypothesized that the effect of abusive supervision on headache may be modified by the genetic variability in *NRCAM*; i.e., the rs2300043 C allele.

In the present study we demonstrate that headache in the general working population is associated with an abusive leadership and *NRCAM* genotype interaction.

Methods

Data collection

The data were based on a probability sample of 5,000 employees randomly drawn from The Norwegian Central Employee Register collected by Statistics Norway. This register is an official registry of all Norwegian employees, as reported by employers. Sampling criteria were adults from 18 to 60 years of age employed in Norwegian enterprises. Questionnaires were distributed by the Norwegian

Postal Service in 2015. A total of 1,608 persons (32%) returned the questionnaire. Saliva collection kits were also sent to those subjects who gave consent. Of these, 1,205 returned the saliva sample kit and the questionnaire without missing data. Responses were treated anonymously, and informed consent was given by the subjects. The survey was approved by the Regional Committee for Medical Research for Eastern Norway.

Instruments

In the questionnaire, the respondents were asked to indicate their experience of certain supervisors behaviours that constitute abusive supervision, using a 5-item version of Tepper's 2,000 scale, with response categories ranging from 0 to 4 ('never', 'rarely', 'once in a while', 'quite often' and 'very often or always') [13, 35]. Cronbach's alpha for abusive supervision was 0.87. Respondents were also asked to report experienced levels of headache during the last 12 months. The response categories for headache ranged from 0 to 3 ('not bothered', 'a little bothered', 'considerably bothered', 'seriously bothered').

Genotyping

Genomic DNA was extracted from saliva using Oragene RNA sample collection kit (DNA Genotech Inc. Kanata, Ontario, Canada). Single nucleotide polymorphism (SNP) genotyping was carried out using predesigned TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA, USA). Approximately 10 ng genomic DNA was amplified in a 5 µL reaction mixture in a 384-well plate containing 1x TaqMan genotyping master mix (Applied Biosystems) and 1x assay mix, the latter containing the respective primers and probes. The probes were labelled with the reporter dye FAM or VIC to distinguish between the two alleles. In accordance with the procedure in our earlier studies [6, 7], an ABI 7900HT sequence detection system was used. Negative controls were included in every run. Approximately 10% of the samples were re-genotyped and the concordance rate was 100%.

Statistical analysis

For the abusive supervision variable, a mean value was calculated from the 5 items in the questionnaire. Ordinal logistic regression was conducted to assess potential associations of abusive supervision, gender, and genotype with headache. The ordinal logistic regression analyses were first stratified by gender. In these analyses, the main effects (without any interaction term) were assessed in step 1, whereas the two-way interaction terms (abusive supervision x genotype) were included in step 2. In addition, an ordinal logistic regression analysis with three-way interactions were conducted (including gender in the interaction term) to formally statistically test any gender differences observed in the stratified analyses of step 2. A Chi square test calculator was used to assess deviation from the Hardy-Weinberg equilibrium [36]. All other statistical analyses were conducted using Stata SE 16.0. Statistical significance was accepted at the p<0.05 level.

Results

A total of 1,185, i.e., 567 (48%) men and 618 (52%) women, were successfully genotyped regarding *NRCAM* rs2300043 (see Tables 1 and 2). The data showed that the distribution within the male cohort was 68 (12.0%) with CC, 265 (47.0%) with CG and 234 (41.0%) with the GG. For the female cohort the distribution was 82 (13.2%), 302 (48.8%) and 234 (37.8%), respectively. The mean experienced abusive supervision scores were 0.15 (SD=0.34) for males with the CC variant, 0.17 (SD=0.38) for those with the CG variant, and 0.21 (SD=0.46) for those with the GG variant. For women the mean experienced abusive supervision scores were 0.26 (SD=0.47), 0.15 (SD=0.41) and 0.14 (SD=0.38), respectively. Males with the CC variant showed a distribution amongst the 4 categories regarding headache as follows: 44.1% 'not bothered', 39.7% 'a little bothered', 16.7% 'considerably bothered' and 0% 'seriously bothered'. For males with the CG and GG variant the distribution was 51.6, 35.8, 10.1, and 48.2, 35.0, 13.6 and 2.10%, respectively. The distribution in the female cohort with the CC variant was 29.2, 52.4, 15.9 and 2.43%. The CG and GG variant showed a distribution of 33.1, 38.4, 20.5, 7.96, 41.4, 19.2 and 4.17%, respectively. No deviation from the Hardy-Weinberg equilibrium ($\chi^2=1.0475$, $p=0.32$) was observed.

Regarding SNP rs2300043, the results from the regression analyses of the linear associations are shown in Table 3. In men (Table 3 left, step 1) the analysis without the interaction term only revealed a trend towards a positive covariation between abusive supervision and headache (OR 1.41, CI 0.94–2.10). In men (Table 3 left, step 2), when the Abusive supervision x rs2300043 interaction was entered, the analyses showed a much stronger correlation between abusive supervision and headache (OR 6.43, CI 1.88–21.9, effects given CC and zero abusive supervision). Also, a significant Abusive supervision x rs2300043

interaction was observed, indicating a weaker relationship between abusive supervision and headache for G carriers. The analysis of the female cohort revealed a positive significant association between abusive supervision and headache (OR 1.71, CI 1.23–2.37) (Table 3 right, step 1), but no significant interactions were observed (see Figure 1 for rs2300043 data summary).

The three-way interaction analysis revealed that the association between abusive supervision and headache was weaker for women vs. men with CC (Table 4).

Discussion

The data of the present study supported our hypothesis that the effect of abusive supervision on headache may be moderated by the genetic variability in the gene encoding *NRCAM*. In particular, a very high odds of headache among men with rs2300043 CC exposed to abusive supervision was demonstrated. This suggests that the rs2300043 C allele in men may reduce tolerance of social stress in the workplace. Hence, our data support the idea that the *NRCAM* and its protein may be important for maintenance of adaptive neuronal processes and responses during stress exposure.

Due to its presence in both the hypothalamus, the pituitary gland and a vast number of brain areas [28], *NRCAM* might be involved in the many processes related to the stress-induced neuronal activity that ultimately leads to changed sensory or emotional neuronal activity. For example, stress may activate the HPA-axis, increase circulating glucocorticoids (CORTs) [37, 38], which in turn affects the brain e.g., hippocampus [39, 40], amygdala [41] and prefrontal cortex [38, 42]. These areas are important for memory, emotions, and pain. Thus, it is tempting to speculate that exposure to repeated social stress, i.e., abusive supervision, might be associated with neural maladaptive changes in the brain.

Table 1: Characteristics of the male subjects by *NRCAM* genotype rs2300043; CC, CG and GG.

	Range	CC		CG		GG		Sum
		n (%)	Mean (SEM)	n (%)	Mean (SEM)	n (%)	Mean (SEM)	
Subjects		68	12.0	265	47.0	234	41.0	567
Headache	0	30	44.1	137	51.6	113	48.2	
	1	27	39.7	95	35.8	82	35.0	
	2	11	16.7	27	10.1	32	13.6	
	3	0	0.00	3	1.13	5	2.10	
Abusive supervision	0 to 4	0.15	0.04	0.17	0.02	0.21	0.02	
Age		43.8	1.21	45.9	0.60	46.7	0.61	

N, number of subjects; SEM, standard error of mean.

Table 2: Characteristics of the female subjects by NRCAM genotype rs2300043; CC, CG and GG.

	Range	CC		CG		GG		Sum
		n (%)	Mean (SEM)	n (%)	Mean (SEM)	n (%)	Mean (SEM)	
Subjects		82	13.2	302	48.8	234	37.8	618
Headache	0	24	29.2	100	33.1	81	34.6	
	1	43	52.4	116	38.4	97	41.4	
	2	13	15.8	62	20.5	45	19.2	
	3	2	2.43	24	7.94	10	4.27	
Abusive supervision	0 to 4	0.26	0.05	0.15	0.02	0.14	0.02	
Age		43.5	1.17	44.7	0.56	43.7	0.61	

N, number of subjects; SEM, standard error of mean.

Table 3: Ordinal logistic regression analysis of the effect of abusive supervision on headache; main effects and two-way interaction (Abusive supervision^xrs2300043) stratified by gender. Adjusted for age. Number of observations=1.185.

	Men			Women		
	Adjusted OR	p-Value	95% CI	Adjusted OR	p-Value	95% CI
Step 1						
Main effects						
Abusive supervision	1.41	0.089	(0.94, 2.10)	1.71	0.001	(1.23, 2.37)
NRCAM rs2300043						
CC	Ref	–	–	Ref	–	–
CG	0.73	0.225	(0.44, 1.21)	1.31	0.227	(0.84, 2.04)
GG	0.89	0.686	(0.53, 1.50)	1.06	0.789	(0.67, 1.67)
Step 2						
Abusive supervision	6.43	0.003	(1.88, 21.9)	1.05	0.872	(0.59, 1.94)
NRCAM rs2300043						
CC	Ref	–	–	Ref	–	–
CG	4.16	0.099	(0.76, 22.6)	0.54	0.268	(0.18, 1.60)
GG	7.58	0.017	(1.43, 39.9)	0.47	0.202	(0.15, 1.48)
Two-way interaction						
CC	Ref	–	–	Ref	–	–
CG	0.22	0.033	(0.05, 0.88)	2.01	0.083	(0.91, 4.45)
GG	0.16	0.008	(0.04, 0.62)	1.87	0.142	(0.80, 4.36)

OR, odds ratio; CI, confidence interval; reference group, CC genotype; Syntax STATA, step 1, by gender, sort, ologit headache abusive supervision age i.rs2300043; Step 2, by gender, sort, ologit headache abusive supervision age i.rs2300043 c.abusive supervision#i.rs2300043. Bold values indicate statistical significance.

Although the study was designed to examine the possible role of the NRCAM during exposure to social stress, the mechanism of possible maladaptive processes in different brain regions is beyond the scope of the present study. However, based on the theoretical link between NRCAM and neuronal development, plasticity, interactions with numerous other intra- and extracellular molecules [43], it seems plausible that social stress, through NRCAM could be associated with supraspinal pain processing. In addition, previous data suggest that deletion of NRCAM results in a delay in peripheral and central Na⁺ channels [33].

Sodium channels are highly important in the conduction of action potentials in pain-conducting pathways, and are highly expressed in both free nerve endings and unmyelinated C-fibres [44]. If NRCAM affects conduction in the peripheral nervous system, it may indirectly affect pain processing in many brain regions. Also, with the high density and its role in the commissural fibres in the corpus callosum, the NRCAM molecule has a crucial role in connecting the two hemispheres. This in turn, may affect several processes of the higher brain centres.

Previous data suggest that rs2300043 C may be linked to psychiatric disorders in males [45]. Although the

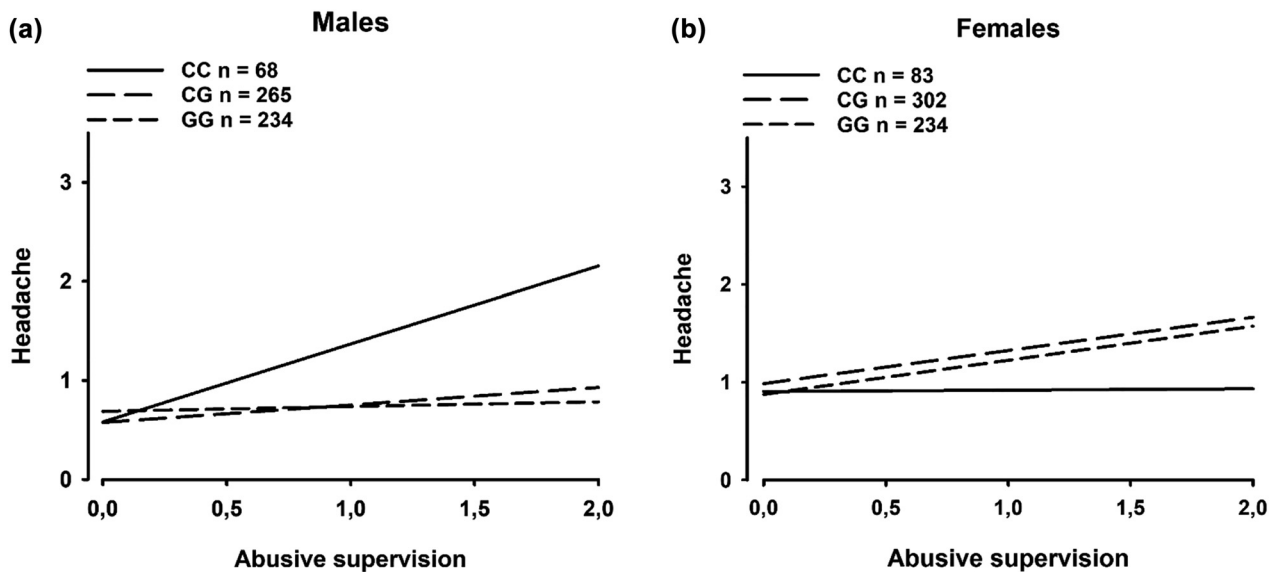


Figure 1: The association between abusive supervision and headache.

(a) Headache in male subjects with NRCAM CC, CG and GG exposed to abusive supervision. Adjusted for age. (b) Headache in female subjects with NRCAM CC, CG and GG exposed to abusive supervision. Adjusted for age.

Table 4: Ordinal logistic regression analysis of the effect of abusive supervision on headache, three-way interaction (Gender^xGenotype^x Abusive supervision).

	Adjusted OR	p-Value	95% CI
rs2300043 – gender difference			
Female vs. male (CC)	0.19	0.014	(0.05, 0.71)
Female vs. male (CG)	1.52	0.299	(0.68, 3.36)
Female vs. male (GG)	1.91	0.109	(0.86, 4.23)

OR: odds ratio, CI: confidence interval; Syntax STATA, ologit headache age i.gender i.rs2300043 i.gender#i.rs2300043 c.abusive supervision#i.rs2300043 c.abusive supervision#i.rs2300043 #i.gender, or. Bold values indicate statistical significance.

NRCAM is located on a non-sex chromosome, our data showed clear gender differences regarding rs2300043. Hence, the present findings support the idea that men and women may be different with regard to how they respond to psychosocial stressors [5, 6, 46, 47] and how they experience pain [48–50]. Recent observations from our group show that men exposed to bullying at the workplace report more pain than women in the same situation [5, 6].

Since *NRCAM* is expressed throughout our whole life, it is clear that this gene has an important role in both the young and adult brain [51]. Moreover, earlier observations indicate that *NRCAM* also in adults may affect synaptic plasticity and structural rewiring [43, 52]. Hence, the recently discovered relationship between *NRCAM* and psychiatric disorders [53], addiction [43],

neurodegeneration [54] and neuropathic pain [29] – which also may be linked to or triggered by environmental factors – is only the beginning of our understanding of the *NRCAM* gene. Conclusive evidence of *NRCAM*'s role in sensory processes and to what extent it affects the pain matrix in the brain remains to be investigated.

Conclusions

This study supports previous findings [55] on abusive supervision as a detrimental social stressor in contemporary working life and highlights the importance of organizational efforts to reduce the occurrence of such leadership behaviour. Extending previous research, the present results indicated that the association between abusive supervision and headache in men with the *NRCAM* rs2300043 C allele was stronger than in other men, and in women with the C allele. This suggests that carrying one or two copies of this allele may, in males, reduce the tolerance to social stress such as exposure to repeated negative acts from a superior. In contrast, the *NRCAM* rs2300043 C allele was not associated with increased report of headache during exposure to social stress in women; actually, a trend towards the opposite pattern was observed. We conclude that more knowledge about the *NRCAM* gene may be important for a more nuanced understanding of stress-induced pain such as headache.

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The survey was approved by the Regional Committee for Medical Research for Eastern Norway (REK 2014/1725).

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