**Genetic predictors of recovery in low back and lumbar radicular pain**

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**Abstract**

Previous data suggest that persistent back pain may be associated with genetic variability. In this study, we assessed the correlation between 8 single nucleotide polymorphisms (SNPs) (VDR, COL11, MMP1, MMP9, IL-1α, IL-1RN, OPRM1, COMT) and pain recovery in patients with low back pain (LBP) and lumbar radicular pain (LRP) over a 5-year period. In total, 296 patients with LBP or LRP were followed for 5 years. All the patients underwent standardized clinical examination and completed pain and function questionnaires. Univariate linear regression was used to estimate the association between the genetic variants, and recovery evaluated as pain intensity at rest at 5-year follow-up. Associations with p values <0.1 were included in the multivariable analysis, adjusting for pain intensity at baseline, age, gender, smoking, BMI and LBP/LRP. Pain intensity at 5-year follow-up was associated with VDR rs731236 (B=-0.5, 95%CI -0.9 to -0.1, p=0.017), MMP9 rs17576 (B=0.5, 95%CI 0.1 to 0.9, p=0.022) and OPRM1 rs1799971 (B=-0.8, 95%CI -1.4 to -0.2, p=0.006) in the univariate analyses. Interestingly, MMP9 rs17576 and OPRM1 rs1799971 remained significant (p=0.026 and p=0.007) in the multivariable model. The data demonstrated that the rare allele of MMP9 rs17576 was associated with poor pain recovery, whereas the rare allele of OPRM1 rs1799971 was associated with better pain recovery at 5-year follow-up in the LBP and LRP patients. In particular the present study suggest that the OPRM1 rs179971 A>G in men is associated with better long-term pain recovery. Each SNP explained only about 2% of the variance. Nevertheless, we conclude that the MMP9 rs17576 and OPRM1 rs1799971 genotypes may affect 5-year recovery in patients with low back and lumbar radicular pain.

**1. Introduction**

Previous data show that low back pain (LBP) has a lifetime prevalence of 70% (2). Lumbar radicular pain (LRP), also referred to as “sciatica”, account for only 5-10% of these low back pain conditions. Although most back disorders are benign, many have a slow recovery (13, 39). In regard to LBP, this condition may have a muscular aetiology (28). However, back disorders can also be related to degenerative changes in the intervertebral discs or in the spine. If such changes cause mechanical compression of the nerve roots, this may lead to LRP. In addition, biochemical mediators released after disc herniation may influence neuronal excitability and promote pain (34).

LBP and LRP are multifactorial phenomena. Age, smoking, body weight, height, occupational load, mental stress and perceptual processes may all contribute to development of persistent LBP and LRP (3, 18, 24, 38, 40). Moreover, genetic variability that influences susceptibility to environmental factors may influence the risk of chronic pain (1, 32). Earlier data suggest that the heritability of back pain range from 30% to 45% (37). Several lines of evidence show that genetic factors, which are important for degenerative changes, inflammation and pain perception, also play a role in low back pain conditions.

For example, genetic variants in genes encoding proteins such as vitamin D receptor (VDR), collagens (COL) and matrix metalloproteinases (MMPs) may affect degeneration of the intervertebral discs (10, 35). Previous studies indicate that genetic polymorphisms related to inflammation in genes encoding interleukin 1 (IL-1α), interleukin-1 receptor antagonist (IL-1RN) and interleukin-6 (IL-6) may also promote persistent LRP (17, 25, 27, 33). Moreover, genetic variability that is important for opioid, dopaminergic, adrenergic and serotonergic signalling may affect supraspinal modulation of nociceptive processing (41-43). Several previous studies demonstrate a link between genetic variability in the gene encoding opioid receptor mu 1 (OPRM1) and pain recovery in LRP patients (14, 29). In addition, genetic variability related to the enzyme catechol-O-methyltransferase (COMT) affects cortical pain processing and the risk of chronic LBP (7).

Hence, several genetic variants have been suggested to be of importance for persistent LBP and LRP. To our knowledge, this is the first study addressing the link between genetic factors and pain recovery over a 5-year period. The aim of the present study was to test a panel of 8 SNPs, namely; VDR rs731236, COL11 rs1676486, MMP1 rs1792750, MMP9 rs17576, IL-1α rs1800587, IL-1RN rs2234677, OPRM1 rs1799971 and COMT rs4680 regarding pain recovery in LRP and LBP patients. The present data suggest that genetic factors may predict the long-term recovery in patients with low back and lumbar radicular pain.

**2. Methods**

*2.1 Study population*

LRP and LBP patients were recruited differently. Participants with LRP were recruited at the outpatient clinic at Oslo University Hospital (OUH) Ullevaal and Haukeland University Hospital (HUH) between 2007 and 2009. The inclusion criteria were age between 18 and 60 years, lumbar disc herniation on MRI with corresponding distribution of pain in lower limbs and positive straight leg raising test. The exclusion criteria were cauda equina syndrome, lumbar spinal stenosis, previous spinal surgery for a herniated disc at the same level or lumbar fusion at any level, generalized musculoskeletal pain, inflammatory rheumatic disease, diabetic polyneuropathy, cardiovascular disease (NYHA class III and IV), cancer, psychiatric disease, drug misuse and alcoholism, recent surgery (within 1 month), pregnancy, poor proficiency in the Norwegian language and non-European-Caucasian ethnicity. In total 270 LRP patients were included and followed over 5 years. The dropout rate in the first year was 9%. Two hundred fifty-one LRP patients were allocated to 5-year follow up with a response rate of 76%.

Participants with LBP were recruited at the outpatient clinic at OUH between 2009 and 2011. The inclusion criteria at baseline were age between 18 and 65 years and persisting low back pain. The exclusion criteria were lumbar disc herniation on MRI with corresponding distribution of pain in lower limbs, positive Laseque, cauda equina syndrome, lumbar spinal stenosis, structural deformity of the vertebral column, previous surgery on the back, generalized muscular and skeletal pain, inflammatory rheumatic diseases, diabetic mellitus with polyneuropathy, comprehensive cardiac disease, cancer or other serious diseases. In total, 148 LBP patients were included and followed up with at 4 months and one year. The dropout rate in the first year was 7%. One hundred thirty-six LBP patients were allocated to 5-year follow-up with a response rate of 78%.

It was assumed that around 180 patients were needed in order to detect differences between rare/rare, rare/common and common/common groups assuming an allele dependent model, allel frequence 1:4, power of 0.8, p=0.05 , SD pain 20mm and a pain difference between extreme groups of 20 mm.

The study was conducted in accordance with the Helsinki Declaration. The Regional Committee for Medical Research Ethics (reference number 2014/1754) and the Norwegian Social Science Data Service approved the study protocol and all the participants gave their written informed consent at baseline and at 5-year follow-up.

*2.2 Clinical procedures and outcome measures*

All patients underwent a standardized clinical examination, which included assessment of sensory and motor functions including straight leg raising and completion of standardized pain and function questionnaires. At baseline, socio-demographic variables, including gender, age, smoking habits and BMI were registered and MRI obtained for all patients. In addition, function was assessed using the validated Norwegian version of the Oswestry Disability Index (ODI), scale 0-100%, where 0% = no disability at all and 100% = very severe disability at baseline and 5-year follow-up (12).

Pain intensity was recorded using the visual analogue scale (VAS) with anchor values from 0 (no pain) to 10 (worst possible pain) at rest during the last week at baseline and at 5-year follow-up (ref her).

*2.3 Genotyping*

In patients with LRP, genomic DNA was extracted from whole blood cells using a FlexiGene DNA isolation kit (Qiagen), whereas in patients with LBP genomic DNA was extracted from saliva using an Oragene DNA sample collection kit (DNA Genotech Inc.) according to the manufacturer’s instructions. SNP genotyping was carried out using predesigned TaqMan SNP genotyping assays (Applied Biosystems). Approximately10 ng DNA was amplified in a 5 µl reaction mixturein a 384-well plate containing 1x universal TaqMan master mixand 1x assay mix, the latter containing the respective primersand probes. The probes were labeled with the reporter dyes FAM or VIC at the 5’end to distinguish between the two alleles. The reactions were performed on an ABI 7900HT sequence detection system (Applied Biosystems) using the following program: 95°C for 10 min, followed by 40 cycles at 95°C for 15 s and 60°C for 1 min. Negative controls containing water instead of DNA were included in every run. Genotypes were determined using the SDS 2.2 software (Applied Biosystems). Approximately 10% of the samples were re-genotyped and the concordance rate was 100%. The SNPs tested are listed in Table 1.

*2.4 Statistical analysis*

Simple linear regression analysis was used to estimate the correlation between the candidate genes VDR, COL11, MMP1, MMP9, IL-1α, IL-1RN, OPRM1 and COMT and resting pain intensity at 5-year follow-up as well as. An-allele dependent model was assumed, such that the effect of the genotype rare/rare was expected to be twice the effect of the genotype rare/common when compared to the genotype common/common. VDR, MMP-9 and OPRM1 showed correlation with p<0.1 and were used for further analysis in a multivariable linear regression model including potential confounding effects of the covariates baseline pain, LRP/LBP, age, gender, smoking (yes/no) and BMI. All candidate genes and covariates with p<0.1 were entered in the final model to evaluate the relationship between the candidate genes in addition to assessing the association between these genes and pain recovery.

Additional univariate and multivariate linear regression analysis in women and men separately was performed to evaluate the association of OPRM1 G allele with LBP/LRP.

An univariate linear regression analysis was also performed to estimate the correlation between the candidate genes VDR, COL11, MMP1, MMP9, IL-1α, IL-1RN, OPRM1 and COMT and disability (ODI score) at 5-year follow-up. VDR showed correlation p< 0.1 and further analysis in a multivariate model was performed to evaluate the association between this SNP and disability at 5 year.

All models were checked for collinearity (no collinearity revealed). All the statistical analysis was performed using the SPSS (version 22) statistical package. A p-value < 0.05 was set as the level of statistical significance.

**3. Results**

*3.1 Characteristics of study population*

The study population comprised 296 patients, including 128 females (43.2%) and 168 males (56.8%), aged 18 to 60 years (mean 42.1 ± 9.9). At baseline, 99 patients (33.4%) smoked on a daily basis (Table 2). At 5-year follow-up the LBP patients reported more pain (3.7 ± 2.9) than the LRP patients (2 ± 2.1). The LBP patients also reported worse function (ODI 28.2 ± 14.3) than the LRP patients (ODI 15.53 ± 14.8).

*3.2 Genetic predictors*

A significant association between pain intensity at rest at 5-year follow-up (VAS rest 5 years) and the VDR rs731236 (p=0.017) SNP, the MMP9 rs17576 (p=0.022) SNP and the OPRM1 rs1799971 SNP (p=0.006) was found. In the multivariable models adjusted for pain intensity at baseline, LRP/LBP, gender, age, smoking and BMI, only the MMP9 rs17576 SNP and the OPRM1 rs1799971 SNP showed correlation with p<0.1 and were kept in further analysis (Table 3). Pain location (LRP/LBP) had a large impact on the results of multivariable regression analyses, as did the covariate pain at rest baseline (p<0.001, p<0.001). In the final model with the MMP9 rs17576 SNP and the OPRM1 rs1799971 SNP, corrected for pain intensity baseline and LRP/LBP, each gene showed an independent contribution to pain recovery (p=0.026, p=0.007) (Table 3). In accordance with our hypothesis, presence of the rare allele of the MMP9 rs17576 SNP was associated with poor pain recovery. However, patients with the rare allele of the OPRM1 rs1799971 SNP in men reported better pain recovery. The MMP9 rs17576 SNP explained 1.8% (R²=0.018) and the OPRM1 rs1799971 SNP explained 2.5% (R²=0.025) of the variance in pain intensity at 5 years.

In addition a significant a association between disability at 5-year follow-up (ODI 5 year) and the VDR rs731236 (p=0.017) SNP was found but in the multivariate models adjusted for disability at baseline, LRP/LBP, gender, age, smoking and BMI this association did not remain significant.

**4. Discussion**

Many studies have shown that lumbar disc degeneration is associated with LBP and LRP (4, 5, 36). Previous data also suggest that genetic markers may be linked to the same degenerative disc phenomenon (9, 36). For example, two independent Japanese cohorts show that the MMP9 rs17576 A>G is associated with lumbar disc herniation (8, 15). In line with these findings, our data showed that the MMP-9 rs17576 A>G, previously linked to tissue degeneration, was associated with slow recovery.

Earlier data also suggest that the MMP-1 rs1799750 1G>2G, may be associated with painful degenerative conditions (6, 30). Moreover, the COL11 rs1676486 G>A has previously been linked to increased risk for LRP (23, 26), whereas the VDR rs731236 T>C may be associated with disc degeneration (8, 35). In addition, several lines of evidence suggest that genetic variability in genes encoding inflammatory cytokines may be associated with persistent back pain (20, 37). For example, the IL-1α rs1800587 C>T may be associated with more pain at one year in LRP patients (25, 33). However, no relationship between genetic variability in these genes and pain recovery was observed in our study.

OPRM1 may be crucial for sensory processing and modulation of back pain and other pain conditions. Two previous studies that emanate from our LRP cohort reported a positive association between the OPRM1 rs179971 A>G and better recovery of pain in men at 1-year follow-up (14, 29). Moreover, earlier observations show that the OPRM1 rs1799971 A>G may be associated with higher pressure pain thresholds (11) and lower cortical responses to experimental pain stimuli (21). In accordance with these earlier observations, the present data suggest that the OPRM1 rs1799971 A>G in men is associated with better long-term pain recovery.

Like the OPRM1 genotype, the genetic variability related to the COMT enzyme may be important for pain. The COMT enzyme metabolizes catecholamines and thus modulates adrenergic, noradrenergic and dopaminergic signalling in the CNS as well as in the peripheral tissue. Therefore, many supraspinal processes including nociceptive modulation may be affected by genetic factors that influence on the COMT enzyme. Interestingly, previous data (31) suggest that the COMT rs4680 G>A may be associated with increased pain after spine surgery. Moreover, a positive correlation between the same SNP and long-lasting pain after disc herniation has been demonstrated (16). No relationship between the COMT genotype and pain recovery was, however, observed in the present study.

In the present study, we did not check for psychosocial covariates, although psychosocial factors, such as anxiety, depression and somatization, may contribute to chronic low back and lumbar radicular pain (22). Therefore, indirect effects of MMP-9 rs17576 and OPRM1 rs1799971 on pain cannot be excluded. Still, together with individual factors like gender, age, smoking, obesity and education level, genetic predisposition may be a prognostic factor in LBP patients as well as LRP patients (22, 24). Thus, development of persistent pain may be multifactorial. In contrast to earlier studies with shorter follow-up (19), however, our LBP patients reported more pain than our LRP patients at 5-year follow-up. This emphasizes that the maintenance of persistent pain is also probably a dynamic process. The pain mechanisms at 1, 2 and 5 years may be different.

In summary, the present data demonstrated that the rare allele of MMP9 rs17576 was associated with poor pain recovery, whereas the rare allele of OPRM1 rs1799971 was associated with better pain recovery in low back and lumbar radicular pain patients. Hence, although the causal relationship between these SNPs and the pain remains to be investigated, our results support the hypothesis that genetic factors involved in tissue degeneration and pain perception may predict long-term recovery in these patients. However, each SNP explained only about 2% of the variance, emphasizing the multifactorial nature of LBP and LRP.

**List of abbreviations**

COMT: catechol-O-methyltransferase, COL: collagen, IL: interleukin, LBP: low back pain, LRP: lumbar radicular pain, MMP: matrix metalloproteinase, OPRM1: opioid receptor mu 1, SNP: single nucleotide polymorphism, VAS: visual analogue scale, VDR: vitamin D receptor.

**Conflict of interest statement**

The authors declare no conflict of interest.

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**Figure legends**

**Figure 1: Flow diagram of study population**

LRP (Lumbar radicular pain). LBP (Low back pain). OUH (Oslo University Hospital). HUH (Haukeland University Hospital).