Author's response to reviews

Title: Subjective health complaints in patients with lumbar radicular pain and disc herniation are associated with a sex - OPRM1 A118G polymorphism interaction: a prospective 1-year observational study

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Author's response to reviews: see over
Response letter

Dear Editor

Thank you very much for your positive responses to our work and for giving us the opportunity to improve our manuscript. We also thank the reviewers for their constructive criticism.

Below are the reviewers’ comments (italic font), followed by our corresponding reply (normal font). Paragraph numbering refers to the submitted manuscript. Changes made in the revised manuscript are highlighted in red. Removed text is not shown.

All authors have reviewed and approved the revised manuscript.

We hope that you will find the revised manuscript acceptable for publication in BMC Musculoskeletal Disorders.

Best regards,
Eivind Hasvik

Reviewer # 1 (Richard Crist)

Reviewer’s report:

Major compulsory revisions: N/A

Minor essential revisions:

1. All instances of the gene name OPRM1 should be italicized.

Reply: We agree, and have now throughout the manuscript italicized the gene name.

2. There is no mention of correcting the p-values for the multiple statistical tests that were run in the analysis. If this multiple testing correction wasn’t already done, it needs to be performed. The table legends or methods should note if the p-values are corrected or uncorrected. Any p-values that are < 0.5 before correction and > 0.5 after correction should be considered nominally significant and not truly statistically significant.

Reply: The reviewer is right that complex data analyses and a large number of tests may be challenging. However, the p-values could be corrected for multiple testing by for example Bonferroni correction. In that case, our data are still truly statistical significant. In accordance with the comment of the reviewer, the following text has been added in Analyses and statistics (page 8, para 1): “The four comparisons were corrected with the Bonferroni method. A p value < 0.0125 (0.05/4) was chosen as the significance level.” Moreover, we now choose to present only data essential to our main hypothesis. One sentence in Analysis and statistics (page 8, para 1), “Differences in patient characteristics ...”, and two sentences in Results (page 9, para...
There were significant differences ...” and “Among the AA carriers ...”, as well as the corresponding p-values in Table 1, are therefore removed.

3. While it is informative to analyze sex differences within the genotypic groups as in Table 1, it would also be beneficial to analyze differences between the genotypic groups. For example, it is important to know if women with the AA genotype have different characteristics than women who are G carriers. It is also important to discuss these differences in the results and discussion sections, which are now largely focused on comparing male G carriers to female G carriers.

Reply: We agree. The difference between especially females AA versus *G and males AA versus *G also should be addressed. Hence the reviewer is right that the analyses may be extended. Thus, we have removed the following sentence from the abstract: “No significant sex difference was found among homozygote A carriers.” Further, we have changed Analysis and statistics (page 7, para 3) by adding the following sentence: “Analyses were performed separately for female *G versus male *G carriers, female AA versus female *G carriers, male AA versus male *G carriers, as well as female AA versus male AA carriers, using a linear mixed effects model approach.” We have also included the findings in Results (page 10, para 3), which now reads “The SHC score did not differ significantly between female AA and *G carriers, F(1, 63) = 1.63, p = 0.206, between male AA and *G carriers, F(1, 48) = 2.48, p = 0.122 or between female and male AA carriers, F(1, 88) = 0.63, p = 0.43.” Finally, in Discussion (page 10, para 1) we have added the sentence “No difference was found between female AA and *G carriers, male AA and *G carriers or female and male carriers of the AA genotype.”

4. On page 11, the first full sentence says “As shown in the present study, the OPRM1 A118G polymorphism also seems to affect nociceptive and supraspinal neuronal signaling in humans...” This seems like an overstatement given that the present comparison between genotype and subjective health complaints doesn't directly address those mechanisms.

Reply: We realize that this may be an overstatement, and have therefore removed the term; “As shown in the present study”. The sentence now reads; “Hence, we think the OPRM1 polymorphism in a sex-specific manner also may affect supraspinal neuronal signaling in humans.“

5. In the conclusion, the phrase "a sex-specific polymorphism" should be changed since it sounds like the polymorphism is sex-specific rather than the effect of the polymorphism being sex-specific.

Reply: The sentence is changed to “The present data indicate that SHC in patients with radicular pain and disc herniation may be influenced by a polymorphism in the OPRM1 gene in a sex-specific manner.”

Discretionary revisions:
1. Referring to the different alleles as "A118" and "118G" is somewhat confusing and ultimately unnecessary since there is only one polymorphism being discussed in the manuscript. They can be referred to as simply the A and G alleles. Likewise referring
to the polymorphism as “the OPRM1 A118G” is not necessary after the first instance in the manuscript.

Reply: Good point. We have altered the names as suggested by the reviewer.

Referee # 2 (Frances Williams)

Reviewer’s report:
The authors have submitted a well written manuscript outlining a precisely described study examining genotype in low back pain in patients with proven disc prolapse and radicular pain. Pain was measured at baseline and at 1 year follow up and subjective health complaints were also documented at both time points. It is slightly ambiguous at the outset whether the outcome of interest is pain or subjective health complaints.

Major revisions:
The final linear mixed model is not clear - what is the outcome variable and why is the sample so small (n=23)?

Reply (regarding outcome variable): The final SHC outcome represents SHC scores during the study time span. However, the final model did not include interactions with time. We agree that this is not clearly communicated in the text. In Analyses and statistics (page 8, para 1), we have therefore added the following sentences; “The outcome variable was SHC during the study time span. Both baseline and 1-year scores were included in the model. This was done to examine change over time by testing interactions between SHC and time.” Additionally we have added more information about the final model in Results (page 9, para 2), by including the following sentence; “When including SHC x time interaction the overall model fit was significantly reduced and this interaction was therefore not included in the final model.”

Reply (regarding sample size): In total 118 patients were included in the study. However, as expected from earlier reports (Olsen et al. 2012), not more than 23 of 118 participants were G carriers. Interestingly this previous report demonstrated a specific pain difference between *G carriers. Our hypothesis was therefore that sex difference between *G carriers also could be observed in the present study. To underpin our hypothesis driven analyses, we have now, in the Introduction (page 5, para 1), mentioned this earlier study and added the following text; “Previous data have demonstrated sex differences between male and female G-allele carriers regarding pain [20]. Our hypothesis was therefore that the effect of the OPRM1 G-allele could be different in men and women regarding the report of subjective health complaints.”

Minor revisions:
Analyses and statistics: should read “decision to test for random effects of pain was based on previous WORK SHOWING genotype differences Results: “Patient characteristics according to sex and genotype are”.

Reply: Thanks. These errors have now been corrected.
These results would be enhanced by giving the values from the table, not just the p value so the reader can be confident they are interpreting table correctly

Reply: As pointed out by the reviewer, we may help the readers when it comes to interpretation of the final linear model in Table 2. Thus, a new sentence is now added in Results (page 9, para 2). The text now reads; “This effect of sex had a clear influence on SHC \(b = 6.59, 95\% \text{ CI} 1.2, 11.37\), whereas the effect of pain \(b = 0.92, 95\% \text{ CI} 0.12, 1.72, p = 0.025\) and prior pain duration \(b = 0.14, 95\% \text{ CI} 0.04, 0.025, p = 0.01\) was less pronounced. Additionally we have added more information about the final model, by including the following sentences; “The subject-specific random factors had a significant effect in the final model \(b = 1.75, 95\% \text{ CI} 0.85, 3.63, p = 0.007\).” and “When including SHC x time interaction the overall model fit was significantly reduced and this interaction was therefore not included in the final model.”

Table 2 - please improve title to reflect more accurately the outcome of interest - is it baseline SHC or follow-up SHC?

Reply: In accordance with the comment of the reviewer, we have added more info about this beneath Table 2; referring to SHC during the study time span and Pain score (0-10). The text beneath Table 2 now additionally reads “Both baseline and 1-year scores were included in the analysis.”