Reviewer's report

Title: Genetic contribution of catechol-O-methyltransferase variants in treatment outcome of low back pain: a prospective genetic association study

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Reviewer: Frank Skorpen

Reviewer's report:

General:
Omair et al. have investigated the possible impact of four common SNPs and resulting haplotypes in the COMT gene on the outcome of low back pain (LBP) treatment in 93 patients after 7-11 years follow up. The study population was a mixture of patients treated with posterolateral fusion (n=60) or cognitive therapy and exercises (n=33). LBP was assessed using the Oswestry Disability Index (ODI) and Visual Analog Score (VAS) at baseline and at follow up. The authors report a significant association between the SNP rs4680 (Val158Met) and reduction in LBP when assessed by VAS, but not with ODI. No statistically significant association was observed with COMT haplotypes.

Major Compulsory Revisions:

1. There is no information on the use of analgesics or other medication that may modulate pain experience in these patients. Opioids, NSAIDs and also antidepressants are commonly prescribed drugs to patients with chronic LBP and are likely to impact both the patients’ general functioning as well as their pain report. If used by these patients, the authors should provide this important information and also include pain medication as a covariate in their analysis.

2. The authors report a significant association between post-treatment VAS LBP and the AA genotype of rs4680 in a recessive model (AA versus AG + GG), whereas no association was seen with neither ODI nor VAS when applying an additive model. On the other hand, when stratifying on rs4680 genotypes, the greatest improvement in VAS-LBP was seen with the heterozygous genotype (which from Figure 1 seems to be significant). Moreover, when analyzing the total cohort (93 patients) least improvement was seen with GG group, but when including the 60 fusion patients only, least improvement was seen with the AA genotype. These findings are difficult to interpret as the recessive model assumes that an effect is detectable when two copies of an affected allele are present, which fits poorly with the data obtained after stratification on genotypes and after sub analysis. The authors should discuss these findings in the context of the assumed functional effect of the Val158Met polymorphism on COMT activity.

Minor Essential Revisions:
1) The associations do not stand correction for multiple testing, implying that the study is not sufficiently scaled to detect true associations. Thus, there is a possibility that the findings are merely false positives. It should be stated in the abstract that the p-values presented are not formally corrected for multiple testing and that the study is to be considered as explorative.

2) It is stated in the abstract that five polymorphisms in the COMT gene were genotyped. However, as one of these (rs2097603) were not analyzed further due to genotyping failure it sounds better to say that four SNPs in the COMT gene were successfully genotyped.

Typographical errors:
1) COMT should not be in italics when referring to the enzyme. E.g. page 4 line 7 from the bottom, page 8 lines 11, 12, 13.
2) Table 2: GRS, abbreviation for genotyping success rate should probably be GSR.

Discretionary Revisions:

The mean VAS-LBP change for the rs4680 GG group of the total cohort was -12.9, and -29.2 for the fusion patients only - which is a huge difference and indicates major differences in VAS change between the two treatment groups. In order to understand the background for these differences, it would be informative to have the characteristics for the patients receiving cognitive intervention and surgery presented separately.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests