Reviewer's report

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

**Version:** 1  **Date:** 14 December 2011

**Reviewer:** Jules Desmeules

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This is a prospective genetic study on 93 individuals suffering from LBP that were randomized in two previous trials designed to evaluate the efficacy of surgery (segmental spinal fusion) vs. a conservative treatment regimen that combined cognitive therapy and active exercises.

Recruiting for these trials extended over a period of 5 years, ranging from 7 to 11 years prior to the present study. All 93 West European individuals presented with LBP for more than 1-year duration that did not respond to non-operative care. They showed radiographic evidence of moderate degenerative disc disease (involving 2 segments or less) and an ODI score of at least 30 out of 100 points.

At baseline and at 7-11 years follow up, subjects were given standardized questionnaires for assessing ODI and VAS LBP scores. In addition, since COMT is a candidate gene that may help explain some of the inter-individual differences in pain sensitivity and response to analgesic treatment, genotype was determined for each subject. Therefore the goal of the present study was to look for an association between COMT polymorphism and the changes in VAS and ODI scores in LBP patients.

**COMMENT:**

1. Please, give a brief summary of the results of the two previous randomized trials. The lack of association found in this study would be consistent with an absence of significant difference between the groups.

2. 9 subjects who underwent "late" surgery (done between the previous trials and this one) were added to the surgery group. Please, verify if these patients had an impact on the results of your analysis?

3. Please, give some details on power calculations. For example if a power was set at 80% what would be the smallest difference that could be detected by the analysis?

4. Please, give the threshold (and references) of the "genotype success rate" that was used in this study.

5. Please, give a more detailed explanation on how the mean effect size was calculated.

6. Recessive analysis shows that heterozygote individuals benefited most from the interventions (surgical or conservative). This observation invalidates the
hypothesis of a "dose-effect" of the COMT polymorphism. This is consistent with the lack of association found in the additive model that shows that, at least, the effect is not growing regularly.

7. The reported standard deviations would be consistent with a skewed distribution. Please, repeat the main analysis on the median.

8. Please, give a more detailed explanation on how the VAS was used (experimental conditions) and what was measured exactly (current pain, pain over the last week, "overall" pain, ...). Was the VAS used in accordance with validated experimental conditions (please provide references)?

9. "Painful experiences" can be influenced directly and indirectly at any given time by a great number of factors. Some are psychological, sociological or cultural, some others are physiological either non-genetically related like a lack of sleep or caffeine/alcohol/drug blood concentration or concomitant headache at the time of the experiment and some are genetically dependant like the activity of a relevant enzyme. Among all these factors the genetic impact is most likely marginal. In order to evaluate its contribution in a regression model, one would need to control for all the other factors (at least for the most important ones). Please, give more details on how these factors were taken into consideration and if not, please, justify.

10. Please, provide a more detailed description on how the haplotypes association analysis was done. How was the SNP dimension combined with the haplotypes?

11. Please, justify the pooling of the operated on and non-operated on patients for this analysis?

12. And then please, provide an explanation on why the response of the GG individuals who were operated on is so different from the response of the non-operated GG's (while the "surgery effect" seems absent for the AA and the AG's)? It seems that there could be an interaction between the groups (surgery vs conservative) and the genotypes...

13. Therefore, please, give more details on the analysis of residuals. Was the normality tested?