Reviewer's report

Title: TRAIL gene 1595C/T polymorphisms contribute to the susceptibility and severity of intervertebral disc degeneration: a data synthesis

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Reviewer: Wei Yang

Reviewer's report:

This is a systematic review of the association between a TRAIL gene SNP 1595C/T with the IDD trait. The study have been carried out carefully following the PRISMA guidelines. Extensive statistical analyses have been performed. However, the results are obviously limited mostly due to the small number of studies available for review, and all studies were Han Chinese subjects, which the authors have discussed as limitations in the manuscript.

Some minor problems should be considered.

In the abstract: 'Patients with lower grade IDD had more genotypes or alleles'. Did you mean "Patients with lower grade IDD had higher frequency of the TT genotypes and the T allele"?

The search strategy is not very specific based on Table S1 from the additional files. Item #1 in the table doesn't make much sense to me. This selects any paper mentioning the TRAIL gene "OR" SNP. I think it be involving both the TRAIL gene "AND” SNP. The lack of specificity is shown by the number of studies have been included in the very beginning (198), and with the vast majority excluded later on. Most of the excluded studies didn't involve the TRAIL gene (126).

Fig1. "Additional records identified through other sources (n=0)". It is not clear from the manuscript what additional records have been attempted to identify.

In the study selection part, the inclusion and exclusion criteria have been made complementing each other. They should actually serve different purposes. Please refer to the guidelines here
Looking at table 1 made me wonder if the 3 studies use different strategies to select subjects, because gender compositions are very different across studies. Ages are also different. It would be great to include their specific study designs in table 1, and discuss whether that contributes to heterogeneity when performing meta-analysis.

Even though the authors' effort to evaluate and present all possible genetic inheritance models should be appreciated, performing many tests raises the concern of multiple comparisons. It might be more desirable to focus on the few top models. The methods section mentioned they "choose the best model before calculating the OR for each model", but the results (table 3) showed that all models have been evaluated.

Table 3 are showing essentially the same information as figure 2, table 4 the same as figure 3. It might be better to keep the summary tables in the main text, and move the figures to supplemental materials.

In the results section (page 7 line 32), "the Shapiron-Wilk W test for normal distribution was applied". It is not clear why normality test is needed and how it could be applied on genotype data and a binary trait.

Page 7 line 41, "The null hypothesis was as follow(s): OR1(CTvsTT) = OR2(CCvsTT)". How is it different compared to testing OR(CTvsCC)=1? Also, association between the SNP with IDD is equivalent to test whether any of the OR(CTvsTT), OR(CTvsCC), OR(CCvsTT) is different from 1, not OR1(CTvsTT) = OR2(CCvsTT).

Page7 line 45-50, "theta1=logOR1=0 (P for OR1>0.05) and theta2=logOR2>0(P for OR2<0.05), indicating that the recessive model (CC vs. CT+TT) was the optimal model". The OR estimations should be shown together with the p values, because what more important to tell if the model is optimal is the effect sizes, but the p values could be significance/insignificance due to sample sizes.
Page 8 line 22 "No significant heterogeneity was found in the recessive model" What does heterogeneity mean in this context? It probably refers to difference in the included studies for meta-analysis. But "heterogeneity" is also used to indicate different sources/mode of genetic effects for genetic studies.

Page 9 line 12 "No evidence of publication bias was observed (Egger's test p=0.276; Begg's test P=0.296)" Given that only 3 publications were considered in the test, it is likely to have low power for detecting real publications biases.

Page 9 line 41 "revealing a complete linkage of genotypes at loci 1595". What does it mean by "complete" linkage? Also, be careful with terms like "linkage" / "association" as they usually refer to specific methods in genetic epidemiology.

Page 11 line 12. Instead of "the sample sizes were smaller", maybe "the sample sizes were relatively small"

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

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