Reviewer's report

**Title:** Age-of-onset-dependent Influence of NOD2/CARD15 gene variants on Disease behaviour and treatment in Crohn's disease

**Version:** 1 **Date:** 18 November 2012

**Reviewer:** silvia vidal

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In the present manuscript, authors analyzed the association between the presence of NOD2 variants and clinical phenotype of pediatric onset Crohn's disease patients. They particularly focused on osteoporosis and growth failure because delayed growth is a well established feature of pediatric onset CD.

NOD2 variants have already been associated with markers of disease severity and specific phenotypes (ileocolitis) in other pediatric-onset CD cohorts. Other authors have reported that NOD2 genotype was not correlated with growth retardation or growth failure. Lower mass index and higher PCDAI have also been reported in patients with NOD2 variants.

Some of the associations have already been published in other cohorts. However, the originality of the manuscript is based on the association between bone mass density/osteoporosis and NOD2 variants. The number of patients was not enough for a complete study of each three NOD2 variants. However, grouping the three NOD2 variants allowed them to reach significant conclusions.

In order to improve the quality and rigor of the manuscript, I would like to suggest the following comments:

**Major compulsory revisions:**

1) Authors indicated differences between carriers of NOD2 variants and wild type patients in the text results. However, some of these differences were not statistically significant (underweight at time of diagnosis, longer duration,..).

2) According to the legend of Figure 2, BMI was only available from 49 of patients. How many were wild type or NOD2 variant?. There were visible differences in the graph but they were not statistically significant. A very small number of patients in one of the groups could explain this apparent contradiction.

3) The authors have not clarified the impact of NOD2 polymorphisms towards osteoporosis. They have only analyzed the impact of several clinical aspects in BMD, regardless of NOD2 (page 10).

4) In Figure 5, response to therapy was evaluated according to age onset. However, the analysis in the other figures (other clinical parameters) was the % of pediatric or adult onset patients. Two different methods of analysis could complicate the interpretation of results. I would suggest a similar evaluation for therapy (separating pediatric and adult onset).

**Minor essential revisions:**
Table 1) at the title of the Table, authors indicated 203 patients instead of 201
Table 2) some results were expressed differently. i.e. 22(35%) and 25/34%
Figure 1) Authors should indicate at the figure (not only legend) which graph is
pediatric or adult onset (it would facilitate the comprehension)

Discretionary revisions:
Discussion could be reduced

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a
statistician.

**Declaration of competing interests:**
I declare that I have no competing interests