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

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Reviewer: Maria Francisca Gonzalez-Escribano

Reviewer's report:

In the manuscript entitled “Age of onset dependent influence of NOD2/CARD15 gene variants on disease behaviour and treatment in Crohn’s disease” Posovszky et al. investigated whether the contribution of mutations in NOD2/CARD15 to the phenotype of the disease and extra-intestinal manifestations (osteoporosis) is different in patients with paediatric and adult onset age. To reach their aims, they study the three mutations in NOD2/CARD15 which have been associated with the disease in a cohort of 201 patients: 85 paediatrics and 116 adults. They collected demographic data of patients and also localization, behaviour, activity and other clinical parameters as well as osteopenia and osteoporosis.

The influence of these NOD2 mutations in paediatric CD has been investigated and some of these reports are not mentioned in this manuscript (Russell RK et al J Pediatr Gastroenterol Nutr. 2004 and Shaoul R et al. Dig Dis Sci. 2009). In my opinion, the weakness of this manuscript lies in two points. One is the sample size which is too low for the successive stratifications made. The other problem is the way in which the results are presented, too long and confusing. The manuscript could improve if the authors show only the most relevant results for their objectives in a clearer way.

Other questions:

1. They need to define how they calculate the onset age and what threshold they use to split paediatric and adult onsets.

2. There are discrepancies concerning numbers in different sections of the manuscript. For example, according with the heading of Table 1, total number of patients is 203, but in the text and inside the Table 1, the authors register a total of 201 patients. In Table 1 and text they say that they have 48 individuals with NOD2 mutations in the adult onset group, nevertheless, according to data in supplementary information this number is 46. The authors should carefully checked all the data included in Tables and text in order to correct these mistakes.

3. The authors use the term "NOD2 SNPs" throughout the manuscript. to refer to individuals bearing NOD2 mutations. This is wrong and could be misinterpreted by readers.

4. According to Table 1, means of age at diagnosis for paediatric patients were 13.9 (range 7-18) for patients with mutations and 12.1 (range 1.18) for patients
without any mutation, nevertheless there are 11 and 14 patient included in the A2 stratum (17-40 y) of these groups. Means this that all these patients were 18 years old at diagnosis? In this case, I suggest establish only two groups older and younger than 18 year at diagnosis.

5. In my opinion the Figures are not necessaries. Data of Figure 1 could be included in Table 1, data of Figure 2 in Table 2 and the rest are included or could be included in the text.

6. Some data probably interesting are not shown for example data of BMD in patients with homozygous status for NOD2 mutations.

7. Table in supplementary information, patients should be split in single dose (heterozygous) and double doses (homozygous and compound heterozygous). These data could be included in Tables 1 and 2. The data relating to the specific mutations could be left as supplementary information.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**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