Reviewer's report

Title: A case-only study of gene-environment interaction between genetic susceptibility variants in NOD2 and cigarette smoking in Crohn’s disease aetiology

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Reviewer: Angharad Morgan

Reviewer's report:

The authors investigated gene-environment interactions between CD associated NOD2 alleles and cigarette smoking in a large sample of patients with CD. It is the largest study to date investigating gene-environment interactions in CD and the first to employ a case-only design. The manuscript is very well-written.

The study found an interaction between the 1007fs variant and smoking, although the increased risk of CD for smokers with this variant was lower than expected. There was no interaction with the other two NOD2 SNPs. The study does have limitations but these are clearly addressed in the manuscript. The findings are not of great consequence but the authors do not pretend them to be. However the study is an important contribution to the area of CD genetics. Many are aware of the likely importance of gene-environment interactions in complex disease such as CD but few such investigations are reported in the literature. Hopefully this study will encourage further similar work by other research groups.

Do the authors have access to sub phenotype data, to test if the interaction results in an increased risk of a particular sub phenotype such as disease location or behaviour?

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