

### **Answers to reviewer 03257023**

1. The title reads as "The unappreciated role of TNFSF15 in gastrointestinal diseases". However the manuscript is not related to all gastrointestinal diseases but only confined to Crohn's disease and ulcerative colitis. Also, it does not make clear why the role of this gene is "unappreciated".

*We have changed the title to "The role of TNFSF15 in the intestinal inflammatory response".*

2. The Abstract does not deal with all gastrointestinal disorders but only mentions Crohn's disease, ulcerative colitis and diverticular disease. Hence the Abstract does not go with the Title.

*We have adjusted the abstract to focus more on the diseases mentioned in the text.*

3. The review is very brief in nature. It is not clear, whether this is a review or an editorial written in respect of an Original Article that is being published at the same time in the Journal.

*The aim of the article is to serve as an editorial and a brief review, outlining how TNFSF15 is a gene worthy of further study due to its role in a multitude of diseases.*

4. Diverticular disease is mentioned in the initial part, but no studies relating diverticular disease to TNFSF15 either by genetic linkages or by way of pathophysiology are mentioned in the review.

*Studies have been added, showing association between TNFSF15 variants and surgical diverticular disease as well as a common risk haplotype between diverticular disease and Crohn's disease.*

5. The last sentence of the Abstract mentions that "Furthermore, we summarize what is currently known of TNFSF15 control region variants and how they can be used to predict susceptibility to IBD as well as to establish a patient's risk of requiring surgical intervention". Unfortunately any discussion of this aspect is missing in the text of the review.

*The abstract has been rewritten and the specific study by Connelly et al, 2014 has been added and cited within the text.*

## Answers to reviewer 03538924

“The unappreciated role of TNFSF15 in gastrointestinal diseases” by Tanya Kadiyska et al. was a review article which introduced the role of TNFSF15 in gastrointestinal diseases. It is well written and good paper for the readers.

However, several points remain to be addressed.

Major point:

1. The direct contribution of TNFSF15 to DD was not described in this manuscript. Several genetic association studies should be added (e.g., Connelly TM et al. Ann Surg 2014).

*We have added the mentioned studies to the text and a new paragraph which serves to describe their findings*

2. TNFSF15 is the second strongest susceptibility gene to Primary biliary cholangitis (PBC) in Asian populations (Nakamura M et al. Am J Hum Genet 2012; Kawashima M et al. Hum Mol Genet 2017; Qiu F et al. Nat Commun 2017). Additionally, rs4979462 had been identified as the primary functional variant in TNFSF15 (Hitomi Y et al. Hum Genet 2015; Sun Y et al. Sci Rep 2016). Therefore, the contribution to the pathogenesis of PBC should be described in this manuscript.

*We have included a paragraph that describes briefly the pathogenesis of PBC and the GWAS that tie TNFSF15 and PBC. Further comments on this specific disease would be greatly appreciated.*

Minor point: 3. P.4, L.17, TL1A is a longer “splicing” variant.

*Corrected.*