Title: Genetic contribution to motility disorders of the upper gastrointestinal tract

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We made substantial changes according to your and reviewers' suggestion and hopefully it is now suitable for publication. We thank the reviewers suggestions that significantly improved the clarity and relevance of our editorial.

Thank you very much for your consideration.
With best regards,

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The manuscript has been improved according to the suggestions of reviewers:

Answer to reviewers

Reviewer 1

The authors summarized current findings regarding genetic contribution, especially polymorphisms, to the upper GI motility disorders. The manuscript is well written, based on the published reports including authors' works.

Minor points should be corrected.

1. Tables 1-4 are not included in the text.
2. Please locate each table in the text.
3. 'In the table 1' (p7) should be 'table 2'.
4. TRL-2 (p7, table 2) should be TLR-2

We thank the reviewer for the helpful suggestions. We corrected each of the points and the text has been corrected accordingly.

Reviewer 2

This is a narrative review of genetic contributions to motility disorders of the upper gastrointestinal tract. The authors have reviewed genetic factors in achalasia, hypertrophic pyloric stenosis and functional dyspepsia. The review is partly an update of a previous review by the main author on genetic factors in achalasia (ref #39). There are a number of sweeping statements and unclear points that may need the attention of the authors to this review:

1. The basis for reviewing the above three diagnostic groups is unclear. The authors claim that "oesophageal achalasia and functional dyspepsia are the most representative motility disorders of the upper GI-tract". This is perhaps incorrect. The typical motility disorders are achalasia and gastroparesis. Functional dyspepsia is a much more nebulous term that may encompass many different disease mechanisms and pathophysiologies connected only by a similarity in symptoms. A specific motor disturbance has not been described in functional dyspepsia. Moreover, the last paragraph of the introduction says that oesophageal achalasia, functional dyspepsia and hypertrophic pyloric stenosis are "three of the best characterized and most common upper GI dysmotilities". It is unclear how hypertrophic pyloric stenosis came into this and again gastroparesis is a much better characterized motility disorder than functional dyspepsia. Please explain why the three diagnoses were chosen and give the readers a better explanation why the three should be included in a review and why gastroparesis should not be included.

We thank the reviewer and we agree that this point needs to be clarified.
We actually have chosen these pathologies for the following reason:

1) **hypertrophic pyloric stenosis represents a well characterized motor dysfunction of infants, and its early age of onset suggests that the contribution of genes in its pathogenesis is predominant;**
2) **idiopathic oesophageal achalasia can be considered a paradigmatic example of upper-GI motility disorder of adults and recent evidences suggest a pregnant genetic background;**

3) **as far as functional dyspepsia, we partially agree with the reviewer about its nebulous pathogenesis. Although symptom's generation may depend on multiple factors not primary related to gastric dysmotility, the role of impaired gastric motility (i.e. impaired fundus accommodation, altered antral motility and impaired gastric emptying) has been largely recognized. In addition, given the high prevalence of FD and in keeping with emerging data about its association with some genes, we decided to treat FD rather than idiopathic gastroparesis, whose association with genetic factor is not similarly supported by literature.**
These concepts have been clarified in the revised manuscript, however should the reviewer consider necessary to add a part on idhiopathic gastroparesis, we will do.

2. The sentence "Although this hypothesis is still far from fully explaining the pathogenesis of the disease, this introduces the concept that a given subject…" is unclear. The first part should be revised. It is unclear what the word "this" in the beginning of the second part refers to.

We thank the reviewer and we rephrased the sentence accordingly. Hopefully it is now clearer.

3. The sentence "In fact, both the association between HLA DR or DQ, especially DQA1 *0103 and DQB1 *0603 and achalasia 25-27 and the oligoclonality of the T-cell population infiltrating the LES 24 supported this hypothesis" is unclear. What do the authors mean with the oligoclonality of the T-cell population (which T-cell population?); how does this support the hypothesis; and which hypothesis is being referred to?

We thank the reviewer and we agree that this point needs to be clarified.
Although the pathogenesis of achalasia remains unclear, the hypothesis we referred to indicates that achalasia is an immune-mediated destruction of the LOS neurons, likely triggered by a virus (i.e. HSV); being virus infection widely diffused the reason whereby in only some individuals infections are able to induce a LOS neurodegeneration is probably due to a genetically based abnormal immune response.
In keeping with this we put our efforts to summarize all the data showing in achalasia patients a significant association with genes encoding for proteins involved in the immune response. In addition. In this context we believe that the findings by Facco et al showing a significant activation of CD3+T cells infiltrating the LES in achalasia patients further support our interpretation.

4. It is perhaps not so wise to start sentences with "In fact" or "As a matter of fact" since very little in science can be described as facts. Most of our pieces of evidence are observations or interpretations.

We apologize for this and we changed the text accordingly.

5. The sentence that starts with "The lack of any association between the same SNP in the iNOS was also excluded by a Spanish group…" needs to be revised. Either the lack of association was confirmed OR the association was excluded!

We corrected the sentence.

6. The authors refer to a work of their own (ref #36) that has yet not been published, only an abstract, and this makes it difficult for the reader to understand the significance of this particular finding. I also think that the increase in the risk for achalasia that follows from and increased

production of NO needs some kind of explanation, since achalasia usually results from death of NO-producing neurons.

Totally agree, the reference was deleted.

7. SNPs polymorphisms is a tautology, since P in SNP stands for polymorphism.

This expression was changed in the revised version of the manuscript.

8. The sentence "Since FD is one of the most prevalent FGIDs, a certain genetic influence is suggested by both symptoms familial clustering and twin studies reported for IBS" assumes that FD and IBS are similar with regard to genetic influences but I am in doubt if this is a correct assumption. Do the authors mean that all FGIDs have a similar genetic influence? What is there to suggest that FD and IBS are similar with regard to genetic influence?

We agree with the reviewer that although all FGIDs share common pathophysiological mechanisms a given genetic influence could be supposed for both FD and IBS, however this was not our assumption and goes beyond our intention. The study we referred to showed indeed symptoms familial clustering and twin studies reported for all FGIDs, but in our case we only focused on FD. We modified the text to make it clearer.

9. The expression "symptoms generation" should be either "symptom generation" OR "generation of symptoms"!

We corrected the typos.

10. The sentence that ends with "…and both symptoms or impaired gastric accommodation and emptying in a small subgroup of dyspepsia patients" does not make sense. What is it the authors are tryi…….

Please would you apologize for the editing errors. This sentence was changed in the revised version of the manuscript.