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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 44662

Title: Contribution of Ghrelin Genetic Alterations to Functional Gastrointestinal Disorders Pathogenesis

Reviewer's code: 00038999

Reviewer's country: Denmark

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-22

Date reviewed: 2018-11-28

Review time: 6 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[ ] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[Y] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Koutouratsas et al have written a review article on the potential role of ghrelin in the pathogenesis of functional GI disorders (FGID). The paper gives a short but comprehensive overview of the field and would be interesting for the readership of WJG.

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Specific comments 1. Paper title: the paper is not focused solely on genetic alterations of ghrelin and therefore the title may be somewhat misleading. The authors could consider revising it. 2. The authors provide criteria for their literature search. However, the paper appears to be a narrative review and should probably be identified as such. 3. Please spell out "SNP" the first time it appears in the text. 4. In page 8, there is strikethrough text. Please decide whether this is to be included in the paper or not. 5. In the chapter of "Functional dyspepsia" (2nd paragraph) the authors note that ghrelin "…. plays a role in the regulation of gastric motility". However, in the previous page, they note that "… at physiological concentrations, ghrelin does not appreciably affect gastric motility" (end of first paragraph). Please clarify. 6. If the paper is to be re-reviewed please insert page numbers. 7. p.11."Keeping in mind that the acylated form of ghrelin exhibits physiologic activity….". Please specify which physiologic activity is meant. As the authors have shown in table 1 and mentioned earlier in the paper, both the acylated form of ghrelin and des-acy ghrelin, have physiologic actions which may also be opposing. 8. p. 11, 2nd last paragraph, 2nd last line: please change "wield" to "yield" 9. Irritable bowel syndrome section, 3rd line: "Bloating could be often be present…" please omit one "be"

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 44662

Title: Contribution of Ghrelin Genetic Alterations to Functional Gastrointestinal Disorders Pathogenesis

Reviewer's code: 00055041

Reviewer's country: Italy

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-27

Date reviewed: 2018-12-03

Review time: 6 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The review is interesting and more actuality

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 44662

Title: Contribution of Ghrelin Genetic Alterations to Functional Gastrointestinal Disorders Pathogenesis

Reviewer's code: 02461118

Reviewer's country: United States

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-22

Date reviewed: 2018-12-03

Review time: 11 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This mini review summarizes that the genetic variations of the hunger hormone, ghrelin, are associated with functional gastrointestinal disorders (FGIDs) pathogenesis. This review requires a substantial revision. To improve the quality, I have following

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suggestions and comments: 1. The introduction section briefly mentions the prevalence of FGIDs in the first paragraph. Several studies have reported much variation in the prevalence of FGIDs between western and Asian countries. The variation range of the FGIDs prevalence should be included with references. 2. Replace Reference [5] to the reference of original studies in the introduction. 3. Add the reference for "Ghrelin is a brain-gut axis peptide that was isolated from stomach cells and was found to be the endogenous ligand for growth hormone (GH) secretagogue receptor" in the introduction. 4. Provide a table for genetic alterations/expression of ghrelin and association with FGIDs (separate table for two distinct FGIDs (functional dyspepsia, FD and irritable bowel syndrome, IBS). It will be better to present these genetic association with symptoms of FD and IBS. Also, conclude if there are any differences observed in ghrelin SNPs in the different populations studied. I also suggest checking if any studies reported ghrelin expression according gender. 5. Provide a figure for the pathway and physiological actions of how ghrelin works (via ENS to CNS). 6. There are already many studies on the role of ghrelin in FGIDs and ghrelin agonist for management of FGIDs (see References below). How is this review different than others? Mention this in the introduction. 7. Ghrelin is an endogenous growth hormone secretagogue receptor ligand and it has been shown to exert prokinetic effects on GI motility. Its use in clinical practice is limited because of the short half-life of ghrelin. This is why ghrelin receptor agonists with enhanced pharmacokinetics were developed; they accelerate gastric emptying and improve symptoms of gastroparesis in animal models and humans. How, this review article explores these clinical scenarios and how genetic alterations in ghrelin may be helpful for new targets for medicine. 8. In the section "GHRELIN BIOCHEMISTRY, PHYSIOLOGY, AND PATHOPHYSIOLOGY" details of ghrelin biochemistry are presented. I think the biochemistry discussion should be very brief and this section should be more focused on ghrelin physiology. 9. Provide the future

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directions for the genetic research which may be carried out in the ghrelin hormone or receptor. 10. Conclusion section needs to be revised extensively. 11. On the page 9, check the deleted sentences and references. 12. Check references if any references are missing. References: 1. Tack J, Camilleri M. New developments in the treatment of gastroparesis and functional dyspepsia. Curr Opin Pharmacol. 2018 Sep 20; 43:111-117. 2. Zatorski H, Mosinska P, Storr M, Fichna J. Relamorelin and other ghrelin receptor agonists - future options for gastroparesis, functional dyspepsia and proton pump inhibitors-resistant non-erosive reflux disease. J Physiol Pharmacol. 2017 Dec;68 (6):797-805. 3. Fukui H, Xu X, Miwa H. Role of Gut Microbiota-Gut Hormone Axis in the Pathophysiology of Functional Gastrointestinal Disorders. J Neurogastroenterol Motil. 2018 Jul 30;24(3):367-386. 4. Camilleri M. Novel therapeutic agents in neurogastroenterology: advances in the past year. Neurogastroenterol Motil. 2014 Aug;26 (8):1070-8. 5. Sanger GJ, Furness JB. Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. Nat Rev Gastroenterol Hepatol. 2016 Jan;13 (1):38-48.

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