Author's response to reviews

Title: Genetic mutations in SPINK1, CFTR, CTRC genes in acute pancreatitis

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Author's response to reviews: see over
Dear Editor,

We would like to submit our manuscript entitled ‘Genetic mutations in SPINK1, CFTR, CTRC genes in acute pancreatitis’ by Koziel D et al., for consideration for publication in your journal BMC Gastroenterology.

The following changes were introduced according to the reviewers’ comments:

Date: 04 March 2015

1. The introduction is still very long. Mechanistic aspects of PRSS, SPINK and CFTR can be summarised in the discussion.
   Shortened according to the reviewer’s comment.
   The majority of people with PRSS1 p.N29I and p.R122H mutations, as well as SPINK1 p.N34S, are predisposed to fall ill in childhood without any other detected risk factors. The progression of the disease is slow and the clinical image may be equivalent to that of recurrent acute pancreatitis [12,13,14].
   Mechanistic aspects of PRSS, SPINK and CFTR summarizes in the discussion.

Page 11

SPINK1 is a specific trypsin inhibitor and an acute phase protein which is secreted by the acinar cells. SPINK1 protein plays a role in the prevention of premature activation of zymogen that is catalyzed by trypsin within the pancreatic duct system or the acinar tissue. A reactive site in the protein serves as a specific target substrate for trypsin. SPINK1 polymorphisms are common in the general population (approximately 2%) but are shown to be significantly associated with pancreatitis [12].

Page 13,14

Recent studies suggest an important role of CFTR in the development of pancreatitis, particularly through its role in intraluminal pH regulation from bicarbonate secretion and the flushing of ductal proteins. Secretory granules of pancreatic acinar cells co-release protons (H+) with digestive enzymes during normal pancreatic secretion. Diminished ductal bicarbonate secretion and consequent reduced alkalinisation of the acinar lumen may promote the development of pancreatitis, since acidification of the pancreatic lumen can lead to a loss of tight junction integrity, allowing the leakage of digestive enzymes into the pancreatic duct lumen and interstitial space [23]. Stressors such as oxidative damage, overloading the protein folding capacity of the ER, trigger the unfolded protein response [24].

2. Details of claudin are not necessary and should be removed.
   Details of claudin have been removed.

Page 5

Studies conducted in recent years confirmed that CLDN2 mutation may increase the risk of CP by interaction with alcohol consumption. The c.592A>C mutation in CDS CLDN2 causes the change of amino acid from Met to Leu. Physiologically, Claudin-2 protein encoded by the CLDN2 gene is expressed at low levels, co-forming tight junctions (a type of sealed cellular connection) between pancreatic duct cells. When subjected to stress, acinar pancreatic cells abnormally produce high quantities of Claudin-2 protein which may lead to pancreatitis by means of aberrant distribution of ion transport between acinar cells and lumen [18].

Page 13,14

Tables 1-5 have been included in appropriate places in the text.
4. The title of the Tables are still embedded within the main text.
   The titles of Tables have been removed from the text.
5. The title probably needs 'genes' after 'CTRC'.
The title of the article has been changed.
Genetic mutations in SPINK1, CFTR, CTRC genes in acute pancreatitis
6. The authors did not understand the comment made about 33 references being too many for a short manuscript. Hence, they have deleted only reference No. 33. They should try and reduce the references quoted.
References No. 12, 13, 14, 18 have been deleted.
7. Language needs to be improved.
The language has been revised from the editorial aspect and corrected by a native speaker.

We believe our findings would appeal to the readership of *BMC Gastroenterology*. We look forward to hearing from you at your earliest convenience.
All authors have approved the manuscript and agree with its submission to *BMC Gastroenterology*.

Yours Faithfully,

Dorota Koziel, Stanisław Gluszek, Artur Kowalik, Małgorzata Chłopek, Liliana Pięciak