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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 7133
Title: Cationic trypsinogen (PRSS1) and serine protease inhibitor Kazal 1 (SPINK1) mutations in subjects with idiopathic early onset chronic or idiopathic recurrent acute pancreatitis in Mexico City.
Reviewer code: 02548398
Science editor: Huan-Huan Zhai
Date sent for review: 2013-11-06 15:59
Date reviewed: 2013-11-07 20:36

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

Manuscript: ID:02548398 ESPS Manuscript NO: 7133 Title: Cationic trypsinogen (PRSS1) and serine protease inhibitor Kazal 1 (SPINK1) mutations in subjects with idiopathic early onset chronic or idiopathic recurrent acute pancreatitis in Mexico City. Authors: Mario Pelaez-Luna, Guillermo Robles-Diaz, Samuel Canizales-Quinteros, Maria T Tsuie-Luna Review: Summary: The authors present data of 19 patients with early onset chronic pancreatitis or idiopathic recurrent pancreatitis from Mexico in which sequencing of PRSS1 and SPINK1 was performed. Two new PRSS1 and 3 SPINK1 variants (one new) were found. Major points: The approach for the identification of chronic pancreatitis (CP) variants is not sufficient. Although, it might not change the picture dramatically I would suggest to sequence all exons of PRSS1, SPINK1, CTRC, CPA1 in these patients and in the 50 controls. Maybe it will even be possible to investigate more controls. The data presented so far are interesting. Since, the PRSS1 variants are new, functional analyses of these variants might help to understand their role in CP better. The same might be true for the new SPINK1 variant. With this approach the paper could be improved from my point of view. In parts (Introduction, Discussion) it seems that the paper needs to be rewritten to make the points made clearer and to give it a red line. Minor points: The references are quite a huge number, maybe a reduction is possible. The number of patients is rather low to give a solid picture of the mutation distribution in Mexico, but the newly described variants make the manuscript interesting (if they have functional consequences). How have the controls been recruited?

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Title: Cationic trypsinogen (PRSS1) and serine protease inhibitor Kazal 1 (SPINK1) mutations in subjects with idiopathic early onset chronic or idiopathic recurrent acute pancreatitis in Mexico City.
Reviewer code: 02547932
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
ESPS Manuscript number: 7133 Cationic trypsinogen (PRSS1) and serine protease inhibitor Kazal 1 (SPINK1) mutations in subjects with idiopathic early onset chronic or idiopathic recurrent acute pancreatitis in Mexico City. Pelaez-Luna et al. In this manuscript 19 individuals with pancreatitis were examined for mutations in PRSS1 (exon 2 and 3) and SPINK1 (exon3). The number of individuals tested is relatively small and genetic testing was restricted to 3 exons of two genes. Testing for CTRC, CPA1 and CFTR was not done. The consequence of the newly identified mutations remains unclear. No functional data were obtained for PRSS1 p.V39E (not p.V39A ?), p.N42S and SPINK1 p.V46D. All three variants seem to be private variants detected in single individuals only. In collaboration with other research groups, functional analyses should be performed for these 3 variants. I believe, that the group of Prof Sahin-Tóth in Boston as well as the group of Claude Férec in Brest or even other groups might be willing to collaborate and to test these variants. Functional data will greatly improves the conclusion of the manuscript. Replication of PCR in the SPINK1 p.V46D index case and paternity test in the parents might be done. The main text as well as references might be shortened. The manuscript is very long for what it has to say. Minor points: "early onset" pancreatitis: 4 affected subjects are older than 40 years. Early onset might not be really appropriate. The figures in the table differ from the figures in the abstract (range 13-40 vs. range 15-48 years) Figures: Both can be omitted. The information given by pherograms is relatively low. Table: The table should be restricted to the individuals with positive findings (1, 6, 8, 15, and 19). References: The manuscript has more references as individuals investigated. This should be an

original paper not a review. References might be limited to the essential literature i.e. 20-30 references at max. References are not unified in style (e.g. ref. 24) or cite wrong names (Audrézet ref. 26). Sharer (ref. 41) might be cited together with Cohn and colleagues earlier in the main body. Some references cannot be correct: e.g. ref. 41 (Sharer 1998) does not deal with SPINK1 mutations, which were described two years later. Also Sibert (ref. 48) contains data of the pre-genetic era.

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Title: Cationic trypsinogen (PRSS1) and serine protease inhibitor Kazal 1 (SPINK1) mutations in subjects with idiopathic early onset chronic or idiopathic recurrent acute pancreatitis in Mexico City.
Reviewer code: 02548374
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Your work has relevance because it brings new information about a population that has not yet been studied and describes the occurrence of new mutations. The study of patient's relatives contributes to understanding the impact of the occurrence of mutations and helps to investigate the presence of other cofactors that may have collaborated to the development of pancreatitis. You have obtained sufficient number of patients because the inclusion criteria were restricted to the defined characteristics of an uncommon disease. It allowed to select patients most likely to have these genetic mutations. Direct sequencing was used for the genetic study and is the most adequate technique for the proposed research. The presentation of the results and discussion is well prepared and allows you to reach the conclusions. I would add a few suggestions that could contribute to presenting what is currently being studied. In the fourth paragraph of the Introduction you report that mutations of SPINK1 gene may have a role in the phenotypic presentation of the pancreatitis. I suggest you to describe some examples and include the reference. I suggest you to mention the N34S mutation in the sixth paragraph of the Introduction, because it is the most often found in the SPINK1 gene in patients with chronic pancreatitis. In the 10th. paragraph of the Discussion you refer to the paper presented by Bernardino et al. This was the only work that studied the SPINK1 and PRSS1 genes in Brazil. I would like to remind that our group published a study in 2009 (da Costa MZ, et al. Pancreatology), however it refers to another gene, the CFTR. For this reason I would suggest this sentence to be clear that you refer to SPINK1 and PRSS1 genes. I congratulate you for choosing this subject and for the presentation of your work. The study of genetics in pancreatic diseases is

crucial to better understand the pathogenesis of this diseases, but it still has been developed by few researchers.