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ESPS Peer-review Report
Name of Journal: World Journal of Biological Chemistry
ESPS Manuscript NO: 7729
Title: Functional analysis of human Na+/K+-ATPase FHM2 mutations expressed in Xenopus oocytes (re-submission of No. 7676)
Reviewer code: 01004042
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-11-30 23:17
Date reviewed: 2013-12-03 02:51

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	[Y]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[Y] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The aim of this work is Functional characterization of ATP1A2 mutations that are related to Familiar Hemiplegic Migraine (FHM). The approach is to express mutants of this protein in oocytes and examine the location and function of this protein. In general the work is straight forward and interesting. There are minor errors in writing. However, there is a major flaw in this work. "To reduce ouabain sensitivity, the mutations Q116R and N127D were introduced in the α2-subunit. This construct is herein referred to as WT." Thus WT is already mutated. In the judgement of this reviewer, one cannot conclude that the consequences of the mutations would have been the same if the control was not already mutated even though the initial mutations are in a different domain of the protein. This raises doubt on validity of any of the conclusions of this work.

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Name of Journal: World Journal of Biological Chemistry
ESPS Manuscript NO: 7729
Title: Functional analysis of human Na+/K+-ATPase FHM2 mutations expressed in Xenopus oocytes (re-submission of No. 7676)
Reviewer code: 00197104
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-11-30 23:17
Date reviewed: 2013-12-10 21:09

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] 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

In continuation to previous work, the authors have studied the functional impact of 7 new mutations in the alpha2 subunit of the NaK ATPase. They show that these mutations that are related to familial and sporadic hemiplegic migraine have different effects on enzyme activity and trafficking to the plasma membrane. The technical quality of the work is good, and the data are convincing and well discussed. Minor comments: - A careful rereading is necessary to correct a few typos (for example familial instead of familiar in familiar hemiplegic migraine, aim and introduction sections). - In the paragraph “Functional consequences” of the discussion ref 26 has been used instead of ref 15 (about P979L mutation)

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Name of Journal: World Journal of Biological Chemistry
ESPS Manuscript NO: 7729
Title: Functional analysis of human Na+/K+-ATPase FHM2 mutations expressed in Xenopus oocytes (re-submission of No. 7676)
Reviewer code: 00503000
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-11-30 23:17
Date reviewed: 2014-02-18 23:01

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] 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	[Y] Major revision

COMMENTS TO AUTHORS

The authors study the functional consequences of seven mutations related to familial and sporadic hemiplegic migraine, in the alpha2 subunit of the NA, K ATPase. This is an interesting work that complements previous works of the authors. I consider that some issues needs to be resolved before publication. Major comments: -Due to the methodological strategy employed, the authors are studying mutations in an already mutated protein. To strengthen their conclusions, the author need to provide some evidence that the mutations introduced in the WT have no further consequences in the protein and the mutants they are studying -Western blot analyses lack a loading control - The authors must provide statistical analyses of their data. Minor comments: -In the title, the abbreviation should be changed for the complete name of the disease -In the whole manuscript, familiar must be changed for familial

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ESPS Peer-review Report
Name of Journal: World Journal of Biological Chemistry
ESPS Manuscript NO: 7729
Title: Functional analysis of human Na+/K+-ATPase FHM2 mutations expressed in Xenopus oocytes (re-submission of No. 7676)
Reviewer code: 00504439
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-11-30 23:17
Date reviewed: 2014-02-28 16:14

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

The authors provide a firm and well performed studies on WT and mutant pumps, I have very few comments, since the authors did not number the MS I will try to inform about the location of my points. 1- Introduction page, the authors mention that K binding stimulates dephosphorylation and conformational change E2 to E1 without mentioninig the role of cytoplasmic ATP in inducing the E1 form. 2-Results, under electrogenic Na,Na exchange. and not "und" 3-From the abstract I have got the impression that K1003E has no impact on pump function, yet the mutation produces a clear shift in Na,Na exchange, because the affinity of the third Na site can be changed independently, it would be more precise to say that K1003 had no impact on K interaction,