Author's response to reviews

Title: A study in Polish patients with cardiomyopathy emphasizes pathogenicity of phospholamban (PLN) mutations at amino acid position 9 and low penetrance of heterozygous null PLN mutations

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Version: 2 Date: 9 January 2015

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

Thank you for review of our paper “A study in Polish patients with cardiomyopathy emphasizes pathogenicity of phospholamban (PLN) mutations at amino acid position 9 and low penetrance of heterozygous null PLN mutations” by Truszkowska et al., the invitation to resubmit and the forwarded Reviewer’s comments. We have revised the manuscript and the changes introduced due to forwarded comments are described below. We hope that in the present version you will find the paper suitable for publication in *BMC Medical Genetics*.

EDITORIAL REQUIREMENTS:

Comment: Please update your ethics statement to include the name of the ethics committee that approved your study.

Answer: In line 72 we now state that ‘..the study protocol was approved by the local bioethics committee (Ethics Committee of the Cardinal Wyszynski Institute of Cardiology).’

Reviewer: Madhu Khullar

Comment: Minor Essential Revisions: Authors have discussed that c.116A>C:p.Leu39Ter (rs111033560), a null variant of PLN leads to truncated protein and is pathogenic, and extrapolate these findings to c.9_10insA:(p.Val4Serfs*16) null variant identified by them in their cohort, the supporting laboratory data for this is not provided. In fact this variant does not appear to be associated with cardiomyopathy, hence a general statement “our results and the data reported in the literature indicate that in humans 213 heterozygous null PLN mutations either have low penetrance or are not pathogenic” may not be correct and should be modified accordingly.
Answer: We have modified the statement so that it now reads: ‘Thus, our results and the data reported in the literature indicate that in humans heterozygous null PLN mutations may have low penetrance or may be not pathogenic.’

Please note that our discussion of rs111033560 (Leu39Ter) pathogenicity was meant to differentiate between subjects homozygous and heterozygous with emphasis on the observation that reported carriers of a single dose of the variant are mainly asymptomatic or only weakly affected. As we write in line 208-210: ‘.. there are a total of 16 described family members with Leu39Ter mutation from whom only two were clearly affected (DCM and HCM, respectively), four had left ventricular hypertrophy and ten were asymptomatic [7, 8].’ Please note that these data are fully consistent with our observation that the null PLN variant found by us (c.9_10insA:(p.Val4Serfs*16) appears also not to be associated with cardiomyopathy. This is even more so, if you take into account the fact that all the subjects reported previously came from families in whom occurrence of other genes than PLN causing cardiomyopathy was possible.

Reviewer: Perundurai Dhandapany

Comment: ‘Needs some language corrections before being published’

Answer: We made an exhaustive effort to correct the English. In particular, we had the paper checked by a native speaker.

ADDITIONAL CHANGES:

In addition we noticed an error in the name of a variant in PLN and changed it in the whole manuscript (previous incorrect name “c.9_10insA:(p.Val4Serfs*16) and current correct name “c.9_10insA:(p.Val4Serfs*14)”.

Best Regards,

Prof. Rafał Płoski