Author's response to reviews

Title: Selective acquired long QT syndrome (saLQTS) upon risperidone treatment

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

Please find the revised version of the manuscript entitled: “Selective acquired long QT syndrome (saLQTS) upon risperidone treatment”.

We are very pleased that our manuscript was well received by the reviewers and is being considered for publication in BMC Psychiatry. We would like to thank the reviewers for their constructive comments that let us improved the manuscript. All of the modifications appear as track-changes (highlighted in green), denoting where the original text has been modified. Below you will find detailed answers to all the specific comments and questions of the reviewers.

1. Dr Zareba did not have any specific comments, and he did not request additional experiments. We would like to thank Dr Zareba for finding our paper « of importance in its field ».

2. Dr Guicheney found unnecessary the sequence of KCNE1 presented in the figure and this panel of the figure has been discarded. The figure legend has been modified accordingly.

According to the suggestion made, we indicated IC50 for KCNH2 inhibition of the 3 studied drugs in the figure legend.

The reviewer asked also to state clearly whether the patient was treated by other drugs. This information was already present in the previous version of the manuscript (Fig. 1A ). We modified the text in order to make this point more intelligible.

Finally, Dr Guicheney suggested that « a screening of all LQT genes (…) could lead to a target and in vitro pharmacology confirmation ».

There are at least 13 genes with a well-documented role in the long QT syndrome (LQTS). In the congenital forms of LQTS the pathogenic mutations in these genes are
found in up to 70% of cases (Napolitano 2005, Berge 2008, Itoh 2009). The acquired (drug-induced) form of LQTS, is considered as a *forme fruste* of the congenital LQTS variant and both forms are believed to have a common genetic background (Kannankeril 2010). The incidence of the mutations in the aforementioned genes is similar in acquired and congenital LQTS (Itoh 2009).

In our genetic analysis we have screened two major genes implicated in LQTS (*KCNH2* and *KCNQ1*) and two less frequently involved genes (*KCNE1* and *KCNE2*). Mutations in *KCNH2* and *KCNQ1* frequently occur in LQTS and are thought to be responsible for the majority of cases with known genetic background (Hedley 2009). Screening of some other genes, especially *SCN5A*, *KCNE1* and *KCNE2*, increases the detection rate of the pathogenic mutations. The mutations in *SCN5A* are probably responsible for around 5% of LQTS cases, making *SCN5A* the third most commonly involved gene in LQTS (Hedley 2009, Bokil 2010).

Following the reviewer’s suggestions, we have completed the analysis and the whole coding regions of the *SCN5A* gene was sequenced but no mutation or significant polymorphism was found in our patient. This information has been now implemented in the text of the manuscript.

It cannot be formally excluded that further expanding of genetic screening on all of the genes implicated in the LQTS could lead to the identification of causative mutations in our case. However, the mutations in the five most important genes that we have already sequenced (*KCNH2*, *KCNQ1*, *KCNE1*, *KCNE2* and *SCN5A*) are responsible for probably more than 95% of cases of LQTS with known genetic background (Hedley 2009, Bokil 2010, Itoh 2009, Schwartz 2009). Therefore the probability that such a mutation will be found when all the genes are screened is minimal. More importantly, assuming that a mutation in one of the remaining LQTS-related genes is found, its causative role will be very difficult to prove on the basis of a single clinical case.

This point of view seems to be shared by Dr Guicheney, who proposes to perform “*in vitro* pharmacological confirmation”. However, in order to convincingly establish a causative role of such a mutation (assuming that it is identified), a whole panel of experiments would need to be performed (cloning of the gene, expression in an *in vitro* cell system, study on the affinity of risperidone and other antipsychotics to the WT and mutated protein, their effect on the function of the potassium channel in the presence and absence of the mutation, etc.). This, even though certainly interesting, would obviously be out of the scope of this revision. In fact, the amount of experimental work necessary to convincingly document a molecular mechanism would make it a completely new project, largely exceeding the frames of a “case report” format, the format we have initially submitted to *BMC Psychiatry*. However, in order to address the reviewer’s comment in the text, we added a sentence in the “conclusions” section, pointing to this limitation of the present study.
We agree with Dr Guicheney that the main limitation of this work is «the fact that no explanation was found». However it is only rarely the case in this type of publications (a single-case report). Importantly, we have found that a KCNH2-independent mechanism could be involved in drug-induced long QT syndrome. This is a novel and potentially important finding, taking into account that the preclinical screening of novel drugs is based on the assessment of their capacity to block KCNH2 only, the protein considered as a common drug target according to the current paradigm.

We hope that you will now find the revised version of the manuscript acceptable for publication in *BMC Psychiatry*.

Dr Maciej Lazarczyk

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**References**