Reviewer’s report

Title: Identification of novel KCNQ1 and KCNH2 mutations and the protective effect of KCNH2 SNP K897T in Long QT Syndrome families

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Reviewer: Pascale Guicheney

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The article of Zhang et al reports KCNQ1 and KCNH2 mutation screening in LQTS families. It is a well-written, detailed manuscript but with no major confirmed new findings.

They present a large LQTS family with 42 genotyped family members, 31 carriers of a novel KCNQ1 L187P missense mutation, including 5 members with a history of syncope. They also identified some other mutations including a novel 2-bp insertion in KCNH2.

In a mid-size family, they found two co-segregating variants, A490T and K897T. In 7 mutation carriers, 3 had a syncope and there was no family history of cardiac death.

Table 1 that gives minimum and maximum QTc values needs more methodological explanations. What is the potential interest of this presentation compared to a mean QTc value measured from lead II?

A large part of the discussion concerns the role of the T987 allele as a cis factor which could reduce the QTc length compared to reports in the literature of cases with A490P or A490T and no associated K897T variant.

The previous reports made their conclusions on single families - which is not enough - and on the basis of the association of a LQTS mutation and the K897T variant located on cis or trans.

It is known that other variants in ionic channels, NOSAP1... influence QTc length. Other potent modifiers may be present in addition in these families and it is thus difficult to be certain about the specific role of the T897 allele in these families. The presence of other known variants should be studied to compare the families and their influence on severity.

These important limitations should be introduced in the article.

The potential differential effect of a cis or trans variant on a LQTS mutation is an interesting point which should be answered by other methods.