LETTERS TO THE EDITOR

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A note on the prevalence of cardiac ion channelopathies in the sudden infant death syndrome

In the December 2014 issue of Europace, Wong and Behr1 published a review on the role of undiagnosed inherited cardiac conditions in sudden unexplained death in infants and children, which I read with great interest. In their Table 1, Wong and Behr2 provide the reader with data on the frequency of mutations in ion channel-related genes in cases of sudden infant death syndrome (SIDS). For example, a frequency of 1.0% is listed for mutations in the KCNQ1 gene, with reference to three studies on cohorts of SIDS cases (their references 30–32, which I cannot repeat here because of the restrictions put on the number of references accompanying a letter to the editor). However, in the 275 SIDS cases of these three studies a total of 7 mutations in KCNQ1 were found. Accordingly, one would expect a frequency of 2.5% (7/275) rather than 1.0%. If one takes into account that only 4 of these 7 mutations can be classified as functionally significant, as we did in our 2011 study,2 one still arrives at a frequency of 1.5% (4/275). This number of 1.5% changes into 1.0% if one takes into consideration, as we also did in our 2011 study,2 that there are another two studies, on a total of 134 SIDS cases, in which no functionally significant mutations in KCNQ1 were found. This brings the total number of SIDS cases studied to 409 and the frequency of functionally significant mutations in KCNQ1 to 1.0% (4/409).2

Similar concerns hold for the other frequencies of SIDS-associated mutations in ion channel-related genes that are listed by Wong and Behr1 in their Table 1. I cannot escape the impression that these frequency data are taken from our 2011 study,2 albeit without an appropriate reference, without realizing that our data include studies with a zero yield of mutations and account for the likelihood of a mutation to be functionally significant. This impression is strengthened by several discrepancies between statements in the text and the actual frequencies listed in the table. For example, Wong and Behr1 state that ‘LQT12-associated α1-syntrophin (SNTA1) mutations have also been demonstrated in 3% of a cohort of 292 SIDS cases,’ with reference to the study by Cheng et al.3 whereas their Table 1 shows a frequency of 1.0%, without any further explanation (which is that only 3 out of the 8 mutations found appear functionally significant4–6). Similar discrepancies hold for statements regarding the frequency of mutations in the GPD1-L and GJA1 genes (1.3 vs. 0.9% and 0.7 vs. 0.3%, respectively).

In summary, the reader of the review by Wong and Behr1 should be aware of the apparent origin of their data on frequencies of SIDS-associated mutations in ion channel-related genes and of the way these data were derived. Furthermore, it is important to note that additional data have become available since the publication of our 2011 study,2 e.g. through the study by Glengarry et al.4 which are not accounted for in the review by Wong and Behr1.

References

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Author’s reply

We thank Dr Wilders1 for his kind interest in our review and for pointing out the inconsistencies in our table of SADS and SIDS gene yields.2 We agree with his approach in his own previous review on SIDS3 that utilized criteria to identify the mutation yield with a greatest likelihood of pathogenicity. Unfortunately, we were remiss in not referring to his article and apologizing for the oversight. In order, however, to be consistent with the SADS data yields, we have redrafted the table to reflect putative mutations rather than likely mutations (Table 1). This includes his suggested study4 that was not known to us at the time of the manuscript submission as well as other studies5–24 to ensure accuracy. The redrafted table includes additional data from other and more recent molecular autopsy studies in SIDS and SADS. The frequency of putative pathogenic mutations in associated genes is specified in ranges to demonstrate the different yields seen in different studies and to better reflect the existing data.

References
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