Author's response to reviews

Title: Exome sequencing identifies a mutation in the ACTN2 gene in a family with idiopathic ventricular fibrillation, left ventricular noncompaction, and sudden death

Authors:

Christopher Semsarian (c.semsarian@centenary.org.au)
Richard Bagnall (r.bagnall@centenary.org.au)
Laura Molloy (l.molloy@centenary.org.au)
Jon Kalman (Jon.Kalman@mh.org.au)

Version: 3 Date: 21 May 2014

Author's response to reviews: see over
We thank the reviewers for his/her comments and have amended the manuscript (highlighted in yellow) as follows:

**Referee 1**

No revisions needed.

**Referee 2**

1. It is debatable whether or not the family shows the degree of heterogeneity suggested by the authors. Indeed, the presence of LVNC and DCM in this kindred would have swayed many to proceed with targeted testing of a DCM panel, which would have identified the ACTN2 mutation.

We acknowledge that the ACTN2 mutation would have been identified with a comprehensive cardiomyopathy gene diagnostic testing panel that includes minor disease-associated genes and have added this to the Discussion (page 12).

2. The individual considered as "IVF" is not well described. It is quite possible this individual is along the spectrum of DCM, with LVNC with preserved LV function. MRI images of this patient showing completely normal LV structure would be helpful.

Individual III:3 had an out of hospital cardiac arrest while visiting London. An MRI was performed at the Royal Brompton Hospital in London and revealed normal left and right ventricular indexed dimensions and function, with no evidence of myocardial fibrosis, and no features of cardiomyopathy. This additional information has been added to the Results section (page 7). MRI images are not available. No further MRI has been performed since an ICD was subsequently implanted while in London.

**Referee 3**

1. The pedigree trees of figure 4 are very important and should be improved. I presumed that * denotes a haplotype that had been inferred and this should be stated in the figure legend. The position of the haplotypes of a particular individual should reflect the position of his/her parents. It would make sense to consistently present, for instance, the father on the left and the mother on the right in the 2 pedigrees.

Note added to Figure 4 legend. Presentation of Figure 4 pedigrees and haplotypes has been improved as suggested.

2. ACTN2 and RYR2 VNTR are not so well known by contrast to poly(AC) such as D1S2670, D1S285 and D1S2678. It would be useful to give more details on the primers used for the 2 VNTR and the PCR conditions as a supplemental table.

PCR primer sequences, and physical and genetic positions of all tested markers have been added as Supplemental Table 2. PCR amplification conditions have been added to the methods section (page 6).

3. A Table should give the physical position and genetic position of the tested markers eventually by inferring the genetic position from the physical position in case of markers absent from the genetic map.

Information added as Supplemental Table 2.