Dear editor,

our manuscript has been revised as recommended. We believe, that all concerns of both reviewers should now be resolved. In the following we describe our changes in detail.

Reviewer 1: Stefan Waldmüller

Discretionary Revisions
1 Addressed: Block "In family 16 ……physical examination" was moved behind the description of family 5.
2 A section genotype-phenotype correlation was included into results as the last paragraph. A corresponding sentence was inserted into discussion, paragraph 2: "Although the number of mutations is too small to prove statistically significant, it is remarkable that all sudden deaths at or before the age of 35 occurred in families with splice mutations, while no sudden death was observed in families with missense mutations"

Minor Essential Revisions
1 Implemented
2 Implemented
3 Implemented
4 Implemented
5 Checked (according results, first paragraph)
6 Implemented
7 Implemented
8 Implemented
9 Implemented
10 Implemented (misspelling in line 15)
11 Implemented
12 Implemented
13 Implemented
14 Implemented (line 3)

Major Compulsory Revisions

1. a) Addressed: "Including relatives of twelve families, a total number of 42 mutation carriers was identified of which eleven (26.2%) had at least one adverse event."

b) Addressed: "Considering the twelve families and six single patients with mutations, 45 individuals with cardiomyopathy and nine with borderline phenotype were identified. Among the 45 patients, 23 (51.1%) suffered from an adverse event."

c) Addressed: "...At least one adverse event occurred in eleven of twelve families."

2. Implemented (also in results, section “adverse clinical events”, first sentence; “cardiac” deleted in second sentence)

3. Please refer to the appropriate Methods sections of the revised manuscript.

4. Please refer to the appropriate Methods sections of the revised manuscript.

5. All 14 mutation-negative family members were examined at least by echocardiography. As a result of these examinations the open symbols in figure 1 indicate “unaffected. However, in only one of these cases MRI was performed due to other reasons and 6 of 14 echocardiographies were performed by external cardiologists. The accuracy of echocardiography is discussed in discussion, para 2, sentence 2. As it is misleading and not correct, line 5 was changed in “...if screened positive for a mutation, for additional cardiac MRI.”

6. Has been addressed in the revised manuscript, refer to the new Table 1.

7. Also 2. of Reviewer P. McKeown: We addressed the novel mutations’ relevance in the appropriate results chapter by pointing out that four of the seven mutations lead to a significant change of the amino acid sequence, namely two splice site mutations, one frameshift mutation and one nonsense mutation. A fifth mutation affected an important phosphorylation site. The two other mutations, both missense mutations, were shown to affect highly conserved amino acid positions.

8. Patient I-2 of family 5 had only borderline hypertrophy in presence of arterial hypertension. As in II-6 trabeculation did not fulfil criteria for noncompaction this
finding is of unknown significance and the patient therefore considered as normal. Therefore, first sentence on page 12 was changed in “… had no certain pathological findings.”

9 Addressed: “… Based on twelve families and six single patients, a total number of 42 mutation carriers was identified, of which eleven had at least one adverse event. A total number of any adverse event occurred in 23 of 45 (51.1%) cardiomyopathy cases. Eleven individuals of seven families suffered from sudden death between 13 and 67 years of age. In three families, a sudden death occurred at or before the age of 35 years. Any adverse event occurred in eleven of twelve families and in two of six single mutation carriers.

10 The discussion was shortened as recommended: The section from "These additional..." until "...unless contraindicated" was removed and the paragraphs combined. As a consequence, the citation Moon et al. was removed.

As suggested, the section from "The youngest ..." to "...are mutation carriers" was moved into results last paragraph (Adverse clinical events) as appropriate.

11 Addressed by the following sentences added into the last paragraph of discussion: "Mutations in other likely candidate genes for HCM were not found in any of the index patients. As to the heterogeneity of the genetic causes of cardiomyopathies, additional mutations in less likely or hitherto unknown disease genes cannot be excluded. Moreover, yet unknown disease modifiers might have had a modulating effect on the disease phenotype."

Reviewer 2: Pascal McKeown

Major Compulsory Revisions

1 ECG data were inserted into table 2. Therefore, this table had to be converted into horizontal format

2 Please refer to our response to point 7 of reviewer Waldmueller.

3 Addressed in discussion, last paragraph, line 3 (“...and the prevalence of atrial fibrillation”) and line 5 (“In our retrospective evaluation of affected families, it can not be excluded, that other conditions have can lead to the adverse events.”)

4 "premature atrial fibrillation" was changed into "high susceptibility for atrial fibrillation"

5 Figure 1 was corrected: Family 5, patient I-2, dashed symbol replaced by open symbol. Family 12, patient II-6, black symbol replaced by dashed symbol. Patient IV-5 was classified as borderline because cardiac MRI was suggested superior as compared to echocardiography.

Table 1: Family 12 column affected was changed into 5 (3) and genotyped persons into 8. Family 13 column affected into 2 (1). Family 14 column affected the number within brackets was deleted.

Table 2: Family 5: Diagnosis and echo data between II-6 and III-2 were changed, as it is correctly described in the text of results section.

6 Both patients from family 6 and single patient 7 were examined by external cardiologists. Although examination records clearly stated the prevalence of a
hypertrophic cardiomyopathy during echocardiography, a precise measure of maximum wall thickness was not provided. Standard M-mode measures of septal thickness are not equivalent with maximum wall thickness e.g. in apical forms hypertrophy. Therefore, these measures were assigned as not available.

7 "EPS: electro-physiological study" was completed by brackets with "programmed ventricular stimulation"

8 Unfortunately no post-mortem material was available for any of the deceased family members. The statement regarding patient IV-3 from family 12 refers to ante-mortem findings by the responsible pediatric cardiologist.

9 Please refer to our response to point 3 of reviewer Waldmueller.

10 Has been addressed in the appropriate Methods section.

Minor Essential Revisions
1 Pedigree position removed
2 Addressed
3 Corrected
4 First line was deleted.
5 "evidence-based" was replaced by "guideline-conform"
6 "died due to" was replaced by "became a victim of"

We are now positively looking forward to your response.

Sincerely,
Philipp Ehlermann, MD