Author's response to reviews

Title: BRAF mutations in thyroid tumors from an ethnically diverse group

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Author's response to reviews: see over
Dear Editors-in-Chief,

MS: 2082191337776657

We are pleased for the invitation to revise and resubmit our manuscript entitled

**BRAF mutations in thyroid tumors from an ethnically diverse group**

We have included a point-by-point response to the comments of the reviewers and hope that our revision has suitably addressed the comments.

Thank you very much for your efforts.

Yours sincerely,

H.-J. Schulten, Ph.D.

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**Letter to the Comments of the Reviewers**

**Reviewer 1**
Comment 1: explain if they used sample microdissection or if pathologist chose samples with majority of cancer/tumor cells (certain percentage?)
Reply: A pathologist (JM) has reviewed each case and only sections with not less than 70% of abnormal or tumor cells, respectively were chosen. This statement has been included in the Methods chapter.

Comment 2: discuss allele enrichment methods that would probably help to detect more mutations in this region
Reply: The purpose of the study was to utilize Sanger sequencing as the method of choice to detect mutations with sensitivity and accuracy that confirms with similar BRAF
mutational studies on thyroid cancer performed in other populations and enables us to compare the results on the same detection level. However, we regard the comment of the reviewer as a suggestion to employ allele enrichment in further studies with vague mutational results.

Comment 3: explain what thyroid disorders/lesions were included for consideration of positive or negative family history and why they were chosen
Reply: We included all histological types of thyroid carcinomas (TC), i.e. PTC, FVPTC, micro PTC, FTC, and non-WDTC for consideration of positive or negative family history. All TC may have capsular invasion or may have other signs of progression; however, only capsular invasion was significantly related with positive family history in our series. We have listed the histological types of TC in the respective sentence of the Results chapter and replaced the term “thyroid disease” with “TC” in the respective sentences of the Discussion and Conclusion chapter.

Comment 4: balance the conclusion: “Other remarkable findings include correlation of capsular invasion with family history of thyroid disease.” Although statistically significant, this association seems to be weak as data on family history was only available from ca. 26% of cancer patients and multiple not fully defined thyroid disorders were included.
Reply: only thyroid carcinomas (TC) were included in statistical evaluation and we rephrased the conclusion remark: Other notable findings include correlation of capsular invasion with family history of TC whereas BRAF mutational status disclosed only limited associations with clinicopathological factors in our series.

Comment 5: reconsider if the Figure 1 is necessary for this manuscript. If you think that it is necessary please include an arrow in Figure 1 for “minimally invasive focus” as probably most of the readers are not pathologists.
Reply: We agree with the reviewer that the majority of readers may not be pathologists; however, histopathological review of all cases was a substantial part of the study and figure 1 represents a demonstration of histopathological criteria used to distinguish
different types of thyroid tumors with new/rare BRAF mutations. We included the recommended arrows.

Reviewer 2
Comment 1: I have one suggestion that authors should specify the exact number of tumors for which they had fresh frozen tissues.
Reply: We have included the number of native and FF samples in the Methods chapter.

Comment 2: Authors should mention, if microdissection was carried out to separate tumor cells.
Reply: We have addressed this comment in reply to the first comment of reviewer 1.