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CORRESPONDENCE

RE: HABP2 G534E Mutation in Familial Nonmedullary Thyroid Cancer

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In a recent brief communication in the Journal, Zhang et al. reported the *HABP2* G534E variant as causal in nonmedullary thyroid cancer (NMTC)(1), a finding that seemed consistent with the original report involving *HABP2* in NMTC (2). These conclusions were based on the presence of *HABP2* G534E in six cases from four different families out of total 29 families included in the study. However, owing to unavailable samples, in the three out of the four families *HABP2* G534E was detected only in one case per family. *HABP2* G534E is known to occur at a high frequency of 2% to 6% in the general Caucasian/white population and hence should not be referred as a "mutation" as Zhang et al. suggested (3–7). Given the high population frequency of this variant, there is a high probability (>10%) that *HABP2* G534E will be present in four out of 29 families by chance. Additionally, in the kindred, where *HABP2* G534E was detected in three cases (two sisters and one nephew), the probability of sharing the variant between affected individuals is also very high (12.5%) independent of the disease phenotype. Therefore, we believe that the results from Zhang et al. do not support the causality of *HABP2* G534E in NMTC primarily because the variant and cosegregation data presented in the study are either absent or very weak.

The limitations of the Zhang et al. study are especially concerning on the background of various recent studies that casted serious doubt on the causal role of *HABP2* G534E in NMTC (3–7). We recently published a large case-control study consisting of more that 2000 NMTC patients and more than 5000 control subjects of European ancestry where we failed to detect the association between *HABP2* G534E and NMTC risk, even after stratifying the cases by age of onset and histological NMTC subtypes (3). A second recent independent study also reported a similarly negative association (and family cosegregation) between *HABP2* G534E and papillary thyroid cancer (4). We also have unpublished data on Hispanics where we fail to detect any causal effects of this variant on NMTC risk. Hence, studies in multiple ethnic populations, using case-control as well as families, do not support a low- or high-penetrant effect of *HABP2* G534E on NMTC risk. In light of these contradictory findings and the inadequate data provided by Zhang et al., it is necessary to exercise extreme caution in assigning NMTC causality to *HABP2* G534E as it could have serious consequences in clinical decision-making.

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