Response to "Single nucleotide polymorphisms and development of hereditary medullary thyroid cancer in V804M RET families: Disease modification or linkage disequilibrium?"

To the Editors:

We appreciate your thoughtful comments regarding our paper.[1] With our response, we hope to address the issues that were presented.

Our research purpose in analyzing these 2 "independent" families was in no way to perform a genome-wide association study (GWAS). GWAS requires hundreds to thousands of individuals from independent families (affected/unaffected) to be tested to determine genotype/phenotype associations. As stated in our conclusion, we consider the single nucleotide polymorphisms (SNPs) we identified to be candidates for further GWAS study and invite collaboration with other researchers to determine the significance of these SNPs. Other published studies have presented similar data.[2-10] We believe that our data, although limited, may encourage additional researchers to study the impact of SNPs, and to collaborate with other researchers to establish the clinical relevance of these SNPs.

To determine linkage disequilibrium, additional family members would need to be genotyped to establish phase and to determine whether the SNPs we identified are "linked" to the RET V804M mutation. Previous studies have shown linkage between RET G691S and S904S mutations.[11] Because we had limited data in this study, we did not complete a linkage analysis, and instead referred to previous studies that have shown linkage. We do appreciate the reviewer's suggestions and preliminary analysis of our families.

We, too, find the G691S SNP to be very interesting both in our data and those of previously published studies.[4,6,12,13] As stated, the G691S polymorphism is a missense mutation and does have genetic modifying potential.[11] We agree that additional functional studies need to be completed.

Figures 1 and 2 and Table I[1] were provided to demonstrate genotype, including heterozygous versus homozygous SNP carriers, as well as phenotype, including who was affected with thyroid cancer, hyperparathyroidism, and C-cell hyperplasia.

It is stated in our Methods section that sequencing was completed on exons 10, 11, 13, 14, 15, and 16 of the RET proto-oncogene. Although we have listed many of those persons in Table I, we do agree that we should have a way to indicate on our pedigree those who we also have genotyped for SNP data that we may not have pathology and those who were omitted from Table I, because we would not be able to show a SNP to pathology correlation. In Table I, if no SNPs were detected in exons 11, 13, 14, and 15, this is indicated by an "empty cell," as mentioned in the key below Table I.

We agree that SNP results on patients who did not have the V804M mutation is needed to complete a proper GWAS analysis. Unfortunately, we have not been able to secure full cooperation from these 2 families to secure such data.

Although we appreciate the comments from Drs. Machens and Dralle that our data are "scant" in supporting that G691S and S904S may have a disease-modifying role in the development of medullary thyroid carcinoma, we believe our data and the other published studies of G691S suggest that it may have a disease-modifying role. Our impression is that they may misinterpret the negative results of G691S and S904S as not reporting negative results. Based on our data of no medullary thyroid carcinoma results in the SNP-negative family members, the "infinite" odds ratio was reported based on the mathematical definition. We agree that additional, large GWAS studies are needed to further clarify our findings and the findings of other researchers. As suggested by Dr. Tobias Carling of New Haven, Connecticut, in our Discussion section, we plan to utilize the International HapMap Consortium Web site to determine the actual frequency of these SNPs in the general population so that we can establish a "control" population.

We welcome any additional comments or suggestions that Drs. Machens and Dralle may have.

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