Response to Letter to the Editor: “p.Val804Met, the Most Frequent Pathogenic Mutation in RET, Confers a Very Low Lifetime Risk of Medullary Thyroid Cancer”

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W e thank Drs Machens and Dralle for their interest in our work on the penetrance of RET p.Val804Met and for highlighting the very recently published German series and French series of RET mutation carriers (1, 2). Of note, both publications report sizeable historic case series from large testing centers that each comprise a combination of index cases and family members. p.Val804Met comprises 9.4% and 17.2%, respectively, of RET mutations detected, with penetrance estimated to be 51% in the German series.

In our article we had examined a “quasi-population series” unselected for presence of cancer in which RET p.Val804Met is observed at allele frequency 1.97 × 10⁻⁴ (11 mutations in 27,899 individuals) (3). Using this observation, applying a lifetime risk of medullary thyroid cancer (MTC) of 1 in 3000, an attribution of RET to MTC (genetic heterogeneity) of 20% and estimation that p.Val804Met constitutes 25% of pathogenic mutations in RET (allelic heterogeneity), the frequency with which RET p.Val804Met is observed is consistent with a lifetime risk (penetrance) for MTC of 4% (95% CI: 0.9% to 8%).

This observed disparity in estimates of penetrance between series ascertained on the basis of phenotype vs population data serves to highlight one of the key issues currently challenging clinical cancer genetics. Unexpectedly high frequencies of pathogenic mutations in TP53 and DICER have also been reported from population data, likewise suggesting penetrance for these genes in this context may be lower (4, 5).

Inclusion of index cases will invariably result in upwards bias of penetrance estimates. Even when evaluating penetrance prospectively in unaffected relatives, ascertained through cascade testing of index cases (themselves ascertained on the basis of phenotype 1/2 familial disease), it is difficult to quantify the degree of upward inflation in estimation of penetrance caused by overrepresentation of genetic modifying factors compared with the population average. Analysis of mutation frequency in population series enables estimation of the average penetrance in the population unbiased by ascertainment.

However, as we highlight in our sensitivity modeling, this approach is predicated on parameter estimation. The predicted penetrance will vary if the estimates for the parameters are modified. For example, if p.Val804Met is estimated to constitute 45% rather than 25% of pathogenic mutations in RET, the estimated lifetime risk would rise to 8%. We had presented an estimate of lifetime risk of 46% (95% CI: 1% to 82%) generated by applying a combination of upper estimates for all parameters [lifetime risk of MTC (1/1000), allelic heterogeneity (45%), and genetic heterogeneity (40%)], serving to exemplify the upper bound on sensitivity testing.

Overall, our data strongly support an average penetrance of RET that is much lower than figures of penetrance derived from analysis of series ascertained based on phenotype. This penetrance figure would be applicable in instances when a RET mutation is ascertained as a ‘secondary finding’ in genetic testing undertaken for
other reasons or through testing via a broad cancer panel in an unrelated tumor. We therefore highlight caution regarding truly “prophylactic” (i.e., preemptive) thyroidectomy in these circumstances and instead suggest monitoring of calcitonin with thyroidectomy to be undertaken in response to biochemical aberration.

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References