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"

Clare Turnbull,[1,2,3,4] Chey Loveday,[1] Louise Izatt,[4] and Sian Ellard[5]

[1]Division of Genetics and Epidemiology, The Institute of Cancer Research, London SW7 3RP, United Kingdom; [2]William Harvey Research Institute, Queen Mary University, London EC1M 6BQ, United Kingdom; [3]National Cancer Registration and Analysis Service, Public Health England, London SE1 6LH, United Kingdom; [4]Department of Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London SE1 9RT, United Kingdom; and [5]Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter EX1 2LU, United Kingdom

We 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 $^{+/-}$ 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

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 6 June 2018. Accepted 12 July 2018.
First Published Online 18 July 2018

Abbreviation: MTC, medullary thyroid cancer.

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.

Acknowledgments

Correspondence and Reprint Requests: Clare Turnbull, MD, PhD, Division of Genetics and Epidemiology, The Institute of Cancer Research, 15 Cotswold Road, Sutton, London SM2 5NG, United Kingdom. E-mail: clare.turnbull@icr.ac.uk.

Disclosure Summary: All authors have nothing to declare.

References

1. Lebeault M, Pinson S, Guillaud-Bataille M, Gimenez-Roqueplo AP, Carrie A, Barbu V, Pigny P, Bezieau S, Rey JM, Delvincourt C, Giraud S, Veyrat-Durebex C, Saulnier P, Bouzamondo N, Chabbert M, Blin J, Mohamed A, Romanet P, Borson-Chazot F, Rohmer V, Barlier A, Mirebeau-Prunier D. Nationwide French study of RET variants detected from 2003 to 2013 suggests a possible influence of polymorphisms as modifiers. *Thyroid*. 2017;**27**(12):1511–1522.
2. Machens A, Lorenz K, Weber F, Dralle H. Genotype-specific progression of hereditary medullary thyroid cancer. *Hum Mutat*. 2018; **39**(6):860–869.
3. Loveday C, Josephs K, Chubb D, Gunning A, Izatt L, Tischkovitz M, Ellard S, Turnbull C. p.Val804Met, the most frequent pathogenic mutation in *RET*, confers a very low lifetime risk of medullary thyroid cancer [published online ahead of print 23 March 2018]. *J Clin Endocrinol Metab*. doi: 10.1210/jc.2017-02529.
4. de Andrade KC, Mirabello L, Stewart DR, Karlins E, Koster R, Wang M, Gapstur SM, Gaudet MM, Freedman ND, Landi MT, Lemonnier N, Hainaut P, Savage SA, Achatz MI. Higher-than-expected population prevalence of potentially pathogenic germline TP53 variants in individuals unselected for cancer history. *Hum Mutat*. 2017;**38**(12):1723–1730.
5. Kim J, Field A, Schultz KAP, Hill DA, Stewart DR. The prevalence of DICER1 pathogenic variation in population databases. *Int J Cancer*. 2017;**141**(10):2030–2036.