Author's response to reviews

Title: Mutation analysis of SDHB and SDHC: Novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma-pheochromocytoma.

Authors:

Jean-Pierre Bayley (J.P.L.Bayley@lumc.nl)
Ivonne van Minderhout (I.J.H.M.van_Minderhout@lumc.nl)
Marjan M Weiss (m.m.weiss@lumc.nl)
Jeroen C Jansen (J.C.Jansen@lumc.nl)
Peter H.N. Oomen (p.h.n.oomen@int.azg.nl)
Fred H. Menko (FH.Menko@vumc.nl)
Barbara Pasini (barbara.pasini@unito.it)
Barbara Ferrando (barbara.ferrando@unito.it)
Nora Wong (nwong@onc.jgh.mcgill.ca)
Lesley C. Alpert (lesley.alpert@mcgill.ca)
Rosie Williams (Rosy.Williams@smnhst.swest.nhs.uk)
Edward Blair (Ed.Blair@orh.nhs.uk)
Peter Devilee (P.Devilee@lumc.nl)
Peter E.M. Taschner (P.Taschner@lumc.nl)

Version: 4 Date: 5 October 2005

Author's response to reviews: see over
Mutation analysis of SDHB and SDHC: Novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma-pheochromocytoma.
Bayley et al

Reply to Reviewers

Reviewer: Anne-Paule Gimenez-Roqueplo

The points made by the reviewer are well taken:

1) We have now adjusted the text of the results section:

"The variant was not found in a Dutch control population of 328 chromosomes (although it should be noted that such a group is not an appropriate ethnic control to exclude the possibility of a non-functional Turkish polymorphism). The functionality of all missense mutations should be interpreted cautiously, and particularly in a case such as this as this is only the second report of a missense mutation of SDHC and the patient presented without a family history."

2) The level of urinary catecholamines in the patients described were ascertained by entirely standard methods.

3) The legend of table 1 has now been extended to include an explanation of the allele frequency.

Reviewer: Hartmut P.H. Neumann

1) The reviewer finds that some passages of the manuscript are "difficult to read, since there are both sporadic HNP cases and familial PGL cases analysed and the results of sporadic HNP cases are summarized with previously reported sporadic HNP cases of the same group of researchers". We have tried to clearly separate the description and discussion of these two groups, and we are not aware of any passage in the text where they are extensively discussed together. The reviewer also notes "We do not learn, if the sporadic HNP cases are related". We discuss sporadic cases, which to us means individuals with no known family history. In order to clarify these points and address the comments of the reviewer we have now included the following text in paragraph 1 of the discussion:

In light of the known role of founder mutations in Dutch PGL cases [1], it seems likely that the majority of apparently 'sporadic' cases are related to other patients carrying the same mutation, rather than being true sporadic cases carrying de novo somatic or germline mutations. This seems particularly likely in the case of the very common SDHD mutation Asp92Tyr (D92Y) which accounts for 19 of the 24 sporadic SDHD cases, but may also explain the prevalence of the c.423+1G>A SDHB mutation.

The point about 'sporadic' raised by the reviewer is important as it is clear that its meaning is open to interpretation. To clearly establish what we understand 'sporadic'
to mean in this type of study, we have now added a definition in both the abstract and in the introduction.

It is not clear to us why the reviewer would expect a table describing a summary of all familial PGL cases including those with SDHD mutations, when this article is a description of a mutation analysis of SDHB and SDHC.

We discuss the results from our previous study in so far as it if relevant to the results and patients with sporadic PGL included in this study. This illustrates, we believe, the point that the vast majority of PGL cases in the Netherlands are not related to SDHB or SDHC, but to SDHD. We agree with the reviewer that such an overview may be of interest, given the unique position of the Netherlands regarding the extensive prevalence of founder mutations of SDHD in PGL cases here, but feel that the current article is not the place to conduct a review of SDHD-related PGL.

2) "CSGE should be explained in the abstract and familial pheochromocytoma – paraganglioma may read and / or instead of –."

This has now been complied with.

3) "Background: Paragraph two „…and both Astuti et al. (8) and others“. Who are „others“? In the next sentence ending with „play a major role in hereditary pheochromocytoma“, a reference is needed."

This has now been complied with.

4) "In the paragraph „Mutation analyses and sequencing“: „All suspect peaks“ (of SSCP): In SSCP you find aberrant bands not peaks”.

This referred to the CGSE technique but may have been poorly phrased, and has now been changed.

5) "Next sentence: „…the remaining two being submitted for direct sequencing of SDHB based on a suspicious clinical history.“ Here is unclear if SSCP or CSGE, the used screening methods for mutations, revealed normal results. This would be important, since one can obtain information regarding the sensitivity of the used screening methods".

This has now been clarified.

6) Results section: The case with the polymorphism adds only confusion and can be deleted.

This has now been complied with.

7) Discussion: The 10% rule is in general attributed to Manger and Gifford who published a review in J Clin Hypertension (2002) showing this „rule“ again, a better reference compared to (29). The „at least“ 25%“ are the message of a paper of Neumann et al. NEJM 2002 and should be given as a reference.

The appropriate Gifford reference and Neumann references have now been added.

The reviewer also states, "The discussion on prevalence of pheochromocytoma is misleading, I think. I am convinced that most pheochromocytoma are currently detected clinically using available imaging and endocrine means". This is the personal opinion of the reviewer, and does not address the fact of the prevalence of pheochromocytoma at autopsy [2,3]. While we do not feel that this
discussion would mislead readers, we have now adjusted the text to adopt a more cautious tone, in the light of a limited number of (published) autopsy studies, and the resulting speculation of eventual phenotypic conversion [4] should future screening methods make an effective identification of all pheochromocytoma cases possible.

Reference List


