Reviewer's report

Title: The SDH Mutation Database. An online resource for succinate dehydrogenase sequence variants involved in pheochromocytoma and paraganglioma.

Version: 3 Date: 7 July 2005

Reviewer: Anne-Paule Gimenez-Roqueplo

Reviewer's report:

General

As far as I know, there have been no SDH mutation databases built up to now. The authors should be congratulate for this useful iniative for all the members of the medical community involved in the management of patients with paraganglioma (pgl) and pheochromocytoma (pheo) syndromes. The main efforts have been made on the design on the SDH database and the collection of the mutations published since 2000 with the first publication showing the identification of SDHD as the paraganglioma hereditary gene (Bora Baysal et al., Science). The authors have collected 50 mutations on SDHD and 60 mutations on SDHB.

I have some major and minor recommendations.

1) Major: I recommend to delete the SDHA gene mutations from the database and the text which are targeted to physicians involved in the management of patients with pheo and pgl for two main reasons.

1. Up to now there have been no reports of pgl/pheo in heterozygous subjects, like fathers or mothers of children affected by Leigh syndrome, with a SDHA mutation. There are no indications to screen this gene in pgl/pheo indications. The few SDHA cases published so far have only a neurologic disease.

2. Moreover the analysis of SDHA gene is difficult because 1) there is a pseudogene, 2) there are two different SDHA isoforms and 3) SDHA is a highly polymorphic gene. The best way to analyze is to screen the cDNA obtained from leukocytes, fibroblastes or muscular mRNA. If some laboratories worldwide decide to directly sequence the SDHA gene from constitutive DNA there are likely to be some diagnosis errors due to a misinterpretation of several missense variants.

2) Minor:

Manuscript: The authors have compiled all previously SDHs mutations published so far. They observed some differences in the type, the number of SDH mutations as well as in the concerned exon. But the identification of SDH mutations is recent and up to now some groups have not reported all their data. They are probably less than 6000 SDH subjects in the world. It is too early to draw definitive conclusions particularly for the low rate of SDHC mutations which could be underestimated by the presence of intragenic deletions (see Baysal, J Med Genet, 2004) which are not searched by most of the laboratories and for the absence of mutations in exons 5 or 8 on SDHB.

I recommend the authors modify their discussion to moderate their conclusions. More definitive conclusions concerning SDH genotype-phenotype correlations could be done in one or two years when different world teams have all entered their genetic data in the database.

Database structure: This database will be very important for the interpretation of new missense variants which are highly frequent on SDHB gene.

I recommend the authors:

1) separate polymorphisms (which appeared in the disease column ?)-like p.Ser68Ser in SDHD-, from mutations -like p.Arg22X in SDHD- and unclassified variants –like c.-12G>A on SDHC- into
one special column in the database. I think it will be more convenient to separate into 3 different pages each type of variants classified as mutations, polymorphisms and unclassified variants for the 3 genes.

2) give the ethnic origin of the tested patients and controls which could explain some differences in some allelic frequencies, for example p.Ser8Ser for SDHB.

3) include somatic data such as 1) the measurement of SDH activity which is the best tool to determine the functionality of a SDH mutation, and 2) the loss of the wild type allele in the tumor.

4) clearly define all the abbreviations (PC, PGL, ..) and asterisks used

5) delete the DNA:Allele 2 column which is useless for an autosomic dominant disease such as pheo/pgl syndrome

6) include all references in the database and in the text of the manuscript. For example there are no reference for p.Trp47X on SDHB and several papers are not referenced in the text.

On the whole the future role of the curator consisting in including non-previously SDH mutations on the SDH database will be very important for the quality of the database and also for the patients and their families. The inclusion of non-functional SDH variants in the database as causative mutations would lead to useless clinical screening and family testing for the patients. The authors are SDHD experts. I suggest they convince several (SDHB, SDHC, SDHD) experts into joining them in a scientific committee to validate the new submitted mutations according to strict criteria before being included in the database.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No