Reviewer's report

Title: An unexpected, mild phenotype of glucocorticoid resistance associated with glucocorticoid receptor gene mutation Case report and review of the literature

Version: 1 Date: 28 May 2017

Reviewer: Laura C Matthews

Reviewer's report:

Molnar and colleagues present a case report describing a rare mutation in the glucocorticoid receptor, a nuclear receptor which mediates a broad range of actions important to development, metabolism and immunity. The introduction is thorough, and well referenced, and the results are well described. However I have a few specific concerns, that need to be addressed before this manuscript is suitable for publication.

1) The figure presented is not of sufficient quality and is not informative to the reader in its current form. I include links to similar published studies for reference.

https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-017-0413-8
https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-017-0404-9
https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-017-0412-9
https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-017-0407-6

My suggestions:

(a) the existing figure needs additional detail, with labels,

(b) a schematic of the the exon structure of the GR gene,

(c) a schematic of the protein structure of GR, with functional domains labelled, and the site of the mutation indicated.

This information is detailed in the introduction and the presence of a diagram would better support the text.
2) It seems from the text that the sister of the index consented to biochemical tests and genetic screening. Can this data also be included?

3) Some of the studies described in table 2 are not included in the reference list. Table 2 needs to be referenced properly.

4) The discussion lacks sufficient reference to, and description of other GR mutations reported in the literature. Several, additional references should be included, and discussed (although, I think some of these refer to studies described in table 2). If not already included, these should be summarised in Table 2.

Kino et al 2001 Pathologic human GR mutant has a transdominant negative effect on the wild-type GR by inhibiting its translocation into the nucleus: importance of the ligand-binding domain for intracellular GR trafficking. J Clin Endocrinol Metab 86:5600-5608

Trebbe et al 2010 Familial Glucocorticoid Resistance Caused by a Novel Frameshift Glucocorticoid Receptor Mutation J Clin Endocrinol Metab 95: E490-E499

Charmandari et al 2008 A novel point mutation in the amino terminal domain of the human glucocorticoid receptor (hGR) gene enhancing hGR-mediated gene expression. J Clin Endocrinol Metab 93:4963-4968

Charmandari et al 2006 Functional characterization of the natural human glucocorticoid receptor (hGR) mutants hGR R477H and hGR G679S associated with generalized glucocorticoid resistance. J Clin Endocrinol Metab 91:1535-1543


Charmandari et al 2005 A novel point mutation in the ligand-binding domain (LBD) of the human glucocorticoid receptor (hGR) causing generalized glucocorticoid resistance: the importance of the C terminus of hGR LBD in conferring transactivational activity. J Clin Endocrinol Metab 90:3696-3705
McMahon et al 2010 Neonatal complete generalized glucocorticoid resistance and growth hormone deficiency caused by a novel homozygous mutation in helix 12 of the ligand binding domain of the glucocorticoid receptor gene (NR3C1). J Clin Endocrinol Metab 95:297-302


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

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