Reviewer’s report

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

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Reviewer: Miles Pufall

Reviewer's report:

The manuscript "An unexpected, mild phenotype associated with glucocorticoid receptor gene mutation, Case report and review of the literature" describes the presentation of a patient with infertility. In the workup for the patient, it was concluded that she had partial resistance to glucocorticoids. As a result, the authors sequenced the glucocorticoid receptor and identified a mutation within the ligand binding domain, and specifically AF2: R714Q. This paper provides a valuable example of how GR mutations have the potential to manifest as different pathologies.

Although nicely reported, I have a few issues with the paper as written:

1) The authors claim that the R714Q mutation is in AF2. Most structures of the GR-LBD (Eric Xu and others) classify the cofactor binding pocket composed in which the LXXLL motif sits as AF2. The position of R714 is quite far from this pocket and might be better described as being within the LBD.

2) On Page 4, the authors refer to the LBD as containing both AF1 and AF2. Although AF2 is almost always associated with the LBD, most (if not all) publications identify AF1 as being a region surrounding residue 200 within the N-terminal domain of GR. There may be other surfaces that bind GRIP1 on the LBD, but they are not commonly referred to as AF1.

3) It is not clear how this mutation might decrease hormone binding. If this is known from other work, it should be discussed.

4) I was confused by how the pathology was classified as Chrousos syndrome. How is Chrousos syndrome defined? What is the hormonal and dex suppression profile of Cushings? Exactly how does this patient differ from the Cushings profile?
5) In the abstract, it says that administration of dex caused suppression of cortisol at midnight, however on page 8 it is not clear whether cortisol levels were normal at night with or without dex. Please clarify.

In short, although this paper provides a useful correlation between a GR mutation and glucocorticoid-related syndrome, how this syndrome differs from Cushings or other glucocorticoid insensitivity pathologies is not clear. Without clear definitions of Chrousos syndrome, Cushings syndrome, and how the patients profile matches one over the other, this work will not allow the community to confidently associate this mutation with a specific kind of glucocorticoid insensitivity.

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

No

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

No

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

No

**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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