Reviewer’s report

Title: The novel p.Cys65Tyr mutation in NR5A1 gene in three siblings with 46,XY disorders of sex development

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Reviewer: John Achermann

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In this report, Fabbri et al describe a novel heterozygous change in the gene encoding steroidogenic factor-1 (NR5A1) in three individuals from a single kindred with 46,XY DSD (severe penoscrotal hypospadias, inguinal gonads) and their mother who has evidence of primary ovarian insufficiency.

The clinical features are not entirely novel but add to the very limited number of cases where there are reportedly “normal” testosterone concentrations in early life or at puberty, and potentially progressive ovarian dysfunction in females. The “traditional” diagnosis in such situations could be androgen insensitivity (X-linked) or 5 alpha reductase deficiency (autosomal recessive) so considering this relatively common and emerging condition of sex-limited dominant NR5A1 dysfunction is important for counseling families appropriately.

The amino acid change reported here is predicted to disrupt a key zinc finger involved in nuclear receptor DNA binding interactions. Although functional work is not undertaken the modeling and protein predictions – as far as can be said – is fairly convincing.

Major compulsory revisions

1) The use of language needs very careful attention, especially to the use of articles (“the”) and plurals. Examples from the first few lines include: Case presentation: “presenting”; background “encoded by NR5A1 gene” “NR5A1 gene sequence includes” “The SF1 protein contains 461 amino acid”

2) The abstract, case histories and discussion all refer to a potential developing adrenal insufficiency (“Considering the slightly elevated ACTH levels in all three patients with 46,XY DSD it may be inferred that p.Cys65Tyr mutation might probably present a late-onset effect upon adrenal function, justifying a long term follow-up on such patients”). This of course is an important point that is relevant to SF-1, and has been put forward many times, but this would be the first cases to my knowledge where this has actually occurred. I think the statement is too strong based on basal hormone levels (perhaps in stressed individuals) and several ACTH measurements over time in non stressed conditions, low dose (physiological) ACTH stimulation tests, and cortisol day curves would all be needed to address any subtle adrenal dysfunction in more detail. If these data are not available I would tone down the use of “might probably”, which in itself is not grammatically useful. I would stick with “might”, but encourage the authors to
obtain more data, over time if needed.

3) The spontaneous puberty data and serial testosterone data in the proband are very important. Can the authors discuss any assessment of gender identity? This child had a relatively late sex reassignment from female to male. There is a trend clinically to assign to male sex more frequently than previously. Outcome data from cases such as these are very useful and more details of evaluation or description of gender identity or sex role would be very useful.

Minor essential revisions

4) background : 3 beta HSD correct gene name HSD3B2, DAX1 is NR0B1

5) Is the testosterone value described in the second sibling unstimulated? In the third sibling is the pre-hCG testo of 0.66 really “normal” at 2 months of age when there is peak reactivation of HPG axis. Are there data on presence or absence of Mullerian structures in cases 2 and 3?

6) P5 methods – greek alpha symbol doesn’t come out in 5 alpha in my manuscript

Discretionary revisions

7) As noted above, recent cases describing testosterone production in NR5A1 families include misdiagnosis as AR in infancy by Wu JY et al (Clin Endocrinol 2012) and testosterone production in puberty, with a differential diagnosis of 5 alpha reductase deficiency type 2 or 17 beta HSD type 3 (Tantawy S et al, Eur J Endocrinol 2012). This is one of the strengths of the paper and could be discussed in more detail.

8) Primary ovarian insufficiency is a better term than premature ovarian failure, especially as there is a potential progressive insufficiency in this case. The potential benefits of making a diagnosis of NR5A1 disruption should be highlighted for the genetics community as there are important counseling issues. These relate not just to the diagnosis, differential diagnosis and variable mode of inheritance described above, but to being able to identify women at risk of developing primary ovarian insufficiency (mothers, maternal aunts etc) and allowing appropriate monitoring, reproductive counseling and potentially preemptive assisted reproductive techniques.

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

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests