Reviewer's report

Title: Deleterious Genetic Variants in Ciliopathy Genes Increase Risk of Ritodrine-induced Cardiac and Pulmonary Side Effects

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Reviewer: Martin A Kennedy

Reviewer's report:

This manuscript describes an exploratory study to understand genetic factors that may predispose to severe adverse drug reactions (ADRs) with the drug ritodrine, a short-acting β2 adrenoreceptor agonist used to prevent premature labour. The analysis focused on 13 women who suffered serious cardiac and pulmonary side effects. Whole exome analysis was applied and non-synonymous substitution variants were evaluated as possible contributing factors to these ADRs.

This is an interesting cohort, and exome analysis is a reasonable approach to seek strongly penetrant genetic factors that may underlie side effects. That said, discovering variants and proving they are relevant to the ADR will be challenging in a small cohort such as this.

Major issues:

Presumably the patients are of Korean ethnicity? This important detail is not specified. 1000G data is used for calling and filtering variants. How well represented would Korean variants be in this dataset? By discarding detected variants not represented in the 1000G data is there not a risk that important ethnic-specific variants may have been lost? There should be some clarification and discussion around these issues.

For the rare-variant association tests (line 136-149) what are the implications of the use of multiple gene lists (particularly in terms of multiple testing correction), and to what degree are these gene lists correlated? It seems unnecessarily complex to use multiple gene sets for this analysis.
The comment on line 167 about the 28 identified genes "with deleterious variants" should be edited to indicate that these were "variants predicted deleterious by SIFT".
Were these mutations confirmed by a resequencing method?
A collection of rare variants were found to be overrepresented in the cases, in ciliopathy-related genes as well as drug metabolising genes. Given the difficulties in obtaining a replication cohort for this type of study, and the lack of functional knowledge around the mechanisms of action of this drug or its metabolism, these variants can only be regarded as candidates that are associated with the adverse reactions. The authors acknowledge this in line 242, indicating that the findings are speculative, but their conclusions (line 271 onwards) are phrased inappropriately strongly when claiming that they "identified rare deleterious variants affecting ritodrine-induced … side effects". This should be rephrased as "rare predicted deleterious variants associated with…". The final sentence (line 275-276) should focus on the need for replication studies to clarify the validity of these variants.

Minor issues:
Abstract conclusions (Line 23-24) should be softened to read "may be associated with" rather than "are associated with".
What is the prevalence of the side effects observed in this study?
In line 51 this statement is unclear ".the mechanism of ritodrine…"; does this refer to mechanism of therapeutic action, or mechanism underlying side effects?
Were the healthy controls drug exposed (line 67)? Why did the control group include males?
Need a specific comment on lack of replication of CACNA1C involvement in cardiac side effects as described by Baek et al. (2017).
Line 233: the drug targets ADRB2 protein, not the gene.
It would be useful for the authors to indicate their views on the validity of the prior CACNA1C association observed for ritodrine side effects, given that they did not observe CACNA1C variants in this study.

Typo/grammar
Line 2: tocolytics>tocolytic
Line 15: "Most of them" is vague - does this refer to the 28 genes?
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.

I recommend additional statistical review

**Quality of written English**

Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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