Reviewer’s report

Title: COPA syndrome in an Icelandic family caused by a recurrent missense mutation in COPA

Version: 0 Date: 02 Sep 2017

Reviewer: Lawrence Nogee

Reviewer’s report:

This is a well written report of three individuals in one family with lung and joint disease who were found by WGS to have a mutation in COPA that arose de novo in the mother and segregated with disease in the family. The same variant had been previously identified in a family with a similar phenotype in the original description of COPA mutations and the authors conclude that the recurrence of this mutation in an apparently unrelated family with a different ethnic background supports that the region of the gene harboring the mutation may be prone to mutations.

I have several minor suggestions for improvement:

1.) As this is only the second report of this mutation, perhaps calling it the "second occurrence" rather than recurrence (line 148) would be more appropriate. In addition, as a different mutation in the same region of the gene was identified in the original report in two different families, that finding also indicated that this region of the gene may be prone to mutations.

2.) In the introduction (lines 75 -79) it would be worth mentioning that pulmonary hemorrhage may be a presenting feature of the lung disease in subjects with COPA syndrome, even though that was not the case in this family.

3.) There are a number of findings described in the lung biopsies beyond "follicular bronchitis". If there are images available from the biopsies, it would be worth including these in the supplementary material.

4.) While the authors provide information in the text that allows the reader to infer the age of the subjects at the time of pulmonary function tests or imaging studies, it would be more helpful to list the ages of the subjects in the figures and tables rather than the calendar year the studies were obtained.

5.) There seems to be a discrepancy between the text in the supplementary material ("Genetic Analysis" section) and supplemental figure 4. The text indicates that a private variant in COBL also segregated with disease, yet the figure indicates that there was a single private variant (in COPA) identified. While the function of COBL is unknown, this information should be included in the figure. In addition a table of the 16 rare variants shared by all affected family members would be very helpful to include in the supplemental data, including the genes, chromosomal locations and the nature of the variants. While this information would not alter the authors'
conclusion that the identified COPA variant was responsible for disease, it might prove very valuable to other investigators and clinicians in trying to understand the variability in phenotypic expression and which genes might act as modifiers of the phenotype.

**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

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