Reviewer’s report

Title: Compound heterozygous LPIN2 pathogenic variants in a patient with Majeed syndrome with recurrent fever and severe neutropenia: case report

Version: 0 Date: 18 Sep 2019

Reviewer: Christian Babbs

Reviewer's report:

General Comments:

Majeed syndrome is rare and so reports should be encouraged to build a better picture the natural history of this disease. In addition to its value as a case report this work contains two novel contributions: i. identification of a novel mutation and ii. the severity of the neutropenia. Regarding the first point, the novel mutation identified is a 4bp deletion leading to a frameshift and premature termination codon so this clearly pathogenic. The very severe neutropenia is potentially interesting but neutropenia has been reported previously in Majeed Syndrome, as the authors themselves point out. Perhaps the it should be highlighted in the abstract and introduction that neutropenia is a known feature of Majeed Syndrome and is worse in this particular patient.

This work needs extensive editing to correct the English as currently some of the meaning is obscured.

Some of the terminology should be rewritten to improve readability, for example it could be pointed out that erythrocyte sedimentation rate and C-protein reactivity are markers of inflammation.

The description of the of erythroblast abnormalities on page 3 (lines 77 and 78) needs to be rewritten as it is very unclear in its current form: "Red blood cell is proliferous and active, metarubricyte was dominated with small, hollow and distorted mature erythrocyte"

The patient and mutation reported in Roy 2019 (PMID: 31377798 DOI: 10.1093/rheumatology/kez317) should be included in Table 1 and Figure 2 and in the discussion in reference to the phenotypic variability seen in Majeed Syndrome.

Specific Comments:

Phenotypic variability has been previously reported in Majeed Syndrome (eg Rao et al 2016) so the authors should acknowledge that the disease is already known to be highly variable.

The values for neutrophil count should be given per mm3 rather than per L to allow easy comparison with existing literature.
It should be stated whether IL-1 blockade was tried in this case.

MRI scans of the patient's limbs should be included if available.

One page 3 (line 100) it is stated that the splice variant was previously reported in reference 2, when in fact it is in reference 3.

The term "variable severity" is used several times and it is not clear what it refers to as variable severity is a well-known feature of Majeed Syndrome. If it means the disparity between the mild anaemia and severe neutropenia this should be made clear. Clarification that Majeed Syndrome is known to be variable and include neutropenia and this patient has more severe neutropenia is the main conclusion that needs to be modified, in my opinion.

On page 4 line 130-131 the further information regarding the lipin domains should be given.

Is it possible this patient has no functional Lipin2 protein? We would have to know the consequence of the aberrant splicing, perhaps the patient's LPIN2 cDNA should be sequenced to better define this?

Table 1 is very unclear and the references should be more clearly given and the the column headings need to be improved (G should be changed to Gender?).

In Figure 1 normal chromatograms should be shown and the 4 deleted base pairs should be annotated in case of the deletion, in the case of the point mutation the chromatograms should be annotated with the intron/exon boundary.

In Figure 2 the c.2327+1G>C change should be shown below the line (perhaps still in red) to highlight that this is a previously discovered variant. Also previous literature and gene browsers show 20 exons in LPIN2, whereas Figure 2 shows only 19. This should be checked and clarified.

**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.

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

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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