Reviewer’s report

Title: Novel mutations of STXBP2 and LYST associated with adult haemophagocytic lymphohistiocytosis with Epstein-Barr virus infection: a case report

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Reviewer: Jennifer Below

Reviewer's report:

The authors present a case report of hemophagocytic lymphohistiocytosis and attribute the observed hyper-inflammatory disorder to a digenic (or potentially polygenic) model including pathogenic mutations observed in STXBP2 and LYST.

In general, I find the paper to be clearly written and of interest to the readership of BMC Medical Genetics, but substantial details of the genetic analysis are lacking.

1. What exome sequencing approach was used? On DNA isolated from what tissue?

2. What quality control measures were applied to the exome sequence data? What data quality metrics were used to filter variants?

3. Were the parents of the probands also exome sequenced? Or were the specific variants of interest genotyped based on the findings in the proband?

4. It is not clear how the authors came up with the list of genes in which they report observed variants. Did they restrict their search to only a list of candidate genes? If so, those should be clearly defined and justified.

5. Table 1 lists the frequencies for the observed variants as being extremely common- if what they are referring to is a population frequency, which I think can't be right. My guess is that maybe they are referring to the proportion of reads that support the alternate allele? If so, this is not a particularly useful metric without knowing the total number of reads mapping to the locus.
6. I would actually like to see the population based allele frequencies given for each putatively pathogenic variant in the Han population (this can be readily looked up in the ExAC database (http://exac.broadinstitute.org) or dbSNP or similar.

7. "undetermined genetic mutations" - should be something like "variants of unknown significance"?

8. The authors claim that the variants are "novel", but it's not clear what they mean: "Two-generation pedigree analysis showed that the mutations were inherited from her parents" - novel? The variants are all inherited, so they are not de novo. If the mean that the variant has never been seen before, they should report what resource they base that assertion on, eg novel to what database/population?

9. There is no discussion of variant filtering for pathogenicity. How were variants annotated and filtered? Were non-coding pathogenic variants considered? Such as splice site variants or covered promoter regions?

10. The authors propose that heterozygous hits to two genes resulted in the phenotype, but the mom's NK cell function looks worse than the proband's; it would aid readers if the authors gave some additional background on what has been seen before as associated with pathogenic variants in these genes.
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.

Unable to assess

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

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