Reviewer’s report

Title: Two monogenic disorders masquerading as one: Severe congenital neutropenia with monocytosis and non-syndromic sensorineural hearing loss

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Reviewer: Peter Bross

Reviewer's report:

The manuscript describes clinical and genetic investigation of a family pedigree with numerous members displaying neutropenia, monocytosis, and hearing loss phenotypes in varying combinations. Whole exome sequencing of an individual with all three phenotypes and one with neutropenia and hearing loss reveals a novel gene variation in the GFI1 gene, a known neutropenia with monocytosis associated disease gene and a variation in the MYO6 gene that has previously been associated with hearing loss. Six other family members with pertinent clinical phenotypes were then investigated for these two variations. All investigated clinically affected neutropenia patients are heterozygous for the GFI1 gene variation supporting disease association. With the exception of one individual with 'clinically unconfirmed hearing loss', all other investigated individuals with hearing loss are heterozygous for the MYO6 gene variation, supporting also this association between phenotype and presence of gene variation. The study is well-described, however, has some unclarities. The conclusion in the abstract (We present a case illustrating the benefits of a broad screening approach that allows identification of polygenic determinants of complex human phenotypes) appears to overexaggerate the case: exome sequencing in only two individuals will only in a limited number of cases reveal the genetic determinants; WES has also only been interrogated for variations in previously described disease genes for these phenotypes; the set-up may be applicable to di- and oligo-genic conditions, but not in this form for polygenic diseases. In the discussion, the argument for association of the GFI1 variation with 'clinically unconfirmed hearing loss' in patient V5 is too speculative.

Specific points:

Background, lines 39-44. The relevance and context of the information on the benefits of administration of G-CSF is unclear. The connection to the acronym in the last sentence of the conclusions is unclear.

Methods, line 29: what does 'filtering out systematic errors' mean? The prediction servers and frequency in the population checks support/weaken the case for disease association.

Results: The information that two patients were investigated with whole exome sequencing should be mentioned in the results section and the respective individuals marked in Fig. 1.

Results, first paragraph: use 3 letter amino acid notation consequently (instead of N382S).

Discussion, last paragraph: What is the overall sequence conservation when this is a 'very highly conserved region'? And give the reference for the statement that it encodes the globular domain.
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:

Acceptable

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