Author’s response to reviews

Title: A novel deletion mutation in KMT2A identified in a child with ID/DD and blood eosinophilia

Authors:

haixia zhang (zhhxia520@163.com)
Bingwu Xiang (xbwfey@163.com)
Hui Chen (wzchenhui@126.com)
Xiang Chen (chenxiangfey@163.com)
Tao Cai (tcai@nih.gov)

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Author’s response to reviews:

Point-by-point response

Editor’s suggestions:

1. I think that your manuscript, though of potential interest, needs to be deeply revised and restructured in formal and content aspects.

Response: Many thanks to Dr. Lidia Larizza for the opportunity to revise the manuscript.

2. As underlined by both reviewers you should investigate/rule out additional causes of the peculiar hematological phenotype (eosinophilia) of your patient, and report clearly which WDSTS signs he manifests.

Response: Based on the whole-exome analysis, no additional deleterious mutations in known causal genes (Suppl. Table 1) are found to cause the phenotypes in the patient we presented. Also, more discussion is provided in the revised manuscript.
3. Secondly you should use the nomenclature for genetic variants recommended by HGVS guidelines. Table 1, in the present format mixes up germline and somatic KMT2A mutations hence not enhancing the comprehension of the specific described case.

Response: The nomenclature of the mutation is revised according to the HGVS guidelines. Since HGMD has increased the number of mutations in the updated professional version, we have revised the Table 1 and related context, which separates germline (in most cases) mutations from somatic mutations.

4. The manuscript should be edited for English language. You should take into account the multiple shortcomings raised by the reviewers to have the revised manuscript suitable for consideration in BMC Medical Genetics.

Response: The revised manuscript has been reviewed by native English speakers.

Cristina Gervasini (Reviewer 1):

The manuscript by Zhang and colleagues reports on one patient affected by intellectual disability, developmental delay and blood eosinophilia found carrier of KMT2A mutation. The clinical presentation of the proband is sufficiently detailed, as the molecular test.

The discussion is superficial: the genotype–phenotype correlation is presented unclear and difficult to read. Several inaccuracies are present.

There are criticisms which should be addressed in order to improve the manuscript and further support the discussion.

Response: Many thanks for Dr. Gervasini’s time and thoughtful suggestions.
1. A more detailed discussion about the KMT2A mutation in patients with WDSTS phenotype and in patients without a clear WDSTS phenotype should be reported.

In the Background section the authors should describe that different phenotypes associated to KMT2A mutations have also been reported. In addition, the effect of somatic and germline KMT2A mutations should be discussed separately.

Response: In the revised version, we have introduced the clinical differences between WDSTS vs. isolated ID/DD, as well as the present mutation spectrum in Table 1 and context. Also, we briefly discussed somatic and germline mutations in the manuscript.

2. As a general comment, the genotype-phenotype correlation can be better developed. An effort is requested in order to comment the relationship of KMT2A mutations and the corresponding phenotypes, taking into account the peculiar hematological phenotype.

Do the Authors investigate additional possible causes of this clinical sign other than KMT2A mutation?

Response: We did not find any other potential causes for the persistent blood eosinophils observed in the present case. In Discussion, we suggested a further validation of the eosinophilia in additional cases with KMT2A mutations.

3. I think that the 5 categories presented in Table 1 and discussed in the last paragraph of the Case report section ("To analysis the relation between phenotypes of the child and genotypes of the KMT2A gene, we systematically reviewed related literatures and etc etc." ) is very difficult to read.

The Authors should rewrite this part presenting the phenotype associated to KMT2A mutations taking into account the phenotype of their proband. For example, a comment on the presence/absence of the WDSTS clinical signs in the proband should be added. In any case, in Table 1 (if maintained) the references are to be added.

Response: Thanks for the suggestion. We replaced the Table 1 by focusing on genotyping comparison of two major phenotypes: WDSTS vs. isolated ID/DD. We also revised the whole manuscript substantially.
4. A more detailed comment is requested to discuss the genic localization of the described mutation. At our knowledge, this is the KMT2A earlier truncating mutation so far described (Figure 3). Its localization could afflict the mRNA and/or protein stability and then the effect should be further discussed.

Response: Based on the analysis of updated HGMD database, we depicted 22 ID/DD-causing mutations in the revised figure 3. Associated discussion is presented in the context and figure legends.

5. The comment of the last paragraph of the Discussion and conclusion section "When we compared whether genotypes and phenotype were related, by a large amount of literature, etc etc" should be rewrite to give a final but simply message to the readers.

Response: Revised accordingly.

6. Figure 3: the figure represents the KMT2A protein structure, but the mutations are reported in a mixed form: there are mutations as nucleotide changes and other as protein changes: please homogenize the form of the described mutations

Response: All mutations shown in figure 3 are now presented at amino acid level in the HGVS style. We don’t include mutations that are not given predicted amino acid positions by HGMD in the diagram of figure 3, but include all of mutations in the revised Table 1.

7. Figure 3: in the figure are not present all the mutations previously described: for example, the 27 novel additional KMT2A mutations reported in the recent paper by Baer et al. 2018 should be added

Response: Recently, many mutations have been added into the updated HGMD. We have revised the paper accordingly, and cited the paper by Baer, et al.
8. Additional minor revisions:

a) background the sentence "Lysine methyltransferase 2A (KMT2A) plays an important role in the early brain development and hematopoiesis by regulating histone H3 lysine 4 (H3K4) methyltransferase activity." should be rewrote.

Response: The sentence in the abstract has been rewritten to: The KMT2A gene encoded lysine methyltransferase plays an essential role in regulating gene expression during early development and hematopoiesis.

b) Case report: "p:25Rfs" is in an incorrect form, please follow the guidelines for correct nomenclature at HGVS site (http://varnomen.hgvs.org/)

Response: The affected transcript and protein by the given mutation have been renamed in HGVS style using the online Mutalyzer (https://mutalyzer.nl/name-checker):

c.74delG; p.(Gly26Alafs*2)

c) Case presentation: in the sentence "To analysis the relation between phenotypes of the child and genotypes of the KMT2A gene, we systematically reviewed 2 related literatures and several major genetic databases, such as HGMD, Development, and OMIM (Figure 3)." The reference "figure 3" is improper

Response: We revised “To analysis” to “To analyze..”, and deleted “(Figure 3)”.

d) Discussion : The sentence "The KMT2A gene is one of the H3K4 methyltransferases" is improper: the gene is not an enzyme, please change the sentence

Response: The sentence now is revised to “The KMT2A gene encodes one of the H3K4 methyltransferases..”
Yongguo Yu, Ph.D., M.D., (Reviewer 2): Zhang et al. reported the clinical phenotypes of a 3.5-year-old boy, including intellectual disability, developmental delay and blood eosinophilia, and then found that he carried a de novo heterozygous frameshift mutation (c.74delG;p:25Rfs) in the KMT2A gene by trio-based whole exome sequencing. These findings will not only contribute to expanding the phenotypical spectrum in patients with KMT2A mutations, but also shed new insight into the role of KMT2A in eosinophil metabolism. However, some problems need to be revised:

Response: Many thanks for Dr. Yu’s time and good suggestions.

1. Supplying ACMG/AMP assessment results;

Response: A reference of the ACMG assessment is added. The mutation is predicted to be a very strong pathogenic mutation.

2. English language needs to be modified, such as the last paragraph in Case presentation, "To analysis the relation between phenotypes of ......";

Response: Grammar and typos have been checked, and revised accordingly.

3. According to authors' description and the current evidence, persistently elevated eosinophil may result from mysterious variants in blood disease--associated gene. Thus authors should supply candidate variants associated with blood disease in trio--wes as supplementary, and provide reasons for exclusion.

Response: To find mutated genes associated with the “blood eosinophilia” phenotype, we searched PubMed. Mutations in six different genes are found in several disorders, which now are summarized to the Suppl. Table 1. In our whole-exome analysis, no deleterious mutations are found in any these genes.