Reviewer’s report

Title: De Novo Variants in the KMT2A (MLL) Gene Causing Atypical Wiedemann-Steiner Syndrome in Two Unrelated Individuals Identified by Clinical Exome Sequencing

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Reviewer: Wendy D Jones

Reviewer’s report:

CASE REPORT: De Novo Variants in the KMT2A (MLL) Gene Causing Atypical Wiedemann-Steiner Syndrome in Two Unrelated Individuals Identified by Clinical Exome Sequencing

Strom et al

These individuals reported by Strom et al with de novo MLL mutations are an important and useful addition to knowledge about Wiedemann-Steiner syndrome. This is a rare condition with currently only 9 individuals reported in the literature and only 5 individuals reported with MLL mutations. The report highlights previously unreported features of WSS which would make an important contribution to the literature and knowledge of this condition. New types of mutation are also reported in MLL in association with WSS (splice site and missense) which will also make a significant contribution to the literature.

The case presentations, and molecular finding sections are well written. With significant improvement, particularly of the background section, I feel this article would be suitable for publication in your journal.

Major Compulsory Revisions

1. Intellectual disability and developmental delay have not been reported in all individuals with all of these conditions (e.g. Weaver syndrome has been reported in association with normal intelligence in some individuals): Remove this sentence or reword... ‘All of these conditions have been reported in association with developmental delay and or intellectual disability’.

2. Background on Wiedemann-Steiner syndrome should be further elaborated on in the background section. There are 9 cases in the literature. 5 have been recently found to have mutations in MLL.

Patient 2
Pre/ Perinatal History

3. The presence of a sacral tuft suggests sacral hypertrichosis, but it would be important in general for clinicians observing a sacral tuft not to miss spina bifida, suggest authors comment on their interpretation of this finding and whether there
was any evidence of a neural tube defect / investigations were carried out for this. If spina bifida has been ruled out, it might be more appropriate to call this sacral hypertrichosis / localized hypertrichosis so as not to confuse the literature. This hypertrichosis should also be mentioned in the conclusions.

4. The conclusions should highlight the newly reported features which will be very useful for the literature: micro-opthalmia, micrognathia, 3-4 finger syndactyly, premature eruption of adult teeth.

Minor Essential Revisions

Background:

5. Histoneopathy is not to my knowledge a recognized term: Remove this and instead use conditions caused by mutations in genes encoding chromatin-modifying enzymes instead. (this term is also used later in the section).

6. Wiedemann-Steiner syndrome has been spelt incorrectly.

‘Without exception however, these disorders affect brain development and lead to developmental delay and/or intellectual disability’.

7. Intellectual disability and developmental delay have not been reported in all individuals with all of these conditions (e.g. Weaver syndrome has been reported in association with normal intelligence in some individuals): Suggest removing this sentence or rewording… ‘All of these conditions have been reported in association with developmental delay and or intellectual disability’.

As these “histoneopathy” disorders are all exceedingly rare in the population, only a small number of cases have been reported, and therefore the complete phenotypic spectrum of many of them have not been well described. Thus while careful phenotyping remains critical for clinical diagnosis, it will often be insufficient to distinguish between related disorders.

8. Some of the conditions listed above have a relatively large number of reported cases compared to others. Suggest rewording ‘As these disorders are rare with some only having a small number of reported cases the complete phenotypic spectrum of many of them have not been well described.’

Patient 2
Pre/ Perinatal History

‘An ocular prosthetic was placed at X months’

9. Please insert age at which prosthetic was inserted or change, e.g. to an ocular prosthetic was required.

Molecular Testing
10. The control population used (e.g NHLBI data) should be stated in this section.

‘Given that typical human exomes carry between zero and five high confidence de novo coding variants (internal data)’

11. Reference other research studies here (as well as internal data) as data on this is known and available in the literature.

‘Other variants of uncertain clinical significance in GFI1B, PCDH15 and MED13 were identified. Detailed variant information for the above mentioned variants can be found in Supplemental Materials 3b. No other variants were identified in patient 2 which were consistent with an autosomal or X-linked recessive or sporadic mode of inheritance’

12. Sporadic suggests non genetic – change this to X-linked, autosomal recessive or new dominant inheritance. It would also be important to state that the variants identified in GFI1B, PCDH15 and MED13 are heterozygous

Conclusions

‘Generally, the clinical diagnosis of WSS is broad, with no specific clinical features or gene mutation required for diagnosis’.

13. This is not true, the patients reported have a distinctive facial appearance, short stature and intellectual disability. Remove this sentence. A sentence about the variability of the condition could be used instead.

14. The authors talk about the location of the missense mutation identified in patient 1. This is likely to be pathogenic given the fact it is de novo and that the phenotype is supportive. The mutation may affect splicing and it would be useful for the authors to carry out splice site prediction / cryptic splice site analysis (based on bioinformatic tools) if possible.

This report highlights the value of full trio clinical exome sequencing for individuals with atypical syndromic features and developmental delay

15. It is unclear what this sentence means, suggest instead ‘….for individuals with multiple-congenital-abnormalities and developmental delay whose features are not consistent with one particular syndrome’.

16. The authors mention other gene variants they found in the two individuals and these are listed in the tables in the supplementary information. It would be useful to discuss why these were discounted i.e. there were no features to suggest this condition and / or the mutation in MLL was felt to explain all of the phenotype.

Table 1.

17. Please could the authors reference where the 5 patients they are comparing
too have come from (ie reference paper) and make it clear they have MLL mutations. To distinguish between the nine patients in the literature reported under the name Wiedemann-Steiner syndrome (i.e. not all the previously reported individuals have mutations).

Figure 1.

18. Photograph C is quite dark and hard to see facial features, suggest removing this.

19. Figure 2.

20. Please give further information about where the alignment is from and the technology used.

21. Supplementary figure 1.

22. This would be improved with the addition of base numbers.

Discretionary Revisions

23. Suggest change of title name to:

24. Case report: De novo mutations in KMT2A (MLL) in two individuals expand the phenotypic spectrum of Wiedemann-Steiner syndrome.

25. This is because, there are only a small number of cases reported and it is therefore likely that the full phenotypic spectrum is not known. The current title may lead to diagnostic confusion.

Background:

26. ‘Surprisingly, a significant number of these have been linked to genes involved in histone modification and chromatin remodeling’

27. Line 3: Suggest removing surprisingly (this is subjective).

Case presentation

28. Suggest using past tense for clinical examination findings, height was …, weight was …etc.

29. ‘Similar to the loss of epigenetic control seen in Rett Syndrome [MIM: 312750], these disorders are thought to be characterized by global changes in gene expression throughout development leading to unpredictable physical manifestations.’

30. Suggest removing the last 5 words of this sentence or rewording (eg leading to abnormalities in a multiple body systems). And perhaps use ‘result from’ as opposed to ‘characterised by’

Conclusions
31. The little boy has Micro-ophthalmia – the authors could also mention also in the conclusions that there were no variants in other genes associated with micro-ophthalmia.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests