Reviewer's report

Title: A missense founder mutation in VLDLR is associated with Dysequilibrium Syndrome without the quadrupedal locomotion

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Reviewer: Kym Boycott

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Reviewers Comments for BMC Medical Genetics Submission:
A missense founder mutation in VLDLR is associated with Dysequilibrium Syndrome without the quadrupedal locomotion

General Comments: Ali and coauthors present two apparently unrelated families who share a homozygous missense mutation in the VLDLR gene. The missense mutation is well characterized, the clinical presentations are detailed and the review of the literature is very helpful.

Major Compulsory Revisions

1. In the title and conclusion of the main text, the authors state that the mutation is a founder mutation. There is no molecular evidence presented regarding this conclusion – for instance microsatellite or SNP markers were not used to show an area of IBD shared between the two families. The authors must either change the interpretation of the data (as they state in the abstract ‘possible founder effect’) or provide the evidence.

Minor Essential Revisions

Abstract:

1. Page 2, Line 7: Change sentence “The quadrupedal locomotion … in all three genes” to “Quadrupedal locomotion in this syndrome has been reported in association with mutations in all three genes.”

2. Page 2, Line 12: should be ‘homozygous missense mutation' not ‘missense homozygous mutation’.

3. Page 2, Line 18: Remove the last sentence of the results section as it is redundant – also stated in the conclusion.

4. Page 2, Line 20: As there has been no significant expansion of the phenotypic spectrum by the patients reported here, the authors should change the conclusion to instead reflect the expanded mutation spectrum associated with VLDLR, and add the word homozygous ('identified the first homozygous missense mutation'), as there has been at least one missense mutation previously described (Boycott et al., 2009).
Background
5. Page 3, Line 5, Background: references [1-3] should be [1,3,8].
6. Page 3, Line 6, Background: references [8-9] should only be [9].
7. Page 3, Lines 10-12: remove sentence “Patients with those disorders….the first few years of life” as this sentence is simply repeating the information provided in the prior sentence.
8. Page 3, line 14: change ‘localized the gene’ to ‘localized a gene’
9. page 3, line 19: remove the space between p.I779fsX3

Materials and Methods: no comments
DNA Methodologies: no comments

Results:
10. Page 5, Line 16: Family 1: Given that short stature is characteristic, it would be helpful to include the height percentile.
11. Page 5, Line 19: Family 1: The authors should provide more detailed description of the cerebellar hypoplasia (areas involved) and not just refer to it as ‘characteristic’ – to what?
13. Page 6, Line 1: Family 2: The authors should provide more detailed description of the cerebellar hypoplasia (areas involved).

Identification of a pathogenic missense mutation: no comments

Discussion:
14. Page 6, Line 25: The authors should remove number sign before OMIM # 224050.
15. Page 6, Line 26: The authors should change upper case to lower case C for Cerebellar hypoplasia.
17. Page 6, Line 30: The authors should change “In this manuscript, we report” to “In this report, we describe…”
18. Page 7, Line 15: The authors should remove “Some of the features…are variable.” as this sentence does not contribute to the paper.

Conclusions:
19. Page 8, Line 20: The authors should change the sentence to reflect that the spectrum of VLDLR mutations has been expanded, not the phenotypic spectrum. The patients described in this report have a very typical phenotype for VLDLR-associated cerebellar hypoplasia, and the authors state this in the discussion. In addition, as previously noted, founder effect should be removed unless supported by additional analysis or can be changed to ‘possible’ founder effect.
Bibliography:
20. Please change the bibliography style to match that of the BMC Medical Genetics Journal:
Authors: Title. BMC Med Genet [year], [volume number]:[article number].

Table:
21. Page 13, Table 1: Please indicate the number of patients that have been identified in each publication (i.e. affected with each mutation)
22. Page 13, Table 1: ‘Absent inferior vermis’ might be better described as ‘Hypoplastic inferior vermis’
23. Page 13, Table 1: Use of +/- should be used in some of the categories that are variable in presentation – e.g. seizures – not all patients in a particular report will have had this feature.

Figure Legends:
24. Legends for Fig 2 and 3: Instead of ‘affecteds’, please change this term to ‘affected individuals’ or ‘affected persons’.

Pedigree:
25. Page 15, Pedigree 2: As patient III-12 was not examined and not clearly affected, please indicate in some other way than a completely shaded circle.

Discretionary Revisions
26. Page 8, Paragraph 2: The paragraph “Kaya et al…. does not really strengthen or add to the paper and could be removed and the authors consider a paragraph outlining the utility of identity by descent mapping with candidate gene sequencing and/or exome sequencing to rapidly come to a diagnosis in such families. This addition would strengthen the paper to emphasize the utility of these methods for rare diseases.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

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.