Author’s response to reviews

Title: Inclusion of joint laxity, recurrent patellar dislocation, and short distal ulnae as a feature of Van Den Ende-Gupta syndrome: A case report

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Inclusion of joint laxity, recurrent patellar dislocation, and short distal ulnae into the Van Den Ende-Gupta syndrome clinical spectrum: A case report

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BMC Medical Genetics

Dear Editor,

Thank you for considering the manuscript. We have revised (changes were highlighted in yellow as per your instructions) it as follows:

Bhavana Dave, Ph.D (Reviewer 1): The case report is regarding a rare autosomal recessive Van Den Ende-Gupta Syndrome (VDGES) in two siblings born to consanguineous parents and presenting with joint laxity, recurrent patellar dislocation, and short distal ulnae, which have hitherto not been associated with the clinical constellation of the syndrome. The report is well presented with appropriately depicted images justifying the inclusion of the phenotypic features
in the spectrum of VDGES syndrome. The description and figures are adequately described in support of the diagnosis of VDGFS. The rarity of this recessive disease, family history of consanguineous parents, scarcity of published reports, supportive molecular and clinical findings, and clearly described additional non-typical clinical features in both siblings with pictorial depiction makes this case report interesting.

Response: We thank the reviewer for the kind comments. No response is required

Some minor suggested changes:

1. Page 5 - The first paragraph should describe how and at what age the cases were referred to the clinician.

Response: Done. See lines 93-94

2. Page 5 line 91- please include the underlined words in the line. The phenotypes of …..siblings, a male and a female, were…

Response: Done. See line 95

3. Page 8 line 176 space between Hospital & research Center

Response: Done. See line 192

4. Page 8 line 187-188. Please include the underlined words in the lines - Authors' contribution: All authors …. and are in agreement…….manuscript. All authors have read…….manuscript.

Response: Done. See line 204

5. Page 8 line 190- If there are no acknowledgements remove the title and remove the word- None.

Response: Done. Acknowledgements removed
6. Page 11 line 249 hands of "male sibling" instead of "brother"

Response: Done. See line 270

7. Page 11 line 252 Figure legend should read: Figure 2: Radiologic images of classic features of the VAGDS syndrome (instead of demonstration of other....).

Response: Done. See line 273

8. Page 11 line 257 Figure 3: A) legend should read the appearance.....of the "female sibling" instead of "sister"

Response: Done. See line 278

9. The clinical features are getting lost in the table. If possible, Table 1 may be reformatted in three columns; each comment can be abbreviated in title. For e.g. "Constant" features in 90-100% cases; "Common" features in 40-89% cases; "Infrequent" features in less than 40% cases. List features under each column.

Response: Done. See revised Table 1
Sulman Basit, PhD (Reviewer 2): The authors have sequenced SCARF2 gene in 2 patients with VDEG syndrome from a consanguineous family and identified a homozygous missense mutation. This mutation has already been reported by Anastasio and colleagues (2010). Authors proposed to include some extra clinical features to the spectrum of VDEG syndrome.

Some limitations exist

Major Concern:

1. In consanguineous marriages, biallelic or even triallelic mutations in two distinct genes or co-inheriting genetic modifiers may well be considered. I would suggest whole exome sequencing to identify other variants segregating with the phenotype which might explain the additional common phenotype in patients.

2. Both patients share some unusual features and SCARF2 protein does not fully explain the pathogenesis of most of the clinical features of VDEGS as mentioned by authors on page 7, 2nd paragraph. This is another reason to consider the possibility of co-inheriting variants.

Response: We realize that this is a limitation of our study. These valuable comments we added to our discussion in lines 171-177

Minor Comment

I would suggest replacing title with "Inclusion of joint laxity, recurrent patellar dislocation, and short distal ulnae as a feature of Van Den Ende-Gupta syndrome: A case report"

Response: Done. See title change in line 2

Abstract; conclusion, please replace "short distal ulnae should be included in the VEDGS phenotype" with "short distal ulnae should be included as a part of clinical spectrum of VEDGS"

Response: Done. See line 50

Page 5, case presentation, last paragraph, reference 4 is wrongly cited. Please cite Anastasio et al., 2010.

Response: Done. See line 118
Bassam R. Ali (Reviewer 3): This manuscript describes a case report on two siblings with typical features of VDEGS caused by a previously reported mutation in SCARF2. The authors rightly suggest that joint laxity, recurrent patellar dislocation, and short distal ulnae should be included in the diagnosis of VDEGS. However, patellar dislocation and short distal ulnae have been reported previously in other patients with VDEGS leaving joint laxity as the only novel feature. I therefore, feel that this report adds very little knowledge to the literature.

Response: we think our report is of value because:

1. Although recurrent patellar dislocation, and short distal ulnae were reported before, these 2 features were only reported in one and two cases; respectively. Hence these 2 features were not considered as features of the syndrome in all previous reviews. The fact that both siblings in our report had the 2 features confirm that they are part of the spectrum.

2. We report new manifestations of joint laxity which have not been previously reported: Digital joint laxity present in digits adjacent to digits with contracture (camptodactyly), and flat feet

3. We present the results of the most complete literature review, grouping clinical features by frequency of observation

4. We bring the attention of the geneticists to the presence of a canine model (this was never mentioned in all previous human case reports), Most interesting, the model show patellar laxity in the phenotype

We hope considering these points by the reviewer

Jennifer Below (Reviewer 4): The authors detail what is presumed to be a unique presentation of Van Den Ende-Gupta Syndrome in a pair of siblings from a consanguineous Saudi family. Phenotypic features include those typical for the syndrome, as well as joint laxity, patellar dislocations, and short distal ulnae. The siblings have a homozygous mutation (c.773G>A) in SCARF2 which is known to cause this syndrome. The authors also present the results of a literature review, grouping clinical features by frequency of observation.

Major critiques:

1. There is no acknowledgement of other potential genetic or environmental explanations for this unique phenotypic presentation. Could this phenotypic presentation be due to interaction or a distinct recessive phenotype in this consanguineous sibling pair? The authors mentioned
that the cases have two unaffected siblings. The unaffected siblings' genotypes could provide additional evidence of causality. Did the unaffected siblings share any symptoms with the cases?

Response: we have added this point to the discussion (see lines 171-177)

2. It is unclear if Marden-Walker syndrome is mentioned because it was considered in diagnosis of the presented cases. This should be clarified.

Response: this is now clarified (see lines 167-170)

Minor critiques:

1. Due to the rarity of this syndrome, it may be more useful to specify the number of observations of each phenotypic feature, rather than binning them into such wide categories. This will give a better idea of how many other features are observed as rarely as the unique ones reported here.

Response: We have put the percentages in the Table as suggested by the first reviewer. In the discussion we mentioned the number of cases of the rare features regarding joint laxity, patellar subluxation, and short ulnae

Note to the Editor:

One of the reviewers requested deleting Acknowledgements because there were none. If the journal requires putting it in the declarations regardless, I will add it

Thank you again

On behalf of the authors

M Al-Qattan