Reviewer’s report

Title: Identification of two novel COL10A1 heterozygous mutations in two Chinese pedigrees with Schmid-type metaphyseal chondrodysplasia

Version: 0 Date: 03 Aug 2019

Reviewer: Sadaf Naz

Reviewer's report:

The authors report the identification of two new variants in COL10A1 associated with MCDS.

I have the following comments:

Major comments:

1. There are 54 COL10A1 variants reported as of today (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=COL10A1) and current literature. At least two are in the signal peptide, another in the triple helical domain. This should be corrected in the manuscript and supplement. All, except one variant, are reported to be dominantly inherited. The authors need to propose genotype-phenotype correlations after considering genetic and phenotypic descriptions of all reported patients with COL10A1 variants with their comparison with the phenotype in the two families presented here.

2. Please remove "Despite the significant clinical and radiological features found in MCDS patients, there is still no systematic description in terms of the phenotype and heredity characteristics of MCDS nowadays." This is not correct.

3. The authors need to define atavism and what they are specifically labeling as such.

4. The convention in naming individuals in pedigrees is I:1 or I-1 and not I1. This should be corrected in the manuscript.

5. The authors should indicate in materials and methods and pedigree legend or figure, all individuals who participated in the study.

6. The manuscript requires editing for writing the manuscript in scientific style and removing grammatical errors.

7. The conservation of amino acids in figure 3E should include diverse vertebrate species arranged in order (at least one each from mammals, birds, reptiles, amphibians and fish).
Minor Comments:

Title
1. Please change the title of the manuscript. It is too long and grammatically incorrect.

Abstract
1. Please remove "However, the research about unusual phenotype features of MCDS is rare". The authors do not present unusual phenotype features of MCDS in the abstract or point out what they are anywhere else in the manuscript.
2. Remove "Then" from "then the spatial model of type X collagen (α1) C-terminal noncollagen…"
3. Remove "members exhibited evident irregular dominance." Replace with "the phenotype exhibited irregular dominance"
4. Here and elsewhere in the manuscript remove words such as "remarkably", "extremely" when presenting data.

Background
1. Remove "Besides" from "Besides, the distinctive clinical features of MCDS…"
2. Please revise "confirmed pathogenic gene". It is not the gene but variants which are pathogenic.
3. Please revise "…and elaborates the rules of the disease." Please write it scientifically, and only after thorough review of literature with genotype-phenotype correlations.

Methods
1. Please remove "Then" from "Then we sequenced the whole-exome of all available affected individuals.."
2. Please indicate here what frequency criteria were used for identifying common SNP. "…which rejected common single nucleotide polymorphism (SNP) sites".
Results

1. Please rephrase "...and there was a trend that male patients were significantly more severe than females." to "male patients were significantly more severely affected than females." Please also point to data and numbers which supports this.

2. Please remove "Interestingly" from "...interestingly, the two novel mutations were not found in ExAC and gnomAD database,"

3. Please write wild type instead of wild in the following statement "... hydrophobicity of wild residue". Please make this change in other places in the manuscript as well.

Discussion

1. Please rephrase the following so it is grammatically correct: "Moreover, the presentations of II1 in family 1 was normal absolutely including relatively moderate stature without any deformity,..."

2. Please rephrase the following "...which was similar with a mutation-attacking person who exhibited normal phenotype in a previous report". The word "mutation-attacking" is not correct.

3. Please rephrase "...irregular dominance of these MCDS patients." Dominance is of traits, not patients.

4. Please rephrase "...patients that onset age was only around 6 months old, but conversely there was only short stature in those abnormal development occurred in 10 months old or later." This is grammatically incorrect.

5. Please reword "...and 15 patients of 28 males 227(54%) and 5 patients of 16 females (31%) were.." to "...and 15 of 28 male patients 227(54%) and 5 of 16 female patients (31%) were.."

6. Please revise, "Moreover, despite the trend that male patients were more severe than females was presented in family 2, we still could not draw a firm conclusion due to the rather small sample size." This is grammatically incorrect.

7. Please remove "as for" and "it" from the following "As for the molecular structure of type X collagen, it is a homotrimer..."

8. Please remove "Obviously" from "Obviously, all of the identified mutation sites of MCDS associated with COL10A1 including mutations in present study were located in NC1 domain..."
9. Please revise "On the other hand, the content of correctly folded homotrimer of collagen X reduced accordingly, and functional haploinsufficiency became the most probable cause of the clinical phenotype in MCDS."

10. Please remove "definitely" from "….pathogenic molecular mechanism of nonsense mutations in MCDS definitely"

11. Revise "Nevertheless, it was completely different that the process of COL10A1 missense mutations results in MCDS" so that it is grammatically correct.

12. Please change appeared to appears in the following "….appeared to be a disruption of collagen..

13. Please change "In present study, one of the novel substitutions (p.Phe589Ile) locate on hydrophobic area and the other (p.Lys616Glu) on the surface of assembled trimer." To "In the present study, one of the substitutions (p.Phe589Ile) affects a hydrophobic area and the other (p.Lys616Glu) is predicted to affect the surface of assembled trimer."

14. Please change "…which seriously impacts the assembly and stability of hydrophobic channel of collagen X trimerization possibly." To … which may seriously impact the assembly and stability of hydrophobic channel of collagen X trimerization."

15. Please change "And the other substitution (p.Lys616Glu) transfers the alkaline residue site to acidity,.". One, sentence should not start with "and". Two, "transfers" should be replaced by "changes". Three, acidity should be replaced by "acidic residue".

16. Please shorten the following "To our knowledge, the present study is the first report about COL10A1 missense mutations in Chinese pedigrees with MCDS, which lays the foundation for genetic research of MCDS in Chinese and further elaborates phenotype features and heredity characteristics of MCDS. In addition, dominant negative effect may be playing an important role in development of MCDS [16,28], but it has not been fully confirmed and still needs further experimental verification." Language editing is also required here.

17. Please revise "Besides, our research preliminarily elaborated several rules on occurrence and development of the disease based on the two MCDS...". This statement needs to be grammatically correct and should also supported by data presented elsewhere after contrasting with other studies.

18. Please delete "We also summarized the underlying pathogenic mechanisms of COL10A1 mutations."
Table 1:
1. Please change "have extra performance" to "have additional phenotypes"

Legends

Figure 2
1. Please change were to are in the following, "...irregularity of the growth plates of distal femur (white arrows) were shown in X-ray image..."

2. This should be re-worded to be scientifically and grammatically correct "plates and even hip (white arrows) (C). In family 2, the boy, proband, showed a deformity of the lower extremities (D) and similar radiological presentations (white arrows) (E) with proband in family 1. However, proband's mother in family 2 exhibited almost normal appearance in X-ray image..."

Figure 4
1. "The two substitutions p.Phe589Ile and p.Lys616Glu were illustrated in the ribbon protein modeling with two mutually perpendicular perspectives, which showed that two substitutions were located in different subunits". Please rephrase after consulting manuscript descriptions of ribbon diagrams.

2. Please change following "Furthermore, changes in present study and mostly previous mutations (supplementary data) were located in NC1 domain." To "Changes in the present study and most previous variants (supplementary data) are located in NC1 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:

Not suitable for publication unless extensively edited

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