Title: Submicroscopic Subtelomeric Aberrations in Chinese Patients with Unexplained Developmental Delay/ Mental Retardation

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Author's response to reviews: see over
Dear editor,

Thanks for your prompt response to our submission “Submicroscopic Subtelomeric Aberrations in Chinese Patients with Unexplained Developmental Delay/ Mental Retardation” (MS ID 1055168432339396). I strongly realize that the reviewers have read our manuscript thoroughly and seriously, and give us many good suggestions, which are all very helpful. I have carefully revised our manuscript according to all the reviewers’ advices point to point.

The reply to editorial requests and reviewers is at the end of this letter.

Best wishes,
Sincerely yours,
Dr. Ye Wu
Editorial Requests

We request that you make some formatting changes to the manuscript, details of these changes are just below. Your cover letter should include details on how the requested formatting changes have been incorporated into the manuscript.

Ethics

Please document ethical approval. Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm). A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Consent

Informed consent must be documented. Please confirm that parental consent was obtained. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

Reply: This research was approved by Medical ethics committee of Peking University First Hospital. The informed consent was obtained from the parents.

Reviewer 1

The authors report on "Submicroscopic subtelomeric aberrations in Chinese patients with unexplained DD/MR". Although dealing with already well known findings, I think that the paper might be of some interest to the Journal's readership. There are, however, a number of minor essential revisions with which the authors should comply:

1) Concerning the MR, were the patients formally tested? If yes, please state, in the METHODS, the tests used for the assessment.

Reply: Patients were tested with Gesell Developmental Schedules or Wechsler intelligence scale for children.

2) In the RESULTS, pag. 7, there is 1 patient missing. The authors report on 23/24 patients. Only later, reading through the paper (particularly studying the TABLE 2), it
emerges that most probably, they entered 23/24 patients (leaving out patient 1518), due to the lack of confirmation of CNV by the Affymetrix SNP array 6.0. Is this true? Please specify clearly in the text, to avoid any confusion!!!

Reply: Subtelomeric CNV found by MLPA in Patient 1518 was not confirmed with SNP array.

3) From TABLE 2 it emerges that patient 419 does not have microcephaly, but, in the DISCUSSION (pag. 9, line 13) it is said that he had microcephaly!!! Please, amend accordingly.

Reply: Patient 419 does not have microcephaly. I have amended it in the manuscript.

4) From TABLE 2 it emerges that in the deleted interval of patient 419 there are 20 genes, but, in the DISCUSSION (pag. 9, line 17) it is said that "The deleted region contains 21 genes"!!! Please, amend accordingly.

Reply: “20” is corrected. I have amended it in the manuscript.

5) In the DISCUSSION-Subtelomeric duplications-, pag. 13, lines 7-9, the last two sentences should be amended as follows "Our finding supports the observation made by Battaglia et al. [49], who suggested that the critical region underlying the phenotype of dup 3q is in 3q29".

Reply: I have amended it in the manuscript.

6) In the REFERENCES list, references 49 and 50 should become respectively 50 and 51, and the following reference should be added as reference 49: "Battaglia A., Novelli A., Ceccarini C., Carey JC. Familial complex 3q;10q rearrangement unravelled by subtelomeric FISH analysis. Am J Med Genet 2006, 140A: 144-150.

Reply: I have added this important reference in the list. Another reviewer gave me a suggestion to add additional two references (Ref. 31 and 32), so the ref. 49 and 50 become 52 and 53 respectively.

Reviewer 2
The BMC Medical Genetics manuscript “Submicroscopic subtelomeric aberrations in Chinese patients with unexplained developmental delay/mental retardation” by Wu et al. reports the results of MLPA and SNP array (Affymetrix 6.0) analyses of the subtelomeric chromosome regions in 451 children with DD/MR from mainland China.

1) Page 4, line 9

However, microscopic techniques cannot detect microdeletions and duplications in interstitial regions or at the functional endings of the chromosomes (subtelomeric regions)

change to:

However, microscopic techniques cannot detect interstitial or terminal subtelomeric microdeletions and microduplications

Reply: I have amended it in the manuscript.

2) Page 4, line 2 from bottom

These aberrant regions associated with DD/MR are likely to contain undiscovered candidate genes

Rewrite this sentence

Reply: “These aberrant regions are likely to contain undiscovered candidate genes associated with DD/MR”.

3) Page 5, line 8

Subtelomeric aberrations were identified, their exact sizes obtained, and possible candidate genes proposed.

change to:

Subtelomeric aberrations were identified, their exact sizes were defined, and possible candidate genes are proposed.

Reply: I have amended it in the manuscript.

4) Page 5, line 5 from bottom

All 451 subjects were Chinese children from the Departments of Pediatric Neurology

Provide the name of the hospital. In the affiliations, there is no such department.

Reply: I have amended it in the manuscript.
5) Page 6, lines 5-6
in one of the first genes following the centromeric repeats. This should read in one of the genes just proximal to the telomeric repeats.
Reply: I have amended it in the manuscript.

6) Page 6, line 6 from bottom
combination of a SNP array with aCGH in a single chip meant the size of each aberrant region could be accurately defined
change to:
combination of a SNP array with aCGH probes in a single chip enabled the accurate definition of the size of each aberrant region
Reply: I have amended it in the manuscript.

7) Page 7, Results, lines 4-7
15pter del in 5; 4pter del in 4; 13pter del in 3
Delete the locations of short arms of acrocentric chromosomes (13pter and 15 ter). They are confusing.
Reply: This is the original data from MLPA. I explained it in the next paragraph.

8) Page 8, line 5 from bottom
deletions in 8p23.3, terminal 7q, terminal 15q and 14q32.3, as well as 22q13
Be consistent and provide the (sub)band designation for all subtelomeric regions
Reply: I have amended it in the manuscript.

9) Page 9
The Authors should cite the following papers:
and

Reply: I have added the important references.

10) Page 12
This paragraph is supposed to describe “Subtelomeric aberrations smaller than previous reports”; however, the Authors discuss also patients with larger rearrangements.

Reply: The deletions we found in terminal 11q, 8p, 7q and 14q are smaller than previous report. The 22q13.3 duplication we found is also smaller than previous reports, and in this section we described the patients with deletions containing the same region in 22q.

11) Page 12, line 4
The terminal 14q deletion found in this patient is the smallest reported to date, and was in 14q32.33.

Reply: I have amended it in the manuscript.

12) Page 12, lines 2-3 from bottom
The deleted region in patient 390 was 2.68Mb, from 4.69 Mb to 4.96 Mb

Change to
The deleted region in patient 390 was 268 kb in size, extending from 4.69 Mb to 4.96 Mb,

Reply: I have amended it in the manuscript.

13) Page 12, line 12
22q 13.33 deletion

change to
22q13.33 deletion

Reply: I have amended it in the manuscript.
“Submicroscopic Aberrations in Chinese Patients with Unexplained Developmental Delay/Mental Retardation” by Wu. et al. This report is very well prepared and will add valuable information to the body of literature on microdeletion/duplication of subtelomeric region. This reviewer has the following comments:

1. It will benefit the reader to define Mental Retardation by including IQ ranges.

Reply:
I add the following descriptions in the Introduction section: “MR is defined as a significant impairment of both cognitive (IQ <70) and social adaptive functions, with onset before 18 years of age. MR can not be diagnosed until the child is older than 5 years, when the intelligence measurements are reliable. For children younger than 5 years, the term “DD” is usually used.

In the Methods section: “IQ<55, assessed with Gesell Developmental Schedules or Wechsler intelligence scale for children”.

2. The conclusion in the abstract needs revision. The following sentence “Four deleted subtelomeric regions and the duplicated region found in this study were smaller…..” The size of the copy number changes may not be as important as the presence or absence of a dosage sensitive gene in the region.

Reply: I have amended it in the abstract.

3. Case 1729 with a GAIN on 22q13.3 involving the SHANK gene is very interesting; more discussion on the phenotypic correlation would be helpful.

Reply: Patient 1729 had some facial dysmorphisms, CHD, microcephaly and growth delay. She was only seven months old, so the phenotype of autism is too early to be assessed.

4. Please discuss case 1467 with 874Kb deletion but no phenotypic descriptions are provided.

Reply: This patient only presented with DD and microcephaly. Some descriptions for this patient have been added into the last paragraph in the Discussion section.
5. Cases 1947, 1711, 2126 and 2026 appear to be cryptic unbalanced translocations. For clarification, it is important to perform FISH analysis on the patients as well as their parents.

Reply: Only for patient 337, who had 2pter del+ 4pter dup, FISH analysis was performed. For the other four patients with complex aberrations, FISH was unavailable. The aberrations might result from balanced translocations in one of the parents.