Author’s response to reviews

Title: Mutations in WDR62 gene in Pakistani families with autosomal recessive primary microcephaly

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Author’s response to reviews: see over
Dear Editor,

Here we are submitting our revised manuscript entitled, “Mutations in WDR62 gene in Pakistani families with autosomal recessive primary microcephaly” by Kousar et al. as research article for publication in BMC Neurology.

We have incorporated all the suggestions of Associate Editor mentioned in the email to improve the manuscript. Thank you for your time and efforts to review our manuscript for publication in BMC Neurology.

Sincerely,

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Author Response:

The authors have addressed to their best the comments raised by the reviewers. I would suggest some further minor changes to improve the clarity of the manuscript (and shorten it) before it can be published. For clarity, these suggested changes are reported in red. The text between ?? ?? refers to the original text of the article.

1. Abstract:
   a. Methods: As part of a large study to detect the genetic basis of primary microcephaly in Pakistan, homozygosity mapping and?
   b. Results: Four out of 100 families recruited in the study revealed linkage to the MCPH2 locus on chromosome 19?
   c. Conclusion: Our data indicate that WDR62 mutations cause about 4% of autosomal recessive primary microcephaly in Pakistan.

   • The above three sections of the abstract are corrected as per suggestion of the reviewer.

2. Introduction
   Remove the second paragraph completely (?MCPH is primary considered?.. decreasing neuronl number and a MCPH-like phenotype?), it is repetitive of what is later represented in discussion in more detail.

   • Corrected as suggested by the reviewer.

3. Subjects and Methods:
   a. Study subjects
   ? by conforming to Helsinki Declaration and local legislations. As part of a large study to address the prevalence and genetic basis of primary microcephaly in Pakistan, 100 families were initially identified and recruited based on the reduced head circumference of affected individuals assessed during field visits in different areas of the Pakistan. Affected probands of cooperative families were clinically examined at?
b. **WDR62 sequencing**

WDR62 gene was sequenced in one obligate carrier and two affected members from each of the four families linked to the MCPH2 locus by PCR, amplifying?

- The above two sections of the subjects and methods are corrected as per suggestion of the reviewer.

4. **Results:**
   a. *By homozygosity mapping, four families resulted in linkage with the MCPH2 locus harboring the WDR62 gene. Three families (MCP26, MCP35, MCP67) were located in villages near Lahore in the Punjab province of Pakistan, while fourth family (MCP3) originates from Abbottabad in the Khyber Pakhtunkhw province. The evaluation of the affected individuals? ? ? ? (MRI) scan could not be performed.***

   b. *DNA sequencing analysis of the entire coding region of WDR62 gene identified two truncating mutations (of which one novel) and two previously reported missense mutations (Fig. 3). The novel mutation in family MCP67 is a single base pair transversion in exon 15 of the gene (c.1942c>t) resulting in a premature stop codon (p.Q648X). In family MCP26?.*

   - Result section is modified to incorporate both the suggestions of the reviewer.

5. **Discussion:**

?families originating from Punjab and Khyber Pakhtunkhw province. The p.Val1314ArgfsX18 truncating mutation identified in family MCP26 had already been reported in a Turkish family (3), as well as in affected members of a Caucasian family (2)? ??better comparison. In family MCP67, harbouring the truncating mutation p.Q648X, the affected subjects also have severe clinical course and ill-defined gyral pattern on brain imaging, in line with the hypothesis that truncating mutations in the WDR62 gene are associated with severe microcephaly and associated brain malformations (2). Indeed, truncating mutations may lead to nonsense mediated decay*

   - Corrected as suggested by the reviewer.
6. Conclusion

beside ASPM, WDR62 gene is a relevant contributor for autosomal recessive primary microcephaly in Pakistan, being responsible for about 4% of cases.

- Corrected as suggested by the reviewer.