Author's response to reviews

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

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Version: 2  Date: 18 August 2011

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

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 tried our best to incorporate the suggestions of worthy reviewers to improve the manuscript. The point by point response to reviewer’s suggestions is attached with this letter. Thank you for your time and efforts to review our manuscript for publication in BMC Neurology.

Sincerely,

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Author Response:

Reviewer 1:

1. Figure 2: the legend needs more detail (e.g. which planes are shown), are these images distorted?
   - The new image file (Figure 2) is created to avoid distortion and information regarding the plane of CT scan is now incorporated in the figure legend.

2. It is not clear if you have just tested 4 MCP families and all 4 happen to carry WDR62 mutations. Given the family numbering schema, it seems that you have access to scores of MCP families - put the results in context in terms of how many families have been screened for WDR62 (and/or other) mutations.
   - This study is part of an ongoing project aimed for the identification of the genetic players responsible for microcephaly in the Pakistani population. In this regard our group has a collection of 100 multiplexed families with autosomal recessive microcephaly. The findings in the significant number of families have already been published and were precisely reviewed this year by Mahmood et al. (Orphanet Journal of Rare Diseases 2011,6:39). During the screening of known microcephaly genes in 100 collected families, only these four families showed linkage to MCPH4 locus carrying WDR62 gene. The related information is also incorporated in the results section of the manuscript.

Reviewer 2:

1. The main limitation of the paper is the scarceness of neuroimaging documentation regarding the patients. From the pedigrees depicted in figure 1, it appears that there are ten living affected subjects, but only the CT scan from one affected subject is presented. Neuroimaging was not available for patients of family MCP26, but what about the others? The authors state that “the affected individuals of families MCP3 and MCP35, carrying known missense mutations, showed milder symptoms and simplified gyral patterns (data not shown)”, while it would be very useful to show these additional data and give them emphasis.
• The quality of the figure 2 has been improved and new figure 2 is uploaded. As these families were identified during field visits, consequently one individual from each family was taken to Children Hospital, Lahore. As a result, axial CT scans were only available from one affected individual of each family except MCP26. Secondly due to the moderate mental retardation, the affected individuals of these families did not cooperate during travel and neuroimaging, as mentioned in the manuscript regarding our efforts to carry out MRI for affected individual of MCP67. However, available clinical details of the affected individuals of MCP3 and MCP35 have been incorporated in the manuscript.

2. The authors conclude that WDR62 gene is a major contributor for autosomal recessive primary microcephaly in Pakistani population, but do not specify whether additional microcephaly families have been excluded for linkage to the WDR62 region, and therefore not considered for this paper. Also, it would be important to know the ascertainment criteria (how were the families referred to the authors?). These data would give us a more accurate estimate of the prevalence of WDR62 mutations, at least according to the recruitment method adopted.

• This study is part of an ongoing project aimed to identify the genetic players responsible for microcephaly in the Pakistani population. In this regard, our group has a collection of 100 multiplexed families with autosomal recessive microcephaly, but only mentioned four families showed linkage to WDR62 gene. All these families (100) were initially identified due to the reduced head circumference in the affected individuals during the field visits of various areas of the Pakistan.