Author's response to reviews

**Title:** A novel deletion mutation in the TUSC3 gene in a consanguineous Pakistani family with autosomal recessive nonsyndromic intellectual disability

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**Author's response to reviews:** see over
March 22, 2011

Editor
BMC Medical Genetics

Dear Sir,

Here we are submitting our revised manuscript, “A novel deletion mutation in the TUSC3 gene in a consanguineous Pakistani family with autosomal recessive nonsyndromic intellectual disability” by Khan et al. as research article for publication in BMC Medical Genetics.

We have incorporated reviewer suggestion in the manuscript. We also certify that the data in the manuscript is original and presently not submitted to any other journal for publication. It is further certified that current study conforms to Helsinki Declaration and local legislation. Written informed consents were obtained from parents/guardians of patients to publish their photographs. Please also find below the point by point response to reviewer comments.

Thank you for your time and efforts to review our manuscript for publication in BMC Medical Genetics.

Sincerely,

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Response to Reviewers

Reviewer 1: Derek Morris

Discretionary Revisions

1. Abstract: "with autosomal recessive NSID" should be added to the first sentence of the Conclusion.
   - Corrected as suggested by the reviewer.

Reviewer 2: Eric Morrow

1. Please report the genome-wide LOD scores. For example, it would be ideal to see that this 8p locus reached a genome-wide significance. Also are there other loci in the pedigree with high LOD scores? Reporting these values would help the readers understand the strength of the putative locus and if there are other loci that might be considered.
   - As SNP based genome-wide scan was performed on selected individuals (Affected: IV-11, IV-12, IV-13 and IV-14; Normal: IV-15, IV-16) of this large family, so significant LOD scores cannot be achieved due to missing genotypes and phases of many individuals. Resultantly genome-wide data was analyzed with homozygosity mapper and dCHIP to find possible homozygous by decent (HBD) regions, which revealed a single HBD region on chromosome 8 as presented in figure 2. Methods and results sections have been revised to incorporate this information along with the modification of figure 1 and addition of the figure 2.

2. The authors nicely test the frequency of the CNV in the Pakistani population, 246 controls. The authors should also report if there are any other CNVs in this gene that are common.
   - According to the database of genomics variants (http://projects.tcag.ca/variation/), 57 CNVs have been reported in the HBD region identified in this family, but 27 involve TUSC3 gene. The detailed analysis of the CNV data indicates that all the
presently identified TUSC3 involving CNVs exist in the heterozygous state. This information is also incorporated in the manuscript.

3. The authors report the patient's head circumference in cm and the authors might consider also reporting the normalized value based on population measures.

- We agree with the reviewer, but unfortunately population based data is not currently available for our population. As a result, head circumference of the affected individuals were compared with the normal individuals of the family, which indicate significant head circumference reduction in the affected individuals.

4. How do the authors know that TUSC3 is the only mutated gene in the pedigree and/or genetic interval? The authors might consider sequencing MCPH1 to see if there are mutations in this gene as well.

- Keeping in view the significance of MCPH1 gene, it was also sequenced for pathogenic mutation but the sequence analysis only revealed the presence of the known SNPs in exon 1 (rs2305023), 6 (rs2442513) and 8 (rs930557 and rs2920676). This clearly indicates the involvement of TUSC3 gene in this family with autosomal recessive NSID. This information is incorporated in the result section of the manuscript.