

Author's response to reviews

Title: A novel HSF4 gene mutation (p.R405X) causing autosomal recessive congenital cataracts in a large consanguineous Pakistani family

Authors:

Naheed Sajjad (naheedsaj@yahoo.com)
Ingrid Goebel (ingrid.goebel@uk-koeln.de)
Naseebullah Kakar (naseebkhan_kakar2003@yahoo.com)
Abdul M. Cheema (amcheema@buitms.edu.pk)
Christian Kubisch (christian.kubisch@uk-koeln.de)
Jamil Ahmad (jamil_48@yahoo.co.in)

Version: 2 **Date:** 17 September 2008

Author's response to reviews: see over

Comments by Reviewer # 1

1. Method, Linkage analysis: the marker allele frequencies and their source should be given.

Marker allele frequencies have been mentioned in the linkage analysis section and table 1.

2. Results: were any unrelated controls sequenced?

Yes, we have sequenced altogether 167 healthy controls (76 from Pakistan and 91 from Germany) further supporting the causative nature of the identified transition, which now is explicitly mentioned in the manuscript.

Comments by Reviewer # 2

1. Markers: The markers used should be stated including their genetic and physical distances in relation to HSF4 should be stated. A table showing the LOD score...

The genetic distance for each of the markers covering the HSF4 locus is now included in the text, moreover the physical position is now given in the text as well as in Figure 1. A table containing the LOD scores at different recombination fractions is added in the revised manuscript.

2. The NM or Genebank ID for HSF4 should be given...

We now added the information about the used reference sequence (i.e. NM_001040667) for isoform B of HSF4 in the text of the revised manuscript. We moreover included the nomenclature of the mutation in isoform A. As requested, we also added the information about exon 11 in the results section.

3. Restriction digestion: in the methods the authors should state the expected.....

As requested, the expected allele sizes for wild type and mutant alleles have been incorporated in the Methods section. We moreover improved figure 1 according to the constructive criticisms of the reviewer now including a revised lane numbering, data on the physical position of markers and microsatellite haplotypes. Moreover, we included and the sizes of products after restriction digest in figure 1.

4. Controls: Even though the mutation segregates and has a major effect.....

See also point 2 of reviewer 1. Pakistani controls and additional German controls have been analyzed, showing that the mutation is neither present in ethnically matched individuals nor in a very different ethnic background. This family is living in Pakistan for the last 20 years and belongs to a rather big ethnic group in Quetta-Pakistan so that the Pakistani controls are well suited.

5. Conclusion: the conclusion is weak and unimaginative.

The conclusion is modified and now is more precise according to the work and title.

Comments by Reviewer # 3

1. One aspect that was found surprisingly absent was that though.....

See also comments to previous reviewers. As requested, marker data along with haplotype bars have been added into pedigree drawing. Moreover, data on additional markers covering other cataract loci have been added in additional table 1.

2. It would be better to state in the methods section how many individuals were.....

The number of affected and unaffected individuals used in this study has been mentioned in the Methods section.

3. How many normal controls were screened? This detail is missing.....

See comments of previous reviewers, the information about controls is now given.

There is an error in the references, with the same paper by.....

We modified the References section accordingly.