Author's response to reviews

Title: The Clinical And Molecular Spectrum Of Galactosemia In Patients From The Cape Town Region Of South Africa

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PDF covering letter
Dear Clare,

**Re: Revision of manuscript “The clinical and molecular spectrum……….. Henderson et al**

We have now revised our manuscript and addressed all the issues raised by the reviewers. These points are listed below and the action taken described.

I trust that the reviewers will be satisfied with the corrections made.

We look forward to finality on this manuscript.

Yours sincerely

Howard Henderson

**Reviewer 1 – Prof Derek Applegarth**

1. Compulsory revisions:
   
   *All have been implemented*

2. Discretionary revisions:

   *We have added the following sentence*

   “This is in accord with the S135L carrier frequency data from the Northern regions of South Africa, which suggest a similar newborn incidence of approximately 1/22 500 (8)”

**Reviewer 2 – Prof Juergen Reichardt**

1. This population is to date only poorly characterised.

   *We are only too aware of and frustrated by this situation: one of the difficulties of research in a developing country with a huge discrepancy in the quality of medical care available to the small 1st world component and the huge, largely black, 3rd world population.*

2. M&M: The authors must provide references for their biochemical assay methodologies.

   *The only assays not referenced were those of the thin-layer chromatography. We have now provided details of our TLC method and included a relevant reference (3).*

3. M&M: References for the Q188R and S135L mutations and the accompanying frequency statements must be included.

   *We have complied and included 2 additional references ie (6),(7)*

We initially developed a restriction PCR primer for this mutation, which was used in patient diagnosis. However when, screening the large number of blood spots for determining carrier frequency we had to use a less costly PCR assay. We therefore developed an ARMS assay as it avoids the use of costly restriction enzymes. Both assays are equally effective in picking up the S135L allele. We have explained this in the text.

5. Discussion: reporting on carrier frequencies:
Our mistake, we are of course, talking of patient incidences. This has been corrected in the text.

We have now included these data and references in the text.

7. TABLE 1 and text: Reporting patient numbers as a %.
We acknowledge that the sample size is small and have given all data as fractions (ie. 9/9) where necessary.

8. Fig 1: remove
This figure can be dispensed with and we have done so.

Reviewer 3 – Dr LJ Elsas

1. The points raised by Dr Elsas are very interesting and have intrigued us for many years. Unfortunately we are unable to comment on these issues as our Black patients (S135L/S135L) are invariable born into a primary health-care environment and none have been maintained on a lactose restricted diet, in fact all have been lost to follow up. We have therefore been able to assess their clinical outcome. In contrast, our Q188R homozygotes have been treated by dietary restriction and their clinical outcome is in accord with that of patients managed in the UK/USA. Given these gross differences in management we are unable to comment on the reportedly “milder” phenotype attached to the S135L mutation; this assertion remains a very intriguing aspect of galactosemia.

We have added two sentences to the conclusion section outlining the above.