Author's response to reviews

Title: Molecular Testing for Adult Type Alport Syndrome

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Major revision: We are grateful to several reviewers for asking us to provide evidence of the frequency of the 3 common mutations in the US population. A more careful analysis of all adult type mutations showed more of these than we had appreciated, so that the relative frequency of the three mutations in this assay is lower than we had estimated, but still substantial. Details are now provided in Table 2. The C1564S, R1649R, and R1677Q mutations have not been found in populations outside the US, to our knowledge. Clinical sensitivity of the assay has been changed to 75%.

The method is targeted to the 3 specific mutations. Detection of additional is possible if the mutation is under the probe. It is expected that the Tm will be different as demonstrated by the different melts of R1677Q and R1677X.

Under Minor Essential Revisions.

We do believe that amino acid substitutions in the NC1 domain usually result in relatively mild disease. Our genotype-phenotype correlations including this observation have been submitted for publication (Bekheirnia et al). In this series, the mean age of ESRD for missense mutations in the NC1 domain was 34 years versus 28 years for the collagenous domain (p = 0.014).

The error on Figure 1 was corrected.

Names of genes and number of mutation were corrected

No polymorphism were observed in our patient samples but were not expected because all positive samples are with an identical haplotype. No polymorphisms were observed in WT controls or negative samples.

UNG denaturation was changed by UNG enzyme inactivation