Reviewer's report

Title: Frequency of Fabry disease in male and female haemodialysis patients in Spain

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Reviewer: Eduard Paschke

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The paper describes a case finding study for Fabry disease among 911 male and female haemodialysis patients from Spain. 5.5% of males and 34% of females were selected for alpha galactosidase (AGAL) activities in dry blood spots, respectively, and subjected to gene analysis. New Fabry alleles were identified in a male and a female patient, respectively, accompanied by a reduction of AGAL activity in the expected low range. Furthermore, two unrelated, clearly affected males and two sisters were found with a mutation (R118C), previously found in an unsymptomatic newborn. Finally, two individuals (1 male, 1 female) carried the known allele D313Y, currently in discussion for being a pseudoallele.

The methodology used is appropriate, the results are in consistence with previous findings in other patient groups and add interesting new data to the problems of biochemical and genetic diagnosis of Fabry disease.

Some details in the selection process should be clarified:

1) Similar screening concepts have recently been used by others, e.g. among patients with renal insufficiency (e.g. Merta et al European Renal Association Nephrol Dial Transplant. 2007 Jan;22(1):179-86) and hypertrophic cardiomyopathy (Montserrat et al (2007) J Am Coll Cardiol 2007;50:2399–403), with lower cutoffs for residual AGAL activity, which prompted some discussion on the proportion on females that would probably be missed by activities above thresholds (Linthorst et al, J Am Coll Cardiol (2008)51(21):2082; author reply 2082-3).

An estimate on the presumable percentage of high outliers according to the increased cutoffs used based on own results mentioned (Molecular study, p. 9, line 3-7), or at least a comment on the problem (including the “logistic” problems, also mentioned in the authors reply to Linthorst) would clearly improve understanding.

2) In table 1 some of the reported activities clearly even exceed the defined cutoffs (Patient 4 (female;94%), 7 (female; 124%)and 8 (male; 46%)).

What was the reason for selecting them?

Furthermore, the residual activities in % of mean normal values should be added.
(p 2,5,7) in each of the 8 cases. Lack of leucocyte activities should be indicated by a clear symbol (e.g. n.d; not determined; instead of empty space) and some minor spelling errors (e.g. decimal point instead of comma, etc.) should be corrected.

Taken together, I recommend to accept the paper after minor revisions.

Level of interest
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- An article of importance in its field

Quality of written English
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- Acceptable

Statistical review
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- the manuscript does not need to be seen by a statistician.

Declaration of competing interests
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- none