Reviewer's report

Title: Focal Segmental Glomerulosclerosis: Molecular Genetics and Targeted Therapies

Version: 1 Date: 23 March 2015

Reviewer: Duncan Johnstone

Reviewer's report:

Although there are a large number of reviews on this subject, the authors address some questions that are usually not addressed. Overall this is a good review.

Minor issues not for publication.

There are grammatical errors that distract from the reading.

a. Introduction, 2nd to last sentence. “Studies were deployed.” Awkward verb choice.

b. Genetic causes of FSGS. 2nd sentence. For example: (a) SD-associated molecules…

This sentence has no verb. The authors are trying to use a colon to denote a series of examples, (a, b, c, etc) but they do not use the colon and semicolon correctly. The entire next section does not follow grammatical rules. “Upstream regulator…” ends in a semi-colon, then goes to example (b), again not following rules of grammar. The same occurs with the transition from “on actin dynamics…” and “AD FSGS.”

c. “Does the result of genetic testing affect….”

“Most studies indicated…” Use the same tense as the rest of the document.

d. “Alternative and Novel therapies for FSGS”

“disease mechanisms while (awkward)

More than a grammatical error:

1. “Structural and Functional Podocyte Deficits”

“… numerous gene products are required to construct the podocyte body, primary and secondary foot processes (FP). For example, nephrin, (NPHS1) and podocin are the major components of the slit diaphragm.”

- The second sentence does not follow logically from the first. The slit diaphragm is part of the tertiary foot process intercellular junction. No examples of gene products involved in the body, primary or secondary foot process are listed by the authors.

2. Genetic causes of FSGS, last paragraph before starting “2. Circulating Factors of FSGS.”
“The renal biopsy may predict…”

- The descriptors on a renal biopsy are not sufficiently specific to predict the presence of 2 APOL1 risk alleles. More data are needed. The best example of the difficulties of going from renal biopsy descriptors to a conclusion about etiology (or about the patient’s genetic background) is in the subject of identifying with high certainty whether an adult with biopsy-proven FSGS has primary or secondary disease. While there are a few findings that are quite suggestive of FSGS secondary to obesity or obesity-related glomerulopathy, for the most part the renal biopsy descriptions of primary and secondary FSGS can be frustratingly similar.

3. “Circulating Factors of FSGS” 1st paragraph

- The role of suPAR as the circulatory factor has been controversial. In part, this is because suPAR has also been described as a disease marker for many inflammatory states, including asthma, non-obese diabetes, cardiovascular risk scores, all-cause admission to the ICU, hantavirus, gastric cancer, and other cancers. Secondly, in additional to the conflicting studies cited by the authors (references 61-63) there is additional conflicting data from Meijer B et al, KI 2014 vol 85; Sinha A et al, K 2015 vol 85; and Spinale JM et al, 2015 KI vol 87. At this point, I would suggest removing suPAR as the “identified” or the “likely” circulatory factor.

4. “Does the result of genetic testing impact decisions…”

- I suggest addressing the role of donors with known APOL1 risk alleles, or with suspected APOL1 risk alleles. There is one opinion paper on this (Cohen DM et al, Transplantation 2011), but there is not much data on donors. Should candidates with 2 APOL1 risk alleles be excluded from donation? How about candidates with 1 APOL risk allele?

5. “Treatment of SR FSGS.”

- This section is largely a good, balanced review of a single study. However, there is more to the treatment of FSGS. This section does not review the data of other studies to address questions such as: how effective is steroid treatment in adults; how often is there spontaneous remission of adult FSGS (Wetzels’ group has published data on a high rate of spontaneous remission in adults), what is the best steroid-sparing agent for short-term and long-term outcomes in adults, and more. The KDIGO recs are mentioned at the end, and might work better to launch the discussion of this section.

6. “Alternative and Novel therapies for FSGS”

- The data on Rituximab acting in a B-cell independent manner are interesting but too preliminary for a review.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests