Reviewer's report

Title: Autosomal dominant polycystic kidney disease in a family with mosaicism and hypomorphic allele

Version: 1 Date: 15 November 2012

Reviewer: Ying-Cai Tan

Reviewer's report:

This is a well-written, concise case report, but the major conclusion was not so sound.

Major Compulsory Revisions:

1. The author claimed the missense change p.Thr2250Met to be a hypomorphic allele, however, the hypomorphic effect was not so clear. His father manifested as a typical PKD patient who had PKD1 frameshift mutation with ESRD at age 52. Beside this PKD1 frameshift mutation, he had another missense change, p.Thr2250Met, which the author considered to be hypomorphic. However, the difference in the age of ESRD between he and his father was only 7 years (45 vs. 52). He looked more like a typical PKD1 patient rather than a patient with a PKD1 frameshift mutation and a hypomorphic mutation in trans. The typical such case reported by Rossetti S et al presented disease in utero (Rossetti S et al 2009, reference 4), a disease onset age much earlier than the case here.

2. In addition, in the discussion section, the author said that this missense change was reported in ADPKD Mutation Database as a likely pathogenic mutation, but when I queried the same database (Nov. 2012), it listed this change as likely neutral. The difference might be due to the different time of querying database, which got updated. However, a prediction of likely neutral is more consistent with phenotype of the patient, which showed not so much different on age of ESRD compared with his father. Thus this missense change behaved more like polymorphism rather than hypomorphic.

3. The author stated that the frameshifting mutation p.Val1105ArgfsX4 was identified in the patient and his father, and was also visible in his grandmother but at a lower level as a result of mosaicism, however, only the patient’s sequencing eletropherogram was shown. It’s better to show them side by side with his father and grandmother’s sequencing result.

Minor Essential Revisions:

1. The patient’s grandmother was found to have 10% chromosomes possessed the frameshifting mutation by HRM study. Did the author ever analyze the patient and his father’s DNA with the same method? If so, what’s the result?

2. In the abstract, the author claimed this family was unlinked to PKD1 and PKD2 loci, but a PKD1 pathogenic mutation was identified, apparently the disease was link to PKD1. Negative result in linkage analysis did not mean the disease was not link to PKD1 or PKD2 gene. This sentence needs to be rephrased.
**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Acceptable

**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