Reviewer's report

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

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Reviewer: Sandro Rossetti

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Autosomal Dominant Polycystic Kidney Disease in a family with mosaicism and hypomorphic allele by Reiterova J et al.

This is a very interesting paper outlining the genetic basis of strong intra-familial phenotype variability in a pedigree with PKD1 disease. To date, intra-familial phenotype variability is observed in ADPKD, and this is at least in part due to the co-inheritance of additional PKD1 or PKD2 genetic variants, mosaicism and/or genetic modifiers. In this pedigree, the mild, PKD2-like disease phenotype in the mother switches into a more severe, PKD1-like phenotype in the affected son and particularly in the affected grand-son, who inherits a likely hypomorphic allele from the apparently unaffected mother. Interestingly, the mildly affected grand-mother is a mosaic, with only 10% affected chromosome in peripheral lymphocytes, and the apparently unaffected mother of the proband did reveal some cysts after careful imaging analysis. Hence, this report is intriguing in showing the presence in the same pedigree of mosaicism and a hypomorphic allele in trans; also it helps to clarify the disease-association of a variant, T2250M, the interpretation of which has been challenging; finally, it shows that having a family member reaching ESRD at age 70y is not automatically indicative of PKD2 disease, but may overlap with mild PKD1 disease. This is very important information for genetic counseling.

I only have some minor comments:

1) It is a bit concerning that the apparently unaffected sister was used as a living-related kidney donor. In fact, it appears that she has a few cysts and she is a carrier of T2250M. How do the authors feel about the possibility that both the donor and the recipient may suffer consequences form this, should the “T2250M-kidneys” develop additional cysts in the future. The authors could comment a bit in the paper about this difficult choice that the clinicians involved here have done.

2) When the authors describe in the paper that the family is apparently unlinked, showing that 2 unaffected individuals carry the at-risk haplotype (through the proband’s paternal uncle): to the expert reader it is obvious that this is due to the mosaicism in the grand-mother. In fact the at-risk haplotype runs with the disease mutation only in 10% of the chromosomes, and with the wild-type chromosome in 90% of the cells (at least in the peripheral lymphocytes), explaining why the same haplotype is found in both. However, I fear that the non expert reader may
be tricked by this and not understand this subtle situation. The authors could write this out in a bit more detail to make this transition clear-cut.

**Level of interest:** An article of importance in its field

**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