Reviewer's report

Title: Common Variants in Mismatch Repair Genes Associated with Increased Risk of Sperm DNA Damage and Male Infertility

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Reviewer: JOAQUIN GADEA

Reviewer's report:

Authors evaluated the relationship between SNP in mismatch repair genes and infertility. They studied 21 SNPs in 5 MMR genes. They reported 3 different SNPs that looks like to be related to infertility. Two of them are also related to an increase in sperm DNA damage.

This reviewer considers this manuscript is relevant and offers original information that could help to understand the genetic basis of some male infertility cases.

My main concern is related to the spermatology area of this manuscript and the design of the study that will have importance in the possible clinical application of this valuable information.

First at all, the 3 groups of study are based in fertility (control and idiopathic infertility) and sperm concentration (<20 or > 20 x 106 spermatozoa/mL). However, the control group was not divided according the same criteria of sperm concentration. So I suggest to evaluate your data from 4 groups (fertile <20 x 106 spermatozoa/mL; fertile >20 x 106 spermatozoa/mL, infertile <20 x 106 spermatozoa/mL; infertile >20 x 106 spermatozoa/mL). So, it would be possible to relate the SNP and sperm concentration and SNP and fertility in a more adequate way.

Sperm concentration is only one of the parameters to evaluate the normal semen quality and spermatogenesis process. Other sperm parameters as motility, viability, morphology and total number of sperm in the ejaculate could be of interest to study.

In the text, concentration values (low or high) are assimilated to impaired or normal spermatogenesis. In opinion of this reviewer it is not a precise an accurate language. Please review this concept.

Some specific questions

Introduction

I suggest including some words related to the relationship between SNP and infertility, and supported by some references. For example:

Carrell DT, Aston KI. The search for SNPs, CNVs, and epigenetic variants associated with the complex disease of male infertility. Systems Biology in Reproductive Medicine 2011: 17-26.


Methods
Subjects and sample collection

How many azoospermic cases are in the case 1 group?
What criteria were used to classify as “normal semen quality”?
All patients has data from at least two semen assessments, what value are you using for classify by concentration, mean value, the best one, the worst one?

DNA fragmentation analysis

Semen samples were frozen – 70ºC. Please, give more information about this process.
It is well known that cryopreservation resulted in a significant increase in percentage sperm DNA fragmentation (Thomson et al. Hum Reprod 2009;24: 2061-2070).

Did the authors evaluate the cryopreservation effect on DNA fragmentation in this experiment?

Results

Please show in a table the sperm parameters from the samples (control and patients) as mean±sem (motility, concentration, volume, viability, morphology, TUNEL, etc).

Please show the DNA fragmentation values in percentage not in logarithmic values in the text and figure 1. (for example 11.82 % not 2.47, 26.57% not 3.28).

Discussion

Smoking effect reported in table 1 is not discussed.
Discussion must improve. The relation between SNPs and infertility must be reevaluated.

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.