Reviewer’s report

Title: BasePhasing: a highly efficient approach for preimplantation genetic haplotyping in clinical application of balanced translocation carriers

Version: 0 Date: 12 Dec 2018

Reviewer: Yanwen Xu

Reviewer’s report:

The authors developed a high performance cost effective method to distinguish balanced translocation carriers from normal embryos in clinical application of PGT-SR. The principal of this method which was named Basephasing by authors, was still a PGH technology. The study utilized cell line GM16457 and two balanced translocation families to confirm the effectiveness. Results of Basephasing were consistent with the ones from karyomap-12-based PGH. The authors considered that Basephasing was one of the most suitable methods with the advantages of simple operation procedures, accurate results and very low cost.

Major problems:

1. Theoretically, ASA bead chip, which was designed based on Asian populations, should provide more information for Chinese populations. According to the figure 2A, MAF values of ASA were mostly concentrated in the 0-0.06 compared with karyomap-12. There was no significant difference in the number of SNPs between the ASA and Karyomap-12 at MAF value > 0.3. Please explain SNPs with which MAF value are more valuable for linkage analysis. Did this increase in the number of SNPs with MAF between 0-0.06 actually make any difference for analysis?

2. In results, "For more analyzable information, chromosomes were divided into segments of the same size (2Mbp), called windows". Please explain the rationale for setting this fragment to 2Mb?

3. Call rate values of two chips per sample were listed in table 3. It seems like the higher the SNP numbers of chip, the higher the call rate value. So, is B Allele Freq plot greater? Please provide B Allele Freq plot for the same sample of two chips.

4. Validation of Basephasing was only based on very limited samples, including a single cell line and two translocation families. Had the unaffected embryos been transferred? Please give pregnancy outcomes and the results of prenatal diagnosis.

5. Please discuss risks or limitations of this method.

Minor problems:
1. In the background of abstract, the authors described "There were no suitable methods to efficiently distinguish balanced translocation carrier embryos from normal ones in clinical application". Since several papers have been published using different platforms, it should be more cautious to describe current situation in this sentence.

2. PGH results in Table 3 showed almost 50% normal/carrier rate in embryos from two translocation families, which was higher than both theoretical data and published data. Please present results in detail.

3. In discussion, authors stated that "8/9 of the gametes would be abnormal in couples with a reciprocal translocation, and 2/3 with a Robertsonian translocation", which is wrong, even the results in Table 3 denied the proportions of abnormal gametes in reciprocal translocations in this paper.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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