Mu Yuan, Endocrinol Metab Syndr 2015, 4:4
http://dx.doi.org/10.4172/2161-1017.C1.008

OMICS International
conferenceseries.com

3rd International Conference on
Endocrinology
November 02-04, 2015 Atlanta, USA

Effects of assisted reproductive technology on the DNA stability and its epigenetic modification in the offspring

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Since the birth of Louise Brown, the world's first *in vitro* fertilisation (IVF) baby 30 years ago, more than 6 million children have been born worldwide with assisted reproductive technology (ART), and in some countries ART infants account for more than 1% of the birth cohorts (Pinborg et al., 2013). However, the health of the offspring conceived by ART has been a big concern with the increasing application of ART to solving infertility problems for its unnatural conception procedures. The incidences of low birth weight (?) and birth defects (Hansen et al., 2005; Lie et al., 2005) have been found more often among infants conceived by ART. Interference of ART to the gametogenesis and preimplantation embryo development resulted in the alteration of epigenetic reprogramming (Manipalviratn et al., 2009) or genomic sta bility (Manipalviratn et al., 2009; Feng et al., 2008) , which was deduced to be the causes of abnormalities in ART children. However, the association of ART with de novo genetic aberrations is still in dispute (Caperton et al., 2007; Riccaboni et al., 2008). Dynamic mutation is one type of DNA alteration, distinguished by unstable trinucleotide repeat expansion or contraction (Rosales-Reynoso et al., 2009). Compared with other gene loci, the frequency of dynamic mutation is much higher because its copy number alteration of trinucleotide repeats within a certain range of these genes will not result in any phenotypic change. Thus, the frequencies of dynamic mutations are a relatively sensitive index DNA instability analysis.

To determine the stability degree of the dynamic mutation genes in ART offspring, seven common dynamic mutation genes were selected, which include Dentatorubral-pallidoluysian atrophy (DRPLA), Huntington disease (HD), Spinobulbar muscular atrophy (SBMA), Dystrophia myotonica-protein kinase (DMPK), Myotonic dystrophy 1 (DM1) and Fragile X syndrome (Fra X). The peripheral blood and umbilical blood were collected from 75 IVF families (75 couples and 100 babies), 72 ICSI families (72 couples and 91 babies) and 99 natural conceived families (99 couples and 100 babies). The ratios of dynamic mutation were screened in the IVF and ICSI babies with the naturally conceived babies as the control.

2,466 transmissions were identified in ART offspring, with 2.11% (n=52/2,466) of alleles being unstable. In the control group, the frequency of dynamic mutation was 0.77% (n=10/1,300). Statistical significance was found between the ART group and the control group ($P<0.01$). The unstable transmission alleles were detected in 32of 1,288 alleles (2.48%) in IVF offspring and 20 of 1,178 alleles (1.70%) in ICSI offspring, both of which were significantly different from naturally conceived babies ($P<0.01$ and $P<0.05$, respectively). However, there were no significant differences in the size of mutational repeats, the rates of expansion or contraction among the three groups ($P>0.05$). The repeat copy numbers of the examined genes in all parents and their babies were found to be within the normal ranges.

To further investigate how ART affects the genome instability in the offspring, 52 ART conceived singleton placentas (32 IVF and 20 ICSI) and 32 comparative naturally conceived placentas were collected, and the DNA damage repair associated genes were analysed.

Results showed that gene expressions of PMS2, RPA1, XPA, MSH2 and MSH6 were significantly higher in the IVF and ICSI groups than in the control group. Both IVF and ICSI groups showed significant different DNA methylation rate of OGG1, RPA1, PMS2, MSH6 and XPA compared with the natural group. Meantime, the protein expressions of PMS2, MSH6 and MLH1 in the ICSI group were also significantly higher than in the IVF and control groups. Therefore, ART procedures and infertile background could result in mild genomic instability, which could result from the alteration of epigenetic modification like DNA methylation of DNA damage repair associated genes.

Biography

Mu Yuan is now a PhD student in his 2nd year in Zhejiang University in China. He has published 2 papers in 2015 (one of which has just been accepted).

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