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Title

THE MECHANICS OF ANEUPLOIDY: CHROMOSOME STRUCTURE AND PATIENT AGE

Authors:
C. Briton-Jones; L. Sekhon; J. A. Lee; R. Marie A. Moschini; M. Duke; A. B. Copperman

Affiliations:

1. Reproductive Medicine Associates of New York, 635 Madison Ave 10th Floor New York, New York, United States, 10022

2. Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, Klingenstein Pavilion 1176 Fifth Avenue 9th Floor New York, New York, United States, 10029

Objective:
The mechanical association of chromosomal formation to patient age remains poorly understood. Previous studies have been unable to fully investigate the age-aneuploidy dynamic due to most chromosomal aneuploidies being lethal to embryonic development prior to implantation. Comprehensive chromosomal screening (CCS) of blastocysts allows for previously unobtainable insight into the biology of aneuploidy. This study investigated aneuploidy in embryos derived from autologous oocytes to better understand the chromosome specific influences of patient age on the mechanisms of aneuploidy.

Design:
Retrospective cohort analysis

Materials and Methods:
All patients undergoing autologous IVF cycles with embryonic aneuploidy screening by targeted comprehensive chromosome screening (qPCR) or next generation sequencing (NGS) from January 2012 to February 2017 were included. Donor oocyte IVF cycles and translocation carriers were excluded. Trophectoderm cells, obtained via blastocyst biopsy during culture day 5 to 7, underwent CCS. Patients were segregated by the proportions of embryos that showed aneuploidy for a specific chromosome and age (<35 years old (YO) and ≥35 YO). Affected chromosomes were grouped according to size (A-C: large (chromosomes 1-12, X); D-G: small (chromosomes 13-22, Y) and centromere position, using standard karyotype criteria. Chi-square test was used to determine statistical significance where $P<0.05$.

Results:
A total of 6751 blastocysts from 1244 patients were analyzed using qPCR or NGS for detection of chromosomal aneuploidy (Table 1). Aneuploid embryos derived from women <35 YO had a 48.1% incidence of chromosomal loss or gain in the A, B and C group chromosomes as compared to 40.8% in women ≥35 (p= 0.03). When comparing chromosome gains of aneuploidy, women < 35 had 27.38% errors in the A+B+C chromosomes as compared to 21.6% in women ≥ 35 (p=0.012). In women <35, 44.8% of the aneuploid embryos showed errors in the smaller chromosome groups: D, E, F and G; compared to 54.7% in women ≥ 35 (p=0.007).

Conclusions:
This study is first to characterize different chromosomal patterns of aneuploidy in blastocyst stage embryos. Aneuploid embryos derived from women <35 have a higher proportion of errors in the larger chromosomes whereas women ≥35 are more likely to contain errors in the smaller chromosomes. The findings supports a theory proposed by Lamb et al (2005) that telomeric exchanges resulting in aneuploidy are more common in younger women and pericentromeric exchanges are more common in older women.

References:
Lamb, NE; Yu, K; Shaffer, J; Feingold, E and Sherman, SL. (2005) Association between age and maternal age and meiotic recombination for trisomy 21. Am. J. Hum. Genet., 76: 91-99.

Support:
None.

Table 1:
Proportion of aneuploid embryos and chromosomal specific aneuploidy by chromosome group.

	Patients	Embryos biopsied	Proportion aneuploid	Proportion of aneuploidy affecting groups A-C	Proportion of aneuploid affecting groups D-G	Proportion of aneuploid gains affecting groups A-C	Proportion of aneuploid losses affecting groups A-C
Under 35 years old	427	2910	28.9	48.1*	44.8**	27.4**	20.7
Over 35 years old	817	3841	43.4	40.8*	54.7**	21.6**	19.2

*P<0.05; **P<0.01