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Title:

PARENTAL HETEROCHROMATIC CHROMOSOMAL VARIANTS ARE NOT ASSOCIATED WITH AN INCREASED RISK OF EMBRYO ANEUPLOIDY

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Objective

Common cytogenetic polymorphisms detected by parental karyotype analysis include heterochromatin regions of chromosomes 1, 9, 16 and Y and also prominent acrocentric short arms, satellites and stalks. Although polymorphic variants are commonly found in the general population and considered to be 'normal' by cytogeneticists, some studies have questioned whether these variants are correlated with an increased rate of reproductive failure due to embryo aneuploidy. (Morales R et al., Dong Y et al.) This study aimed to evaluate if couples who carry a heterochromatic variant are at risk of experiencing increased rates of embryo aneuploidy.

Design:

Retrospective, cohort analysis.

Materials and Methods:

The study included couples who were tested with G-banding karyotype analysis on peripheral blood lymphocytes and underwent a PGT-A cycle between Jan, 2012 and March, 2018. Couples who were detected to be carriers of balanced translocations, inversions, mosaicisms, or pathogenic polymorphisms were excluded from the analysis. Trophectoderm biopsies (Day 5-7) were analyzed by Next-Generation Sequencing or quantitative polymerase chain reaction (qPCR). Participants were classified by couple karyotype (Group A: at least one patient was reported to be a carrier of a heterochromatic variant; Group B: both patients were reported as "normal".) Data were evaluated using Student T-tests, Fisher's and χi2 tests when appropriate, a generalized estimating equation (GEE) model that accounted for patients who underwent multiple cycles adjusting for potential cofounders was used. A sample size of 42 patients per group was needed to detect a 30% difference in implantation rates with 80% power (A=0.05).

Results:

A total of 946 couples were analyzed, a 5.0% (n=48) prevalence of heterochromatic variants was found. The most common variant types found were non-pathogenic pericentric inversions on chromosome 9 (33.3%) and any heterochromatin block variants (qh) on sexual chromosomes (22.2%). Heterochromatic variants were more common on male partners (33/48, 68.7%) than females (15/48, 31.2%). Heterozygosity in the patient or partner was observed in all couples with a heterochromatic variant. A total of 869 IVF/PGT-A cycles were included in the analysis (Group A: n=48; Group B: n=82). A total of 4017 trophectoderm biopsies were analyzed. Demographic, stimulation parameters and embryological variables, were comparable among cohorts (Table 1). No significant difference was observed in embryo ploidy rates among groups. No association was found with the presence of a heterochromatic chromosome variant and the

odds of aneuploidy in a GEE model that controlled for age, BMI, AMH, and embryo age at biopsy (L'Beta= -0.04, CI95% -0.16 – 0.07; OR 0.95, CI95% 0.8-1.07, p=0.46). A sub-analysis adjusting for the gender of the heterochromatic variant carrier found no association with the odds of aneuploidy (L'Beta= 0.025, CI95% -0.20 – 0.25), OR 0.11, CI95% 0.8-1.28, p=0.82).

Conclusions:

The relationship between 'normal' chromosomal variants and reproductive outcome remains highly contested. The statistically significantly higher incidence of heterochromatic variations found in infertile individuals stresses on the need to evaluate their role in infertility and subfertility. It has been reported that epigenetic, genetic, and chromosomal modifications could be associated with certain complex disorders such as infertility and poor obstetrical outcome. Our study's findings showed that there is no association between parental heterochromatic chromosome variants and subsequent embryo aneuploidy rates. Ploidy rates do not appear to be affected in couples when at least one patient is reported to be a carrier of a normal karyotype variant. Further analysis on infertile population at the molecular level, may unveil potential relationships between parental chromosomal variants and embryological chromosome segregation errors.

Support:

None.

Table 1:

Comparison analysis of demographic, oocyte stimulation, embryological and ploidy variables of the populations analyzed.

869 cycles. (4017 embryos).					
Variable	Variant carrier		Normal Karyotype		
	n=48	cycles	n=821	cycles	
	Mean	SD	Mean	SD	p value
OocyteAge	36.22	4.22	36.37	4.16	0.81
BMI	22.82	3.61	28.42	143.12	0.27
SrgDay	12.06	1.42	12.91	13.88	0.11
GndCumulativeDose	3988.47	1562.28	3769.04	1337.67	0.27
SrgE2	2321.91	880.83	2447.39	1170.89	0.35
SrgP4	0.86	0.42	0.94	0.54	0.27
D3FSH	6.44	3.78	6.09	3.37	0.57
AMH	3.70	4.65	3.28	3.45	0.52
BAFC	12.23	6.68	12.33	5.97	0.91
EggsRetrieved	15.85	9.56	15.77	8.49	0.95
M2 Eggs	12.02	8.11	11.78	7.07	0.81
Fertilized eggs	9.35	6.89	9.54	6.03	0.83
Embryos biopsied.	5.62	4.67	4.69	3.67	0.18
Aneuploid embryos	2.70	2.60	2.08	1.89	0.11
Euploid embryos	2.57	2.73	2.44	2.67	0.73
Inconclusive results	0.33	0.93	0.17	0.63	0.24
Euploid embryos rate (embryos-%)	121/264	45%	1951/3753	52%	0.61
Aneuploid embryos rate (embryos-%)	127/264	48%	1660/ 3753	44%	0.98
Inconclusive reports rate (embryos-%)	20/264	7%	142/3753	3.7%	0.32