American Society for Reproductive Medicine 2018 Scientific Congress & Expo
October 6 to 10, 2018 ● Denver, Colorado, USA

Title:

THE PRESENCE OF A POLYMORPHISM IN THE MATERNAL MTHFR GENE DOES NOT CORRELATE WITH THE INCIDENCE OF EMBRYONIC ANEUPLOIDY

Authors:
Carlos Hernandez-Nieto, MD[1], Joseph A. Lee, BA[1]; Dmitry Gounko MA[1]; Enrique Cervantes MD[1]; Martha Luna-Rojas MD[1]; Alan B. Copperman, MD[1,2]; Benjamin Sandler, MD[1,2]

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:
Methylenetetrahydrofolate reductase (MTHFR) plays an important role in catalyzing the conversion of 5, 10 methylenetetrahydrofolate into 5-methylenetetrahydrofolate, the predominant circulating form of folate in humans. Variations in the sequence of MTHFR gene have been implicated in the sub-fertile population and may influence embryo development, implantation and aneuploidy rates. Additionally, the viability of euploid embryo may suffer as a result of potential MTHFR gene polymorphism's effect on multiple essential processes including meiosis, embryogenesis and pregnancy initiation. (Enciso M, et al. 2016). This study seeks to analyze the proportion and odds of embryo aneuploidy in patients detected as carriers of the most common types of MTHFR gene mutations.

Design:
Retrospective

Materials and Methods:
Patients who underwent IVF with preimplantation genetic testing for aneuploidy (PGT-A) from Jan 2012-January 2018 were included. Trophectoderm biopsies (Day 5-6) were analyzed by Next-Generation Sequencing (NGS) or quantitative Polymerase Chain Reaction (qPCR). Natural language processing was used from the study site's electronic medical records to identify patients who were tested for MTHFR. Female patients were analyzed depending on their carrier status for a MTHFR mutation (homozygote A1298c, heterozygote A1298C, homozygote C677T, heterozygote C677T, or compound A1298c + C677T). Detected balanced translocations, severe male factor and ovum donation cases were excluded from the analysis. A sample size of 93 patients per group was needed to detect a 20% difference in aneuploidy rate with 80% power (A=0.05).

Results:
Of 6,249 cycles, an 11% prevalence of polymorphism was found on the entire population. 748 patients were included in the analysis, in this tested population the prevalence of any MTHFR mutation was 75.9%. (n=568). Patients without a MTHFR polymorphism (n=180) were used as controls. The most common mutated allele was C667T. 46.3% (n=263) followed by A12898C 35.2% (n=200) and the compound mutation (A1298C+C677T) 18.4% (n=105). No significant differences were found in patient demographics, stimulation, or embryology parameters (Table 1). Overall the aneuploidy rate was similar among non-MTHRF carrier patients (49%) as compared with all MTHFR mutation carriers (50%, p=0.69). Also, no difference was found when comparing homozygous, heterozygous, or combined MTHR mutations (p=0.73) (Table 2). After the data was evaluated using a Generalized Estimating Equation (GEE) model that accounted for patients who underwent multiple cycles, controlled for oocyte age, AMH, BMI, and number of embryos biopsied per cycle; no association was found with the presence of any MTHFR variant and the odds of aneuploidy (L'Beta 0.83, CI95% 0.60-1.14), p=0.26). There was a positive association with increasing oocyte age with the odds of aneuploidy OR 0.19, (CI95% 0.15-.0.24, p= <0.0001). After a multivariate logistic regression analysis controlling for the same cofounders mentioned above, no association was found with the odds of aneuploidy when analyzing the different types of alleles were observed ((A1298C, OR 1.22 (0.74 - 1.99, p=0.42); (C677T, OR 0.87 (CI95% 0.54 - 1.40, p=0.58); (compound, OR 1.19 (CI95% 0.64-2.22, p=0.56)) (Table 3.).

Conclusions:
Personalized and genomic medicine is expanding the understanding of how genetic variants can impact human condition and healthcare. By using big data and a systems-based approach, this study demonstrated the presence of the most common MTHFR genotype variants are not associated with the rate of embryo aneuploidy. Our findings remain consistent with the current reproductive knowledge base that increased age correlates with elevated odds of aneuploidy. Although, after controlling for age and other potential cofounders, patients who have a MTHFR polymorphism did not experience increased odds of embryo aneuploidy.

Support:
None.

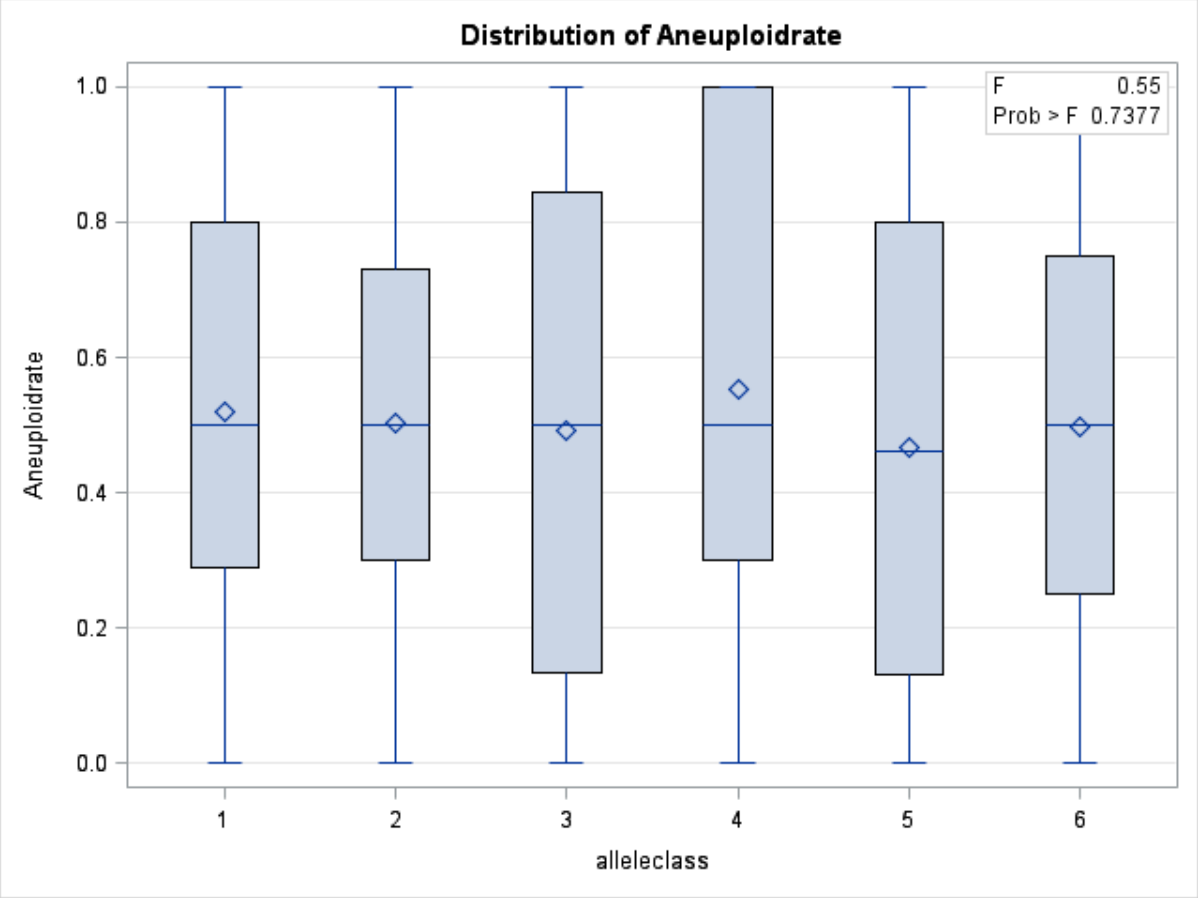
Bibliography:
1. Enciso, M., Sarasa, J., Xanthopoulou, L. et al. Hum Genet (2016) 135: 555.

Table1:
Demographic characteristics of populations analyzed.

	NO MTHFR polymorphism		Positive MTHFR polymorphism			
	n=180		n=568			
	Mean	SD	Mean	SD	p value	significance
Oocyte Age	36.60	4.12	37.24	4.13	0.06	NS
Body Mass Index	22.91	3.99	23.57	4.49	0.09	NS
Gravida	2.00	1.77	1.97	1.82	0.85	NS
Parity	0.52	0.66	0.41	0.69	0.07	NS
Day of surge	12.13	1.49	12.02	1.45	0.38	NS
Gnd Cumulative Dose	3830.71	1413.95	3757.00	1340.54	0.52	NS
Srg Estradiol	2281.97	1053.34	2282.68	1107.91	0.99	NS
Srg Progesterone	1.00	0.46	0.92	0.64	0.08	NS
Day 3 estradiol	43.14	21.53	47.14	30.46	0.07	NS
Day 3 progesterone	0.38	0.18	0.43	0.36	0.01	NS
Day 3 LH	4.01	3.01	4.14	2.80	0.66	NS
Day 3 FSH	6.05	3.15	6.07	3.52	0.95	NS
AMH	2.81	2.12	2.99	3.51	0.61	NS
BAFC	11.50	5.34	11.76	5.97	0.63	NS
Endometrial Thickness At Surge	9.64	2.42	9.66	1.98	0.920	NS
# Eggs Retrieved	15.63	8.40	15.03	8.67	0.42	NS
M2 count	11.29	6.51	11.35	6.93	0.92	NS
Zygote Count	9.01	5.56	9.00	5.77	0.98	NS
Embryos biopsied	4.98	3.81	4.76	4.23	0.52	NS
Aneuploid embryos	2.27	2.05	2.11	2.17	0.37	NS
Euploid embryos	2.42	2.60	2.24	2.64	0.42	NS
Other result - inconclusive	0.28	0.95	0.40	2.03	0.28	NS
Aneuploid rate %	0.49	0.34	0.50	0.36	0.67	NS

Table 2:

Aneuploidy rate per Type of MTHFR polymorphism. Heterozygous, Homozygous, Compound. ANOVA							
Rates	Negative Mutation	C677T Heterozygous	C677T Homozygous	A1298C Heterozygous	A1298C Homozygous	Compound Mutation	p value
N	n=180	n=187	n=76	n=148	n=52	n=105	
Aneuploidy rate	49.60%	52.00%	50.10%	49.20%	55.30%	46.70%	
Aneuploid blasts / Biopsied blasts	409/887	425/909	171/399	288/666	105/219	210/508	0.73



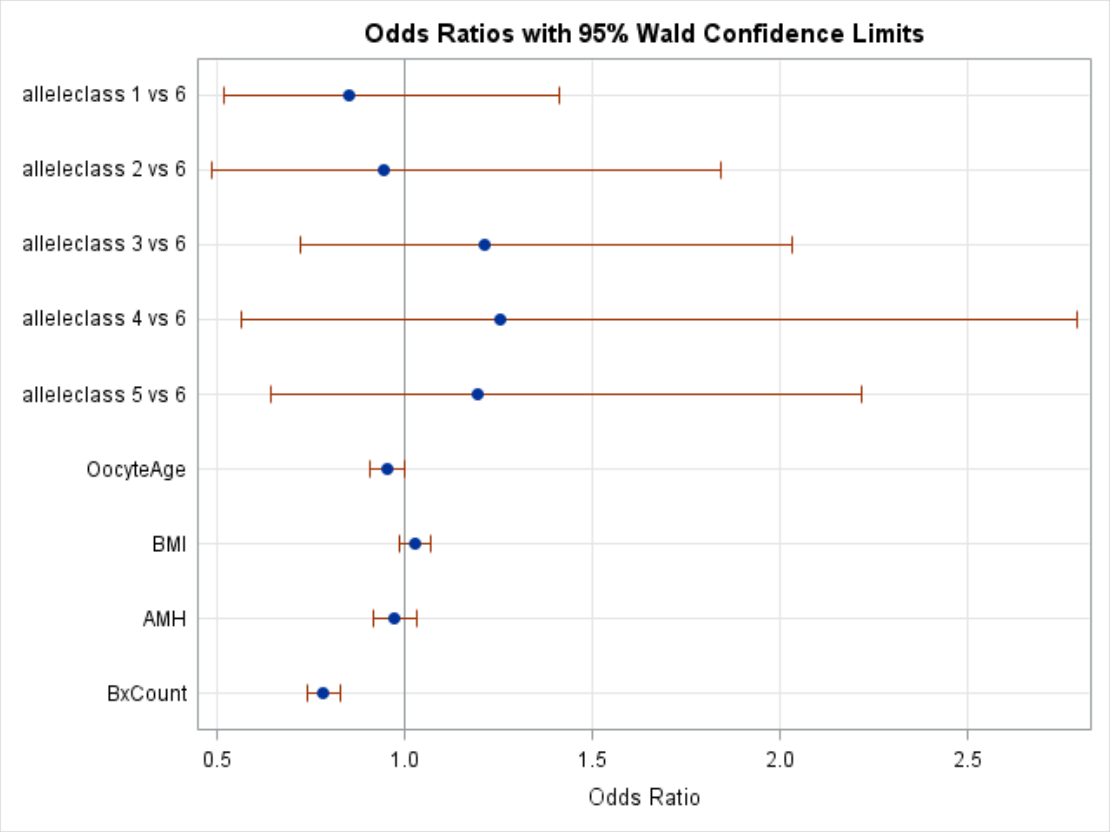
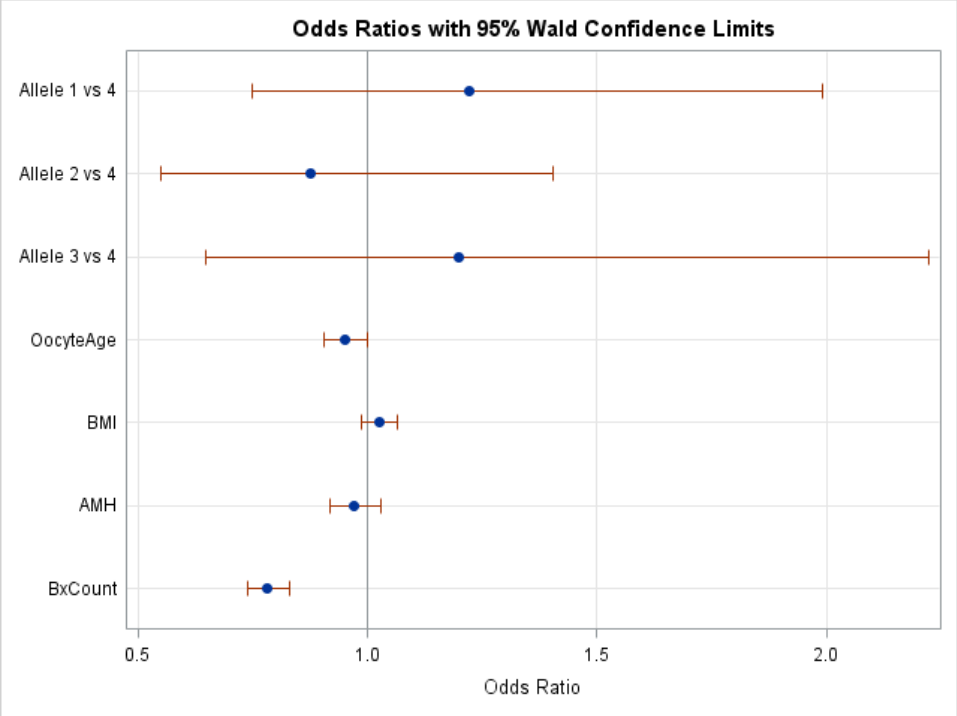
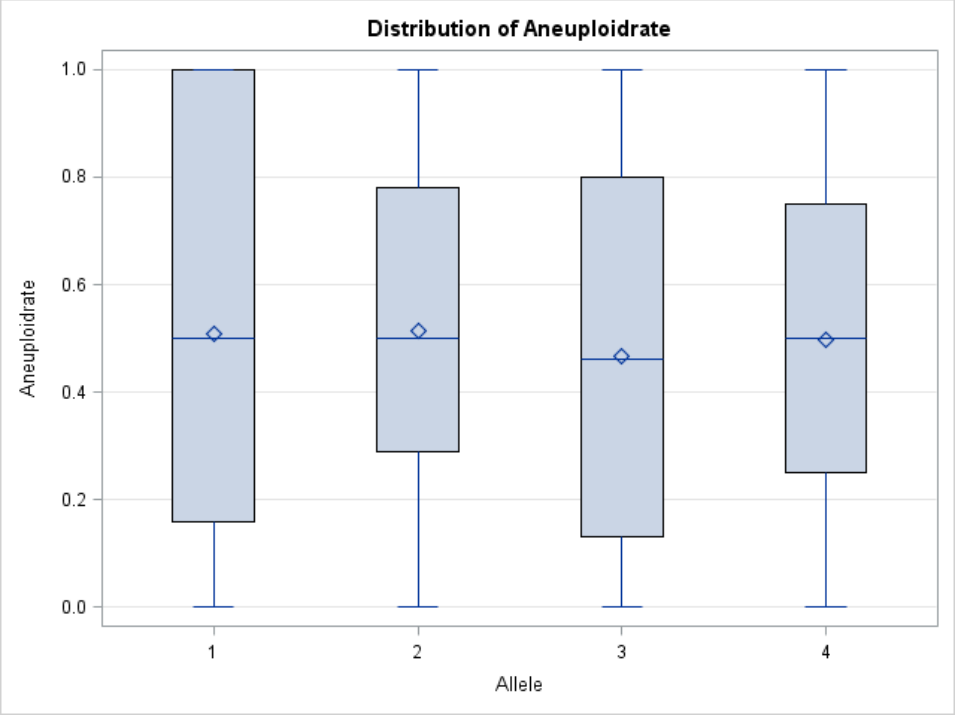


Table 3:

Aneuploidy rate per Type of allele. C677T, A1298C, Compound or control. ANOVA with Tukey's Studentized Range and multivariate logistic regression controlling for oocyte age, BMI, AMH and blasts biopsied.					
Rates	Negative Mutation	A1298C	C677T	Compound Mutation	p value
N	n=180	n=200	n=263	n=105	
Aneuploidy rate	49.60%	50.80%	51.40%	46.70%	0.69
Aneuploid blasts / Biopsied blasts	409/887	393/885	596/1308	210/508	
Odds of aneuploidy	Reference	OR 1.22 (0.74 - 1.99, p=0.42).	OR 0.87 (CI95% 0.54 - 1.40, p=0.58)	OR 1.19 (CI95% 0.64-2.22, p=0.56)	


Odds Ratios with 95% Wald Confidence Limits
Allele 1 vs 4
Allele 2 vs 4
Allele 3 vs 4
OocyteAge
BMI
AMH
BxCount
0.5
1.0
1.5
2.0
Odds Ratio


Distribution of Aneuploidrate
Aneuploidrate
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Allele