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In the name of God

OB-GYN congress
Bahman 98

Preimplantation genetic screening should be used in all in vitro fertilization cycles in women over the age of 35 years: AGAINST: Pre-implantation genetic screening should not be used in all IVF cycles in women over the age of 35 years

BJOG Debate
William Ledger
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There is little doubt that the appropriate use of PGD can be beneficial. The detection of a recessive mutation in an embryo can obviate transfer and thereby avoid a termination of pregnancy or the birth of a child with a severe disability.

PGS (PGT-A) can reduce time to pregnancy and avoid the distress of repeated miscarriages or failed transfers in specific subgroups of patients (Rodrigo et al. *Biomed Res Int* 2014;2014:517125); however, the evidence suggests that the universal use of PGT-A is premature.

Rates of embryonic aneuploidy are low below 37 years of age, and several large single-centre and national studies have failed to find improvement in livebirth rates for women younger than 37 years of age (Kang et al. *Fertil Steril* 2016;106:597–602; Chang et al. *Fertil Steril* 2016;105:394–400).
A recent large randomized controlled trial failed to show improvement in cumulative livebirth rate for women aged 36–40 years after PGT-A.

SET vs DET

In several RCT showed decrease LBR in SET in comparison to DET

Worldwide live births following the transfer of chromosomally “Abnormal” embryos after PGT/A: results of a worldwide web-based survey

Abstract: Purpose Preimplantation genetic testing for aneuploidy (PGT-A) has become increasingly controversial since normal euploid births have been reported following transfer of embryos diagnosed as “abnormal.” There is an increasing trend in transferring “abnormal” embryos; but it is still unknown how many IVF centers transfer “abnormal” embryos and with what efficiency.

Methods: We performed a worldwide web-survey of IVF centers to elucidate PGT-A related practice patterns including transfer
of human embryos found “abnormal” by PGT-A. Participating centers reflected in vitro fertilization (IVF) cycles in the USA,
Canada, Europe, Asia, South America, and Africa.

Results: 20% of IVF units reported transfers of
chromosomally “abnormal” embryos, and 56% of these took place in the USA, followed by Asia in 20%. Remarkably, 106
(49.3%) cycles resulted in ongoing pregnancies (n = 50) or live births (n = 56). Miscarriages were rare (n = 20; 9.3%).

Conclusions: The transfers of “abnormal” embryos by PGT-A offered robust pregnancy and live birth chances with low miscarriage rates. These data further strengthen the argument that PGT-A cannot reliably determine which embryos should or should not be transferred and leads to disposal of many normal embryos with excellent pregnancy potential.

PGT-A may lead to the unnecessary discarding of healthy embryos that are wrongly diagnosed as aneuploid, a loss that is particularly damaging to the chances of livebirth for an older patient with few chances left. PGT-A is costly, with a patient aged 36–37 years incurring a cost of approximately $30,000 for a 90% likelihood of attaining a euploid embryo. In many jurisdictions, this outlay could cover several further unscreened IVF cycles, giving a significantly higher chance of a livebirth per dollar spent (Goldman et al. *J Assist Reprod Genet* 2018;35:1641–50).

We know that the technology is imperfect: PGT-A can erroneously call euploid embryos as aneuploidy (Tiegs et al. *J Assist Reprod Genet* 2016;33:893–7) and we do not know what to do with apparently mosaic embryos (Greco et al. *N Engl J Med* 2015;373:2089–90).

Aneuploid embryo transfer

PGDIS Statement on the transfer of mosaic embryos

Oocyte maturation arrest

Case1:

A 30-year-old female with a 6-year history of primary unexplained infertility was referred to our center. Routine infertility investigation revealed that her ovulatory cycle was regular, and that her fallopian tubes were patent.

The concentrations of endocrine hormones in her serum were
normal

The sperm concentration, motility, and morphology of her spouse were normal, and the karyotypes of both individuals were
normal.

Oocyte maturation arrest

She had 2 IVF cycle

First one: 23 oocytes retrieved and all of them were immature

Second one: 19 oocyte

3 in GV

16 in MI

The oocytes were cultured overnight in culture medium for in vitro maturation. However, 24 h later no polar body was extruded.

The patient’s elder sister also presented with primary unexplained infertility and experienced a failed IVF attempt at another IVF center.

Several genes involved in oocyte maturation in mice were identified
Two genes in human
TUBB8
PATL2
TUBB8 (Tubulin beta 8: The protein encoded by this gene represents the primary beta-tubulin subunit of oocytes and the early embryo. Defects in this gene, which is primate-specific, are a cause of oocyte maturation defect 2 and infertility.)

Sequencing analysis identified the heterozygous TUBB8 mutation
c.1054G > T in both sisters, which was not detected in their mother and inherited from their father.
Mutations at these amino acids could affect the folding or stability of
b-tubulin, thus impairing microtubule behavior and spindle assembly by dominant negative effects.

The comprehensive mutational and phenotypic spectrum of TUBB8 in female infertility

European Journal of Human Genetics, 20 April 2018

Inherited or de novo variants in the TUBB8 gene accounted for 30% of individuals affected by oocyte maturation arrest.
In 87 patients from unrelated families diagnosed with oocyte maturation or
early embryonic were genotyped for TUBB8 and 30 patients carrying TUBB8 variants.

Thus, TUBB8 mutation screening might not only be a genetic diagnostic marker for patients with oocyte maturation arrest, but might also have clinical implications for evaluating the competence of patients' functional oocytes with first polar body (PB1).

Biallelic Mutations in PATL2 Cause Female Infertility Characterized by Oocyte Maturation Arrest

The American Journal of Human Genetics 101, 609–615, October 5, 2017

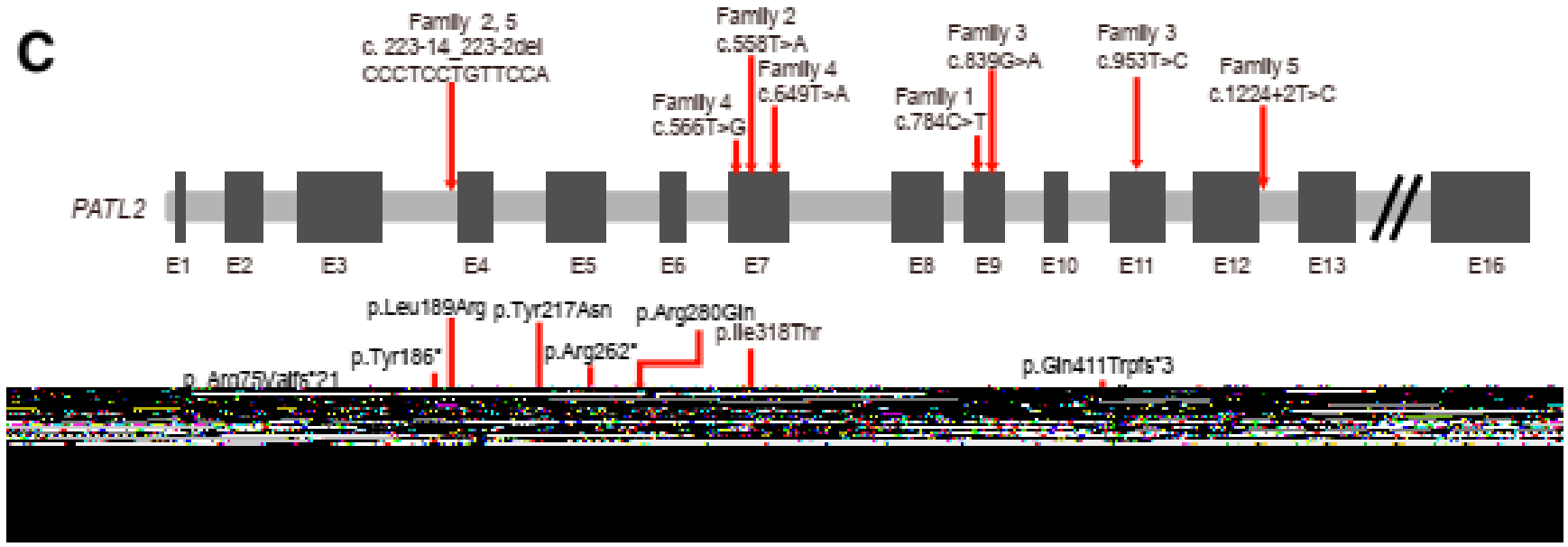
TUBB8 mutations account for around 30% of the individuals with oocyte MI arrest, but the genetic causes of human oocyte GV arrest
remain to be elucidated, and other genetic causes of MI arrest are largely unknown.

PATL2 gene Cause Female Infertility

a homozygous nonsense mutation of PATL2 (c.784C>T [p.Arg262*]) were identified in a consanguineous family with a phenotype characterized by human oocyte germinal vesicle (GV) arrest. According to the description reported by the individual, almost all the oocytes retrieved were arrested at the *GV stage*.

Subsequent mutation screening of PATL2 in a cohort identified four additional independent individuals with compound-heterozygous PATL2 mutations with slight phenotypic variability.

Autosomal Recessive
Encode an RNA binding protein
Oocyte maturation, Meiotic arrest


C
Family 2, 5
c. 223-14_223-2del
CCCTCCTGTTCCA
Family 2
c.558T>A
Family 4
c.649T>A
Family 4
c.566T>G
Family 1
c.784C>T
Family 3
c.839G>A
Family 3
c.953T>C
Family 5
c.1224+2T>C
PATL2
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E16
p.Leu189Arg
p.Tyr217Asn
p.Arg280Gln
p.Ile318Thr
p.Tyr186*
p.Arg262*
p.Gln411Trpfs*3

Fertilization Failure

Case2

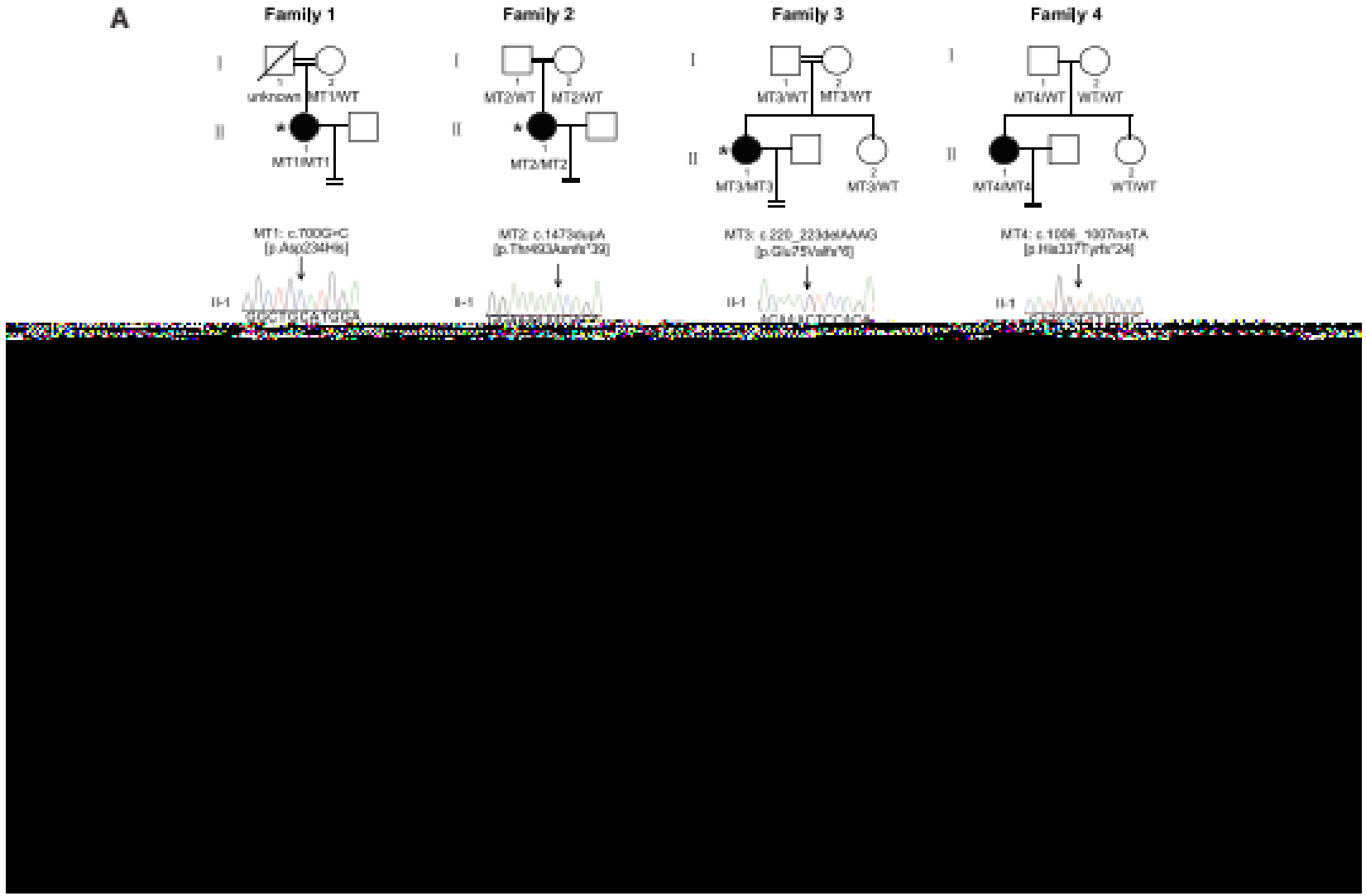
A 35 years old woman with primary infertility of unknown cause for 7 years.
She had normal menstrual cycles.
Her spouse had normal sperm counts and their sperm had normal morphologic features and motility and the karyotypes of both individuals were normal.
Her parents are consanguineous.
She had one failed ICSI attempt, in which eight PB1 oocytes were retrieved but could not be fertilized

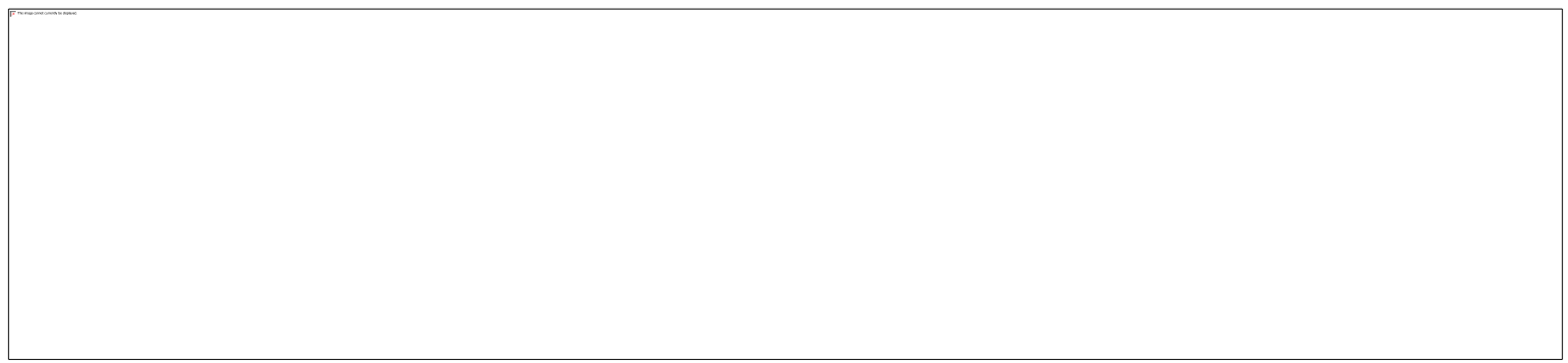
Genetics

Three genes have been identified for fertilization in human.

- ZP2
- TLE6
- WEE2

Patient had a homozygote mutation in WEE2
Autosomal Recessive
Oocyte specific protein tyrosine kinase (cdc2)
Ooocyte maturation and fertilization


A
Family 1
Family 2
Family 3
Family 4
I
II
unknown
MT1/WT
MT1/MT1
MT2/WT
MT2/WT
MT2/MT2
MT3/WT
MT3/WT
MT3/MT3
MT3/WT
MT4/WT
WT/WT
MT4/MT4
WT/WT
MT1: c.700G>C
[p.Asp(234His]
MT2: c.1473dupA
[p.Thr493Asnfs*39]
MT3: c.220_223delAAAG
[p.Glu75Valfs*6]
MT4: c.1006_1007insTA
[p.His337Tyrfs*24]
II-1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Panel for Fertility

Analysis of all known genes associated with fertility. Enables an accurate diagnosis.

The panel for fertility covers **141 genes**. All of these genes are sequenced simultaneously. We interpret all genes associated with the patient's phenotype, referred to as a gene set. In Addition, mtDNA is part of the enrichment.

Ovarian dysgenesis
AR, BMP15, CFTR, FSHR, HARS2, HSD17B4, MCM9, MRPS22, NR5A1, NUP107, PSMC3IP, SOHLH1

Recurrent pregnancy loss, early embryonic arrest and thrombophilia
F2, F5, MTHFR, NLRP2, NLRP5, PADI6, PATL2, PROC, PROS1, SERPINC1, SERPINE1, SYCE3, SYCP3, TACR3, THBD, TUBB8, WEE2

Treatment?

Thank You