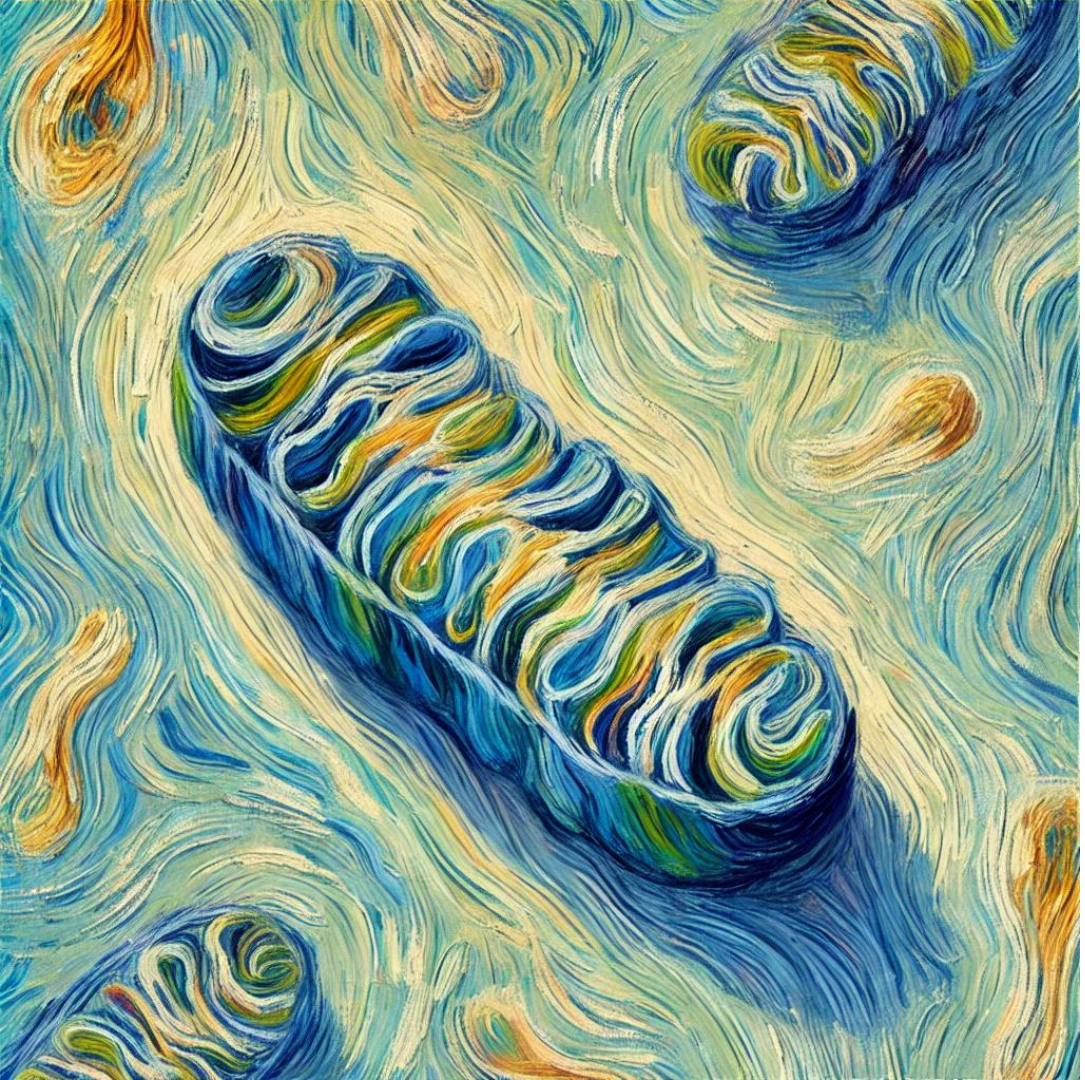

Mitochondrial genotype associating with low birthweight after ART

Claudia Spits

GENETICS
REPRODUCTION
AND
DEVELOPMENT

Image created with the assistance of OpenAI's ChatGPT

nature communications

Article

https://doi.org/10.1038/s41467-024-45446-1

Children born after assisted reproduction more commonly carry a mitochondrial genotype associating with low birthweight

Received: 10 December 2022

Accepted: 23 January 2024

Published online: 09 February 2024

Check for updates

Joke Mertens[1], Florence Belva[2], Aafke P. A. van Montfoort[3], Marius Regin[1], Filippo Zambelli[4], Sara Seneca[1,2], Edouard Couvreu de Deckersberg[1], Maryse Bonduelle[2], Herman Tournaye[5,6], Katrien Stouffs[1,2], Kurt Barbé[7], Hubert J. M. Smeets[8,9], Hilde Van de Velde[5,10], Karen Sermon[1], Christophe Blockeel[5,11] & Claudia Spits[1]

OXFORD hro

Human Reproduction Open, 2025, **2025(1)**, hoae074

https://doi.org/10.1093/hropen/hoae074

Advance Access Publication Date: December 30, 2024

Original article

The interplay between mitochondrial DNA genotypes, female infertility, ovarian response, and mutagenesis in oocytes

Annelore Van Der Kelen[1,2,†], Letizia Li Piani[1,3,4,5,†], Joke Mertens[1], Marius Regin[1], Edouard Couvreu de Deckersberg[1], Hilde Van de Velde[1,3], Karen Sermon[1], Herman Tournaye[1,3], Willem Verpoest[1,3,6], Frederik Jan Hes[1,2], Christophe Blockeel[1,3], and Claudia Spits[1,*]

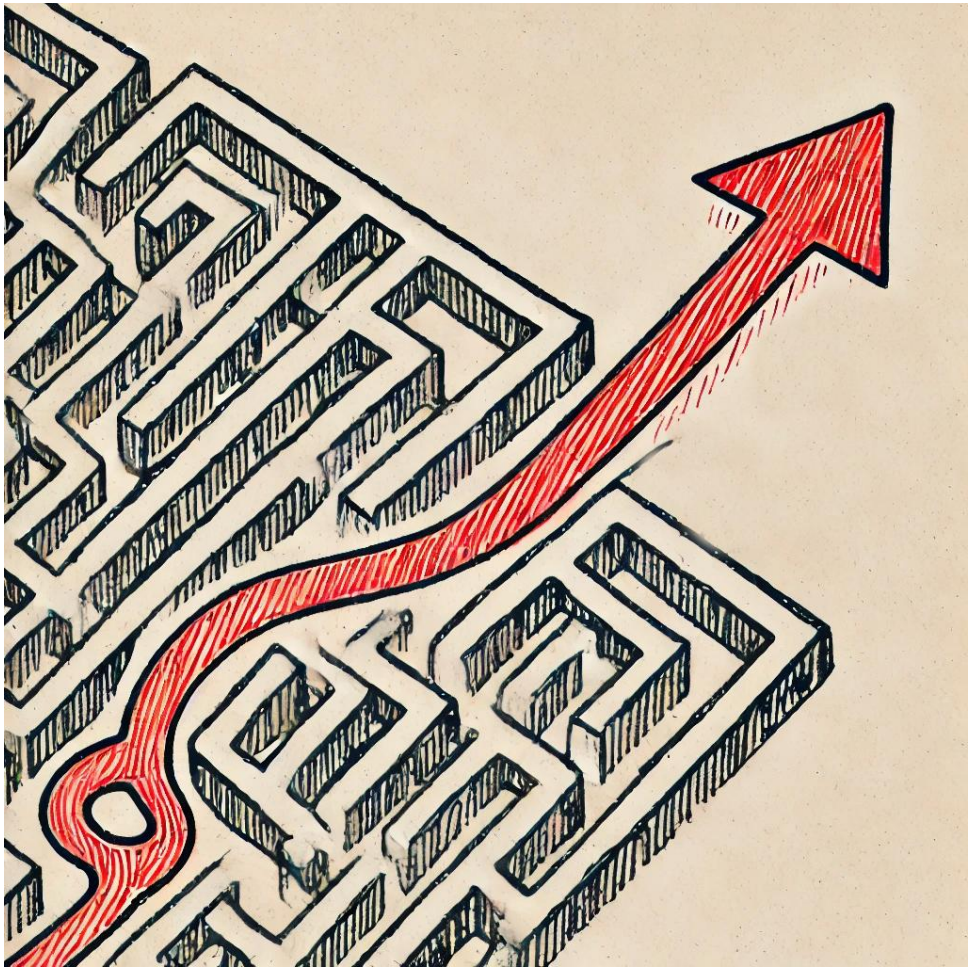

Image created with the assistance of OpenAI's ChatGPT

Human embryonic stem cells commonly display large mitochondrial DNA deletions

To the Editor:
Mitochondria play an important role in early embryogenesis and contribute to the unique biology of stem cells. Undifferentiated human and mouse embryonic stem cells (ESCs) contain relatively few spherical and immature mitochondria, similar to those in human and other mammalian preimplantation embryos[1]. The number and maturity of mitochondria increases upon differentiation, concurrent with the switch from glycolysis to oxidative phosphorylation (OXPHOS) for energy production[1]. Conversely, human somatic mitochondria undergo morphological and functional changes during reprogramming to induced pluripotent stem cells (iPSCs)[2], with a shift from OXPHOS to glycolysis. Furthermore, attenuating mitochondrial function in undifferentiated human (h) ESCs increases the mRNA levels of the pluripotency genes *NANOG*, *POU5F1* (*OCT4*) and *SOX2*, compromises the cells' differentiation potential and increases the

Stem Cell Reports
Article
ISSCR
OPEN ACCESS

Random Mutagenesis, Clonal Events, and Embryonic or Somatic Origin Determine the mtDNA Variant Type and Load in Human Pluripotent Stem Cells

Filippo Zambelli,[1,2] Joke Mertens,[1] Dominika Dziedzicka,[1] Johan Sterckx,[3] Christina Markouli,[1] Alexander Keller,[1] Philippe Tropel,[4] Laura Jung,[5] Stephane Viville,[5,6] Hilde Van de Velde,[1,3] Mieke Geens,[1] Sara Seneca,[1,7] Karen Sermon,[1] and Claudia Spits[1,*]

Van Haute & Spits et al., 2013, Zambelli et al., 2018

Human oocytes and embryos commonly carry mtDNA mutations

Molecular Human Reproduction Vol.13, No.3 pp. 149–154*, 2007
Advance Access publication on January 26, 2007 doi:10.1093/molehr/gal112

mtDNA point mutations are present at various levels of heteroplasmy in human oocytes

Lorraine Jacobs[1,2], Mike Gerards[1], Patrick Chinnery[3], John Dumoulin[4], Ireneaus de Coo[5], Joep Geraedts[1] and Hubert Smeets[1,6]

Am. J. Hum. Genet. 57:239–247, 1995

Rearranged Mitochondrial Genomes Are Present in Human Oocytes

Xi Chen,[1,*] Robert Prosser,[2] Simonetta Simonetti,[1,†] James Sadlock,[1] Georgiana Jagiello,[2,3,4] and Eric A. Schon[1,3]

Departments of [1]Neurology, [2]Obstetrics and Gynecology, and [3]Genetics and Development, and [4]The Center for Reproductive Sciences, Columbia University, New York

RBMOnline - *Vol 1. No 3. 96–100 Reproductive BioMedicine Online webpaper 2000/010 on web 1/12/00*

Articles

Mitochondrial DNA point mutation in human oocytes is associated with maternal age

Dr Jason Barritt received his MSc in 1995 in Human Genetics and his PhD in 1998 in Human Anatomy (reproductive) from Virginia Commonwealth University. His PhD dissertation was on "Mitochondrial DNA rearrangements in human oocytes and embryos". He then moved to the Institute for Reproduction Medicine and Science as a postdoctoral fellow to continue his mitochondria work with both Dr Carol Brenner and Dr Jacques Cohen. Dr Barritt has published numerous articles on mtDNA heteroplasmy after cytoplasmic transplantation, as well as on mtDNA mutations and rearrangements in human oocytes and embryos.

Dr Jason Barritt

Jason A Barritt, Jacques Cohen, Carol A Brenner[1]

Molecular Human Reproduction Vol.13, No.3 pp. 149–154*, 2007
Advance Access publication on January 26, 2007 doi:10.1093/molehr/gal112

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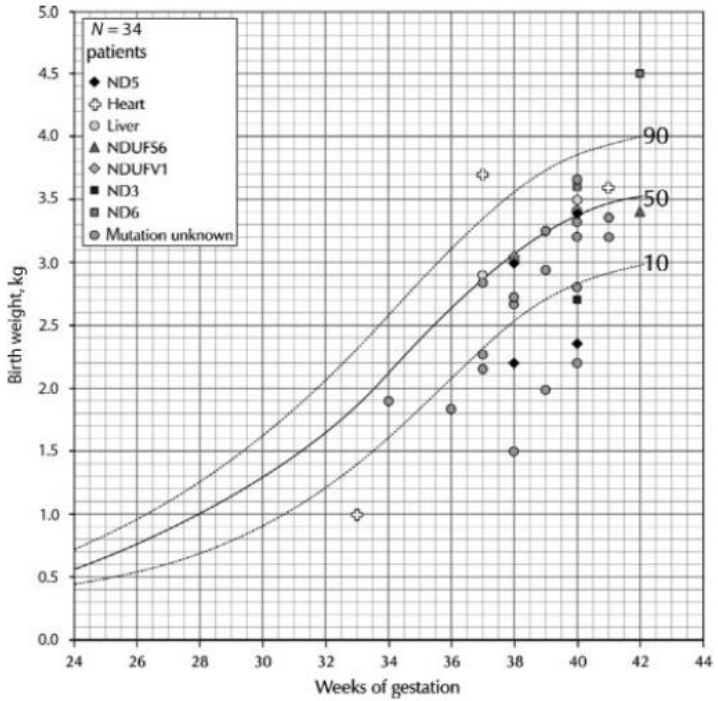
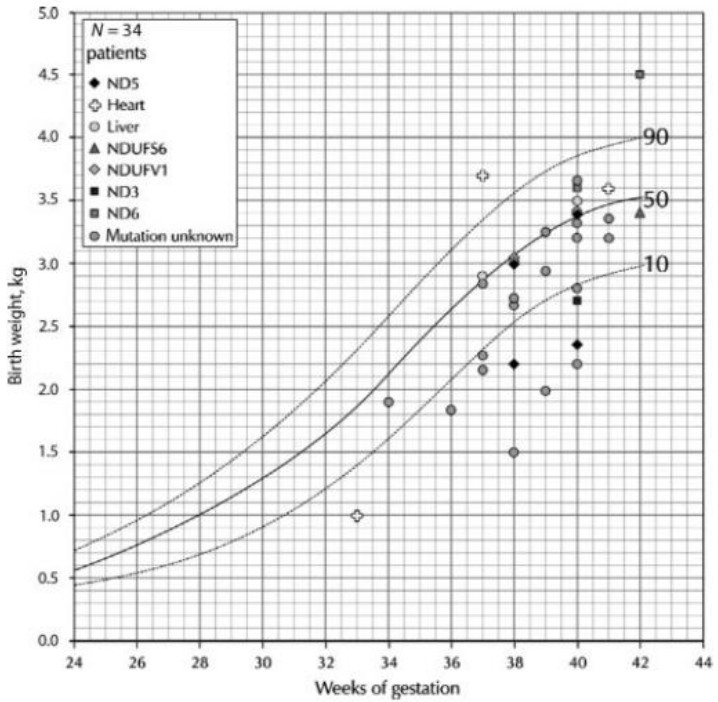
mtDNA mutations associate to low birth weight



Gibson et al., 2008
Kleist-Retzow et al., 2003

mtDNA mutations associate to low birth weight and endocrine disorders



Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Endocrine disorders in mitochondrial disease ☆

Andrew M. Schaefer [a,*], Mark Walker [b], Douglass M. Turnbull [a], Robert W. Taylor [a,*]

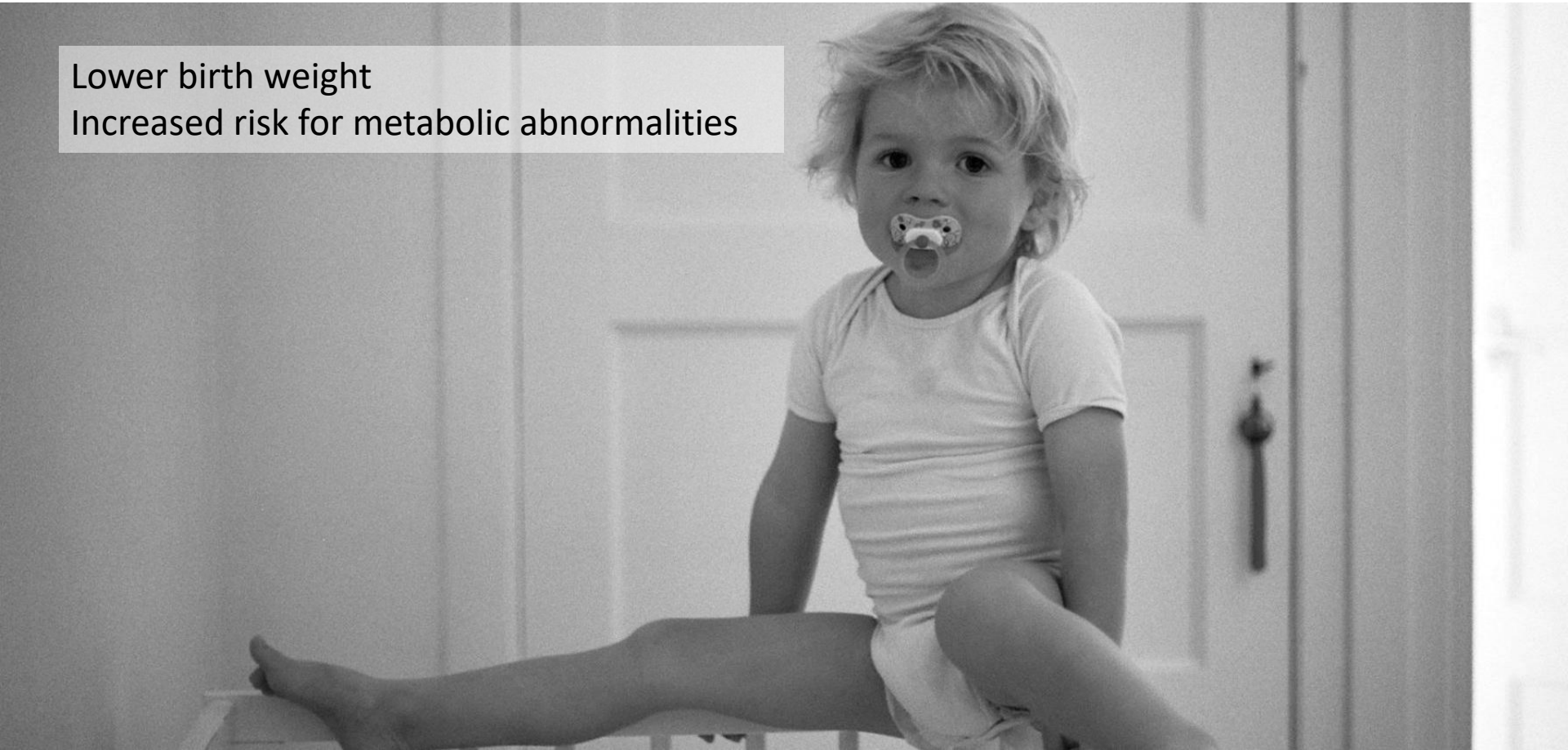
Diabetes **Hypoadrenalism**

Hypoparathyroidism

Hypogonadism

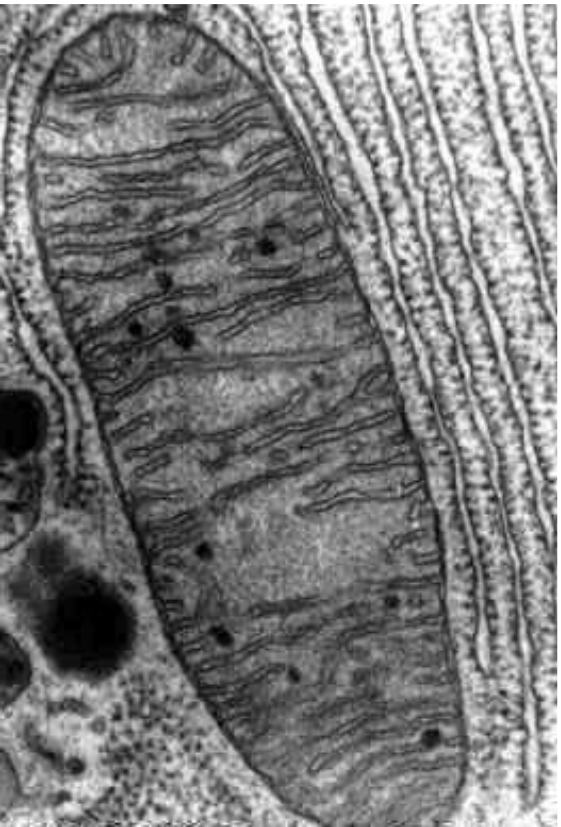
Gibson et al., 2008
Kleist-Retzow et al., 2003

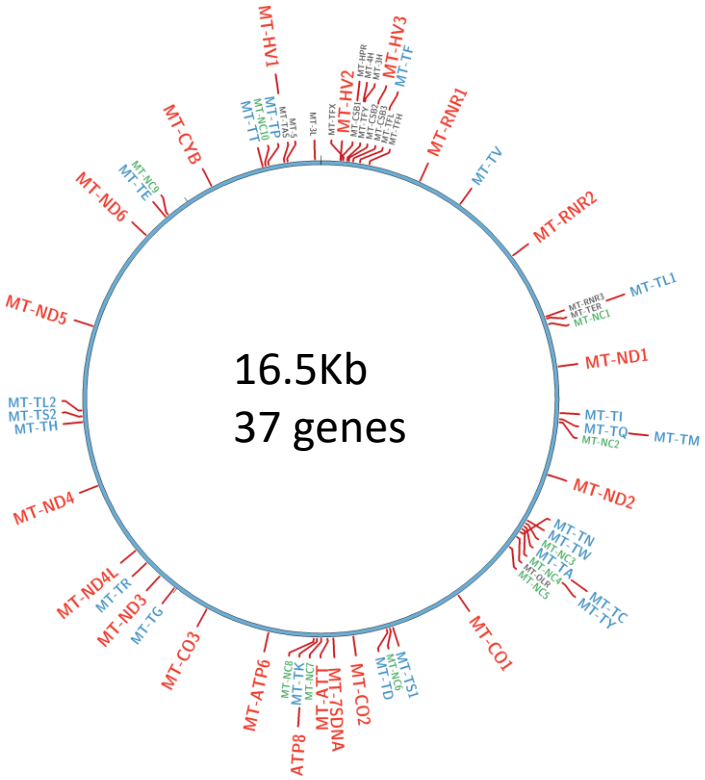
Over ten million ART children



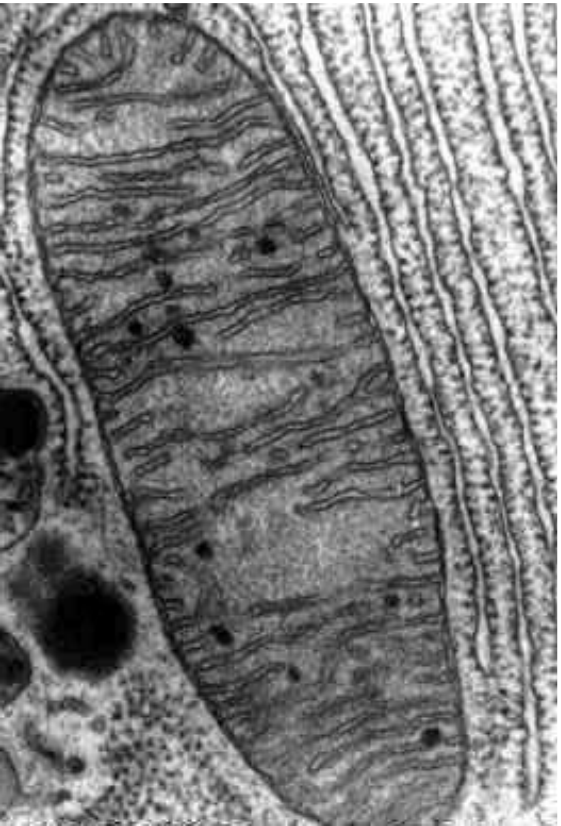
Lower birth weight
Increased risk for metabolic abnormalities

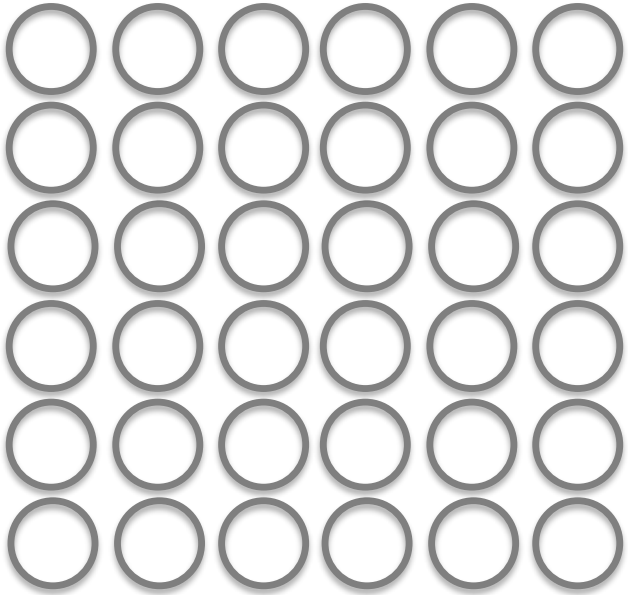
Hypothesis: an increased mitochondrial DNA mutation load could cause these differences





The mtDNA can be homoplasmic or heteroplasmic





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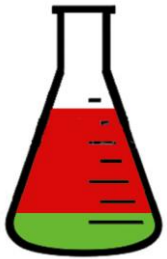

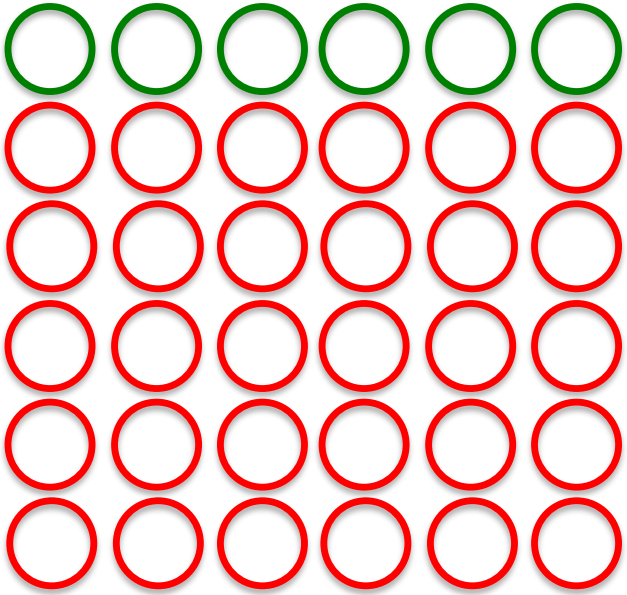

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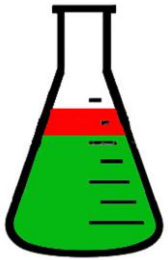

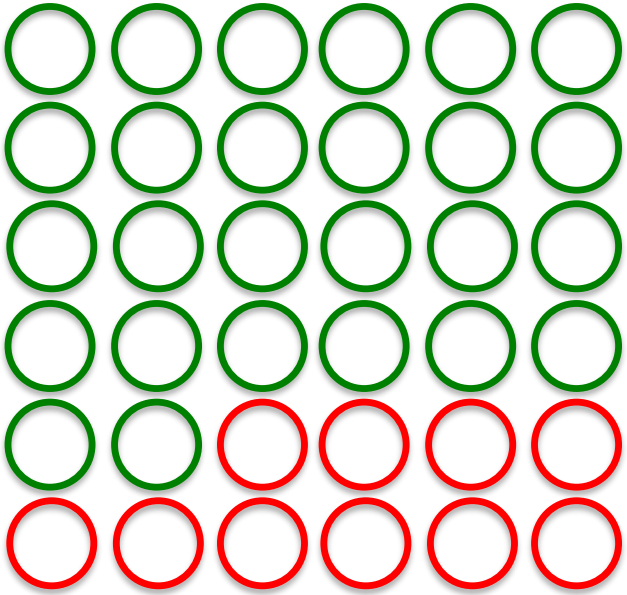

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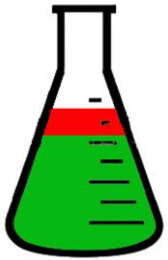
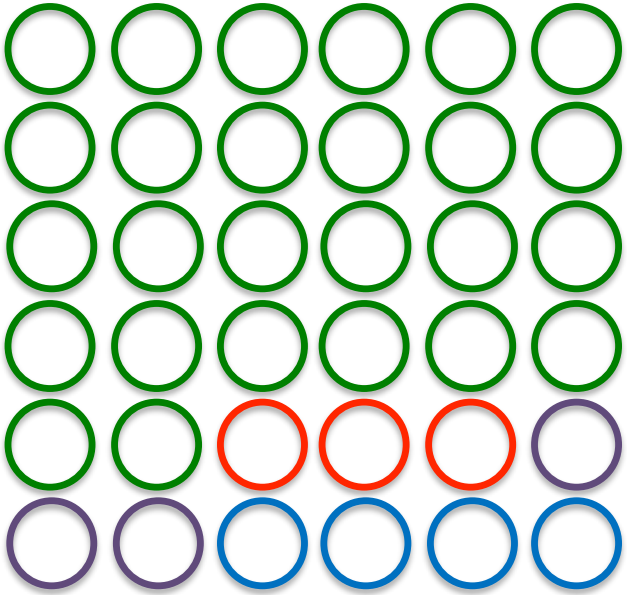
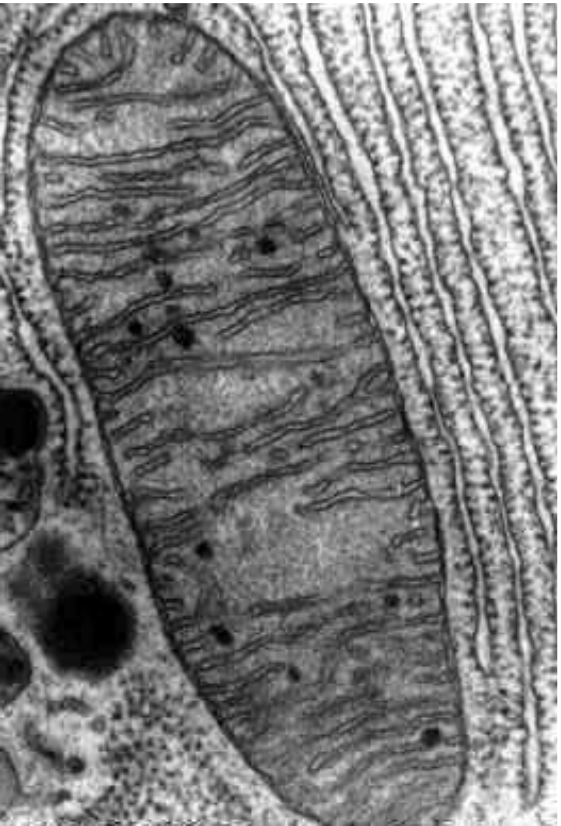




Hypothesis: an increased mitochondrial DNA mutation load could cause the differences seen in ART children



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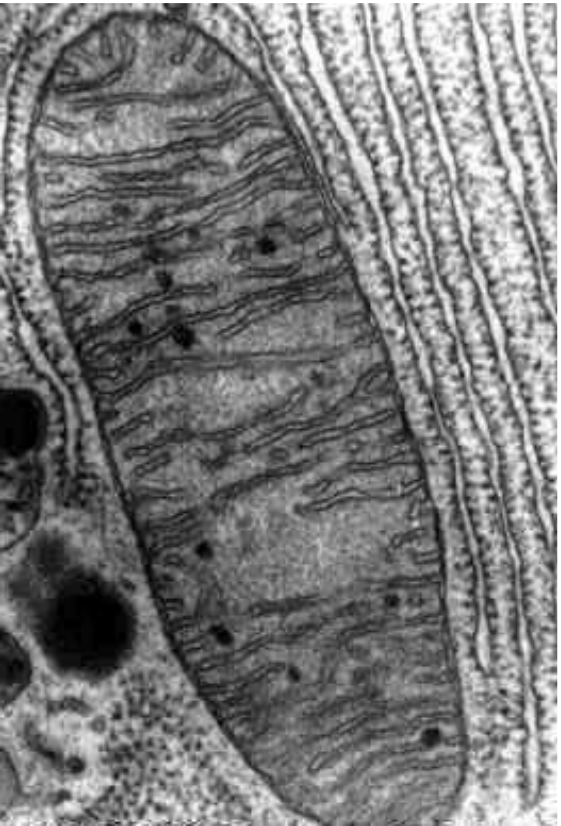

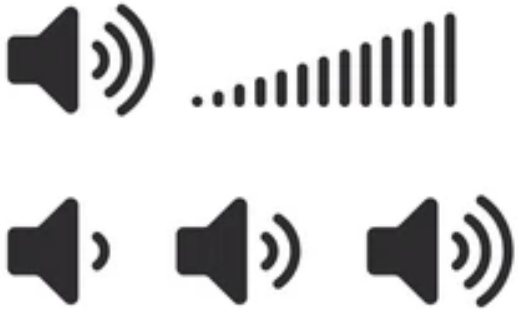

Association to ageing or ovarian stimulation?

Molecular Human Reproduction Vol.11, No.11 pp. 785–789, 2005
Advance Access publication December 22, 2005 doi:10.1093/molehr/gah227

Mitochondrial DNA deletions in rhesus macaque oocytes and embryos

T.C.Gibson[1], H.M.Kubisch[2] and C.A.Brenner[1,3]

Reproduction, Fertility and Development, 2012, **24**, 945–952
http://dx.doi.org/10.1071/RD11212

Impaired mitochondrial function in murine oocytes is associated with controlled ovarian hyperstimulation and *in vitro* maturation

Hongshan Ge[A,B,D], Theodore L. Tollner[C], Zhen Hu[B], Mimi Da[A], Xiaohe Li[A], HeQin Guan[B], Dan Shan[B], Jieqiang Lu[A], Changjiang Huang[A,B] and Qiaoxiang Dong[A,B,D]

Molecular Human Reproduction, Vol.22, No.4 pp. 261–271, 2016
Advanced Access publication on January 20, 2016 doi:10.1093/molehr/gaw003

molecular human reproduction ORIGINAL RESEARCH

Oocyte mitochondrial deletions and heteroplasmy in a bovine model of ageing and ovarian stimulation

Elizabeth R. Hammond[1,†], Mark P. Green[2,3,4,†], Andrew N. Shelling[1], Martin C. Berg[2], John C. Peek[5], and Lynsey M. Cree[1,5,*]

Repeated Ovarian Stimulations Induce Oxidative Damage and Mitochondrial DNA Mutations in Mouse Ovaries

HSIANG-TAI CHAO,[a] SHU-YU LEE,[b] HORNG-MO LEE,[c] TIEN-LING LIAO,[b] YAU-HUEI WEI,[d] AND SHU-HUEI KAO[b]

Mitochondrial dysfunction may link to infertility


J Assist Reprod Genet (2011) 28:773–783
DOI 10.1007/s10815-011-9588-7

REVIEW

The contribution of mitochondrial function to reproductive aging

Yaakov Bentov · Tetyana Yavorska · Navid Esfandiari · Andrea Jurisicova · Robert F. Casper

Oocyte competence

- mtDNA copy number
- Membrane potential

mtDNA disease and infertility

- POLG may influence the age of menopause
- Deletions and sperm motility
- Variants and POI


CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2017: 91: 199–207
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Published by John Wiley & Sons Ltd
CLINICAL GENETICS
doi: 10.1111/cge.12896

Invited Review

Genetics of mitochondrial dysfunction and infertility

Demain L.A.M., Conway G.S., Newman W.G. Genetics of mitochondrial dysfunction and infertility.
Clin Genet 2017: 91: 199–207. © John Wiley & Sons A/S. Published by

L.A.M. Demain[a,b], G.S. Conway[c,d] and W.G. Newman[a,b]


Molecular Human Reproduction, Vol.19, No.8 pp. 486–494, 2013
Advanced Access publication on April 23, 2013 doi:10.1093/molehr/gat026

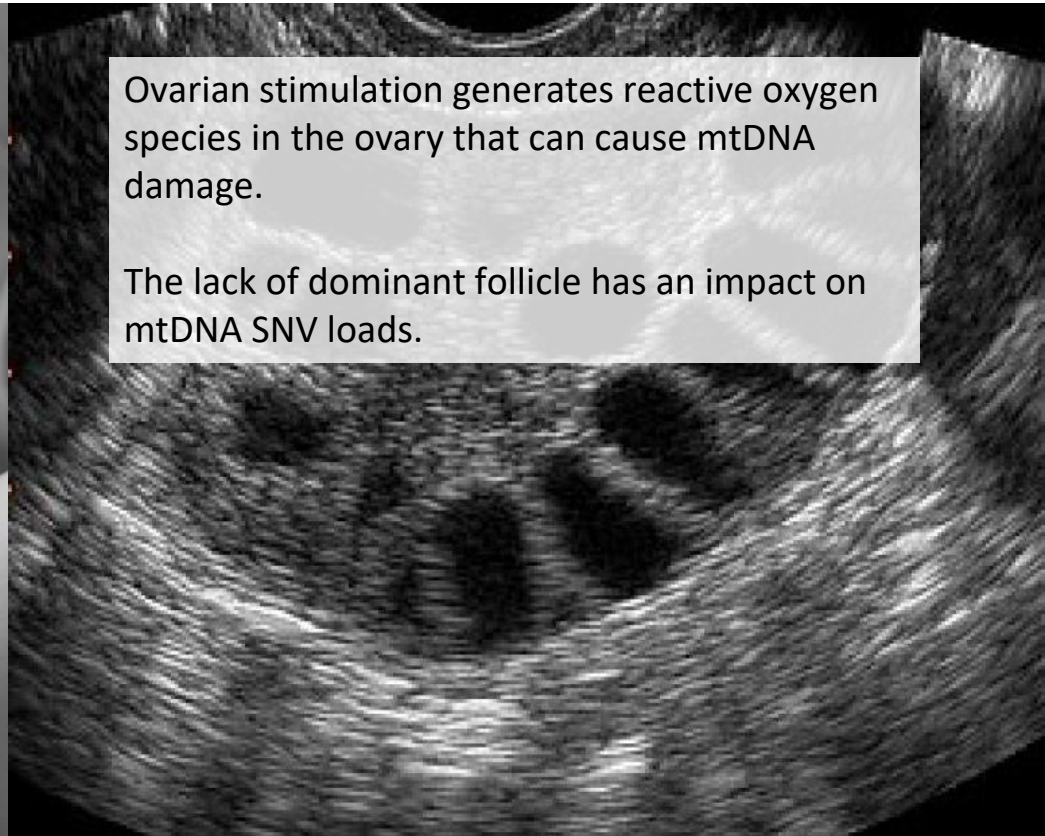
MHR NEW RESEARCH HORIZON *Review*

Maternal obesity, infertility and mitochondrial dysfunction: potential mechanisms emerging from mouse model systems

Natalia M. Grindler and Kelle H. Moley*

Hypothesis: female infertility and/or ovarian stimulation
can be linked to mtDNA mutations which are transmitted to the children

Women with a modestly increased mutation load show reduced fertility.



Ovarian stimulation generates reactive oxygen species in the ovary that can cause mtDNA damage.

The lack of dominant follicle has an impact on mtDNA SNV loads.

Do ART individuals carry a different mtDNA variant landscape?

Analysis of the mtDNA of 181 control and 270 ART individuals
Mapped all variants:

- homoplasmies: haplogroups and beyond
- heteropasmies

Mertens et al., 2024, Nature Communications

Do ART individuals carry a different mtDNA variant landscape?

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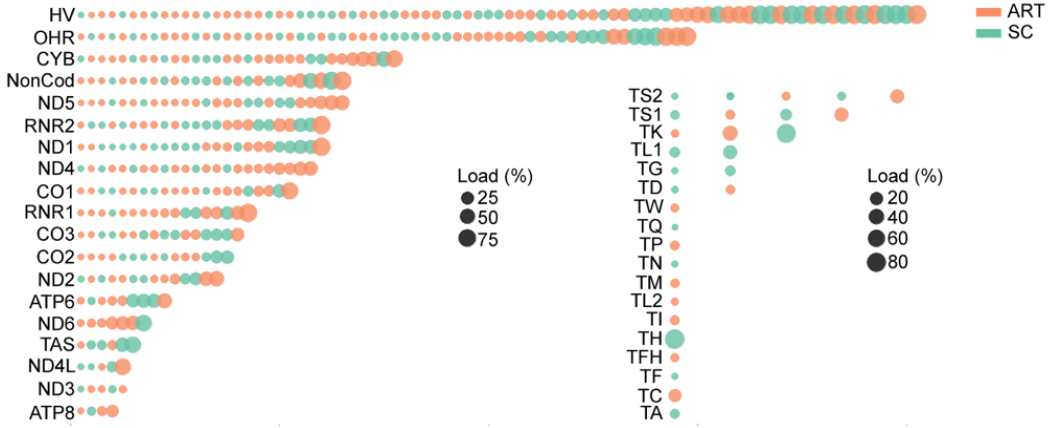

1- HV: 60%, CO3: 5%
2- RNR2: 3%
3- no variants...

Mertens et al., 2024, Nature Communications

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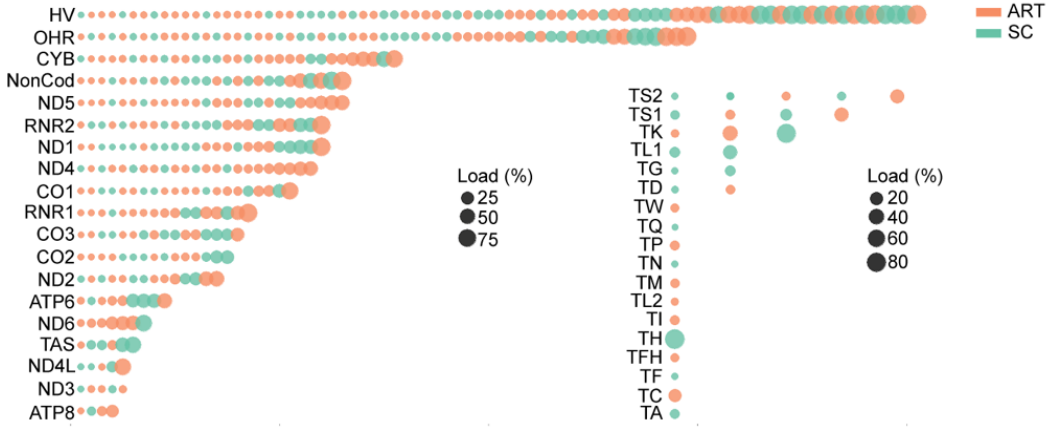

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16.000-dimensional table
37-dimensional table

Mertens et al., 2024, Nature Communications

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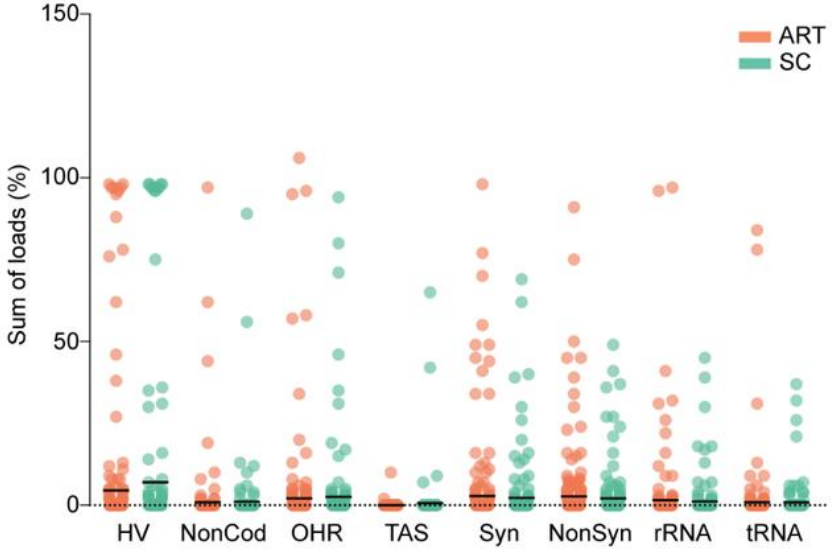

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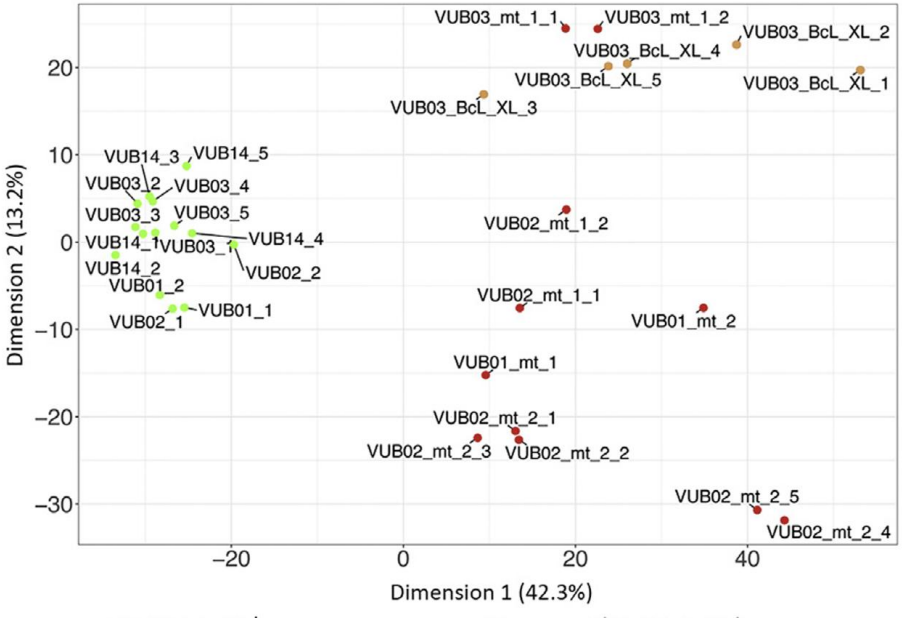

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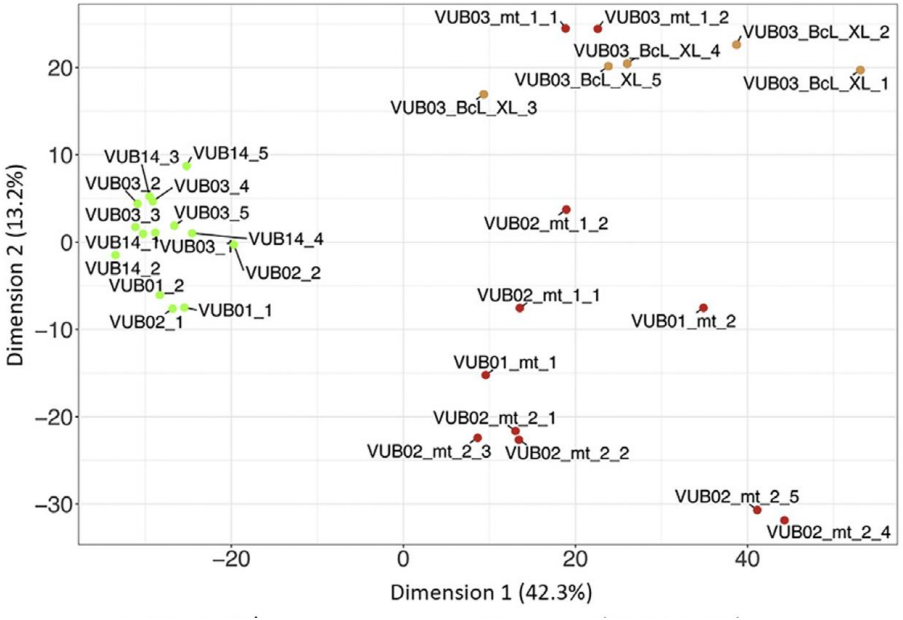

	Factor/Dimensions			
	1	2	3	4
HV	0.003	-0.203	-0.131	0.835
Non-coding	0.052	-0.067	0.737	-0.158
OHR	-0.009	-0.249	-0.194	-0.506
TAS	0.797	-0.230	-0.046	-0.069
Synonymous	0.668	0.356	0.016	0.093
Non-synonymous	0.121	0.713	0.098	0.099
rRNA	-0.114	0.554	-0.205	-0.104
tRNA	-0.081	-0.001	0.638	0.198

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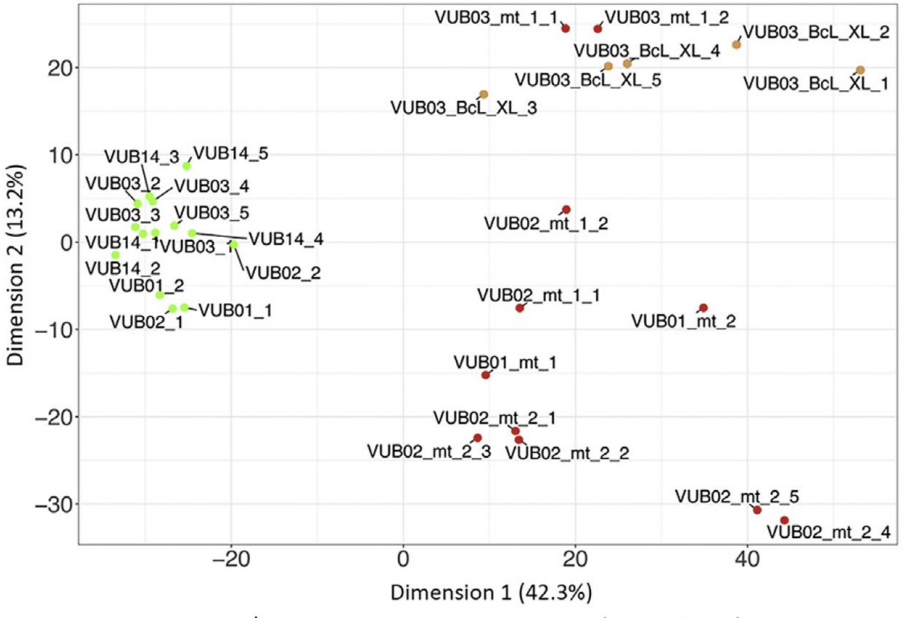

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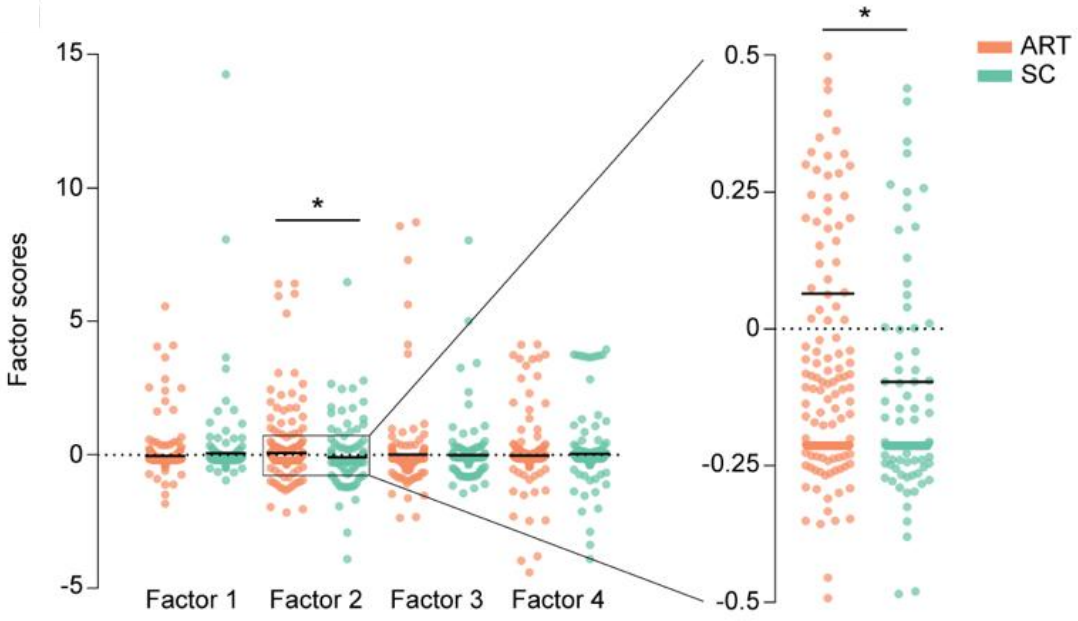
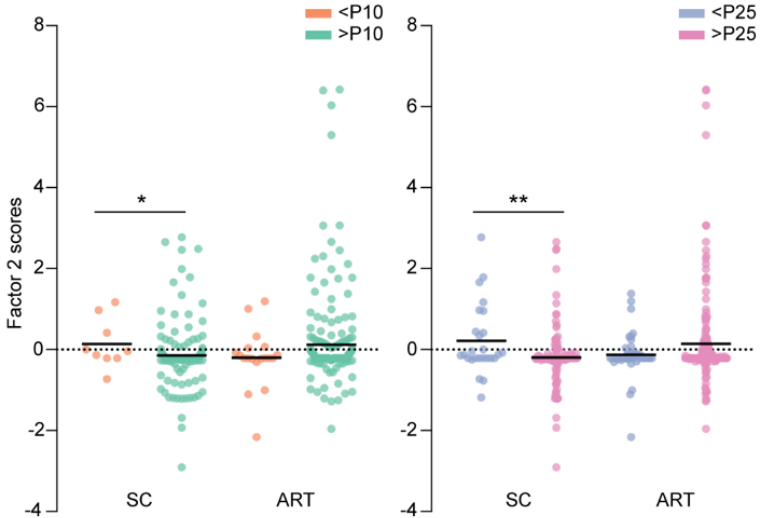
Do ART individuals carry a different mtDNA variant landscape? **A bit**



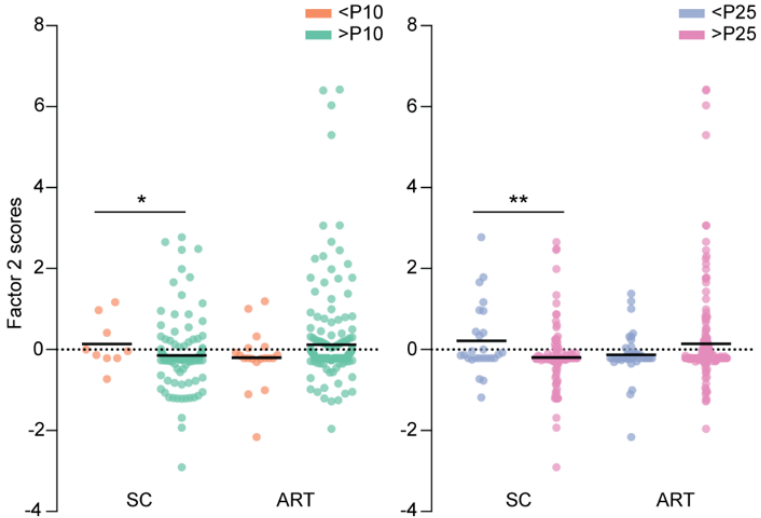
Do these differences associate to birthweight?

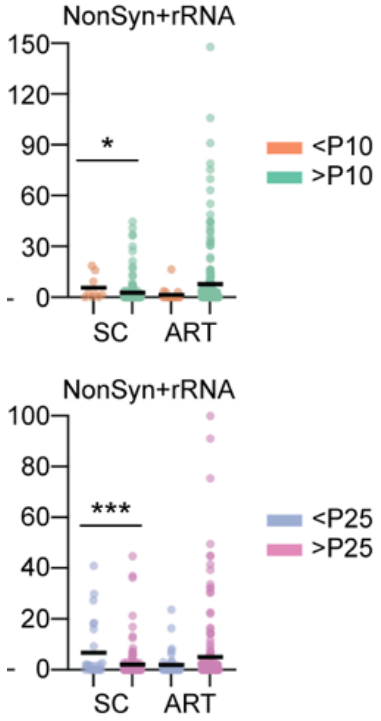


<P10 is about <2.5Kg, <P25 is about <3Kg, mean about 3.4Kg

Do these differences associate to birthweight?

Yes, but apparently only in SC





<P10 is about <2.5Kg, <P25 is about <3Kg, mean about 3.4Kg

What is happening with the ART children?

Old UZBrussel and Cook medium have a strong impact on BW

Further evidence that culture media affect perinatal outcome: findings after transfer of fresh and cryopreserved embryos FREE

Ewka C. Nelissen ✉, Aafke P. Van Montfoort, Edith Coonen, Josien G. Derhaag, Joep P. Geraedts, Luc J. Smits, Jolande A. Land, Johannes L. Evers, John C. Dumoulin

Human Reproduction, Volume 27, Issue 7, July 2012, Pages 1966–1976,
https://doi.org/10.1093/humrep/des145
Published: 02 May 2012 **Article history** ▾

Do these differences associate to birthweight?

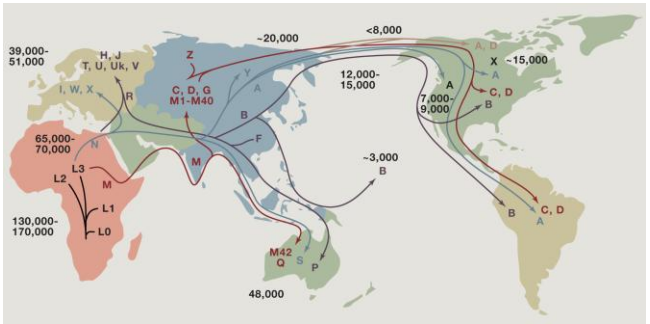
Heteroplasmies

- non-synonymous and rRNA coding variants

Do these differences associate to birthweight?

Heteroplasmies
- non-synonymous and rRNA coding variants

Homoplasmies
- tRNA variants
- Haplogroups



Do these differences associate to birthweight?

Yes, especially for <P25, with odds 2.974

Heteroplasmies

- non-synonymous and rRNA coding variants

Homoplasmies

- tRNA variants
- Haplogroups

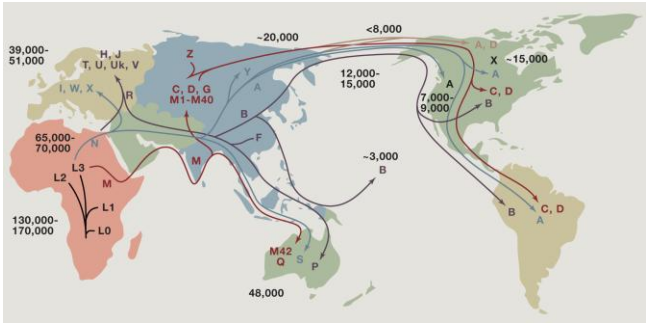
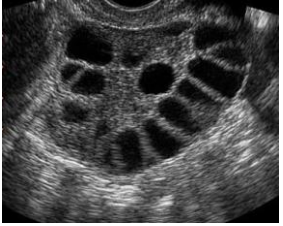


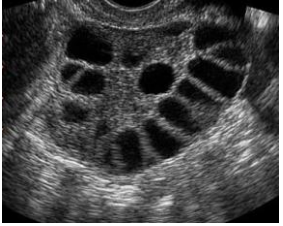
Table 2 | Binary logistic regression to predict a birthweight under the 10th or 25th percentile in SC individuals and ART individuals exposed to Vitrolife® culture medium

	Exp(B)	95% C.I. for Exp(B)	Significance
P10 in SC and ART Vitrolife®			
Smoking	7.211	1.552–33.496	0.012
Pregnancy hypertension	14.045	1.185–166.410	0.036
Haplogroup K1	4.952	1.075–22.813	0.040
tRNA homoplasmies	7.518	1.850–30.553	0.005
Heteroplasmic non-synonymous and rRNA variants	2.180	642–7.400	0.212
P25 in SC and ART Vitrolife®			
Maternal age	1.129	1.036–1.231	0.006
Haplogroup I	5.774	1.125–29.624	0.035
Haplogroup J	2.248	0.783–6.455	0.132
Haplogroup T	0.146	0.018–1.165	0.069
tRNA homoplasmies	2.405	0.796–7.264	0.120
Heteroplasmic non-synonymous and rRNA variants	2.974	1.439–6.2144	0.003



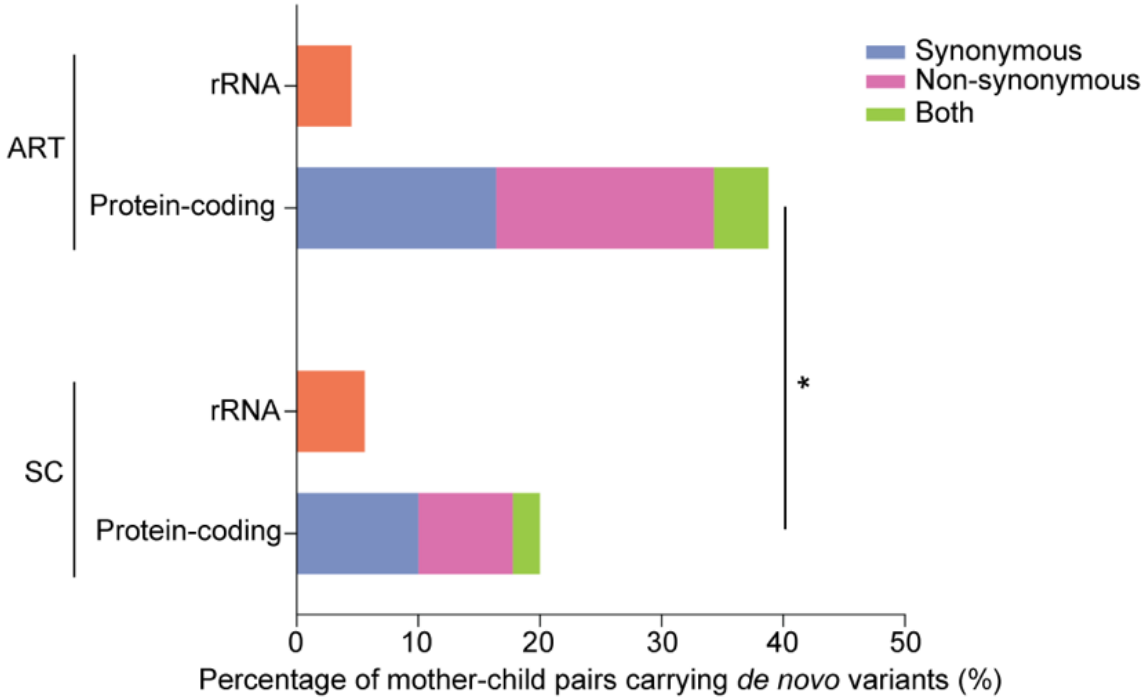
Where are these heteroplasmic variants coming from?

Study the mtDNA of 157 mother-child pairs

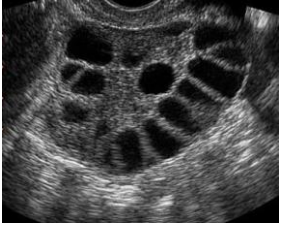


Where are these heteroplasmic variants coming from?

ART children carry more *de novo* protein and rRNA coding variants



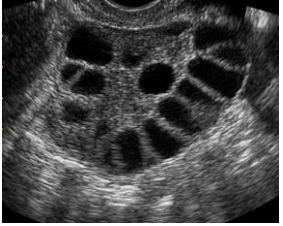
N=157



Where are these variants coming from?

113 oocytes donated in natural menstrual cycles and after OS from the same donors

157 mother-child pairs



Where are these variants coming from?

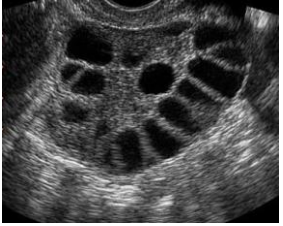
Maternal ageing and controlled ovarian stimulation

113 oocytes donated in natural menstrual cycles and after OS from the same donors

157 mother-child pairs

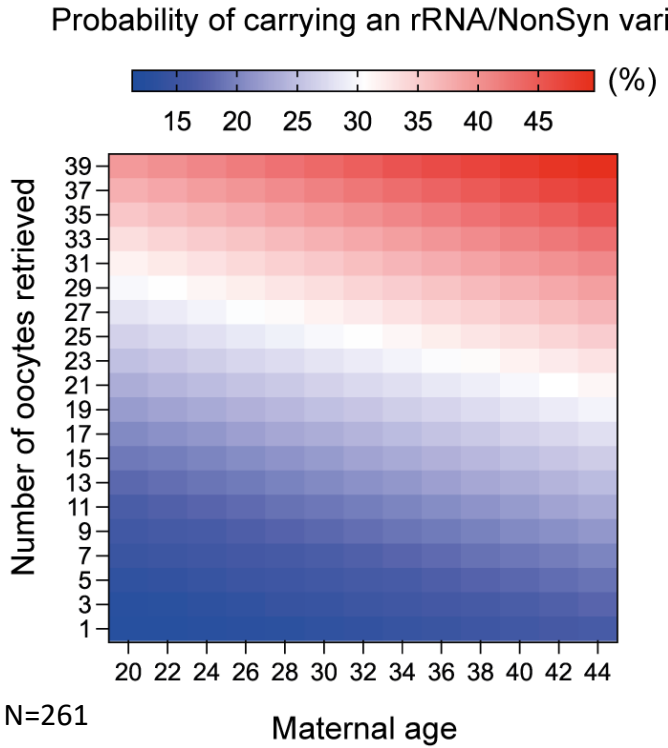
Table 5 | Generalized linear model regressions with Poisson distribution on de novo variants in mother-child pairs and oocytes

	(B)	95% Wald C.I.	Significance
Total number of de novo variants in mother-child pairs and oocytes (*N* = 170)			
Maternal age	0.037	0.024–0.050	<0.001
rRNA de novo variants in mother-child pairs and oocytes (*N* = 170)			
Maternal age	0.054	0.10–0.097	0.015
Total number of de novo variants in oocytes (*N* = 113)			
Maternal age	0.079	0.031–0.127	0.001
Oocytes retrieved	0.017	−0.004–0.037	0.110
Total number of de novo non-synonymous and rRNA variants in oocytes (*N* = 113)			
Maternal age	0.033	−0.003–0.068	0.074
Oocytes retrieved	0.021	0.006–0.036	0.007



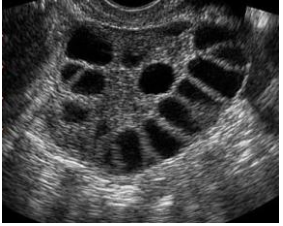
Where are these variants coming from?

Maternal ageing and controlled ovarian stimulation



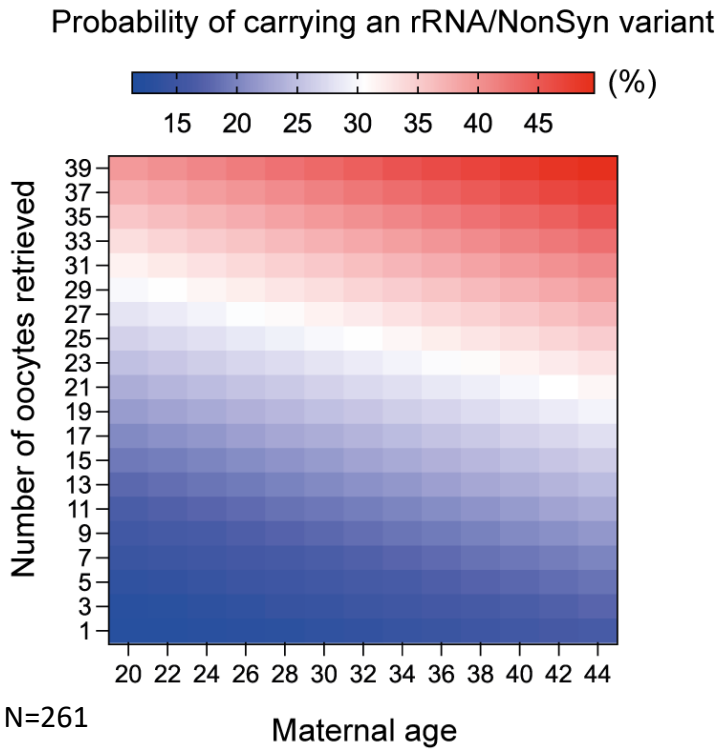
N=261

Van Der Kelen & Li Piani et al., Human Reproduction Open, 2025



Where are these variants coming from?

Maternal ageing and controlled ovarian stimulation

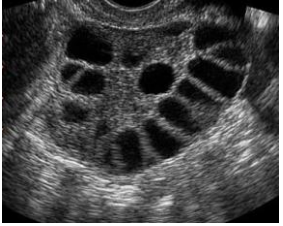


N=261

To have 1 euploid embryo in women aged 40 years, 19 oocytes are required (Esteves *et al.*, 2019)

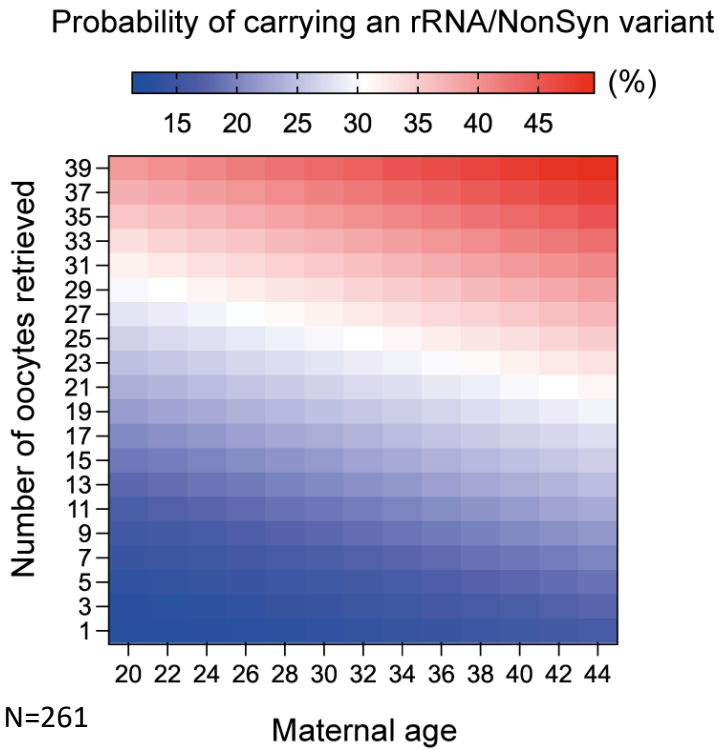
In this range, the likelihood for an oocyte to carry a potentially harmful heteroplasmic variant is 25%

Van Der Kelen & Li Piani et al., Human Reproduction Open, 2025



Where are these variants coming from?

Maternal ageing and controlled ovarian stimulation



N=261

To have 1 euploid embryo in women aged 40 years, 19 oocytes are required (Esteves *et al.*, 2019)

In this range, the likelihood for an oocyte to carry a potentially harmful heteroplasmic variant is 25%

This is 1.5-times higher than the general population (15.6%, Wei *et al.*, 2019)

Van Der Kelen & Li Piani et al., Human Reproduction Open, 2025

Take home messages

1. rRNA and non-synonymous variants
   associate with lower birthweight percentiles

2. They occur more frequently in ART individuals due to
   1. *de novo* mutagenesis associated with maternal aging
   2. ovarian stimulation-induced large oocyte cohorts

3. Association ≠ causation: more research needed!
   1. currently looking into perinatal outcomes vs ART treatment factors

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