
MARCH 19 - 23
PCRS 2025
PACIFIC WAVES - EXPLORING SCIENTIFIC FRONTIERS IN AN EVOLVING SOCIETY
INDIAN WELLS, CA
PACIFIC COAST
REPRODUCTIVE
SOCIETY

Genetic Testing Panels for IVF Failure:

The Answer We've Been Waiting For?

Meaghan Doyle, MS, LCGC (she/her)

Licensed Certified Genetic Counselor

Founder, DNAide Genetic Counselling

Disclosures

- Nothing to Disclose

Needs Assessment Statement and Expected Learning Outcomes

- At the end of this session participants should be able to:
  - summarize the nonsyndromic phenotypes currently associated with single gene causes of IVF failure
  - evaluate the benefits, risks, and limitations of clinical genetic testing for genes related to nonsyndromic causes of IVF failure
  - argue for the importance of pre- and post-test genetic counseling when considering genetic testing for nonsyndromic causes of IVF failure

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Outline

- Current landscape of genetic testing for infertility
- Introduction to gene panels
- Examples of gene discovery
- Clinical utility of gene panels for IVF failure
- Genetic Counseling
- Q&A

Language

- Sperm-factor
- Egg-factor
- People with testes
- People with ovaries
- People with a uterus/person carrying a pregnancy
- Language used in the literature
- Male/female

Current Landscape

Genetic Testing for Infertility

Standard Genetic Testing

Sperm-Factor	Egg-factor
• Karyotype • *CFTR* • Y Chromosome Microdeletion	• Karyotype • *FMR1*

Standard Genetic Testing

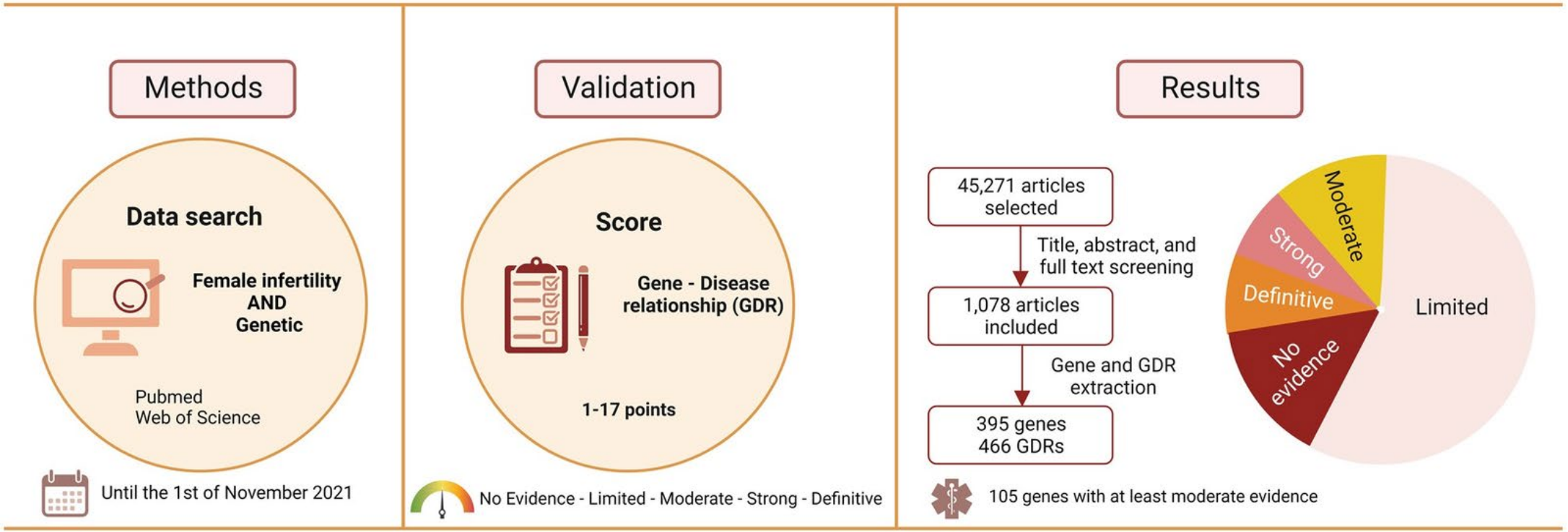
Sperm-Factor	Egg-factor
• Karyotype • *CFTR* • Y Chromosome Microdeletion	• Karyotype • *FMR1*

Carrier screening is designed to assess risk to future children, not diagnose patients

JOURNAL ARTICLE

A systematic review and evidence assessment of monogenic gene–disease relationships in human female infertility and differences in sex development FREE

105 genes with at least moderate evidence of a relationship with female infertility/DSDs



What are gene panels?

- Genetic test
- Analyze many genes at one time related to indication for testing
- May be predesigned by the testing laboratory
- Customization options may be available

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Benefits of gene panels

- Typically same cost and turnaround time of testing a single gene
- Helpful when phenotype overlaps with many genetic etiologies

Downsides of gene panels (for IVF failure)

- More on this later…

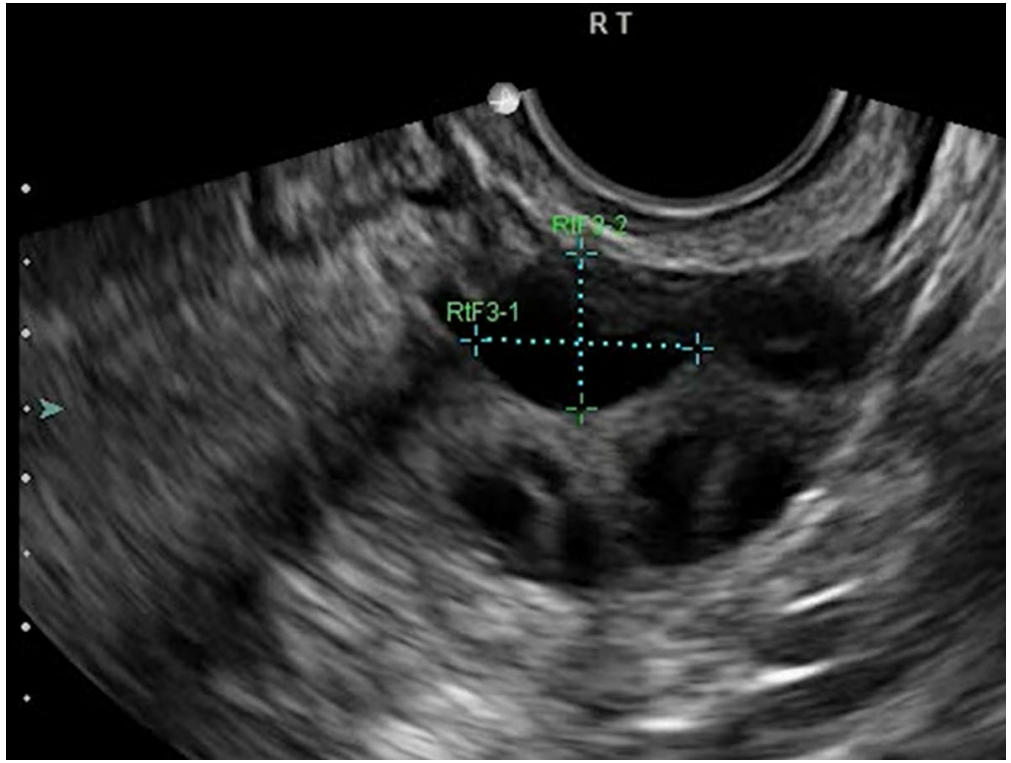
Gene Discovery

Infertility and IVF Failure

Empty Follicle Syndrome

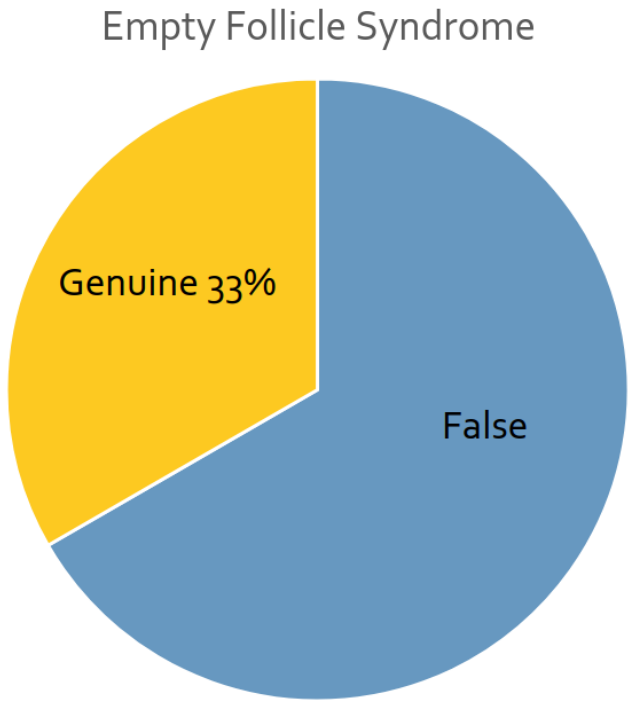
Follicles and COCs

- Follicles: fluid-filled structures in the ovaries where eggs develop
- COCs: Cumulus-oocyte complexes
  - Extracted from follicular fluid during egg retrieval



Empty Follicle Syndrome (EFS)

- False EFS: failure to take trigger medication correctly
- Genuine EFS:
  - Dysfunctional folliculogenesis
  - Ovarian aging
  - Genetic factors



Genuine Empty Follicle Syndrome

REPORT

A Recurrent Missense Mutation in *ZP3* Causes Empty Follicle Syndrome and Female Infertility

Tailai Chen,[1,2,3,7] Yuehong Bian,[1,2,3,7] Xiaoman Liu,[1,2,3] Shigang Zhao,[1,2,3] Keliang Wu,[1,2,3] Lei Yan,[1,2,3] Mei Li,[1,2,3] Zhenglin Yang,[6] Hongbin Liu,[1,2,3] Han Zhao,[1,2,3,*] and Zi-Jiang Chen[1,2,3,4,5,*]

- Large family
- Multiple females with primary infertility
- Variant in *ZP3* identified as the cause

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Proband III-10

- 28yo
- 8 years of primary infertility
- Normal infertility assessment
- IVF #1: 11 follicles >14mm in diameter, normal estradiol level, 11 COCs retrieved
- 9 of 11 had no oocyte

REPORT

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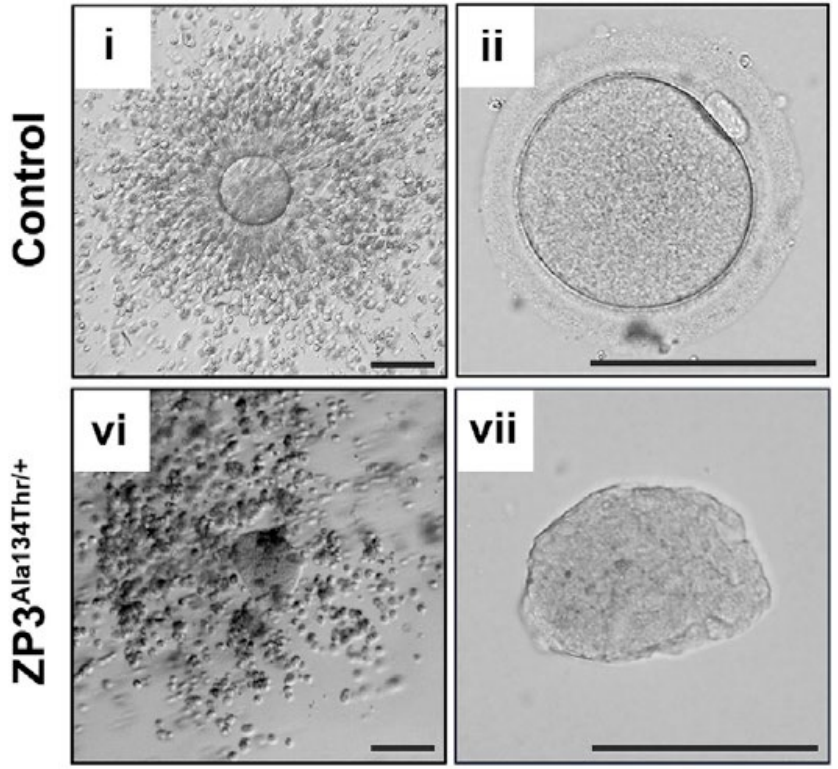

Proband III-10

- IVF #2: 6 follicles >14 mm, normal estradiol
  - 4 empty follicles
  - 2 COCs retrieved, both containing degenerated oocytes lacking a zona pellucida

REPORT

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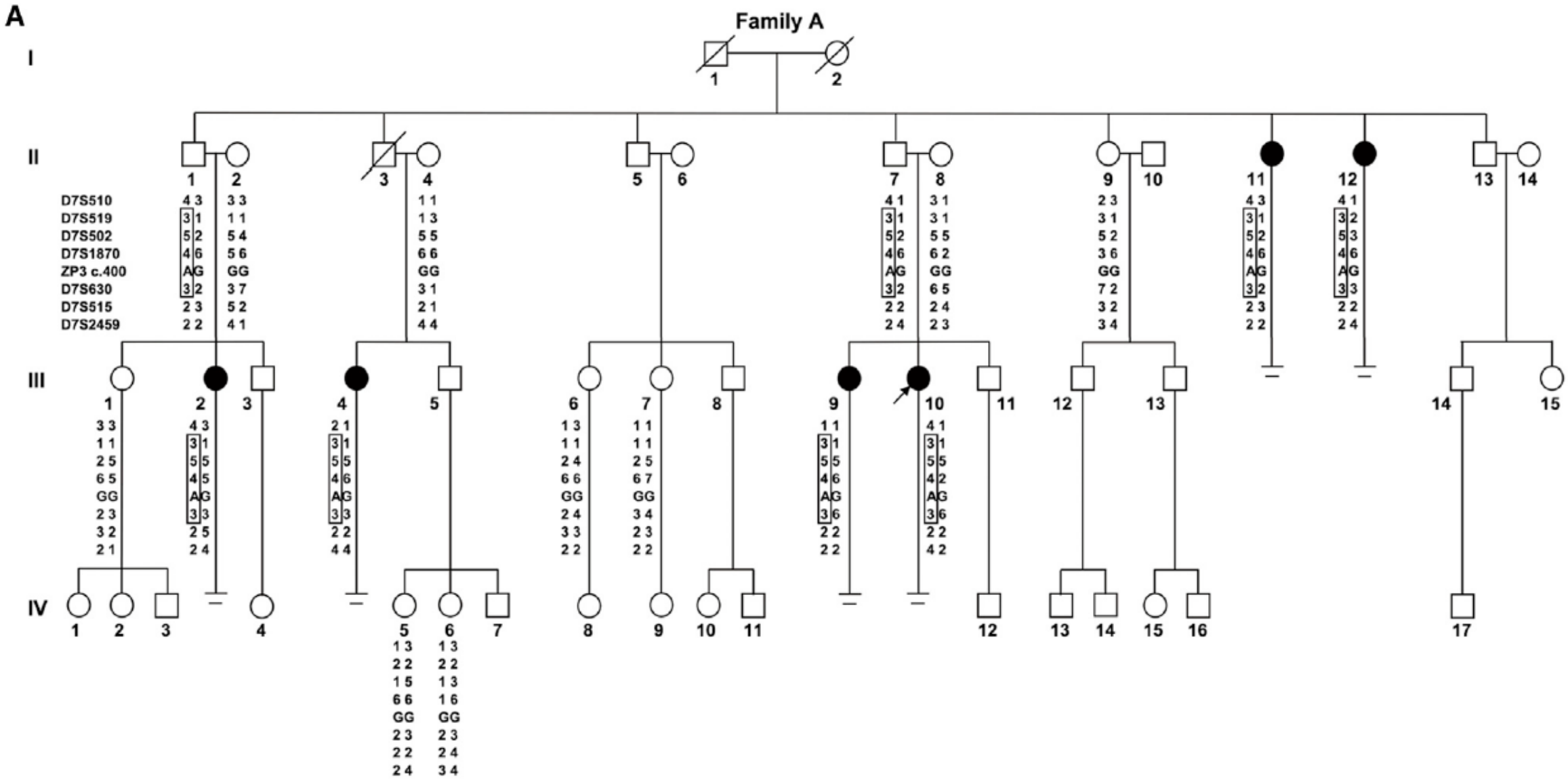
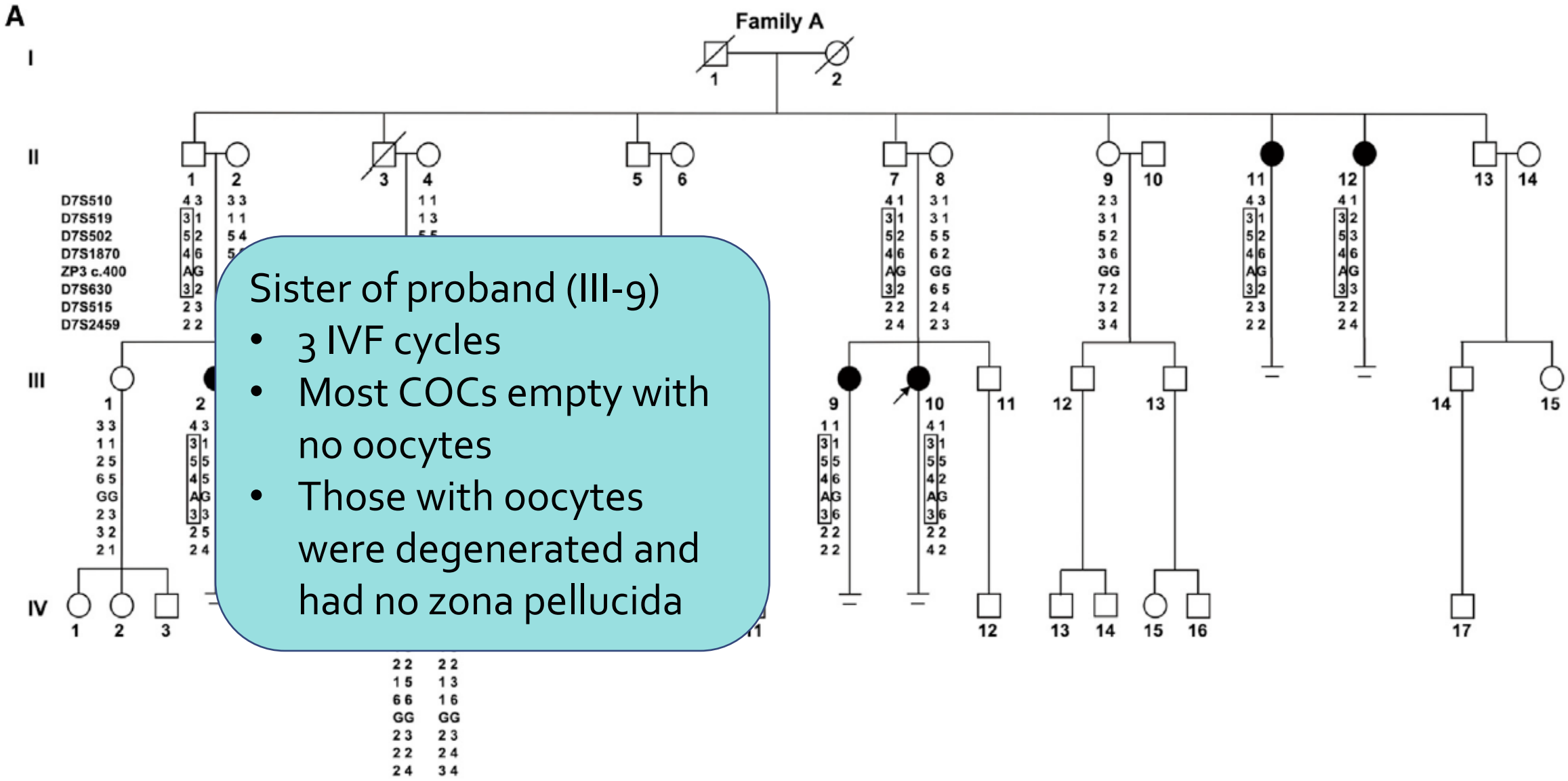
Tailai Chen,[1,2,3,7] Yuehong Bian,[1,2,3,7] Xiaoman Liu,[1,2,3] Shigang Zhao,[1,2,3] Keliang Wu,[1,2,3] Lei Yan,[1,2,3] Mei Li,[1,2,3] Zhenglin Yang,[6] Hongbin Liu,[1,2,3] Han Zhao,[1,2,3,*] and Zi-Jiang Chen[1,2,3,4,5,*]

Proband III-10

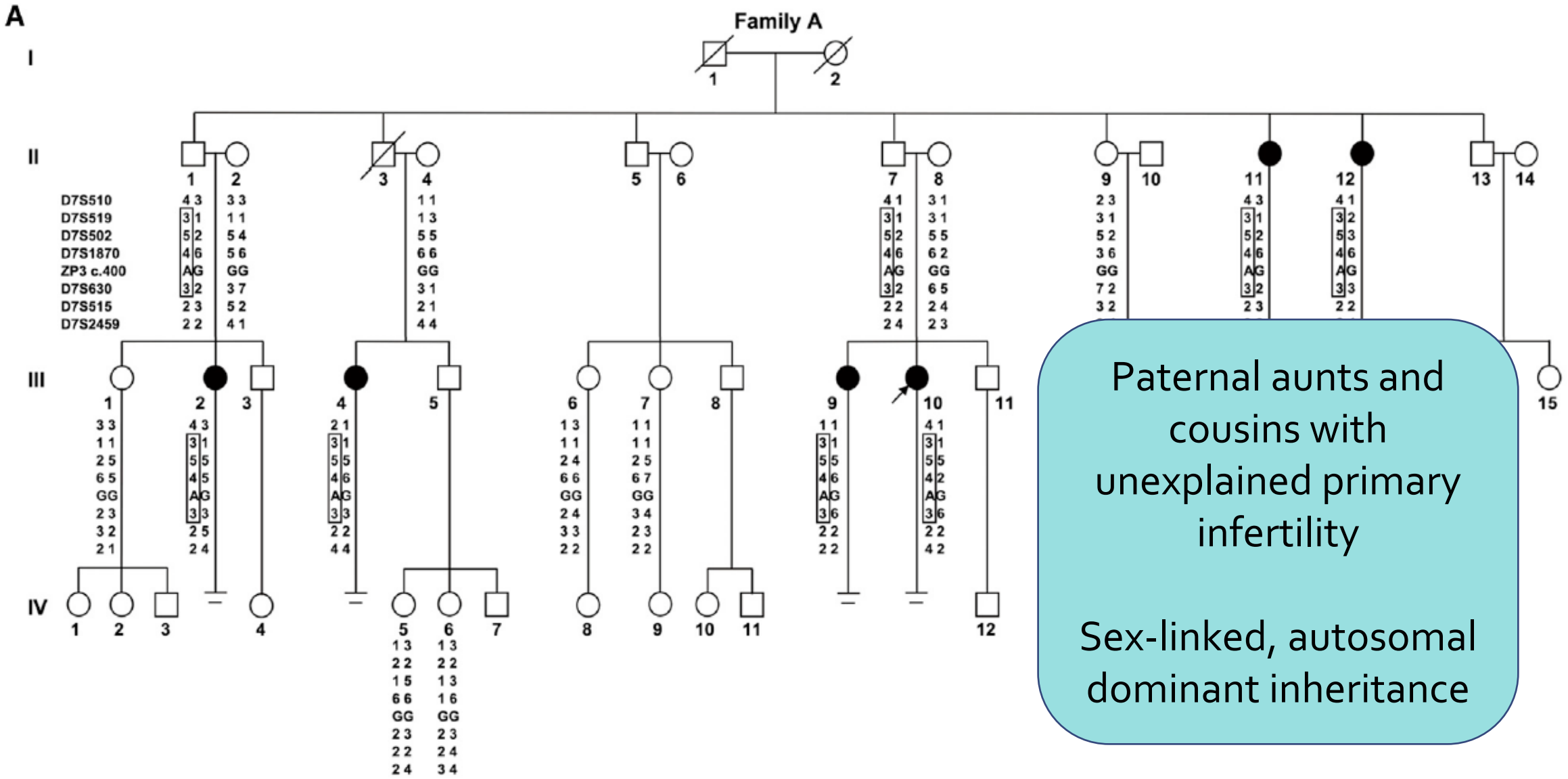
- IVF #3: 7 follicles >14mm, normal estradiol
  - 7 COCs retrieved, all empty


A
Family A
I
II
III
IV
D7S510
D7S519
D7S502
D7S1870
ZP3 c.400
D7S630
D7S515
D7S2459



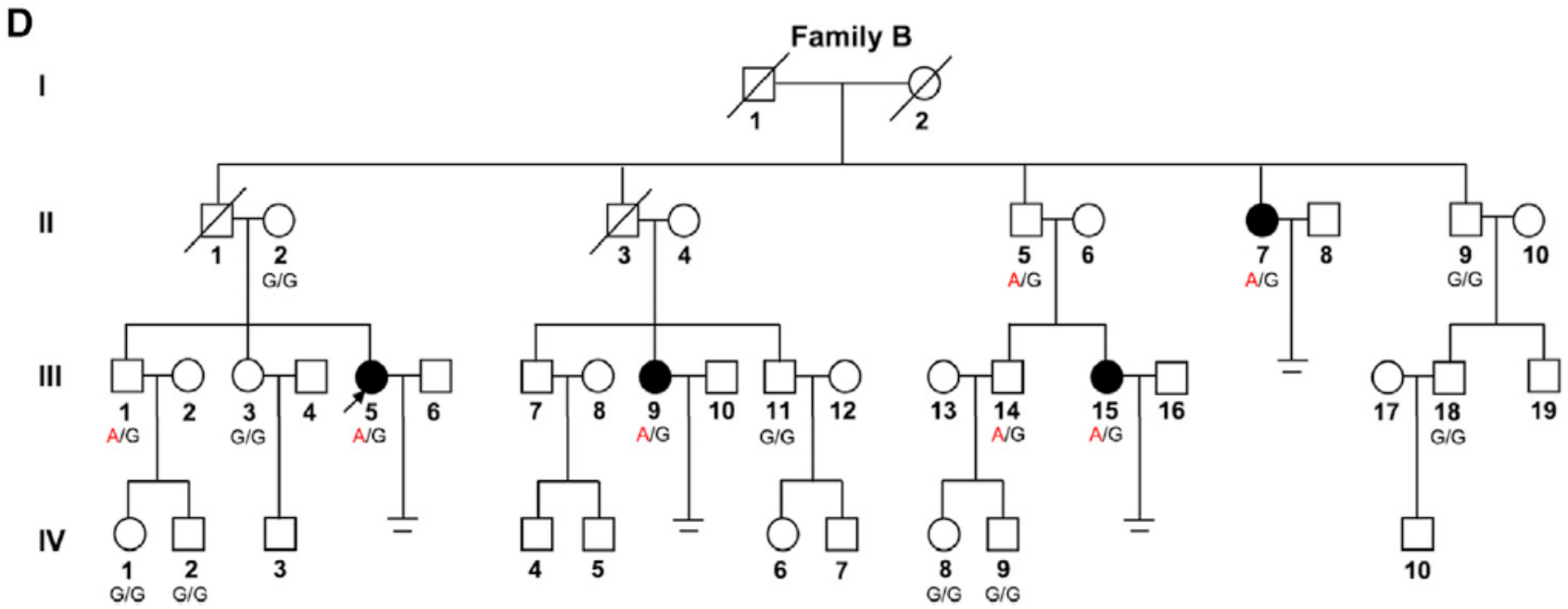
Sister of proband (III-9)

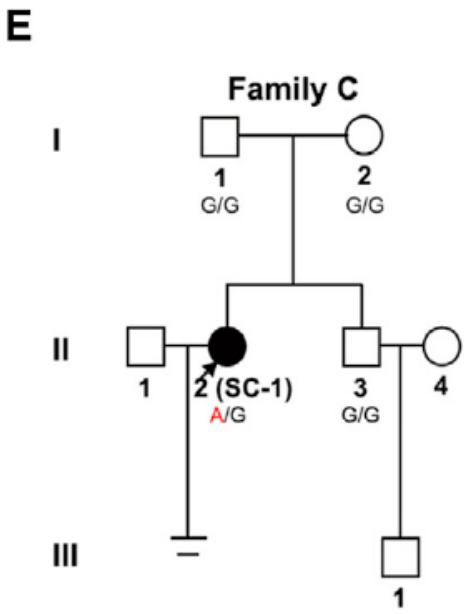
- 3 IVF cycles
- Most COCs empty with no oocytes
- Those with oocytes were degenerated and had no zona pellucida



Paternal aunts and cousins with unexplained primary infertility

Sex-linked, autosomal dominant inheritance





ZP3 sequencing subsequently identified the same variant in 2 other families with the same phenotype

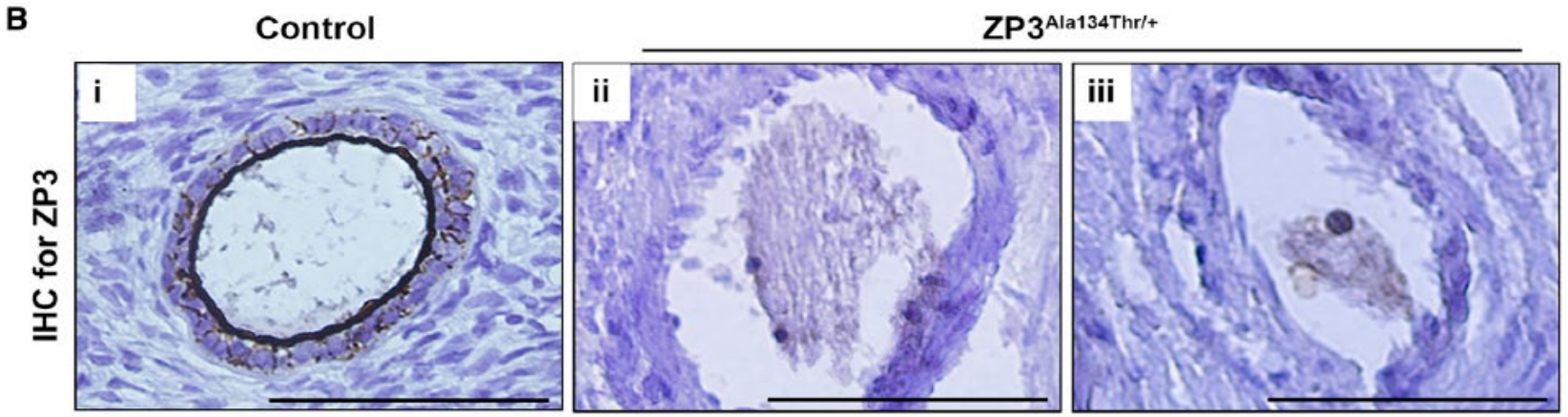
c.400G>A

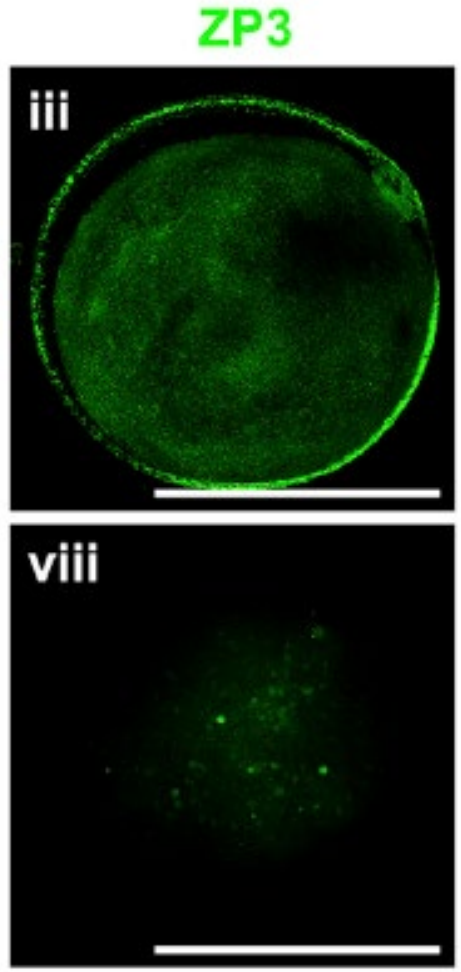
ZP3

- Encodes ZP3 glycoprotein, a component of human zona pellucida (ZP)
  - Only expressed in the oocyte
- ZP is a thick extracellular coat surrounding mammalian oocytes
- ZP functions include:
  - Recognizing gametes
  - Supporting oocyte-follicle cell communication
  - Protecting the oocyte

ZP3

- Ovarian biopsy via laparoscopy prior to ovulation
  - Egg donor as control





ZP3 Phenotype

- Genuine empty follicle syndrome
- Oocyte death
- Abnormal zona pellucida

Genetic Cause Identified

- Significant family history of the same (rare) phenotype
- Multiple rounds of IVF with the same phenotype, not improving with protocol changes

Sperm-factor gene

With possible treatment

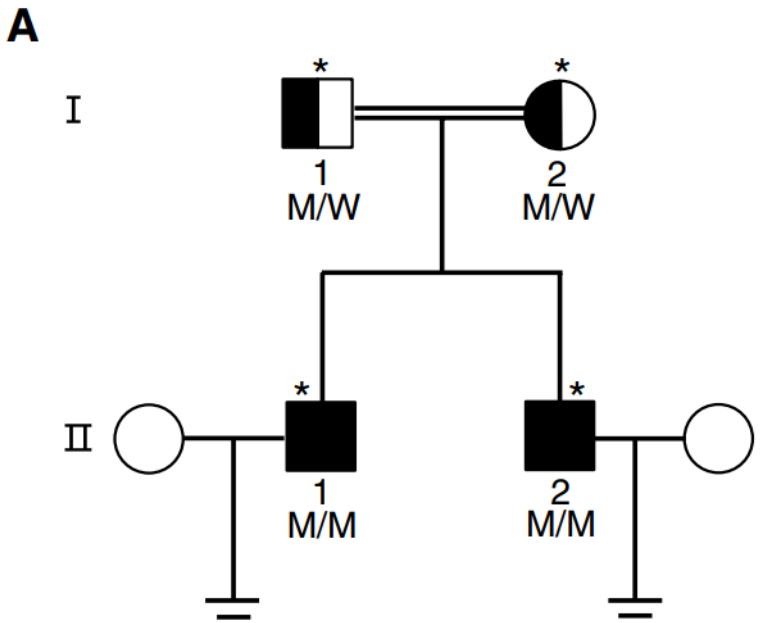
Disruption in *ACTL7A* causes acrosomal ultrastructural defects in human and mouse sperm as a novel male factor inducing early embryonic arrest

Aijie Xin[1,2]*, Ronggui Qu[1]*, Guowu Chen[1]*, Ling Zhang[1,3,4]*, Junling Chen[1], Chengqiu Tao[3], Jing Fu[1], Jianan Tang[2], Yanfei Ru[2], Ying Chen[1], Xiandong Peng[1], Huijuan Shi[2†], Feng Zhang[1,2,3,4,5†], Xiaoxi Sun[1,4,6†]

- Consanguineous family
- Two brothers with unexplained infertility
- Normal semen analysis
- Insemination with conventional IVF resulted in no fertilized oocytes
- ICSI was successful but all embryos arrested at the 4 or 5 cell stage
- Both had healthy live births with donor sperm

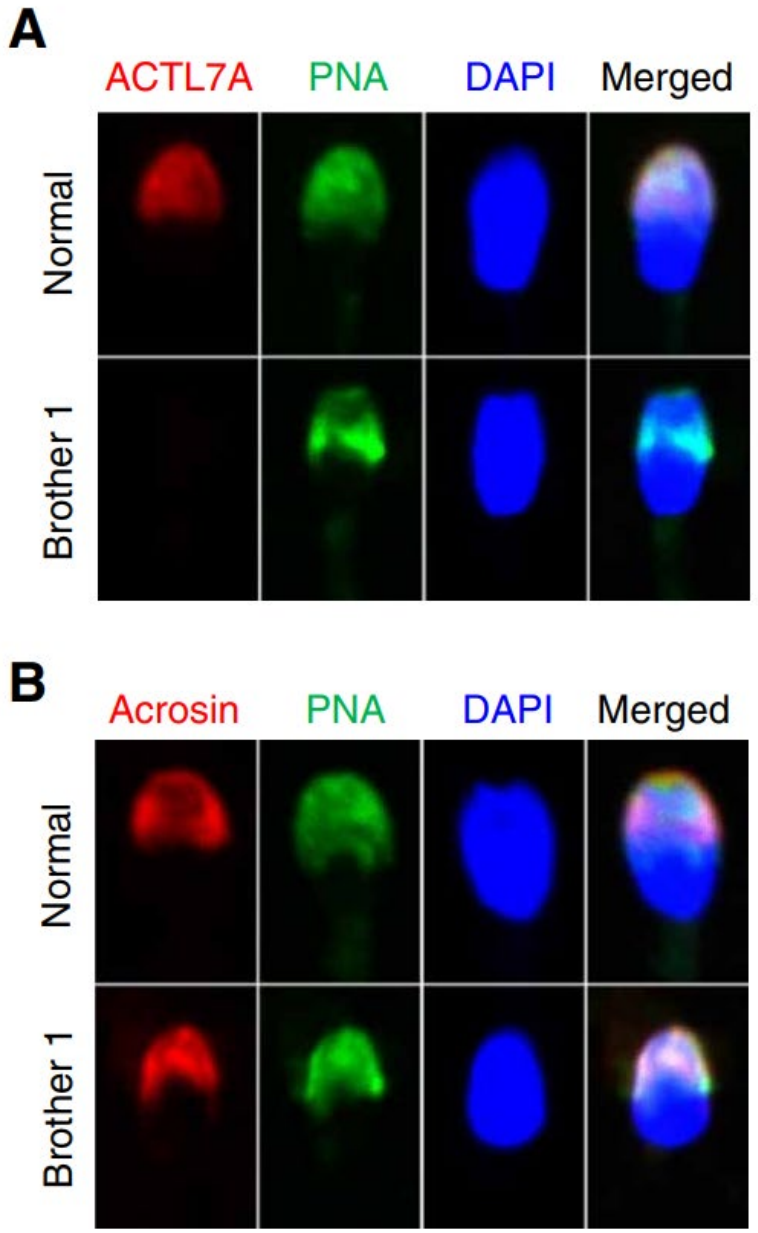
Genetic Evaluation

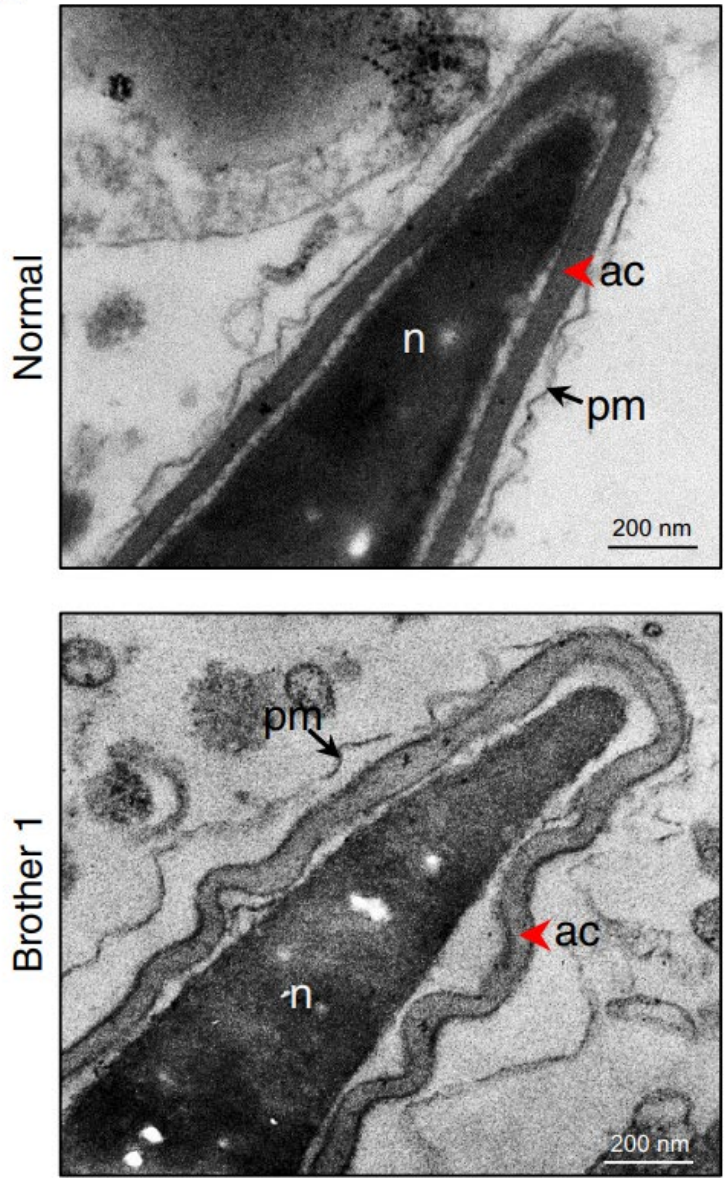
- Whole exome sequencing performed on both brothers and their parents
- Novel homozygous *ACTL7A* variant identified



ACTL7A

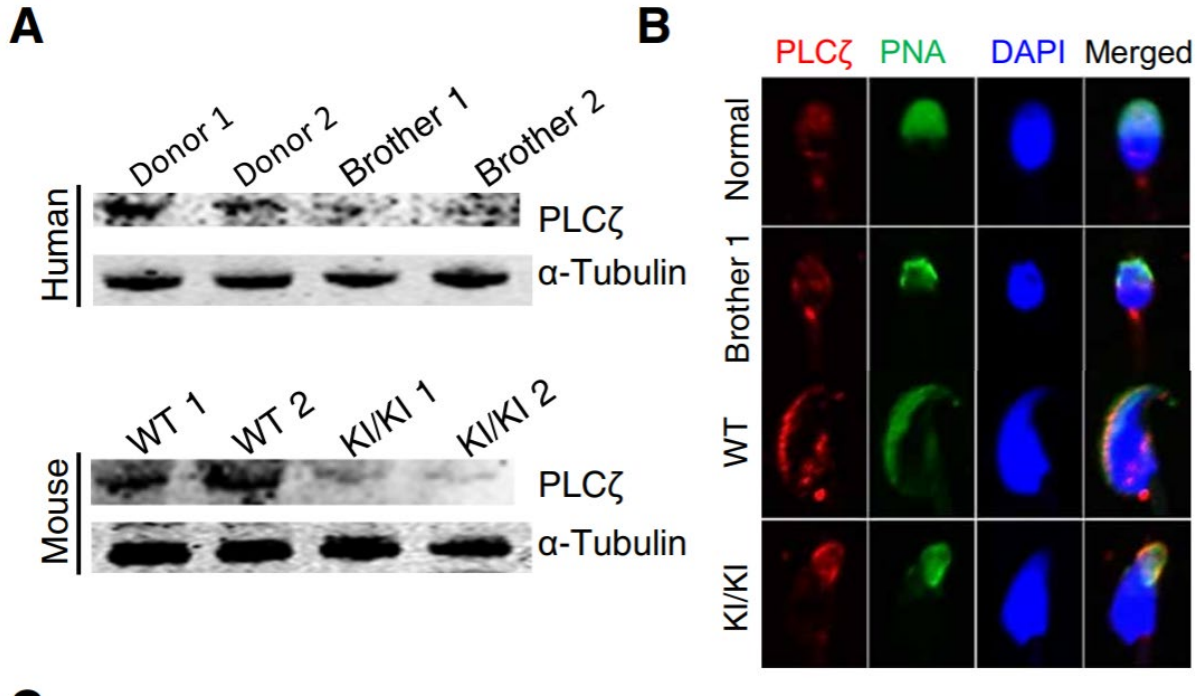
- ACTL7A is localized to the acrosome
- Homozygous *ACTL7A* variants may cause acrosomal defects in human sperm
- *ACTL7A* male knockout mice were infertile





Mouse Models

- ACTL7A mouse knockouts were infertile but ICSI did not rescue fertilization
- PLCζ was lacking in mice and human sperm
  - Oocyte activation/fertilization
  - Initiation of embryonic development



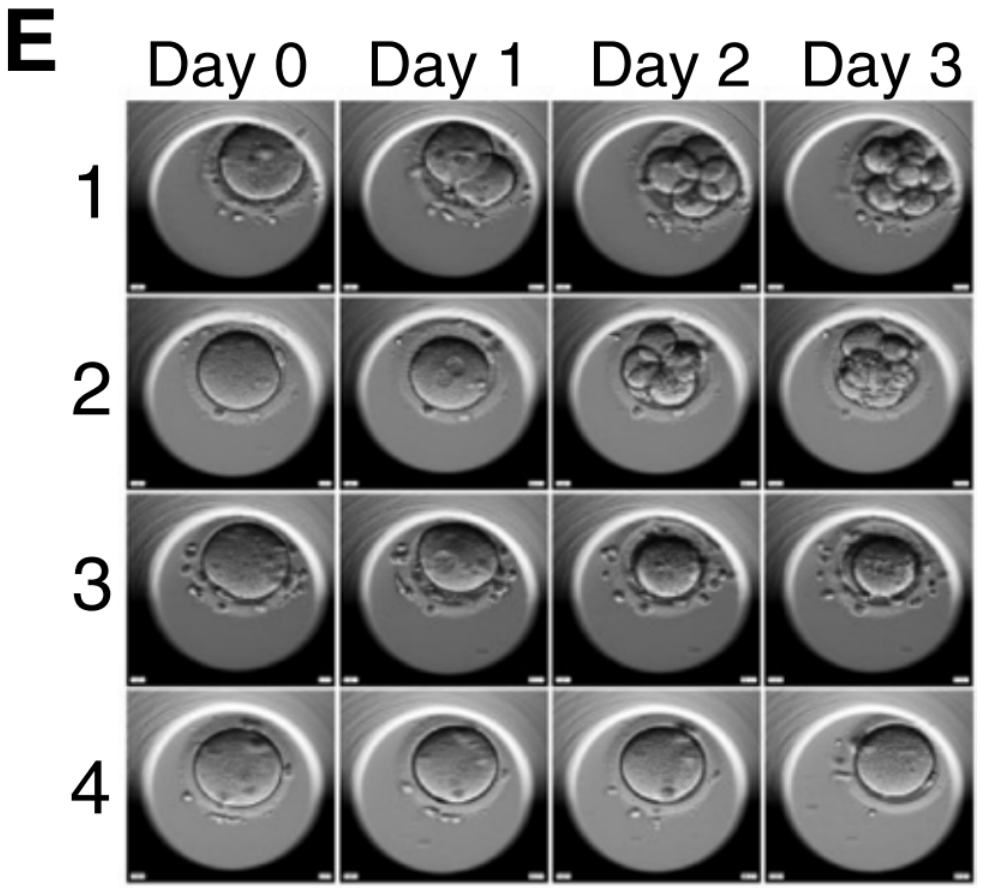
Treatment option?

- Artificial oocyte activation with strontium chloride
  - Viable embryos in mice
- Mouse offspring were fertile
  - No significant differences vs. control group

Treatment option?

- Brother 2 attempted a cycle with this treatment
- Two good quality day 3 embryos
- Implantation unsuccessful

  39yo partner



ACTL7A

- Unexplained infertility prior to IVF
- Fertilization failure with conventional IVF
- Successful fertilization with ICSI
- Early embryonic arrest
- Possible treatment with artificial oocyte activation

Genetic Cause Identified

- Consanguinity
- Two relatives with identical phenotypes
- Protocol issue not suspected

TUBB8

One gene, many phenotypes

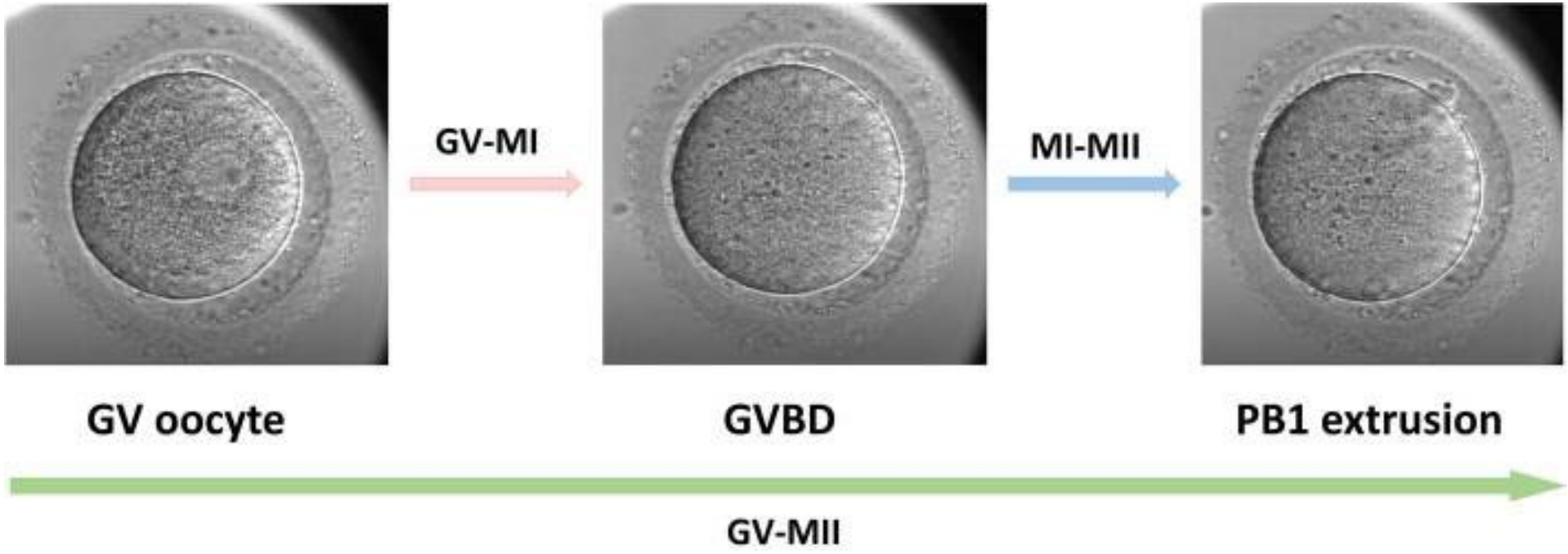
Published in final edited form as:
N Engl J Med. 2016 January 21; 374(3): 223–232. doi:10.1056/NEJMoa1510791.

Mutations in *TUBB8* cause human oocyte meiotic arrest

Ruizhi Feng[1,*], Qing Sang[1,*], Yanping Kuang[2,*], Xiaoxi Sun[3,*], Zheng Yan[2,*], Shaozhen Zhang[2,*], Juanzi Shi[4], Guoling Tian[5], Anna Luchniak[6], Yusuke Fukuda[6], Bin Li[2], Min Yu[3], Junling Chen[3], Yao Xu[1], Luo Guo[8], Ronggui Qu[1], Xueqian Wang[1], Zhaogui Sun[9], Miao Liu[9], Huijuan Shi[9], Hongyan Wang[1], Yi Feng[10], Ruijin Shao[11], Renjie Chai[12], Qiaoli Li[1], Qinghe Xing[1], Rui Zhang[13], Eva Nogales[13,14], Li Jin[1], Lin He[1,15], Mohan L. Gupta Jr.[6,7], Nicholas J. Cowan[#,5], and Lei Wang[#,1]

- 4 generations of “female infertility as a consequence of oocyte meiosis I arrest”
- WES to 23 additional patients following the identification of *TUBB8* as a candidate gene
- Assessed the role of TUBB8 in detail

Oocyte Development



GV oocyte
Prophase I arrest
(Germinal vesicle)

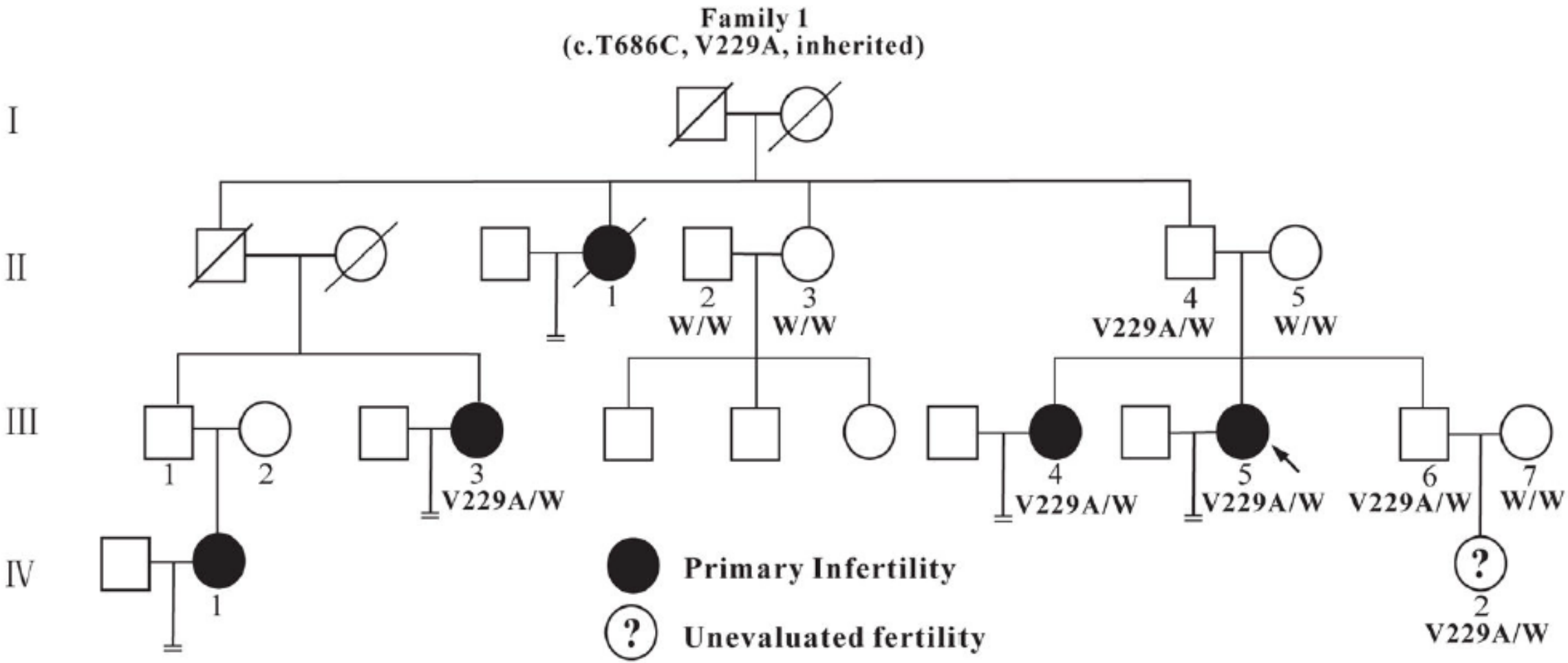
MI oocyte
GV breaks down
(metaphase I)

MII oocyte
First PB is extruded
(metaphase II)

Image from Yang et al., 2021

Oocyte maturation and development

- Eggs must be at the MII stage for fertilization to be possible
- Oocyte maturation arrest: egg development arresting before the MII stage
- Prior to this paper being published no genes responsible for oocyte maturation arrest had been identified


Family 1
(c.T686C, V229A, inherited)
I
II
III
IV
1
2
W/W
3
W/W
4
V229A/W
5
W/W
1
2
3
V229A/W
1
4
V229A/W
5
V229A/W
6
V229A/W
7
W/W
?
2
V229A/W
Primary Infertility
?
Unevaluated fertility

Clinical details and IVF/ICSI outcome in patients from families 1–7

	Case	Age (years)	Duration infertility (years) of	Previous IVF/ICSI cycles	Total No of oocyte retrieved	Stage of Oocyte (Number)
Family-1	III-4 (V229A)	37	8	1	4	MI(3)+abnormal morphology oocyte(1)
Family-1	III-5 (V229A)	32	10	2	21	MI(21)
Family-2	II-2 (D417N)	37	9	5	37	GV(7)+MI(30)
Family-3	II-1 (S176L)	34	10	4	43	GV(3)+MI(40)
Family-4	II-1 (R262Q)	37	10	2	12	MI(12)
Family-5	II-1 (M363T)	25	4	3	18	GV(1)+MI(17)
Family-6	II-1 (R2K)	33	7	2	54	GV(2)+MI(52)
Family-7	II-1 (M300I)	26	6	2	26	MI (26)

- Ages ranging from 25-37
- 1-5 IVF cycles
- 4-54 oocytes retrieved
- No MII oocytes with most arresting at MI

TUBB8

- β-tubulin 8
- Expressed at high levels in different stages of human oocyte development
- Essentially absent in mature sperm and somatic tissues
- Accounts for nearly all of the β-tubulin in human oocytes and early embryos
- Needed for the oocyte spindle

TUBB8 - Further Research

- 2 further studies on women with IVF/ICSI failure
  - 37.2% had TUBB8 variants

REVIEW

The comprehensive variant and phenotypic spectrum of *TUBB8* in female infertility

Wei Zheng[1] · Huiling Hu[2] · Shuoping Zhang[1] · Xilin Xu[2] · Yong Gao[3] · Fei Gong[1,2] · Guangxiu Lu[1,2] · Ge Lin[1,2]

Received: 29 December 2020 / Accepted: 2 May 2021 / Published online: 10 May 2021

- WES on “100 infertile female subjects and 100 controls”
- Evaluate pathogenicity of *TUBB8* variants and compare phenotypes

Variety of Phenotypes observed

- Oocyte maturation arrest
- Poor/no fertilization
- Complete cleavage failure
- Embryonic arrest before blastocyst formation
- High frequency of abnormal fertilization (1PN and MPN)

Multiple Inheritance Patterns

- Mostly autosomal dominant
- Some autosomal recessive

* 616768

TUBULIN, BETA-8; TUBB8

Alternative titles; symbols

TUBULIN, BETA, CLASS VIII

HGNC Approved Gene Symbol: TUBB8

Cytogenetic location: 10p15.3 ***Genomic coordinates (GRCh38): 10:46,455-76,621***
(from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
10p15.3	Oocyte/zygote/embryo maturation arrest 2	616780	AD, AR	3

TUBB8 is not the only gene with multiple phenotypes

Gene	Paper	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4	Inherita
BTG4	2020 Zheng et al., H	Cleavage failure				AR
CDC20	2021 Huang et al., M	Oocyte maturation arrest	Early embryonic arrest			AR
CDC20	2021 Xu et al., The I	Oocyte maturation arrest	Fertilization Failure	Early embryonic arrest		AR
CDC20	2021 Zhao et al., Ide	Oocyte maturation arrest	Fertilizating Failure			AR
FBXO43	2021 Wang et al., FI	Early embryonic arrest				AR
KHDC3L	2018 Wang Novel m	Early embryonic arrest				AR
LHCGR	2011 Yariz et al., Inh	Empty follicle syndrome				AR
LHCGR	2017 Yuan et al., Ge	Empty follicle syndrome				AR
NLRP2	2019 Mu Mutations	Early embryonic arrest				AR
NLRP5	2019 Mu Mutations	Early embryonic arrest				AR
NLRP5	2022 Tong et al., Mu	Early embryonic arrest				AR
OOEP	2022 Tong et al., Mu	Early embryonic arrest				AR
PADI6	2016 Xu et al., Muta	Early embryonic arrest				AR
PADI6	2018 Wang Novel m	Early embryonic arrest				AR
PANX1	2021 Wang et al., H	Oocyte death				AR
PANX1	2019 Sang et al., A p	Oocyte death				AD
PATL2	2017 Chen et al., Bi	Oocyte maturation arrest	Fertilization Failure	Early embryonic arrest		AR
PATL2	2018 Christou-Kent	Oocyte maturation arrest				AR
PATL2	2020 Liu et al., Nove	Oocyte maturation arrest				AR
PATL2	2021 Cao et al., The	Oocyte maturation arrest				AR
REC114	2019 Wang et al., H	Multiple pronuclei	Early embryonic arrest			AR
TLE6	2018 Wang Novel m	Early embryonic arrest				AR
TLE6	2015 Alazami et al.,	Cleavage failure	Early embryonic arrest			AR
TRIP13	2020 Zhang et al., B	Oocyte maturation arrest	Cleavage failure			AR
TUBB8	2020 Sha et al., Nov	Multiple pronuclei				AD
TUBB8	2016 Feng et al., Mu	Oocyte maturation arrest				AD
TUBB8	2016 Feng et al., Mu	Oocyte maturation arrest	Early embryonic arrest			AD, AR
TUBB8	2017 Chen et al., No	Oocyte maturation arrest	Fertilization Failure	Early embryonic arrest		AD, AR
TUBB8	2021 Zheng et al., T	Oocyte maturation arrest	Fertilization Failure	Cleavage failure	Early embryonic	AD, AR
TUBB8	2022 Yao et al., Mu	Oocyte maturation arrest				AD, AR
WEE2	2018 Sang et al., Ho	Fertilization failure				AR
WEE2	2021 Jin et al., Nove	Fertilization failure				AR
ZP1	2014 Huang et al., M	Abnormal zona pellucida				AR
ZP1	2020 Okutman et al	Oocyte maturation arrest				AR
ZP1	2022 Loeuillet et al.	Oocyte maturation arrest				AR
ZP3	2017 Chen et al., A	Empty follicle syndrome	Abnormal zona pellucida			AD
ZP3	2021 Zhang et al., A	Empty follicle syndrome	Abnormal zona pellucida			AD

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NLRP5	2022 Tong et al., Mu	Early embryonic arrest				AR
OOEP	2022 Tong et al., Mu	Early embryonic arrest				AR
PADI6	2016 Xu et al., Muta	Early embryonic arrest				AR
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TUBB8	2016 Feng et al., Mu	Oocyte maturation arrest				AD
TUBB8	2016 Feng et al., Mu	Oocyte maturation arrest	Early embryonic arrest			AD, AR
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TUBB8	2022 Yao et al., Mu	Oocyte maturation arrest				AD, AR
WEE2	2018 Sang et al., Ho	Fertilization failure				AR
WEE2	2021 Jin et al., Nove	Fertilization failure				AR
ZP1	2014 Huang et al., M	Abnormal zona pellucida				AR
ZP1	2020 Okutman et al	Oocyte maturation arrest				AR
ZP1	2022 Loeuillet et al.	Oocyte maturation arrest				AR
ZP3	2017 Chen et al., A	Empty follicle syndrome	Abnormal zona pellucida			AD
ZP3	2021 Zhang et al., A	Empty follicle syndrome	Abnormal zona pellucida			AD

There are many genes being discovered, and as research evolves, we are learning that the phenotypes and inheritance patterns are not straightforward

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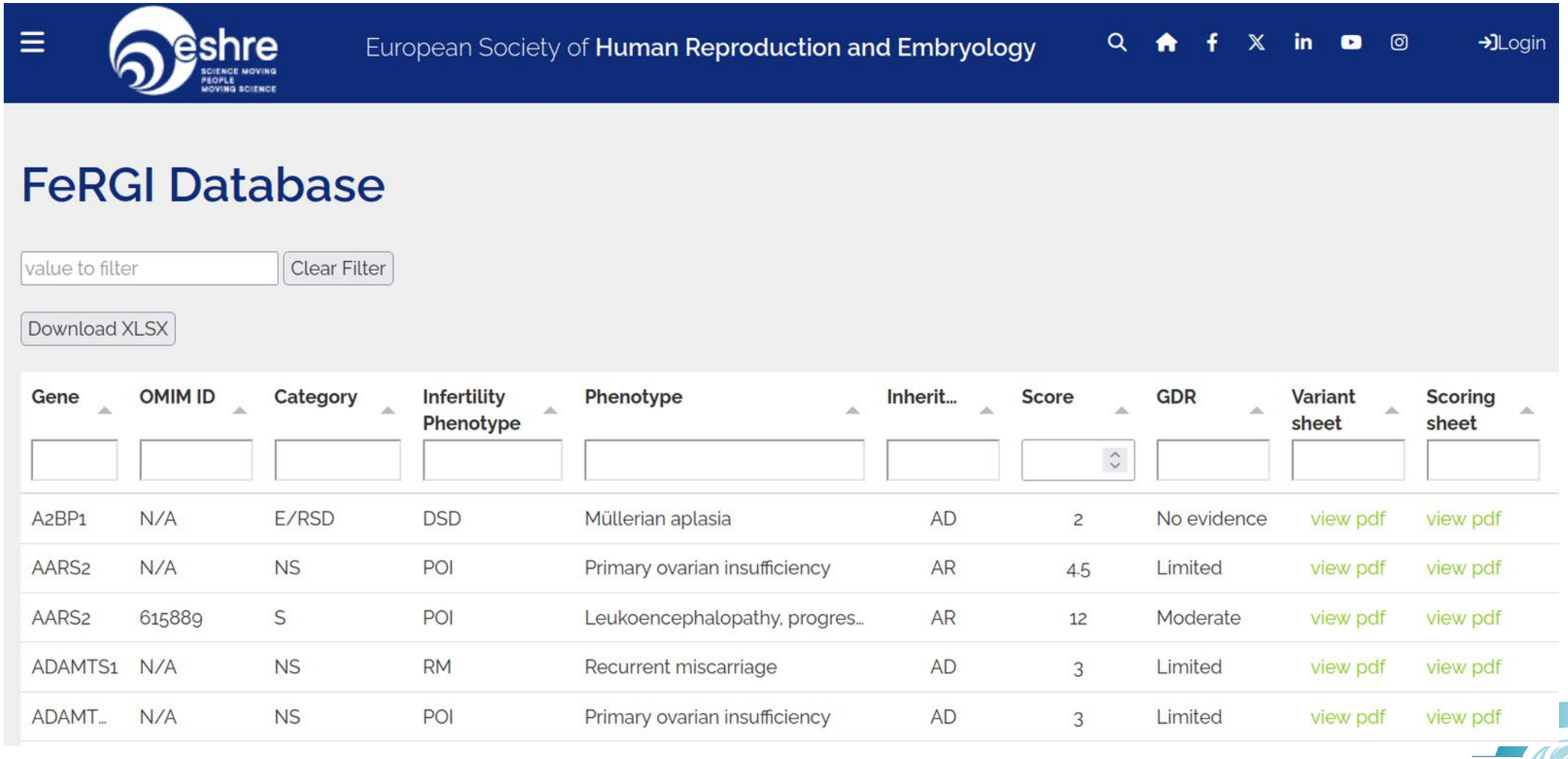
KHDC3L	2018 Wang Novel m	Early embryonic arrest				AR
LHCGR	2011 Yariz et al., Inh	Empty follicle syndrome				AR
LHCGR	2017 Yuan et al., Ge	Empty follicle syndrome				AR
NLRP2	2019 Mu Mutations	Early embryonic arrest				AR
NLRP5	2019 Mu Mutations	Early embryonic arrest				AR
NLRP5	2022 Tong et al., Mu	Early embryonic arrest				AR
OOEP	2022 Tong et al., Mu	Early embryonic arrest				AR
PADI6	2016 Xu et al., Muta	Early embryonic arrest				AR
PADI6	2018 Wang Novel m	Early embryonic arrest				AR
TUBB8	2016 Feng et al., Mu	Oocyte maturation arrest				AD
TUBB8	2016 Feng et al., Mu	Oocyte maturation arrest	Early embryonic arrest			AD, AR
TUBB8	2017 Chen et al., No	Oocyte maturation arrest	Fertilization Failure	Early embryonic arrest		AD, AR
TUBB8	2021 Zheng et al., T	Oocyte maturation arrest	Fertilization Failure	Cleavage failure	Early embryonic	AD, AR
TUBB8	2022 Yao et al., Mu	Oocyte maturation arrest				AD, AR
WEE2	2018 Sang et al., Ho	Fertilization failure				AR
WEE2	2021 Jin et al., Nove	Fertilization failure				AR
ZP1	2014 Huang et al., M	Abnormal zona pellucida				AR
ZP1	2020 Okutman et al	Oocyte maturation arrest				AR
ZP1	2022 Loeuillet et al.	Oocyte maturation arrest				AR
ZP3	2017 Chen et al., A	Empty follicle syndrome	Abnormal zona pellucida			AD
ZP3	2021 Zhang et al., A	Empty follicle syndrome	Abnormal zona pellucida			AD

There are many genes being discovered, and as research evolves, we are learning that the phenotypes and inheritance patterns are not straightforward

Female Reproductive Genetics Initiative



Gene	OMIM ID	Category	Infertility Phenotype	Phenotype	Inherit...	Score	GDR	Variant sheet	Scoring sheet
A2BP1	N/A	E/RSD	DSD	Müllerian aplasia	AD	2	No evidence	view pdf	view pdf
AARS2	N/A	NS	POI	Primary ovarian insufficiency	AR	4.5	Limited	view pdf	view pdf
AARS2	615889	S	POI	Leukoencephalopathy, progres...	AR	12	Moderate	view pdf	view pdf
ADAMTS1	N/A	NS	RM	Recurrent miscarriage	AD	3	Limited	view pdf	view pdf
ADAMT...	N/A	NS	POI	Primary ovarian insufficiency	AD	3	Limited	view pdf	view pdf

https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Reproductive-Genetics/FeRGI/Database

Basic informations	Answer reviewer 1	Answer reviewer 2
Assessor code reviewer	*F1*	*H1*
Date of curation	11/07/2022	9-7-2022
Curated gene	*TUBB8*	*TUBB8*
Possible synonyms used for gene name	bA631M21.2	*bA631M21.2*
OMIM phenotype	Oocyte/zygote/embryo maturation arrest 2	Oocyte/zygote/embryo maturation arrest 2
OMIM disease ID	616780	616780
References describing patients	27989988, 27273344, 26789871, 33009822, 32063091, 32524331, 32316999, 30297906, 29671363, 29877102, 29661911, 33809228, 28652098, 34509376, 34160777, 33059025, 32949002, 29704226	27989988, 27273344, 26789871, 33009822, 32063091, 32524331, 32316999, 30297906, 29671363, 29877102, 29661911, 33809228, 28652098, 34509376, 34160777, 33059025, 32949002, 29704226
Step 1: Inheritance informations	Answer reviewer 1	Answer reviewer 2
Incidence	N/A	Familial and sporadic
Reported inheritance	Autosomal dominant and recessive	Autosomal dominant and recessive
Inheritance in animal models	Autosomal recessive	Autosomal recessive
Additional evidence: pLi* and/or o/e scores (for pLoF)	pLI=0.02 and o/e=0.62	pLI = 0.02 o/e = 0.62
Conclusion inheritance in HUMAN	Autosomal dominant and recessive	Autosomal dominant and recessive

https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Reproductive-Genetics/FeRGI/Database

Summary clinical validity assessment	Reviewer 1	Reviewer 2
Clinical validity score of reviewers	17	17
Clinical validity score difference between reviewers	0	
Clinical validity status	Agreement	
Final clinical validity score (average)	17	
Final clinical validity classification (see Tab scores and classifications)	Definitive	

https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Reproductive-Genetics/FeRGI/Database

Phenotypes – Egg-provider (IVF Failure)

- Genuine Empty Follicle Syndrome
- Oocyte Death
- Abnormal Zona Pellucida
- Oocyte Maturation Arrest
- Fertilization failure
- Cleavage failure
- Multiple pronuclei
- Early embryonic arrest

Phenotypes – Egg-provider

- Primary ovarian insufficiency
- Hypogonadotropic hypogonadism
- Recurrent miscarriage
- Recurrent triploidy
- Recurrent molar pregnancy
- Recurrent implantation failure

Phenotypes – Sperm Provider

- Fertilization failure
- Conventional IVF failure
- ICSI failure
- Early embryonic arrest
- Morphological abnormalities
- Azoospermia

Clinical Utility

of gene panels for IVF failure

Types of Gene Panels

Pre-designed

- Genes are curated by the testing lab
- Infertility panels currently on the US market focus on syndromic infertility
- Laboratories want a high diagnostic yield

Custom

- Genes are selected by the clinician
- More flexibility
- Higher level of genetic expertise required

Custom Panels

Narrow

- Genes known to produce phenotype seen in your patient
- Genes with high levels of evidence
- Pro: less chance of uncertain findings

Broad

- Genes related to "male" or "female" infertility
- Genes with less evidence
- Pro: uncertain finding today may be a diagnostic finding tomorrow

Custom Panels

Narrow	Broad
• Genes known to produce phenotype seen in your patient • Genes with high levels of evidence • Pro: less chance of uncertain findings	• Genes related to "male" or "female" infertility • Genes with less evidence • Pro: uncertain finding today may be a diagnostic finding tomorrow

What makes a genetic diagnosis?

1. A well researched gene known to be related to the patient's phenotype

2. Genetic variant(s) that we know impact the gene function

3. Inheritance pattern matching:
   - Number of variants detected
   - Family history

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- **A well researched gene known to be related to the patient's phenotype**
- Genetic variant(s) that we know impact the gene function
- Inheritance pattern matching
  - Number of variants detected
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Genes of Uncertain Significance (GUS)

- Newly discovered genes
- Minimal research, phenotype may not be fully defined
- Testing laboratory may be suspicious that gene is relevant to your patient but can't say conclusively

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Many of the genes identified related to IVF failure may be GUSs

Genes of Uncertain Significance (GUS)

Variants in Genes Possibly Associated with Reported Phenotype:

- Custom panels with variants in GUSs identified may not have infertility phenotypes included in the gene descriptions

What makes a genetic diagnosis?

- A well researched gene known to be related to the patient's phenotype
- **Genetic variant(s) that we know impact the gene function**
- Inheritance pattern matching
  - Number of variants detected
  - Family history

Variant pathogenicity

Variant pathogenicity

- Location within the gene (hot spot/critical regions)
- Prevalence in case/control studies
- *In vitro* analysis tools
- Testing relatives

Variant of uncertain significance (VUSs)

- Not enough evidence to classify a variant as pathogenic or benign
- Common in genes that are newly discovered
- Cannot be used for diagnostic purposes

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VUSs are common in genetic testing for IVF failure

What makes a genetic diagnosis?

- A well researched gene known to be related to the patient's phenotype
- Genetic variant(s) that we know impact the gene function
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  - Number of variants detected
  - Family history

Inheritance Pattern

- If autosomal recessive
  - Single variant identified is not sufficient for diagnosis
- If autosomal dominant
  - Which parent was the variant inherited from?

Testing Relatives

- Female infertility
  - Variant inherited from mother - unlikely to be pathogenic

REVIEW

The comprehensive variant and phenotypic spectrum of *TUBB8* in female infertility

Wei Zheng[1] · Huiling Hu[2] · Shuoping Zhang[1] · Xilin Xu[2] · Yong Gao[3] · Fei Gong[1,2] · Guangxiu Lu[1,2] · Ge Lin[1,2]

Received: 29 December 2020 / Accepted: 2 May 2021 / Published online: 10 May 2021

- 16 of the reported 102 *TUBB8* variants assessed could be classified as likely pathogenic (LP)
- For patients with LP variants, donor eggs may be the most feasible for conceiving at present
- Pathogenicity of all *TUBB8* variants couldn't be evaluated in this study
  - Lack of DNA from parents

When panels might be useful

- Same phenotype in multiple cycles despite protocol changes
- Most/all of the follicles/oocytes/embryos affected
- Suspicious family history
- Consanguinity
- Patient is interested in answers
- Possible insight into outcome of treatment
- Informative for family members

Genetic Counseling

MARCH 19 - 23

PCRS 2025

PACIFIC WAVES - EXPLORING SCIENTIFIC FRONTIERS IN AN EVOLVING SOCIETY

Prep

- Establish physician relationship
- Obtain records
- Obtain family history via questionnaire

Pre-test counseling

- Review personal and family medical history
- Discuss other limitations and considerations
- Review logistics
- Discuss result disclosure protocols
- Emphasize testing is optional
  - Facilitate decision-making re: testing
- Emotional support

Post-test counseling

- Check-in
- Disclose results
- Explain what they mean
- Discuss further testing if needed
- Physician to determine if findings explain phenotype
- Emotional support
- Encourage keeping in touch

The answer we've been waiting for?

The answer we've been waiting for?

- Significant advances in gene discovery for IVF failure
- Results *may*:
  - Explain phenotype
  - Guide decision to move to donor gametes
  - Guide treatment
  - Provide insight to other family members on fertility status
- High chance of uncertain results
- Fertility genetics expertise is needed before testing and when interpreting results

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Q&A

Meaghan Doyle, MS, LCGC (she/her)
meaghan@DNAide.com
@MeaghanDoyleGC