Meiosis interrupted: the genetics of female infertility via meiotic failure

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Abstract

Idiopathic or ‘unexplained’ infertility represents as many as 30% of infertility cases worldwide. Conception, implantation, and term delivery of developmentally healthy infants require chromosomally normal (euploid) eggs and sperm. The crux of euploid egg production is error-free meiosis. Pathologic genetic variants dysregulate meiotic processes that occur during prophase I, meiotic resumption, chromosome segregation, and in cell cycle regulation. This dysregulation can result in chromosomally abnormal (aneuploid) eggs. In turn, egg aneuploidy leads to a broad range of clinical infertility phenotypes, including primary ovarian insufficiency and early menopause, egg fertilization failure and embryonic developmental arrest, or recurrent pregnancy loss. Therefore, maternal genetic variants are emerging as infertility biomarkers, which could allow informed reproductive decision-making. Here, we select and deeply examine human genetic variants that likely cause dysregulation of critical meiotic processes in 14 female infertility-associated genes: *SYCP3*, *SYCE1*, *TRIP13*, *PSMC3IP*, *DMC1*, *MCM8*, *MCM9*, *STAG3*, *PATL2*, *TUBB8*, *CEP120*, *AURKB*, *AURKC*, and *WEE2*. We discuss the function of each gene in meiosis, explore genotype-phenotype relationships, and delineate the frequencies of infertility-associated variants.

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Introduction

Healthy, chromosomally normal (euploid) eggs and sperm are essential to implantation, full-term pregnancy and healthy infant development. The contribution of low-quality eggs to female infertility is not fully understood, partly because human egg scarcity limits robust investigations. Egg quality decreases with increasing maternal age, but other causes of poor egg quality likely exist (Lindsay & Vitrikas 2015, Ruebel & Latham 2020). Despite being of an optimal maternal age and the absence of reproductive pathology, many women have difficulty conceiving (Nandi & Homburg 2016) or endure recurrent idiopathic miscarriage (El Hachem *et al.* 2017). Why some women face exceptional difficulty conceiving and carrying a pregnancy to term is poorly understood. For these patients, the genetic determinants of egg quality may offer an answer.

During meiosis, oocytes must faithfully segregate their chromosomes in two rounds of division to create a euploid zygote upon fertilization. One-half of all spontaneous abortions are aneuploid; these comprise the largest fraction of chromosomally abnormal pregnancy losses (Hassold 1986). A significant proportion of these pregnancy losses are attributed to errors in meiosis.

Errors in meiotic processes, such as chromosome synapsis, crossing over and spindle building can impair chromosome segregation and cause aneuploidy. Aneuploidy is more frequently observed in oocytes than in spermatocytes (Bernardini *et al.* 2000, Hassold & Hunt 2001, Bell *et al.* 2020). Understanding the molecular and genetic underpinnings of how meiosis is regulated is key to unlocking the mystery of the origins of human aneuploidy.

Genomic approaches, including next-generation sequencing and cytogenetic arrays, have begun to identify relationships between clinical infertility phenotypes and maternal gene variants. The disease of infertility includes a spectrum of patient fecundity levels, including subfertility (i.e. any degree of reduced fecundity) (American College of Obstetrics and Gynecology 2019). Identifying subfertility-associated literature is difficult because of the way cases and controls are typically defined: once a patient becomes pregnant and passes a threshold of gestation, the patient may be considered fertile. Alternative methods of defining subfertility have emerged, such as time-to-pregnancy and blastocyst aneuploidy measurements. Because these methods of subfertility assessment are not widely adopted, the clinical phenotypes associated with

errors in meiosis encompass a list of diagnoses. After reviewing the literature using PubMed search terms such as ‘female infertility’ and ‘fertility’, we identified the principal clinical phenotypes associated with aneuploid egg production and subfertility as: primary ovarian insufficiency (POI) (Primary ovarian insufficiency is the terminology preferred by the National Institutes of Health. Other works, including those cited in this review, may use the term ‘premature ovarian failure’ (POF). Both terms refer to the same condition (Committee opinion 2014), oocyte arrest and embryonic arrest, fertilization failure, recurrent pregnancy loss and early menopause. Note that POI refers to secondary amenorrhea before 40 years of age, whereas early menopause is defined as secondary amenorrhea between the ages of 40 and 45 years old (Edmonds 2012).

The genes associated with these clinical phenotypes span a wide range of meiotic processes. Here, we review selected human gene variants that may cause infertility or subfertility by impacting landmark cellular meiotic processes. We divided these processes into four groups: (1) prophase I; (2) meiotic resumption; (3) meiosis I (MI) chromosome segregation; and (4) meiotic cell cycle regulation. Recent reviews have discussed genetic drivers of female infertility through non-meiotic mechanisms such as altered ovarian reserve and ovarian function, defective follicle activation and growth (Yatsenko & Rajkovic 2019) and syndromic causes of infertility (Zorrilla & Yatsenko 2013, Jedidi *et al.* 2019). Another recent review discussed female infertility caused by DNA repair dysregulation (Veitia 2020). To avoid redundancies, we took a deep dive to describe only a selection of gene variants that impact female gamete viability and/or quality by disrupting these four

key meiotic processes. We discuss example genes and indicate the remainder of genes we identified in Figs 1, 2, 3, 4 and 5. We review the genes by presenting them in a biologically relevant temporal order in which they function (Fig. 1). To provide context, we first describe the biological function of these genes during the meiotic process, often using findings from model organism studies, then consolidate findings from case studies, and, when possible, report functional assessments of the human gene variants.

Prophase I: making and repairing double-strand breaks

After pre-meiotic DNA replication, oocytes enter meiotic prophase I to prepare for homologous recombination (Fig. 1), an essential process for double-strand break (DSB) repair and successful MI chromosome segregation. Prophase I begins with chromosome DSBs initiated by the SPO11 topoisomerase (de Massy *et al.* 1995, Keeney & Kleckner 1995, Keeney *et al.* 1997, Bergerat *et al.* 1997) and is followed by homologous chromosome pairing and synapsis through the formation of the synaptonemal complex (SC). In parallel, DSB repair occurs. Repair can occur through homolog crossing over, leaving physical linkages (chiasmata) between the homologs. Chiasmata are essential to hold homologs together until anaphase I. Therefore, at least one crossover per homolog must occur, lest an aneuploid egg form after completion of MI. Notably, defects in prophase I can also give rise to POI because oocytes with persistent DNA damage undergo apoptosis and are culled from the ovarian reserve. Consistent with this hypothesis, most POI patients are subfertile: only 5–10% of POI patients eventually

Figure 1 Overview of steps in oocyte meiotic maturation vulnerable to infertility-causing genetic variants. The oocyte matures through discrete meiotic phases, requiring genes that are susceptible to dysregulation by genetic variants; those associated with female infertility phenotypes are listed below each phase. Prophase I involves a program of synapsis, cohesion, and recombination. After the diplotene stage of prophase I, oocytes arrest in the dictyate stage of prophase I until puberty and while it grows in size. Upon ovulation, oocytes resume meiosis and initiate a burst of maternal RNA translation. To complete meiosis I, the spindle forms and, under the governance of the spindle assembly checkpoint, homologous chromosomes segregate. The spindle reflects one from a mouse oocyte. After an asymmetric cytokinesis, oocytes arrest at metaphase II awaiting fertilization. After fertilization, inhibition of CDK1 induces meiosis II completion. Exact stoichiometry is not depicted. Check marks (✓) indicate those genes discussed in this review. Created using BioRender.com.

Figure 2 Meiotic prophase I and maturation are disrupted by female infertility-associated gene variants. The synaptonemal complex (purple box) scaffolds homologous chromosomes and is composed of two lateral elements (SYCP2/3) and central elements SYCE1 (shown), SYCP1, SYCE2, SYCE3, and TEX12 (not shown). TRIP13 removes HORMA domain proteins (HORMADs), permitting synaptonemal complex assembly. The meiotic cohesin complex (green box) joins sister chromatids. In parallel with synaptonemal complex assembly, recombination (blue box) begins with double-strand breaks via SPO11. This requires the MRE11-RAD50-NBS1 (MRN) complex. Recombinases RAD51 (not shown) and DMC1 facilitate strand invasion into a chromosome's homolog. HFM1 may also be essential for stable strand invasion (Guiraldelli *et al.* 2013). At double-strand breaks, the MCM8/9 helicase facilitates RAD51 recruitment and DNA synthesis. BRCA2 is proposed to localize to DSBs via MEILB2, and recruits RAD51 and DMC1 (Zhang *et al.* 2019a). A PMSC3IP-MND1 heterodimer stabilizes the RAD51 filament. BRCA1 may also stabilize the RAD51 filament in meiosis (Scully *et al.* 1997, Li *et al.* 2018). MEIOB is essential for maintenance of RAD51 and DMC1 foci (Souquet *et al.* 2013). The resulting double Holliday junction is stabilized by the MSH4/5 heterodimer. The MSH4/5 complex recruits the MLH1/MLH3 heterodimeric endonuclease, which processes most crossovers. Exact stoichiometry is not depicted. Underlined gene products are implicated in infertility. Check marks (✓) indicate gene products discussed in this review. Created using BioRender.com.

conceive and maintain a pregnancy (Welt 2020). The following eight genes (Table 1) are essential regulators of distinct prophase I steps (Figs 1 and 2) and variants within these genes are associated with female infertility.

The synaptonemal complex and chromosome synapsis

The synaptonemal complex (SC), which forms during homologous chromosome synapsis, is a symmetrical, zipper-like protein complex that bridges two homologs (Fig. 2) (Fawcett 1956, Moses 1956). Three protein types comprise the SC: a central element, running parallel

to the chromosome arms; transverse elements flanking the central element; and lateral elements coating the inner faces of the chromosome arms and framing the transverse elements (Costa *et al.* 2005, Dunne & Davies 2019). The lateral elements of the SC assemble first. Lateral element proteins, SYCP2 and SYCP3, form a heterodimeric scaffold on chromosomes. The scaffold grows outward along the length of chromosomes, with chromatin forming perpendicular loops (Offenberg *et al.* 1998, Yang *et al.* 2006). Female mice deficient in the SYCP3 homolog, *Scp3*, have significantly more embryo death than their wildtype (WT) counterparts.

Increased maternal age amplifies this phenotype: rates of embryo death in *Scp3*-deficient mice increase with age. As a result, *Scp3*-deficient female mice have a shorter reproductive lifespan than do WT female mice. At a cellular level, *Scp3*-deficient oocytes have greater

proportions of chromosomes not linked by chiasmata, likely because chiasmata fail to form (Yuan *et al.* 2002). Therefore, *SYCP3* dysfunction in humans could lead to infertility, specifically pregnancy loss and accelerated reproductive aging (reviewed in detail in Geisinger & Benavente 2016).

An *SYCP3*-specific sequencing screening of 26 women with three or more spontaneous miscarriages before ten weeks of gestation provided initial evidence for correlating *SYCP3* malfunction with female infertility. The screening identified two women with heterozygous point mutations (NM_153694.1:c.IVS7-16_19delACTT and NM_153694.1:c.657T>C), both of which occur in putative splice sites of *SYCP3*. To ascertain their biological impact on meiosis, the putative splice-site variants were introduced into mouse testes. This analysis showed that the NM_153694.1:c.657T>C variant had a higher unspliced-to-spliced transcript ratio than the WT gene, while the NM_153694.1:c.IVS7-16_19delACTT variant did not change the splicing transcript ratio. The protein product of the NM_153694.1:c.657T>C variant was unable to form homopolymeric fibers in cultured somatic cells, whereas WT *SYCP3* formed thick looped-shaped fibers (Bolor *et al.* 2009).

The association between *SYCP3* NM_153694.1:c.657T>C and infertility was corroborated by targeted sequencing of 200 women, half of whom had recurrent pregnancy loss (RPL) of unknown cause and half of whom had successful pregnancies as controls (Sazegari *et al.* 2014). Of note, another study of 101 women with histories of at least three undiagnosable pregnancy losses did not identify the allele (Mizutani *et al.* 2011). These findings suggest that, although *SYCP3* variants are linked to RPL in terms of both molecular characterization and patient genetic sequence data, *SYCP3* variants are not the sole etiology of RPL.

Figure 4 Spindle assembly and chromosome segregation are vulnerable to female infertility-associated genetic variants. Schematic of microtubule nucleation (green box) and the chromosomal passenger complex (purple box). Microtubules are composed of tubulin, a heterodimeric polymer of α - and β -tubulin. *TUBB8* encodes a β -tubulin. CEP120 may also act in meiotic spindle building, as it does in mitosis. The chromosomal passenger complex (purple box) is comprised of the illustrated components, with either Aurora kinase (AURK) B or C as the catalytic subunit. AURKC expression is exclusive to meiosis and participates in chromosome alignment, kinetochore-microtubule attachment correction, and spindle building; in meiosis, AURKB also supervises kinetochore-microtubule attachment. Note that the spindle reflects a mouse oocyte. Exact stoichiometry is not depicted. Underlined gene products are implicated in infertility. Check marks (✓) indicate gene products discussed in this review. Created using BioRender.com.

Figure 5 Exits from meiosis I and II are targets for infertility-causing genetic variants. Schematic of meiosis I cytokinesis and meiosis II cell cycle exit. During cytokinesis, actin filaments and myosin II form a contractile ring at the cleavage furrow. POF1B binds to non-muscle actin filaments and shares homology with myosin. Upon fertilization, an increase in intracellular calcium leads to activation of Ca^{2+} /CaM-protein kinase II (CaMKII). CaMKII, in turn, activates WEE2 through phosphorylation. Activated WEE2 represses the maturation promoting factor (MPF), comprised of cyclin B1 and CDK1, by phosphorylating CDK1. This decrease in MPF activity, in concert with APC- and CDC20-mediated cyclin B1 decay, triggers exit from meiosis II. Exact stoichiometry is not depicted. Underlined gene products are implicated in infertility. Check marks (✓) indicate gene products discussed in this review. Created using BioRender.com.

After the lateral element assembles, the transverse filament and central element of the SC assemble between homologs. SYCP1, a central element protein, initiates this process by localizing between the lateral elements of two homologs and recruiting additional central element proteins, including synaptonemal complex central element protein 1, SYCE1 (Costa *et al.* 2005). SYCE1 is an essential component of the central element. For instance, mouse oocytes that lack SYCE1 fail to assemble the central element of the SC, a critical step in synapsis. *Syce1*^{-/-} oocytes and spermatocytes have homologs that pair but do not form SCs. As a result, *Syce1*^{-/-} spermatocytes arrest in meiotic prophase I, and the ovaries of *Syce1*^{-/-} mice are small and depleted of follicles; both sexes are therefore sterile (Bolcun-Filas *et al.* 2009). The absence of follicles in *Syce1*^{-/-} mice parallels POI (Welt 2018).

In humans, *SYCE1* variants are associated with POI. For example, a novel 0.16 MB microdeletion (hg19:g. 135,092,227_135,256,027del) spanning *SYCE1* and a cytochrome-encoding gene, *CYP2E1*, was identified via SNP array. One of 89 POI patients had this heterozygous microdeletion. This patient had menarche at age 14 but stopped menstruating at age 21, marking the onset of POI (McGuire *et al.* 2011). The association between POI and *SYCE1* mutation was strengthened by whole-exome sequencing of a consanguineous family with multiple POI cases. In this study, two sisters harbored a single homozygous nonsense mutation in *SYCE1* (NM_130784.2:c.613C>T), generating a truncated 205-amino acid protein. Both sisters (ages 16 and 17) had primary amenorrhea. Their heterozygote parents and brothers were fertile and healthy, suggesting autosomal recessive inheritance of the allele. A healthy, fertile sister and 90 ethnically matched controls lacked the allele (de Vries *et al.* 2014).

Importantly, the biological impact of the *SYCE1* c.613C>T variant has been assessed by creating a humanized mouse model. Female mice homozygous for the equivalent mutation lacked follicles and oocytes, and, similar to the family described, heterozygote mice were unaffected. Chromosomes in homozygous mutant gametes failed to synapse during prophase I (Hernandez-Lopez *et al.* 2020). This study demonstrates that this *SYCE1* variant recapitulates the infertility phenotype in mouse and results in disrupted chromosome synapsis. Subsequent studies of POI patient cohorts that used SNP arrays also demonstrated enrichment of *SYCE1* variants in POI patients (Zhen *et al.* 2013, Jaillard *et al.* 2016, Tsuiko *et al.* 2016). Additionally, whole-exome sequencing of a family containing two members with POI identified a gross deletion encompassing part of the *SYCE1* locus (Zhe *et al.* 2020). The functional consequence of this deletion or of the truncating variant are unknown, but the generation of this humanized mouse model offers a promising avenue to interrogate the molecular relationship between SYCE1 function and subfertility.

Homologous recombination and genome integrity

HORMA domain (HORMAD) proteins accumulate on unsynapsed chromosomes and promote SPO11-mediated DSBs (Mao-Draayer *et al.* 1996, Woltering *et al.* 2000, Goodyer *et al.* 2008, Shin *et al.* 2010). SPO11-mediated DSB formation requires the MRE11-RAD50-NBS1 (MRN) complex (Alani *et al.* 1990, Cao *et al.* 1990, Nairz & Klein 1997, Garcia *et al.* 2011, Girard *et al.* 2018). Thyroid hormone receptor interactor 13 (TRIP13 or PCH2) is an AAA+ ATPase that, in meiosis, catalyzes the removal of the meiosis-specific HORMADs, HORMAD1 and HORMAD2, from

Table 1 Female infertility-associated genetic variants affecting prophase I and meiotic entry. Genes are listed in order of appearance in text; their variants are listed in order of publication year. Frequencies of small (<1kb) genetic variants were identified in gnomAD v2.1.1 and ExAc v1.0 via ANNOVAR. Allele frequencies of structural variants reflect those of overlapping variants of the same type (i.e. deletion (DEL), duplication (DUP) etc.), rather than of exact matches; the gnomAD variant ID of the variant used is indicated.

Gene	DNA variant	Protein variant	Key phenotype	Reference	Allele Frequency		
					gnomAD exomes ¹	ExAc ²	gnomAD genomes ³ gnomAD SVs ⁴
<i>SYCP3</i>	NM_153694.1:c.553-16_19del	Intronic variant	Recurrent pregnancy loss	Bolor et al. (2009)[†]	NF	NF	NF
<i>SYCP3</i>	NM_153694.1:c.657T>C	SDS variant	Recurrent pregnancy loss	Bolor et al. (2009)[†]	5.63E-05	6.83E-05	6.83E-05
<i>SYCP3</i>	NM_153694.1:c.657T>C	SDS variant	Recurrent pregnancy loss	Mizutani et al. (2011)[†]	5.63E-05	6.83E-05	6.83E-05
<i>SYCP3</i>	NM_153694.1:c.657T>C	SDS variant	Recurrent pregnancy loss	Sazegari et al. (2014)[†]	5.63E-05	6.83E-05	6.83E-05
<i>SYCE1</i>	NC_000010.10:g.135092227_135256027del	Structural variant	POI	McGuire et al. (2011)[†]	N/A	N/A	N/A
<i>SYCE1</i>	NM_130784.2:c.613C>T	p.Q205*	POI	DeVries et al. (2014)	NF	NF	1.52E-03 (gnomAD DEL_10_115557)
<i>SYCE1</i>	NC_000010.10:g.135254039_135377532dup	Structural variant	POI	Jaillard et al. (2016)[†]	N/A	N/A	4.97E-02 (gnomAD DUP_10_31262)
<i>SYCE1</i>	NC_000010.10:g.135256762_135379710dup	Structural variant	POI	Tsuiiko et al. (2016)[†]	N/A	N/A	4.97E-02 (gnomAD DUP_10_31262)
<i>SYCE1</i>	NC_000010.10:g.135281682_135377532dup	Structural variant	POI	Bestetti et al. (2019)[†]	N/A	N/A	4.97E-02 (gnomAD DUP_10_31262)
<i>SYCE1</i>	NC_000010.10:g.135281682_135378761dup	Structural variant	POI	Bestetti et al. (2019)[†]	N/A	N/A	4.97E-02 (gnomAD DUP_10_31262)
<i>SYCE1</i>	NC_000010.10:g.135252327_135378761dup	Structural variant	POI	Bestetti et al. (2019)[†]	N/A	N/A	4.97E-02 (gnomAD DUP_10_31262)
<i>SYCE1</i>	NC_000010.10:g.135252327_135378761del	Structural variant	POI	Bestetti et al. (2019)[†]	N/A	N/A	4.97E-02 (gnomAD DUP_10_31262)
<i>SYCE1</i>	NC_000010.10:g.135281682_135404523dup	Structural variant	POI	Bestetti et al. (2019)[†]	N/A	N/A	1.52E-03 (gnomAD DEL_10_115557)
<i>TRIP13</i>	NM_004237.4:c.77A>G	p.H26R	Oocyte maturation arrest	Zhang et al. (2020b)	9.19E-06	3.21E-05	4.97E-02 (gnomAD DUP_10_31262)
<i>TRIP13</i>	NM_004237.4:c.518G>A	p.R173Q	Oocyte maturation arrest	Zhang et al. (2020b)	7.95E-06	1.65E-05	4.97E-02 (gnomAD DUP_10_31262)
<i>TRIP13</i>	NM_004237.4:c.907G>A	p.E303K	Oocyte maturation arrest	Zhang et al. (2020b)	1.60E-05	1.65E-05	4.97E-02 (gnomAD DUP_10_31262)
<i>TRIP13</i>	NM_004237.4:c.592A>G	p.I198V	Oocyte maturation arrest	Zhang et al. (2020b)	NF	NF	NF
<i>STAC3</i>	NM_004237.4:c.739G>A	p.V247M	POI	Xiao et al. (2019)[†]	NF	NF	NF
<i>STAC3</i>	NM_001282716:c.877_885del	p.293_295del	POI	Xiao et al. (2019)[†]	NF	NF	NF
<i>STAC3</i>	NM_001282716:c.891_893dup	p.297_298insAsp	POI	Xiao et al. (2019)[†]	NF	NF	NF
<i>STAC3</i>	NM_001282716:c.291dup	p.N98Qfs*2	POI	Franca et al. (2019)[†]	NF	NF	NF
<i>STAC3</i>	NM_001282716:c.1950C>A	p.Y650*	POI	Colombo et al. (2017)[†]	NF	NF	NF
<i>STAC3</i>	NM_01282717:c.677C>G	p.S227*	POI	He et al. (2018)	3.98E-06	8.24E-06	3.19E-05
<i>STAC3</i>	NM_012447.2:c.1573+5G>A	p.L490Tfs*10	POI	Le Quesne Stabej et al. (2016)	1.19E-05	NF	NF
<i>STAC3</i>	NM_012447.3:c.1947_1948dup	p.Y650Sfs*22	POI	Caburet et al. (2014)	NF	NF	NF
<i>STAC3</i>	NC_000007.13:g.99786485del	p.F187fs*7	POI	Heddar et al. (2019)	NF	NF	NF
<i>STAC3</i>	NM_001282716.1:c.659T>G	p.L220R	POI		NF	NF	NF

	NM_001282716.1:c.3052del	p.R1018DfsTer14	POI						
STAC3	NC_000007.13:g.99794799G>A	p.R321H						NF	NF
MCM8	NC_000020.10:g.5948227G>A	p.E341K	Early menopause risk					NF	NF
MCM8	NC_000020.10:g.5948227G>A	p.E341K	Early menopause risk					0.0451	0.0451
MCM8	NC_000020.10:g.5948227G>A	p.E341K	Early menopause risk					0.0451	0.0378
MCM8	NC_000020.11:g.5954739T>A	Intronic variant	Early menopause risk					0.0451	0.0378
MCM8	NM_001281520.1:c.1954-1G>A	p.V652Wfs*6, p.V652_Q664del, or p.V652_E721del	POI					NR	
		p.L491fs*88						3.98E-06	8.25E-06
MCM8	NM_001281520.1:c.1469_1470insTA		POI					NF	NF
MCM8	NM_032485:c.446C>G	p.P149R	POI					NF	NF
MCM8	NM_001281520.1:c.482A>C	p.H161P	POI					NF	NF
MCM8	NC_000020.10:g.5948227G>A	p.E341K	Early menopause risk					NF	NF
MCM8	NC_000020.11:g.5954739T>A	Intronic variant	Early menopause risk					0.0451	0.0451
MCM8	NM_001281522.1:c.925C>T	p.R309*	Growth retardation, recurrent pilomatricomas, primary amenorrhea					NF	NF
MCM8	NM_032485.4:c.351_354del	p.K118Efs*5	POI					7.96E-06	8.24E-06
MCM9	NM_017696.2:c.1732+2T>C	SDS variant	POI, short stature					NF	NF
MCM9	NM_017696.2:c.394C>T	p.R132*	POI, short stature					1.33E-05	
MCM9	NC_000006.11:c.672_673delinsC	p.Q225Kfs*4	POI, mixed polyposis, colorectal cancer					7.97E-06	8.24E-06
MCM9	NM_017696.2:c.1483G>T	p.E495*	POI, short stature					NF	NF
DMC1	NM_007068.3: c.106G>A	p.D36N	POI					NF	NF
PSMC3/P	NM_016556.2:c.600_602del	p.E201del	46,XX ovarian dysgenesis					NF	NF
PSMC3/P	NC_000017.10:c.489C>G	p.Y163*	POI					NF	NF
PSMC3/P	NM_016556:c.496_497del	p.R166Afs	POI					NF	NF
PSMC3/P	NM_016556:c.430_431insCA	p.L144*	POI					NF	NF

*Reference sequence or reference sequence version number not reported; ¹Frequency in gnomAD v2.1.1 exomes; ²Frequency in ExAc v1.0; ³Frequency in gnomAD v2.1.1 genomes;

⁴Frequency in gnomAD SVs v2.1; NF, not found; N/A, not applicable; SDS, Splice donor site; POI, Primary ovarian insufficiency.

synapsed chromosome axes (Fig. 2) (Wojtasz *et al.* 2009, Chen *et al.* 2014a). The processes of DSB formation and HORMAD removal are susceptible to dysregulation by infertility-associated genetic variants. For example, variants in *NBN* (*NBS1*), a gene essential for DSB generation (Fig. 2), also lead to POI and Nijmegen breakage syndrome, a syndrome of microcephaly, recurrent cancer and infertility (Warcoin *et al.* 2009, Tucker *et al.* 2018, Szeliga *et al.* 2019, Fievet *et al.* 2020). In addition, several variants in *TRIP13* have been linked with female infertility phenotypes both in mouse models and in clinical settings. *TRIP13* (or *PCH2*) is an AAA+ ATPase that, in meiosis, catalyzes the removal of the meiosis-specific HORMADs, HORMAD1 and HORMAD2, from synapsed chromosome axes (Fig. 2) (Wojtasz *et al.* 2009, Chen *et al.* 2014a). Male and female *Trip13*-knockout mice are sterile; female *Trip13*-knockout mice undergo oocyte atresia resulting in POI (Li & Schimenti 2007).

In contrast to the oocyte atresia phenotype in mouse, human *TRIP13* variants are linked with oocyte maturation arrest (Table 1). The first is a homozygous missense variant in exon 1 (NM_004237.4:c.77A>G), found in three patients with infertility. Two other infertility patients had compound heterozygous variants. One patient's compound heterozygous variants lie in exons 5 and 10 (NM_004237.4:c.518G>A and NM_004237.4:c.907G>A), the latter of which encodes the AAA+ ATPase domain. The other patient's compound heterozygous variants lie in the AAA+ ATPase domain (NM_004237.4:c.592A>G; NM_004237.4:c.739G>A) (Zhang *et al.* 2020b). Each patient had primary infertility despite regular menstrual cycles. During IVF cycles, MI oocytes could be retrieved, but attempts to mature the oocytes failed. In the patients with the homozygous mutation and one of the compound heterozygous mutations (NM_004237.4:c.518G>A; NM_004237.4:c.907G>A), nearly all oocytes were arrested in metaphase I (Zhang *et al.* 2020b). However, in the patient with the other compound heterozygous mutations (NM_004237.4:c.592A>G; NM_004237.4:c.739G>A), 14 mature eggs were retrieved. Twelve of these eggs fertilized, but all subsequently arrested at the eight-cell stage. *In vitro* ATPase assay of the NM_004237.4:c.739G>A variant compared to WT *TRIP13* showed significantly diminished ATPase activity; the other *TRIP13* variants identified (Table 1) had no change in ATPase activity (Zhang *et al.* 2020b). Finally, the effects of these *TRIP13* variants on HORMAD2 have been interrogated. Ectopic expression of WT *TRIP13* in HeLa cells decreased total HORMAD2 protein content, but HORMAD2 levels were unchanged by ectopic expression of the NM_004237.4:c.739G>A, NM_004237.4:c.907G>A, and NM_004237.4:c.77A>G *TRIP13* variants (Zhang *et al.* 2020b). These data suggest that these three variants may impair HORMAD2 removal. Interestingly, the

clinical phenotype of patients harboring these variants is not POI, as it is in mouse, suggesting that the impact of *TRIP13* mutation acts later during chromosome segregation (Fig. 1).

After DSBs are generated, DNA is resected and vulnerable single-stranded DNA remains. In mammals, two homologs of the bacterial recombinase RecA, RAD51 and DMC1, assemble on the single-stranded DNA, search for homologous DNA sequences and promote strand invasion. Proteasome 26S ATPase subunit 3-interacting protein (PSMC3IP), also called homologous-pairing protein 2 (HOP2) (Leu *et al.* 1998), heterodimerizes with MND1 to stimulate DMC1 and RAD51 activity. PSMC3IP/MND1 stabilizes DMC1 and RAD51 filaments on single-stranded DNA and catalyzes the capture of double-stranded DNA (Fig. 2) (Sansam & Pezza 2015). *Hop2*- and *Dmc1*-knockout mice lack ovarian follicles and have small ovaries, suggesting that loss of these DNA-repair proteins is associated with infertility phenotypes (Pittman *et al.* 1998, Petukhova *et al.* 2003).

Similar to the mouse knockout phenotypes, variants in both *DMC1* and *PSMC3IP* are associated with POI (Table 1). A homozygous *DMC1* missense variant (NM_007068.3:c.106G>A) was found in a consanguineous family with male and female infertility. At the time of the study, the female patient was 30 years old, had been infertile for at least 3 years and was diagnosed with POI at age 20 (He *et al.* 2018). The *DMC1* variant in this family lies in the helix-3 turn-helix DNA-binding motif conserved between RAD51 and DMC1. *In silico* analysis predicts that the substitution alters hydrogen bonds within the structure, suggesting that the variant interrupts DNA interactions (He *et al.* 2018). Several other proteins essential in the process of strand invasion are implicated in infertility (Fig. 2), including *BRCA1*, *BRCA2* and *HFM1* (Oktay *et al.* 2010, 2020, Valentini *et al.* 2013, Wang *et al.* 2014a,b, Pu *et al.* 2016, Lin *et al.* 2017, Lambertini *et al.* 2018, Turan *et al.* 2018, Weinberg-Shukron *et al.* 2018, Caburet *et al.* 2020, Porcu *et al.* 2020, Zhe *et al.* 2019, Turan & Oktay 2020), suggesting that this process is particularly important for fertility.

Three studies have identified *PSMC3IP* variants unique to patients with subfertility. A homozygous 3-bp deletion in the conserved C-terminus of *PSMC3IP* (NM_016556.2:c.600_602del) was found in five patients with 46,XX ovarian dysgenesis. All affected patients had primary amenorrhea and their ovaries were undetectable on ultrasound (Zangen *et al.* 2011). Subsequently, a homozygous C-terminal truncation in exon 6 of *PSMC3IP* (NC_000017.10:c.489C>G) was identified. In this family, two sisters and one brother were homozygous for the mutation and had primary amenorrhea or azoospermia (Al-Agha *et al.* 2018). This sexually monomorphic phenotype mirrors that of the *Hop2*-knockout mice. The most recent detection

of *PSMC3IP* POI-associated variants was in a woman who had two variant alleles of *PSMC3IP* predicted to be pathogenic (NM_016556:c.496_497del and NM_016556:c.430_431insGA). On ultrasound, ovaries and follicles were undetectable (Yang *et al.* 2019b). In contrast, a cohort of 50 Swedish women with POI did not have any pathogenic variants of *PSMC3IP* (Norling *et al.* 2014), highlighting the genetic complexities that give rise to this syndrome. The mechanism by which the mutations disrupt *PSMC3IP* is unknown.

DSBs are genotoxic and DNA repair is therefore critical for cell survival and genome integrity. Many DNA helicases are recruited during this process to protect the structural integrity of single-stranded DNA. Among these helicases is the complex formed by minichromosome maintenance proteins 8 and 9 (MCM8 and MCM9) (Gozuacik *et al.* 2003, Yoshida 2005). MCM8 and MCM9 form a hexameric helicase, which promotes RAD51 recruitment and DNA synthesis at sites of DSBs (Fig. 2) (Park *et al.* 2013, Natsume *et al.* 2017, Hustedt *et al.* 2019). Both male and female *Mcm8*-knockout mice are sterile. The oocytes from *Mcm8*^{-/-} mice cannot undergo DSB repair and their ovaries are small and adenoma-ridden. Upon histological examination, their primary follicles are shrunken and dysmorphic (Lutzmann *et al.* 2012). In contrast, the consequence of *Mcm9* knockout is sexually dimorphic. Female knockouts are sterile and completely lack oocytes. However, male knockout mice are fertile, but have fewer germ cells than their WT counterparts (Hartford *et al.* 2011, Lutzmann *et al.* 2012). Primary follicles are completely absent in the ovaries of *Mcm9* knockout mice (Lutzmann *et al.* 2012).

Reports of mixed reproductive-somatic syndromes associated with *MCM8/9* variants indicate that this complex is essential in both human germ cells and somatic cells. One investigation identified two *MCM9* variants, each in separate consanguineous families bearing daughters with POI and short stature. One variant alters a splice donor site (NM_017696.2:c.1732+2T>C), generating a truncated splice variant, while the other variant generates a premature stop codon (NM_017696.2:c.394C>T). When ectopically expressed in human HEK293T cells, truncated MCM9 failed to localize to sites of DNA damage (Wood-Trageser *et al.* 2014). A subsequent study identified a child of a consanguineous family with primary amenorrhea, short stature, and recurrent pilomatricomas (benign hair follicle tumors). This patient had a truncating mutation in exon 9 of *MCM8* (NM_001281522.1:c.925C>T) (Heddar *et al.* 2020). Moreover, a homozygous *MCM9* truncation (hg19:c.672_673delinsC) in a consanguineous family was linked with POI and gastrointestinal polyposis (Goldberg *et al.* 2015), a pathology classically associated with variants in genome stability genes (Grady & Carethers 2008). Heterozygotes in the family had no reproductive pathologies, but rather late-onset gastrointestinal tumors (Goldberg *et al.* 2015).

Several studies have linked *MCM8/9* variants with POI (Table 1), strengthening the association between the complex and female infertility.

Menopause represents the end of the female reproductive lifespan. Although there is a spectrum of causes of early menopause, one associated cause is depletion of the ovarian reserve, such as in POI (Edmonds 2012). Analyses of several genome-wide association studies (GWAS) indicate that *MCM8* variants are associated with early menopause. A SNP in exon 9 of *MCM8* (NC_000020.10:g.5948227G>A) was first identified as associated with early natural menopause in the Nurse's Health Study and the Women's Genome Health Study (He *et al.* 2009). A subsequent study found that NC_000020.10:g.5948227G>A increased the risk of early menopause by 85% (Murray *et al.* 2011). An investigation of age-of-menopause-associated SNPs in Hispanic women corroborated NC_000020.10:g.5948227G>A and identified a novel variant, NC_000020.11:g.5954739T>A, as linked with early menopause (Chen *et al.* 2012). Additional studies using population-level data reinforced the association between NC_000020.10:g.5948227G>A and early menopause (Carty *et al.* 2013, Coignet *et al.* 2017). Two studies, a meta-analysis of 6510 patients (Chen *et al.* 2014b) and a GWAS of 2455 patients (Spencer *et al.* 2013), sought the age of menopause-associated alleles in African-American women. In contrast to the findings described previously, neither of these studies found *MCM8* alleles associated with early menopause. These studies collectively demonstrate an abundant range of fertility phenotypes associated with *MCM8/9* helicase complex variants, which are complicated by ethnicity differences and a variety of alleles. Other work that identified infertility-linked variants in recombination, such as *MEIOB*, *MSH4*, *MSH5* and *MLH3* corroborate the essential role of recombination in fertility (Fig. 2) (Mandon-Pepin *et al.* 2008, Ferras *et al.* 2012, Pashaiefar *et al.* 2013, Carlosama *et al.* 2017, Guo *et al.* 2017, Caburet *et al.* 2019). Therefore, some genes associated with early menopause function in meiotic recombination, which illustrates unifying etiology of POI and some cases of early menopause.

In both mitosis and meiosis, cohesin complexes provide cohesion between sister chromatids and between homologous chromosomes; cohesion is essential for DSB repair by homologous recombination (Birkenbihl & Subramani 1992, Sjogren & Nasmyth 2001, Sonoda *et al.* 2001, Schar *et al.* 2004, Atienza *et al.* 2005). Together, two hinge-like SMC proteins, a kleisin and a stromalin form a ring-shaped cohesin complex (Fig. 2) (Chiu *et al.* 2004). During pre-meiotic DNA replication, cohesin complexes join homologous chromosomes along their arms and sister chromatids at their centromeres (Klein *et al.* 1999, Buonomo *et al.* 2000, Pasierbek *et al.* 2001). One subunit gene, stromal antigen protein 3 (*STAG3*) is expressed exclusively during

meiosis (Pezzi *et al.* 2000, Prieto *et al.* 2001). Molecular and clinical studies of STAG3 indicate that it is essential for both mouse and human gametogenesis and fertility. *Stag3* perturbation in mouse causes gametes to arrest in prophase I and *Stag3* knockout mice of both sexes are sterile (Hopkins *et al.* 2014, Winters *et al.* 2014). At a molecular level, the chromosomes in *Stag3* knockouts cannot crossover because intact cohesin is required for DSB repair (Hopkins *et al.* 2014). Additionally, STAG3 accumulates on microtubules in mouse oocytes and may be required for kinetochore-microtubule attachments to prevent aneuploidy (Zhang *et al.* 2017).

Similar to findings in mouse, STAG3 dysfunction in humans is associated with reduced oocyte viability. For example, a homozygous truncation mutation (NC_000007.13:g.99786485del) was identified in four sisters. Each presented with POI between ages 17 and 20. The premature stop codon interrupts the STAG domain in exon 7, thereby removing exons 8–34. Heterozygote family members did not have POI, indicating autosomal recessive inheritance. Notably, one patient homozygous for the NC_000007.13:g.99786485del allele developed bilateral ovarian cancer at age 19, but the relationship between this allele and ovarian cancer is unknown (Caburet *et al.* 2014). Subsequent studies have identified other *STAG3* mutations associated with POI (Table 1). All of these cases share several features. First, the patient is either homozygous for a variant allele or is compound heterozygous for two variant alleles, suggesting that POI-causing *STAG3* mutations are autosomal recessive. Second, all affected patients had primary amenorrhea. Finally, all affected patients examined via ultrasound had a structural gynecologic problem. Most often, patients had streak ovaries and, sometimes, they had small uteri. This clinical phenotype mimics *Stag3* knockout in mouse, but defects in kinetochore-microtubule attachments have not been evaluated likely because of the severity of POI. Interestingly, other variants of *STAG3* exist that have not been linked to POI and their clinical phenotype is unknown. For example, 569 missense variants are listed for this gene in the gnomAD database. Given *STAG3*'s critical role in meiosis and the large number of *STAG3* genetic variants, there may be undescribed fertility phenotypes, such as embryonic death or aneuploidy, associated with other *STAG3* variants.

Meiotic resumption: regulating translation and building a spindle

After completion of homologous recombination, oocytes arrest in the final stage of prophase I where they will eventually grow in size within follicles. During the growth phase, oocytes are transcriptionally active, but once they are fully grown, transcription ceases. Beginning at puberty and recurring in each menstrual cycle, a luteinizing hormone (LH) surge triggers ovulation and meiotic resumption. Meiotic resumption

is the period between the exit from prophase I arrest and entry into metaphase I (Figs 1 and 3). It shares similar regulatory features of the mitotic G2/M cell cycle transition, such as CDK1-dependent nuclear envelope breakdown and spindle building (Solc *et al.* 2010). To build a spindle, mouse oocytes use aggregated clusters of microtubule-organizing centers (MTOCs) to nucleate microtubules to form the meiotic spindles (Schuh & Ellenberg 2007). In human oocytes, however, a RAN-dependent chromatin-driven pathway nucleates microtubules (Holubcova *et al.* 2015).

Translation repression

During oocyte growth and oogenesis, transcription and translation are tightly controlled. Oocyte maturation, fertilization and preimplantation embryonic development occur without transcription and rely on translation of stored maternal RNAs. Once oocytes resume meiosis, there is a regulated burst of maternal RNA translation. One negative regulator of oocyte translation is Protein Associated with Topoisomerase II Homolog 2 (PATL2). In *Xenopus laevis* eggs the PATL2 homolog, P100, complexes with the cytoplasmic polyadenylation element binding (CPEB) ribonucleoprotein complex and binds transcripts to repress translation (Fig. 3A) (Marnef *et al.* 2010). Loss of *Patl2* caused decreased translational repression in mouse (Christou-Kent *et al.* 2018). P100 protein levels decrease rapidly after nuclear envelope breakdown, which marks meiotic resumption, thereby allowing translation of maternal RNAs (Marnef *et al.* 2010, Nakamura *et al.* 2010). Litter sizes from *Patl2*-knockout female, but not male, mice are reduced. Significantly more metaphase I-arrested oocytes were found in *Patl2*^{-/-} mice than in WT, although some prophase I oocytes harvested from *Patl2*^{-/-} mice reached meiosis II. Importantly, the arrested oocytes have significantly more spindle morphology defects and misaligned chromosomes. These data suggest that *Patl2* loss reduces oocyte quality by changing the regulation of mRNA transcripts, which makes it a strong candidate to cause human subfertility.

Two *PATL2* variants were identified in two families with female infertility (Maddirevula *et al.* 2017). In both cases, the affected patients had oocyte maturation defects but had regular menstrual cycles. Neither family reported male infertility. In one family, two sisters presented with infertility at ages 27 and 35. Both tried to conceive for over six years and all IVF cycles failed because only prophase I-arrested oocytes were retrieved. In the second family, two sisters had several years of infertility characterized by retrieval of only prophase I-arrested oocytes. Positional mapping and whole-exome sequencing of these patients found two homozygous variants of *PATL2*, a truncation (NM_001145112.1:c.478C>T) in the first family and a missense mutation (NM_001145112.1:c.1108G>A)

in the second family. Three fertile males in this study were homozygous for *PATL2* variants (Maddirevula *et al.* 2017). Several other *PATL2* mutations have been identified in female patients with infertility caused by oocyte maturation defects (Table 2). The phenotypic spectrum of patients with *PATL2* variants sometimes includes early embryonic arrest and phenotypic heterogeneity. One hypothesis for the complexity in phenotypes is that differences in cis-regulatory elements cause variable penetrance (Wu *et al.* 2019). Other unidentified mutations in interacting proteins may also compound or dilute the phenotype. In aggregate, these results suggest that the most common phenotype of *PATL2* variants is oocyte maturation defects. Although the structure of P100 is solved (Rother *et al.* 1992), the molecular biology of *PATL2* variants is otherwise unexplored. However, infertility-linked variants in another translational regulator, *NANOS3*, suggest that translational regulation may be a key pathogenic mechanism in infertility (Wu *et al.* 2013, Santos *et al.* 2014, Sousa *et al.* 2016).

Spindle building

Because the spindle is essential for chromosome segregation, variants in genes encoding spindle components could cause infertility. Microtubules are composed of α - and β -tubulin heterodimers, and *TUBB8* is the only primate-specific isotype of the β -tubulin family (Fig. 4). It contributes virtually all of the β -tubulin in primate oocytes (Feng *et al.* 2016a). *TUBB8* was first identified as a genetic correlate for human infertility in a family with at least four generations of female infertility (Feng *et al.* 2016a). Two family members underwent IVF. In both cases, the retrieved oocytes were either morphologically abnormal or, more often, MI-arrested. Subsequently, six additional families with *TUBB8* mutations and infertility were identified (Feng *et al.* 2016a) (Table 2). In each family, retrieved oocytes had either a morphologically abnormal or an absent spindle. When the mutant forms of *TUBB8* were overexpressed in HeLa cells or microinjected into mouse oocytes, spindles were unipolar or absent (Feng *et al.* 2016a).

Until recently, *TUBB8* function was poorly characterized, perhaps because its expression is limited to primate oocytes. New work shows that *TUBB8*'s numerous mutations give rise to a range of developmental arrest phenotypes (Table 2). Subsequent studies have identified several other *TUBB8*-variant phenotypes. One phenotype is fertilization failure (Feng *et al.* 2016b, Chen *et al.* 2017, 2019, Wang *et al.* 2018). Other phenotypes include, two-pronuclear zygotes with complete cleavage failure (Yuan *et al.* 2018), four-cell or eight-cell embryonic arrest (Feng *et al.* 2016b, Chen *et al.* 2017, 2019) and implantation failure (Chen *et al.* 2019). Perplexingly, there is no unifying genetic inheritance pattern of patients with *TUBB8* variants;

the cohorts include heterozygotes, homozygotes, and compound heterozygotes. The variants span all four exons of *TUBB8* and its two functional domains.

Nearly all of the patients with *TUBB8*-deficient oocytes underwent years of repeated IVF procedures, despite bearing oocytes that could not complete development. However, women with *TUBB8* mutations and oocyte maturation defects were able to successfully conceive with egg donation (Lanuza-Lopez *et al.* 2020). *TUBB8* is thus a strong candidate for clinical validation as a predictive biomarker of IVF failure so that patients may consider egg donation earlier.

Centrosomal Protein 120 (CEP120) plays an essential role in mitotic microtubule nucleation and therefore is likely required for successful meiosis and fertility (Fig. 4) (Mahjoub *et al.* 2010). Whole-exome sequencing of infertile patients revealed enrichment of a *Cep120* variant (NM_153223.3:c.2840G>A) in patients with disproportionately high rates of embryonic aneuploidy in their corresponding maternal age group (Tyc *et al.* 2020). When the identified variant was expressed in mouse oocytes, microtubule nucleation efficiency decreased and metaphase I chromosome misalignment increased, which resulted in increased frequency of egg aneuploidy at metaphase II.

Although mitotic cells form spindles using centriole-containing centrosomes, mammalian oocytes lack centrioles (Manandhar *et al.* 2005). Mouse oocytes contain acentriolar MTOCs. CEP120 localized to the forming MTOCs and ectopic expression of the variant reduced microtubule nucleation, which could contribute to unequal pulling forces on kinetochores upon anaphase I onset (Tyc *et al.* 2020). However, because human oocytes use a chromatin-based nucleation pathway, further evaluation of a role for CEP120 in human oocytes is warranted. Importantly, this study is the first whole-exome sequencing analysis in a cohort of subfertile patients grouped based on the proportion of *in vitro* fertilized embryos that are aneuploid. Such approaches help to develop biomarkers for age-independent risk of oocyte aneuploidy.

Chromosome segregation

Following meiotic resumption, oocytes continue to build the spindle and align chromosomes at the metaphase plate (Figs 1 and 4). The spindle is essential to segregate homologous chromosomes in anaphase I and, after fertilization, sister chromatids in anaphase II. To ensure euploid egg formation, spindle microtubules must correctly attach to kinetochore complexes that dock at centromeres. In meiosis I, sister chromatid kinetochores act as a unit and attach to microtubules that nucleate from the same spindle pole. However, in meiosis II, sister kinetochores will attach to microtubules from opposite poles. Gene variants appear to impact each of these steps and cause infertility.

Table 2 Female infertility-associated genetic variants affecting meiotic resumption. Genes are listed in order of appearance in text; their variants are listed in order of publication year. Frequencies of small (<1 kb) genetic variants were identified in gnomAD v2.1.1 and ExAC v1.0 via ANNOVAR.

Gene	DNA variant	Protein variant	Key phenotype	Reference	Allele frequency		
					gnomAD exomes ¹	ExAC ²	gnomAD genomes ³
PATL2	NM_001145112.1:c.784C>T	p.R62*	OM arrest	Chen <i>et al.</i> (2017)	0	NF	NF
PATL2	NM_001145112.1:c.558T>A;	p.Y186*	OM arrest	Chen <i>et al.</i> (2017)	NF		
PATL2	NM_001145112.1:c.223-14_223-2del	p.R75Vfs*21			0.0002	5.55E-05	0.0003
PATL2	NM_001145112.1:c.953T>C;	p.I318T	OM arrest	Chen <i>et al.</i> (2017)	6.50E-06		
PATL2	NM_001145112.1:c.839G>A	p.R280Q		Chen <i>et al.</i> (2017)	5.19E-05	5.05E-05	3.19E-05
PATL2	NM_001145112.1:c.649T>A;	p.Y217N;	OM arrest	Chen <i>et al.</i> (2017)	6.49E-06		
PATL2	NM_001145112.1:c.566T>G	p.L189R			6.49E-06		
PATL2	NM_001145112.1:c.1224+2T>C;	p.Q411Wfs*3;	OM arrest	Chen <i>et al.</i> (2017)			
PATL2	NM_001145112.1:c.223-14_223-2del	p.R75Vfs*21			0.0002	5.55E-05	0.0003
PATL2	NM_001145112.1:c.478C>T	p.R160*	OM arrest	Maddirevula <i>et al.</i> (2017)	3.25E-05		
PATL2	NM_001145112.1:c.1108G>A	p.G370R	OM arrest	Maddirevula <i>et al.</i> (2017)	6.60E-06		
PATL2	ENST0000043130:c.478C>T	p.R160*	OM arrest	Christou-Kent <i>et al.</i> (2018) [†]	3.25E-05		
PATL2	c.778G>A;	p.V260M;	OM arrest	Wu <i>et al.</i> (2019) [†]	NF		
PATL2	c.223-14_223-2del	p.R75Vfs*21			0.0002	5.55E-05	0.0003
PATL2	c.1273A>C	p.T425P;	OM arrest	Wu <i>et al.</i> (2019) [†]	NF		
PATL2	c.898C>T	p.Q300*			NF		
PATL2	c.877G>T	p.D293Y;	Embryonic arrest and OM arrest	Wu <i>et al.</i> (2019) [†]	NF		
PATL2	c.223-14_223-2del	p.R75Vfs*21			0.0002	5.55E-05	0.0003
PATL2	c.716del	p.N239fs*9;	Embryonic arrest and OM arrest	Wu <i>et al.</i> (2019) [†]	NF		
PATL2	c.223-14_223-2del	p.R75Vfs*21			0.0002	5.55E-05	0.0003
PATL2	NC_000015.9:c.1528C>A	p.P510T	OM arrest	Liu <i>et al.</i> (2020) [†]	NF		
PATL2	NC_000015.9:c.1376C>A	p.S459Y	OM arrest	Liu <i>et al.</i> (2020) [†]	NF		
TUBB8	NM_177987:c.527C>T	p.S176L	OM arrest	Feng <i>et al.</i> (2016a) [†]	NF		
TUBB8	NM_177987:c.1249G>A	p.D417N	OM arrest	Feng <i>et al.</i> (2016a) [†]	NF		
TUBB8	NM_177987:c.5G>A	p.R2K	OM arrest	Feng <i>et al.</i> (2016a) [†]	NF		
TUBB8	NM_177987:c.785G>A	p.R262Q	OM arrest	Feng <i>et al.</i> (2016a) [†]	NF		
TUBB8	NM_177987:c.900G>A	p.M300I	OM arrest	Feng <i>et al.</i> (2016a) [†]	NF		
TUBB8	NM_177987:c.1088T>C	p.M363T	OM arrest	Feng <i>et al.</i> (2016a) [†]	NF		
TUBB8	NM_177987:c.686T>C	p.V229A	OM arrest	Feng <i>et al.</i> (2016a) [†]	NF		
TUBB8	c.426_427insG	p.T143Dfs*12	OM arrest	Feng <i>et al.</i> (2016b) [†]	NF		
TUBB8	c.80_100del	p.E27_A33del	OM arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	c.1043A>G	p.N348S	Embr. arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	c.628A>G	p.I210V	Embr. arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	c.853A>C	p.T285P	OM arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	c.527C>T	p.S176L	OM arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	c.713C>T	p.T238M	Embr. arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	c.784C>T	p.R262W	OM arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	c.763G>A	p.V255M	OM arrest	Feng <i>et al.</i> (2016b) [†]	NP		
TUBB8	ENST00000309812.4:c.10A>C	p.I4L	OM arrest	Feng <i>et al.</i> (2016b) [†]	2.12E-05	6.77E-05	0.0005
TUBB8	ENST00000309812.4:c.209C>T	p.P70L	OM arrest	Chen <i>et al.</i> (2017)	0	2.75E-05	3.19E-05
TUBB8	ENST00000309812.4:c.1057G>A	p.V353I	Embr. arrest	Chen <i>et al.</i> (2017)	1.21E-05	8.44E-06	
TUBB8	ENST00000309812.4:c.35G>A	p.C12Y	OM arrest	Chen <i>et al.</i> (2017)	NF		

TUBB8	ENST00000309812.4:c.580G>A, ENST00000309812.4:c.1245G>A	p.E194K; p.M415I	Embr. arrest	Chen et al. (2017)	NF	
TUBB8	ENST00000309812.4:c.5G>T	p.R2M	OM arrest	Chen et al. (2017)	NF	
TUBB8	ENST00000309812.4:c.613G>A	p.E205K	Embr.arrest	Chen et al. (2017)	NF	
TUBB8	ENST00000309812.4:c.990G>A	p.M330I	Embr. arrest	Chen et al. (2017)	NF	
TUBB8	Gross whole-gene deletion	N/A		Wang et al. (2018)	NF	
TUBB8	NM_177987.2:c.292G>A	p.G98R	OM arrest	Yuan et al. (2018)	3.58E-05	3.18E-05
TUBB8	NM_177987.2:c.322G>A	p.F108K	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1205dup	p.M403Hfs*3	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.426dup;	p.T143Dfs*12;	OM arrest	Chen et al. (2019)	3.58E-05	3.18E-05
TUBB8	NM_177987.2:c.322G>A	p.F108K	OM arrest	Chen et al. (2019)	3.30E-05	3.19E-05
TUBB8	NM_177987.2:c.10A>C	p.I4L	Embr. arrest	Chen et al. (2019)	0	
TUBB8	NM_177987.2:c.1000C>G	p.Q334E	Embr. arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1072C>G	p.P358A	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1073C>T	p.P358L	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1171C>T	p.R391C	Embr. arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1270C>T	p.Q424*	OM arrest	Chen et al. (2019)	8.16E-06	3.37E-05
TUBB8	NM_177987.2:c.1286C>T;	p.T429M;	N/A	Chen et al. (2019)	2.92E-05;	3.50E-05
TUBB8	NM_177987.2:c.1301_1327del	p.434_442del		Chen et al. (2019)	6.87E-05	3.40E-05
TUBB8	NM_177987.2:c.181C>A	p.P61T	Embr. arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.527C>T	p.S176L	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.721C>T	p.R241C	Embr. arrest	Chen et al. (2019)	1.64E-05	0
TUBB8	NM_177987.2:c.1057G>A	p.V353I	Embr. arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1061G>A	p.C354Y	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1228G>A	p.E410K	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1249G>T	p.D417Y	Embr. arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.292G>A	p.G98R	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.523G>A	p.V175M	OM arrest	Chen et al. (2019)	8.90E-06	
TUBB8	NM_177987.2:c.722G>A	p.R241H	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.735G>C	p.Q245H	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.763G>A	p.V255M	Embr. arrest	Chen et al. (2019)	2.12E-05	0.0005
TUBB8	NM_177987.2:c.763G>A	p.V255M	OM arrest	Chen et al. (2019)	2.12E-05	0.0005
TUBB8	NM_177987.2:c.883G>C	p.D295H	Embr. arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.1099T>C	p.F367L	OM arrest	Chen et al. (2019)	NF	
TUBB8	NM_177987.2:c.600T>G	p.F200L	Embr. arrest	Chen et al. (2019)	0	
TUBB8	NM_177987.2:c.735G>C	p.Q245H	OM arrest	Lanuza-Lopez et al. (2020)	NF	
TUBB8	NM_177987.2:c.845G>C	p.R282P	OM arrest	Lanuza-Lopez et al. (2020)	NF	
TUBB8	NM_177987.2:c.763G>A	p.V255M	OM arrest	Lanuza-Lopez et al. (2020)	2.12E-05	0.0005
TUBB8	NM_177987.2:c.178G>C	p.V60L	OM arrest	Zhao et al. (2020a)	NF	
TUBB8	NM_177987.2:c.1130T>C	p.L377P	OM arrest	Zhao et al. (2020a)	NF	
TUBB8	NM_177987.2:c.260C>T	p.P87L	Embryonic implantation failure; fertilization failure	Zhao et al. (2020a)	NF	
TUBB8	NM_177987.2:c.1172G>A	p.R391H	Embr. arrest	Zhao et al. (2020a)	NF	
TUBB8	NM_177987.2:c.608A>G	p.D203G	Embryonic implantation failure	Zhao et al. (2020a)	NF	
TUBB8	NM_177987.2:c.728C>T	p.P243L	OM arrest	Zhao et al. (2020a)	NF	
TUBB8	NM_177987.2:c.1103T>C;	p.I368T;	OMn arrest	Zhao et al. (2020a)	NF	

(Continued)

Table 2 Continued.

Gene	DNA variant	Protein variant	Key phenotype	Reference	Allele frequency		
					gnomAD exomes ¹	ExAc ²	gnomAD genomes ³
TUBB8	NM_177987.2:c.382dup	p.D128Gfs*27	OM arrest	Zhao <i>et al.</i> (2020a)	NF		
	NM_177987.2:c.80_100del;	p.E27_A33del;			NF		
	NM_177987.2:c.1103T>C	p.I368T			NF		
	NM_177987.2:c.82C>T;	p.H28Y;			2.48E-05;	4.29E-05	
TUBB8	NM_177987.2:c.148_154delinsCACACACAGGCCAGCG	p.Y50_N52delinsHHHEAS-GATPVLPPNVHHH	Embr. arrest	Zhao <i>et al.</i> (2020a)	NF		
	GTGCGACCCCGCTCTCC				0	8.41E-06	
	CCACCCACGTGCACACAC	p.Q134*;			NF		
	NM_177987.2:c.400C>T;	p.D118G			NF		
TUBB8	NM_177987.2:c.353A>G	p.C239S	Embryonic implantation failure; fertilization failure	Zhao <i>et al.</i> (2020a)	NF		
	NM_177987.2:c.716G>C				0		
	NM_177987.2:c.662C>T	p.T221I			0		
	NM_177987.2:c.1139G>A	p.R380H			0		
TUBB8	NM_177987.2:c.1163T>C	p.M388T	Embr. arrest	Zhao <i>et al.</i> (2020a)	NF		
	NM_177987.2:c.236G>A	p.G79E			NF		
	NM_177987.2:c.293G>A	p.G98E			NF		
	NM_177987.2:c.148T>C	p.Y50H			0		0
TUBB8	NM_177987.2:c.743C>T	p.A248V	Embr. arrest	Zhao <i>et al.</i> (2020a)	NF		
	NM_177987.2:c.893A>G	p.N298S			NF		
	NM_177987.2:c.940G>T	p.A314S			NF		
	NM_177987.2:c.1187A>G	p.H396R			NF		
TUBB8	NM_177987.2:c.728C>G	p.P243R	Embryonic implantation failure; embr. arrest	Zhao <i>et al.</i> (2020a)	NF		
	NM_177987.2:c.497C>T	p.T166I			NF		
	NM_177987.2:c.12C>G	p.I4M			NF		
	NM_177987.2:c.1164G>A	p.M388I			NF		
TUBB8	NM_177987.2:c.49G>A	p.G17S	Embryonic implantation failure	Zhao <i>et al.</i> (2020a)	5.24E-06		
	NM_177987.2:c.1076G>A	p.R359Q			7.96E-06	1.66E-05	3.19E-05
	NM_177987.2:c.736C>G	p.L246V			NF		
	NM_177987.2:c.925C>T	p.R309C			1.22E-05	8.58E-06	0.0002
TUBB8	NM_177987.2:c.535G>C	p.V179L	OM arrest	Zhao <i>et al.</i> (2020a)	NF		
	NM_177987.2:c.82C>T;	p.H28Y;			2.48E-05	4.29E-05	
	NM_177987.2:c.398T>C	p.F133S			NF		
	NM_153223.3:c.2840G>A	p.R947H			NF		
CEP120			Increased egg aneuploidy relative to maternal age	Tyc <i>et al.</i> (2020)			

¹Reference sequence or reference sequence version number not reported; ²Frequency in gnomAD v2.1.1 exomes; ³Frequency in ExAc v1.0; ⁴Frequency in gnomAD v2.1.1 genomes. NF, not found; NP, reference sequence not provided; OM, oocyte maturation; Embr., embryonic.

The Aurora kinases (AURK) are serine/threonine kinases critical in mitosis and meiosis. Mammals have three isoforms: A, B, and C. AURKB and AURKC are members of the chromosomal passenger complex (CPC), essential for faithful chromosome transmission in meiosis by allowing correction of improperly attached kinetochore microtubules (Fig. 4) (Sharif *et al.* 2010, Balboula & Schindler 2014). Female *Aurkc*-knockout mice are subfertile and their oocytes frequently have chromosome misalignment (Schindler *et al.* 2012). Female *Aurkb*-knockout mice, however, are significantly less fertile than *Aurkc*-knockout mice and undergo premature age-related infertility (Nguyen *et al.* 2018).

Anaphase I onset in oocytes with chromosome misalignment often leads to aneuploidy. A protective *AURKB* mutation (hg19:g.8111091A>G) was identified in a patient who had low embryo aneuploidy relative to her age (39 years old, 33% aneuploid blastocysts) (Nguyen *et al.* 2017). Compared to mouse oocytes expressing WT *AURKB*, oocytes expressing the *AURKB* NC_000017.10:c.T116C variant more rapidly aligned their chromosomes when challenged with a microtubule regrowth assay. These data indicate that this gain-of-function *AURKB* variant protects against aneuploidy. Women who harbor this variant may have longer reproductive lifespans. Maternal *Aurkb* variants have also been associated with more complex aneuploid phenotypes, including a fetus with abnormal brain and skull development (anencephaly) with >10% aneuploid cells (Lopez-Carrasco *et al.* 2013). These results suggest that *AURKB* catalytic function is closely tied to egg ploidy where increased kinase function facilitates euploidy, while decreased kinase function can cause aneuploidy.

The difference in the impact of *Aurkb* and *Aurkc* loss on female mouse fertility is reflected in human fertility. *AURKC* expression is almost exclusive to germ cells (Fellmeth *et al.* 2015) and the first three embryonic division cycles (Avo Santos *et al.* 2011). *AURKC* variants are associated with spermatogenesis defects leading to male infertility (reviewed in Coutton *et al.* 2015, Quartuccio & Schindler 2015), but *AURKC* dysfunction in female infertility is more sparsely described. An *AURKC* deletion has been detected in infertile men, but two fertile sisters also harbored the deletion (Dieterich *et al.* 2009). However, because the *Aurkc*-knockout phenotype in female mice is smaller litter sizes, not sterility, a potential subfertility effect of *AURKC* defects in human females may be subtle and potentially overlooked.

Meiotic cell cycle regulation: maintaining arrests and controlling exits

To maintain prophase I arrest and to trigger exit from the metaphase II arrest (Figs 1 and 5), the activity of maturation promoting factor complex (MPF), which consists of a heterodimer of CDK1 and CCNB1 (cyclin

B) (Han *et al.* 2005), must be inhibited. This inhibition is accomplished by phosphorylation on a tyrosine residue in CDK1 and regulation of cyclin B stability. Aberrant regulation of CDK1 activity could alter the precision in timing required for fertilization. Indeed, several genes involved in the transition out of metaphase I and arrest at metaphase II are implicated in infertility, including *POF1B* and *CDC20* (Fig. 5) (Lacombe *et al.* 2006, Ledig *et al.* 2015, Weinberg-Shukron *et al.* 2015, Huang *et al.* 2019, Oral *et al.* 2019, Wang & Liu 2020, Zhao *et al.* 2020b).

WEE2 oocyte meiosis inhibiting kinase (WEE2 or WEE1B) is an oocyte-specific tyrosine kinase that phosphorylates and inhibits CDK1 (Figs 3B and 5); in prophase I, this phosphorylation maintains arrest, but, after fertilization, it promotes meiotic exit (Han *et al.* 2005, Oh *et al.* 2010, 2011). In rhesus macaque and mouse oocytes, *Wee2* knockdown causes some prophase I-arrested oocytes to resume meiosis prematurely (Han *et al.* 2005, Hanna *et al.* 2010). In humans, WEE2 inhibitors are being studied as hormonal contraception, suggesting that WEE2 may play a role in human reproduction (Hanna *et al.* 2019).

WEE2 variants are associated with fertilization failure after intracytoplasmic sperm injection (ICSI). In the first identified cases of WEE2-associated fertilization failure, metaphase II eggs were retrieved from four women ranging in age from 27 to 37. The WEE2 mutations were all homozygous (Table 3). In each case, the patients underwent menarche at an appropriate age, had regular menses, and generated polar-body-extruding oocytes. However, ICSI was unsuccessful and pronuclei failed to form. Surprisingly, the microinjection of WT-WEE2 cRNA into the four patients' eggs rescued the fertilization failure phenotype, and two pronuclei formed. Two of the four oocytes developed into euploid blastocysts, while the others arrested (Sang *et al.* 2018). No further clinical follow-up was described. The homozygous inheritance of the mutation and the phenotype rescue with WT WEE2 suggests autosomal recessive inheritance.

When the identified mutants were expressed in mouse oocytes, polar body extrusion and phosphorylated CDK1 decreased significantly compared to controls (Sang *et al.* 2018). These data suggest that, in patients with these WEE2 variants, WEE2 is unable to sufficiently inactivate CDK1, resulting in impaired meiotic exit and pronucleus formation. Subsequently, WEE2 mutants were associated with patients who, despite having regular menses, had eggs that could not form pronuclei upon ICSI (Dai *et al.* 2019, Yang *et al.* 2019a, Zhang *et al.* 2019b, Zhao *et al.* 2019, Zhou *et al.* 2019). However, one patient with a WEE2 mutation (NM_001105558.1:c.1228C>T) demonstrated a different phenotype: poor-quality embryos. Of 30 eggs, three formed normal-looking 2-pronuclei zygotes and three formed abnormal 3-pronuclei zygotes. Of the 2-pronuclei zygotes, all later arrested after cleavage

Table 3 Female infertility-associated genetic variants affecting cell cycle regulation. Variants are listed in order of publication year. Frequencies of small (<1 kb) genetic variants were identified in gnomAD v2.1.1 and ExAc v1.0 via ANNOVAR.

Gene	DNA variant	Protein variant	Clinical phenotype	Reference	Allele frequency		
					gnomAD exome ¹	ExAc ²	gnomAD genome ³
WEE2	NM_001105558.1:c.700G>C	p.D234H	Fertilization failure	Sang et al. (2018)	NF		
WEE2	NM_001105558.1:c.1473dup	p.T493Nfs*39	Fertilization failure	Sang et al. (2018)	NF		
WEE2	NM_001105558.1:c.220_223del	p.E75Vfs*6	Fertilization failure	Sang et al. (2018)	NF		
WEE2	NM_001105558.1:c.1006_1007insTA	p.H337Yfs*24	Fertilization failure	Sang et al. (2018)	NF		
WEE2	NC_000007.13:c.598C>T	p.R200*	Fertilization failure	Zhou et al. (2019) [†]	1.61E-05	2.50E-05	9.56E-05
WEE2	NC_000007.13:c.1319G>C	p.W440S	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.293_294ins	p.P98P fsX2	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	CTGAGACACGACCCCAACC	p.Y526D	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.1576T>G	p.H331N	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.991C>A	p.T435M fsX31	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.1304_1307del	p.K114N fsX20	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.341_342del	p.Q288H	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.864G>C	p.Q288H	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.1A>G	p.Q?	Fertilization failure	Zhao et al. (2019) [†]	NF		
WEE2	NM_001105558:c.1261G>A	p.G421R	Fertilization failure	Dai et al. (2019)	NF		
WEE2	NM_001105558.1:c.585G>C	p.K195N	Blastocyst arrest after fertilization or fertilization failure	Dai et al. (2019)	2.01E-05		
WEE2	NM_001105558.1:c.1228C>T	p.R410W	Fertilization failure	Dai et al. (2019)	NF		
WEE2	NM_001105558.1:c.1006_1007dup	p.H337Yfs*24	Fertilization failure	Dai et al. (2019)	NF		
WEE2	NM_001105558.1:c.1006_1007dup	p.H337Yfs*24	Fertilization failure	Dai et al. (2019)	NF		
WEE2	NM_001105558.1:c.1136-2A>G	p.G379Efs*6/ p.D380Lfs*39	Fertilization failure	Dai et al. (2019)	NF		
WEE2	NM_001105558:c.619C>T	p.R207C	Fertilization failure	Yang et al. (2019a)	NF		
WEE2	NC_000007.13:c.1228C>T	p.R410W	Fertilization failure	Zhang et al. (2019b) [†]	2.01E-05		
WEE2	NC_000007.13:c.725G>C	p.R242P	Fertilization failure	Zhang et al. (2019b) [†]	NF		
WEE2	NC_000007.13:c.997T>C	p.S333P	Fertilization failure	Zhang et al. (2019b) [†]	NF		
WEE2	NC_000007.13:c.1221G>A	p.D408Vfs*1	Fertilization failure	Zhang et al. (2019b) [†]	NF		
WEE2	NC_000007.13:c.220_223del	p.E75Vfs*6	Fertilization failure	Zhang et al. (2019b) [†]	NF		
WEE2	NC_000007.13:c.1006_1007insTA	p.H337Yfs*24	Fertilization failure	Zhang et al. (2019b) [†]	NF		
WEE2	NC_000007.13:c.1286_1288del	p.G429del	Fertilization failure	Zhang et al. (2019b) [†]	NF		
WEE2	NC_000007.13:c.220_223del	p.E75Vfs*6	Fertilization failure	Zhang et al. (2019b) [†]	NF		
WEE2	NC_000007.13:c.598C>T	p.R200*	Fertilization failure	Zhang et al. (2019b) [†]	1.61E-05	2.50E-05	9.56E-05
WEE2	NC_000007.13:c.1184G>A	p.G395E	Fertilization failure	Zhang et al. (2019b) [†]	4.01E-06		

[†]Reference sequence or reference sequence version number not reported; ¹Frequency in gnomAD v2.1.1; ²Frequency in ExAc v1.0; ³Frequency in gnomAD v2.1.1 genomes, exomes.

Figure 6 Population frequencies of infertility-associated variants. The population allele frequencies of the female infertility-associated variants listed in Tables 1, 2 and 3 were identified in the gnomAD database (v2.1.1). The number of variants that had a non-zero allele frequency in gnomAD and the total number of variants in each gene are denoted in parentheses after the gene name. Genes for which no reported infertility-associated variants are present in the gnomAD database are not included in the figure. For each allele, dot color represents an associated reproductive phenotype (see key). Multiple phenotypes are represented by two-color dots. Frequencies are shown on $\log_{10}$ scale.

(Dai *et al.* 2019). The data from this patient show that *WEE2* mutations may be associated with additional undiscovered oocyte quality phenotypes that impact embryonic development.

Conclusion

This review identified 251 reports of female patients with infertility-associated genotypes; some appeared frequently either within a given study, such as *SYCE1* NC_000010.10:g.135254039_135377532dup in Bestetti *et al.* (2019), or across multiple studies, like *MCM8* NC_000020.10:g.5948227G>A. Other reports, such as that of *CEP120* NM_153223.3:c.2840G>A, were unique. In the gnomAD database, the population frequencies of the variants identified in this review range from not found to common (>2%) (Fig. 6). Most variants were either not found in the population database or were extremely rare, reflecting severe reproductive phenotypes associated with these variants that diminish evolutionary fitness, such as oocyte maturation arrest. In contrast, more common infertility variants tend to be associated with less severe reproductive phenotypes, such as increased risk of early menopause (*MCM8*) or increased egg aneuploidy (*CEP120*).

The range of reproductive phenotypes caused by meiotic dysregulation brings into focus the fundamental goal of fertility biomarker development: informed reproductive decision-making. Patients with pathologic variants in meiotic genes deserve realistic expectations of their fertility. For example, several patients with *WEE2* variants that cause fertilization failure underwent a decade of fertility treatments with no success. It is critically important to identify and validate infertility-associated variants in meiotic genes so that clinicians can clearly assess future fertility.

This review shows that variants in meiotic genes can cause infertility. How do we bridge the gap between the literature reviewed here and the future of genetic fertility assessments? The most pressing problem in clearly identifying the molecular pathophysiology of oocyte-based infertility is the imprecision of the disease

phenotype. The spectrum of subfertility is particularly problematic. A common treatment course in the United States is that, after having difficulty conceiving, a couple is referred to a fertility clinic. If conception occurs, the patient would leave the fertility clinic and continue prenatal care with an obstetrician. Patients such as these may be subfertile, rather than sterile, but there are very few studies conducted on such patients due to the transition of care. Clear metrics of subfertility and difficult conception are beginning to emerge. Increased use of metrics such as time to conception and blastocyst aneuploidy rate in assessing fertility status and the development of additional metrics will open the door to better understanding the etiology of subfertility.

The second opportunity for improvement in genetic infertility research is increasing the quality and standardization of genotype-phenotype associations. Currently, candidate variants are inconsistently experimentally validated; often, the initial study does not conduct further experiments after a candidate variant is identified. Increased collaboration between clinical researchers and basic scientists will produce a comprehensive picture of the genotype-phenotype association. In the absence of collaboration, study authors should actively facilitate future investigations by clearly reporting their results and depositing their data in public databases. This includes providing detailed clinical information when reporting an associated genotype. As such, we recommend that all researchers investigating genetic mechanisms of infertility follow two sets of standards: (1) the international nomenclature guidelines of the Human Genome Variation Society (den Dunnen *et al.* 2016) and (2) the sequence variant causality guidelines published by a working group convened by the US National Human Genome Research Institute (MacArthur *et al.* 2014). Studies that adhere to these guidelines provide the foundation for follow-up research and can lead to strong clinical associations.

Given the apparent causal relationships between the meiotic genes that drive major meiotic processes described here and their clinical phenotypes, it is

possible to envision a future in which maternal genetic biomarkers complement existing clinical approaches to infertility. Genetic evaluations could occur before a patient attempts to conceive or after an initial infertility diagnosis. In the interim, there are likely many undiscovered genotype-phenotype associations in meiotic-cause infertility. Together, the infertility and meiosis communities can develop new prognostic indicators of conception success.

Declaration of interest

Karen Schindler is an Associate Editor of Reproduction. Karen Schindler was not involved in the review or editorial process for this paper, on which she is listed as an author.

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Author contribution statement

K S and J X conceived of the work. L B and K S interpreted the data and wrote the manuscript. L B, K T, W E, and K M collected data. L B performed ANNOVAR variant frequency retrieval. J X provided the server and technical computational advice. K T, J X, K S, and L B critically revised the article.

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