Identification of Novel Causative Genes and Variants of Female Infertility

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ABTRACT

Female infertility is a highly complex and heterogeneous condition. Despite its growing global prevalence, the current knowledge around the genetic contributors to its etiology is lacking. In this research project, patients experiencing recurrent reproductive loss were investigated for potential genetic dispositions. Genomic DNA isolated from patients' blood samples were sent for whole exome sequencing. The exome data were filtered for damaging rare biallelic variants in genes with potential roles in reproduction. This led to the identification of the novel homozygous likely pathogenic variant, c.626G>A, p.Trp209*, in the *TERB1* gene of a patient diagnosed with premature ovarian insufficiency. In addition, a second homozygous pathogenic *TERB1* variant, c.1703C>G, p.Ser568*, was identified in an infertile woman with an azoospermic brother, also homozygous for her variant, who was previously reported in the literature. TERB1 is involved in the movement of chromosomes during meiotic prophase I to enable homologous chromosome pairing and recombination. It has an established role in human male infertility. This report adds *TERB1* to the short list of genes associated with human infertility in both sexes and expands the current understanding of the genetic contributors to female infertility.

RÉSUMÉ

L'infertilité féminine est une condition très complexe et hétérogène. Malgré sa prévalence mondiale croissante, les connaissances actuelles sur les facteurs génétiques de son étiologie sont insuffisantes. Dans le cadre de ce projet de recherche, des patientes souffrant de pertes de reproduction récurrentes ont été examinées pour déterminer si elles présentaient des prédispositions génétiques potentielles. L'ADN génomique isolé à partir des échantillons de sang des patients a été envoyé pour le séquençage de tous les exomes. Les données des exomes ont été filtrées à la recherche de variants biallélіques rares et dommageables au niveau protéinique dans des gènes jouant un rôle potentiel dans la reproduction. Cela a conduit à l'identification d'un nouveau variant homozygote, prédit d'être probablement pathogène, c.626G>A, p.Trp209*, dans le gène *TERB1* d'une patiente chez qui on a diagnostiqué d'une insuffisance ovarienne prématurée. En outre, un deuxième variant pathogène homozygote de *TERB1*, c.1703C>G, p.Ser568*, a été identifié chez une femme infertile avec un frère azoospermique, également homozygote pour son variant, qui avait déjà été décrit dans la littérature. TERB1 est impliqué dans le mouvement des chromosomes pendant la prophase méiotique I pour permettre l'appariement et la recombinaison des chromosomes homologues. Il joue un rôle établi dans l'infertilité masculine humaine. Ce rapport ajoute *TERB1* à la courte liste des gènes associés à l'infertilité humaine dans les deux sexes, élargissant ainsi la compréhension actuelle des facteurs génétiques de l'infertilité féminine.

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LIST OF ABBREVIATIONS

LH: Luteinizing hormone

AMH: Anti-Mullerian hormone

HSG: Hysterosalpingography

HyCoSy: Hysterosalpingo-contrast sonography

MRI: Magnetic resonance imaging

GnRH: Gonadotropin releasing hormone

FSH: Follicle stimulating hormone

HH: Hypogonadotropic hypogonadism

CHH: Congenital hypogonadotropic hypogonadism

POI: Premature ovarian insufficiency

POF: Primary ovarian failure

DOR: Diminished ovarian reserve

hCG: Human chorionic gonadotropin

IVF: In-vitro fertilization

IVM: In-vitro maturation

PRPT: Platelet rich plasma therapy

PCOS: Polycystic ovary syndrome

CC: Chlomiphine citrate

ART: Assisted reproductive technology

PID: Pelvic inflammatory disease

SC: Synaptonemal complex

DSB: Double-stranded break

ZP: Zona pellucida

ARC: Arcuate nucleus

AVPV: Antroventral periventricular

ICSI: Intracytoplasmic sperm injection

WES: Whole exome sequencing

VUS: Variant of uncertain significance

MTC: Meiotic telomere complex

LINC: Linker of nucleoskeleton and cytoskeleton

PI: Primary infertility

EFS: Empty follicle syndrome

EEA: Early embryonic arrest

OMA: Oocyte maturation arrest

ZCF: Zygotic cleavage failure

RMC: Recurrent miscarriage

RHM: Recurrent hydatidiform mole

MC: Miscarriage

UF: Uterine fibroids

CHM: Complete hydatidiform mole

IF: Implantation failure

OD: Oocyte death

PA: Primary amenorrhea

FF: Fertilization failure

GD: Gonadal dysgenesis

OMD: Oocyte maturation defect

PEL: Preimplantation lethality

MLID: Multi locus imprinting disorder

HPO: Hypothalamus-pituitary-ovary axis

SCMC: Subcortical maternal complex

BPA: Bisphenol A

TNFa: Tumor necrosis factor alpha

VEGF: Vascular endothelial growth factor

NOBOX: Homeobox protein NOBOX

SC: Synaptonemal complex

SYCE1: Synaptonemal Complex Central Element Protein 1

DSB: Double stranded break

NBN: Nibrin

DMC1: DNA Meiotic Recombinase 1

PSMC3IP: PSMC3 Interacting Protein

MCM8: Minichromosome Maintenance 8 Homologous Recombination Repair Factor

MCM9: Minichromosome Maintenance 9 Homologous Recombination Repair Factor

MEIOB: Meiosis Specific With OB-Fold

MSH4: MutS Homolog 4

MSH5: MutS Homolog 5

PATL2: PAT1 Homolog 2

TUBB8: Tubulin Beta 8

LHCGR: Luteinizing Hormone/Choriogonadotropin Receptor

TERB1: Telomere Repeat Binding Bouquet Formation Protein 1

TERF1: Telomeric Repeat Binding Factor 1

SUN1: Sad1 And UNC84 Domain Containing 1

KASH5: KASH Domain Containing 5

LINC: Linker of Nucleoskeleton and Cytoskeleton

NMD: Nonsense mediated decay

MasoNMD: Making sense of nonsense mediated decay

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FORMAT OF THESIS

This thesis is written in the manuscript format.

CONTRIBUTION OF AUTHORS

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CHAPTER 1 - INTRODUCTION

1.1 Female Infertility

1.1.1 Definition and Epidemiology

Female infertility is characterized as the inability to achieve clinical pregnancy with a healthy partner after 12 months of regular unprotected intercourse (1). For patients of age 35 and older, clinical evaluation is commenced after 6 months of unsuccessful attempts at pregnancy. This timely evaluation is necessary because of the rapid decline of fertility with increasing age. Infertility can be categorized as primary or secondary: patients with primary female infertility have no previous conceptions, whereas patients with secondary female infertility are unable to conceive after having at least one previous successful pregnancy (2).

Globally, infertility affects 10-15% of the general population, of which 35% are due to female factors (3). The high prevalence of infertility is attributable to the complexity and intricacy of the biological events that must be completed successfully to develop functional gonads, produce viable gametes, achieve conception, and preserve the pregnancy (3). In female factor infertility, compromised oogenesis, aberrant neuroendocrine signaling, or anatomically and functionally defective reproductive organs can induce this phenotype (3).

1.1.2 Evaluation

An individual or a couple failing to conceive for a sustained period may seek medical attention for potential fertility complications. In the case of heterosexual couples, the healthcare professional can concurrently evaluate both male and female factors. This assessment includes acquiring partners' medical, sexual, and lifestyle histories, performing physical examinations, as well as analyzing biological samples. From a medical history standpoint, patients' age, previous and/or current diagnoses and treatments, medications, and family history are considered (1,4,5). For sexual history, couples'

duration of infertility, intercourse frequency and length, and any sexual dysfunction should be taken (1,4,5). Lastly, history on lifestyle factors that can impact fertility, such as smoking, alcohol and recreational drug use, exercise, and diet, is considered (1,4,5).

To evaluate male infertility, semen samples can be collected, after about 3 days of abstinence, and analyzed for volume, sperm count, motility, progression, morphology, and sperm DNA fragmentation, if needed (4). Semen analyses, in addition to the physical examination, provides greater insight into whether a male factor contributes to the infertility.

The female reproductive anatomy and cycle are incredibly complex, which can pose difficulty when evaluating patients for female factors. In addition, unlike collecting and analyzing semen samples to assess sperm parameters, it is difficult to comprehensively study the quality and viability of oocytes without invasive methods. Therefore, the diagnostic process for female infertility is considerably more extensive and requires healthcare professionals to utilize reproductive history, physical examinations, as well as laboratory tests and imaging to create a global picture of the patient's condition (1, 5-7). Reproductive history includes patient's age at menarche, menstrual cycle interval and duration, presence and severity of concomitant molimina such as breast tenderness, bloating, and cramps, during a menstrual period, past gynecological diagnoses (for example, sexually transmitted infections, pelvic inflammatory disease, endometriosis), treatments, surgeries (primarily abdominal and pelvic), and family history of reproductive problems (6, 7). Fertile patients are more likely to have a regular menstrual cycle, flow, and molimina (1).

Physical examination and clinical tests aim to assess the ovarian function and reserve, uterine shape, size and cavity, and patency of the fallopian tubes (1, 8). Compromised ovulation accounts for up to 40% of the female infertility cases (9) and it usually disrupts menstruation, leading to amenorrhea (absence of menstruation for at least 6 months) (10), oligomenorrhea (infrequent menstruation every 6

weeks to 6 months) (11), or irregular cycles. To evaluate ovulatory function, healthcare professionals can measure the patient's midluteal phase (day 21 or roughly a week before expected period) serum progesterone levels (8, 12). A progesterone concentration of 3 ng/mL or higher usually indicates recent ovulation (8). In addition, ovulation predictor kits that measure urinary luteinizing hormone (LH) levels can detect the mid-cycle LH-surge-driven increase in the LH concentration, which indicates ovulation (1).

Similar to assessing ovarian functions, several methods can be utilized to assess ovarian reserve, which refers to the quantity of oocytes remaining in the ovaries (13). As women age, the number of viable oocytes reduces, leading to a decline in ovarian reserve (8). An earlier or accelerated decline in women of reproductive age can indicate reduced reproductive potential (13). Therefore, measuring ovarian reserve is important when evaluating fertility. Ovarian reserve can be assessed through endocrinological tests and clinical imaging. Anti-Mullerian hormone (AMH) is produced by the granulosa cells of the growing follicles (14). Serum AMH concentrations do not fluctuate during or between periods, thus, measurements can be taken at any given day of the cycle (13). However, age-specific differences should be taken into consideration, as AMH concentration decreases with increasing age (15). Serum AMH levels can be used clinically to estimate the number of oocytes in the ovary (14). A normal serum AMH concentration ranges from 1.0-3.5 ng/mL and indicates normal ovarian reserve (1). Concentrations lower than 1.0 ng/mL can be associated with diminished ovarian reserve. Transvaginal ultrasonography is an imaging technique used to count the number of antral follicles (> 9 mm in diameter) in the ovaries during early follicular phase (1, 13). A total antral follicle count below 7 per ovary is considered low (8).

Although female infertility due to uterine cavity anomalies are comparatively rare, it is still crucial to assess the uterine cavity to rule out the possibility of such abnormalities. During the follicular

phase, the uterine lining proliferates, forming the endometrium, for the blastocyst to implant (16, 17). Therefore, a functional uterus is required to carry out a pregnancy. Uterine abnormalities can be examined with hysterosalpingography (HSG), which can reveal congenital or acquired defects, such as polyps, and confirm if the fallopian tubes are open or blocked (1,8). Hysterosalpingo-contrast sonography (HyCoSy) is an imaging alternative to HSG that can also be used when evaluating the uterine cavity as well as the fallopian tubes (18). HyCoSy, unlike HSG, does not expose patients to radiation and instead relies on transvaginal ultrasound for assessment (19). With respect to accuracy, HSG and HyCoSy show comparable results. Moreover, higher-resolution imaging technologies such as magnetic resonance imaging (MRI) can be used to improve the characterization of the abnormalities detected by HSG or sono-HSG (8). Although it is the most invasive method, hysteroscopy can provide a more definitive diagnosis in addition to an opportunity to immediately treat intrauterine pathologies surgically (1).

Diseases affecting the fallopian tubes hinder oocyte transportation into the uterus (20). To assess tubal patency, HSG, sono-HSG, or HyCoSy can be used to evaluate for possible proximal and distal tubal occlusions (5, 7). However, for patients with suspected endometriosis or pelvic adhesions due to a history of pelvic infection or surgery, laparoscopy is may be used to detect peritubal adhesions (5).

1.1.3 Causes and Management

A variety of factors may lead to female infertility, of which commonly include ovulatory disorders, endometriosis, pelvic adhesions, tubal abnormalities, and hyperprolactinemia (1, 21).

1.1.3.1 Ovulatory Disorders

Ovulation refers to the release of an oocyte from the ovary following the dominant follicle's rupture (22). It is associated with the mid-cycle LH surge that induces the weakening of the ovarian wall to induce follicular eruption. The term "ovulatory disorders" is used to describe conditions in which

ovulation is absent (anovulation) or irregular (oligoovulation). The recent ovulatory disorder classification proposed by the International Federation of Gynecology and Obstetrics has established four categories based on anatomical origin: Type I: Hypothalamic, Type II: Pituitary, Type III: Ovarian, and Type IV: Polycystic Ovary Syndrome (23).

1.1.3.1.1 Hypothalamic and Pituitary Origin

The hypothalamus is a neuroendocrine organ and secretes Gonadotropin Releasing Hormone (GnRH) (24). GnRH's distinct secretion pattern, pulsatile or surge release, from the medio-basal hypothalamus determines its biological impact on anterior pituitary and, thus, is a point of regulation in the reproductive axis. The GnRH secretion pattern is determined by Kisspeptin, a molecule produced by a small cluster of cells called KNDy neurons found in both the arcuate (ARC) and antroventral periventricular (AVPV) nuclei of hypothalamus. Depending on the brain region from which it is secreted, the impact Kisspeptin has on the GnRH secretion pattern will differ. Kisspeptin released from ARC KNDy neurons will act through its receptor, KISS1R, and promote pulsatile GnRH secretion, while AVPV KNDy neurons will promote surge GnRH release.

An ovarian follicle is composed of three different cell types: granulosa, theca, and the oocyte (25). During the follicular phase of menstrual cycle, the pulsatile, low-frequency GnRH secretion stimulates its receptor, GNRHR, on the anterior pituitary to secrete follicle stimulating hormone (FSH) and luteinizing hormone (LH) (26). FSH acts through its transmembrane receptor on the granulosa cell membrane to induce granulosa cell proliferation and aromatase synthesis (26, 27). Aromatase is an enzyme involved in steroidogenesis and is required for the conversion of androstenedione produced by theca cells into estrogen, in response to LH (26, 28). As follicles mature, eventually a dominant antral follicle forms which continues estrogen production (27). At high concentrations, estrogen will bind to the ER-alpha receptors on the AVPV kisspeptin neurons, enhancing Kiss1 production. This then

translates into the GnRH surge release as well as negative feedback on FSH secretion. Surge GnRH release from the hypothalamus induces a mid-cycle surge LH release from the anterior pituitary, which induces ovulation (28). GnRH deficiency or absent pulsatility can disrupt FSH and LH secretion, resulting in decreased sex steroid levels, follicular growth abnormalities, and ultimately, anovulation (1). Abnormalities in the anterior pituitary can impact its endocrine function, causing reduced gonadotropin secretion and ovulatory dysfunction, leading to infertility (29). These abnormalities include and are not restricted to conditions that impact anterior pituitary's glandular activity such as hypopituitarism, anatomical defects, as well as environmental factors that may damage the gland, such as radiation exposure (29).

Hypogonadotropic hypogonadism (HH) can be congenital or acquired due to abnormalities at the hypothalamic or pituitary level that impair gonadotropin production, or secretion and cause decreased gonad activity (30, 31). Congenital HH (CHH) arises from genetic defects that impair GnRH neuron migration or network development. As a result, these patients are deficient in GnRH and, consequently, experience primary amenorrhea and lack secondary sexual characteristic development (32). Acquired HH arises from extrinsic factors and/or stressors that alter the hypothalamic-pituitary axis function or structure. This includes medications, psychological stress, and metabolic syndromes (1, 32). Depending on the type of HH, different treatment strategies should be utilized. Hypogonadism in CHH should be addressed via hormone replacement therapy (32). The formulation for adult females most frequently used includes natural human estrogens (17-beta-estradiol) and progestins. To induce ovulation in women with anovulatory infertility, a recent study showed that human menopausal gonadotropin and letrozole can be administered (33). Another option is the administration of pulsatile GnRH, which has been recorded to have a high success rate (32). For acquired HH, the specific anomaly responsible of the condition should be addressed. For example, patients experiencing acquired HH due

to obesity can benefit from reversing their phenotype through weight loss only (1). In addition, sustained opioid consumption may lead to acquired HH (32). Exogenous opioids act through hypothalamic opioid receptors and disrupt the normal GnRH secretion required for FSH and LH secretion from the anterior pituitary (34). With reduced FSH and LH levels, sex steroid production from the gonads is also reduced, leading to acquired HH. Although there is insufficient data on treatments for opioid-induced HH in women, reducing administered opioid dose, DHEAS therapy and testosterone replacement therapy make up the proposed treatment options (35, 36).

1.1.3.1.2 Ovarian Origin

Ovaries are the female gonads. In these oval-shaped organs, ova are produced through oogenesis and embedded to mature until ovulation (37). In addition to storing the female gametes, ovaries also have endocrine function and are the site of estrogen and progesterone production. As a part of the hypothalamus-pituitary-ovarian axis, ovaries are regulated by the gonadotropins that promote follicular growth, sex steroid production, and ovulation (37). Defects that prevent normal ovarian function can lead to ovulatory disorders. Primary ovarian insufficiency (POI) or premature ovarian failure (POF) is characterized as the occurrence of 4-6 months of secondary amenorrhea and follicular exhaustion before the age of 40 (38-40). Patients with POI or POF can present with elevated basal FSH levels (>30-40 mlU/mL) and hypoestrogenism (<50 pg/mL) (38). For the majority of POI cases, the biological mechanisms that lead to premature ovarian reserve depletion is unidentified (41). However, evidence for both genetic and environmental contributors have been documented extensively in the literature (39).

Due to the significantly reduced chances of spontaneous pregnancy in POI patients, assisted reproductive technologies are viable options to attempts at conceiving (42). If the patient has a sufficient residual ovarian reserve, gonadotropin-mediated ovarian stimulation can be considered (43). However, since POI patients often poorly respond to stimulation, multiple in-vitro fertilization (IVF) cycles might

be needed for successful conception. If the patient does not respond to ovarian stimulation, using donor eggs can be an option. In addition to donor eggs, patients can also choose to use donor embryos.

Presently, multiple experimental therapies are being investigated to alleviate the burden of infertility that accompanies POI. One propose novel method is the platelet rich plasma technology (PRPT), which encompasses the intraovarian injection of plasma with high platelet concentration rich in growth factors to induce primordial follicle development and differentiation (43). Although clinical trials have rather recently began for this method, there are already mixed results produced. For example, in their 2019 study, Pantos et al. treated one menopausal woman (age 46) and two POI patients (ages 27 and 40) with PRPT (44). Upon treatment, all three menstruations recovered. In the 27-year-old patient, a decrease in FSH levels were observed as well as a minute increase in her AMH levels. Remarkably, all three patients were able to achieve complication-free spontaneous pregnancy 2-6 months following the treatment. Despite its promise, important to note that PRPT treatment results vary from person to person, and not all individuals receiving the treatment can benefit from it (43). In fact, in a randomized control trial, researchers reported that PRPT does not increase the number of oocytes retrieved for IVF (45). In this paper, of 83 patients <38 years old with poor ovarian response to stimulation (several rounds with less than 3 oocytes retrieved), 41 underwent PRPT and 42 did not, acting as the control group (45). Contrary to the findings of Pantos et al., no significant difference was observed between the number of MII oocytes retrieved from the PRPT and control group. However, the researchers note that PRPT has not been standardized yet, and thus results should not be generalized.

The diminished ovarian reserve (DOR) observed in POI can also occur independently. The decrease in the quantity of eggs in women in their mid-40s is a physiologically normal phenomenon. The occurrence of this phenotype in younger women is characterized as pathologic DOR, which could be defined as any of the risk factors of poor ovarian response and/or an abnormal ovarian reserve test,

such as an antral follicle count of less than five or seven, and AMH < 0.5-1.1 ng/mL (40, 46). In contrast to patients with POI who are infertile, women with DOR can still have regular menses and despite having fewer oocytes than normal, they can still conceive (47, 48). The etiology behind pathologic DOR is unclear, however, congenital and environmental factors have been implicated (49). DOR patients seeking to conceive can undergo controlled ovarian stimulation, where high FSH doses (300-450 IU/day) are administered to boost the number of mature follicles (1, 50). The follicular growth can be monitored by transvaginal ultrasounds to identify mature follicles to induce ovulation by administering human chorionic gonadotropin (hCG) (1). Ovulation induction is followed by intrauterine insemination 24-36 hours after the hCG shot. Alternatively, patients can also undergo IVF (50). If the patient does not respond to ovarian stimulation, using a donor egg to achieve pregnancy is recommended.

1.1.3.1.3 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women. Depending on the evaluation criteria applied, PCOS prevalence can range from 6-10% to 14-19% (51, 52). According to the Evidence-based Guideline for the Assessment and Management of Polycystic Ovary syndrome, to make the diagnosis of PCOS in adults, two out of the following three criteria are necessary: 1) oligoovulation or anovulation; 2) clinical and/or biochemical evidence of hyperandrogenism with elevated total testosterone levels, or free testosterone; and 3) polycystic ovaries demonstrated on ultrasound (52). In addition, other conditions that can cause the patient's symptoms must be excluded.

PCOS is a highly heterogeneous condition with complex and diverse pathogenetic mechanisms. Aberrations in multiple distinct physiological pathways have been implicated in PCOS manifestation. From an endocrine lens, hyperandrogenism observed in PCOS patients is an outcome of excess androgen production in the ovaries, which can be attributed to changes in the hypothalamus-pituitary-

ovarian (HPO) axis in women (52). It is hypothesized that alterations at the level of kisspeptin neurons in the hypothalamus leads to an increase in GnRH pulse frequency in women with PCOS, which in return increases LH production while FSH levels remain unmodified or slightly decreased. Elevated LH then stimulates androgen production in theca cells, increasing testosterone levels. It is proposed that excess testosterone may halt follicular growth and lead to antral follicle accumulation in the ovaries. Granulosa cells present in these resting follicles produce excess AMH, which is believed to contribute to the PCOS phenotype by inhibiting FSH action required for primary follicle recruitment and maturation (51, 53).

From an environmental perspective, endocrine disruptors can dysregulate steroidogenesis and contribute to the development of the PCOS phenotype (54). One example is bisphenol-A (BPA), a plasticizer that leads to excess androgen production in theca cells by disrupting aromatase synthesis in the granulosa cells (55). Aromatases enzymes that convert androgens to estrogens. P450aro aromatase produces estrone from testosterone in granulosa cells (56). Since estrone is the precursor for estrogen, disruptions in the P450aro expression may lead to the hyperandrogenism phenotype in PCOS (57).

Additionally, current literature suggests a strong association between PCOS and insulin resistance, an impairment in tissue response to insulin (58, 59). Around 65-95% of patients with PCOS present insulin resistance and a compensatory elevation in serum insulin levels (hyperinsulinemia). Insulin resistance in PCOS is attributed to a disruption in the insulin signaling cascade downstream of insulin receptor activity. This leads to overproduction of insulin, a regulator of ovarian function (60). In response to the increase in serum insulin, androgen production in theca cells heightens, further contributing to the hyperandrogenemia (61).

There are multiple steps that can be taken to address PCOS related infertility. The first line of treatment is encouraging a healthy diet and regular exercise to help manage insulin resistance and

hyperandrogenism associated with PCOS (62). Losing weight is an important feature in the management of PCOS. Second line of treatment is ovulation induction through clomiphene citrate (CC) or, as increasingly evident, preferably letrozole. CC is a selective estrogen receptor modulator and acts by blocking estrogen receptor signaling in the hypothalamus to increase GnRH pulse amplitude (62). This translates to an increase in gonadotropin production which then induce follicular maturation.

In the past, women who did not respond to CC were given letrozole, an aromatase inhibitor which prevents androgen's conversion to estrogen in the ovaries. This altered estrogen level blocks the estrogen-driven hypothalamic negative feedback, and the subsequently increased gonadotropin levels induce ovulation (62). Although both lines of treatment are shown to be effective in ovulation induction, a systemic review and meta-analysis published in 2023 by Abu-Zaid et al. comparing the efficacy of CC showed that women treated with CC had a lower pregnancy and live birth rate than women treated with letrozole (63). Because CC can act as an anti-estrogenic agent, it can hamper endometrium thickening and cervical mucous secretion, two processes that require estrogen signaling (64, 65). In fact, in their paper, Abu-Zaid et al. reported that endometrial thickness in women treated with letrozole is significantly higher than in the CC treated patients (63), while Tepper et al. reported a decrease in cervical mucous secretion in CC treated women (65). Since endometrial thickening is required for the endometrial mucosa to become receptive to implantation, the study by Abu-Zaid et al suggested that this difference in pregnancy rate could be attributed to the anti-estrogenic role of CC. As a third line of treatment, women who fail to respond to ovulation induction may turn to assisted reproductive technologies (ART), such as IVF or in-vitro maturation (IVM) of eggs. The IVF treatment is initiated with stimulation of the ovaries by injecting daily exogenous gonadotropins (1). Transvaginal ultrasound is used to track follicular maturation (66). When at least three follicles grow to become 18 mm in diameter, hCG shot is given to drive LH surge required for the final oocyte maturation (66, 67). 35 to 38

hours after administering hCG, ultrasound-guided transvaginal aspiration is used to retrieve the mature oocytes which are placed in a dish (66). Intracytoplasmic sperm injection (ICSI) or insemination is used to fertilize the oocytes. Three- or five-days post-fertilization, the embryo is transferred into the uterus for implantation (1, 66).

1.1.3.2 Endometriosis

Endometriosis is a chronic inflammatory condition characterized by the implantation of endometrial tissue outside of the uterine cavity (1, 68). Patients with endometriosis can experience chronic pain in the pelvic region and fertility complications. About 5-10% of women are affected by endometriosis, making it a globally prevalent condition (69). A widely accepted etiology is retrograde menstruation, where the menstrual blood flows backwards through the fallopian tubes and into the pelvis rather than out of the vagina (70). When the viable endometrial cells carried by menstrual blood implant into the peritoneal cavity and grow, endometriosis may arise (68, 71). Although 76-90% of women with patent fallopian tubes experience retrograde menstruation, only some experience endometriosis (72). A possible explanation for this discrepancy is the differences in peritoneal fluid's immunological activity and composition in women with and without endometriosis. The peritoneal fluid of endometriosis patients are more concentrated with immunological factors, including activated macrophages and neutrophils (73). Their cytokine products, including tumor necrosis factor alpha (TNFa), interleukins, and proinflammatory angiogenic factors like vascular endothelial growth factor (VEGF), can support the endometrial lesion's implantation and growth in the peritoneal cavity (73, 74). In fact, Rana et al. has reported an altered immune microenvironment in the peritoneal cavity of endometriosis patients, with enhanced cytokine synthesis and secretion (74).

In addition to retrograde menstruation, there are multiple other theorized pathogenetic mechanisms for endometriosis formation. For example, one metaplasia theory suggests that peritoneal

cell's differentiation into the endometrial tissue leads to endometriosis (68, 72). Although it is postulated that growth factors and cytokines have a role, no specific agent has been identified yet. Similar to retrograde menstruation, another hypothesis postulates that endometrial stem cells can regurgitate into the peritoneum and implant, generating ectopic endometrial implants (75). Despite the abundance in number of theories proposed, the retrograde menstruation hypothesis remains to be the dominantly accepted one.

There are multiple mechanisms in which endometriosis may lead to female infertility. It can lead to pelvic adhesions (discussed below) and disrupt the tubal-ovarian anatomical relationship (76). As an inflammatory condition, endometriosis can disrupt ovulation due to an increase in inflammatory cells and factors in the peritoneal fluid (77). In addition, endometriosis can lead to implantation failure due to the biochemical changes in the endometrial lining that hamper the blastocyst's attachment. To address endometriosis-related infertility, surgery and/or ART can be used (78). Laparoscopy is a surgical intervention utilized to remove endometriotic lesions (79). It can also aid in treating organs that might have been damaged due to endometriosis. In patients with more severe endometriosis-related anatomical defects, such as tubal occlusions, IVF can be advised (74).

1.1.3.3 Pelvic Adhesions and Tubal Factors

Pelvic adhesion is a condition where adjacent organs within the pelvis are bound together by scar tissue (80). It can compromise fallopian tubal patency, disrupting egg release and transport (81). Infections such as pelvic inflammatory disease (PID) can cause adhesion formation and lead to infertility (1). PID arises from infections that ascend from the cervix into the upper reproductive tract (82). Roughly 85% of PID cases are due to sexually transmitted bacteria, predominantly *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. The infection can induce inflammatory response in the uterus, ovaries, and/or fallopian tubes, and cause scarring, adhesions, or tubal obstructions. Such structural

damages to the reproductive organs can interfere with ovum transportation and lead to infertility (82, 83). In addition to the sexually transmitted bacteria, aerobic and anaerobic bacteria resident to the normal vaginal flora can also cause PID in a polymicrobial fashion, with anaerobes being the predominant invaders (84, 85). The available data on the anaerobic mechanism of pathogenesis suggests that ascending anaerobic invasion of the upper genital tract can lead to tissue damage at the fallopian tube level, facilitating infection acquisition (86).

Early detection and treatment of PID is crucial to mitigate the risk of developing infertility. Timely intervention with antibiotics against the causative bacterial strain can clear up the infection with minimal anatomical damage (82). However, in unattended PID, severe injuries to the reproductive organs might render IVF compulsory to increase chances of achieving pregnancy (87).

The fallopian tube is a highway connecting the ovaries to the uterus (83). Impairments to its structure and function can lead to tubal factor infertility, which accounts for roughly 22% of the female infertility cases (1). The predominant tubal factor is tubal blockage. In addition to the sexually transmitted bacteria described above that damage and obstruct the fallopian tubes, congenital defects, ischemic nodules, polyps, and injuries from tubal surgeries can also prevent normal tubal function and cause infertility (83). For tubal-factor infertility, IVF is usually the first line of treatment (1).

1.1.3.4 Hyperprolactinemia

Hyperprolactinemia is a condition characterized by elevated serum prolactin levels (88). Prolactin is a peptide hormone secreted by the anterior pituitary that induce milk production in pregnant and lactating women. In most cases, the pathologic increase in prolactin is due to prolactinoma, a benign tumor of the anterior pituitary that drives excessive prolactin production (89). Biochemically, prolactin suppresses the expression of a hypothalamic factor, kisspeptin, that induces GnRH release (88). The excess prolactin levels in hyperprolactinemia translates into abnormal repression of GnRH activity and,

consequently, decreased gonadotropin levels. Due to a lack of ovarian stimulation, patients with hyperprolactinemia can experience hypogonadism, amenorrhea, and ultimately, infertility. Hyperprolactinemic individuals can be treated with dopamine receptor agonists such as bromocriptine to shrink the prolactinoma, which can reduce prolactin production and restore fertility (91).

1.1.4 Genetics of female infertility

Genetic factors have been extensively documented in the pathogenesis of female infertility, with roughly 10% of cases being attributable to genetic defects (92). From chromosomal abnormalities to single nucleotide variants, aberrant genetic make-up can impair oogenesis, oocyte maturation, ovarian reserve maintenance, endocrine signaling, fertilization, implantation, and early embryonic development, leading to infertility (3).

Oogenesis refers to the formation of the female gamete, oocyte (91). In humans, between the second and seventh month of gestation, around 7 million oogonia are produced from primordial germ cells through rapid mitotic divisions in the fetal ovaries (94). This number plummets drastically after the seventh month as programmed cell death eliminates a substantial portion of the oogonia. This is a normal physiological process to control the quality of oocytes and eliminate some of the ones with chromosomal abnormalities due to impairments in critical processes such as synapsis, recombination, and DNA repair (95). After this degeneration, the ovarian reserve will be approximately 1 million oocytes at the time of birth, among which only 300,000 will survive to puberty and approximately 400 will be ovulated (93, 94). However, genetic abnormalities may alter this apoptotic program and lead to an exaggerated elimination of oocytes (3). Since the ovarian reserve dictates reproductive potential, women with depleted number of oocytes may experience infertility. Newborn ovary homeobox-encoding protein (NOBOX) is a transcription factor involved in follicular development and ovarian reserve maintenance (3, 97). Oocyte loss in NOBOX deficient mice is accelerated during ovarian

development (98). In humans, biallelic *NOBOX* variants have been reported in women with POI (99, 100).

Following oogonia depletion, remaining cells enter meiosis and are called primary oocytes (93). Meiosis includes two rounds of cellular division: meiosis I and II (101). Each division is split into four distinct stages: prophase, metaphase, anaphase, and telophase. The primary oocytes first enter meiotic prophase 1 where homologous chromosomes pair up (synapse). For synapsis to occur, chromosomes must first move towards their homologs. Several proteins have been shown to be involved in this process in mice, including TERB1, TERB2, and KASH5. Homozygous variants in *KASH5* have been reported in patients with POI and, more broadly, infertility (102-104). During synapsis, homologous chromosomes are linked to one another via a protein complex called synaptonemal complex (SC) (105). SC has three counterparts, one of which is synaptonemal complex central element protein 1 (SYCE1). Biallelic variants in *SYCE1* have been reported in women with POI (106, 107).

Synapsis is not random; only the complementary sequences on the maternal and paternal chromosomes can pair up, which are called the homologous chromosomes or regions (108). This alignment is important for when the genetic material between homolog pairs is exchanged through recombination (101, 105). Recombination is often referred to as the "hallmark of prophase 1" as it is the source of genetic diversity in gametogenesis. For recombination to take place, DNA double-stranded breaks (DSB) form on the maternal and paternal chromosomes (108). The broken ends of the opposite chromosomes then crossover, exchanging homologous genetic materials. Once the exchange is complete, the DSBs are repaired. DSB formation is initiated by a meiosis-specific endonuclease, SPO11, accompanied by the tri-protein MRN complex required for mediating the repair response (105, 109). Nibrin (NBN), a protein component of the MRN complex, acts as a DNA damage sensor and promotes DSB repair (110). Biallelic nonsense mutations in NBN have been reported in a female with POI (111).

The single stranded DNA exposed from DSB generation attaches three proteins, one of which is DNA meiotic recombinase 1 (DMC1) (105). DMC1 is stabilized by PSMC3 interacting protein (PSMC3IP). Biallelic variants in DMC1 have been reported in patients with POI and DOR (104, 112). PSMC3IP variants have also been reported in POI (113-118) as well as ovarian dysgenesis and primary amenorrhea (105). Following the exchange of chromosomal fragments, DNA repair proteins restore the DSB. Cells with unrepaired for erroneously repaired DNA enter cell-cycle arrest and get eliminated through apoptosis (3). Minichromosome maintenance complex components 8 (MCM8) and 9 (MCM9) are DNA repair proteins that form a helicase and induce DNA production at the DSB location (104). Biallelic variants in both of these genes have been reported in women with POI (105). In addition to MCM8 and MCM9, DNA repair proteins with biallelic variants implicated in female infertility include meiosis specific with OB-fold (MEIOB) (118-121), mutS homolog 4 (MSH4) (87-90), and mutS homolog 5 (MSH5) (121).

Once homologous chromosomes finish recombination and enter the final stage of prophase 1, oocytes enter meiotic arrest (93,105). While this arrest is maintained until the start of puberty, oocytes remain transcriptionally active and continue to grow in their follicles until they fully mature. In contrast to transcription, translational processes are halted in arrested oocytes. This repression is achieved by oocyte translation suppressor proteins, such as protein associated with topoisomerase II homolog 2 (PATL2) (105). Biallelic PATL2 variants have been associated with oocyte maturation defects in several patients with primary female infertility (122, 123**)**. In both instances, patients had regular menstrual cycles and normal ovarian reserve. However, all oocytes retrieved for IVF were mostly arrested at the germinal vesicle stage.

With the start of puberty and menstruation, around once every 28 days, an LH surge induces ovulation and arrested oocytes resume meiosis, entering metaphase I (105). During this time,

microtubules build meiotic spindles required to segregate the chromosomes aligned at the metaphase plate. Tubulin beta 8 (TUBB8) is a primate-specific microtubule subunit (124). Biallelic variants in *TUBB8* were identified in several patients with primary infertility due to oocyte maturation defect (124, 125). Following alignment, homologous chromosomes are pulled towards opposite poles in anaphase I and the division is completed in telophase I, finalizing meiosis I (93, 105). At the end of the first meiotic division, two haploid cells of different sizes are formed: a large secondary oocyte and a much smaller first polar body (93). Also described as mature eggs, secondary oocytes enter meiosis II, arrest at metaphase II, and only continue meiosis if fertilization occurs (105).

Fertilization is a biochemical process that entails the fusion of sperm with an egg to form a diploid zygote (108, 126). Upon ejaculation into the vaginal canal, spermatozoa migrate through the uterus towards the fallopian tube's ampulla, the site of fertilization (127). By the time they reach the egg, capacitation is completed, a process that allows sperm to penetrate across follicular cells and the zona pellucida (108). Zona pellucida is a glycoprotein-rich extracellular layer that coat the resident oocyte of the follicle (128). The matrix is composed of four main zona pellucida glycoproteins: ZP1, ZP2, ZP3, and ZP4 (129). Binding of capacitated sperm to ZP1, ZP3 and ZP4 triggers acrosome reaction which releases hydrolytic enzymes onto zona pellucida (108). ZP2, on the other hand, only binds to acrosome-reacted sperm and prevents multiple sperm from fusing with the oocyte (polyspermy) (130). Only the spermatozoa that complete acrosome reaction can penetrate through zona pellucida, among which only one can fuse with the oocyte (131). Fertilization failure due to biallelic variants in *ZP1* and *ZP2* have been reported in infertile women with oocyte degeneration and empty follicle syndrome (97, 132, 133).

After successful fertilization, the secondary oocyte must exit the metaphase-II arrest to complete meiosis II. WEE2 oocyte meiosis inhibiting kinase is required for the second meiotic resumption and the succeeding pronuclei formation (108). Biallelic WEE2 variants were identified in unrelated women with

primary infertility. Despite having normal menstrual cycles, all IVF attempts with oocytes from these patients were unsuccessful due to fertilization failure. In addition to ZP1, ZP2, and WEE2, some of the other proteins implicated in human fertilization failure include CDC20 (134).

When no fertilization takes place, the secondary oocyte remains under meiotic arrest and is eliminated from the body through menstruation (93). The reproductive cycle and potential is heavily regulated through endocrine signaling, specifically by the HPO axis. As discussed above, GnRH is a hypothalamic hormone that stimulates the downstream gonadotropin synthesis Surge GnRH release promotes surge LH release, which induces the ovulation of the dominant follicle expressing LH receptor (LHCGR). Biallelic variants in *KISS1R* and *GNRHR* have been identified in patients with congenital HH (135, 136). Additionally, biallelic variants in FSH receptor gene, *FSHR*, and *LHCGR* have been associated with POI and empty follicle syndrome, respectively (137, 138).

Female infertility is clinically and genetically a highly heterogeneous condition. Although physical, laboratory, and imaging assessments can provide great insight, genetic tests have become a critical part of patient evaluation to better determine the cause of patients' infertility. In a clinical setting, karyotyping and *FMR1* premutation analysis are the methods most frequently used to identify a genetic predisposition and correspondingly plan the most effective assisted reproduction treatment (139). However, these tests are unsuitable to detect rare monogenic defects. In recent years, with the advancement and increasing accessibility of sequencing technologies, there has been a rise in the identification of single-gene defects associated with female infertility. Despite this advancement, from hundreds of genes that are estimated to be involved in female infertility (3), only around 70 have been associated with female infertility in humans.

Increasing sequencing efforts can associate novel variants and genes with female infertility. This is especially important for patients interested in using assisted reproductive technologies, as these costly

treatments may not work for them. An example from the literature is patients with *TUBB8* variants. According to a 2023 study reporting 9 primary female infertility patients with *TUBB8* variants, none of the women were able to conceive naturally or through IVF and ICSI (140). In both treatments, oocyte quality is an important success factor and *TUBB8* variants have been associated with oocyte maturation defects, as previously described. Thus, donor eggs are currently the best line of treatment for patients with disease-causing variants *TUBB8* variants (140). In cases like this, early screening for pathogenic variants in reproductive genes can help avoid unnecessary fertility treatments that would not work for the patient, saving them from both the emotional and financial burden of repeated failed treatments.

In this project, we worked on identifying novel genes and variants in patients experiencing recurrent reproductive failure, including female infertility. To facilitate and standardize the patient recruitment process, a questionnaire titled "Questionnaire for Participants with Recurrent Reproductive Failure" was created. In summary, the questionnaire investigates the patient's menstrual characteristics (length, flow, regularity, existence of pain), pregnancy history, medical history (sexually transmitted infections, surgeries, contraceptives, medications, previous diagnoses), partner's history (sexually transmitted infections, past pregnancies, medical conditions, blood relationship), family history (blood relationship between parents or grandparents, existing medical, genetic, or fertility problems), pregnancy history of the mother and sisters, and family pedigree. The complete questionnaire is included below.

Patients were recruited from collaborators across the world, with a significant number of participants being of Egyptian origin. Since September 2022, 53 blood-extracted DNA from patients and family members from 17 Egyptian families, of which 12 are consanguineous, have been submitted for whole-exome sequencing (WES). Of the patients analyzed, 1 had ≥2 molar pregnancies, 8 had ≥5 miscarriages with no live births, and 12 had ≥5 years of infertility with no live births. We hypothesize that there are underlying genetic dispositions that could explain patients' phenotypes.

Objective 1. Identifying candidate genes and variants inherited under the recessive model in patients using whole-exome sequencing.

Objective 2. Validating and segregating the candidate variants among available family members.

Objective 3. Identifying additional patients with variants in the same novel gene identified.

CHAPTER 2 - MANUSCRIPT

A Report of Two Homozygous *TERB1* Protein-Truncating Variants in Two Unrelated Women with Primary Infertility

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2.1 Abstract

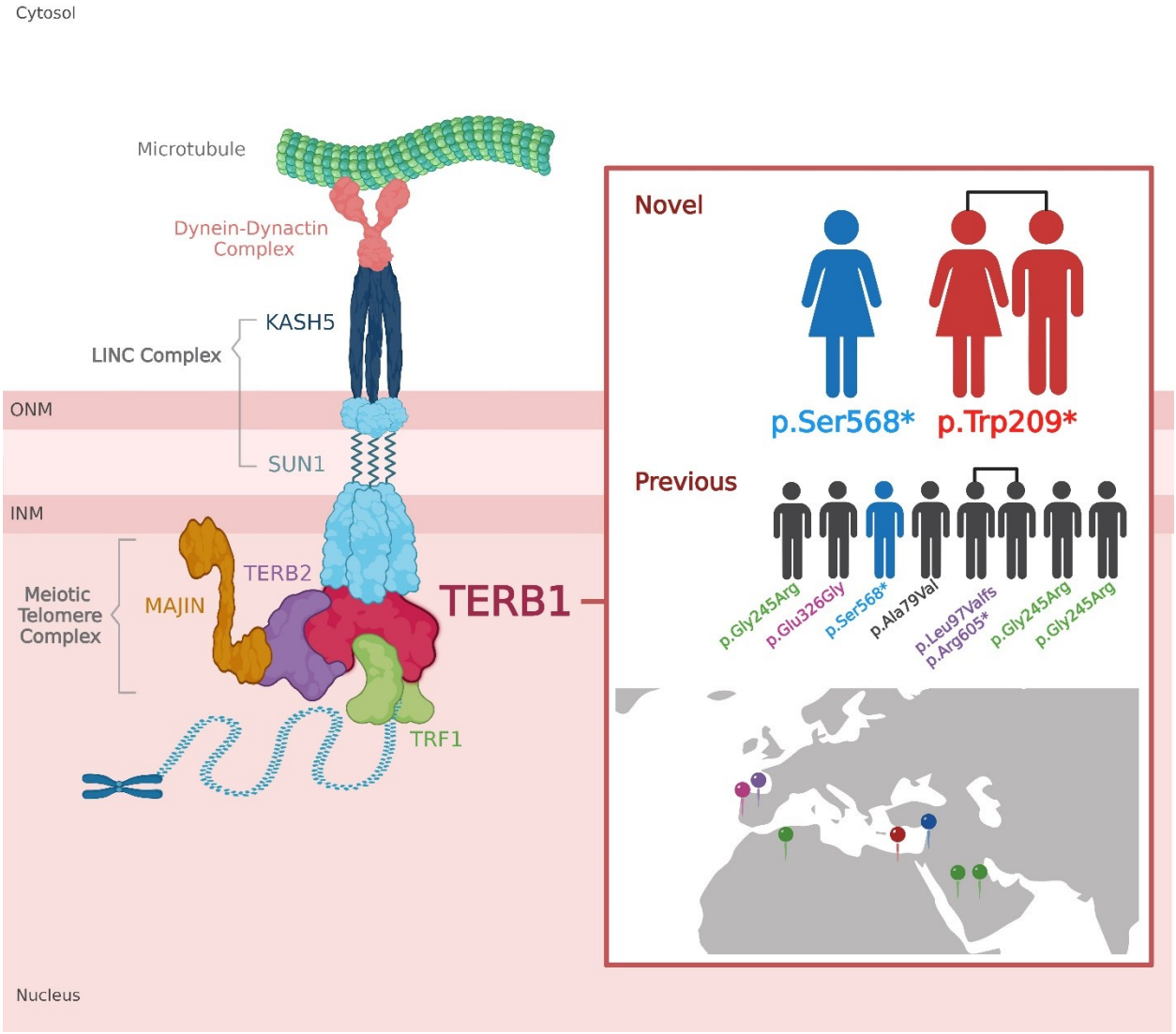
Purpose: To investigate the genetic etiology of patients with female infertility.

Methods: Whole Exome Sequencing was performed on genomic DNA extracted from the patient's blood. Exome data were filtered for damaging rare biallelic variants in genes with possible roles in reproduction. Sanger sequencing was used to validate the selected variants and segregate them in family members.

Results: A novel homozygous likely pathogenic variant, c.626G>A, p.Trp209*, was identified in the *TERB1* gene of the patient. Additionally, we report a second homozygous pathogenic *TERB1* variant, c.1703C>G, p.Ser568*, in an infertile woman whose azoospermic brother was previously described to be homozygous for her variant.

Conclusions: Here, we report for the first time two homozygous likely pathogenic and pathogenic *TERB1* variants, c.626G>A, p.Trp209* and c.1703C>G, p.Ser568*, respectively, in two unrelated women with primary infertility. *TERB1* is known to play an essential role in homologous chromosome movement, synapsis, and recombination during the meiotic prophase I and has an established role in male infertility in humans. Our data add *TERB1* to the shortlist of Meiosis I genes associated with human infertility in both sexes.

Keywords: *TERB1*, female infertility, genetics, meiosis, mutation



Graphical abstract. Summary of the main message of the manuscript. The schematic diagram on the left is used to portray TERB1 protein interactions as well as the multiprotein mechanism that drives chromosome movements for homologous pairing. The panel on the right summarizes the novel variants identified in the reported patients and the previously reported variants in *TERB1*. Siblings are indicated with the pedigree sibship lines. The pins on the map are color-coded for the variants reported and are positioned to show each patient's ethnicity.

2.2 Introduction

Infertility is defined as the inability to conceive after a year of unprotected intercourse [1]. This disorder, affecting globally 15% of the general population [2], can be categorized into two groups: primary and secondary. Unlike primary infertility, secondary infertility patients have had previous successful pregnancies [3]. Due to the complex nature of human reproductive physiology, there is notable variety in how infertility is manifested. In women, ovulatory problems make up the majority of infertility cases. Among these are polycystic ovarian syndrome, premature ovarian insufficiency (POI), and hormonal irregularities caused by hypothalamic dysfunction [4]. In men, abnormalities in sperm count, morphology, motility, and function can lead to infertility [5], with up to 15% of these cases being attributable to genetic defects [6].

Over the years, the growth in access to whole-genome and exome sequencing technologies has facilitated associating many genes of the reproductive axis with human infertility [2]. Although genetic defects in various biological processes, including gonad formation, hormonal regulation, and meiosis, have been described to cause infertility, pathogenic variants in genes contributing to gamete quality and production have been highlighted to have the most severe impact on reproductive success [2]. However, despite the high frequency of infertility, improved insight into its biological mechanisms, and the availability of sequencing technologies, the genetic and pathophysiological heterogeneity of infertility render numerous causative genes and variants undiscovered.

Here, we report two homozygous stop-gain variants in the telomere repeat binding bouquet formation protein 1 (*TERB1*) gene in two unrelated infertile women from familial cases. So far, *TERB1* variants have only been reported in infertile men. Our findings show, for the first time, that they are also associated with primary female infertility.

2.3 Clinical Case Reports

Case 1. The first family analyzed in this study is of Egyptian origin and includes a female (patient ID 2105) with five years of primary infertility due to diminished ovarian reserve, and her brother (patient ID 2104) with ten years of infertility with three partners due to non-obstructive azoospermia (Figure 1a). The parents of the infertile siblings are first cousins. Clinical findings of the infertile female are summarized in Table 1.

Table 1 Clinical data of patient 2105.

Parameter	**Measurement**
Age at menarche	13
Menstrual cycle	30 days, lasting 3-5 days
Luteinizing Hormone levels	Elevated (18.5 IU/L)
Follicle Stimulating Hormone levels	Elevated (22.3 IU/L)
Anti-Mullerian Hormone levels	Severely decreased (0.3 ng/mL)
Ovary size	Small ovaries Right → 1,96 x 1,70 x 1,52 Left → 2,26 x 1,07 x 1,51
Partner sperm parameters	Normal sperm parameters Ejaculate volume = 2 mL Sperm count = 60 million/ejaculate Sperm motility = 85% Progressive motility = 54% Morphology index = 40%

The clinical data was acquired on day 2 of menses when the patient was 26 years and 8 months old. The reference level of the hormones at follicular phase are the following: Luteinizing Hormone = 1-12 IU/L [7], Follicle Stimulating Hormone = 1-9 IU/L [7], Anti-Mullerian Hormone = 2-6.8 ng/mL [8].

Case 2. The second infertile female is from a previously reported family (Figure 1b) consisting of two unaffected siblings and an infertile non-obstructive azoospermic male who is homozygous for a pathogenic protein-truncating *TERB1* variant, c.1703C>G, p.Ser568* [9]. The fertility status of the second homozygous brother is unknown. The affected sister has an unfulfilled wish to have a child for 4-5 years and had one spontaneous pregnancy that resulted in a very early miscarriage. Afterwards, medically assisted reproduction treatment did not result in pregnancy. No DNA was available from the infertile sister prior to publishing the original report.

2.4 Results

Case 1. To potentially identify the genetic etiology of infertility in this family, whole exome sequencing was performed on 2105 using blood DNA. Given the parents are first cousins and did not have problem conceiving, the recessive mode of inheritance of the defect was prioritized. Exome data were filtered according to the criteria described in the Materials and Methods and resulted in the identification of two genes with candidate variants: a novel homozygous stop-gain variant, NM_001136505.2:c.626G>A, p.Trp209*, in *TERB1,* and two novel multiple heterozygous nonsynonymous variants, NM_053006:c.2T>A, p.M1K and NM_053006: c.728G>T, p.C243F, in *TSSK2* (Supplementary Figures 1 and 2). The identified variants were classified as likely pathogenic, likely pathogenic, and likely benign, respectively [15]. Sanger sequencing was used to validate and segregate the candidate variants, which led to the confirmation of the *TERB1* variant (Figure 1a) and the exclusion of the *TSSK2* variants since c.2T>A, p.M1K was not validated in the patient (Supplementary Figures 1 and 2).

The *TERB1* variant is located in a run of homozygosity of 11.1-Mb on chromosome 16 and was predicted by the R package *masonmd* (Make Sense of nonsense-mediated decay (NMD)) [19] and Mutation Taster [20] to trigger NMD. Segregation analysis showed that this variant is also homozygous in the affected azoospermic brother, while the three unaffected siblings and parents are all heterozygous carriers (Figure 1a). To exclude the presence of any other recessive causative variants responsible for the infertility of the azoospermic brother, we next performed exome sequencing on his blood DNA and filtered the exome data under the same criteria described above. Our analysis did not reveal any other candidate gene with plausible recessive variants that may explain the phenotype of the infertile brother (Supplementary Figure 1).

TERB1 is involved in the pairing of homologous chromosomes during meiotic prophase I [21] and has an established role in the causation of male infertility due to meiotic arrest and consequently azoospermia (Table 2). Based on its function, the phenotype of the affected brother, and the pathogenicity classification of the variant, we conclude that the novel homozygous likely pathogenic variant, c.626G>A, p.Trp209*, in *TERB1* is the most plausible candidate to explain the infertility of the two siblings.

Case 2. DNA analysis of the infertile sister revealed that she is also homozygous for the *TERB1* variant found in her brother, NM_001136505.2:c.1703C>G, p.Ser568* (Figure 1b). The variant was also predicted by *masonmd* [19] and Mutation Taster [20] to trigger NMD.

2.5 Discussion

In this paper, we report a novel likely pathogenic protein-truncating variant, p.Trp209*, in the *TERB1* gene of an infertile woman and her azoospermic brother. We also report a second infertile female, from a previously described family [9], who is homozygous for another pathogenic protein-truncating variant in *TERB1*.

Table 2 Previously reported recessive *TERB1* variants.

Reference	**Patient ID**	**Variant***	**Zygosity**	**ACMG Classification by Varsome**	**Phenotype**
Kherraf et al., 2022 [22]	P0145	c.733G>A, p.Gly245Arg	Hom	VUS (4P : 0B)	NOA
Salas-Huetos et al., 2021 [9]	Individual 2	c.977A>G, p.Glu326Gly	Hom	VUS (1P : 1B)	NOA
	M2073**	c.1703C>G, p.Ser568*	Hom	Pathogenic	NOA
Krausz et al., 2020 [23]	M468	c.236C>T, p. Ala79Val	Hom	VUS (2P : 0B)	NOA
	10-200 & brother	c.289_290del, p. Leu97Valfs*7	Multiple Het	Pathogenic	NOA
		c.1813C>T, p. Arg605*		Pathogenic	NOA
Alhathal et al., 2020 [24]	19DG1792	c.733G>A, p.Gly245Arg	Hom	VUS (4P : 0B)	NOA
	19DG1816		Hom		NOA

*All variants are provided in NM_001136505.2. **Previously reported male proband whose infertile sister is reported in this study. 'Hom' and 'Multiple Het' are short for homozygous and multiple heterozygous, respectively. 'VUS' is for variant of uncertain significance, 'P' for pathogenic points, and 'B' for benign points. 'NOA' stands for non-obstructive azoospermia.

TERB1 encodes for a 727 amino acid nuclear protein consisting of two ARM, one coiled-coil, one TERF1-interacting, and one Myb domains (Figure 1c) [21]. TERB1 plays a critical role in the attachment of telomeres to the nuclear envelope and is required for homologous chromosome movement, pairing, synapsis, and recombination. It interacts with the telomeric repeat binding factor 1 (TERF1 in humans and *trf1* in mice) and mediates the assembly of the meiotic telomere complex (MTC) [25], which includes another TERB protein, TERB2, and membrane-anchored junction protein (MAJIN) [26], a transmembrane protein of the inner nuclear membrane. The MTC localizes to the nucleus and anchors the chromosomes to SUN domain-containing protein 1 (SUN1), another transmembrane protein of the inner nuclear membrane, and KASH domain-containing protein 5 (KASH5), a transmembrane protein of the outer nuclear membrane [27]. SUN1 and KASH5 form the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex and attach the MTC to the Dynein-Dynactin complex in the cytoplasm [28]. Altogether, these interacting proteins between the chromosomes in the nucleus and the cytoplasmic cytoskeleton ensure the rapid movement of homologous chromosomes for pairing, synapsis, and recombination [29].

In mice, deleterious mutations in any of *Terb1* [26], *Terb2* [26], *Majin* [26], *Sun1* [30], or *Kash5* [31] result in the loss of germ cells, gonadal dysgenesis, and infertility in both sexes. In humans, biallelic variants in *TERB1* [9, 22-24], *TERB2* [9], *MAJIN* [9], *SUN1* [32], and *KASH5* [32] have been shown to cause non-obstructive azoospermia. However, of these five genes, only biallelic variants in *KASH5* have so far been reported in infertile women (Supplementary Table 1). Some of these women had primary infertility due to POI [33, 34] while others had diminished ovarian reserve and/or recurrent miscarriage [35].

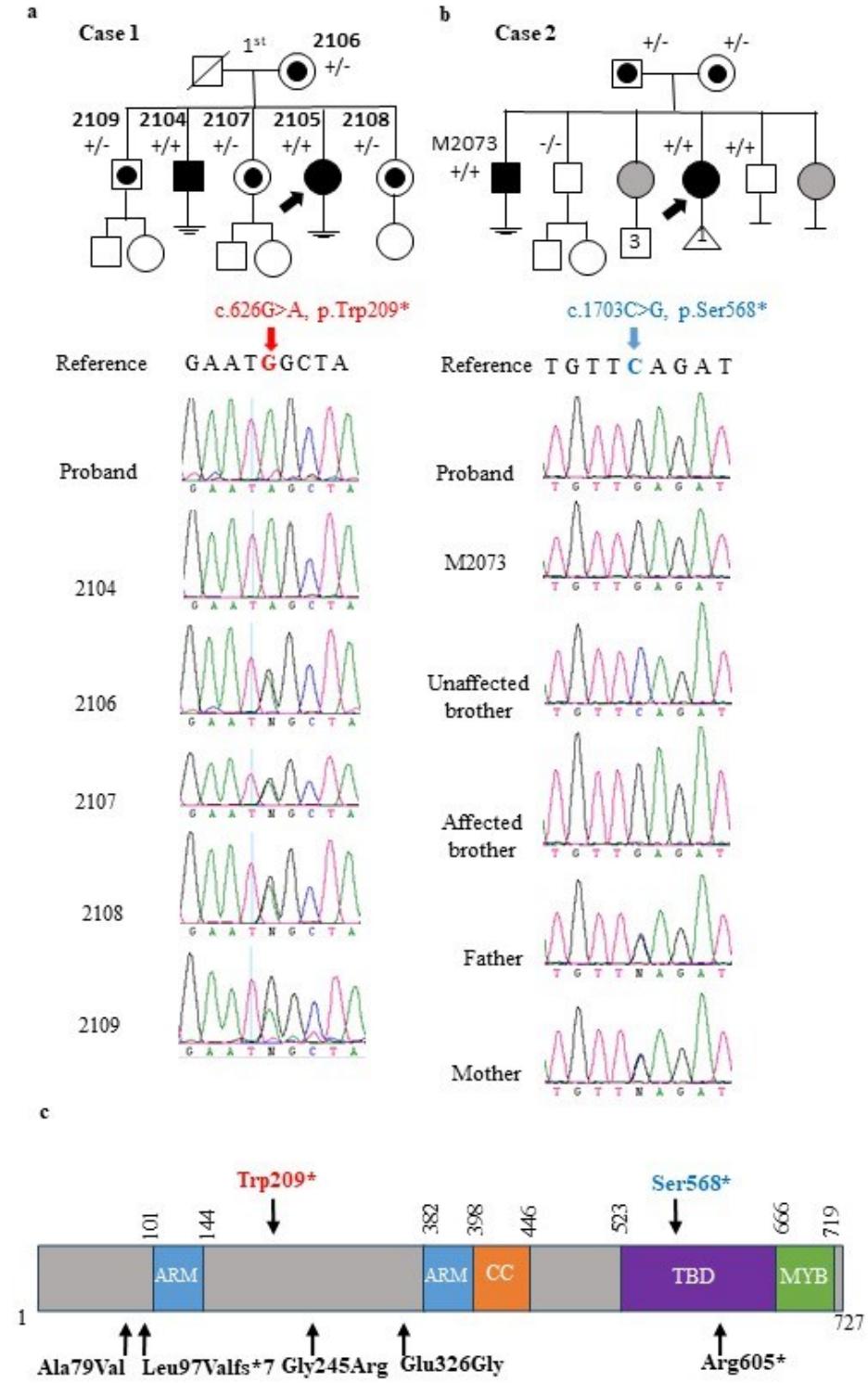
In addition to the members of the MTC and LINC complexes, recessive defects in approximately 50 Meiosis I genes have been shown to cause infertility in both male and female mice [36]. However, to our knowledge, biallelic variants in about 20 Meiosis I genes have been reported to cause male and

female infertility in humans (Summarized in Supplementary Table 1). Results from both mice and human studies have demonstrated a consistent difference in the severity of the phenotype between the two sexes. While in men, deleterious variants cause mostly a complete arrest of Meiosis I and lead to non-obstructive azoospermia, in women, the meiotic arrest appears to be partial and results in a spectrum of reproductive outcomes, ranging from infertility to POI, diminished ovarian reserve, early embryonic arrest after medically assisted reproduction, recurrent molar pregnancy and/or miscarriage (Supplementary Table 1). This sexual dimorphism was described a long time ago in mice [36, 37] and humans [38]. However, due to the phenotype-based nature of human studies, this spectrum of diverse reproductive outcomes seen in women adds another layer of complexity to the highly heterogeneous entity of female infertility, consequently, hampering and delaying the identification of its causative genes and associated variants.

Herein, we describe, for the first time, the association of recessive pathogenic *TERB1* variants with primary female infertility in two unrelated families. Our report adds *TERB1* to the, as of yet, short list of Meiosis I genes associated with human infertility in both sexes.

Fig. 1 Identification of the likely pathogenic and pathogenic *TERB1* variants in two families with primary female infertility. **a** The family pedigree and chromatograms for Case 1. **b** The family pedigree [9] and chromatograms for Case 2. '+/+' and '+/-' indicate family members who are homozygous and heterozygous for the variant, respectively. '-/-' indicate family members with wildtype alleles. The black filled circle and square represent the infertile female and azoospermic male, respectively. Grey circles indicate genetically not tested individuals. Symbols with the black dot represent the heterozygous carriers. Black arrow indicates the proband. Triangle represents miscarriage. The fertility status of M2073's homozygous brother is unknown. **c** Schematic representation of the human *TERB1* protein and its functional domains. Interdomains are indicated in grey, and the domains are colored. ARM, indicates armadillo repeats; CC, coiled-coil domain; TBD, TRF-1 binding domain; MYB, and Myb-like domain.

Mutated amino acids above the protein structure are the *TERB1* variants found in our patients (red: novel, blue: reported in [9]), while those below the protein structure in black are the *TERB1* variants reported in previous literature.



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CHAPTER 3 – GENERAL DISCUSSION

Human infertility has a global prevalence of 10-15%, where approximately 35% of cases are due to female factors (3) and 30% due to male factors (140). Despite their similar proportional contribution, the number of genes with biallelic variants reported in male infertility is nearly five times higher than in female infertility, with an estimated 156 and 62 genes respectively (Table 3) (96, 141-143). This research project establishes a novel association between deleterious variants in *TERB1,* a gene previously implicated in male infertility, and primary female infertility. The two homozygous variants, c.626G>A, p.Trp209* and c.1703C>G, p.Ser568*, were found in two unrelated women, Case 1 and Case 2 respectively, from consanguineous families. The novel c.626G>A, p.Trp209* variant was identified in our lab, while the second variant, c.1703C>G, p.Ser568*, was initially identified in the azoospermic brother of Case 2 and was reported in a paper analyzing the genetics of male infertility (144). With this finding, I added *TERB1* to the short list of genes with biallelic variants reported in human female infertility.

Table 3: Genes with reported biallelic variants associated with human female infertility. Genes reported in both female and male infertility are bolded.

Category	Gene	Protein Function	Phenotype (XX)	Summary of Reports (XX)	References*
Ovarian development	*POF1B*	Actin-binding protein	POI	Multiple cases, including familial	1, 2
	NANOS3	Primordial germ cell maintenance	PI	1 familial case	3
Folliculogenesis	*GDF9*	Follicle development	POI	Multiple cases, including familial	4, 5
	BMP15	Follicle development	POI	Multiple cases, including familial	6, 7, 8
	BMPR15	Follicle development	POI	1 case	9
	NOBOX	Follicle development - transcription factor	POI	Multiple cases, including familial	10, 11
HPO axis activity	***KISS1R***	GnRH release	HH	Multiple cases, including familial	12, 13, 14
	GNRHR	Gonadotropin release	HH	Multiple unrelated cases	15
	FSHR	Follicle maturation	POI, HH	Multiple cases, including familial	16, 17, 18
	LHCGR	Ovulation	EFS, PI, POI	Multiple cases, including familial	19, 20, 21
Meiosis initiation	***STRA8***	Meiotic initiation	POI	1 case	22
	MEIOSIN	Meiotic initiation	POI	2 cases	22, 23

Homologous chromosome pairing and synapsis	***KASH5***	Chromosome movement	POI	Multiple cases, including familial	24, 25, 26
	SHOC†	Synaptonemal complex assembly	POI	1 case	22
	SPO16	Synaptonemal complex assembly	POI	1 case	27
	TRIP13	Synaptonemal complex assembly	EEA, OMA, ZCF, PI	Multiple unrelated cases	28, 29
	SYCE1	Synaptonemal complex subunit	POI	Multiple unrelated cases	30, 31
	SIX6OS1	Synapse formation	POI	2 cases	32, 33
	HFM1	Synapse formation	POI, DOR, RMC	Multiple cases, including familial	34, 35
	STAG3	Cohesin complex subunit. Synapse formation	POI	Multiple cases, including familial	36, 37, 38, 39
	PSMC3IP	Strand exchange stimulation	POI	Multiple cases, including familial	40
Recombination and chromosome separation	*REC114*	DSB formation	EEA, PI	Multiple cases, including familial	41
	TOP6BL	DSB formation	PI, RHM, MC	Multiple unrelated cases	42, 43
	MEI4	DSB formation	DOR	Multiple cases, including familial	44
	MEI1	DSB formation	RMC, RHM, UF, CHM, PI, EEA, IF	Multiple unrelated cases	43, 45
	XRCC2	DSB repair	POI	1 case	22
	MCMDC2	DSB repair	POI	1 case	22

	MCM8	DSB repair	POI	Multiple cases, including familial	46, 47, 48
	MEIOB	DSB repair	POI, PI, MC	Multiple cases, including familial	49, 50
	ZSWIM7	DSB repair	POI	Multiple cases, including familial	51, 52
	BRCA2	DSB repair	POI	Multiple unrelated cases	53, 54
	SPIDR	DSB repair	POI, OD	Multiple cases, including familial	55, 56
	MCM9	DSB repair	POI, HH, OD	Multiple cases, including familial	57, 58, 59
	DMC1	DSB repair	POI, DOR	Multiple cases, including familial	60, 61
	SPATA22	DSB repair	POI, PI	Multiple cases, including familial	62, 63
	HROB	DNA repair	POI, PA	Multiple cases, including familial	2, 64
	FANCM	Crossover suppression and regulation	POI	Multiple cases, including familial	65, 66, 67
	MSH4	DNA mismatch repair, crossover formation and homolog segregation	POI	Multiple cases, including familial	68, 69, 70
	MSH5	DNA mismatch	POI	1 familial case	71

		repair, crossover formation & homolog segregation			
	REC8	Homologous chromosome and sister chromatid separation	POI	1 case	2
Meiosis regulation	*MAD2L1BP*	MI and MII checkpoint protein	POI, OMA	1 case	72
	CDC20	MI and MII checkpoint protein	OMA, EEA, PI	Multiple unrelated cases	73, 74, 75
	WEE2	MI and MII arrest maintenance	FF, PI	Multiple cases, including familial	76, 77, 78
	FBXO43	MII arrest maintenance	EEA	Multiple unrelated cases	79
	MOS	MII arrest maintenance	EEA, PI	Multiple unrelated cases	80, 81, 82
Oocyte maturation and fertilization	*NUP107*	Nuclear pore complex component	GD, POI	2 cases	83, 84
	FIGLA	Transcription factor	POI	2 cases	85, 86
	TUBB8	Meiotic spindle assembly	EEA, OMA, PI,	Multiple cases, including familial	87, 80
	PABPC1L	Maternal mRNA translation activation	POI, OMA, EEA	Multiple cases, including familial	89, 90
	PANX1	Channel protein	OD, PI	Multiple unrelated cases	91, 92
	BTG4	Maternal mRNA decay	EEA, ZCF	Multiple unrelated cases	93, 94, 95
	PATL2	Maternal mRNA	PI, OMA	Multiple cases,	96, 97, 98

		translation repressor		including familial	
	SOHLH1	Transcription factor	HH	Multiple cases, including familial	99, 100
	DIS3	RNA degradation	POI	1 familial case	101
	ASTL	Fertilization regulation	PI, OMA, FF	Multiple unrelated cases	102, 103
	ZP1	Component of zona pellucida. Oocyte development. Sperm binding and acrosome reaction induction.	PI, EFS, OMD	Multiple cases, including familial	104, 105, 106, 107
	ZP2	Component of zona pellucida. Oocyte development. Acrosome-reacted spermatozoa penetration.	FF, PI, EFS, OMD	Multiple cases, including familial	108, 109
	ZP3	Component of zona pellucida. Oocyte development. Sperm binding and acrosome reaction induction.	EFS, POI	Multiple unrelated cases	22, 110
Early embryonic development	*TLE6*	Member of the subcortical maternal complex	EEA, PEL, PI	Multiple cases, including familial	111, 112, 113, 114
	OOEP	Member of the subcortical	EEA	1 case	115

		maternal complex			
	PADI6	Member of the subcortical maternal complex	EEA, PI, RMC, RHM, MLID	Multiple cases, including familial	116, 117, 118, 119
	NLRP2	Member of the subcortical maternal complex	EEA, MLID	Multiple unrelated cases	120, 121
	NLRP5	Member of the subcortical maternal complex	EEA, FF, RHM, OMA, RMC, PI, FF, MLID	Multiple cases, including familial	122, 123, 124, 125

POI: premature ovarian insufficiency, PI: primary infertility, HH: hypogonadotropic hypogonadism, EFS: empty follicle syndrome, EEA: early embryonic arrest, OMA: oocyte maturation arrest, ZCF: zygotic cleavage failure, RHM: recurrent hydatidiform mole, MC: miscarriage, DOR: diminished ovarian reserve, RMC: recurrent miscarriage, UF: uterine fibroids, CHM: complete hydatidiform mole, IF: implantation failure, OD: oocyte death, GD: gonadal dysgenesis PA: primary amenorrhea, FF: fertilization failure, OMD: oocyte maturation defect, PEL: preimplantation embryo lethality, MLID: multilocus imprinting disturbances.

*References for Table 3 can be found in the Appendix.

The 62 female infertility genes can be categorized into nine distinct categories based on their respective reproductive function: ovarian development, HPO axis activity, folliculogenesis, meiosis initiation, homologous chromosome pairing and synapsis, recombination and chromosome separation, meiosis regulation, oocyte maturation and fertilization, and early embryonic development (Table 3). Interestingly, all reported genes, directly or indirectly, have a role in gamete production, maturation, and maintenance.

Of the 62 known genes, 39 (63%) are involved in folliculogenesis or meiosis, of which 27 (69%) are involved in homologous chromosome recombination, with roughly half of them encoding DNA

repair proteins. DNA repair is an important process in prophase I to fix the double-stranded breaks generated to drive meiotic recombination between homologous chromosomes as well as to restore any mismatched base pairs for faithful DNA inheritance in gametes. If homologous recombination is impaired, faulty gametes will either get eliminated via apoptotic processes, arrest and fail to mature, or lead to early embryonic loss after fertilization or implantation. Interestingly, defects in 22 (82%) genes involved in homologous recombination have been reported in patients with POI (Table 3), highlighting the role of meiotic genes in maintaining the oocyte pool and normal ovarian functions.

Following folliculogenesis and meiosis, variants in 13 genes involved in oocyte maturation and fertilization make up 21% of known genes for female infertility. Rather than the production of oocytes, these genes are required for the proper growth of oocytes and crucial to produce mature eggs equipped with the biological materials and the appropriate structure to successfully get fertilized and produce viable embryos. The roles of these genes vary from coding for structural components of ovarian follicles and oocytes to regulators of maternal mRNA translation. Oocyte maturation and fertilization gene defects have been associated with 10 different reproductive outcomes. Unlike in meiosis and folliculogenesis gene defects, the phenotype frequencies are more heterogeneous in this category. Oocyte maturation arrest (6 genes), primary infertility (6 genes), and POI (5 genes) are the most reported phenotypes. An explanation for this distribution can be the role of the protein products in maturing the oocytes of the already-established ovarian reserve rather than producing it. Because of this, depending on how the gene defect impacts the established oocyte pool, different phenotypes can be observed in patients. A similar phenotypic trend can be observed in patients with mutations in genes involved in early embryonic development. All genes reported in this category are members of the subcortical maternal complex (SCMC) expressed specifically in oocytes and early embryos (146). SCMC is required for the establishment of de novo maternal methylation and post-fertilization cleavage events that proceed zygote through the first embryonic divisions. Aligning with its role, defects in several

members of the SCMC genes have been reported in patients with early embryonic arrest. However, similar to oocyte maturation and fertilization genes, a spectrum of phenotypes is observed in patients with defects in these genes and include but are not limited to primary infertility, recurrent molar pregnancies, and recurrent miscarriages.

Among the 62 genes reported to cause female infertility, 28 (45%) have been also implicated in male factor infertility (Table 3). Intriguingly, 24 out of the 28 are meiotic genes (86%), with the remaining 4 involved in HPO axis signaling (14%). Given that meiosis and HPO axis signaling are biological entities common to both sexes, it is logical that they are the two categories of genes with biallelic variants associated with infertility in both men and women. However, there is a stark difference between their contribution to the overall pool of genes identified in the two sexes. While these 28 genes make up 45% of all known female-infertility-associated genes, they account for only 20% of all known male-infertility-associated genes. This disproportionality can be seen as a testament to how little is known about the genetic causes of female infertility.

Abnormal sperm parameters account for 65-80% of male infertility cases (4). Thus, semen analysis is a valuable assessment to evaluate for male infertility. Due to the male reproductive physiology, sperm samples can be readily collected to assess spermatozoid concentration, motility, and morphology. A normal ejaculate has a volume of >1.5 mL and a spermatozoid count of >39 millions. Because the high number of available gametes, morphological and functional assessments can also be done without being limited by the sample size. If an abnormality observed in the sperm, further genetic testing can be performed to identify its cause. Comparatively, female reproductive physiology renders oocytes inaccessible. Female gametes are embedded within the ovarian tissue. Although ultrasound imaging and endocrinological measurements (such as AMH levels) can provide insight into the ovarian reserve, to directly assess oocyte morphology, more invasive methods must be utilized to retrieve the egg.

Oocyte retrieval is a clinical procedure used as a part of medically assisted reproductive treatments, such as IVF. The number of oocytes collected per stimulation in healthy patients ranges from 8-18 oocytes (142), which is significantly smaller than the spermatozoid concentration observed in a normal ejaculate. Thus, the sample size to assess gamete morphology is small to begin with in female infertility. In addition, some patients may fail to respond to stimulation, resulting in the retrieval of a limited amount of or no eggs and hindering the analysis of oocyte morphology. When egg retrieval is successful, several processes can be examined under the microscope including polar body extrusions, fertilization, and zygotic cleavage formation. Although any abnormalities can be detected at these preimplantation stages, once the embryo transfer is completed, unless the product of conception is retained beyond 6 weeks, it is difficult to possibly get an idea about the physiological defects that might have led to the pregnancy loss. Overall, due to the complexity of female reproduction, there are many barriers along the way to understanding and evaluating a potential genetic contributor to patients' infertility.

In addition to the obstacle created by the small number and inaccessibility of oocytes, female infertility's phenotypic spectrum further complicates its studies and diagnoses. In female infertility of genetic origin, patients often experience a combination of reproductive failures such as amenorrhea, miscarriages, molar pregnancies, and fertilization or implantation failures. In fact, almost half of the 62 female infertility genes have been associated with multiple phenotypes. One example is the homozygous damaging variant in the *MEIOB* gene identified in a patient with POI, one hydatidiform mole, and one early miscarriage (147). Because clinically these three entities are considered distinct reproductive failure forms (infertility, molar pregnancy, and miscarriage), a combination of reproductive outcomes can pose an additional hurdle in suspecting a genetic predisposition to the patient's condition. In addition, these phenotypes could also manifest differently with respect to age. Literature suggests that as women get older, the quality of their oocytes decline (95). Thus, depending on the affected gene and

defect severity, women who reproduce early may be able to conceive successfully and experience infertility only at an older reproductive age.

The advent of next generation sequencing and the identification of several additional genes associated with different forms of reproductive failure in affected siblings and even the same patient is increasing the awareness of the clinicians to the overlapping manifestations of these conditions. With this increasing awareness, more and more patients partake in genetic screening and contribute to research around genetics of reproduction. This allows not only the identification of additional genes associated with reproductive failure, but also provides patients with an explanation to why they might not be achieving pregnancy, freeing them from the mental burden of the unknown.

CHAPTER 4 – CONCLUSION AND FUTURE DIRECTIONS

Female infertility is a complicated entity with diverse manifestations. As the global infertility rates elevate, it is essential to investigate and identify the genetic contributors of this prevalent condition to provide patients with the correct diagnosis and prevent the consequent emotional and financial burden of undergoing fertility treatments. To achieve this, genetic testing efforts should be amplified across populations. This project makes a novel association between damaging biallelic *TERB1* variants and female infertility, contributing to the current understanding of the field.

In addition to the *TERB1* variant, below are the additional findings and projects I will be working on for the remainder of my degree:

1) Additional biallelic variants in genes implicated in reproduction have been identified in our patients. 2136 is a female patient from a consanguineous family with a reproductive history of 12 years of primary infertility, six early miscarriages, three failed ICSI trials, and one complete hydatidiform mole. In this patient, exome filtering identified a homozygous stop-gain variant, NM_001163560:c.814C>T:p.R272*, in *MEIOB,* a gene previously associated with female infertility (83-85). This case is included in a second and bigger manuscript that is currently being improved.
2) Roughly 50 single heterozygous protein-truncating variants were identified and validated in our POI patient cohort without a recessive defect identified. These variants will also be included in the manuscript mentioned above.
3) Compound heterozygous protein truncating *NLRP2* variants were identified in patient 2168 who have had 4 miscarriages and 1 failed ICSI trial. Additional experiments are currently being conducted to assess the impact of these variants on the mRNA.

CHAPTER 5 – MASTER REFERENCE LIST

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APPENDIX

Centre universitaire de santé McGill
McGill University Health Centre

Questionnaire for Participants with Recurrent Reproductive Failure
(Recurrent spontaneous abortions, Molar pregnancies, Infertility)

Name:……..……..……..……

Date of Birth:..……..……..

Medical Card Number (for identification only):……..……..

Address:...…….....

Phone Number:…….……

Email:……..……..…….

Physician's Name and Hospital:…….....……

Ethnic Group & Country of Origin of Participant:……

Partner:…….……..……

For how many years have you been trying to conceive and/or had unprotected sexual intercourse?
.....

Age at first pregnancy (successful or not):…….…….……..

Number of term pregnancies:…….……..

Please complete the following page for additional details on your pregnancy/pregnancies:
Obtain details of ALL pregnancies in chronological order. Types of pregnancies, their outcomes, and complications if any:

Live birth (**LB**)
Still birth (**SB**) (Loss of baby after 28 weeks of pregnancy)
Miscarriage (**MC**)
Termination of pregnancy (**TOP**) (clarify if undesired pregnancies, fetal abnormalities, or maternal conditions necessitating ending the pregnancy)
Hydaditiform mole (**HM**)
Invasive mole (**IV**)
Choriocarcinoma (**CC**)
Blighted ovum (**BO**)
IVF (failed or successful in vitro fertilization)
In uterine insemination (**IUI**)

	1st	**2nd**	**3rd**	**4th**
Pregnancy type (see categories above)				
Month, Year				
Spontaneous conception? (if no, name drug)				
Gestational age (number of weeks of pregnancy at childbirth or when D&C was performed)				
D&C?				
Any other complication during pregnancy/delivery?				

	5th	**6th**	**7th**	**8th**
Pregnancy type (see categories above)				
Month, Year				
Spontaneous conception? (if no, name drug)				
Gestational age (number of weeks of pregnancy at childbirth or when D&C was performed)				
D&C?				
Any other complication during pregnancy/delivery?				

In the case of molar pregnancies or other gestational trophoblastic diseases, did you require chemotherapy? If yes, please provide details:.....

The following questions are about the patient's menses and medical history:

How many days does your period last (in days)?.....

Please describe your period flow (light, normal, heavy):…….

Do you experience pain with your menses (if yes, how much?):……

Have you ever had any pelvic infection (STD, PID, chlamydia, gonorrhea), vaginitis or other vaginal infection?..... …….
.....

Have you had any surgery in the pelvic area (uterus, tubes, ovaries, or cervix?):…….
……

Have you ever had an infection in the abdomen or pelvis after surgery?.....

Have you ever had treatment to your cervix?.....

Have you ever used any oral contraceptive medications or intrauterine contraceptive devices (IUCD)? Explain the name of the drugs/devices used, when and for how long?
.....
.....

Have you had an x-ray of your uterus and tubes? If yes, what were the findings?
.....

Have you ever had your karyotype checked and if so, what as it?.....
……

Have you ever experienced absence of periods or irregular menstrual cycles (if yes, for how long)?
……...……

Have you been diagnosed with diminished ovarian reserve? If yes, please answer the following:

- When and how were you diagnosed?
- What was your antral follicle count (number of follicles in each ovary during your menstruation)?
- What was your serum anti-mullerian hormone (AMH), serum follicle stimulating hormone (FSH), and serum estradiol levels on day 2-3 of the menstrual cycle?

.....

……

……

Have you ever had medication for inducing ovulation? If yes, please explain:……

.....

Do you have any of the following?	**Yes** ✓	**No** ✖	**Don't know** **?**
▪ Thyroid disorder or imbalance			
▪ Endometriosis			
▪ Scar tissue or adhesions			
▪ Hashimoto's disease			
▪ Polycystic ovary syndrome (PCOS)			
▪ Lupus (systemic lupus erythematosus, SLE)			
▪ Antiphospholipid syndrome			
▪ Anti-cardiolipin antibodies			
▪ Any other autoimmune disease			
▪ Any other disease			

Do you have any additional medical conditions you would like your physician to know about?

……

……

The following questions are about the patient's partner:

Has your partner had a sexually transmitted disease (STD)?.....
.....

Has your partner had any previous pregnancies, successful or not, with partners other than yourself?.....
……

Does your partner have any children from previous partners? If yes how many?.....
.....

Are you aware of any medical condition linked to infertility or not in your partner?.....
……

Has your partner had a spermogramme?.....

Has your partner had his karyotype checked?.....
Is there a blood relationship between you and your partner?.....

Is there a blood relationship between your parents or grandparents?.....
……

Is there any medical condition in your family or that of your partner?.....
……..……

Are there fertility problems in your family or that of your partner?.....
.....

Is there a history of babies born in either of your families who have genetic problems?.....
……

Pregnancy details of your mother and sisters. Indicate the number of each.

	Livebirth or Stillbirth	Preterm (Childbirth before 38 weeks of pregnancy)	Spontaneous Abortion or Miscarriage	Termination of pregnancy OR therapeutic abortion	Hydaditiform Mole	Infertility	Twins
Mother	……	……	……	……	……	……	……
Sister 1	……	……	……	……	……	……	……
Sister 2	……	……	……	……	……	……	……
Sister 3	……	……	……	……	……	……	……

Explain in your own terms what makes you believe that this patient may have a genetic defect and indicate any relevant observations or test results.

.....

.....

.....

.....

.....

.....……

……

Family History/Pedigree

Legend:

- Livebirth (LB)
- Stillbirth (SB)
- Spontaneous abortion (SA)
- Termination of pregnancy (TOP), indicate the reason
- Invasive mole (IM)
- Choriocarcinoma (CC)
- Blighted ovum (BO)
- Hydaditiform mole (HM)
- Oocyte maturation defect (OMD)
- Embryonic arrest during the preimplantation period
- Infertility

I……

……

Grandparents

II……

……

Parents

III……

……

Participant

IV……

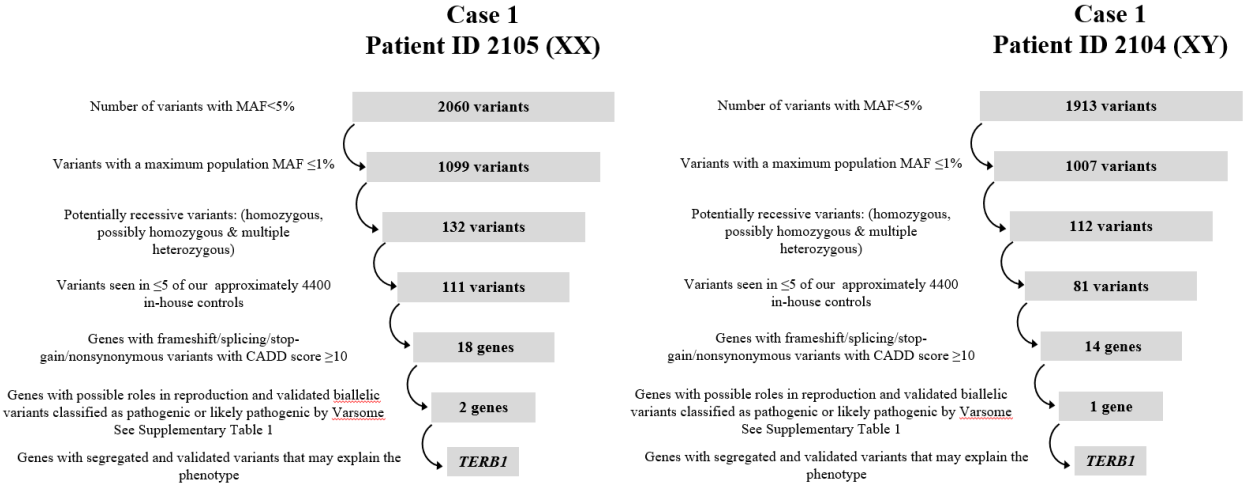
……

Offspring

Supplementary Figures and Table

Supplementary Figure 1: Exome data filtering scheme for patients 2105 and 2104.

The raw variant data acquired from Whole Exome Sequencing were initially filtered for variants with minor allele frequency (MAF) <5%. The resulting 2060 and 1913 variants were then filtered, in order, according to 1) maximum population MAF, 2) zygosity, 3) frequency in in-house control, 4) variant type and Combined Annotation Dependent Depletion (CADD) score, and 5) gene role and Varsome classification. The remaining candidates were either validated and segregated or excluded using Sanger sequencing. This process resulted in the identification, validation and segregation of the novel homozygous stop-gain variant, NM_001136505.2:c.626G>A, p.Trp209*, in *TERB1* of the infertile sister (2105) and azoospermic brother (2104). The numbers adjacent to the filtering criteria reflect the number of variants or genes that remained upon applying the specific criterion.



Supplementary Figure 2: The 18 and 14 genes with candidate variants in 2105 and 2104, respectively. Orange highlighted variants are found in both siblings. Sanger sequencing was done on variants indicated in black frames, which are classified as pathogenic, likely pathogenic, or of uncertain significance by the ACMG guidelines using Varsome, and are found in genes with potential roles in reproduction. The crossed-out, likely pathogenic *TSSK2* variant in patient 2105 was not confirmed by Sanger sequencing, excluding the gene as a candidate. Bolded is the likely pathogenic *TERB1* variant that was validated in both patients and segregated with the phenotype, making it the most plausible candidate to explain our patients' phenotypes.

Patient 2105 (female) Candidate Genes and Variants

Position	Zygosity	Protein Change	Gene	CADD	ACMG Classification by Varsome	Gene Name
chr1:181695216	multiple het	p.E720K	CACNA1E	25.7	Uncertain significance	Calcium Voltage-Gated Channel Subunit Alpha1 E
chr1:181702165	multiple het	p.L962F	CACNA1E	17.33	Likely Benign	
chr1:206224794	multiple het	p.M118I	AVPR1B	27.1	Likely Benign	Arginine Vasopressin Receptor 1B
chr1:206230910	multiple het	p.R348Q	AVPR1B	14.05	Likely Benign	
chr6:106960613	hom	p.P133T	CRYBG1	16.87	Likely Benign	Crystallin Beta-Gamma Domain Containing 1
chr12:48482722	hom	p.F81C	SENP1	24.7	Benign	SUMO Specific Peptidase 1
chr12:49420968	hom	p.S4927R	KMT2D	11.36	Uncertain significance	Lysine Methyltransferase 2D
chr12:52754768	hom	p.R253C	KRT85	23.4	Likely Benign	Keratin 85
chr16:53720481	hom	p.V214I	RPGRIP1L	22.7	Likely Benign	RPGRIP1-like
chr16:66819763	**hom**	**p.W209***	**TERB1**	**37**	**Likely Pathogenic**	**Telomere Repeat Binding Bouquet Formation Protein 1**
chr16:66969389	hom	p.G15R	CES2	12.11	Uncertain significance	Carboxylesterase 2
chr16:68279421	hom	p.A31V	PLA2G15	22.4	Likely Benign	Phospholipase A2 Group XV
~~chr22:19118914~~	~~multiple het~~	~~p.M1K~~	~~TSSK2~~	~~25.2~~	~~Likely Pathogenic~~	Testis-Specific Serine Kinase 2
chr22:19119640	multiple het	p.C243F	TSSK2	16.08	Likely Benign	
chr22:19766797	hom	p.P355R	TBX1	13.53	Likely Benign	T-Box Transcription Factor 1
chr22:19776368	hom	p.R283Q	GNB1L	23.6	Likely Benign	G Protein Subunit Beta 1 Like
chr22:21188907	hom	p.L104F	PI4KA	22.3	Likely Benign	Phosphatidylinositol 4-Kinase Alpha
chrX:23749032	hom	p.P19L	ACOT9	22.9	Uncertain significance	Acyl-CoA Thioesterase 9
chrX:70147159	hom	p.L420Q	SLC7A3	26.8	Likely Benign	Solute Carrier Family 7 Member 3
chrX:74293709	hom	p.R273Q	ABCB7	18.27	Benign	ATP Binding Cassette Subfamily B Member 7
chrX:79984337	hom	p.Y434H	BRWD3	12.55	Likely Benign	Bromodomain And WD Repeat Domain Containing 3

Patient 2104 (male) Candidate Genes and Variants

Position	Zygosity	Protein Change	Gene	CADD	ACMG Classification by Varsome	Gene Name
chr1:181695216	multiple het	p.E720K	CACNA1E	25.7	Uncertain significance	Calcium Voltage-Gated Channel Subunit Alpha1 E
chr1:181702165	multiple het	p.L962F	CACNA1E	17.33	Likely Benign	
chr1:206224794	multiple het	p.M118I	AVPR1B	27.1	Likely Benign	Arginine Vasopressin Receptor 1B
chr1:206230910	multiple het	p.R348Q	AVPR1B	14.05	Likely Benign	
chr5:169812358	hom	p.Y32H	KCNMB1	25.4	Uncertain significance	Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 1
chr8:54163408	hom	p.A64S	OPRK1	25.7	Uncertain significance	Opioid Receptor Kappa 1
chr8:120865444	hom	p.R65H	DSCC1	35	Uncertain significance	DNA Replication And Sister Chromatid Cohesion 1
chr12:48482722	hom	p.F81C	SENP1	24.7	Benign	SUMO Specific Peptidase 1
chr12:49420968	hom	p.S4927R	KMT2D	11.36	Uncertain significance	Lysine Methyltransferase 2D
chr12:52754768	hom	p.R253C	KRT85	23.4	Likely Benign	Keratin 85
chr16:66819763	**hom**	**p.W209***	**TERB1**	**37**	**Likely Pathogenic**	**Telomere Repeat Binding Bouquet Formation Protein 1**
chr21:34635671	hom	p.A472T	IFNAR2	20.2	Likely benign	Interferon Alpha And Beta Receptor Subunit 2
chr21:34947948	hom	p.F388L	SON	23	Likely Benign	SON DNA and RNA Binding Protein
chr21:40177902	hom	p.A93V	ETS2	10.14	Benign	ETS Proto-Oncogene 2, Transcription Factor
chr22:19766797	hom	p.P355R	TBX1	13.53	Likely Benign	T-Box Transcription Factor 1
chr22:19776368	hom	p.R283Q	GNB1L	23.6	Likely Benign	G Protein Subunit Beta 1 Like

Supplementary Table 2: The table summarizes the recessive variants in meiosis I genes that have been reported to cause infertility in both females and males. To curate a list of meiosis I genes, PubMed search engine was used with the following keywords in different combinations to find review papers on genes involved in meiosis: meiosis, meiosis I, genes, genetics, meiotic genes, crossover, homologous recombination, and infertility. From the review papers extracted, a list of only genes involved in meiosis I was generated using the GeneCards database to confirm the role of the genes in meiosis I. Next, a second PubMed search was done to identify the variants reported in human infertility for each meiosis I gene using different combinations of the following keywords: gene name, variant, mutation, female infertility, male infertility, infertility, primary ovarian insufficiency, azoospermia, and reproduction. Genes with causative biallelic variants reported for at least one female and one male patient were then compiled in a table. The final table includes all such variants for the meiosis I genes reported in infertility in both sexes. POI stands for premature ovarian insufficiency; NOA: non-obstructive azoospermia; DOR: diminished ovarian reserve; SCO: Sertoli cell-only syndrome; RPL: recurrent pregnancy loss; RMC: recurrent miscarriage; RHM: recurrent hydatidiform mole; UF: uterine fibroids; CHM: complete hydatidiform mole; PI: primary infertility; EA: embryonic arrest; IF: implantation failure; HM: hydatidiform mole; MC: miscarriage.

Supplementary table 2: Summary of reported meiosis I gene variants in female and male infertility in humans

Gene	Patient ID	Sex	Protein Change	Zygosity	Phenotype	Reference
DMC1	IV-1	Female	c.106G>A, p.Asp36Asn	Homozygous	POI	[1]
	IV-2	Male			NOA	
	G2-A	Male	c.28delG, p.Glu10Asnfs*31	Homozygous	NOA	[2]
	G2-B	Female			DOR	
	G2-C	Female				

FANCM	II-1 & II-2	Female	c.5101C>T, p.Gln1701*	Homozygous	POI	[3]
	1	Female	c.1972C>T; p.Arg658*	Homozygous	DOR	[4]
	2	Female				
	3	Female	c.5101C>T, p.Gln1701*	Homozygous	POI	
	4	Female				
	5	Female	c.5791C>T; p.Arg1931*	Homozygous	POI	
	B.1, B.2	Male	c.1491dupA, p.Gln498Thrfs*7	Multiple heterozygous	NOA and SCO	[5]
			c.4387-10A>G, p.Arg1436_Ser1437insLeuLeu*			
	Subject 3	Male	c.5101C>T, p.Gln1701*	Homozygous	NOA	
	Subject 4	Male	c.5791C>T, p.Arg1931*	Homozygous	NOA	
	IV:1, IV:2, IV:3	Male	c.1946_1958del, p.Pro648Leufs*16	Homozygous	oligoasthenospermia and azoospermia	[6]
	Patient 6	Female	c.3088C>T, p.Arg1030*	Multiple heterozygous	POI	[7]
			c.5791C>T, p.Arg1931*			
	P6649 and P6649-B	Male	c.1778delG, p.Arg593Glnfs*76	Multiple heterozygous	NOA	[8]
			c.1663G>T, p.Val555Phe			
	P6612	Male	c.1972C>T, p.Arg658*	Homozygous	NOA	
	P0138	Male	c.5791C>T, p.Arg1931*	Homozygous	NOA	[9]
HFM1	Affected sister 1 & 2	Female	c.1686-1G>C	Multiple heterozygous	POI	[10]
			c.2651T>G, p.Ile884Ser			
	Sporadic patient	Female	c.2206G>A, p.Gly736Ser	Multiple heterozygous	POI	
			c.3929_3930 delinsG, p.Pro1310Argfs*41			
	POI-6	Female	c.3100G>A, p.Gly1034Ser	Multiple heterozygous	POI	[11]
			c.1006+1G>T			
	Family 1, II-1	Male	c.3490C>T, p.Gln1164*	Homozygous	NOA	[12]
	Family 2, II-1	Male	c.3470G>A, p.Cys1157Tyr	Homozygous	NOA	
	5	Female	c.2410G>T, p.Glu804*	Homozygous	POI	[13]
	P0369	Male	c.3588+1G>A	Homozygous	NOA	[9]
	IV-4	Male	c.1832-2A>T	Homozygous	NOA	[14]
	P1	Male	c.1355G>A, p.Arg452Gln	Homozygous	NOA	[15]
	P2	Male	c.2562_2563del, p.Glu856Asnfs*56	Multiple heterozygous	NOA	
			c.4126del, p.Glu1376Argfs*49			
	P3	Male	c.2487_2491del, p.Lys829Asnfs*23	Multiple heterozygous	NOA	
			c.3490C>T, p.Gln1164*			
	II-3 & II-2	Female	c.2680+3_2680+4delAT	Multiple heterozygous	DOR & RPL	[16]
			c.1978-2A>C			
	Family 2, Patient II-1	Female	c.2899del, p.Ile967Phefs*2	Homozygous	POI	[17]
	Family 1, II-1	Female	c.1730-1G>T	Homozygous	POI	[18]
	Family 1, II-2	Male			NOA	
KASH5	NOA008, II-2 & II-3	Male	c.1604T>A, p.Leu535Gln	Homozygous	NOA	[19]
	IV-1	Male	c.590T>C, p.Leu197Pro	Homozygous	NOA	[20]
	IV-2	Female			POI	
	III-1 & III-2	Female	c.747G>A	Homozygous	POI	[21]
	IV-2	Female	c.1270_1273del	Homozygous	RMC	[22]
	IV-3	Female			RMC	
	IV-4	Male			NOA	
	IV-5	Female			Infertility	
	IV-6	Female			RMC	
MCM8	IV-1, IV-6, & IV-9	Female	c.446C>G, p.Pro149Arg	Homozygous	POI	[23]
	V-1	Female	c.1954-1G>A	Homozygous	POI	[24]
	V-2	Male			NOA	
	IV-2, IV-3, IV-4, IV-6 & IV-7	Female	c.1469-1470insTA	Homozygous	POI	
	V-5, V-9, V-10, & V-11	Female	c.482A>C, p.His161Pro	Homozygous	POI	[25]
	IV-1 & IV-3	Female	c.351_354delAAAG, p.Lys118Glufs*5	Homozygous	POI	[26]
	1	Female	c.1905+1G>C	Homozygous	POI	[13]
	P0370	Male	c.482A>C, p.His161Pro	Homozygous	SCO	[9]
	P0281	Male				
MCMDC2	P0085	Male	c.1795C>T, p.Arg599*	Homozygous	NOA	[9]
	POI-1640	Female	c.685C>T, p.Gln229*	Homozygous	POI	[27]

MEI1	III-8	Male	c.3307C>T, p.Arg1103Trp	Homozygous	NOA	[28]
	1333	Female	c.3452G>A, p.Trp1151*	Homozygous	RMC, RHM	[29]
	1660	Female			UF	
	1661	Female				
	880	Female	c.1196+1G>A	Multiple heterozygous	RMC, CHM	
			c.2206del, p.Val736Serfs*31			
	1659	Male	c.1196+1G>A	Multiple heterozygous	NOA	
			c.2206del, p.Val736Serfs*31			
	NOA249	Male	c.3002del, p.Ala1001Glufs*42	Homozygous	NOA	[30]
	18-406	Male	c.1088C>T, p.Thr363Met	Multiple heterozygous	NOA	[31]
			c.925C>T, p.Leu309Phe			
	II-1 in Family 1	Female	c.186G>C, p.Lys62Asn	Multiple heterozygous	RHM	[32]
			c.1585T>A, p.Phe529Ile			
	II-1 in Family 2	Female	c.1792+1G>T	Homozygous	PI, EA	
	II-1 in Family 4	Female	c.1585T>A, p.Phe529Ile	Homozygous	PI, EA, IF	
	II-1 in Family 5	Female	c.186G>C, p.Lys62Asn	Multiple heterozygous	PI, EA	
			c.734-2A>C			
	II-1 in Family 6	Female	c.186G>C, p.Lys62Asn	Multiple heterozygous	PI, EA	
			c.734-2A>C			
	II-1 in Family 7	Female	c.1585T>A, p.Phe529Ile	Multiple heterozygous	PI, EA	
			c.745C>T, p.Gln249*			
	III-2 & III-3	Male	c.529+5G>A	Multiple heterozygous	NOA	[33]
			c.2071C>G, p.Gln691Glu			
MEIOB	A1, A2, A3, A4	Male	c.191A>T, p.Asn64Ile	Homozygous	NOA	[34]
	I1 & I2	Male	c.1098delC, p.Ser366fs	Homozygous	NOA	[35]
	MO13, III-10	Female	c.1218G>A	Homozygous	POI, HM, early MC	[36]
	MO13, III-11				POI	
	Family 2, II-1	Female	c.31C>T, p.Arg11*	Multiple heterozygous	POI	[37]
			c.900+1G>A			
	Family1, IV-3	Male	c.400C>T, p.Arg134*	Homozygous	NOA	
	Family 1, V-3	Female	c.258_259del, p.Cys86fs	Homozygous	Oligomenorrhea & infertility	[38]
			c.1072_1073del, p.Met358fs			
	Family 2, IV-3	Female	c.814C>T, p.Arg272*	Homozygous	POI	
	Family 3, II-1	Male	c.1072_1073del, p.Met358fs	Homozygous	NOA	
MSH4	P1, P2	Female	c.2355+1G>A	Homozygous	POI	[39]
	11-127	Male	c.1913C>T, p.Pro638Leu	Homozygous	NOA	[31]
	M1916	Male	c.2261C>T, p.Ser754Leu	Homozygous	NOA	
	F1 II-1	Male	c.1552C>T, p.Gln518*	Homozygous	NOA	[40]
	III-7	Female	c.2261C>T, p.Ser754Leu	Homozygous	POI	[41]
	III-4	Male			NOA	
	M2047	Male	c.1453C>T, p.Gln485*	Multiple heterozygous	NOA	[42]
			c.1686del, p.Val563*			
	AMC-01	Male	c.2198C>A, p.Ser733*	Homozygous	NOA	
	AMC-02	Female			POI	
	P9359	Male	c.805_812del, p.Val269Glnfs*15	Homozygous	NOA	[43]
	P9517	Male	c.1950G>A, p.Trp650*	Multiple heterozygous	NOA	
			c.2179delG, p.Asp727Metfs*11			
	P9540	Male	c.244G>A, p.Gln82Ser	Multiple heterozygous	NOA	
			c.670delT, p.Leu224Cysfs*3			
	P21504	Male	c.2220_2223del, p.Lys741Argfs*2	Homozygous	NOA	
	Family 1, II-1, II2	Female	c.2531-1G>A	Homozygous	POI	[17]
MSH5	III-3 & III-4	Female	c.1459G>T, p.Asp487Tyr	Homozygous	POI	[44]
	M721	Male	c.75dup, p.Ser26Glnfs*42	Homozygous	NOA	[42]
	M2464	Male	c.964C>T, p.Arg322Cys	Homozygous	NOA	
	M1502	Male	c.1857del, p.Ala620Glnfs*9	Homozygous	NOA	
	M1529	Male		Homozygous	NOA	
PSMC3IP	III-5, III-6, IV-2, IV-3 & IV-6	Female	c.600_602del, p.Glu201del	Homozygous	POI	[45]
	III-2, III-3, III-6 & III-7	Female	c.489C>G, p.Tyr163*	Homozygous	POI	[46]
	III-1	Male			NOA	
	FPOI41	Female	c.496_497delCT, p.Arg166Alafs	Multiple heterozygous	POI	[47]
			c.430_431insGA, p.Leu144*			
	P7	Male	c.333delG, p.Arg111fs	Homozygous	NOA	[48]
	II-4	Female	c.206_208delAGA, p.Lys69del	Multiple heterozygous	POI	[49]
			c.189G>T, p.Lys63Asn			
	II-3	Female	c.597+1G>T	Multiple heterozygous	POI	[50]
			c.268G>C, p.Asp90His			

REC8	6	Female	c.1035_1036dup, p.Glu346Glyfs*72 c.624+1G>A	Multiple heterozygous	POI	[13]
	P0088	Male	c.860_861del, p.Pro287Argfs*74	Homozygous	NOA	[9]
SHOC1	11-272 & brother	Male	c.797delT, p.Leu266Glnfs*6	Homozygous	NOA	[31]
	M2012	Male	c.1085_1086del, p.Glu362Valfs*25	Homozygous	NOA	
	M2046	Male	c.945_948del, p.Glu315Aspfs*6 c.1351del, p.Ser451Leufs*23 c.1347T>A, p.Cys449*	Multiple heterozygous	NOA	
	Family 1, two brothers	Male	c.1582C>T, p.Arg528* c.231_232del, p.Leu78Serfs*9	Multiple heterozygous	NOA	[51]
	Family 2, proband	Male	c.1194delA, p.Leu400Cysfs*7	Homozygous	NOA	
	Sporadic patient	Male	c.1464delT, p.Asp489Thrfs*13	Homozygous	NOA	
	Family 1, II-2	Male	c.231_232del, p.Leu78Serfs*9	Homozygous	NOA	[52]
	Family 2, II-1	Male				
	Family3, II-1	Male	c.1978G>A, p.Ala660Thr c.4274G>A, p.Arg1425His	Multiple heterozygous	NOA	
	POI-450	Female	c.231_232del, p.Leu78Serfs*10	Homozygous	POI	[27]
SIX6OS1	P3907	Male	c.958G>T, p.Glu320*	Homozygous	NOA	[53]
	P6032	Male	c.1180-3C>G	Homozygous	NOA	
	PK-INF-543 IV-2 & IV-3	Male	c.204_205del, p.His68Glnfs*2	Homozygous	NOA	
	PK-INF-543 IV-5	Female		Homozygous	POI	
	NOA-1	Male	c.135_136del, p.Lys45Asnfs*5	Homozygous	NOA	[54]
	POI-1	Female			POI	
SPATA22	PK-INF-602, IV-4	Female	c.683-1G>A	Homozygous	PI	[55]
	PK-INF-602, IV-5 & IV-6	Male			NOA	
	P0074	Male	c.1118_1121del, p.Phe373Serfs*6	Homozygous	NOA	[9]
	Family 1, IV-1 & IV-2	Female	c.400C>T:p.R134X	Homozygous	POI	[56]
	Family 1, IV-3 & IV-4	Male			NOA	
	Family 2, II-1	Female	c.31C>T:p.R11X c.900+1G>A	Multiple heterozygous	POI	
STAG3	II-1 & II-2	Female	c.1947_48dupCT, p.Tyr650Serfs*22	Homozygous	POI	[57]
	V-2 & V-3	Female	c.677C>G, p.Ser227*	Homozygous	POI	[58]
	IV-2 & IV-3	Female	c.1573+5G>A, p.Leu490Thrfs*10	Homozygous	POI	[1]
	Proband	Female	c.291dupC, p.Asm98Glnfs*2 c.1950C>A, p.Tyr650*	Multiple heterozygous	POI	[59]
	07-002	Male	c.1759dupG c.2394+1G>A	Multiple heterozygous	NOA	[60]
	II-1 & II-2	Female	c.3052delC, p.Arg1018Aspfs*14 c.659T>G, p.Leu220Arg	Multiple heterozygous	POI	[61]
	II-3	Male	c.1262T>G, p.Leu421Arg c.1312C>T, p.Arg428*	Multiple heterozygous	NOA	[62]
	V-1 & V2	Female	c.877_885del, p.293_295del c.891_893dupTGA, p.297_298insAsp	Homozygous	POI	[63]
	13-567	Male	g.100180673del c.1645_1657del, p.His549Alafs*9	Multiple heterozygous	NOA	[31]
	II-3	Female	c.962G>A, p.Arg321His	Homozygous	POI	[7]
	II-1	Male			NOA	
	Patient	Female	c.3381_3384del	Homozygous	POI	[64]
	IV-1 , IV-6, IV-7 & IV-10	Female	c.968delC, p.Phe187fs*7	Homozygous	POI	[65]
	2	Female	c.2627G>A, p.Gly876Glu	Homozygous	POI	[13]
	III-1 & III-2	Male	c.1942G>A, p.Ala648Thr c.1951_1953del, p.Leu652del	Homozygous	NOA	[66]
	III-3	Female	c.1942G>A, p.Ala648Thr c.1951_1953del, p.Leu652del	Homozygous	POI	

SYCE1	IV-7 & IV-9	Female	c.613C>T, p.Gln205*	Homozygous	POI	[67]
	II-2 & II-3	Male	c.197-2A>G	Homozygous	NOA	[68]
	Proband	Male	c.689_690del, p.Phe230fs	Homozygous	NOA	[69]
	AZO-III13	Male	c.375-2A>G	Homozygous	NOA	[70]
	15-285	Male	c.1_1113del, p.1del371aa	Homozygous	NOA	[31]
	NOA-2	Male	c.271+2T>C, p.Ala66_Leu91delinsVal	Homozygous	NOA	[22]
	POI-2	Female	c.689_690del, p.Phe230Serfs*21	Multiple heterozygous	POI	
			c.475G>A, p.Glu159Lys			
	NOA51	Male	c.689_690del, p.Phe230fs	Homozygous	NOA	[71]
	P3793	Male	c.154C>T, p.Arg52*	Homozygous	NOA	[72]
	P6	Male	c.373A>G, p.Arg125Gly	Homozygous	NOA	[48]
	Family 3, II-1	Female	c.154C>T, p.Arg52*	Multiple heterozygous	POI	[17]
			c.675del, p.Asp22Metfs*29			
	Family 6, II-1	Female	c.271+1G>A	Homozygous	POI	
TOP6BL	1031	Female	c.783dup, p.Glu262*	Homozygous	RHM, MC	[29]
	HM74	Female	c.1501T>C, p.Ser501Pro	Homozygous	RHM	
	V-1	Male	c.483dupT	Homozygous	NOA	[73]
	V-2	Male				
	V-3	Male				
	V-5	Female			PI	
XRCC2	IV-2	Male	c.41T>C, p.Leu14Pro	Homozygous	NOA	[74]
	IV-3	Male			NOA	
	IV-1	Male			NOA	[75]
	IV-2	Female			POI	
	19DG1738	Male	c.643C>T, p.Arg215*	Homozygous	NOA	[76]
ZSWIM7	19DG1770	Male	c.201+1G>T	Homozygous	NOA	
	19DG1869	Male	c.231_232del, p.Cys78Phefs*21	Homozygous	NOA	
	Family 1, Case2657	Male	c.231_232del	Homozygous	NOA	[77]
	Family 2, Case2876	Male				
	Patients 1 &2	Female	c.173C>G, p.Ser58*	Homozygous	POI	[78]
	P20428	Female	c.38T>C, p.Leu13Pro	Homozygous	POI	[79]
	TPOF-GII2	Female	c.231_232delAT, p.Cys78Phefs*21	Homozygous	POI	
	IV-2 & IV-3	Female	c.176C>T, p.Ser59Leu	Homozygous	POI	[80]
	IV-5 & IV-6	Male			NOA	

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