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REVIEW

Genetic factors as potential molecular markers of human oocyte and embryo quality

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Abstract
Successful human reproduction requires gamete maturation, fertilization, and early embryonic development. Human oocyte maturation includes nuclear and cytoplasmic maturation, and abnormalities in the process will lead to infertility and recurrent failure of IVF/ICSI attempts. In addition, the quality of oocytes/embryos in the clinic can only be determined by morphological markers, and there is currently a lack of molecular markers for determining oocyte quality. As the number of patients undergoing IVF/ICSI has increased, many patients have been identified with recurrent IVF/ICSI failure. However, the genetic basis behind this phenotype remains largely unknown. In recent years, a few mutant genes have been identified by us and others, which provide potential molecular markers for determining the quality of oocytes/embryos. In this review, we outline the genetic determinants of abnormalities in the processes of oocyte maturation, fertilization, and early embryonic development. Currently, 16 genes (*PATL2*, *TUBB8*, *TRIP13, ZP1*, *ZP2*, *ZP3*, *PANX1*, *TLE6*, *WEE2*, *CDC20*, *BTG4*, *PADI6*, *NLRP2*, *NLRP5*, *KHDC3L*, and *REC114*) have been reported to be the causes of oocyte maturation arrest, fertilization failure, embryonic arrest, and preimplantation embryonic lethality. These abnormalities mainly have Mendelian inheritance patterns, including both dominant inheritance and recessive inheritance, although in some cases de novo mutations have also appeared. In this review, we will introduce the effects of each gene in the specific processes of human early reproduction and will summarize all known variants in these genes and their corresponding phenotypes. Variants in some genes have specific effects on certain steps in the early human reproductive processes, while other variants result in a spectrum of phenotypes. These variants and genetic markers will lay the foundation for individualized genetic counseling and potential treatments for patients and will be the target for precision treatments in reproductive medicine.

Keywords Human oocyte maturation · Gene mutations · Fertilization · Embryonic development

Introduction

The first IVF procedure was performed in 1978, and over the past four decades, the number of patients undergoing IVF/ICSI attempts has increased worldwide and it is now estimated that more than 6 million babies have been born through IVF/ICSI [1, 2]. However, the success rate of IVF/ICSI is still only around 30–40%. There are two main factors preventing improvement in the success rate. First, there is a lack of good molecular markers for evaluating the quality of oocytes/embryos. Morphological markers are currently used in the clinic for choosing oocytes to be fertilized and embryos to be implanted. However, being morphologically normal does not mean that the oocytes/embryos are normal on the molecular level, which is the key to becoming functional oocytes and viable embryos. Second, a number of patients have experienced recurrent failure of IVF/ICSI attempts for unknown genetic reasons, including oocyte maturation arrest, fertilization failure, embryonic arrest, and implantation failure.

Successful mammalian reproduction requires gamete development, fertilization, and early embryonic development, and defects in any of these processes will result in infertility, recurrent miscarriage, or even birth defects [3–7]. It is well known that maternal factors such as age, sperm factors such as severe oligoasthenozoospermia, and environmental factors

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such as smoking can influence oocyte and embryo quality. However, there are still a number of patients with failed IVF/ICSI attempts for unknown reasons. In this review, we focus on the maternal genetic factors that can contribute to the failure of IVF/ICSI attempts. Human oocytes pass through the germinal vesicle (GV) stage, metaphase I (MI) stage, and finally reach metaphase II (MII), which is the stage at which oocytes can be fertilized [8, 9]. Human oocyte maturation includes nuclear maturation and cytoplasmic maturation. Nuclear maturation refers to the oocyte developing normally into the MII stage and producing haploid cells by extruding the first polar body. Cytoplasmic maturation refers to the series of changes in the oocyte cytoplasm that are required for fertilization, activation, and embryonic development [9]. After an oocyte is ovulated from the ovary, it waits for the sperm to start a new life. Under physiological conditions, sperms travel through the vagina and uterus, finally encountering the oocyte in the oviduct. The sperm pass through the corona radiata and zona pellucida and fuse with the oocyte and begin fertilization. During fertilization, the oocyte completes meiosis, extrudes the second polar body, and forms both the maternal and paternal pronucleus. After fertilization, the zygote undergoes several cleavages to form the blastocyst. Finally, the blastocyst is implanted in the uterus [10–13].

In a study from 1990, four infertile women who had undergone failed IVF attempts and who had three kinds of anomalies in human oocyte development were described. These included failure of oocyte maturation from the GV stage (oocyte GV arrest), failure of polar body formation (oocyte MI arrest), and the absence of oocytes in mature follicular aspirates (empty follicle syndrome) [14]. A few subsequent reports described additional cases with similar phenotypes and other defects in fertilization and early embryonic arrest [15–19]. Although such cases represent a very low percentage of IVF failures, these patients undergo several rounds of stimulations always showing the same outcome, thus suggesting a genetic predisposition. Therefore, it is of importance to uncover the underlying genetic determinants contributing to patients with failure of IVF/ICSI attempts. However, for a long period of time, there have only been a few reports on the genetic causes behind these defects. Recently, more and more causative genes involved in oocyte and embryo development have been identified. In this review, we summarize these recently discovered genetic factors that are responsible for oocyte and embryo developmental defects (Fig. 1).

Methods

A literature search was conducted for all publications in PubMed/Medline until December 2020 using the following search terms: “oocyte maturation arrest”, “oocyte maturation defects”, “fertilization failure”, “early embryonic arrest”, “implantation failure”, and “human embryonic lethality” with possible combinations with the keywords “genetics”, “gene mutations”, “subfertility”, and “infertility”. Any additionally relevant articles identified from the bibliographies of the initially retrieved articles and reviews were also included. Only English-language publications or articles in other languages but with an abstract in English were included. In addition, we focused on studies containing several individuals with mutations in a specific gene because this reduced false positive results and provided strong and convincing evidence for roles of the genes in the corresponding phenotypes. Finally, we did not include studies describing the association between single nucleotide polymorphisms and a particular phenotype because these kinds of studies cannot provide strong genetic evidence.

Results

Oocyte GV arrest and mutations in *PATL2*

Oocytes are initially arrested at the diplotene stage of prophase I until puberty, and these are referred to as GV oocytes. Upon exposure to surging luteinizing hormone, GV oocytes resume meiosis followed by chromatin condensation and breakdown of the nuclear envelope [8]. However, a few infertile patients have been found who suffer recurrent failure IVF/ICSI attempts because their oocytes are always arrested at the GV stage and cannot undergo subsequent maturation. In 2017, we and others identified patients with GV arrest showing a recessive inheritance pattern [20, 21]. Mutations in *PATL2* were identified in some consanguineous families with the GV arrest phenotype, and other phenotypes were subsequently observed. Some families had oocytes arrested at the MI stage or had PB1 oocytes with abnormally large first polar bodies [21]. Most of these PB1 oocytes could not be fertilized or could be fertilized but then underwent subsequent embryonic arrest [21]. We concluded that the phenotypic variability depended on the extent of the effects of the mutations on the PATL2 protein, with greater impairment of the PATL2 protein resulting in oocytes arrested at earlier stages. The role of *PATL2* mutations in oocyte maturation defects was soon confirmed by two other groups [22, 23]. A group from France found that 26% of their patients of North African descent with oocytes arrested at either the GV or MI stage or with atretic cells presented with *PATL2* homozygous mutations, indicating that *PATL2* mutations are a major cause of oocyte maturation defects in this population ($n = 23$) [22]. In another group from China, mutations in *PATL2* were found to account for 44.4% of the individuals with oocyte GV arrest ($n = 9$), suggesting that *PATL2* mutations are the major cause for GV arrest in different ethnic populations [23]. Following these studies, other groups have identified several novel mutations in *PATL2* that are responsible for different phenotypes,

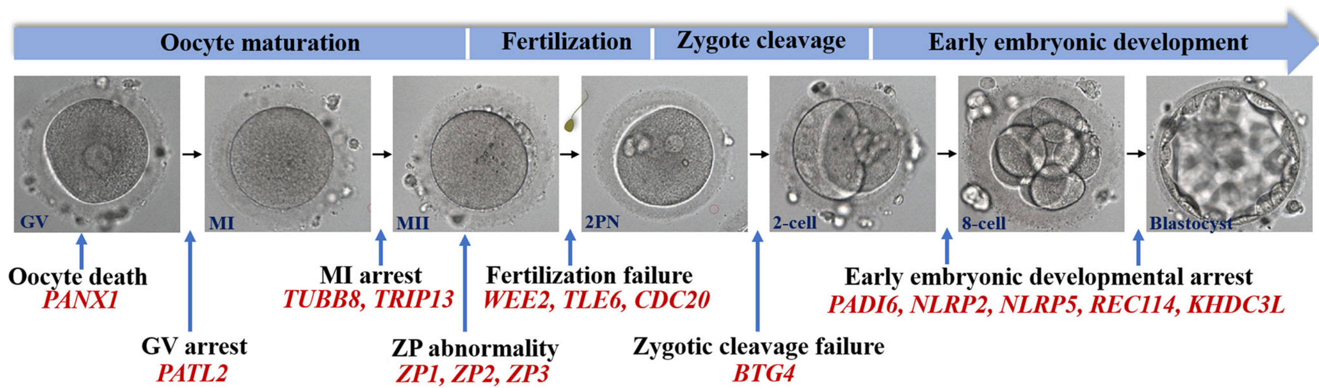

Fig. 1 Recently discovered genetic factors that are responsible for oocyte and embryo developmental defects

including oocyte maturation, fertilization failure, and embryo developmental arrest [24, 25]. The mutations in *PATL2* and resulting phenotypes are listed in Table 1.

Oocyte MI arrest and mutations in *TUBB8 and TRIP13*

The chromosomes begin to condense following oocyte GV breakdown, and bipolar spindles are formed when oocytes reach metaphase I. Meiosis I is completed by extruding the first polar body [8]. In the clinic, some infertile patients have been diagnosed with oocyte MI arrest, and oocytes retrieved from some of these patients do not have the first polar body [14–18, 79]. In 2016, we identified patients with oocyte MI arrest with a dominant inheritance pattern, and we identified mutations in *TUBB8* as responsible for the disease [26]. These mutations were either inherited from the patients' fathers or occurred de novo. Further studies showed that mutations in *TUBB8* account for around 30% of cases of oocyte MI arrest, indicating the dominant role of *TUBB8* in the disease [27–31]. The human β-tubulin family consists of nine β-tubulin isotypes [80], but TUBB8 is the only one to be specifically expressed in human oocytes and early embryos [26], thus indicating that it plays a role in human oocyte spindle assembly and likely contributes to the uniqueness of primate oocyte maturation.

Further studies have shown that recessive inheritance pattern of *TUBB8* is also pathogenic [27–30, 36]. These patients either have homozygous mutations or compound heterozygous mutations, with one rare variant coming from both parents. Mutations in *TUBB8* have been shown to result in the following five phenotypes: (1) oocyte MI arrest [26–35], (2) PB1 oocytes that fail to be fertilized [27–31], (3) PB1 oocytes that can be fertilized, but the embryos fail to cleave [27, 28, 30, 36], (4) PB1 oocytes that can be fertilized and embryos that can undergo cleavage, but ensuing embryonic development is arrested [27–31, 37], and (5) some usable embryos with implantation potential can be obtained but fail to result in pregnancy after implantation [27, 28]. Table 1 includes the published mutations in *TUBB8* and their corresponding phenotypes. Considering the expanding spectrum of *TUBB8* mutations in human oocyte development, fertilization, and early embryonic development, screening for *TUBB8* mutations has potential value for evaluating the functionality of PB1 oocytes and for providing precise diagnoses for infertile patients with recurrent failure of IVF/ICSI attempts.

We further identified bi-allelic missense mutations in *TRIP13*, a new causative gene responsible for oocyte MI arrest [38]. All mutations reduce the protein abundance of TRIP13 and lead to the accumulation of HORMAD2. More importantly, injecting *TRIP13* cRNA into oocytes from one affected individual was able to rescue the phenotype of oocyte MI arrest, which has implications for future therapeutic treatments.

Defects in the zona pellucida and mutations in the ZP protein family

Mature oocytes are surrounded by the extracellular zona pellucida, which mediates sperm binding and penetration and is essential for fertilization [81]. In mice, the zona pellucida is composed of three glycoproteins — ZP1, ZP2, and ZP3 — while in humans it is composed of four glycoproteins — ZP1, ZP2, ZP3, and ZP4 [82, 83]. In mice, knockout of either *ZP2* or *ZP3* causes sterility by destroying the zona pellucida [84, 85]. In 2013, a form of infertility was identified in a family in which the patients had undergone several failed IVF/ICSI attempts, and these patients presented with an autosomal recessive inheritance pattern characterized by abnormal eggs lacking a zona pellucida [39]. A homozygous frameshift mutation in *ZP1* was identified in these patients. In 2017, another form of infertility caused by empty follicle syndrome was found to follow an autosomal dominant inheritance pattern [51]. A recurrent heterozygous missense mutation in *ZP3* was identified in two inherited and in two sporadic cases. These patients had difficulties in retrieving oocytes after hormone stimulation, and an in vitro functional study demonstrated that the mutation impairs the assembly of the ZP proteins and might therefore result in oocyte degeneration. An additional infertile

Table 1 Summary of gene mutations involved in human oocyte and embryo defects

Gene	Mode of inheritance	Phenotype in mutants	Refs
PATL2	AR	Oocyte maturation arrest	[20–25]
		Fertilization failure	[21, 25]
		Early embryonic arrest	[21, 25]
TUBB8	AD, AR, de novo, incomplete dominance, unknown	Oocyte maturation arrest	[26–35]
		Oocytes with large polar body	[27]
		Abnormal fertilization	[30]
		Fertilization failure	[27–29, 31]
		No cleavage	[27, 28, 30, 36]
		Early embryonic arrest	[27–31]
		Embryonic implantation failure	[27, 28]
		Multiple pronuclei formation	[31, 37]
TRIP13	AR	Oocyte maturation arrest	[38]
ZP1	AD, AR	Oocytes without a zona pellucida	[39–42]
		Empty follicle syndrome	[39, 40, 43–49]
ZP2	AD, AR	Oocytes without a zona pellucida	[40]
		Oocytes with a thin zona pellucida	[40, 45, 50]
		Fertilization failure	[50]
		Empty follicle syndrome	[43]
ZP3	AD	Oocytes without a zona pellucida	[40, 41, 51]
		Empty follicle syndrome	[41, 43, 51, 52]
PANX1	AD	Oocyte death	[53]
TLE6	AR	Early embryonic arrest	[47, 54–57]
		Fertilization failure	[54, 55]
		Embryonic implantation failure	[55]
WEE2	AR	Fertilization failure	[58–64]
		Poor fertilization	[64]
CDC20	AR	Oocyte maturation arrest	[65]
		Fertilization failure	[65]
		Early embryonic arrest	[65]
BTG4	AR	Zygotic cleavage failure	[66]
PADI6	AR	Early embryonic arrest	[56, 57, 67, 68]
		Zygotic cleavage failure	[69]
		Recurrent hydatidiform moles	[70]
NLRP2	AR	Early embryonic arrest	[57, 71]
NLRP5	AR	Early embryonic arrest	[57, 71, 72]
		Fertilization failure	[47, 73]
KHDC3L	AR	Early embryonic arrest	[56]
		Recurrent hydatidiform moles	[74, 75]
		Recurrent pregnancy loss	[76]
REC114	AR	Multiple pronuclei formation	[77]
		Early embryonic arrest	[77]
		Recurrent hydatidiform moles	[78]

AD, autosomal dominant; *AR*, autosomal recessive

patient was identified after failure of IVF attempts, and this patient's oocytes either had no zona pellucida or only a very thin zona pellucida [86]. The genetic study indicated that the patient carried both a heterozygous missense mutation in *ZP2* and a heterozygous frameshift mutation in *ZP3*. The two mutations were transmitted from her parents, indicating a

recessive inheritance pattern. The patient was treated by ICSI with an improved culture system and successfully delivered a healthy baby. In another recent study, homozygous mutations in *ZP2* were identified in oocytes from patients in two independent consanguineous families [50]. All of these oocytes were surrounded by a thin zona pellucida that was defective in sperm binding. These oocytes failed to be fertilized by IVF, but they could be fertilized by ICSI and could result in live birth. Mutations in human *ZP1*, *ZP2*, and *ZP3* and their corresponding phenotypes are summarized in Table 1 [39–52].

Discovery of "oocyte death" and mutations in *PANX1*

In 2019, a previously unreported phenotype named "oocyte death" was identified [53]. All the retrieved oocytes showed cytoplasmic shrinkage and darkening before or after fertilization, and heterozygous mutations in *PANX1* were found to be responsible for the phenotype. PANX1 is one of three members of the Pannexin1 family of proteins, which play important roles in cellular communication [87]. Functional studies in HeLa cells and *Xenopus laevis* oocytes indicated that mutations altered the PANX1 glycosylation pattern, thus affecting the subcellular localization of PANX1 in cultured cells and resulting in aberrant PANX1 channel activity [53]. Unexpectedly, knock-in mice with the four different mutations were all healthy and fertile. Further experiments demonstrated that expression of PANX1 in human oocytes is significantly higher than it is in mouse oocytes, which might provide an explanation for the absence of a phenotype in the knock-in mice, and oocyte-specific overexpression of mutant *Panx1* can recapitulate the oocyte death phenotype [53]. These findings indicate that abnormal glycosylation and channelopathy are causes of female infertility.

Fertilization failure and mutations in *TLE6*, *WEE2*, and *CDC20*

After extruding the first polar body, oocytes enter meiosis II and arrest at the MII stage until fertilization [8]. Fertilization involves the transition from meiosis to mitosis and the transition from egg to embryo and thus involves several biological events, including sperm-egg binding, the release of cortical granules, the extrusion of the second polar body, and pronucleus formation [88]. Knockout of a few genes in mice — including *Juno* and *CD9* in oocytes and *Izumo*, *Adam2*, *Adam3*, and *Calmegin* in sperm — causes sterility through fertilization failure [89–94]. However, the genetic factors behind fertilization failure in humans have remained largely unknown. In 2015, three infertile patients in two consanguineous families were reported to have the phenotype of fertilization failure in which several morphologically normal oocytes could be retrieved from the patients during IVF and ICSI, but no zygotes could be formed [54]. A homozygous single mutation in *TLE6* was identified in these patients, and a functional study suggested that the mutation impaired PKA-mediated phosphorylation of TLE6 and prevented the interaction between TLE6 and other subcortical maternal complex (SCMC) proteins [54]. Additional mutations in *TLE6* have been found to be responsible for fertilization failure, early embryonic arrest, and embryonic implantation failure (Table 1) [47, 55–57].

In 2018, we identified homozygous mutations in *WEE2* in patients from four families with fertilization failure [58]. Oocytes from these patients were morphologically normal. After injection of sperm, these oocytes could extrude the second polar body, but they failed to form zygotes. In vitro and in vivo evidence suggests that mutations in *WEE2* significantly decrease the amount of WEE2 protein, leading to abnormal serine phosphorylation of WEE2 and reduced tyrosine 15 phosphorylation of Cdc2, which results in MII exit and subsequent fertilization failure. By injecting *WEE2* cRNA into a patient's oocytes, the phenotype of fertilization failure could be rescued and blastocysts could form in vitro on day 6. Preimplantation screening analysis showed that these blastocysts had normal numbers of chromosomes and did not have large deletions or repetitions in the genome. This provides a potential therapeutic strategy for the treatment of these patients with *WEE2* mutations. Three subsequent studies identified additional mutations in *WEE2* (Table 1), and together these studies suggest that mutations in *WEE2* are the major cause of human fertilization failure [59–64].

Recently, we identified five sporadic cases carrying homozygous mutation or compound heterozygous mutations in *CDC20* [65]. Two of the patients showed the typical phenotype of fertilization failure. Injecting wild type *CDC20* cRNA into patients' oocytes could recuse the phenotype of MI arrest, similar to what was seen in patients with *WEE2* mutations [58]. The other three patients harboring *CDC20* mutations had the phenotype of oocyte MI arrest or early embryonic arrest [65]. This phenotypic variability might be the result of different degrees of impairment resulting from different CDC20 mutations.

Apart from complete fertilization failure, other fertilization problems are also seen in the clinic, such as multiple pronuclei formation. Until now, the genetic factors for multiple pronuclei formation have been largely unknown. A few studies have reported that some patients carrying mutations in *TUBB8* or *REC114* present with multiple pronuclei, and other genetic causes for multiple pronuclei should be investigated further [31, 37, 77].

Zygotic cleavage failure and mutations in *BTG4*

An oocyte and a sperm will first form a zygote after fertilization and then undergo zygotic cleavage to begin embryonic development [88]. For some individuals, morphologically

normal oocytes can be retrieved and successfully fertilized, but they fail to undergo cleavage, thus showing a unique early embryonic phenotype that we named "zygotic cleavage failure (ZCF)" [66]. By whole-exome sequencing, four homozygous mutations in *BTG4* were identified in four independent families with the phenotype of ZCF, and they followed a Mendelian recessive inheritance pattern [66]. BTG4 is a key adaptor of the CCR4-NOT deadenylase complex, which bridges CNOT7 to EIF4E and facilitates the decay of maternal mRNAs in early embryonic development [95]. Functional studies in HeLa cells indicated that *BTG4* mutations altered the protein level of BTG4 or the interaction between BTG4 and CNOT7. In vivo studies further demonstrated that the process of maternal mRNA decay was disrupted in the zygotes of the affected individuals, which provides a mechanistic explanation for the phenotype of ZCF [66]. To date, *BTG4* is the only identified gene responsible for the phenotype of human ZCF.

Early embryonic arrest and mutations in *PADI6*, *NLRP2*, *NLRP5*, *KHDC3L*, and *REC114*

Following normal fertilization and zygotic cleavage, mitosis is initiated in the embryo [88]. With the degradation of maternal RNAs and proteins and the activation of the embryonic genome, embryos undergo further cleavage, differentiation, and development [96, 97]. Studies have shown that the expression of several proteins control specific parts of the process. The SCMC is essential for embryonic activation and subsequent progression past the 2-cell stage [97]. The SCMC consists of FLOPED, PADI6, TLE6, FILIA, NLRP2, and NLRP5, and knockout of the corresponding genes in female mice results in sterility due to embryonic arrest prior to the 4-cell stage [98–102]. In the clinic, early embryonic arrest is commonly observed and is one of the major reasons for failed IVF/ICSI attempts [19]. However, the genetic causes for the phenotype are largely unknown. In 2016, we identified *PADI6* as the first mutant gene responsible for patients with early embryonic arrest [67]. The amount of phosphorylated RNA polymerase II and the expression levels of a few genes involved in zygotic genome activation were reduced in the affected individuals' embryos. Importantly, although oocytes from the patients were morphologically normal, the PADI6 protein was lacking in patients' oocytes, indicating that the phenotype of early embryonic arrest results from defects in oocyte cytoplasmic maturation. In addition to the phenotype of early embryonic arrest, *PADI6* mutations were also shown to be responsible for zygotic cleavage failure and recurrent hydatidiform moles [56, 57, 67–70].

Other mutant genes were further identified. Homozygous and compound heterozygous mutations in *NLRP2* and *NLRP5* were found to be responsible for human embryonic arrest or fertilization failure [47, 57, 71–73]. *Nlrp2* knockout female mice are subfertile and show age-associated maternal fertility [102], while human patients with mutations in *NLRP2* exhibit phenotypic variability (Table 1). Patients carrying homozygous truncating mutations or compound heterozygous truncating or missense mutations in *NLRP2* produce very few viable embryos after IVF/ICSI, while some patients with compound heterozygous missense mutations have a limited number of viable embryos and are able to eventually give birth to live full-term infants after several transplantation attempts [71]. This variability can be explained by the fact that different mutations impair the function of the NLRP2 protein to different extents. Additional novel mutations in genes encoding proteins of the SCMC, including *TLE6*, *PADI6*, and *KHDC3L*, have been identified as being responsible for embryonic arrest at the cleavage stage or morula stage (Table 1). It is worth noting that mutations in *KHDC3L* were previously shown to cause recurrent hydatidiform mole [74, 75]. A study has shown that a novel homozygous frameshift mutation in *KHDC3L* causes early embryonic arrest in which embryos formed after ICSI are fertilized normally but arrest at the morula stage [76]. These studies provide further evidence for the important role of the SCMC in human embryonic development and in recurrent IVF/ICSI failure. In 2019, we identified a new pathogenic gene *REC114* responsible for early embryonic arrest from two consanguineous families [77]. The two patients underwent recurrent IVF/ICSI failure due to early embryonic arrest and carry homozygous splicing or missense mutation in *REC114*. Moreover, it is reported that a homozygous splicing mutation in *REC114*, which is located directly before exon 4 in the splicing region, might cause recurrent hydatidiform moles in humans [78]. *REC114* is an essential factor in meiosis via the formation of a complex with MEI4 and IHO1 at sites of double-strand breaks [103, 104], suggesting that *REC114* is essential for both oocyte meiosis and early embryonic development.

Discussion and conclusion

A number of patients have been identified with recurrent failure of IVF/ICSI attempts caused by abnormalities in gamete and embryo development as well as defects in oocyte maturation. The increasing number of IVF/ICSI cycles being performed provides an unprecedented opportunity for systematically evaluating the phenotypes of oocyte maturation, fertilization, and early embryonic defects. Such work will help identify more novel genes and uncover new signaling pathways, functions, and genetic mechanisms involved in early human reproduction. In the clinic, the quality of oocytes is key for successful IVF/ICSI and for the health of the neonate, but there is currently a lack of molecular markers for evaluating the quality of oocytes. In recent years, a series of genetic factors have been identified as potential markers for

evaluating oocyte quality (Table 1). In these studies, women carrying mutations rarely gave birth, and it was reported that only two mothers carrying *NLPR2* mutations gave birth after several rounds of transplantation [71]. The similar situation was observed in the women with recurrent hydatidiform mole. Elie et al. showed that only 1% of patients carrying biallelic mutations of *NLRP7* could give birth from spontaneous conceptions [105], and for most patients, oocyte donation may be a way to having their own babies. These findings can thus provide some guidance for clinicians to provide genetic counseling. We expect that by whole-exome sequencing and whole-genome sequencing, more and more genetic factors responsible for oocyte quality will likely be identified in the future, which might benefit patients who suffer from these conditions. Such discoveries will help improve the success rate of IVF/ICSI attempts, optimize clinical therapeutic treatment, and provide genetic diagnoses for patients.

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