Maternal effect genes: Update and review of evidence for a link with birth defects

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Summary

Maternal effect genes (MEGs) encode factors (e.g., RNA) that are present in the oocyte and required for early embryonic development. Hence, while these genes and gene products are of maternal origin, their phenotypic consequences result from effects on the embryo. The first mammalian MEGs were identified in the mouse in 2000 and were associated with early embryonic loss in the offspring of homozygous null females. In humans, the first MEG was identified in 2006, in women who had experienced a range of adverse reproductive outcomes, including hydatidiform moles, spontaneous abortions, and stillbirths. Over 80 mammalian MEGs have subsequently been identified, including several that have been associated with phenotypes in humans. In general, pathogenic variants in MEGs or the absence of MEG products are associated with a spectrum of adverse outcomes, which in humans range from zygotic cleavage failure to offspring with multi-locus imprinting disorders. Although less established, there is also evidence that MEGs are associated with structural birth defects (e.g., craniofacial malformations, congenital heart defects). This review provides an updated summary of mammalian MEGs reported in the literature through early 2021, as well as an overview of the evidence for a link between MEGs and structural birth defects.

Background

The genome of the mammalian zygote and early embryo is silent. Consequently, early development events (e.g., genomic imprinting) are under the control of factors, determined by maternal effect genes (MEGs), that are present in the egg prior to fertilization. The transition from maternal to embryonic control of development is gradual, with embryonic genome activation (EGA) occurring in two phases: minor and major EGA. Each phase is accompanied by a wave of maternal transcript degradation.1–4 In mice, minor EGA occurs at the 1-cell stage, and major EGA occurs at the 2-cell stage. In humans, these events occur at the 2-cell and 4- to 8-cell stages, respectively. The impact of variation in MEGs is, therefore, determined early in development. However, the consequences of such variation (e.g., imprinting disturbances) on offspring phenotypes may not manifest until later in development.

Mammalian MEGs

In non-mammalian species, the importance of MEGs in early development is well documented.5–8 In contrast, relatively little is known about the role of MEGs in mammalian development. However, the first mammalian MEGs were reported in 2000,9 and the number of such genes has subsequently increased steadily. Reviews published between 2014 and 2016 collectively included 69 mammalian MEGs.9–11

The majority of mammalian MEGs have been identified in mouse models, using either traditional knockout (TKO) or oocyte-specific conditional gene knockout (oCKO) strategies. In many of these models, the observed phenotype is female infertility due to pre-implantation developmental arrest. However, maternal null genotypes for some MEGs are compatible with post-implantation survival and even viable offspring.12–15 Further, compared with variants that result in the complete absence of the MEG product, those that result in reduced levels of MEG products may give rise to less severe offspring phenotypes. For example, all embryos from females homozygous for a complete loss-of-function Kdm1a oCKO arrest prior to the blastocyst stage, whereas embryos from females homozygous for an oCKO that results in low levels of KDMA1 protein can survive to birth (average litter size, 2.3).16

In mammals, MEGs are involved in a range of functions that are consistent with the events required for early embryonic development and set the stage for subsequent developmental events. These include: cell division (e.g., cytoskeleton assembly), epigenetic reprogramming and imprinting (e.g., DNA methylation, chromatin structure), and the transition from maternal to embryonic control of development (e.g., transcriptional regulation, protein degradation, gene silencing).9,11 In addition, several MEGs encode components of the subcortical maternal complex (SCMC), a multiprotein complex that is uniquely expressed in the oocyte and early embryo and appears to serve multiple functions in early development. Genes encoding components of the SCMC include Khdc3, Nltp2, Nltp5, Ooep, Padi6, Tle6, and Zbed3.17 While the function of the SCMC has not been fully delineated, it is involved in spindle formation and positioning and may also be
involved in regulation of translation, organelle distribution, and epigenetic reprogramming.17–20

### Human MEGs

Identification of the first human MEG, NLRP7, was reported in 2006. This gene is an ortholog of the mouse MEG Nlrp2. NLRP7 was identified as a MEG using linkage analysis and candidate gene sequencing in two families, each with more than one female with a history of recurrent hydatidiform molar pregnancy.21,22 Maternal homozygous or compound heterozygous variants in NLRP7 are now recognized as the major cause of diploid, biparental hydatidiform mole, accounting for approximately 55% of cases.23 These hydatidiform moles are characterized by complete loss of maternal imprinting marks24 and thus represent a severe imprinting disorder.25 Maternal homozygous or compound heterozygous variants in NLRP7 have also been associated with recurrent pregnancy loss26,27 and offspring with multilocus imprinting disorders (MLIDs).28 Although the majority of pregnancies to women carrying pathogenic variants in NLRP7 are associated with adverse outcomes, a small proportion (~1%) result in apparently normal live births.29

Ten additional human MEGs (Table 1) have subsequently been identified through whole-exome or candidate-gene sequencing in women ascertained on the basis of having a child with a MLID. The remaining five human MEGs, three (CDC20, TRIP13, and TUBB8) are involved in spindle assembly, one (PATL2) is involved in mRNA binding, and one (BTG4) is involved in maternal mRNA decay. For each of the genes included in Table 1, variant genotypes have been repeatedly observed in women with relevant phenotypes. In addition to the genes in Table 1, variant genotypes in OOE1, UHRF1, and ZAR1, which are all known to be MEGs in the mouse, have each been reported once in women ascertained on the basis of having a child with a MLID.28

Similar to NLRP7, most human MEGs are associated with a spectrum of outcomes, ranging from zygotic cleavage failure and early embryonic arrest (assessed in embryos from women undergoing in vitro fertilization or inter-cytoplasmic sperm injection) to MLIDs. Mutations in some human MEGs are also associated with effects at earlier time points, including defects in oocyte maturation and fertilization (e.g., CDC20)25, as well as apparently normal live births in a small proportion of pregnancies.

There are no population-based estimates of the number of women with pathogenic variants in specific MEGs, making gene-phenotype correlations difficult to assess. It is, however, clear that offspring phenotypes can vary across women and across pregnancies to the same woman. Variability in the phenotypic consequences of damaging MEG genotypes across women, to some extent, is likely to reflect differences in the underlying genetic variants: Among women carrying two NLRP7 mutations, a small number of live births (6/346 pregnancies) occurred to

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**Table 1. Summary of known human maternal effect genes**

| Gene symbol | Gene name                  | Location      | Phenotypes*            | Maternal genotype | Function                                      |
|-------------|----------------------------|---------------|------------------------|-------------------|-----------------------------------------------|
| BTG4        | BTG anti-proliferation factor 4 | 11q23.1       | ZCF28                 | hom               | maternal mRNA decay                           |
| CDC20       | Cell division cycle 20    | 1p34.2        | EEA, FF, OMA31        | CH, hom           | regulation of spindle assembly checkpoints    |
| KHDC3L      | KH domain containing 3 like | 6q13          | EEA, HM, RPL32–34     | CH, het, hom      | SCMC member                                    |
| NLRP2       | NLR family pyrin domain containing 2 | 19q13.42     | EEA, MLID28,35        | CH, het, hom      | SCMC member                                    |
| NLRP5       | NLR family pyrin domain containing 5 | 19q13.43     | EEA, MLID, NL35,36    | CH, het, hom      | SCMC member                                    |
| NLRP7       | NLR family pyrin domain containing 7 | 19q13.42     | HM, MLID, NL, RPL23,25,28 | CH, het, hom | SCMC member                                    |
| PADI6       | Peptidyl arginine deiminase 6 | 1p36.13       | EEA, HM, MLID, NL, ZCF36,41 | CH, het, hom | SCMC member                                    |
| PAT1        | PAT1 homolog 2             | 15q21.1       | EEA, FF, IF, OMA41–43 | CH, hom           | mRNA binding/inhibition of post-transcription translation |
| TLE6        | TLE family member 6        | 19q13.3       | EEA44,45              | CH, hom           | SCMC member                                    |
| TRIP13      | Thyroid hormone receptor interactor 13 | 5p15.33     | OMA, ZCF36            | CH, hom           | component of spindle assembly checkpoints     |
| TUBB8       | Tubulin beta 8 class VIII  | 10p15.3       | EEA, IF, OMA, ZCF47–49| CH, het, hom | assembly of oocyte spindles                   |

SCMC, subcortical maternal complex; CH, compound heterozygous; het, heterozygous; hom, homozygous.

*Phenotypes observed in pregnancies or offspring of women with genotypes including variant alleles: EEA, early embryonic arrest; FF, fertilization failure; HM, hydatidiform mole; IF, implantation failure; MLID, multilocus imprinting disorder; NL, apparently normal live birth; OMA, oocyte maturation arrest; RPL, recurrent pregnancy loss; ZCF, zygotic cleavage defect/failure.
those carrying missense mutations expected to have mild functional consequences or splice mutations that leave one isoform intact, whereas no live births (0/257 pregnancies) occurred in women carrying at least one protein-truncating mutation.69

The phenotypic consequences of damaging MEG genotypes may also depend on the number of variant alleles that a woman carries. For example, both heterozygous and biallelic mutations in NLRP2 and PAD6 have been identified in women ascertainment through a child with a MLID, whereas only biallelic mutations (homozygous and compound heterozygous) have been identified in women ascertained based on a history of infertility or hydatidiform mole. However, differences in outcomes across pregnancies to the same woman suggest that there are further sources of variability. In addition to stochastic processes, such intra-individual variability may reflect differences in other factors that might influence translation and protein abundance in the oocyte, including maternal environment (e.g., nutritional status), use of artificial reproductive techniques (ART), and maternal age, as well as pre- and post-ovulatory aging.53–56

MEGs and structural birth defects

The potential for MEGs to influence the risk of structural birth defects (i.e., congenital malformations of structures or organs, such as congenital heart defects, craniofacial malformations, and defects of the neural tube) in offspring has been proposed67,68 but has not been widely investigated. However, in a prior review of mammalian MEGs, it was noted that embryos from maternal Dmnt3L TKO mice have structural birth defects (i.e., neural tube defects).10 In addition, in a study of five women who had a child with a MLID due to maternal mutations in NLRP7, one woman also had a child with both an atrial and a ventricular septal defect.36 As this combination of heart defects is relatively rare,59–61 the probability that it would co-occur by chance in a sibship with MLID is low. Further, in a genome-wide study of the association between maternal genes and conotruncal heart defects in offspring, potential MEGs were enriched by 2.3-fold (p < 0.05) among the most significantly associated (i.e., p < 0.05) maternal genes.63 Hence, data from both model systems and humans suggest that the phenotypic spectrum for some MEGs may include structural birth defects.

Although the association of MEGs with adverse reproductive outcomes is increasingly recognized (e.g., Elbracht et al.,25, Gheldof et al.,50 and Yatsenko et al.51), the most recent publication that included a comprehensive list of mammalian MEGs is from 2016,64 and no review has focused on structural birth defects as a potential consequence of alterations in MEGs. Therefore, a comprehensive review of the literature was conducted to identify MEGs reported through February 2021 and to identify the subset of MEGs that have been associated with structural malformations.

Updated list of mammalian MEGs

Research articles published from January 1999 (the year prior to the first reported mammalian MEG) through March 2020 describing mammalian MEGs were identified by searching PubMed for a comprehensive list of relevant terms (e.g., maternal effect genes, embryonic genome activation, subcortical maternal complex, hydatidiform molar pregnancy), followed by review of titles, abstracts, and full text. Details of the search and review process are provided in the Supplemental methods. This process was then repeated weekly through February 2021.

For this review, a gene was considered to be a MEG when (1) there was evidence, in humans, that women carrying potentially damaging variants experienced adverse post-fertilization reproductive outcomes (e.g., recurrent pregnancy loss, hydatidiform moles, offspring with MLID); or (2) studies in animal models, using either TKO or cKO strategies, demonstrated that oocytes devoid of the gene product were capable of in vivo fertilization but subsequent development was abnormal. Genes that have only been associated with pre-fertilization abnormalities (e.g., oocyte maturation arrest) and genes implicated as potential MEGs based only on their expression patterns were not included. Maternal genes for which adverse outcomes were attributable to abnormalities of chromosome number, which may have arisen prior to or after fertilization (i.e., due to meiotic or mitotic errors) were also excluded from the list of MEGs but were retained in a separate list (Table S1). For example, Table S1 includes formin-2 (Fmn2), because female Fmn2−/− mice produce oocytes that do not extrude the first polar body and thus, when fertilized, produce polyploid embryos that are subsequently lost, resulting in a sub-fertility phenotype.63 However, as the search strategy used to identify relevant articles did not include terms specific to abnormalities of chromosome number (e.g., aneuploidy), this list should be considered incomplete.

The search and review process identified 82 genes (Table 2; Table S2) that met the inclusion criteria for a MEG, including 42 genes identified in prior reviews. Genes included in prior reviews that are not included in the current list were excluded either because evidence that the gene is a MEG is based on expression data (e.g., H1fbo64,65) or the observed impact on reproduction occurs prior to fertilization (e.g., female Nobox−/− mice are infertile due to a defect of early folliculogenesis, and in humans mutations in Nobox are associated with primary ovarian insufficiency66,67). For simplicity and to emphasize that the phenotypic consequences of MEGs result from effects on the embryo, all outcomes associated with the 82 MEGs are referred to as “offspring phenotypes,” although in many cases the phenotypes are non-viable (e.g., hydatidiform moles) or early lethal (e.g., zygotic cleavage failure).
| Gene symbol | Gene name | Previously reported |
|-------------|-----------|---------------------|
| Ago2        | Argonaute RISC catalytic component 2 | yes |
| Arida       | AT-rich interaction domain 1A | no |
| Atg5        | Autophagy related 5 | yes |
| BCAR4       | Breast cancer anti-estrogen resistance 4 | yes |
| Bcas2       | BCAS2 pre-mRNA processing factor | yes |
| Bnc1        | Basonuclin 1 | yes |
| Btg4        | BTG anti-proliferation factor 4 | no |
| Cdc20       | Cell division cycle 20 | no |
| Cdx2        | Caudal type homeobox 2 | no |
| CNOT6L      | CCR-NOT transcription complex subunit 6 like | no |
| Clcf.       | CCCTC-binding factor | yes |
| Ctnnb1      | Catenin beta 1 | no |
| CXXC1       | CXXC finger protein 1 | no |
| Dcafl3      | DBD1 and CUL4 associated factor 13 | no |
| DDB1        | Damage specific DNA binding protein 1 | no |
| DGC8        | DGC8 microprocessor complex subunit | no |
| Dicer1      | Dicer 1, Ribonuclease III | yes |
| Dnmt1       | DNA Methyltransferase 1 | yes |
| Dnmt3a      | DNA Methyltransferase 3 alpha | yes |
| Dnmt3l      | DNA Methyltransferase 3 like | yes |
| DPPA3       | Developmental pluripotency associated 3 | yes |
| Dtl         | Denticless E3 ubiquitin protein ligase homolog | no |
| Ecd         | Embryonic ectoderm development | no |
| Elmt2       | Euchromatic histone lysine methyltransferase 2 | no |
| Exosc10     | EXOSC10 | no |
| Ezh2        | Enhancer of zeste 2 polycomb repressive complex 2 subunit | yes |
| Gclm        | Glutamate-cysteine ligase modifier subunit | yes |
| H3F3b (H3-3B) | H3.3 Histone B | no |
| Hina        | Histone cell cycle regulator | yes |
| H2ac1       | HIST1H2AA; H2A clustered histone 1 | yes |
| H2bc1       | HIST1H2BA; H2B clustered histone 1 | yes |
| Hsp70B1     | Heat shock protein 90 beta family member 1 | no |
| Igf2bp2     | Insulin like growth factor 2 mRNA binding protein 2 | no |
| Kdm1a       | Lysine demethylase 1A | no |
| Kdm1b       | Lysine demethylase 1B | yes |

(Continued on next page)
MEG expression patterns

Each MEG that is present in the mouse genome was annotated for its expression category, using the database of the transcriptome in mouse early embryos (DBTMEE). The DBTMEE includes data on RNA abundance and gene-expression categories in mouse meiosis II (MII) oocytes and 1-, 2-, and 4-cell embryos. The information on RNA expression categories in mouse meiosis II (MII) oocytes DBTMEE includes data on RNA abundance and gene-expression category among the mouse MEGs is signed to an expression category. The most frequent gene-expression category among the mouse MEGs is “maternal mRNA” (40%). This category includes genes for which expression is highest in MII oocytes and tends to decline at each subsequent stage. The next most common categories were minor zygotic genome activation (ZGA) (17%, highest expression in 1-cell embryos), major ZGA (11%, highest express in 2-cell embryos), and mid-implantation gene activation (11%, highest expression in 4-cell embryos) (Table S2).

MEG-enriched pathways and gene ontology terms

The identified MEGs (Table 2) were analyzed using GeneAnalytics (LifeMap Sciences) to identify enriched pathways and gene ontology (GO) terms. GeneAnalytics provides a matching score and category (high, medium, and low) for the query set, based on the similarity between genes in the set and genes in an individual pathway or GO term. Fourteen pathways, 45 GO biological processes, and 16 GO molecular processes were ranked as high (Tables S3 and S4). The most highly ranked pathway was chromatin regulation/acetylation (score = 62.14). This pathway includes 255 genes, of which 19 are included in the MEG list. The most highly ranked GO Biological Process was chromatin organization (score = 74.59, 24 MEGs/367 genes), and the most highly ranked GO molecular process was chromatin binding (score = 41.68, 18 MEGs/468 genes). Other processes ranked as high were related to genetic imprinting (e.g., regulation of gene expression by genetic imprinting, score = 34.15) and methylation (e.g., DNA methylation involved in embryo development, score = 27.64; histone lysine methylation, score = 19.42).

MEGs and structural birth defects

Of the 82 mammalian MEGs, eight (10%) have been associated with birth defects in mouse models (Table 3), including one (NLRP2) that is a known human MEG. These eight genes are all involved in methylation and imprinting. Unless noted otherwise, the studies that identified the association between these MEGs and structural birth defects compared offspring from matings involving females homozygous for a TKO or oCKO and wild-type (WT) males (i.e., TKO/oCKO × WT) to offspring from WT × WT matings. Since all offspring from TKO/oCKO × WT matings are heterozygous, any observed phenotype could be due to zygotic haploinsufficiency rather than a maternal effect. This possibility was ruled out when the phenotype was not observed in TKO heterozygotes.

DNA methyltransferase 1 (Dnmt1)

This DNA methyltransferase has a somatic (Dnmt1s) and an oocyte-specific (Dnmt1o) isoform in mice and humans. During pre-implantation development, maternally derived Dnmt1o functions to maintain methylation patterns on differentially methylated domains of imprinted loci. Embryos that develop in the absence of Dnmt1o lose methylation on one-half of the normally methylated parental alleles at imprinted loci, likely due to absence of methylation maintenance during one embryonic cell cycle.

Homozygous Dnmt1o TKOs develop normally. However, compared to WT females, Dnmt1o−/− females have an increased rate of post-implantation losses, with most embryos lost between 14 and 21 days. Using a morphological scoring system, the phenotype of offspring from Dnmt1o−/− TKO females was compared to the offspring of WT females. In embryonic day 9.5 (E9.5) embryos from Dnmt1o−/− females, both the overall morphologic score and scores for individual morphologic features (e.g., heart, caudal neural tube) were significantly lower (indicating delayed development). Further, the proportion of embryos with a significant heart or neural tube closure.

### Table 2

| Gene symbol | Gene name | Previously reported |
|-------------|-----------|---------------------|
| Ubc2        | Ubiquitin conjugating enzyme E2 A | yes |
| Uchl1       | Ubiquitin C-terminal hydrolase L1 | yes |
| Ulnf1       | Ubiquitin like with PHD and ring finger domains 1 | no |
| Yap1        | Yes associated protein 1 | no |
| Yhdf2       | YTH N6-methyladenosine RNA binding protein 2 | no |
| Zar1        | Zygote arrest 1 | yes |
| Zbed3       | Zinc finger BED-type containing 3 | no |
| Zfp3612     | ZFP36 ring finger protein like 2 | yes |
| Zfp57       | ZFP57 zinc finger protein | yes |

*Mouse gene symbol is used unless gene is not present in mouse (human ortholog/gene symbol if different from mouse/rabbit). Indicates whether the MEG was reported in prior reviews by Kim and Lee, Zhang and Smith, or Condic. No mouse ortholog, identified as a MEG in rabbit. Known human MEG. No mouse ortholog, identified as a MEG in humans. Triple knockout of Nlrp9a, b, and c has a maternal effect.
defect, defined as an individual morphological score < 2 (corresponding to a >12-h developmental delay), was higher in the offspring of \(Dnmt1o^{-/-}\) females (heart: WT, 14%; \(Dnmt1o^{-/-}\), 54%; neural tube: WT, 16%; \(Dnmt1o^{-/-}\), 54%). In addition, magnetic resonance microscopy of E9.5 and E11.5 embryos from \(Dnmt1o^{-/-}\) females identified both normal-appearing embryos and embryos with abnormalities including pharyngeal arch defects and failure of caudal neural tube closure.74

Heterozygosity for the \(Dnmt1o\) TKO in females is also associated with adverse offspring phenotypes. Compared to WT females, \(Dnmt1o^{+/+}\) females have a higher rate of post-implantation losses and, at mid-gestation, a modest increase in the frequency of embryos with morphologic abnormalities (WT, 5%; \(Dnmt1o^{+/+}\), 13%).75 The proportion of embryos from \(Dnmt1o^{+/+}\) females with morphologic abnormalities was further increased when ARTs (i.e., superovulation and embryo transfer) were used (\(Dnmt1o^{+/+}\) with ART, 18%).75

**DNA methyltransferase 3 (Dnmt3a)**

This DNA methyltransferase is involved in \(de\ novo\) methylation. In the mouse, the homozygous \(Dnmt3a\) TKO is lethal, but heterozygotes develop normally.76 In oocytes, disruption of \(Dnmt3a\) results in hypomethylation of maternally imprinted genes. This hypomethylation is inherited by, and results in aberrant expression of, maternally imprinted genes in the embryo.77 Embryos from females homozygous for an oCKO of \(Dnmt3a\) die before E11.5 and present with pericardial edema, lack of brachial arches, and open neural tube defects.14,77

**DNA methyltransferase 3 like (Dnmt3L)**

This gene belongs to the Dnmt3 methyltransferase family but lacks a functional methyltransferase domain. Similar to \(Dnmt3a\), \(Dnmt3L\) is required for establishment of maternal methylation imprints during oogenesis,12 likely serving as an accessory factor for \(Dnmt3a\).78 Mice that are homozygous for a TKO in \(Dnmt3L\) develop normally. However, the offspring of \(Dnmt3L^{-/-}\) TKO females fail to develop past E9.5 and present with pericardial edema, exencephaly, and other neural tube defects.12 In embryos from \(Dnmt3L^{-/-}\) TKO females, hypomethylation of maternally imprinted genes appears to vary across embryos and loci (i.e., some loci in some embryos are normally methylated), suggesting that the effects of maternal deficiency of \(Dnmt3L\) are, to some extent, determined by stochastic processes.79

**Lysine demethylase 1B (Kdm1b)**

This histone H3K4 demethylase is required for \(de\ novo\) DNA methylation of some imprinted genes in oocytes, likely because H3K4 demethylation makes imprinted loci more accessible to \(de\ novo\) DNA methylation.80 Mice homozygous for a \(Kdm1b\) TKO develop normally. However, offspring of \(Kdm1b^{-/-}\) TKO females fail to develop past mid-gestation and present with placental defects, growth impairment, pericardia edema, and neural tube defects.80

**NLR family pyrin domain containing 2 (Nlrp2)**

\(Nlrp2\) is a member of the SCMC.81 Mice homozygous for an \(Nlrp2\) TKO are viable.82 However, compared to WT females, \(Nlrp2^{-/-}\) TKO females have fewer and smaller litters, due to losses after E9.5. In addition, they have higher rates of neonatal deaths and offspring with morphological defects including asymmetric limb development, craniofacial abnormalities, missing or small eyes, and micrognathia.81 Compared to embryos and pups from WT females, those from \(Nlrp2^{-/-}\) females differ in methylation and expression at some imprinted loci, suggesting that maternal \(Nlrp2\) may play a role in imprint acquisition or maintenance.81

In humans, maternal \(NLRP2\) mutations have been identified in women undergoing fertility treatments that result in early embryonic arrest and in women with offspring affected by MLIDs.28 In a review of six children with MLID due to maternal effect variants in \(NLRP2\), one also had an omphalocele and a heart defect. While

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**Table 3. Mammalian maternal effect genes associated with structural birth defects in offspring**

| Gene symbol | Gene name | Function | System | Birth defect phenotype |
|-------------|-----------|----------|--------|------------------------|
| Dnmt10      | DNA Methyltransferase 1, oocyte-specific isoform | Maintenance of DNA methylation | TKO | craniofacial, hear and neural tube defects |
| Dnmt3a      | DNA Methyltransferase 3 alpha | \(de\ novo\) DNA methylation | oCKO | lack of brachial arches and open neural tube defects |
| Dnmt3L      | DNA Methyltransferase 3 like | \(de\ novo\) DNA methylation | TKO | exencephaly and other neural tube defects |
| Kdm1b       | Lysine demethylase 1B | histone H3K4 demethylation | TKO | neural tube defects |
| Nlrp2       | NLR family pyrin domain containing 2 | SCMC, acquisition or maintenance of DNA methylation | TKO | craniofacial and skeletal defects; missing or abnormal-sized eyes; micrognathia |
| Tet3        | Tet methylcytosine dioxygenase 3 | DNA demethylation | oCKO | variable multi-organ abnormalities |
| Trim28      | Tripartite motif containing 28 | maintenance of DNA methylation | oCKO | craniofacial malformations; anophthalmia |
| Zfp57       | ZFP57 zinc finger protein | maintenance of DNA methylation | TKO | heart defects |

oCKO, oocyte-specific conditional knockout; TKO, traditional knockout.
omphalocele is common feature of the Beckwith-Wiedemann syndrome, heart defects are not considered to be either major or minor clinical features of this syndrome. 

Tet methylcytosine dioxygenase 3 (Tet3) 
This gene is involved in active DNA demethylation, and the Tet3 homozygous TKO is neonatal lethal. Using an oCKO, Tet3 was identified as a MEG associated with a reduced number of productive matings, increased post-implantation loss with “variable multi-organ abnormalities,” and increased neonatal lethality (survival <1 day after birth). However, only the association with neonatal and increased neonatal lethality (survival <1 day after birth). 

Zfp57 zinc finger protein (Zfp57) 
This zinc finger protein gene is involved in maintenance of DNA methylation. In 2008, Li et al. identified Zfp57 as the first “maternal-zygotic effect” gene, in which the offspring phenotype depends on both the maternal and zygotic genotypes. Specifically, zygotic homozygosity for a Zfp57 TKO is partially neonatal lethal in offspring of females heterozygous for the TKO (percent dead: E18.5, 17%; post-natal day 1 [P1] pup, 45%) and is a more highly penetrant, mid-gestational lethal in offspring of females homozygous for the TKO (percent dead: E11.5–13.5, 38%; E17.5–18.5, 80%). Hence, compared to the zygotic mutant, absence of both maternal and zygotic ZFP57 results in an earlier and more highly penetrant lethal phenotype.

Shamis et al. hypothesized that the mid-gestation lethality observed in the maternal-zygotic Zfp57 mutant might be attributable to abnormal development of the heart. To assess this hypothesis, they evaluated several heart phenotypes in four groups of E14.5 embryos: Zfp57 TKO heterozygous embryos from heterozygous mothers (control), Zfp57 null embryos from heterozygous mothers (zygotic null), heterozygous embryos from null mothers (maternal null), and null embryos from null mothers (maternal-zygotic nulls). Although the impact of the maternal and zygotic genotypes differed by phenotype—for example, atrial septal defects were only observed in the zygotic (44%) and maternal-zygotic (100%) nulls, whereas ventricular septal defects were observed in the maternal (20%), zygotic (20%), and maternal-zygotic (80%) nulls—results of these studies indicate that both maternal and zygotic Zfp57 contribute to heart development.

Discussion

Since the identification of the first mammalian MEG in 2000, the number of recognized MEGs has steadily increased, as has our understanding of the phenotypic consequences of variation within these genes. Based on this review, the number of identified mammalian MEGs associated with non-chromosomal, post-fertilization phenotypes in offspring is 82. In mouse models, these genes are expressed in the oocyte, and their expression patterns are consistent with a model of gradual transition from maternal to embryonic control of development. Further, these MEGs are enriched for genes related to chromatin, methylation, and imprinting, which is consistent with the involvement of these genes in early developmental events.

This review also indicates that the potential phenotypic consequences for MEGs include structural birth defects. Of the 82 identified MEGs, eight (10%) have been associated with structural birth defects, including craniofacial, heart, neural tube, and skeletal defects. These eight MEGs are all involved in methylation and imprinting. A role for methylation and imprinting abnormalities in the etiology of structural birth defects is consistent with the occurrence of such conditions in imprinting syndromes (e.g., omphalocele in Beckwith-Wiedemann syndrome) and has been suggested based on studies of non-syndromic structural birth defects. Further, epigenetic and imprinting differences resulting from ARTs have been suggested as a potential cause for the increased risk of structural birth defects in offspring conceived by in vitro fertilization or intracytoplasmic sperm injection. Consequently, it may be that any association between structural birth defects and
MEGs is limited to the subset of MEGs that are involved in methylation and imprinting. However, given gaps in our current understanding of MEGs and their phenotypic consequences, potential associations between structural birth defects and other categories of MEGs cannot be ruled out.

Filling gaps in our understanding of MEGs is of substantial clinical and public health importance, as the phenotypes that may arise as a consequence of damaging MEG genotypes impact a significant proportion of women. Approximately 14% of couples are infertile, and birth defects occur in approximately 6% of births. Further, the underlying causes of these conditions are often unknown: up to 30% of infertile couples are diagnosed with idiopathic infertility, and approximately one-half of all birth defects cannot be ascribed a specific cause. For these women, reproductive counseling is generally based on empirical data rather than individualized estimates, and their reproductive options are limited.

Variation within MEGs offers a potential explanation for at least a portion of the women with unexplained adverse reproductive outcomes. The identification of women carrying damaging MEG genotypes would provide the opportunity for improved reproductive counseling including: (1) accurate assessment of recurrence risks—the risk of subsequent adverse offspring outcomes in women carrying damaging MEG genotypes can be up to 100%, which is much higher than recurrence risks based on empirical data (e.g., the empirical risk of recurrence for most structural birth defects is less than 5%); (2) improved understanding of potential future outcomes—reproductive counseling generally focuses on recurrence of the presenting condition, whereas women carrying damaging MEG genotypes may be at risk for a spectrum of outcomes (e.g., MLID in the first pregnancy, hydatidiform mole in the next); and (3) personalized reproductive options—women carrying damaging MEG mutations should be offered the option of oocyte donation rather than in vitro fertilization or intra-cytoplasmic sperm injection.

The field of maternal effect genetics has already provided the basis for new testing, counseling, and treatment approaches. For example, women with recurrent hydatidiform moles can be tested for mutations in NLRP7 and KHDCL3, and those who test positive can be informed of the low probability of live births in subsequent pregnancies and the option of oocyte donation. Indeed, several successful pregnancies have been reported following ovum donation in women carrying NLRP7 mutations. In the future, oocyte donation may well be a viable option for women carrying variant genotypes in any MEG that has been convincingly linked to offspring phenotypes.

The current inventory of MEGs and our understanding of the impact of MEGs on offspring phenotypes are, however, far from complete. Future research efforts should seek to expand the number of identified MEGs. Oocytes contain thousands of maternal transcripts and proteins that could influence embryonic development. However, the vast majority of the genes encoding these factors have not been evaluated as potential MEGs.

Mammalian MEGs identified in model systems should be systematically evaluated for their potential roles as MEGs in humans. The majority of MEGs identified in model systems have not been assessed in humans. Although differences in expression patterns may suggest that a gene that acts as a MEG in a model system may not have a corresponding role in humans (e.g., ZFP57), the absence of a transcript in oocytes does not exclude a role for the gene as a MEG, since the cognate protein may be present in the oocyte (e.g., Tong et al., Li et al., and Ohsugi et al.). Thus, while expression patterns might be used to prioritize MEGs for further investigation in humans, a comprehensive assessment of potential human MEGs will likely require evaluation of women presenting with a range of adverse reproductive outcomes.

Another gap in the MEG knowledge base is the lack of detailed information on gene-phenotype correlations. While it is clear that many MEGs are associated with a spectrum of offspring phenotypes, the known phenotypic spectrum for individual MEGs is likely to be incomplete. In model systems, understanding of the phenotypic consequences of individual MEGs is generally limited to phenotypes resulting from complete absence of the gene product on a single genetic background. However, less severe mutations (e.g., hypomorphs) and genetic background may both impact on offspring phenotypes. Further, for any given model, the number of potentially relevant phenotypes that have been evaluated is generally limited. For example, among live-born offspring of female mice homozgyous for a hypomorphic mutation in Kdm1a, the rate of death within 48 h is increased relative to the offspring of WT females (26% versus 5%, respectively) and “...consistent with these animals having more subtle developmental defects.” However, a more detailed assessment for such defects, which could include structural birth defects such as congenital heart defects, has yet to be published.

Understanding of gene-phenotype correlations in humans is also limited for a variety of reasons. In particular, individual studies have generally been restricted to cohorts of women ascertained on the basis of a single phenotype (e.g., MLID), with the phenotypic spectrum defined based on the observed outcomes among all pregnancies to the cohort members. This approach is, however, limited by the relatively small size of most study cohorts, the relatively small number of additional pregnancies to each woman, and potential biases resulting from the initial ascertainment criteria (e.g., mutations identified in women who have a child with a MLID may not be associated with the full spectrum of outcomes resulting from mutations in the gene). In addition, most studies in humans have focused on rare, predicted deleterious variants in protein-coding genes, although maternal variation within non-coding regions (e.g., McJunkin, and common variation in protein-coding genes may also be associated with offspring phenotypes.
Conclusions
The nascent field of maternal effect genetics has already provided important new insights into the causes of a range of adverse reproductive outcomes, as well as the basis for new testing, counseling, and treatment approaches. Given the personal and public health impact of infertility, reproductive loss, structural birth defects, and other developmental disturbances that have been associated with MEGs, research aimed at enhancing the MEG knowledge base is strongly warranted. Future research efforts should include identification and characterization of additional mammalian MEGs, translation of knowledge from model systems to humans, and mapping of gene-phenotype relationships.

Supplemental information
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Declaration of interests
The author declares no competing interests.

Web Resources
Database of transcriptome in mouse early embryos (DBTMEE): https://dbtmee.hgc.jp/index.php
GeneAnalytics: https://geneanalytics.genecards.org/

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