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REVIEW

Genomics of pregnancy loss

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Abstract
Pregnancy loss is the most common obstetric complication occurring in almost 15% of pregnancies. Of the examined products of conception (POC), approximately 60% of pregnancy losses result from chromosomal abnormalities and copy number variations (CNVs) in embryos, but genetic etiologies of euploid pregnancy loss remain largely unexplained. Previous studies suggest that genetic factors make a significant contribution to embryonic mortality. We aimed to review the results of current genomic studies of gene variants associated with miscarriage, including exome sequencing to look for pathogenic variants in the whole exome, as well as high-coverage whole-genome sequencing in families with miscarriages. We compared the lists of genes causative of or predisposing to miscarriage in parents and POCs. Additionally, we summarize novel genetic variants, which may be responsible for embryonic aneuploidy according to WES/WGS studies. Identification of genes that contribute to pregnancy loss is of importance in understanding the biological pathways that can cause pregnancy loss and an informative approach for discovering the key genes for human development. Knowledge of specific genes that contribute to pregnancy loss could also be valued in designing a diagnostic sequencing panel for patients with recurrent pregnancy loss.

Keywords Miscarriage · Pregnancy loss · Genetic variant · Mutation · Whole-exome/whole-genome sequencing · Embryonic lethality

Introduction

Genetic causes of human embryonic death

Low efficiency of reproduction is characteristic of humans as a biological species, with only about a third of conceptions surviving to birth [1–3]. Human embryos are characterized by a high frequency of chromosomal abnormalities [4], which little affect viability in the preimplantation period. As a consequence, the main selection of embryos occurs either during implantation and manifests as low efficiency of natural conception or as unrecognized implantation failures, or soon after implantation (manifests as biochemical losses and miscarriage) [1].

As a result, about 15% of clinically recognizable pregnancies end as miscarriages, 90–95% of which occur in the first trimester of pregnancy [5]. The significance of genetic causes of embryonic mortality at such early stages is very substantial. Although the majority of early pregnancy losses are sporadic, 1–3% of pregnant women suffer from recurrent pregnancy loss (RPL), defined as two or more consecutive pregnancy losses in woman's obstetric history. The impact of genetic factors for miscarriage was proven by the fact that women with miscarriage more often have cases of embryonic death in their pedigree [6], and the frequency of RPL among first-degree relatives of women with idiopathic RPL is six-fold higher in comparison with the general population [7, 8].

Chromosomal abnormalities of the embryo are the most common cause of miscarriage. Almost 50 years of cytogenetic studies of spontaneous abortions have demonstrated abnormality rates of around 50–60% [9–11]. Trisomies are the most frequently detected anomalies (58–61%), followed by monosomy X (8–13%), polyploidies (2–13%), and structural anomalies (7–9%) [12, 13]. Autosomal monosomies

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are rare in spontaneous abortion material (0.8–1.5%) and found predominantly in mosaic state [14–16]. DNA-based methods of molecular karyotyping, such as array comparative genomic hybridization (aCGH) and single-nucleotide polymorphism (SNP) microarray, also made it possible to identify microstructural rearrangements (CNVs, 2–4.4%) and uniparental disomy (UPD, 0.25–0.5%) [17–20].

However, after excluding of abnormal embryo karyotype and maternal causes, such as uterine abnormalities, coagulation, immunological, and hormonal factors of the mother, the causes of 40–50% abortions (with a normal karyotype) most often remain unrecognized. In such cases, pregnancy losses may be caused by other genetic aberrations, including SNVs and indels.

Search for candidate genes in pregnancy loss

Classical linkage analysis is usually used to identify candidate genes, but in the case of pregnancy loss, such analysis is quite difficult to carry out due to the low rate of large pedigrees with reproductive disorders. The meta-analysis of 428 case–control studies identified 21 variants in 13 genes contributing to the RPL development, but due to the large heterogeneity between sampling in these studies, all found associations with RPL were low/moderate [21]. Genome-wide association studies (GWAS), based on genome-wide genotyping of polymorphic markers, have made it possible to map loci and genes potentially associated with the RPL phenotype [22].

In addition, smallest overlapping regions delineation has been used in CNV studies to search for genes responsible for reproductive failure [23]. Recent works on large samples and using higher-resolution methods (high-resolution chromosomal microarrays, low-coverage whole-genome sequencing, CNV sequencing) made it possible to identify loci and genes associated with embryonic loss [19, 24, 25].

Next-generation sequencing (NGS), including whole-genome sequencing (WGS) and whole-exome sequencing (WES), is an effective approach for screening of potential pathogenic variants without prior analysis of genotype–phenotype correlations. Because genetic variants (parental or embryonic) that contribute to embryo loss are subjects of negative selection, many of them would be exist as ultra-rare or de novo variants. Extremely rare genetic variants with large effect sizes could be identified in family-based linkage analyses. However, families affected by pregnancy loss are uncommon due to reduced reproductive capacity, and family-based analysis is not possible in most cases. Therefore, an important advantage of WES, compared with alternative approaches, is the ability to identify extremely rare and de novo genetic variations.

The first study using exome sequencing identified a rare homozygous variant in a highly conserved region of the *CHRNA1* gene in a deceased fetus with non-immune hydrops from the RPL family [26]. In subsequent years, WES studies of miscarriages involved single families [27–32], or non-family samples, for example, women with miscarriage [33]. Often, the attention of researchers was directed to the fetuses with developmental defects identified by ultrasound examination [34–38], and results of these studies reviewed in [39–41]. The phenomenon of miscarriage per se, most cases of which occur in the first trimester, became the object of research somewhat later. More large-scale studies of human miscarriage become possible last years due to cost-effectiveness of whole-exome and whole-genome sequencing technologies. The number of studies of the pregnancy loss by sequencing is growing now [42], although this technology is not routine so far, and interpretation of the WES/WGS results is a challenging issue. The results of such studies and the problems that complicate its implementation are discussed in this review.

Study design in WES/WGS researches identifies causal variants from the maternal or embryonic side

Here, we consider studies using WES and high-coverage WGS for identification of single-nucleotide variants (SNVs) and insertions/deletions (indels) that provide a possibility for identification of the molecular origins of pregnancy loss. Various approaches are possible for studying of pathogenic or significant gene variants in reproduction, which are determined by the sample collection (families, POC, miscarried women). Analysis of different cohorts allows to identify variants that are significant for the maternal or embryonic component of pregnancy maintenance. Most often, samples analyzed to study miscarriage are:

i. Products of conception (POC) (embryos/fetuses, depending on the pregnancy age), this approach is focused on searching for the causes of embryonic death (presumably de novo mutations or inherited homozygous recessive mutations) in the genome of the embryo [30, 35, 43–46].
ii. Women with RPL. After excluding of anatomical and chromosomal causes of pregnancy loss in women, genetic variants that contribute to RPL are analyzed. Some of studies focus on the analysis of specific set of genes that could potentially be associated with RPL (for example, related to immune and hormonal disorders, endometrial and placental dysfunction, coagulation) [33, 47–49]. Other studies use women with normal reproduction as controls [50, 51], but the analysis of small samples reduces the reliability of the differences found.

iii. Couples with miscarriage, where causal variants are searched in the genomes of mothers and fathers [52, 53].
iv. Trios/families (including the abortus and both parents). This approach is the most informative, as it allows to distinguish de novo or inherited variants, which may be important for assigning the pathogenic significance of the identified variant or gene, including the case of compound heterozygotes [31, 54, 55]. Candidate variant detected in one of the family members can be verified in other relatives by Sanger sequencing. Thereby, family analysis increases the diagnostic yield of exome sequencing, for example, in a study on a Chinese population, the diagnostic yield for the trio was 55.9% (19/34) compared to 33.3% (9/27) for the analysis of POC only [38].
v. In addition, the detection of variants which affect embryonic viability is possible in samples of dead fetuses with developmental anomalies. Typically, part of these samples is represented by fetuses with anatomical anomalies established by ultrasound examination, and significant proportion of such fetuses is nonviable and dies spontaneously during the 2nd trimester [28, 34, 36]. But miscarriage is specific cohort with the distinct WES diagnostic yield rate that was found in the study of Xiang et al.: after excluding of the aneuploidies and CNVs, detection rate in the group of the pregnancy termination for fetal abnormality was found 24.2% versus 3.8% in miscarriage group [56]. Possibly, this is due to better knowledge about spectrum of variants related to fetal abnormalities than to pregnancy viability.

Whole-exome sequencing

Though the exome comprises approximately 1% of the human genome, as estimated it cover the majority (85%) of pathogenically significant variants. Since whole-exome sequencing (WES), which detects changes in protein-coding sequences, was first described in 2009, it has led to the identification of abundance of new variants and genes associated with human diseases, including those involved in reproductive disorders. According to the ACMG (American College of Medical Genetics and Genomics) recommendations, WES can be considered a diagnostic test for individuals with phenotypes suggesting a genetic etiology and having a high degree of genetic heterogeneity, and human pregnancy loss satisfies these criteria.

WES detects SNVs and indels with identifying hundreds and thousands of variants per genome. Therefore, the use of bioinformatics strategies is necessary to prioritize the variants most likely responsible for the pathological phenotype such as miscarriage. According to the ACMG recommendations, detected variants are divided into pathogenic, likely pathogenic, uncertain significance, likely benign, or benign. Sequence changes are considered pathogenic and can be supposed causative for the disease if they are absent or very rare in controls, affect the coding part of the gene, located in an evolutionarily conserved sequence, damage the protein (according to bioinformatics tools), and/or there is published data about their association with the disease [57–59]. Disease variant discovery can gain power from classifying genes by their tolerance to inactivation, with predicted loss-of-function (pLoF) variants that render the corresponding genes non-functional. In addition, it is important to trace segregation of variant with the disease in the family or pedigree to determine its significance.

The application of WES has some limitations. Because exome capture biases read coverage, the detection of copy number variants (CNVs) is hardly possible using WES. Exome capture reagents are ineffective in difficult areas of the genome, so not even the entire protein-coding portion of the genome is covered with WES.

Another problem when using WES is the detection of low-level mosaicism. To exclude the misinterpretation of inherited variants as seemingly de novo mutations (as a consequence of low-level gonadal mosaicism in one of the parents), high sequencing coverage (i.e., at 500× or more) is preferred. If mosaicism is inter-tissue, the genotype of lymphocytes of peripheral blood may not correspond to the genotype in other tissues. For example, in a family with four consecutive miscarriages up to 10 weeks and the absence of clinical and chromosomal pathology in parents, WES detected a de novo heterozygous nonsense variant (c.1012G > T) in exon 12 of the *EFTUD2* gene (NM_004247.4), leading to structural changes in the EFTUD2 protein. This variant was absent in DNA from the peripheral blood of both parents, but Sanger sequencing confirmed its presence in three available for analysis abortions. This suggests the presence of parental gonadal mosaicism, and additional WES of DNA from sperm identified the same variant in 13.5% of cells [60].

Since each individual exome carries from several tens to hundreds of causal variants, interpretation and designation of their pathogenic significance is one of the most difficult problems. For example, exome sequencing of 100 women with RPL from the Chinese Han population found an average of 67.4 rare deleterious nonsynonymous variants and 11.6 potential loss-of-function variants in each patient [48]. Another study of 36 POC found 83.633 SNPs and 13.635 indels, and 29.172 SNPs and 3.093 indels were attributed as pathogenic ones [46]. Various prioritization methods are used to narrow the number of genes/variants and select the most pathogenically significant. Some authors identify a set of RPL-associated genes based on the results of

previous studies in human patients and animal models [33, 48]. However, considering that the recurrence of specific variants or affected genes in different studies is quite low, such an approach is unlikely to be optimal at present time. An accumulation of knowledge about genotype–phenotype correlations in intrauterine death and creation of large-scale databases of variants identified in miscarriage will make this approach more productive.

Bioinformatics filters for selection of putative causative variants of DNA sequence rely on the minor allele frequencies (MAFs) in databases; variant type, including missense, nonsense on protein, frameshift, and splice-site variants; predicted loss-of-function (pLoF) variants; variant impact predicted to be protein damaging; and changes in evolutionary conserved sequences. The MAF threshold varies in different studies, usually ranging from 0.001 to 5%. The design of the study [43] based on the assumption that variants caused embryonic lethality are not detectable in live-born individuals. Therefore, variants with MAF = 0 were selected (that absent in the dbSNP, 1000 Genomes, ESP6500, ExAC, and gnomAD databases) [43].

Following selection of the most significant genes/variants, study can be carried out on expanded samples using other methods. For example, in a Bangladeshi woman with a history of 29 abortions from three different spouses and no successful pregnancies, a variant in the *FKBP4* gene was discovered. Sanger sequencing on *FKBP4* in 220 patients and 100 controls found three additional new variants of this gene in patients with miscarriages from Asian populations. Interestingly, none of these variants was found in European women with miscarriage or in matched population controls with normal reproduction [61]. This indicates the possible population specificity of reproductive loss genetics, which must be taken into account when comparing results obtained for samples of different genetic ancestry groups.

Estimation of the pathogenic significance of detected variants also includes testing of animals, usually mice. This can be an assessment of the fertility of mice with a specific mutation or gene knock-out (complete lethality or a reduced number of pups in the litter) or an assessment of gene expression in mouse embryos at various stages: zygotes, blastocysts, etc. [62]. Cell cultures with the mutations introduced by genome editing technologies are another way of experimental confirmation of the variant significance. Choriocarcinoma lines (BeWo, JEG-3, JAr) or immortalized trophoblast cells (HTR8/SVneo, TEV-1, ACH-3P, SGHPL-5, HIPEC65) can be used for this purpose. Recently, the use of trophoblast stem cell cultures has also been developed, which completely correspond to placental cells and have a proper transcriptional profile, in contrast to immortalized cell lines, reviewed in [63]. In cell cultures, the functional properties of trophoblast-like cells with knock-out/knockdown or overexpression of the studied gene are assessed, for example, their ability to migrate and invade or changes in adhesion and apoptosis. Since trophoblast migration and invasion are critical features of implantation and placental development, the effect of variants on cell culture verify variant's significance [62, 64]. In addition, estimation of the ability to express the gene of interest or related genes, as well as to produce protein, can be made.

The gene location in a chromosomal region with the significant effect on reproduction determined by other methods, for example, using the analysis of CNVs and chromosomal rearrangements provide additional confirmation of the gene significance [18, 22, 65].

High-coverage WGS

There is growing evidence that genetic variants in non-coding regions of the human genome may play an important role in the development of human phenotypic traits and diseases. In fact, most variants in genome-wide association studies (GWAS) map to non-coding regions [66]. There is an increasing number of reports about Mendelian diseases that map beyond protein-coding regions of the genome [67]. WGS has the potential to identify practically all forms of genetic variability, including single-nucleotide, structural, and copy number variants. Another advantage of WGS is the ability to detect regulatory genetic variants, including those located in non-coding regions of the genome. In addition, WGS allows the analysis of coding regions with difficult capture, such as CG-rich loci or regions of repeated sequences. Long-read WGS allows analysis of regions that are challenging for short-read sequencing, which is the most common method in WES now. But interpreting of prodigious amount of the resulting genomic data is a separate challenge.

Genome analysis faces several challenges, such as high cost, complexity of processing, clinical interpretation, and storage of huge volumes of data [68]. Compared to WES, the complexity of interpreting sequencing results increases greatly for WGS, and the few WGS of embryonic loss published to date have identified large numbers of potentially deleterious variants; however, the authors discuss only exome variants, probably due to the complexity of analysis and interpretation of variants localized beyond protein-coding regions [32, 45, 69–71]. Therefore, the diagnostic utility of WGS for the study of pregnancy loss remains to be assessed in appropriate samples and pipelines.

The first study using WGS to look for the causes of fetal mortality, published in 2017, was carried out on a large multi-generational pedigree with a total of 19 deaths of male fetuses with a normal karyotype at less than 20 weeks of gestation [32]. Because the mutation had an X-linked recessive pattern of inheritance based on pedigree, WGS

was performed on six family members (five female carriers and healthy male offspring from one of the five women) and identified 293,009 ultra-rare variants with MAF < 0.05%. Of these, 456 variants were found to be nonsynonymous, of which 4 variants were present in all five female carriers and absent in the healthy male family member. However, only two variants were located in genes on the chromosome X (*CCDC120* and *FOXP3*) and thus represented candidate variants. Since *CCDC120* gene is not associated with pathology, this variant was classified as VUS, and *FOXP3* gene considered the most likely candidate. The encoded transcriptional regulator protein is critical for the development and maintenance of regulatory T cells, and a variant in *FOXP3* gene has previously been implicated in a potentially lethal X-linked disease (MIM #304790). Thus, the identified ultra-rare frameshift variant (c.906delT; p.D303fs*87) is the most likely candidate responsible for the repeated death of male fetuses in this pedigree [32].

In 2021, WGS was performed on a consanguineous Saudi Arabian family with four idiopathic miscarriages at 9 weeks of gestation. Genomic analysis of the trio revealed that abortus inherited the NM_017419.3:c.680G > T variant in both copies of the *ASIC5* gene from its heterozygous carrier parents. A search for this variant in an expanded sample of 200 healthy Saudis using PCR and Sanger sequencing did not find a homozygous variant in any individual. Moreover, this variant was new to the Saudi Human Genome Program (SHGP) database, which includes about 9500 genomes. However, heterozygous carrier of this variant was found who was the only daughter of a mother with idiopathic RPL (three consecutive cases of embryonic death in the 9th week of pregnancy) [69].

The lack of family data about variant inheritance seriously complicates the analysis of the results of whole-genome studies. Thus, Buonaiuto et al. carried out full genome sequencing with 30-fold coverage of ten abortuses (6 sporadic and 4 recurrent) with a normal karyotype and revealed 11 M SNPs and 2 M indels. After all filters, the authors prioritized 439 unique variants in 399 genes, and 182 variants were absent in the HGDP dataset, and for the remaining 257 (58.5%), the minor allele frequency is less than 1% in the full HGDP cohort. The authors suspect causative role of variants in the *STAG2*, *FLAD1*, *TLE4*, *FRMPD3*, and *FMNL2* genes [45]. An additional seven genes (*BHLHE40*, *DBN1*, *FOXA1*, *HSPD1*, *PLXNA3*, *SLC35A2*, and *SRF*) were previously identified as associated with miscarriage based on CNV analysis of dead fetuses [24].

Workalemahu et al. analyzed the genomes of members of 4 families with miscarriage, with 3 to 6 cases of prenatal death at different stages and live-born children in each family (22 samples in total). After excluding low-quality samples and prioritization, 28,485 casual SNVs were found in 16 embryos/fetuses from three families [71]. Of these, 22 de novo variants, 6 inherited AD, and 6 X-linked recessive variants were pathogenic. The authors distinguish *DICER1*, *FBN2*, *FLT4*, *HERC1*, *TAOK1*, and *VWA5B2* as the most significant known genes involved in embryo/fetal development and reported in congenital anomalies, highlighting that fetal anomaly phenotypes may share common pathways with recurrent miscarriage [71].

The observed mean de novo loss-of-function SNVs in pregnancy losses was higher than that of the expected (2.0 vs 0.2; $p = 0.01$) and higher than in live births in the same families. Moreover, the SNVs were enriched in > 1 protein-altering genes (p value < 0.001). The findings of higher counts of de novo SNVs in abortions compared with live births, excess of genes with > 1 loss-of-function de novo SNVs, and occurrence of multiple de novo events in a single gene in samples from losses, mean importance of de novo SNVs in the pathogenesis of reproductive losses [70, 71].

In the largest study to date, Byrne et al. examined members of 200 families with miscarriages from 13 to 20 weeks, stillbirths, and neonatal deaths from 20 weeks of pregnancy to 28 days after birth. WGS identified P and LP variants in 52 families and candidate variants or genes (VUS/GUS) were found in an additional 53 families. Considering only cases with the diagnosis "miscarriage," P and LP variants were identified in 3/7 families (42.9%) [70].

Results of WES/WGS studies of miscarriage

To date, about four dozen studies have been published that have used WES or WGS to identify variants in families with pregnancy losses, sometimes in combination with fetal anomalies (Table S1). The majority of these studies carried out analysis of single families [29, 31, 32, 54, 55, 60, 61, 64, 69, 71–77], eight examined samples of women with miscarriage [33, 47–51, 78, 79], two studied couples [52, 53], six examined samples of abortions (POC) [30, 43–46, 80], three studies carried out trio analysis [62, 70, 81], and the remaining studies examined different combinations of subjects [56, 82, 83] (Table S1).

Studies of particular families typically include women with multiple pregnancy losses, in some cases associated with fetal anomalies, and many of these families are consanguineous [30, 64, 73–75, 80]. In such families, variants are almost always found that likely responsible for the phenotype. For example, a homozygous missense variant in the *NOP14* gene was found in abortions from two consanguineous Iranian couples with RPL [73]. In a consanguineous Chinese family with three sisters having RPL, a rare homozygous frameshift variant in the *CAPS* gene was identified in all three patients [64]. Qiao et al. examined 4 families with idiopathic RPL and compound heterozygous variants in the *DYNC2H1* and *ALOX15* genes were found

in 2 families [31]. Some families were specific due to peculiar characteristics of dead embryos, for example, numerous losses of triploid abortions as a result of incompetent second meiotic division in the mother [29, 75] or the death of male fetuses in which variants in the X-linked *FOXP3* and *NSDHL* genes are detected [32, 76].

The majority (78.8%, 41 of 52) of variants found in families were inherited, including 27 (65.9%) maternal, 11 (26.8%) paternal, and 3 (7.3%) variants inherited from both parents. Eleven variants (21.2%) occurred de novo in the embryo. Of the inherited variants, half were autosomal recessive (AR, 53.6%, 22 of 41) (four homozygous and 18 compound heterozygous), four were autosomal dominant (AD) (genes *APOE*, *BNC2*, *CSF1R*, *MBD4*) with reduced penetrance (9.8%, 4 of 41), and four were X-linked recessive (XLR, 9.8%, 4 of 41, all inherited from the mother), while the remaining 26.8% (11/41) were in non-OMIM genes in heterozygous state.

The diagnostic efficiency for sample analysis (women with miscarriage, abortions, or trios) is estimated using the ADR (abnormality detection rate), which is calculated as the ratio of the number of cases with pathogenic or likely pathogenic variants to the total number of cases analyzed. Some authors also include VUS if there is supporting data for variant significance. The use of genomics to identify the genetic causes of prenatal death in samples of fetuses with structural anomalies gives diagnostic results ranging from 14 to 57% [34–36]. For miscarriage samples (both RPL and sporadic cases), ADR varies from 0.3 to 100%, but this figure is quite subjective and depends both on the severity of the filters used due to pathogenic significant results selection and on sample studied (women/abortions/trios). For example, in dead fetuses with structural anomalies, WES gives the diagnostic yield for the trio noticeably higher than for fetal samples only: 24% (11/45) compared to 14% (4/29), in [34], and 56% (19/34) compared to 33% (9/27), in [38]. The ADR may also differ for embryos that die at different stages of pregnancy. Thus, the proportion of cases with diagnostic variants in the first, second, and third trimesters was 30%, 38%, and 17%, respectively [44].

The WES/WGS studies of miscarriage published to date have analyzed more than a thousand cases (POC, women, trios, and families), identifying 357 candidate variants in 254 genes (Table S2). Some studies, especially WGS-based, find dozens of variants per case, so we included in the list only genes that the authors emphasize as top or the most likely ones. It is important that only a few (27) genes (*ALPG(ALPPL2)*, *BPTF*, *BUB1B*, *CCNB3*, *CDH5*, *COL6A3*, *DCHS1*, *FBN2*, *FKBP4F5*, *F11*, *FLT1*, *FSHR*, *FGA*, *HSF1*, *KHDC3L*, *MMP10*, *MMP9*, *MTHFR*, *NEB*, *NLRP7*, *OSBPL5*, *PADI6*, *PLK1*, *REXO4*, *SCN5A*, *TNC*) were found in at least two studies, indicating the heterogeneity and complexity of the pregnancy loss phenotype.

It can be assumed that the set of significant genes may partly differ between abortions and mothers with miscarriage. For mothers, processes such as decidualization and endometrial receptivity, immune response to pregnancy, coagulation, and uterine spiral arteries remodeling are critical for reproductive success. The association of some genes involved in these processes with miscarriage has previously been studied using a candidate approach in patients with RPL [84], and recent WES/WGS studies are also detecting pathogenically significant variants in these genes (Table S1) (for example, F5 [33, 49, 83] and *MTHFR* [83]) in samples of women with miscarriage. Variants critical for embryo viability are most likely included lethal ones. From embryo side, deleterious variants in genes involved in essential cellular processes, such as mitosis, transcription, DNA methylation, cell proliferation, and differentiation, especially in the extraembryonic tissues, are likely to cause embryonic lethality early in pregnancy, considering that most of conceptions did not reach the fetal stage (> 9 weeks postconception). Later in fetal development, defects affecting other processes that required for normal organogenesis and growing should be critical. Indeed, variants in 116 genes were found only in mothers (parents) and in 114 genes were found only in abortions, and Gene Ontology shows enrichment of different biological processes in these two categories of subjects (Fig. 1).

Importantly, the products of some parental genes are directly significant for the embryo development, because about 10% of maternal gene products remain active after fertilization until the blastocyst stage [85]. Numerous maternal effect genes (expressed during oogenesis and determining an embryonic phenotype) are known in human, for example, *TUBB8*, *PLK4*, *MATER*, *TLE6*, *PADI6*, *KHDC3L*, and *ZSCAN4*, and deleterious variants of some of this are found in pregnancy loss genomes. Berkay et al. in a sample of 35 miscarried women detected ten women as heterozygous carriers of recessive variants that could be lethal or disrupt intrauterine development, including genes *WNT6*, *ZAR1*, and *ZSCAN4* [49]. *Zscan4* is one of the best-known genes of early embryonic development; its expression is detected at the 2-cell mouse embryos, and its product is necessary for maintaining genome stability and a normal karyotype in mouse ESCs [86]. Blastocyst growth was interrupted and implantation was not successful in the absence of *Zscan4* activity [87].

Apparently, not only single gene variations in the conception could be a lethality cause; rare variants in several different genes could be incompatible with appropriate in utero development and normal fertility as well [49, 50, 82]. It was found that some patients carried mutations in genes affecting the same biological processes thus suggest that additive/epistatic effects of distinct variants contribute towards RPL etiology [33].

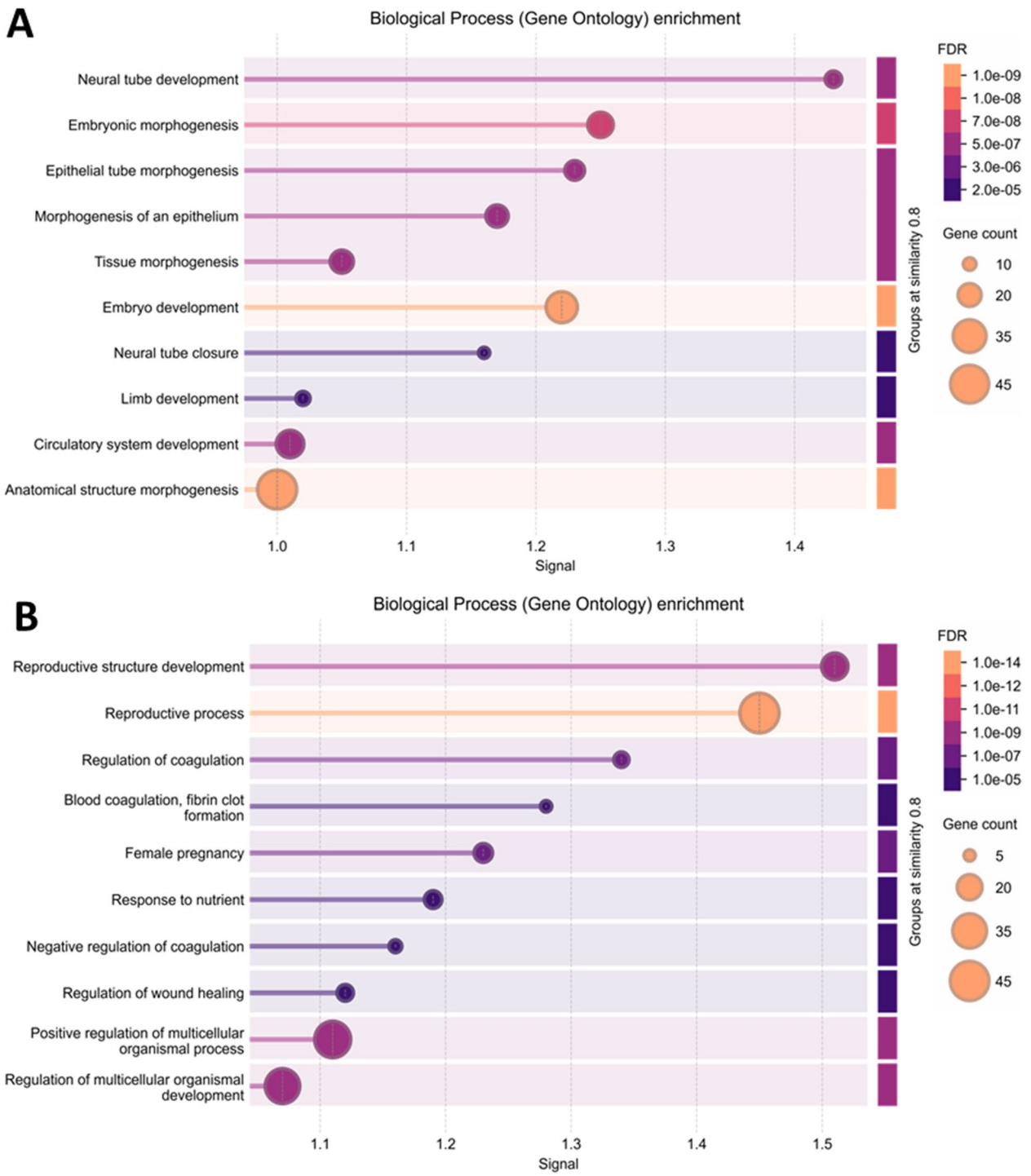

Fig. 1 Biological process enrichment among genes with variants found in abortuses (POC) and in mothers (parents) in WES/WGS studies of miscarriage. This figure utilizes Gene Ontology classification system enrichment by String to analyze gene ontology within two categories of subjects: **A** biological process enrichment for 130 genes from abortuses (POC); **B** biological process enrichment for 134 genes in mothers (parents), offering insights into the diverse biological functions these genes may influence

Analysis of the properties of known genes associated with miscarriage, stillbirth, and termination for fetal abnormality showed that they correspond to broadly expressed, highly evolutionary conserved genes involved in crucial cell differentiation and developmental processes and related signaling pathways, reviewed in [40–42]. Although the results available now provide some insight into the pathogenesis of embryonic mortality, really, most studies describe

DNA sequence variants that have only presumptive associations with the phenotype, especially in non-familial studies. In vitro/in vivo functional studies are required to determine the actual contribution of these genetic variants to human embryonic mortality. For example, such genes as *TEAD4*, *NEDD8*, and *BCAM* were found essential for the establishment of pregnancy, due to its variants or expression changes could be a molecular cause for trophoblast dysfunction and result in early human pregnancy loss [88–90]. Functional analysis for gene competence from the mother's side, for example, *ANXA4*, was carried out on the human endometrial stromal cell line THESCs [79].

At the population level, RPL is a common disease, and the number of causative genes/variants can be very high. In addition, a lot of variants could be located in genes that have not been associated with previously known diseases and missing in the OMIM database. Thus, a research group from Saudi Arabia in a WES study published in 2015 identified seven novel (non-OMIM) candidate genes (*THSD1*, *PIGC*, *UBN1*, *MYOM1*, *DNAH14*, *GALNT14*, and *FZD6*) in 19 families with RPL (37%) [30], and in a later study, they identified 13 more new candidate genes (*MS4A7*, *SERPINA11*, *FCRL4*, *MYBPHL*, *PRPF19*, *VPS13D*, *KIAA1109*, *MOCS3*, *SVOPL*, *FEN1*, *HSPB11*, *KIF19*, and *EXOC3L2*) in 44 families (30%) [35]. The nearly constant proportion of families that harbor candidate variants in genes with no established role in human pathology seems consistent with population study of human lethality [91, 92] and support the assumption about a large number of human embryo lethal genes, many of them have yet to be characterized. This once again emphasizes the need to create a specific database for miscarriage-related variants. Now, such databases are appearing, for example, https://plovdb.ott.ru/ [93].

Search for lethal gene variants in population data

The identification of lethal variants in human genome has the potential to improve interpretation of the clinical exome/genome sequencing data. Defining the molecular cause of embryonic death provides both accuracy of diagnostic for genetic counseling and important scientific contributions by revealing "gene essentiality." Genes are considered "essential" when loss of its function compromises the viability of the individual (for example, embryonic lethality) or results in profound loss of fitness, and these genes govern basic biological information at the cellular, tissue, and organismal levels. Using model organisms, it was shown that in yeast, knockout of 19% of genes is lethal [94], and in mice, a quarter of gene knockouts lead to embryonic lethality [95, 96]. In humans, studies have estimated that ~ 3400 of human genes are essential for embryonic and fetal survival [97]. Typically, the essentiality of human genes is assessed by their importance for the growth of human cell lines or the effect of knocking out orthologous genes in mice. But the list of essential genes in live human individuals may differ noticeably from cell cultures and from mouse, especially in extraembryonic tissues. For example, key regulators of trophoblast lineage specification in rodents (i.e., *Cdx2*, *Eomes*, *Esrrb*, and *Sox2*) do not appear to play essential (or identical) roles in human trophoblasts [98].

Therefore, it is necessary to assess the essentiality of human genes in vivo, and there are two different ways for this purpose. The direct way to outline essential genes involved in human development is to study embryonic loss, and whole-genome/exome studies of miscarriage are appropriate method for identifying such genes and variants. Another way is the analysis of genome sequencing data at the population level, which requires the bioinformatic dissection of huge volumes of data.

Population-based bioinformatics researches are based on assumption that in a randomly mating population certain rate of heterozygous pathogenic/pLoF (predicted loss of function) variants together with the absence of individuals carrying homozygous variants for these genes are consistent with pre/perinatal lethality. An example of such approach is an unprecedented study of the genomes of 1.52 million people from six European populations [91]. Since a rare variant present in 1:500 individuals (frequency 0.2%) is expected to be present in one per million in a homozygous state, the absence of such homozygous variants in a sample of more than 1.5 million people may indicate their lethal effect. The search for homozygosity-deficient variants revealed 25 genes with protein-altering variants that have a strong deficit of homozygosity (10% or less of predicted homozygotes) (Table S3). Interestingly, 11 variants were located in genes that have not been associated with previously known diseases, variants in other 14 genes cause Mendelian diseases. In comparison with genes that did not show a homozygous deficit, genes with a homozygous deficit are 6.6-fold more likely to be linked to autosomal recessive disease ($p = 1.9 \times 10^{-4}$), 15.1-fold more likely to be essential for viability in human cell lines ($p = 9.1 \times 10^{-8}$), and 19.5-fold more likely to result in lethality in knocked out mice ($p = 1.2 \times 10^{-6}$). Analysis of the reproductive history of carriers of pLoF variants in homozygous deficiency genes showed an association between these variants and miscarriage, with the most pronounced effect on the miscarriage rate was in couples carrying pLoF variants in the *DHCR7* gene (OR = 5.3) [91]. It can be assumed that in addition to miscarriage, lethal variants can also cause earlier losses (including RIF), at the implantation stage or soon after and before ultrasound registration of pregnancy, and such losses will not be registered at all [91]. Other bioinformatics research of 125,748 exome sequences from the gnomAD for

different ethnic groups and mouse and human gene function databases identified 138 candidate genes. Although the frequency of heterozygous lethal variants in these genes in the general population is ≥ 0.5%, variants are not found in a homozygous state [92] (Table S4).

Currently, list of genes from WES/WGS studies of miscarriages little overlaps with lists of lethal genes from population analysis [91, 92]. But *DHCR7* and *GBE1* genes were found strongly associated with human lethality (Fig. 2). *DHCR7* gene encodes 7-dehydrocholesterol reductase and is essential for the final step of cholesterol biosynthesis. Mutations in this gene caused an autosomal recessive Smith–Lemli–Opitz's (SLOS) syndrome with multiple congenital anomalies and intellectual disability. There is a discrepancy between the expected incidence of SLOS based on carrier frequency (1/26,500) and the observed incidence of disease (1/3906) that may be explained by a higher rate of pregnancy loss in affected embryos [55, 92]. *GBE1* encodes the glycogen branching enzyme (GBE), which is crucial for the synthesis of glycogen; mutations in this gene are associated with glycogen storage disease type IV (also known as Andersen's disease). GSD IV is a heterogeneous disease, which is known to have hepatic and neuromuscular features as well as the prenatal manifestations, ranged from fetal hydrops and polyhydramnios to miscarriage [99].

Identification of genes important for pregnancy maintenance will make it possible to further study of their functional significance through the gene networks construction. Recently, a gene network of RPL was built based on a GEO dataset. The NF-κB signaling, Foxo signaling, PI3K/AKT, and endometrial cancer signaling pathways were shown to be the most significant pathways in the RPL regulatory network. The key network gene *PLK1* was found to play a protective role against RPL and its expression is decreased in patients with RPL in comparison with the healthy control ($p < 0.01$) [100]. In experiments, in vivo *PLK1* suppression inhibited mitochondrial function and chorionic villi development, and in vitro *PLK1* knockdown induced the NF-κB signaling pathway and activation of apoptosis with simultaneous reducing cell invasion, migration, and proliferation [100]. These data are consistent with two WES studies of patients with miscarriages, where *PLK1* mutations were also found [47, 52]. Genes identified in miscarriage studies can be classified into the following categories: genes with known

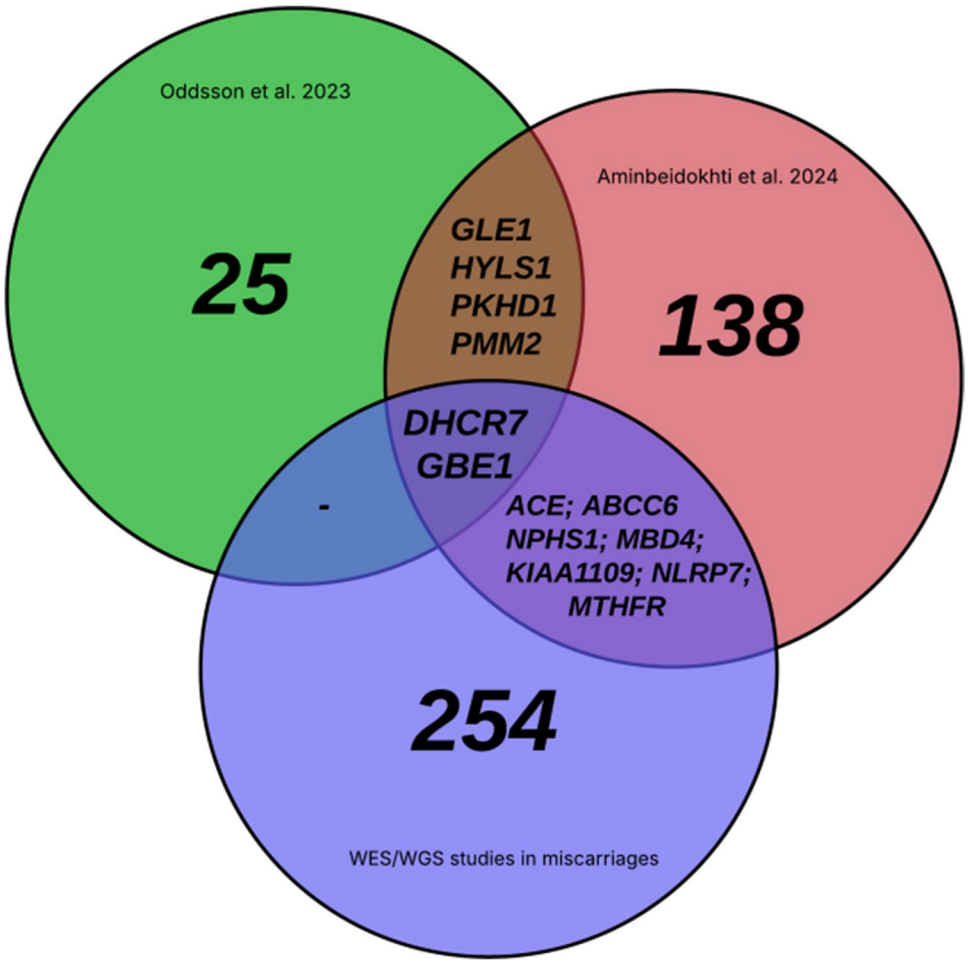

Fig. 2 Overlapping genes with variants are found to be lethal in population studies [91, 92] and in WES/WGS studies of miscarriage

association with embryonic death; genes for which embryonic mortality represents phenotype "expansion" (previously associated with pathology in live-born individuals); genes with no established role in human pathology. It is hard to link such genes with the miscarriage phenotype in cohort studies.

So, genomic studies demonstrated that 3–100% of pregnancy losses have variants of diagnostic value in genes that may contribute to embryo death, supporting the use of WES/WGS as a valuable genetic testing tool in searching for a cause of pregnancy loss. The identification of causative variants provides important information for follow-up parental studies, prenatal counseling, estimation of the recurrence risk, and management of subsequent pregnancies.

Genomics of aneuploidy

Mostly, the search for lethal variants in the genome is carried out in samples of abortions with a normal karyotype, to rule out chromosomal abnormalities as a cause of embryo death. However, variants that affect the occurrence of numerical chromosomal abnormalities in embryos also significantly contribute to the high frequency of pregnancy losses in humans. Chromosomal abnormalities of the embryo are detected in about 50–60% of miscarriages in the first trimester of pregnancy, and the most frequent aberrations are chromosomal aneuploidies (about 75%) and polyploidies (about 10%) [12, 13, 101]. Most trisomies are maternal in origin, with errors occurring during the meiotic division of oocytes. Chromosome segregation errors in oocytes may be sporadic due to maternal age, but there are evidences that some women have a higher rate of aneuploid embryos than average for their age [102, 103]. This echoes data on non-random recurrence of abortus karyotypes in some families with RPL. An increased probability of the same karyotype pattern (recurrent normal or recurrent abnormal) in multiple consecutive abortions was found for RPL patients [104–107]. A large-scale CMA study also revealed repeated cases of loss of embryos with triploid karyotypes [19]. Therefore, the ascertainment of genome variants that affect chromosome segregation in parental meiosis or disturbances in the first mitotic divisions in embryos is of interest for reproductive genetics.

As early as 1997, Delhanty et al. found out that some women produced "chaotic" embryos (with multiple chromosomal abnormalities) more often than others at the same age [108], which suggests that genetic variants in several (some) genes affect chromosome segregation accuracy and predispose women to a higher incidence of aneuploid progeny. A large associative study found no association between genetic variants in women and meiotic aneuploidy [109]. But it was reported that the rs2305957 variant of the *PLK4* gene, the product of which is involved in the regulation of centriole duplication, is associated with an increased risk of mitotic aneuploidy during early embryonic development [109]. Studies of the association of single gene variants with aneuploid pregnancy loss have conflicting results [110]. Single gene variants with an uncertain or no role in aneuploid pregnancy loss included variants in synaptonemal complex protein 3 (*SYCP3*), mitotic polo-like kinase 4 (*PLK4*) and meiotic stromal antigen 3 (*STAG3*) spindle integrity variants, and 5,10-methylenetetrahydrofolate reductase (*MTHFR*) [111]. However, recently published WES studies of women with increased frequencies of aneuploid blastocysts in IVF cycles have identified candidate genes and variants not previously associated with meiotic aneuploidy in the embryo, including genes related to the formation of the cytoskeleton and microtubules, especially a nonsynonymous variant rs2303720 in *CEP120* (centrosomal protein 120) [112]. Variants in genes *TLE6* (c.1397T > C), *IKBKG* (c.169G > A), *BUB1B* (c.1227A > C), *TP73* (c.277G > A), and *AURKC* (c.744C > G), involved in the cell division and chromosome segregation, may be factors predisposing to the occurrence of embryonic aneuploidies [113]. A missense variant in synaptonemal complex central element protein 2 (SYCE2), associated with recombination traits, increases risk of pregnancy loss [114]. In two siblings from consanguineous parents (with poor ovarian response in the female patient with RIF and azoospermia in the male patient), WES identified a novel homozygous splicing variant in Helicase for meiosis 1 (*HFM1*; c.1730-1G > T) that was not reported in public population databases. Embryos of this female harbored chromosomal microduplications of maternal origin [115]. In specific type of pregnancy disturbance, such as recurrent androgenetic hydatidiform mole (OMIM 618431), bi-allelic variants in the *MEI1* gene lead to the elimination of the maternal chromosomes from the oocyte [116]. Thus, WES can be an effective tool for identifying causative variants in patients with an increased risk of embryo karyotype abnormalities.

Machine learning-based classifiers for predicting the embryonic aneuploidy risk in female IVF patients using WES data identified *MCM5*, *FGGY*, and *DDX60L* as potential aneuploidy risk genes [117]. The results of three WES studies of families with multiple cases of triploid abortions up to 12 weeks of pregnancy due to interruption of the maternal second meiotic division are also interesting. In the study of Filges et al. a woman without live birth had 18 consecutive miscarriages in anamnesis; interestingly, the proband's mother also suffered from RPL. Deleterious variants common to the proband and her mother were identified in 47 genes, with priority variants in eight genes whose products are involved in oocyte maturation, oocyte activation, or polar body extrusion (*PLCD4*, *OSBPL5*, *YES1*, *MBD4*, *CSF1R*, *NLRP10*, *CEP250*, and *BNC2*) [29]. In another

study, WES was implemented for two sisters (with a total of 22 abortions) from an Iranian family with consanguineous parents. Due to examination of members of a large pedigree, list of candidate genes was narrowed, with cyclin B3 gene (*CCNB3*) most likely responsible for the phenotype. Both women with RPL were homozygous, and their parents were heterozygous carriers of a new missense variant (p.V1251D) in the *CCNB3* affecting a conservative region in placental mammals [75]. In the study of Liang et al. in the female with recurrent triploid digynic miscarriages were identified candidate variants in two genes: a missense in *EIF4ENIF1* and a stop gain in *HORMAD2* [118]. Thus, in three families with RPL caused by failure to complete the maternal second meiotic division correctly, the candidate genes do not overlap. Possibly, more complex interactions among multiple genes and genetic variants are responsible for higher chromosomal abnormality risk in some patients. Disclosure of the association between maternal (more broadly parental) genetic variants and embryonic aneuploidy risk suggests the potential of using genomic data to predict embryonic aneuploidy risk that is important, for example, in RPL and IVF patients.

Problems and challenges in WES/WGS research of miscarriage

The search for DNA sequence variants leading to embryo loss poses specific challenges, such as:

i. High genetic heterogeneity expected in miscarriage, due to a variety of possible causes of embryonic loss, both from the maternal and the embryonic side, as well as complex interplay between the fetal and maternal genomes and the environment. Due to the genetic heterogeneity of embryonic lethality, the vast majority of variants are not replicated in different studies. So, the accumulation of bulk genome data of dead embryos and their parents is required along with studies of trios and, especially, large pedigrees that make it possible to narrow the number of candidate genes.
ii. Specific genomic landscape. Due to significant influence of extraembryonic tissues on embryo viability, a lot of genetic variants responsible for embryonic mortality could be found in new candidate genes (non-OMIM genes), but it is problematic to link such genes with the miscarriage phenotype in cohort studies and our knowledge about these genes is limited now.
iii. Population-based approaches to a comprehensive genomic assessment of miscarriage are lacked. Most of the information obtained to date is based on studies of individual families or small samples. Because variants in candidate genes identified in small groups or trios are often of indeterminate significance, WES/WGS results, especially rare variants, require replicative studies in larger samples. Interpretation and further study of the identified lethal variants are limited due to the lack of follow-up studies. Moreover, the vast majority of cases of embryonic death does not come to the attention of geneticists at all and are not examined.
iv. Deficiency of databases of variants associated with embryonic lethality. As a result, identification of variants and genes with functional or pathogenic value is often a notably challenging task, and various bioinformatics strategies and methods for prioritization of genetic variants are used. No long-established standards have yet been developed for assessing the pathogenic significance of variants in human miscarriage. As a result, the number of variants can range from several dozen for the specific case [46] to one variant per dozen cases [56].
v. Adequate samples obtaining. Missed abortion samples may undergo maceration, resulting in increased degradation of the genomic DNA. As a result, DNA fragments have smaller sizes and unequal coverage, which can cause the registration of false-positive SNV. For example, low-quality libraries due to DNA degradation of two samples may have contributed to the high number of de novo SNVs observed in these abortions in the study [71]. In addition, there is the possibility of contamination of embryonic samples with maternal tissue.
vi. One of the obvious problems in studies of the genetic etiology of miscarriage is the lack of detailed phenotypic description of early miscarriages. Identification of morphological features not only by ultrasound examination, but also using the transcervical embryoscopy, which allows assessing the morphology of the intact POC [105, 119], in combination with genomic studies will provide the possibility to study the genotype–phenotype correlation in miscarriage.
vii. High degree of somatic mosaicism in placental tissues. A high nucleotide substitution burden was found within bulk placental samples, and placenta is the only healthy human tissue studied so far that has contained clones that are detectable by whole-genome sequencing [120]. In addition, developmental bottlenecks genetically isolate placental tissues from lineages derived from the inner cell mass. These findings revealed extensive mutagenesis in placental tissues and suggest that mosaicism is a typical feature of early development [120, 121].

Conclusion

A feature of the human miscarriage is the predominance of the first trimester pregnancy loss with the significant influence of extraembryonic tissues on embryo viability, in comparison with the tissues and organs of the embryo itself. Currently, all available databases for genotype–phenotype correlations in humans are focused on the pathology of organs in the postnatal period. Creating of special databases for cases of embryonic death, representing the specifics of this group, is of current interest. Comprehensive databases are needed to accumulate the information from sequencing studies and additional tests, including transcriptomic analysis, functional studies, and animal experiments. Such systematization will improve our understanding of the miscarriage causes (https://plovdb.ott.ru/).

Interpretation of sequencing results will be more convincing if DNA samples from abortion and its parents are available, because the family analysis makes it possible to distinguish between inherited and de novo variants. Some genomic studies reveal a predominance of de novo variants in embryos/fetuses [70, 71], and large pedigrees also make it possible to more accurately classify the significance of detected gene variants. RPL families are more likely to be carriers of unfavorable reproductive variants compared with families with sporadic losses.

It is necessary to study the functional significance of the detected genetic variants in appropriate models, since it may differ in cell cultures or in other species, which leads to uncertainty in assessing their pathogenic significance. Additional genetic or experimental data, including transcriptome analysis, gene-specific studies in trophoblast or endometrial cell cultures, and animal models, are needed to prove a causative significance of the identified variant/gene for miscarriage.

In addition, genomic studies of embryos with karyotype abnormalities are important as a new tool for identifying genes and variants that may be responsible for the generation of chromosomal disorders, such as trisomies, monosomy X, triploidy, and tetraploidy, that are typical for human spontaneous abortions as well as complete hydatidiform mole with a high risk of malignancy. Now, the exact genetic causes of aneuploid egg or embryo production remain unclear, making it difficult to diagnose infertility based on individual genetic variants in mother's genome.

Future efforts should be aimed at increasing the number of sequenced cohorts with embryonic death, especially including trios (families) with RPL, with a more detailed characterization of the phenotypic features of pregnancy pathology and the obstetric history of the couples. The accumulation of data about the gene sequence in embryonic death allows identifying genes important in the early human development and distinguishes variants that disrupt the functions of such genes resulting to miscarriage. Knowledge of specific genes that contribute to pregnancy loss could also be valued in designing a diagnostic sequencing panel for patients with recurrent pregnancy loss. Preconceptional screening for such genes can identify at-risk couples for pregnancy losses, allowing preimplantation genetic testing. Even in cases where medical care is not available, the information itself can be important for clinicians and patients in understanding the cause of the disease, making a more accurate prognosis, and assessing recurrence risk.

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Data availability All data are available in supplementary files.

Declarations

Ethical approval Not applicable.

Conflict of interest The authors declare no competing interests.

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