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Bioinformatics Applications in Recurrent Pregnancy Loss

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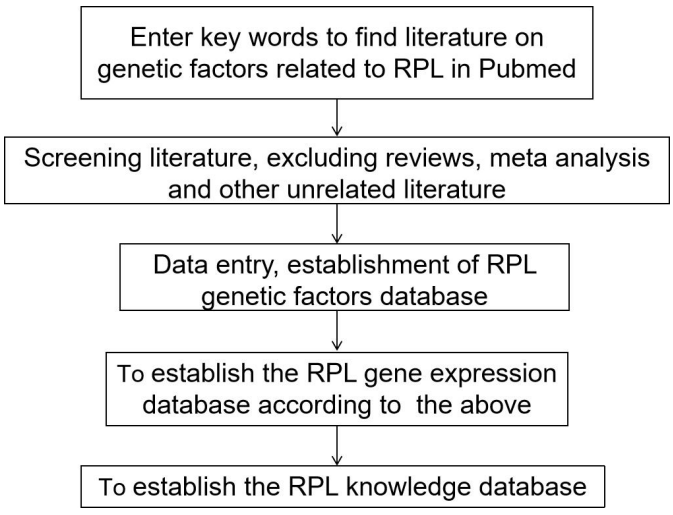
Graphical Abstract



Abstract.

Although accumulating evidence shows that endocrine, thrombotic, immune and other factors related to recurrent pregnancy loss, studies have shown that these factors are ultimately contributed to genetic variation. Therefore, taking a bioinformatics approach to explore the correlation and difference between these genetic variations and their expressions is helpful to understand the underlying genetic mechanism of recurrent pregnancy loss and to efficiently avoid the physical and psychological harm caused by abortion to women.

Recurrent pregnancy loss (RPL) usually means two or more pregnancy failures occured within 20 weeks of conception, with an incidence as great as 3% to 5% of pregnancies [1]. RPL is a complex disease with diverse causes, including heredity, age, antiphospholipid syndrome, uterine anomalies, thrombosis, hormone or metabolic disorders, infection, autoimmunity, sperm quality, lifestyle, and mental, psychological, and environmental factors [2, 3], which brings a substantial adverse impact on

society and female health care. Therefore, understanding the gene regulation network of RPL is beneficial to clarify the etiology of recurrent abortion and possible to prevent another miscarriage through some intervention, which will have great clinical significance and social benefits.

Genetic abnormalities are the main factor of RPL[4]. The correlation between chromosomal abnormalities and abortion has been clear and the relative genetic risk is easy to predict. For example, an abnormal karyotype in either partner, especially featuring a translocation and/or an inversion, is considered to be a cause of RPL, due to unbalanced chromosomal segregation in meiosis, which cause significant chromosomal imbalances (i.e., disomies and nullisomies) in their gametes with subsequent partial aneuploidies in the conceptuses [5, 6]. In theory, the incidence of normal, carrier and imbalances in the offspring of reciprocal translocation, Roche translocation and inversion were 1/18-1/18-16/18, 1/6-1/6-4/6 and 1/4-1/4-2/4, respectively, which are calculated according to the principle of chromosome separation and recombination. With the development of preimplantation genetic test (PGT) technology that derived from in-vitro fertilization (IVF), it is found that the actual genetic risk is quite different from theoretical calculation, which is not only related to the sex of the carrier, but also the location of the breakpoint and the chromosome involved[7-9]. A study by Xie etc. showed that the ratio of euploid and translocation balance embryos in reciprocal translocation and Robert translocation were 27.8% and 44%, the rest of all were aneuploid or translocation imbalance embryos [10]. Wang reported that 104 embryos from 11 Roche translocation carriers were detected, including normal, translocation carriers and unbalanced chromosome embryos were 22%, 19%, 59% [11].

Apart from chromosomal factors, abortion is also related to endocrine, immune, thrombotic, male sperm and other factors. With the development and clinical application of gene detection technology, current studies showed that these so-called clinical factors may eventually be attributed to genetic abnormalities. Examples of SNPs and copy number variants (CNVs) that may contribute to a genetic susceptibility to miscarriage include variances in the following genes: AR, DNMT3, FOXP3, CGB5, NLRP7, TIMP2 and CTNNA3[12-18]. A recent systematic review of 428 case-control studies from 1990 to 2015 evaluated 472 variants in 187 genes [19]. Meta-analysis could only be performed for 36 variants in 16 genes, because the other studies had never been replicated. The investigators reported modest associations between RPL and 21 variants in genes (odds ratio [OR] 0.51–2.37) involved in the immune response (IFNG, IL10, KIR2DS2, KIR2DS3, KIR2DS4, MBL, TNF), coagulation (F2, F5, PAI-1, PROZ), metabolism (GSTT1, MTHFR), and angiogenesis (NOS3, VEGFA). In addition, mutations in the thrombophilia genes, including MTHFR, F2, and F5, and deficiencies in protein C, protein S, and antithrombin III, may also increase the risk of second- or third-trimester loss[20-23].

Epigenetic modifications, including DNA methylation, noncoding RNA, genomic imprinting, and histone modification, refer to the heritable changes in gene functions without changing the genetic genes. Abnormal DNA methylation was found in the decidual chorionic villi of RPL with normal karyotype, especially at the loci of the imprinting genes [24, 25]. Aberrant microRNAs (miRNAs), which are endogenous small noncoding RNAs and ~22 nucleotides, were found in unexplained RPL [26]. Over the past few years, some studies have verified a clear correlation between lncRNAs and

placental development, such as the lncRNAs HOTAIR, HOXA11-AS, and MEG3 and MALAT1, and these lncRNAs appear to be involved in some pregnancy pathologies[27-29].

Above all, genetic abnormalities or variants and related gene expression abnormalities play an important role in RPL. Understanding the correlation between the expression differences of these changes in different populations, different tissues (peripheral blood, amniotic fluid, villi, embryo, etc.) and abortion, is of great significance for clinical abortion counseling and genetic counseling, as well as for the exploration of potential factors of unexplained RPL and the development of beneficial interventions, so as to reduce or avoid abortion risks, improve women's survival quality.

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