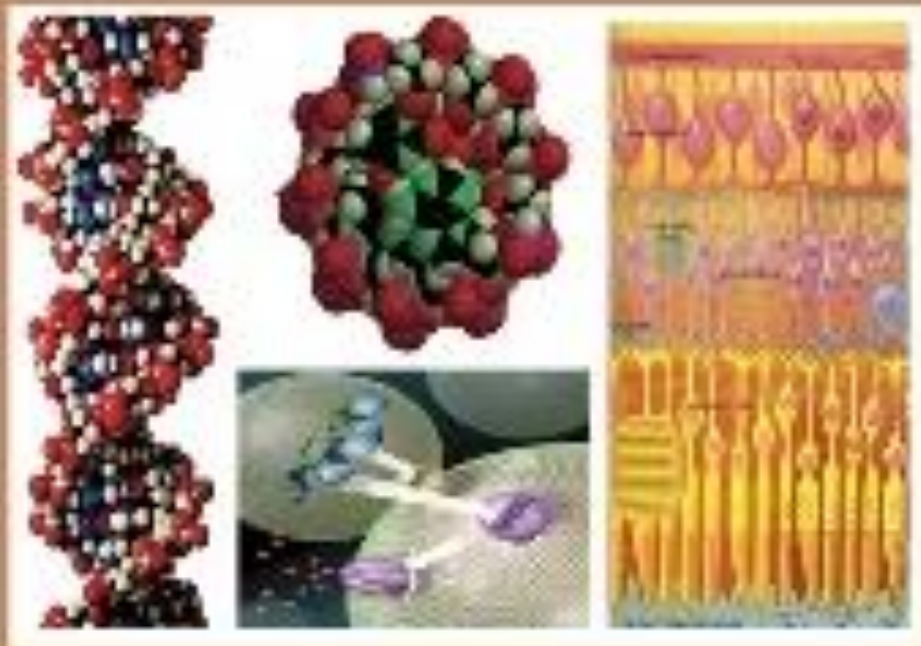




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Correlation Between Long non-coding RNA SOX2OT rs9839776 C>T Polymorphism and Unexplained Recurrent Miscarriages

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ABSTRACT

Recurrent miscarriage (RM) is a severe pregnancy complication that results in the loss of two or more spontaneous pregnancies. RM has several complex reasons. Advances in genetics, immunology, and cell biology have strongly connected non-coding RNAs (ncRNAs) to recurrent miscarriages. NcRNAs regulate placental trophoblast cell processes, which affect trophoblast development, migration, and invagination; they also have a role in breast and ovarian cancer. As a result, their abnormal expression may contribute to the progression of RM. Several investigations have found a connection between RM and genetic polymorphisms that regulate cell migration. Variations in the long non-coding RNA (lncRNA) SOX2OT gene have been associated with a variety of cancer-related illnesses, particularly colorectal cancer, breast cancer, and cancer of the digestive tract. According to a recent study, the long non-coding SOX2OT rs9839776 CT raises the risk of RM. In this review, we explain the existing evidence supporting a relationship between the LncRNA SOX2OT rs9839776 polymorphisms and recurrent miscarriages.

INTRODUCTION

Recurrent miscarriage is the diagnosis for women who experience pregnancy loss twice or more before 20 weeks of gestation with the same male partner (Diejomaoh, 2015)(Garrido-Gimenez & Alijotas-Reig, 2015)(Ngoc *et al.*, 2022). Recurrent miscarriage can be caused by a variety of causes, including genetics, immunology disorders, endocrine abnormalities, unhealthy lifestyles, and reproductive organ anomalies. (Pereza *et al.*, 2017)(Yousefian *et al.*, 2022).

Yet, in around half of patients, their cause is still unidentified, and these people are deemed to have unknown RM. (URM) (Sugiura-Ogasawara *et al.*, 2014) (Gan *et al.*, 2022). Studies have discovered a connection between recurrent miscarriage and the migration function of trophoblasts, despite the fact that the etiology is frequently unknown(F. J. Tian *et al.*, 2018)(J. Wang *et al.*, 2021). Additionally, research indicates that polymorphisms in many genes, including those that control cell migration like IGF-2 and PAI-1, are linked to recurrent miscarriage(Shi *et al.*, 2017)(Mou *et al.*, 2022). As a result, a study into the relationships between genetic polymorphisms that govern the migration of cells, invading cells, and recurrent abortions may help us better understand the etiology of recurrent miscarriage.

The non-coding RNAs (ncRNAs) are RNAs that lack the ability to encode protein molecules. ncRNAs include circular RNAs, long non-coding RNAs, and microRNAs. Even though they don't code for proteins, ncRNAs play crucial roles in biology at the RNA level. For instance, by taking part in chromosomal remodelling, gene transcription, and post-transcriptional modification, they can control a number of crucial life processes (L. Zhu *et al.*, 2021).

Functional Identification of Long Non-Coding RNAs:

Transcribed RNA molecules, also known as long noncoding RNAs (lncRNAs), can be as long as 200 bases or 100 kb. lncRNAs cannot code for proteins since they lack an open reading frame (Bertone *et al.*, 2004)(Amirinejad *et al.*, 2020). lncRNAs play a variety of important biological activities, influencing the synthesis, splicing and translation of specific RNA, DNA, and protein components by binding directly to them. Furthermore, lncRNAs can recruit proteins as well as RNA from either the nucleus or the cytoplasm to form functional complexes. (Quinn & Chang, 2016)(Sufianov *et al.*, 2023). Numerous cellular and carcinogenesis processes are mediated by lncRNAs, including transcriptional regulators, tumorigenesis, cell migration, and invasion (Beermann *et al.*, 2016)(Yangjun Wu *et al.*, 2019)(Loganathan & Doss C, 2023). According to the lncRNA diseases database, Seventeen long non-coding including BCAR4, MALAT1, PVT1 and GAS5, have been revealed to have key roles in the tumor biology of breast cancer and several additional diseases including breast cancer, cardiovascular disease, and recurrent miscarriages (G. Chen *et al.*, 2013)(Bao *et al.*, 2019)(S. Li *et al.*, 2023)(R. Peng *et al.*, 2018)(Che, Yang, *et al.*, 2019)(L. Cao *et al.*, 2022). Modern genomic techniques have proven that lncRNA SNPs (single-nucleotide polymorphisms) are related to a variety of disorders, particularly malignancies, cardiometabolic disorders, and Alzheimer's condition. (Dechamethakun & Muramatsu,

2017)(Y. Tian *et al.*, 2022). The impact of SNPs on operational lncRNAs is attracting considerable attention because of the possibility of influencing the risks of carcinomas, particularly breast cancer. (Romero-Cordoba *et al.*, 2014)(Tang *et al.*, 2017). In addition, a prior study discovered that several lncRNA gene variants linked to breast cancer susceptibility are also linked to vulnerability to recurrent miscarriage (Che, Huang, *et al.*, 2019a).

Growing evidence suggests that lncRNAs play a role during the onset as well as the progression of recurrent miscarriages by controlling the migration and invasion of the trophoblast cells. (Qin *et al.*, 2019)(Yan Zhang *et al.*, 2017)(Yanan Zhang & Wang, 2022). Additionally, some research has discovered that lncRNA polymorphisms have an impact on how lncRNAs are expressed (Xue *et al.*, 2018)(P. Zhang & Sha, 2023). Several lncRNA polymorphisms, like CCAT2 and MALAT1, have been linked to an increased risk of recurrent miscarriages. (Che, Yang, *et al.*, 2019) (Yanan Zhang & Wang, 2022).

SOX2OT, A Long Non-Coding RNA, and Related Diseases:

A genomic study revealed that the SOX2 gene was located within the intron of another gene, termed SOX2-OT. (Fantes *et al.*, 2003a) (Ye & Fan, 2012). The scientists discovered that SOX2-OT comprises a minimum of five exons (latest investigations estimate it possibly includes hundreds of exons) and produces an mRNA-like transcript on the same strand as SOX2. (Fantes *et al.*, 2003b) (Stevanovic *et al.*, 2023). The corresponding transcript is evolutionarily preserved, with the human SOX2-OT transcripts accessible through mouse expression sequence tags sharing 80% nucleotide identity. (Fantes *et al.*, 2003b). Furthermore, the genomic region encompassing the SOX2-OT transcription unit (about 40 kb) is highly conserved across vertebrates (Fantes *et al.*, 2003b)(Stevanovic *et al.*, 2023). Currently, there are only a few investigations on SOX2OT genomic

mutations. (Boraska *et al.*, 2014). A recent study has found that the lncRNA SOX2OT serves as a malignant molecule in the development and progression of various cancers of the human body, including intestinal cancer, carcinoma of the colon, and breast cancer. It may impact malignant cell motility and penetration (L. Han *et al.*, 2018) (Qu & Cao, 2018)(Sun *et al.*, 2018)(Feng *et al.*, 2021)(K. Zhang *et al.*, 2018)(P.-Y. Li *et al.*, 2020). The researcher Tang *et al.* identified that SOX2OT polymorphisms (rs9839776 C>T) have been linked to breast cancer risk because of their effect on SOX2OT expression. (Xiuwu Tang, Yan Gao, Linxiang Yu, Yan Lu, Guanglin Zhou, Lifang Cheng, Kai Sun, Baoli Zhu, Ming Xu, 2017). A number of investigations have shown that certain breast cancer risk-correlated lncRNA polymorphisms have been associated with repeated miscarriages (Qiao *et al.*, 2018)(M. Zhang *et al.*, 2017). According to the findings, SOX2OT gene variants could be associated with recurrent miscarriages (Che, Huang, *et al.*, 2019a). The rs9839776 intron variation within the SOX2OT gene is the only SNP discovered in SOX2OT that showed statistical significance for SOX2OT expression during a genome-wide association study (Boraska *et al.*, 2014). A study in the Chinese community discovered that an SNP (rs9839776 C>T) in the SOX2-OT gene's intronic region is associated with a higher risk of recurrent miscarriages (CT vs. CC: adjusted OR = 1:357, 95%CI = 1:065 1:728, p = 0:0134) (Fang *et al.*, 2019). The investigation in the Turkish Azeri community, however, showed no significant connection between the SOX2OT rs9389776 variant with RM (Gene *et al.*, 2022).

Polymorphism has a significant impact on lncRNA expression, which can be

the root cause of serious pathogenic mechanisms (Xue *et al.*, 2018)(Wei *et al.*, 2018). Further research on the link between lncRNA gene polymorphisms and RM in different groups could improve knowledge of the disease's pathogenesis.

SOX2OT Regulates sox2 Expression:

SRY-box transcriptional factor 2 (SOX2) overlaps transcripts (SOX2-OT) and is a lncRNA that is transcribed in the same direction as *Sox2*. The SOX2-OT gene is found on human chromosome 3q26.33, in a highly conserved area of approximately 750 kb in humans and other species (Shahryari *et al.*, 2015)(Yi *et al.*, 2022). The SOX2-OT gene encodes the crucial controller of stem cell development in embryos pluripotency, the SOX2 gene, within its intronic region. Both SOX2-OT and SOX2 are transcribed in the same way (Amaral *et al.*, 2009) (Messemaker *et al.*, 2018). lncRNAs can alter the expression of neighboring overlapping genes in several ways (Marchese *et al.*, 2017). A number of studies have investigated the regulatory interaction between SOX2-OT along with SOX2 (Figure 1). The majority of cancer studies involving SOX2-OT and SOX2 discovered that elevation of SOX2-OT boosts SOX2 expression in cancer cells (Fig. 1); however, one study indicated that SOX2-OT overexpression had no effect on SOX2 expression (Yuanyuan Wu *et al.*, 2018)(Zhan *et al.*, 2020). One study determined that whenever SOX2-OT becomes overexpressed in adenocarcinoma of the pancreatic duct cells, the luciferase activity of the SOX2 promoter increases significantly, demonstrating that SOX2-OT is an activator of transcription of the SOX2 gene (J. J. Zhang *et al.*, 2017)(Y. Wang *et al.*, 2021).

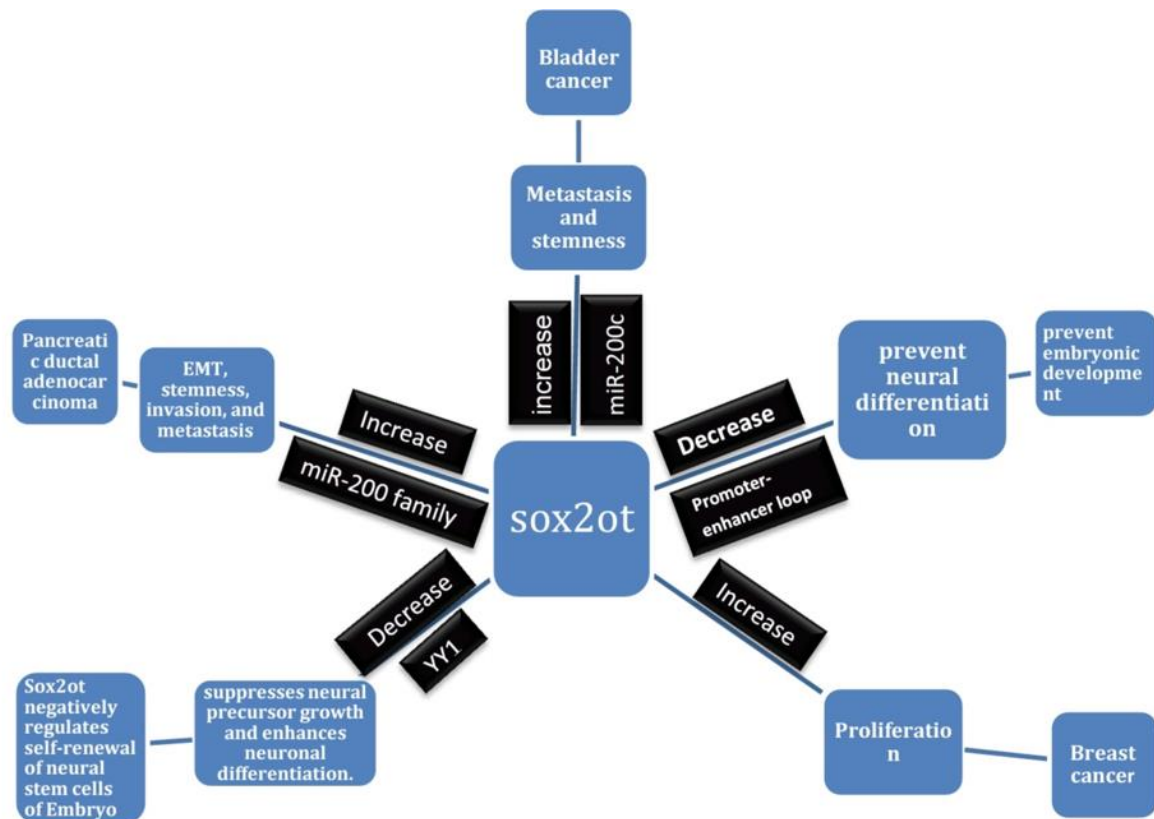


Fig. 1: SOX2-OT regulates SOX2 expression in cancer and brain stem cells. It upregulates SOX2 expression in cancer cells by serving as a miRNA sponge. One study found that overexpressing SOX2-OT boosts the luciferase activity of the SOX2 promoter, indicating that it is a transcriptional activator. According to studies, SOX2-OT interacts with YY1, a transcriptional regulator, and reduces SOX2 expression in neural stem cells. It also weakens the chromatin promoter-enhancer loop, preventing SOX2 transcription in neural stem cells. The regulation of SOX2 expression in tumor cells takes a different approach (Zhan *et al.*, 2020) (Messemaker *et al.*, 2018) (Z. Li *et al.*, 2018) (Knauss *et al.*, 2018) (P. Y. Li *et al.*, 2020).

Note: EMT: epithelial-mesenchymal transition; YY1: Yin Yang-1.

The Effect of ncRNAs on Placental Trophoblast Function:

The placenta is a temporary organ that develops during pregnancy. It attaches to the lining of the mother's uterus and plays a vital part in the development of the embryo by transferring oxygen, vitamins and minerals from the mother to the embryo and removing waste from metabolism, and ammonia from the baby's blood. The placenta also possesses biological activities including hormone secretion and immunological safeguarding, that are closely related to trophoblast growth cells (Baines & Renaud, 2017) (Jeyarajah *et al.*, 2022) (Chatuphonprasert *et al.*, 2018) (Martínez-Razo *et al.*, 2021). The trophoblast is cells forming the outer layer of

a blastocyst with fertilization. Trophoblasts are formed after four days of fertilization, the trophoblast separates from the inner cell mass as a blastocyst (Knöfler *et al.*, 2019) (Dietrich *et al.*, 2022).

After blastulation, the connection between trophoblast, endometrial stroma and uterine lumen epithelium results in implantation, then the first stage of placental development begins (Ali *et al.*, 2020). Describes the effect of LncRNA on the performance of placental trophoblast by regulating trophoblast development, invasion, migration, angiogenesis, cellular death and the ability of these effects to lead to recurrent miscarriage Table 1.

Table 1: The link between LncRNA and numerous malignancies, as well as its impact on trophoblast function, which may lead to RM.

LncRNA	Expression in RM	Effect on trophoblast	Other associated diseases	Reference
HOTAIR	upregulation	Inhibits trophoblast proliferation, migration and invasion	Papillary thyroid carcinoma, epithelial ovarian cancer, primary ovarian insufficiency, recurrent implantation failure and colorectal carcinoma.	(Woo Park et al., 2022) (Zhao et al., 2020) (Cho et al., 2021) (Jung et al., 2016) (Kim et al., 2020) (H. Zhu et al., 2016)
NEAT1	upregulation	Inhibits trophoblast proliferation, invasion and migration	Promote human cell proliferation and migration in cancers such as breast and cervical cancer.	(Xiaodan Liu et al., 2022) (Xiong et al., 2019) (Li Wang & Zhu, 2018) (Teng et al., 2020)
H19	downregulation	Regulation of angiogenesis of extravillous trophoblasts	It regulates breast cancer, colorectal cancer, and hepatocellular carcinoma growth, invasion, and metastasis.	(Zeng et al., 2020) (Bai & Tang, 2020) (F. Peng et al., 2017) (Ding et al., 2018) (Rojas et al., 2022)
TUG1	Not detected yet	Inhibits apoptosis and Enhance trophoblast proliferation, invasion and angiogenesis,	Upregulated ovarian cancer	(Yangjun Wu et al., 2019) (Q. Li et al., 2022) (Kuang et al., 2016)
PVT1	Downregulation	Promote proliferation, migration, invasion and apoptosis	Overexpressed in many human cancers, for example, cervical and prostate cancer	(Shen et al., 2017)(H. Liu et al., 2016)(Yang et al., 2020a)
MALAT1	Downregularion	Enhance angiogenesis and regulate proliferation, migration, invasion and apoptosis	Detected in hepatocellular carcinoma lung and pancreatic cancer	(Y. Wang et al., 2019)(Y. Wang et al., 2018)(Xiaoli Liu et al., 2020)(M. Huang et al., 2019)
SNHG7-1	Downregulation	Promote proliferation, migration, invasion and apoptosis	Promote proliferation of nasopharyngeal carcinoma, and enhance bladder cancer and breast cancer.	(Hu et al., 2020) (Zhan et al., 2020)(Z. H. Li et al., 2020)(Xiang et al., 2019)

LncRNA and Placental Angiogenesis:

Angiogenesis refers to the creation of new blood vessels that assist the transportation of nutrients as well as oxygen from the mother to the embryo, supporting the creation and upkeep of the first trimester (X. Chen *et al.*, 2017). Many studies have demonstrated the relevance of vascular problems in recurrent miscarriages (Vidyadhari et al., 2019). However, abnormal angiogenesis leads to serious reproductive problems like RM (X. Chen *et al.*, 2017). Despite the lack of concrete proof of ncRNAs participation in placental venous and spiral arterial transformation, numerous

investigators have proposed that ncRNAs may influence placental angiogenesis (Zeng *et al.*, 2020). For example, researchers showed that the lncRNA H19, which is highly expressed in early pregnancy human trophoblasts, can control the angiogenic potential of extravillous trophoblasts via the H19/miR-106a-5p/VEGFA pathway (C. Li *et al.*, 2019).

Long Non-Coding RNA and Recurrent Miscarriage:

In recent years, research on lncRNAs has grown in RM. Previously, researchers discovered many lncRNA subgroups that express differently in the villus

of RM patients versus healthy pregnant women, indicating that lncRNAs have a role in the physiology and pathophysiology of RM. These findings revealed that lncRNA may be involved in the occurrence of RM by several mechanisms such as inflammation, apoptosis, or extracellular matrix-receptor interaction.

lncRNAs may regulate the transcription and expression of downstream genes by targeting miRNAs, hence increasing disease development.

1) Directly influence target mRNA expression.

2) Use miRNAs to regulate the synthesis and expression of descending mRNAs of interest (M. Liu *et al.*, 2021)(Leilei Wang *et al.*, 2017)(T. Li *et al.*, 2020).

1-Directly Influence Target mRNA Expression:

Recent research has discovered that lncRNA H19 has a significant expression in embryonic development and plays a definite function in carcinogenesis (Kallen *et al.*, 2013)(L. Yan *et al.*, 2015). According to one study, H19 with GPX4 documented a decrease in the RM group compared to the control group. As a result, H19 can reduce GPX4 mRNA expression, which may result in RM occurrence (Tarangelo *et al.*, 2014). Other lncRNA examples in this pathway include HOTAIR, PVT1, and MALAT1.

2-Target miRNAs to Control the Synthesis and Expression of Subsequent Target mRNA:

PVT1 overexpression suppresses miR-424, reducing the synthesis of miR-424's targeting gene, eIF5A, as well as proliferating and motility (Yang *et al.*, 2020b). (Xiang *et al.*, 2019)discovered that SNHG7-1, a particular lncRNA, influenced trophoblast cell proliferation and invasion while also enhancing the occurrence of RM via the Wnt/-catenin signaling pathway, which intended to bind to miR-34a, thus raising the initiation of RM.

Genetic Susceptibility to Recurrent Miscarriage:

Research has shown that genes associated with susceptibility play a

significant role in the etiology of recurrent abortion (Pereza *et al.*, 2017). Recent study on repeated abortion has identified several susceptibility genes, including MMP2, MMP9, IL-10, TNF- α , CTLA4, FOXP3, and THBD, as linked to recurrent miscarriage (Li Li *et al.*, 2018)(Y. Yan *et al.*, 2021)(Vaziri Nezamdoust *et al.*, 2023)(Dirsipam *et al.*, 2021)(Quintero-Ronderos *et al.*, 2017)(Rahmani *et al.*, 2017)(Bahadori *et al.*, 2014)(Hou *et al.*, 2016). Furthermore, research indicates that certain genes that govern cell migration are connected with vulnerability to recurrent miscarriage (X. Wang *et al.*, 2023)(Hashemi *et al.*, 2018). There are some studies on the number of lncRNA gene polymorphisms associated with various tumors and abnormal expression in many human cancers that have revealed no significant link between their polymorphism and the likelihood of recurrent miscarriage, such as TINCR gene rs2288947 (Y. Liu *et al.*, 2018)(F. Tian *et al.*, 2017)(Xu *et al.*, 2023)(Icduygu *et al.*, 2022)(W. Huang, Zhou, Pi, *et al.*, 2019), and TOX3 gene that is linked with numerous disorders such as cancer of the pulmonary system, ovarian cancer, breast cancer and polystatic ovarian syndrome (Latif *et al.*, 2010)(W. M. Cao *et al.*, 2016)(X. Zhang *et al.*, 2013)(Lin Li *et al.*, 2018)(Gao *et al.*, 2018)(L. Chen *et al.*, 2017)(Bruni *et al.*, 2022). Some studies showed the rs3803662 C>T polymorphism is substantially associated with a higher likelihood of breast cancer (Q. Wang *et al.*, 2016) (Solis-Coronado *et al.*, 2022). The researchers supposed that TOX3 mutation is related to RM. Similar to the genetic polymorphism of lncRNA CCAT2, which is related to both breast cancer and RM(Che, Huang, *et al.*, 2019a), but they did not find any significant correlation with TOX3 rs3803662 polymorphism and repeated miscarriages(W. Huang, Zhou, Li, *et al.*, 2019).

There are studies showed that the lncRNA CCAT2 rs6983267 polymorphism is significantly correlated with an increased possibility of ovarian cancer(J. Han *et al.*, 2017)(Ikoma *et al.*, 2021) and an increased

risk of prostate cancer (M. Zhu *et al.*, 2017). Further research discovered that rs6983267 had a slight connection with breast cancer (He *et al.*, 2017). However, case-control research indicated that this variation contributes to a lower incidence of RM. Thus, it has been proposed that the lncRNA CCAT2 rs6983267 G variant reduces susceptibility to RM, although the rs6983267 G allele plays opposing roles in various disorders (Che, Huang, *et al.*, 2019b).

Conclusion

This review focuses on the most recent advances in long non-coding RNA research and the function and possible molecular pathways of lncRNAs associated with the onset and progression of RM. RM is one of the most important clinical concerns in female reproductive health, having serious consequences for family well-being. As a result, medical research should focus on methods to increase the pregnancy effectiveness rate for women who have had several miscarriages. Extensive research has uncovered new substances, such as immunological variables, have revolutionized the diagnosis and therapy of this disorder. The most recent studies have helped to clarify the role and function of ncRNAs in RM. These studies provided fairly little information, and many of the functions of lncRNAs remain unexplored. ncRNAs expression patterns exceed mRNA expression profiles for discriminating between healthy and sick tissues. As a result, searching for differently expressed ncRNAs in RM will not only provide us with an improved knowledge of the etiology of unexplained RM but also help us identify certain ncRNAs as potential indicators of RM, thereby increasing disease prevention and treatment. Thus, we urge that researchers do larger population studies to demonstrate the therapeutic utility of ncRNAs in identifying and treating early pregnancy conditions such as RM.

Declarations:

Ethical Approval: It is not applicable.

Conflict of interests: The authors declare no conflict of interest.

Authors Contributions: I hereby verify that

all authors mentioned on the title page have made substantial contributions to the conception and design of the study, have thoroughly reviewed the manuscript, confirm the accuracy and authenticity of the data and its interpretation, and consent to its submission.

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