NEAR EAST UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF MEDICAL BIOLOGY AND GENETICS

LNCRNA REGULATION IN HUMAN OOCYTES OBTAINED FROM PATIENTS WITH POLYCYSTIC OVARIES

M.Sc THESIS

Warda RAI

Nicosia
June, 2022

WARDA RAI LNCRNA REGULATION IN HUMAN OOCYTES OBTAINED FROM PATIENTS WITH POLYCYSTIC OVARIES MASTER THESIS 2022

NEAR EAST UNITVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF MEDICAL BIOLOGY AND GENETICS

LNCRNA REGULATION IN HUMAN OOCYTES OBTAINED FROM PATIENTS WITH POLYCYSTIC OVARIES

MSc THESIS

Warda RAI

Supervisor
Prof. Pinar TULAY

Nicosia
June, 2022

Approval

We certify that we have read the thesis submitted by Warda Rai titled **"LncRNA regulation in human oocytes obtained from patients with polycystic ovaries"** and that, in our combined opinion, it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

Examining Committee	Name-Surname	Signature
Head of the Committee:	Prof. Rasime Kalkan	…..…..……
Committee Member*:	Assist. Prof. Özel Yürüker	…..…..……
Supervisor:	Prof. Pınar Tulay	…..…..……

Approved by the Head of the Department

27/06/2022

Prof. Pınar Tulay
Head of Department

Approved by the Institute of Graduate Studies

…../…../20…

Prof. Dr. Kemal Hüsnü Can Başer
Head of the Institute

Declaration

I hereby declare that all information, documents, analysis, and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of the Institute of Graduate Studies, Near East University. I also declare that, as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Warda Rai

27/06/2022

Acknowledgments

First of all, I would like to thank Allah Almighty and my family for the support and trust they have given me during the completion of my thesis.

I would like to thank everyone who dedicates themselves to science for the scientific data and technological opportunities they have provided so far to complete my thesis.

I would also like to express my endless gratitude to Assoc Prof Dr. Pinar Tulay and Hakan Aytaçoğlu for guiding me throughout this process and providing assistance at every stage of my thesis. I would like to state that it would be very difficult to complete my thesis without them, and I would not be able to contribute to science without the knowledge they provided.

Finally, I would like to express my gratitude to all my professors in the faculty of Medical Biology and Genetics, who made me love science, and to everyone who shared their knowledge with me.

Warda Rai

Abstract

LNCRNAS REGULATIONS IN HUMAN OOCYTES OBTAINED FROM PATIENTS WITH POLYCYSTIC OVARIES

Warda Rai

MSc, Department of Medical Biology and Genetics

June, 2022, 54 pages

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder which affects females of reproductive age. It is a condition that often results in the production of cysts in the ovaries leading to problems in ovulation and infertility. PCOS also causes excess facial hair, diabetes, obesity, hyperandrogenism, acne and insulin resistance. Hence it is a syndrome that has multiple conditions which cause several adversities in a patient's life. PCOS affects about 4% to 20% of females at reproductive age and is the leading infertility cause. According to previous studies, there has been upregulation in lncRNA gene expression in PCOS patients in different types of samples. In this study, experiments were conducted to find out the selected lncRNA regulation patterns in human meiosis II stage oocytes, which were obtained from patients suffering from polycystic ovaries (PCO) and women without PCO (control group).

Materials and methods: Human oocytes were obtained from *in vitro* fertilization (IVF) patients at the Near East University Hospital by an expert embryologist. Two groups were formed. The first group involved oocytes from patients with PCO, and the second group consisted of oocytes from patients with no PCO (control group). In total, 13 samples were collected, seven from PCO patients and six from the control group, respectively. RNAs from these samples were extracted, and then cDNAs were manufactured using these extracted RNAs. The expression data of lncRNAs were obtained by using real-time polymerase chain reaction (PCR). The results were analyzed by statistical methods using GraphPad prism software.

Result: The experiment was conducted on a total of 13 samples, out of which seven were attained from PCO patients, and the remaining six were acquired from non-PCO patients. The values attained after statistical methods suggested that expression patterns of *MALAT1*, *AOC4P*, and *NEAT1* in two groups were not statistically significant. This implies that these selected lncRNAs (*MALAT1*, *AOC4P*, and *NEAT1*) may not have a role in the development of polycystic ovaries in human oocytes.

Conclusions and recommendations: *MALAT1*, *AOC4P*, and *NEAT1* were not statistically significant in human oocytes of PCO patients. However, the sample size in this study is very small, so further studies should be designed with a larger sample size to attain even more accurate findings. Further studies will be conducted investigating other non-coding RNAs and lncRNAs which could potentially be affecting PCOS patients adversely.

***Keywords**:* PCOS, lncRNAs, gene regulation

Table of Contents

CHAPTER III

Materials and Methods

CHAPTER IV

CHAPTER V

CHAPTER VI

Conclusion and Recommendations

List of Tables

List of Figures

List of Abbreviations

MNE: Ministry of National Education

***ACTB*:** Actin Bita

AGEs: Advanced Glycation End products

ANOVA: Analysis Of Variance

***AOC4P*:** Amine Oxidase Copper Containing 4, Pseudogene

cDNA: complementary deoxyribonucleic acid

CRC: Colorectal cancer

CTBP1-AS: C-Terminal binding protein 1 antisense

DNA: Deoxyribonucleic Acid

FSH: Follicle-stimulating hormone

GC: Granulosa cell

IGF1: Insulin-like growth factor 1

IVF: In vitro fertilization

LH: Luteinizing hormone

KO: Knockout

LncRNA: Long non-coding ribonucleic acid

***MALAT1*:** Metastasis-associated lung adenocarcinoma transcript 1

MiRNA: Micro RNA

mRNA: messenger ribonucleic acid

mTOR: Mammalian target of rapamycin

***NEAT1*:** Nuclear Enriched Abundant Transcript 1

***NEAT2*:** Nuclear Enriched Abundant Transcript 2

PCO: Polycystic ovary

PCOS: Polycystic ovary syndrome

PCR: Polymerase chain reaction

PI3K/AKT: Phosphotidylinositol-3-kinase/ protein kinase B

RNAs: Ribonucleic acids

SOX13: *SRY-box transcription factor 13*

WT: Wild Type

Chapter I

Introduction

1.1. Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a condition in which there is an abnormal amount of androgen production in the ovaries. Due to this excessive level of androgen present in the ovaries, various sack-like structures called cysts (fluid-filled sacs) are formed hence the name polycystic ovary syndrome. PCOS is a common endocrine abnormality. It impacts 4% to 20% of reproductive-age women around the world (Deswal et al., 2020). PCOS is a significant cause of female infertility. It is a hormonal imbalance condition where excessive androgen in ovaries results in interfering with follicle development and release of the egg during ovulation which causes cyst formation around the ovaries. This causes problems in menstruation, giving rise to conditions like amenorrhea (missing one or more menstrual periods) or oligomenorrhea (fewer than six to eight periods per year). Acne, obesity, insulin resistance, hyperandrogenism, and polycystic ovaries are also some of the outcomes of PCOS. There is an increased incidence of diabetes type II in PCOS patients. In PCOS, there are either insufficient or non-functioning of insulin receptors which causes higher insulin and glucose levels in the blood. This, in turn, causes conditions like obesity, hyperglycemia, and hyperinsulinemia. Studies suggest that obese women have more risk of developing high levels of androgen, leading to hyperandrogenism, which further enhances the symptoms of PCOS (Pasquali, 2006). PCOS is also associated with metabolic disorders like hepatic steatosis, glucose intolerance, dyslipidemia, and hypertension (Liu et al., 2017).

The severity of PCOS symptoms show variation. Some women have a mild form of the condition, and they may not even realize that they have PCOS, while other women have severe symptoms affecting their quality of life and fertility. After menopause, the ovaries stop functioning, and androgen level drops. Thus, the symptoms tend to improve.

However still, PCOS postmenstrual females, when compared with other postmenstrual women, have higher insulin resistance and androgen level (Hsu, 2013).

In PCOS patients, there is a hormonal imbalance. In females, normally, a small amount of male sex hormone, i.e., androgen, is produced by the adrenal glands and the ovaries, which helps in the correct function of the reproductive system. However, unfortunately, in PCOS women, the ovaries and adrenal glands or both produce an excess amount of androgen. An excessive amount of androgen leads to the hair on the body and face, hair loss, obesity, acne, and other symptoms. It also affects the development of ovarian follicles which produce estrogen and progesterone and release the mature oocyte during ovulation. This, in turn, causes the multiple immature follicles to develop, which are also known as cysts. Having an ovarian cyst is one of the many symptoms of PCOS, and this syndrome may happen to women with or without polycystic ovaries. PCOS women also experience insulin resistance in which the body is unable to use insulin effectively because the insulin receptors are either insufficient or are not functioning. If the body cells become resistant to the action of insulin, the sugar level may increase, which in turn promotes the production of more insulin. Insulin normally regulates blood sugar levels, so in PCOS women, there is no regulation of blood sugar as well, which leads to the high glucose level in the blood and high insulin levels. Excess insulin may increase the production of androgen, causing difficulty in ovulation. A type of low-grade inflammation has also been observed in PCOS patients. This low-grade inflammation stimulates polycystic ovaries to produce androgen leading to heart and blood vessel problems (González, 2012). The causes of PCOS are not entirely understood, but it is believed that genetic and environmental factors may contribute significantly.

The genetic influence on the development of PCOS is high. It has been observed that PCOS cases appear to cluster in families. Evidence supports that hyperandrogenemia (presence of an excess amount of androgen) and hyperinsulinemia (presence of excess amounts of insulin) in siblings show hereditability (Franks & McCarthy, 2004; Legro et al., 1998). However, it is not yet confirmed what the exact mode of inheritance of this

syndrome is. It is possible that PCOS is inherited as an autosomal dominant pattern, but there is more chance of it being oligogenic (involving a few genes) or polygenic, involving two or more genes (Franks et al., 1997a; Franks & McCarthy, 2004). Nevertheless, it is also possible that a major change in a single gene could influence the physical traits of a family. The candidate genes for PCOS which have been under the radar and could influence the polycystic ovary syndrome are those genes that are involved in androgen biosynthetic pathways and the genes which affect the action or secretion of insulin.

It has been noticed that the prevalence of PCOS has been rising in relatively constant gene pool populations. This shows that there is a very important role of environmental factors on PCOS. The more obese an individual is, there are more risks of susceptibility to this syndrome. In developed countries, there is an easy access to food, and modern life helps conserve the daily energy, which creates a positive energy balance. Moreover, studies showed that PCOS patients had a high concentration of glycol-toxins and advanced glycation end products (AGEs). AGEs also show a positive correlation between hyperandrogenemia and insulin resistance (Diamanti-Kandarakis et al., 2005). Another example of an environmental effect on PCOS is the use of medication, such as valproic acid. Valproic acid is a fatty acid-containing short-chain and is employed in the treatment of patients suffering from epilepsy, bipolar disorder, migraines, and generalized mood behaviors. This medicine causes stigma of PCOS in women using it. These women developed symptoms of polycystic ovaries, obesity, hyperandrogenism, and anovulation (Franks et al., 1997b). When the use of medication is stopped, the symptoms get reversed (Franks et al., 2001). Recent studies suggest that only obesity caused by the use of valproic acid is enough to develop the phenotype of PCOS (Gambineri et al., 2002).

There is no genetic testing in the diagnosis of PCOS that could confirm 100% whether a person definitely has PCOS or not. However, medical doctors usually start the investigation by discussing the medical history of patients and asking the patients about changes in their menstrual cycle and weight. Pelvic examination is performed by

gynecologists in which reproductive organs are inspected manually and visually for masses, abnormal growth, or other abnormalities. Physical exams detect extra hair growth and acne. PCOS patients also have to go through various blood tests. Blood tests are important because they help to analyze the hormone levels and negate other causes (menstrual abnormalities), which could mimic symptoms like PCOS. An ultrasound test is also performed, which analyzes the ovaries and thickness of the uterus lining. If a patient has two of the following three symptoms, then that patient is diagnosed with PCOS according to the Rotterdam criteria. Irregular ovulation leading to irregular or infrequent periods, a blood test showing excess levels of androgen (a male hormone), or the signs indicating excess male hormones, ultrasound reports can be used to confirm the presence of polycystic ovaries (Azziz, 2006).

There is no definite treatment for PCOS which could completely eradicate it. For some patients, infertility is the main concern, and for others, it is excess hair in different parts of the body (hirsutism). Some patients might be concerned most about the acne on their face, while others might want to reduce their obesity. The treatments include lifestyle changes and medication. Doctors might recommend a low-calorie diet for weight loss and moderate exercise. Losing weight can increase the effect of medications that a PCOS patient might be taking for infertility (Farshchi et al., 2009). In order to regulate the menstrual cycle in PCOS patients, birth control pills (containing estrogen and progesterone) are recommended because they decrease androgen production and regulate estrogen. This can correct excess hair growth, acne, and abnormal bleeding. For patients suffering from infertility, medication like clomiphene, letrozole, metformin, and gonadotropins are recommended (Diamanti-Kandarakis et al., 2010). For reduction of excess hair growth, birth control pills, spironolactone (for patients who are not planning for pregnancy), eflornithine, and electrolysis are often recommended (Kini & Ramalingam, 2018).

It is evident from the above discussion that PCOS is responsible for lots of adverse health conditions, but still, there is no specific cause known behind this syndrome. Furthermore,

there is no cure for this condition; thus, genetic background of PCOS represents a very important field of research to determine causes and possible remedies for this phenomenon. In order to find out what goes wrong in the normal process of fertilization in PCOS, we have to first understand how ovulation and the normal fertilization process occur.

1.2. Formation of Oocytes and Ovulation Process

The females have a finite number of follicles that she is born with. As she grows older, this number keeps on decreasing with the increasing age. Each follicle contains one immature egg, and each ovary has thousands of follicles. There are different stages through which an oocyte passes in order to be converted into a mature ovum. The primordial germ cell is the very first stage which has an embryonic cell that will ultimately transform either into sperm or oocyte cells. During embryo development, these cells translocate themselves to gonads, which ultimately form the testis in males or the ovaries in females. When a primordial germ cell reaches the gonadal ridge, the cells in the vicinity influence the cell to differentiate into oogonium. Oogonia consist of two sets of chromosomes and hence are diploid cells. This means that a human's oogonium will have 23 pairs or 46 chromosomes in total. A process called mitotic cell division occurs in the oogonium during the first five months of prenatal development, due to which oogonium increases in size. In order to be converted into a mature ovum, every oocyte has to pass through two phases of meiotic cell divisions. At this point, the number of oocytes will not increase; rather, they will develop in terms of growth and maturity. This means that towards the end of prenatal development, individual maturation of oocytes starts to occur, and they become primary oocytes. The first phase of meiotic cell division occurs at this stage which results in oocyte growth. But the process of maturation does not occur right away. These oocytes are arrested at meiosis prophase I, and meiotic division reinitiates when luteinizing hormone induces resumption of meiosis at puberty. The next stage of oocyte maturation starts when puberty hits. All the oocytes do not enter meiosis together. Depending upon the reproductive age of women, the number of oocytes going together

into this stage may vary. Every month, a new batch of primary oocytes begins to mature. As soon as the reproductive hormones affect the primary oocyte, it completes its first stage of meiotic cell division, and the process is called oocyte maturation. When the first stage of meiotic cell division ends, one cell divides into two different cells; a smaller polar body (which eventually deteriorate) and a larger secondary oocyte. This secondary oocyte goes into the maturation stage. Following this process, the secondary oocyte enters the second phase of meiotic cell division. At this stage, the secondary oocyte further split into two different cells; a smaller polar body and a larger mature cell. The large mature cell formed is called an oocyte. Similar to the polar body I, the small polar body (polar body II) also disintegrates. At this point, as the oocyte is converted into the oocyte stage of development, ovulation occurs. When ovulation takes place, the follicle releases an oocyte. There are finger-like projections that help in the movement of the oocyte into the fallopian tube as human egg cells cannot move by themselves. When the fallopian tube gets the oocytes, cilia (hair-like small projections) help in the further movement of the oocyte. Fertilization takes place in the fallopian tube. At fertilization, the oocyte becomes ovum by completing meiosis II (Hamilton et al., 1944).

Ovum and sperm cells contain 23 chromosomes each, and they combine during fertilization to form a new cell with 46 chromosomes. The fertilized egg is known as a zygote. The zygote undergoes cleavage divisions, and upon implantation, embryonic development continues.

1.3. Events that occur during oocyte formation in PCOS patients

Normally the anterior pituitary gland located in the brain secretes hormones like follicle-stimulating hormones (FSH) or luteinizing hormones (LH) into the bloodstream, which direct the ovarian function. When these hormones are secreted, the immature eggs are stimulated in the maturation process, and the size of follicles begins to increase. When the eggs become mature, the follicle release estrogen, which is the major female sex hormone. At a certain level of estrogen in the bloodstream, the pituitary gland secretes a flood of luteinizing hormones in the ovaries, which in turn causes the mature follicle to

open and release the egg through a process known as ovulation, and this egg passes down the fallopian tube, where it is fertilized. The immature eggs and follicles that remain disintegrate. If the egg is left unfertilized, the egg and uterine lining are lost during the next menstrual period (Hassan et al., 2014).

In PCOS patients, the pituitary gland may secrete excessive levels of luteinizing hormones into the blood, which disrupts the normal course of the menstrual cycle. Consequently, the follicles may not undergo maturation, and ovulation does not happen that leads to infertility. Some immature follicles may not disintegrate and will persist as fluid-filled sacs known as cysts. High levels of insulin (produced by the pancreas) might be increased in the bloodstream. When too much insulin is paired with excessive levels of luteinizing hormone, the ovaries produce an overabundance of testosterone. Excessive testosterone levels impede ovulation, which can lead to infertility. Many of the physical features associated with PCOS are also caused by high levels of testosterone, such as acne and excessive hair growth. Owing to excess insulin and insulin resistance, PCOS increases the risk of type 2 diabetes, heart disease, hypertension, cholesterol abnormalities, and endometrial cancer (Zhao et al., 2016).

1.4. Long Non-coding RNAs

Non-coding RNAs (ncRNA) do not code proteins and they can be categorized into different types depending on the length. Short ncRNAs have less than two hundred nucleotides, and long non-coding RNAs (lncRNAs) are usually longer and have more than two hundred nucleotides (Djebali et al., 2012a).

According to HUMAN GENCODE, there are about 16,000 lncRNA genes within the genome, but according to some other estimates, this number exceeds a hundred thousand human lncRNAs (Fang et al., 2018; Uszczynska-Ratajczak et al., 2018). This human genome contains lncRNAs and the transcription is mediated by RNA Polymerase II (Pol II) as well as other RNA polymerases and lncRNAs from other intergenic regions (lincRNAs). There is a 7-methyl guanosine (m^7G) cap at 5'end of lncRNAs, and a

polyadenylated tail at 3'end, respectively. The resulting lncRNAs are also spliced just like mRNAs. It is important to observe that enhancer regions are transcribed into enhancer RNAs (eRNAs), and promoter regions are transcribed into upstream promoter transcripts (Wu et al., 2017).

1.5. Gene regulation by lncRNAs

LncRNAs regulate gene expression at multiple levels. They have the ability to modulate the structure of chromatin and its function. They also have an impact on stability, RNA splicing and translation. LncRNAs are also involved in processes such as the development and control of organelles and nuclear condensates (Statello et al., 2020).

1.5.1. Chromatin Regulation

The modulation of chromatin structure and gene expression by complex lncRNA has been unveiled by the recognition of RNA-chromatin interaction across the genome (Bell et al., 2018; Bonetti et al., 2020; Chu et al., 2011; Li et al., 2017). Although the regulatory mechanisms mediated by lncRNA have to be studied separately, RNA has the intrinsic regulatory capability. RNA is negatively charged, and the histone tails are positively charged. Hence, RNA and histone tail can neutralize the opposite charges, which can de-compact chromatin (Dueva et al., 2019). Therefore, the level of gene expression can be altered through this regulation. Mechanistically, chromatin alterations are the result of cis-acting and trans-acting nuclear lncRNAs, but sometimes they occur as a result of their protein affinity that can link both DNA and RNA, and in other instances, it is due to DNA binding in a sequence-specific fashion (Statello et al., 2020).

1.6 The statement of the problem

PCOS is a syndrome that not only affects women leading to infertility but also causes problems like acne, facial hair growth, irregular no periods and diabetes. There is no definite cure for PCOS discovered yet. This study can give information about the lncRNA regulation in oocytes of PCO patients, which might lead us to the path of finding the cause and cure behind this syndrome.

1.7 Significance of the study

There is no study conducted to date which tests the lncRNA regulations in oocytes directly. LncRNAs were proposed to have a n important role in PCOS development, which is one of the major reasons behind infertility. Hence it is important to conduct this research in order to figure out the underlying principles of PCOS and the role of lncRNAs like *MALAT1*, *AOC4P*, and *NEAT1* in the oocyte formation process.

1.8 Study Hypothesis and Goal

The aim of the research was to investigate whether lncRNAs have a differential expression pattern in oocytes from patients with polycystic ovaries and the patients undergoing IVF treatment with no polycystic ovaries. Thus, the purpose was to analyze the regulation pattern of lncRNAs in human meiosis II stage oocytes from patients with PCO.

CHAPTER II

Literature Review and Related Research

2.1. Long Non-coding RNAs in PCOS

PCOS can be affected by various factors such as genetics, environment, and epigenetics, but the etiology of PCOS is still not clear. Cell proliferation, apoptosis, differentiation, and tumorigenesis involve long non-coding RNAs to play a vital part by associations with the modification of chromatin, RNA binding proteins, and endogenous competitive RNA (ceRNA) (Flynn & Chang, 2014; Quinn & Chang, 2015). LncRNAs are important in the development of follicles, according to previous studies. An experimental animal study had failed a successful pregnancy when lncRNA *NEAT1* was knocked out (KO). It was because of dysfunction of the corpus luteum and lower progesterone levels in the serum (Nakagawa et al., 2014a).

Previously published studies investigated lncRNA expression in leukocytes of obtained from PCOS patients (Liu et al., 2015; Qin et al., 2019). Liu et al. (2015) showed that the expression of CTBP1-AS was significantly higher in PCOS patients compared to the control group (Liu et al., 2015). Another research by Qin et al. showed that lncRNA H19 expression levels in leukocytes of PCOS patients were significantly higher compared to the non-PCOS control group (Qin et al., 2019). This suggests that the higher the amount of lncRNA H19 expression, the greater the risk of PCOS (Qin et al., 2019). Hence it was indicated that increased levels of lncRNA H19 may work as a useful biomarker for PCOS patients. However, the shortcomings of these studies must also be considered, which are the fact that the sample size is relatively small and the sample type is leukocytes obtained from peripheral blood. Since PCOS is an endocrine disease, it cannot be alleviated by only peripheral blood leukocyte samples.

Previous studies examined the expression levels of lncRNAs in the cumulus/granulosa cells (GC) obtained from females with PCOS. The gene expression profiles of lncRNA in GC/cumulus cells showed that the majority of the lncRNAs (620 out of 623) were upregulated in the samples obtained from PCOS patients (Huang et al., 2015, Huang et al, 2018; Jiao et al., 2018; Liu et al., 2017). Similarly, Liu et al. (2017) showed that a high number of lncRNAs were upregulated in samples obtained from PCOS patients, i.e., 692 samples were upregulated and 170 down-regulated, respectively (Liu et al., 2017). Thus, it can be assumed that the expression of lncRNAs is usually upregulated in samples obtained from PCOS patients. However, the findings of many studies also have some discrepancies. *MALAT1*, *AOC4P*, and *NEAT1* have been associated with PCOS previously (Chen et al., 2018; Lin et al., 2020; Zhen et al., 2021).

2.1.1. *MALAT1*

Metastasis Associated Lung Adenocarcinoma Transcript 1 (*MALAT1*) gene, which is also called Nuclear Enriched Abundant Transcript 2 (*NEAT2*), is situated on the 11q13.1 chromosome in humans and 19qA in mice, respectively. Its transcription is performed by polymerase II. *MALAT1* was first identified in patients with non-small cell lung cancer by microarray screening of tumor samples. It was found that *MALAT1* was upregulated in tumor samples obtained from cancer patients as well as patients who were diagnosed to have metastasis (Ji et al., 2003). This gene transcript has more than 8000 nucleotides (Ji et al., 2003) and falls into the category of long non-coding RNAs. It is, in fact, one of the most studied long non-coding RNA. *MALAT1* was shown to be highly abundant and broadly maintained among 33 mammalian species (Eißmann et al., 2012; Ji et al., 2003). Furthermore, the interaction between *MALAT1* and serine-and arginine-rich (SR) proteins that participated in splicing regulation was shown previously (Yoshimoto et al., 2016). The average median expression value of this gene across all tissues is 150 TPM (transcripts per million) and ovaries were shown to have the highest level of *MALAT1* expression level with 287 TPM (Aguet et al., 2017). The original classification of *MALAT1* was an intron-less transcript, and it was believed that it has a poly-A tail.

However, it was then identified that *MALAT1* has a number of alternatively spliced isoforms and transcription start locations in transcripts. These isoforms and transcripts show differences in the expression patterns in samples with cancer (Djebali et al., 2012b; Meseure et al., 2016). *MALAT1* was shown to have a direct or indirect role in transcription and/or regulation of splicing of alternative pre-mRNA (Arun et al., 2018). Different studies showed that *MALAT1* had altered pre-mRNA splicing when it was knocked out of the cells (Arun et al., 2016; Malakar et al., 2017; Tripathi et al., 2010). A number of studies also showed a direct effect of *MALAT1* in patients with diabetes and the signaling of insulin (Chen et al., 2018).

In vitro and *in vivo* knockdown of *MALAT1* decreased the proliferation, invasion, and metastasis of human osteosarcoma cells (Dong et al., 2015). Simultaneously, the expressions of proliferating cell nuclear antigen (PCNA), matrix metallopeptidase 9 (MMP-9), phosphorylated PI3Kp85, and Akt were considerably suppressed in *MALAT1*-deficient cells (Dong et al., 2015). These findings suggested that *MALAT1* may inhibit tumor development and metastasis by inhibiting the PI3K/AKT signaling pathway (Dong et al., 2015). The findings of another study indicated that *MALAT1* can affect extracellular matrix catabolism, inflammation, and especially apoptosis in chondrocytes exposed with lipopolysaccharides, which ultimately regulates the evolution of osteoarthritis by targeting PI3K/Akt/mTOR which is a pathway involved in cell cycle regulation (Li et al., 2020).

2.1.2. *AOC4P*

Amine Oxidase Copper containing 4, a pseudogene (*AOC4P*), is located on chromosome 17q21.31 in Homo Sapiens. It is classified as an lncRNA. Studies have shown that *AOC4P* is involved in colorectal cancer (CRC) and gastric cancer (Lu et al., 2016; Zhang et al., 2019). The levels of *AOC4P* were shown to be decreased in cell lines and tissues in epithelial ovarian cancer (Lin et al., 2020). In poorly metastatic epithelial ovarian cancer cell lines, the *AOC4P* expression knockdown helped in the migration or invasion of cells. In highly metastatic epithelial ovarian cancer cell lines, *AOC4P* overexpression causes a

reduction in the capability of these cells to metastasize *in vitro*. *AOC4P* also showed an anti-metastatic role *in vivo*, which was confirmed by tumor dissection and imaging (Lin et al., 2020). However, there is not enough research conducted yet which elaborates on the effect of *AOC4P* in the gene regulation of PCOS. *AOC4P* plays a role in GC progression by targeting signaling pathways such as PI3K/AKT (Liu et al., 2021).

2.1.3. *NEAT1*

Nuclear Enriched Abundant Transcript 1 (*NEAT1*) is a long non-coding RNA that consists of about 3.2kb nucleotides. It is situated on chromosome 11q13.1 in Homo Sapiens. The transcript of *NEAT1* is found to be mostly in the nucleus, whereas some of it is also present in the cytoplasm (van Heesch et al., 2014). Previously published studies showed that this gene is expressed excessively in a lot of solid tumor samples, such as samples obtained from non-small cell lung cancer (Pan et al., 2015) and ovarian cancer (Sun et al., 2016). However, it was also reported that with diverse sorts of cancer, the impact of *NEAT1* can also vary as this gene showed reduced expression in promyelocytic leukemia (Zeng et al., 2014). In endometrial cancer, *NEAT1* expression levels showed a positive correlation with the stage of cancer and metastasis (Li et al., 2016). This gene was shown to be involved in transcription regulation and RNA processing (Chen & Carmichael, 2009; Nakagawa et al., 2014a). Furthermore, *NEAT1* knockout (KO) mice, despite normal ovulation, were unable to have a successful pregnancy. These mice were shown to have corpus luteum malfunction and low progesterone levels (Nakagawa et al., 2014a). Some studies also concluded that interference with *NEAT1* in rats with PCOS resulted in increased levels of miR-381 and reduced IGF1 levels, which in turn improved levels of sex hormones and also caused a reduction in pathological damage of ovarian tissues in rats with PCOS (Zhen et al., 2021). Extremely high levels of *NEAT1* expression may stimulate cell proliferation and block cell death, hence promoting tumor growth *in vivo.* This mechanism may involve *SOX13* regulation and PI3K/AKT pathway activation (Xu et al., 2018).

Chapter III

Materials and Methods

Ethical approval was obtained from Near East University (YDU/2020/76-1011), and informed consent was obtained from all the patients.

3.1. RNA isolation

Human oocytes were obtained from IVF patients at the Near East University Hospital by an expert embryologist. Two groups were formed. The first group involved oocytes from patients with polycystic ovaries (PCO), and the second group consisted of oocytes from patients with no PCO (control group). In total, 13 samples were collected, seven from PCO patients and six from the control group, respectively.

RNA was isolated from single human oocytes using a specific DNA/RNA isolation kit (Norgen RNA purification kit, Canada). Extraction was performed in accordance with the manufacturer's protocol with no alterations. The quality and quantity of the isolated RNA were analyzed using Nanodrop following the manufacturer's protocol.

3.2. cDNA synthesis

cDNA was synthesized using a commercially available kit (Transcript First Strand cDNA Synthesis kit, Canada) using the extracted RNA samples. The manufacturer's protocol was followed for cDNA synthesis with no alterations.

3.3. PCR analysis for gene expression study

Real-time PCR was performed using the cDNA samples to investigate the expression levels of *MALAT1*, *NEAT1* and *AOC4P*, respectively. Optimization for PCR conditions was performed. Different final concentrations of primers ranging from 0.5µM to 2.5µM were tested out. Annealing temperatures ranging from 56°C to 62°C were also tested for different annealing times ranging from 10 to 30 seconds. SYBR green mix (LightCycler® 480 SYBR Green I Master kit, Roche, Germany) was used to detect the expression levels of each lncRNA.

PCR was performed following the manufacturer's protocol with slight changes. A reaction mixture of 5 µl of SYBR green master mix, 2µM final concentrations of forward and reversed primers for *MALAT1* and *NEAT1* and 1µM final concentration of forward and reverse primers for *AOC4P* and 1µl of cDNA was prepared for each reaction. One reaction for negative control was also prepared with 5µl SYBR green master mix and forward and reverse primers, respectively. All of the reaction mixtures were centrifuged for 5 seconds at 6000rpm and then were placed into real-time PCR equipment at the following settings (Table 1).

Table 1.

Table Showing PCR Settings for LncRNAs (MALAT1, NEAT1, and AOC4P)

PCR Steps	**Temperature/Time**	**Cycles**
Initial Denaturation	95°C for 10min	1
Denaturation	95°C for 10sec	40
Annealing	56°C (*MALAT1* and *NEAT1*) / 62°C (*AOC4P*) for 20sec	
Elongation	72°C for 30sec	

The reaction mixtures were prepared in a similar manner for the housekeeping gene. A negative control reaction was prepared in the absence of any cDNA. The reaction mixtures consisted of 5µl of SYBR green master mix, 0.5µM of forward and reverse primers and 1µl of cDNA sample. The real time PCR conditions were same as the *MALAT1* and *NEAT1* (Table 1).

3.4. Statistical analysis

ΔΔCt method was used to normalize gene expression using *ACTB* as a housekeeping gene. Logarithmic values of ΔΔCt values were then evaluated with unpaired student's T-tests and one-way ANOVA on GraphPad prism software.

Chapter IV

Findings and Discussion

In this study, a total of 13 oocytes were used. The details of each sample are shown in table 2. RNA extraction was successfully performed for each sample and the concentration and the purity are shown in table 2.

Table 2.

Table Showing the Patient Details Including Polycystic Ovary Status, Age And BMI.

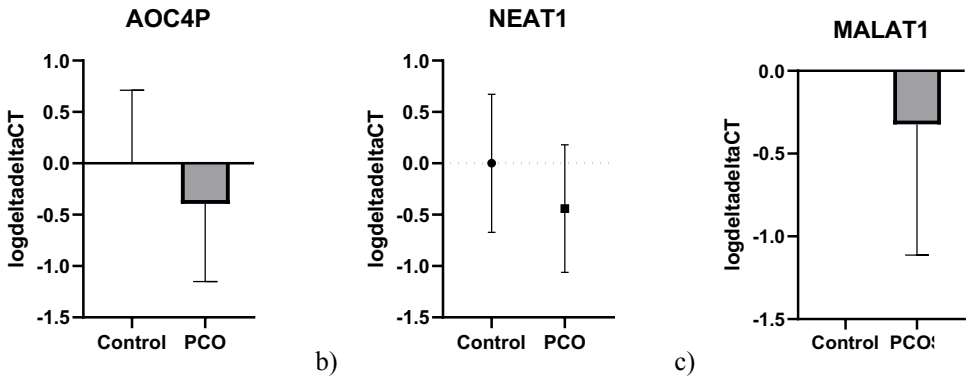
Patient's No.	Groups	Female's Age	BMI	Concentration (ng/µl)	260/280
1	Study group	22	27	10.0	1.52
2	Study group	29	22	11.0	1.48
3	Study group	26	19	12.7	1.46
4	Study group	23	21	11.0	1.50
5	Study group	21	19	9.7	1.51
6	Study group	27	16	9.9	1.52
7	Study group	28	34	12.5	1.53
8	Control group	23	22	10.9	1.56
9	Control group	21	19	10.3	1.53
10	Control group	21	19	10.0	1.52
11	Control group	25	18	10.9	1.56
12	Control group	29	18	11.5	1.51
13	Control group	27	23	10.0	1.52

The real time PCR analysis was performed to investigate the level of gene expression. The ΔΔCt values were calculated using the Ct values obtained from the real time PCR analyses. Normalization was performed against the housekeeping gene. Statistical analysis was performed to examine the statistical significance. Following are the results

of the unpaired student's T-test, which were attained using GraphPad prism software. Figures 1 a, b and c provide the comparison between lncRNA expression values in oocytes of PCO patients and the control group, respectively. The statistical analysis results suggest that these lncRNAs are expressed at similar levels in the oocytes obtained from patients with PCO and the control group ($p>0.005$, table 3).

Figure 1.

Graph Showing Expression Values of AOC4P, NEAT1 and MALAT1 in Oocytes of PCO and the Control Patients.



a) b) c)

Table 3.

P and T Values of lncRNAs (MALAT1, AOC4P And NEAT1) from Unpaired T-test.

LncRNA	P values	T values
MALAT1	0.5026	0.7067
AOC4P	0.3563	0.9629
NEAT1	0.2438	1.232

Chapter V

Discussion

Polycystic ovary syndrome is a hormonal imbalance condition in which there is abnormal production of male sex hormone, i.e., androgen. Due to this abnormality, some women face symptoms like acne, facial hair growth, hyperglycemia, obesity, diabetes type 2, polycystic ovaries, irregularity in menstruation, and infertility. Having PCOS does not mean a person experiences all the symptoms at once. It rather is a condition that may show even combinations of these symptoms. For instance, having polycystic ovaries does not confirm that a woman has PCOS. Women can have PCOS with or without having polycystic ovaries (Carmina & Lobo, 1999).

PCOS is such a complex disease that the main cause behind this syndrome is still unknown. It is believed that there might be some environmental or/and genetic factors behind this condition, but they are yet to be discovered. Previous studies have also been conducted in which lncRNAs' effect on different tissues or sites of the body in PCOS patients have been examined. For example, in one of the previous studies, it was found that knocking out *NEAT1* gene in mice affects the formation of the corpus luteum (Nakagawa et al., 2014b). It was found that *NEAT1* knockout (KO) mice failed to carry out successful pregnancy. However, the analysis on the number of ovulated oocytes in wild-type (WT) mice and *NEAT1* KO mice showed that both groups had almost equal numbers of ovulated oocytes which implied normal ovulation process. When these eggs were inserted into other pseudo-pregnant mothers by *in vitro* fertilization, these eggs showed a normal number of embryos with normal morphology, indicating that there was nothing wrong with oocytes produced in *NEAT1* KO mice (Nakagawa et al., 2014b).

In 2015, Hung et al. carried out an experiment in which they isolated cumulus cells from PCOS patients in order to figure out the patterns of expression of lncRNAs (Huang et al., 2015). They concluded that cumulus cells obtained from PCOS women showed abnormal expression of lncRNAs as compared to normal women indicating that this differential

expression might be a cause behind PCOS and this may affect the oocyte development. According to the results of this study, there was no significant difference in the expression of lncRNAs in oocytes of PCO patients compared to the control samples. However, it is important to keep in mind that this study involved the investigation of only three lncRNAs, i.e., *MALAT1*, *AOC4P*, and *NEAT1*. It is a possibility that other lncRNAs have a role to play in oocytes of PCO/PCOS patients though this area is yet to be explored. Another important point here that may have caused insignificant results is the low sample size, i.e., 13 samples. There is a chance that if the sample size is increased in the experiment, more robust results would be obtained.

In another experiment carried out on Chinese women, it was established that the expression level of CTBP1-AS (a long non-coding RNA) in peripheral blood leukocytes of PCOS patients was higher than in normal women. Hence, this study suggested that there might be some etiological effect of CTBP1-AS upregulation in PCOS patients (Liu et al., 2015). A similar study was conducted again on Chinese women by Qin et al. (2019) in which they tested the lncRNA H19 expression levels in peripheral blood leukocytes of PCOS patients and normal women (control group). They found out that there was upregulation of H19 lncRNA in peripheral blood leukocytes of PCOS patients, and hence this study became the first one to establish any relationship between H19 lncRNA and PCOS (Qin et al., 2019).

In other words, a number of experiments have been conducted in the past investigating the role of lncRNAs in PCOS, but no study has yet experimented on the regulation of lncRNAs directly in oocytes of PCO/PCOS patients. This study is the first, and more research studies should look into the expression and regulation of genes in oocytes. The results of this study showed that the expression of lncRNAs investigated were similar in oocytes of PCO patients and normal patients, respectively.

CHAPTER VI

Conclusion and Recommendations

6.1 Conclusion

In conclusion, there is no significant difference between the expression of *MALAT1*, *AOC4P*, and *NEAT1* in oocytes of PCO patients and the control group, respectively. Previous studies conducted focus on lncRNAs expression in ovaries, peripheral blood leukocytes and cumulus cells. However, this study is the first one to focus on the expression of lncRNAs in oocytes specifically. There is a research gap when it comes to the studies conducted directly on oocytes to find out lncRNA regulations, so further studies should focus on filling this research gap to attain more definite results.

6.2 Recommendations

In future experiments, researchers should also focus on other etiological or genetic factors which could be of importance. Maybe it is the neighboring environment that causes an abnormal environment for oocytes to fertilize or develop into an embryo. Moreover, future studies should also focus on investigating the expression difference of other lncRNAs than *MALAT1*, *AOC4P*, and *NEAT1* as well, in oocytes of PCO/PCOS patients. Increasing the sample size of oocytes can also add up to the reliability and accuracy of future experiments. In addition to lncRNAs, other non-coding RNAs, such as small non-coding RNAs (sRNAs), should also be investigated for playing a role in polycystic ovary syndrome.

CHAPTER VII

References

Aguet, F., Brown, A. A., Castel, S. E., Davis, J. R., He, Y., Jo, B., Mohammadi, P., Park, Y. S., Parsana, P., Segrè, A. v., Strober, B. J., Zappala, Z., Cummings, B. B., Gelfand, E. T., Hadley, K., Huang, K. H., Lek, M., Li, X., Nedzel, J. L., … Zhu, J. (2017). Genetic effects on gene expression across human tissues. *Nature*, *550*(7675), 204–213. https://doi.org/10.1038/NATURE24277

Arun, G., Diermeier, S., Akerman, M., Chang, K. C., Wilkinson, J. E., Hearn, S., Kim, Y., MacLeod, A. R., Krainer, A. R., Norton, L., Brogi, E., Egeblad, M., & Spector, D. L. (2016). Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. *Genes & Development*, *30*(1), 34–51. https://doi.org/10.1101/GAD.270959.115

Arun, G., Diermeier, S. D., & Spector, D. L. (2018). Therapeutic Targeting of Long Non-Coding RNAs in Cancer. *Trends in Molecular Medicine*, *24*(3), 257–277. https://doi.org/10.1016/J.MOLMED.2018.01.001

Azziz, R. (2006). Diagnosis of Polycystic Ovarian Syndrome: The Rotterdam Criteria Are Premature. *The Journal of Clinical Endocrinology & Metabolism*, *91*(3), 781–785. https://doi.org/10.1210/JC.2005-2153

Bell, J. C., Jukam, D., Teran, N. A., Risca, V. I., Smith, O. K., Johnson, W. L., Skotheim, J. M., Greenleaf, W. J., & Straight, A. F. (2018).

Chromatin-associated RNA sequencing (ChAR-seq) maps genome-wide RNA-to-DNA contacts. *ELife*, *7*. https://doi.org/10.7554/ELIFE.27024

Bonetti, A., Agostini, F., Suzuki, A. M., Hashimoto, K., Pascarella, G., Gimenez, J., Roos, L., Nash, A. J., Ghilotti, M., Cameron, C. J. F., Valentine, M., Medvedeva, Y. A., Noguchi, S., Agirre, E., Kashi, K., Samudyata, Luginbühl, J., Cazzoli, R., Agrawal, S., … Carninci, P. (2020). RADICL-seq identifies general and cell type–specific principles of genome-wide RNA-chromatin interactions. *Nature Communications 2020 11:1*, *11*(1), 1–14. https://doi.org/10.1038/s41467-020-14337-6

Carmina, E., & Lobo, R. A. (1999). Polycystic Ovary Syndrome (PCOS): Arguably the Most Common Endocrinopathy Is Associated with Significant Morbidity in Women. *The Journal of Clinical Endocrinology & Metabolism*, *84*(6), 1897–1899. https://doi.org/10.1210/JCEM.84.6.5803

Chen, J., Ke, S., Zhong, L., Wu, J., Tseng, A., Morpurgo, B., Golovko, A., Wang, G., Cai, J. J., Ma, X., Li, D., & Tian, Y. (2018). Long noncoding RNA MALAT1 regulates generation of reactive oxygen species and the insulin responses in male mice. *Biochemical Pharmacology*, *152*, 94–103. https://doi.org/10.1016/J.BCP.2018.03.019

Chen, L. L., & Carmichael, G. G. (2009). Altered Nuclear Retention of mRNAs Containing Inverted Repeats in Human Embryonic Stem Cells: Functional Role of a Nuclear Noncoding RNA. *Molecular*

Cell, *35*(4), 467–478. https://doi.org/10.1016/J.MOLCEL.2009.06.027

Chu, C., Qu, K., Zhong, F. L., Artandi, S. E., & Chang, H. Y. (2011). Genomic Maps of Long Noncoding RNA Occupancy Reveal Principles of RNA-Chromatin Interactions. *Molecular Cell*, *44*(4), 667–678. https://doi.org/10.1016/J.MOLCEL.2011.08.027

Deswal, R., Narwal, V., Dang, A., & Pundir, C. S. (2020). The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. *Journal of Human Reproductive Sciences*, *13*(4), 261. https://doi.org/10.4103/JHRS.JHRS_95_18

Diamanti-Kandarakis, E., Christakou, C. D., Kandaraki, E., & Economou, F. N. (2010). Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. *European Journal of Endocrinology*, *162*(2), 193–212. https://doi.org/10.1530/EJE-09-0733

Diamanti-Kandarakis, E., Piperi, C., Kalofoutis, A., & Creatsas, G. (2005). Increased levels of serum advanced glycation end-products in women with polycystic ovary syndrome. *Clinical Endocrinology*, *62*(1), 37–43. https://doi.org/10.1111/J.1365-2265.2004.02170.X

Djebali, S., Davis, C. A., Merkel, A., Dobin, A., Lassmann, T., Mortazavi, A., Tanzer, A., Lagarde, J., Lin, W., Schlesinger, F., Xue, C., Marinov, G. K., Khatun, J., Williams, B. A., Zaleski, C., Rozowsky, J., Röder, M., Kokocinski, F., Abdelhamid, R. F., … Gingeras, T. R. (2012a). Landscape of transcription in human cells.

Nature 2012 489:7414, *489*(7414), 101–108. https://doi.org/10.1038/nature11233

Djebali, S., Davis, C. A., Merkel, A., Dobin, A., Lassmann, T., Mortazavi, A., Tanzer, A., Lagarde, J., Lin, W., Schlesinger, F., Xue, C., Marinov, G. K., Khatun, J., Williams, B. A., Zaleski, C., Rozowsky, J., Röder, M., Kokocinski, F., Abdelhamid, R. F., … Gingeras, T. R. (2012b). Landscape of transcription in human cells. *Nature*, *489*(7414), 101–108. https://doi.org/10.1038/NATURE11233

Dong, Y., Liang, G., Yuan, B., Yang, C., Gao, R., & Zhou, X. (2015). MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. *Tumour Biology : The Journal of the International Society for Oncodevelopmental Biology and Medicine*, *36*(3), 1477–1486. https://doi.org/10.1007/S13277-014-2631-4

Dueva, R., Akopyan, K., Pederiva, C., Trevisan, D., Dhanjal, S., Lindqvist, A., & Farnebo, M. (2019). Neutralization of the Positive Charges on Histone Tails by RNA Promotes an Open Chromatin Structure. *Cell Chemical Biology*, *26*(10), 1436-1449.e5. https://doi.org/10.1016/J.CHEMBIOL.2019.08.002

Eißmann, M., Gutschner, T., Hämmerle, M., Günther, S., Caudron-Herger, M., Groß, M., Schirmacher, P., Rippe, K., Braun, T., Zörnig, M., & Diederichs, S. (2012). Loss of the abundant nuclear non-coding RNA MALAT1 is compatible with life and development.

Https://Doi.Org/10.4161/Rna.21089, *9*(8), 1076–1087. https://doi.org/10.4161/RNA.21089

Fang, S., Zhang, L., Guo, J., Niu, Y., Wu, Y., Li, H., Zhao, L., Li, X., Teng, X., Sun, X., Sun, L., Zhang, M. Q., Chen, R., & Zhao, Y. (2018). NONCODEV5: a comprehensive annotation database for long non-coding RNAs. *Nucleic Acids Research*, *46*(D1), D308–D314. https://doi.org/10.1093/NAR/GKX1107

Farshchi, H., Rane, A., Love, A., & Kennedy, R. L. (2009). Diet and nutrition in polycystic ovary syndrome (PCOS): Pointers for nutritional management. *Https://Doi.Org/10.1080/01443610701667338*, *27*(8), 762–773. https://doi.org/10.1080/01443610701667338

Flynn, R. A., & Chang, H. Y. (2014). Long Noncoding RNAs in Cell-Fate Programming and Reprogramming. *Cell Stem Cell*, *14*(6), 752–761. https://doi.org/10.1016/J.STEM.2014.05.014

Franks, S., Gharani, N., & McCarthy, M. (2001). Candidate genes in polycystic ovary syndrome. *Human Reproduction Update*, *7*(4), 405–410. https://doi.org/10.1093/HUMUPD/7.4.405

Franks, S., Gharani, N., Waterworth, D., Batty, S., White, D., Williamson, R., & McCarthy, M. (1997a). The genetic basis of polycystic ovary syndrome. *Human Reproduction (Oxford, England)*, *12*(12), 2641–2648. https://doi.org/10.1093/HUMREP/12.12.2641

Franks, S., Gharani, N., Waterworth, D., Batty, S., White, D., Williamson, R., & McCarthy, M. (1997b). The genetic basis of polycystic ovary

syndrome. *Human Reproduction*, *12*(12), 2641–2648. https://doi.org/10.1093/HUMREP/12.12.2641

Franks, S., & McCarthy, M. (2004). Genetics of Ovarian Disorders: Polycystic Ovary Syndrome. *Reviews in Endocrine and Metabolic Disorders 2004 5:1*, *5*(1), 69–76. https://doi.org/10.1023/B:REMD.0000016125.05878.96

Gambineri, A., Pelusi, C., Vicennati, V., Pagotto, U., & Pasquali, R. (2002). Obesity and the polycystic ovary syndrome. *International Journal of Obesity 2002 26:7*, *26*(7), 883–896. https://doi.org/10.1038/sj.ijo.0801994

González, F. (2012). Inflammation in Polycystic Ovary Syndrome: Underpinning of insulin resistance and ovarian dysfunction. *Steroids*, *77*(4), 300–305. https://doi.org/10.1016/J.STEROIDS.2011.12.003

Hamilton, W. J., Dodds, G. H., & Barnes, M. J. (1944). Phases of maturation and fertilization in human ova. *Journal of Anatomy*, *78*(Pt 1-2), 1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1272570/

Hassan, S., Muere, A., & Einstein, G. (2014). Ovarian hormones and chronic pain: A comprehensive review. *PAIN®*, *155*(12), 2448–2460. https://doi.org/10.1016/J.PAIN.2014.08.027

Hsu, M. I. (2013). Changes in the PCOS phenotype with age. *Steroids*, *78*(8), 761–766. https://doi.org/10.1016/J.STEROIDS.2013.04.005

Huang, X., Hao, C., Bao, H., Wang, M., & Dai, H. (2015). Aberrant expression of long noncoding RNAs in cumulus cells isolated from

PCOS patients. *Journal of Assisted Reproduction and Genetics 2015 33:1*, *33*(1), 111–121. https://doi.org/10.1007/S10815-015-0630-Z

Huang, X., Pan, J., Wu, B., & Teng, X. (2018). Construction and analysis of a lncRNA (PWRN2)-mediated ceRNA network reveal its potential roles in oocyte nuclear maturation of patients with PCOS. *Reproductive Biology and Endocrinology*, *16*(1), 1–13. https://doi.org/10.1186/S12958-018-0392-4/FIGURES/5

Jiao, J., Shi, B., Wang, T., Fang, Y., Cao, T., Zhou, Y., Wang, X., & Li, D. (2018). Characterization of long non-coding RNA and messenger RNA profiles in follicular fluid from mature and immature ovarian follicles of healthy women and women with polycystic ovary syndrome. *Human Reproduction*, *33*(9), 1735–1748. https://doi.org/10.1093/HUMREP/DEY255

Ji, P., Diederichs, S., Wang, W., Böing, S., Metzger, R., Schneider, P. M., Tidow, N., Brandt, B., Buerger, H., Bulk, E., Thomas, M., Berdel, W. E., Serve, H., & Müller-Tidow, C. (2003). MALAT-1, a novel noncoding RNA, and thymosin β4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene 2003 22:39*, *22*(39), 8031–8041. https://doi.org/10.1038/sj.onc.1206928

Kini, S., & Ramalingam, M. (2018). Hirsutism. *Obstetrics, Gynaecology & Reproductive Medicine*, *28*(5), 129–135. https://doi.org/10.1016/J.OGRM.2018.03.004

Legro, R. S., Driscoll, D., Strauss, J. F., Fox, J., & Dunaif, A. (1998). Evidence for a genetic basis for hyperandrogenemia in polycystic

ovary syndrome. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(25), 14956–14960. https://doi.org/10.1073/PNAS.95.25.14956

Li, H., Xie, S., Li, H., Zhang, R., & Zhang, H. (2020). LncRNA MALAT1 mediates proliferation of LPS treated-articular chondrocytes by targeting the miR-146a-PI3K/Akt/mTOR axis. *Life Sciences*, *254*, 116801. https://doi.org/10.1016/J.LFS.2019.116801

Lin, X., Tang, X., Zheng, T., Qiu, J., & Hua, K. (2020). Long non-coding RNA AOC4P suppresses epithelial ovarian cancer metastasis by regulating epithelial-mesenchymal transition. *Journal of Ovarian Research*, *13*(1), 1–11. https://doi.org/10.1186/S13048-020-00644-5/TABLES/3

Liu, A. L., Xie, H. J., Xie, H. Y., Liu, J., Yin, J., Hu, J. S., & Peng, C. Y. (2017). Association between fat mass and obesity associated (FTO) gene rs9939609 A/T polymorphism and polycystic ovary syndrome: A systematic review and meta-analysis. *BMC Medical Genetics*, *18*(1), 1–7. https://doi.org/10.1186/S12881-017-0452-1/FIGURES/4

Liu, Y., Ding, W., Yu, W., Zhang, Y., Ao, X., & Wang, J. (2021). Long non-coding RNAs: Biogenesis, functions, and clinical significance in gastric cancer. *Molecular Therapy - Oncolytics*, *23*, 458–476. https://doi.org/10.1016/J.OMTO.2021.11.005

Liu, Y. D., Li, Y., Feng, S. X., Ye, D. S., Chen, X., Zhou, X. Y., & Chen, S. L. (2017). Long Noncoding RNAs: Potential Regulators Involved in the Pathogenesis of Polycystic Ovary Syndrome.

Endocrinology, *158*(11), 3890–3899. https://doi.org/10.1210/EN.2017-00605

Liu, Z., Hao, C., Huang, X., Zhang, N., Bao, H., & Qu, Q. (2015). Peripheral blood leukocyte expression level of lncRNA steroid receptor RNA activator (SRA) and its association with polycystic ovary syndrome: a case control study. *Https://Doi.Org/10.3109/09513590.2014.999763*, *31*(5), 363–368. https://doi.org/10.3109/09513590.2014.999763

Liu, Z., Hao, C., Song, D., Zhang, N., Bao, H., & Qu, Q. (2015). Androgen Receptor Coregulator CTBP1-AS Is Associated With Polycystic Ovary Syndrome in Chinese Women: A Preliminary Study. *Reproductive Sciences 2014 22:7*, *22*(7), 829–837. https://doi.org/10.1177/1933719114565037

Li, X., Zhou, B., Chen, L., Gou, L. T., Li, H., & Fu, X. D. (2017). GRID-seq reveals the global RNA–chromatin interactome. *Nature Biotechnology 2017 35:10*, *35*(10), 940–950. https://doi.org/10.1038/nbt.3968

Li, Z., Wei, D., Yang, C., Sun, H., Lu, T., & Kuang, D. (2016). Overexpression of long noncoding RNA, NEAT1 promotes cell proliferation, invasion and migration in endometrial endometrioid adenocarcinoma. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *84*, 244–251. https://doi.org/10.1016/J.BIOPHA.2016.09.008

Lu, M., Liu, Z., Li, B., Wang, G., Li, D., & Zhu, Y. (2016). The high expression of long non-coding RNA PANDAR indicates a poor

prognosis for colorectal cancer and promotes metastasis by EMT pathway. *Journal of Cancer Research and Clinical Oncology 2016 143:1*, *143*(1), 71–81. https://doi.org/10.1007/S00432-016-2252-Y

Malakar, P., Shilo, A., Mogilevsky, A., Stein, I., Pikarsky, E., Nevo, Y., Benyamini, H., Elgavish, S., Zong, X., Prasanth, K. v., & Karni, R. (2017). Long noncoding RNA MALAT1 promotes hepatocellular carcinoma development by SRSF1 upregulation and mTOR activation. *Cancer Research*, *77*(5), 1155–1167. https://doi.org/10.1158/0008-5472.CAN-16-1508/652513/AM/LONG-NONCODING-RNA-MALAT1-PROMOTES-HEPATOCELLULAR

Meseure, D., Vacher, S., Lallemand, F., Alsibai, K. D., Hatem, R., Chemlali, W., Nicolas, A., de Koning, L., Pasmant, E., Callens, C., Lidereau, R., Morillon, A., & Bieche, I. (2016). Prognostic value of a newly identified MALAT1 alternatively spliced transcript in breast cancer. *British Journal of Cancer 2016 114:12*, *114*(12), 1395–1404. https://doi.org/10.1038/bjc.2016.123

Nakagawa, S., Shimada, M., Yanaka, K., Mito, M., Arai, T., Takahashi, E., Fujita, Y., Fujimori, T., Standaert, L., Marine, J. C., & Hirose, T. (2014a). The lncRNA Neat1 is required for corpus luteum formation and the establishment of pregnancy in a subpopulation of mice. *Development*, *141*(23), 4618–4627. https://doi.org/10.1242/DEV.110544

Nakagawa, S., Shimada, M., Yanaka, K., Mito, M., Arai, T., Takahashi, E., Fujita, Y., Fujimori, T., Standaert, L., Marine, J. C., & Hirose, T.

(2014b). The lncRNA Neat1 is required for corpus luteum formation and the establishment of pregnancy in a subpopulation of mice. *Development*, *141*(23), 4618–4627. https://doi.org/10.1242/DEV.110544

NEAT1 promotes cell proliferation in multiple myeloma by activating PI3K/AKT pathway. (n.d.). Retrieved July 4, 2022, from https://www.europeanreview.org/article/16053

Pan, L. J., Zhong, T. F., Tang, R. X., Li, P., Dang, Y. W., Huang, S. N., & Chen, G. (2015). Upregulation and Clinicopathological Significance of Long Non-coding NEAT1 RNA in NSCLC Tissues. *Asian Pacific Journal of Cancer Prevention*, *16*(7), 2851–2855. https://doi.org/10.7314/APJCP.2015.16.7.2851

Pasquali, R. (2006). Obesity and androgens: facts and perspectives. *Fertility and Sterility*, *85*(5), 1319–1340. https://doi.org/10.1016/J.FERTNSTERT.2005.10.054

Qin, L., Huang, C. C., Yan, X. M., Wang, Y., Li, Z. Y., & Wei, X. C. (2019). Long non-coding RNA H19 is associated with polycystic ovary syndrome in Chinese women: a preliminary study. *Endocrine Journal*, *66*(7), 587–595. https://doi.org/10.1507/ENDOCRJ.EJ19-0004

Quinn, J. J., & Chang, H. Y. (2015). Unique features of long non-coding RNA biogenesis and function. *Nature Reviews Genetics 2015 17:1*, *17*(1), 47–62. https://doi.org/10.1038/nrg.2015.10

Statello, L., Guo, C. J., Chen, L. L., & Huarte, M. (2020). Gene regulation by long non-coding RNAs and its biological functions. *Nature*

Reviews Molecular Cell Biology 2020 22:2, *22*(2), 96–118. https://doi.org/10.1038/s41580-020-00315-9

Sun, C., Li, S., Zhang, F., Xi, Y., Wang, L., Bi, Y., & Li, D. (2016). Long non-coding RNA NEAT1 promotes non-small cell lung cancer progression through regulation of miR-377-3p-E2F3 pathway. *Oncotarget*, *7*(32), 51784. https://doi.org/10.18632/ONCOTARGET.10108

Tripathi, V., Ellis, J. D., Shen, Z., Song, D. Y., Pan, Q., Watt, A. T., Freier, S. M., Bennett, C. F., Sharma, A., Bubulya, P. A., Blencowe, B. J., Prasanth, S. G., & Prasanth, K. v. (2010). The Nuclear-Retained Noncoding RNA MALAT1 Regulates Alternative Splicing by Modulating SR Splicing Factor Phosphorylation. *Molecular Cell*, *39*(6), 925–938. https://doi.org/10.1016/J.MOLCEL.2010.08.011

Uszczynska-Ratajczak, B., Lagarde, J., Frankish, A., Guigó, R., & Johnson, R. (2018). Towards a complete map of the human long non-coding RNA transcriptome. *Nature Reviews Genetics 2018 19:9*, *19*(9), 535–548. https://doi.org/10.1038/s41576-018-0017-y

van Heesch, S., van Iterson, M., Jacobi, J., Boymans, S., Essers, P. B., de Bruijn, E., Hao, W., MacInnes, A. W., Cuppen, E., & Simonis, M. (2014). Extensive localization of long noncoding RNAs to the cytosol and mono- and polyribosomal complexes. *Genome Biology*, *15*(1), 1–12. https://doi.org/10.1186/GB-2014-15-1-R6/FIGURES/5

Wu, H., Yang, L., & Chen, L. L. (2017). The Diversity of Long Noncoding RNAs and Their Generation. *Trends in Genetics*, *33*(8), 540–552. https://doi.org/10.1016/J.TIG.2017.05.004

Xu, H., Li, J., & Zhou, Z.-G. (n.d.). *NEAT1 promotes cell proliferation in multiple myeloma by activating PI3K/AKT pathway*.

Yoshimoto, R., Mayeda, A., Yoshida, M., & Nakagawa, S. (2016). MALAT1 long non-coding RNA in cancer. *Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms*, *1859*(1), 192–199. https://doi.org/10.1016/J.BBAGRM.2015.09.012

Zeng, C., Xu, Y., Xu, L., Yu, X., Cheng, J., Yang, L., Chen, S., & Li, Y. (2014). Inhibition of long non-coding RNA NEAT1 impairs myeloid differentiation in acute promyelocytic leukemia cells. *BMC Cancer*, *14*(1), 1–7. https://doi.org/10.1186/1471-2407-14-693/FIGURES/3

Zhang, K., Lu, C., Huang, X., Cui, J., Li, J., Gao, Y., Liang, W., Liu, Y., Sun, Y., Liu, H., Wei, B., & Chen, L. (2019). Long noncoding RNA AOC4P regulates tumor cell proliferation and invasion by epithelial-mesenchymal transition in gastric cancer. *Therapeutic Advances in Gastroenterology*, *12*, 1756284819827697. https://doi.org/10.1177/1756284819827697

Zhao, L., Zhu, Z., Lou, H., Zhu, G., Huang, W., Zhang, S., & Liu, F. (2016). Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis. *Oncotarget*, *7*(23), 33715. https://doi.org/10.18632/ONCOTARGET.9553

Zhen, J., Li, J., Li, X., Wang, X., Xiao, Y., Sun, Z., & Yu, Q. (2021). Downregulating lncRNA NEAT1 induces proliferation and represses apoptosis of ovarian granulosa cells in polycystic ovary syndrome via microRNA-381/IGF1 axis. *Journal of Biomedical*

Science, *28*(1), 1–14. https://doi.org/10.1186/S12929-021-00749-Z/FIGURES/9

EK:1067-202

YAKIN DOĞU ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMALAR ETİK KURULU

ARAŞTIRMA PROJESİ DEĞERLENDİRME RAPORU

Toplantı Tarihi : 23.01.2020
Toplantı No : 2020/76
Proje No :1011

Yakın Doğu Üniversitesi Tıp Fakültesi öğretim üyelerinden Doç. Dr. Pınar Tulay'ın sorumlu araştırmacısı olduğu, YDU/2020/76-1011 proje numaralı ve **"Expression of genes involved in PI3K/AKT/mTOR pathway in human oocytesobtained frompatients with polycystic ovaries"** başlıklı proje önerisi kurulumuzca değerlendirilmiş olup, etik olarak uygun bulunmuştur.

1. Prof. Dr. Rüştü Onur (BAŞKAN)
2. Prof. Dr. Nerin Bahçeciler Önder (ÜYE) KATILMADI
3. Prof. Dr. Tamer Yılmaz (ÜYE) KATILMADI
4. Prof. Dr. Şahan Saygı (ÜYE)
5. Prof. Dr. Şanda Çalı (ÜYE)
6. Prof. Dr. Nedim Çakır (ÜYE)
7. Prof. Dr. Nurhan Bayraktar (ÜYE)
8. Doç. Dr. Nilüfer Galip Çelik (ÜYE) KATILMADI
9. Doç. Dr. Emil Mammadov (ÜYE)
10. Doç. Dr. Mehtap Tınazlı (ÜYE) KATILMADI

Turnitin Orijinallik Raporu

- İşleme kondu: 05-Tem-2022 14:57 EEST
- NUMARA: 1866876800
- Kelime Sayısı: 8831
- Gönderildi: 1

Thesis Warda Rai tarafından

Benzerlik Endeksi

%15

Kaynağa göre Benzerlik
Internet Sources:
%12
Yayınlar:
%13
Öğrenci Ödevleri:
N/A

1% match (yayınlar)
Z. Al-Omar, B. Ozbakir, P. Tulay. "Differential expression of genes involved in steroidogenesis pathway in human oocytes obtained from patients with polycystic ovaries", Journal of Reproductive Immunology, 2020
1% match (20-Tem-2021 tarihli internet)
https://kms.shanghaitech.edu.cn/bitstream/2MSLDSTB/124924/1/10.1038%40s41580-020-00315-9.pdf
< 1% match (13-Eyl-2020 tarihli internet)
https://www.frontiersin.org/articles/10.3389/fgene.2018.00471/full
< 1% match (24-May-2021 tarihli internet)
https://www.frontiersin.org/articles/10.3389/fimmu.2021.669819/full
< 1% match (19-Oca-2022 tarihli internet)
https://www.frontiersin.org/articles/10.3389/fgene.2021.760416/full
< 1% match (29-May-2022 tarihli internet)
https://www.frontiersin.org/articles/10.3389/fcell.2021.730014/full
< 1% match ()
Liangshan Mu, Xiaoting Sun, Mixue Tu, Dan Zhang. "Non-coding RNAs in polycystic ovary syndrome: a systematic review and meta-analysis", Reproductive Biology and Endocrinology : RB&E
< 1% match ()
Yueh-Ying Hsieh, Fon-Yih Tsuang, Yi-Jie Kuo, Chia-Hsien Chen, Chang-Jung Chiang, Chun-Li Lin. "Biomechanical analysis of single-level interbody fusion with different internal fixation rod materials: a finite element analysis", BMC Musculoskeletal Disorders
< 1% match ()
Yufeng Shi, Honglei Zhai, Sharon John, Yi-Ting Shen, Yali Ran, Giang Hoang, Miao-Hsueh Chen. "Gene Expression Analysis of Environmental Temperature and High-Fat Diet-Induced Changes in Mouse Supraclavicular Brown Adipose Tissue", Cells
< 1% match ()
Amina Soltani, Bela Kajtar, El Husseiny Mohamed Mahmud Abdelwahab, Anita Steib et al. "Is an Immunosuppressive Microenvironment a Characteristic of Both Intra- and Extraparenchymal Central Nervous Tumors?", Pathophysiology
< 1% match (18-Eki-2015 tarihli internet)
http://www.science.gov/topicpages/s/spontaneous+metastasis+development.html
< 1% match (24-Ara-2021 tarihli internet)

https://www.science.gov/topicpages/n/noncoding+rna+lncrna
< 1% match (yayınlar)
Current Topics in Microbiology and Immunology, 2016.
< 1% match (03-Eki-2020 tarihli internet)
https://www.intechopen.com/profiles/40233/kazutaka-yokota
< 1% match (25-Şub-2022 tarihli internet)
https://discovery.researcher.life/download/article/d3b0fe106e993016955f4f5e9ea7b314/full-text
< 1% match (18-Mar-2022 tarihli internet)
https://discovery.researcher.life/download/article/b2780a0d86c134a4ae2ebe966a3bbb97/full-text
< 1% match (04-Kas-2019 tarihli internet)
https://link.springer.com/article/10.1007%2Fs12031-018-1093-3
< 1% match (05-Tem-2022 tarihli internet)
https://link.springer.com/article/10.1007/s13277-014-2631-4?code=876dffb9-9ada-4b56-9f05-51d6eddf0279&error=cookies_not_supported
< 1% match (yayınlar)
Soudeh Ghafouri-Fard, Asghar Ashrafi Hafez, Mohammad Taheri. "Metastasis Associated Lung Adenocarcinoma Transcript 1: An update on expression pattern and functions in carcinogenesis", Experimental and Molecular Pathology, 2020
< 1% match (11-Haz-2022 tarihli internet)
https://d-nb.info/1259417212/34
< 1% match (01-Ara-2020 tarihli internet)
https://eprints.keele.ac.uk/4541/1/AlMnaseerPhD2018.pdf
< 1% match (21-Eyl-2021 tarihli internet)
https://eprints.keele.ac.uk/9263/1/BountaliPhD2021.pdf
< 1% match (16-Tem-2021 tarihli internet)
https://munin.uit.no/bitstream/handle/10037/15809/Thesis.pdf
< 1% match (12-Nis-2020 tarihli internet)
https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2605.2005.00623.x
< 1% match (06-Eki-2020 tarihli internet)
https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2265.2008.03247.x
< 1% match (yayınlar)
Kaixuan Sun, Yinling Xiu, Jianbo Song, Yuexin Yu. "Long Noncoding RNA CTBP1-AS Regulates Ovarian Granulosa Cells Proliferation and Autophagy and Participates in Polycystic Ovary Syndrome", Research Square Platform LLC, 2021
< 1% match (28-Eki-2021 tarihli internet)
https://www.mdpi.com/2072-6694/13/21/5386/htm
< 1% match (26-Tem-2020 tarihli internet)
https://www.mdpi.com/1422-0067/21/8/2947/htm
< 1% match (19-May-2022 tarihli internet)
http://ijrm.ir/article-1-312-en.html
< 1% match (06-Haz-2018 tarihli internet)
http://www.reproduction-online.org/content/151/6/643.full
< 1% match (yayınlar)
Yongqian Chen, Xiaolei Zhang, Yuan An, Bin Liu, Meisong Lu. "LncRNA HCP5 promotes cell proliferation and inhibits apoptosis via miR-27a-3p/IGF-1 axis in human granulosa-like tumor cell line KGN", Molecular and Cellular Endocrinology, 2020
< 1% match (yayınlar)
Peixin Dong, Ying Xiong, Junming Yue, Sharon J. B. Hanley, Noriko Kobayashi, Yukiharu Todo, Hidemichi Watari. "Long Non-coding RNA NEAT1: A Novel Target for Diagnosis and Therapy in Human Tumors", Frontiers in Genetics, 2018
< 1% match (15-Oca-2022 tarihli internet)
https://guttmanlab.caltech.edu/files/2021/11/1-s2.0-S0092867421012307-main.pdf
< 1% match (14-Ara-2021 tarihli internet)

http://www.bioneer.co.kr/literatures/manual/PM-444(V0)%20Multiplex%20PCR%20PreMix.pdf
< 1% match ()
Potratz, Kailey. "Letrozole vs. Clomiphene Citrate for Infertility in Polycystic Ovarian Syndrome", UND Scholarly Commons, 2018
< 1% match (28-Oca-2022 tarihli internet)
http://repository.bilkent.edu.tr/bitstream/handle/11693/76780/Transcriptomic%20alterations%20in%20the%20aged%20brain%20with%20and%20without%20dietary%20and%20dietary-mimetic%20manipulations.pdf?isAllowed=y&sequence=1
< 1% match (yayınlar)
Ying Liu, Wei Ding, Wanpeng Yu, Yuan Zhang, Xiang Ao, Jianxun Wang. "Long non-coding RNAs: Biogenesis, functions, and clinical significance in gastric cancer", Molecular Therapy - Oncolytics, 2021
< 1% match (07-Şub-2022 tarihli internet)
https://bio-protocol.org/bio101/r8843505
< 1% match (25-Haz-2017 tarihli internet)
http://dev.biologists.org/content/develop/143/21/3882.full.pdf
< 1% match (07-Oca-2022 tarihli internet)
https://ebin.pub/the-chemical-biology-of-long-noncoding-rnas-1st-ed-9783030447427-9783030447434.html
< 1% match (14-Ara-2006 tarihli internet)
http://www.empowereddoctor.com/story_187.html
< 1% match (yayınlar)
Chaofan He, Kaixian Wang, Yuanyuan Gao, Chen Wang, Leina Li, Yaping Liao, Ke Hu, Meng Liang. "Roles of Noncoding RNA in Reproduction", Frontiers in Genetics, 2021
< 1% match (yayınlar)
Li Qin, Chui-can Huang, Xiu-min Yan, Yao Wang, Zhong-yi Li, Xiang-cai Wei. "Long non-coding RNA H19 is associated with polycystic ovary syndrome in Chinese women: a preliminary study", Endocrine Journal, 2019
< 1% match (yayınlar)
Wenhao Qu, Ying Cheng, Wei Peng, Tongyu Rui, Chengliang Luo, Jian Zhang. "Reducing the Amount of M1 Microglia by Inhibiting CXCR4 and iNOS Exerts Neuroprotection in a Rat Model of Subarachnoid Hemorrhage", Research Square Platform LLC, 2021
< 1% match (22-Ara-2021 tarihli internet)
https://dmsjournal.biomedcentral.com/articles/10.1186/s13098-020-00544-0
< 1% match (01-Şub-2022 tarihli internet)
https://mdpi-res.com/d_attachment/nutrients/nutrients-14-00512/article_deploy/nutrients-14-00512.pdf
< 1% match (09-Haz-2020 tarihli internet)
https://www.jstage.jst.go.jp/article/endocrj/66/7/66_EJ19-0004/_article
< 1% match (yayınlar)
Annika K Schröder, Sascha Tauchert, Olaf Ortmann, Klaus Diedrich, Jürgen M Weiss. "Insulin resistance in patients with polycystic ovary syndrome", Annals of Medicine, 2009
< 1% match (yayınlar)
Xinyu Wang, Chong Liu, Siwei Zhang, Huiwen Yan et al. "N6-methyladenosine modification of MALAT1 promotes metastasis via reshaping nuclear speckles", Developmental Cell, 2021
< 1% match (22-Haz-2022 tarihli internet)
https://bmcgenomics.biomedcentral.com/track/pdf/10.1186/s12864-022-08679-2.pdf
< 1% match (19-Haz-2018 tarihli internet)
http://genesdev.cshlp.org/content/30/1/34.full
< 1% match (08-Kas-2019 tarihli internet)

http://hss.ulb.uni-bonn.de/2019/5509/5509.pdf
< 1% match (09-Eki-2021 tarihli internet)
https://www.biorxiv.org/content/10.1101/2021.01.06.425556v1.full.pdf
< 1% match (22-Şub-2021 tarihli internet)
https://www.presentica.com/doc/11889403/sample-response-nike-segmentation-and-targeting-pdf-document
< 1% match (28-Eki-2021 tarihli internet)
https://www.researchgate.net/publication/341944819_Exosomal_microRNA-146a_derived_from_mesenchymal_stem_cells_increases_the_sensitivity_of_ovarian_cancer_cells_to_docetaxel_and_taxane_via_a_LAMC2-mediated_PI3KAkt_axis
< 1% match (25-Ara-2021 tarihli internet)
https://www.thefreelibrary.com/The+Role+of+lncRNAs+in+Regulating+the+Intestinal+Mucosal+Mechanical...-a0684111313
< 1% match ()
Felley-Bosco, Emanuela, Rehrauer, Hubert. "Non-Coding Transcript Heterogeneity in Mesothelioma: Insights from Asbestos-Exposed Mice", 'MDPI AG', 2018
< 1% match (yayınlar)
Faezeh Malakoti, Niloufar Targhazeh, Haniye Karimzadeh, Erfan Mohammadi, Milad Asadi, Zatollah Asemi, Forough Alemi. "Multiple function of lncRNA MALAT1 in cancer occurrence and progression", Chemical Biology & Drug Design, 2022
< 1% match (yayınlar)
Shujuan Wu, Zhe Yang, Shaojing He, Lu Han, Menggi Zhou, Jing Yang, Jiao Chen, Gengxiang Wu. "LncRNA AOC4P impacts the differentiation of macrophages and T-lymphocyte by regulating the NF-κB pathways of KGN cells: potential pathogenesis of polycystic ovary syndrome", Research Square Platform LLC, 2022
< 1% match (yayınlar)
Sunny Dholpuria, Manish Kumar, Sandeep Kumar, Parul Sarwalia, Sandeep Rajput, Rakesh Kumar, Sachinandan De, Tirtha K. Datta. "Differential Expression of Newly Identified Long Intergenic Non-Coding RNAs in Buffalo Oocytes Indicating Their Possible Role in Maturation and Embryonic Development", Journal of Cellular Biochemistry, 2017
< 1% match (12-Eki-2020 tarihli internet)
http://bio-bigdata.hrbmu.edu.cn/LncTarD/download/lncTarD.txt
< 1% match (29-Eki-2021 tarihli internet)
https://clinphytoscience.springeropen.com/articles/10.1186/s40816-021-00296-y
< 1% match (06-Nis-2019 tarihli internet)
https://fjfsdata01prod.blob.core.windows.net/articles/files/449097/pubmed-zip/.versions/1/.package-entries/fgene-10-00205/fgene-10-00205.pdf?rscd=attachment%3B+filename%2A%3DUTF-8%27%27fgene-10-00205.pdf&se=2019-04-06T07%3A00%3A44Z&sig=BeA2rSWa%2Blmmj46YOypzpoHJdvWpNeHbNbQuHZARJk8%3D&sp=r&sr=b&sv=2015-12-11
< 1% match (26-Eki-2021 tarihli internet)
https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-021-00749-z
< 1% match (24-Haz-2020 tarihli internet)
https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-020-01219-0
< 1% match (15-Haz-2022 tarihli internet)
https://portlandpress.com/bioscirep/article-split/40/1/BSR20192523/221488/RNA-sequencing-analysis-reveals-the-potential
< 1% match (07-Nis-2020 tarihli internet)
http://tributriathlon.com/munster/polycystic-ovarian-syndrome-diet-pdf.php
< 1% match (10-Ara-2021 tarihli internet)

https://wjgnet.com/1007-9327/CitedArticlesInF6?id=10.1038%2Fnature08975
< 1% match (12-Nis-2022 tarihli internet)
https://www.hgsc.bcm.edu/biblio/export/tagged?f%5Bag%5D=A&f%5Bgenetic-contributions-variation-general-cognitive-function-meta-analysis-genome-wide-associat%5D=
< 1% match (25-May-2022 tarihli internet)
https://www.ingentaconnect.com/contentone/isez/fb/2019/00000067/00000001/art00003?crawler=true&mi=
< 1% match (19-Eyl-2020 tarihli internet)
https://www.researchsquare.com/article/rs-23943/v2
< 1% match (yayınlar)
Li Jin, Qian Yang, Chengliang Zhou, Lanxin Liu, Huihui Wang, Min Hou, Yimei Wu, Fengtao Shi, Jianzhong Sheng, Hefeng Huang. "Profiles for long non-coding RNAs in ovarian granulosa cells from women with PCOS with or without hyperandrogenism", Reproductive BioMedicine Online, 2018
< 1% match (yayınlar)
Yu-dong Liu, Ying Li, Shu-xian Feng, De-sheng Ye, Xin Chen, Xing-yu Zhou, Shi-ling Chen. "Long Noncoding RNAs: Potential Regulators Involved in the Pathogenesis of Polycystic Ovary Syndrome", Endocrinology, 2017
< 1% match ()
Van Rooyen, Desmaré. "An investigation into the biosynthesis and metabolism of adrenal C11-oxy steroids", 2020
< 1% match (yayınlar)
Bei Shi, Di Feng, Matthew Sagnelli, Jiao Jiao, Xiaoli Sun, Xiuxia Wang, Da Li. "Fructose levels are elevated in women with polycystic ovary syndrome with obesity and hyperinsulinemia", Human Reproduction, 2020
< 1% match (yayınlar)
Jingran Zhen, Jiangli Li, Xia Li, Xue Wang, Yaling Xiao, Zhengyi Sun, Qi Yu. "Downregulating lncRNA NEAT1 induces proliferation and represses apoptosis of ovarian granulosa cells in polycystic ovary syndrome via microRNA-381/IGF1 axis", Journal of Biomedical Science, 2021
< 1% match (yayınlar)
Luisa Statello, Chun-Jie Guo, Ling-Ling Chen, Maite Huarte. "Gene regulation by long non-coding RNAs and its biological functions", Nature Reviews Molecular Cell Biology, 2020
< 1% match (yayınlar)
Runju Zhang, Victoria Wesevich, Zhaojuan Chen, Dan Zhang, Amanda N. Kallen. "Emerging roles for noncoding RNAs in female sex steroids and reproductive disease", Molecular and Cellular Endocrinology, 2020
< 1% match (yayınlar)
S. Nakagawa, M. Shimada, K. Yanaka, M. Mito et al. "The lncRNA Neat1 is required for corpus luteum formation and the establishment of pregnancy in a subpopulation of mice", Development, 2014
< 1% match (20-Kas-2020 tarihli internet)
https://jhoonline.biomedcentral.com/articles/10.1186/s13045-018-0606-4

Curriculum vitae

Name Surname: Warda Rai
Date of Birth: 14/05/1997
Title: Student
Education: Master's degree in Medical Biology and Genetics

Degree	Field	University	Year
Bachelor	Biotechnology	University of Veterinary and Animal Sciences	2020
Master	Medical Biology and Genetics	Near East University	2022