Genetic Variant of Alu Ace and its Susceptibility in PCOS

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Abstract: A considerable section of the world's population suffers with PCOS, a frequent infertility disorder. With an 8–13% incidence, it is the most common endocrine illness in women of reproductive age. As the condition is multiple and complicated, it is sometimes difficult to diagnose. The overlap of the disease's origins, the variety of factors that contribute to it, the complexity of its pathophysiology, the variety of signaling pathways and proteins, and the lack of a precise genetic diagnostic test are the causes of this. Although improvements have been achieved in PCOS diagnosis and therapy, little is understood about the key signaling pathways and molecular players involved. In this review, we reviewed the clinical spectrum, genetic variation of ALU ACE associated with PCOS, and the nature of physical and genetic interactions between genetic factors. Understanding the genetic variables and cell signaling mechanisms underlying PCOS would surely help us better grasp the syndrome's pathogenesis. Elevated ACE concentrations in plasma are caused by a genetic variation in the ACE and lead to insulin resistance and hyperandrogenism, both of which are hallmarks of PCOS. As a result, it was suggested that ALU ACE I/D polymorphism contributes to PCOS etiology.

Keywords: PCOS, Polycystic Ovarian Syndrome, ALU ACE, ALU ACE insertion - deletion polymorphism, Pathophysiology.

1. Introduction

PCOS is a Complex metabolic, endocrine, and reproductive disorder affecting approximately 5 - 10% Off the female population in developed countries. [1, 2, 3] PCOS is a prevalent endocrine condition that affects women, particularly those of reproductive age. [1] Stein and Leventhal first described PCOS in 1935. Acne, infertility, hirsutism, IR, cystic ovaries hyperandrogenism, amenorrhea or oligomenorrhea, and obesity can all be signs of PCOS, which can be detected by ultrasonography. [5, 6, 7] PCOS is characterized by consistently secreted amounts of gonadotropin - releasing hormone (GnRH), high levels of luteinizing hormone (LH), and inadequate follicle stimulating hormone (FSH) secretion, all of which contribute to excessive androgen secretions and ovulatory failure.

![Image of enlarged follicle and normal ovary]

Figure 1: Showing Uterus with polycystic ovary
Source: https://images.app.goo.gl/7E55NKhZmpL2VNe87

Furthermore, the majority of PCOS patients develop insulin resistance, which leads to increased androgen production, resulting in lower sex hormone - binding globulin secretions. [8, 9, 10]

PCOS is defined clinically by menstruation irregularity, recurrent anovulation, and polycystic ovaries. [11] Polycystic ovaries have numerous cysts up to 8mm in diameter, each carrying a completely undeveloped egg. The Rotterdam criteria are wider than others, and a diagnosis is given when a person meets two of the following three criteria: oligo and/or anovulation, hyperandrogenism (clinical and/or biochemical), and polycystic ovaries recognised sonographically. [12] PCOS is a complicated collection of illnesses including genetic and environmental influences. Cooper and colleagues discovered PCOS genes in 1968. [13] The PCOS study reported many relatives and siblings show a high rate of PCOS occurrence. The presence of PCOS in the first proband relative in around 55 - 60% of small families has supported the autosomal mode of inheritance. Later, among females with PCOS, monogenic causes of hirsutism, oligomenorrhea, and male pattern baldness were discovered. [14]

Although the actual process of PCOS development remains unknown. PCOS is linked to all gene abnormalities that impact the ovaries directly or indirectly. The condition has been widely examined, but its specificity and mechanism remain unknown.

Prevalence:
Globally, the prevalence of women with PCOS is 5 - 20% in 2012. [15] It is estimated that worldwide - wide in 2016, 105 million women suffered from PCOS. The age groups from 15 - 49 are more suffered from this disease. [16] In the United States, polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders with 4 - 12% in 2018. [17] As per the Survey in 2017, According to the Rotterdam criteria, the prevalence of PCOS in south India is 6% and also discovered that the chances of urban women developing PCOS are 0.1 times higher than those of women in rural India. [18]

Symptoms:
During puberty, PCOS symptoms typically start to manifest around the time of the first menstrual cycle. PCOS can develop later in life, for instance, as a result of severe weight
Complications in PCOS:
PCOS can have a variety of side effects, such as infertility, gestational diabetes, high blood pressure during pregnancy, premature birth or miscarriage, steatohepatitis without alcohol (severe liver inflammation caused by fat accumulation in the liver). The risk of cardiovascular disease is considerably increased by the presence of the metabolic syndrome, a collection of disorders that also includes high blood pressure, diabetes, and abnormal cholesterol or triglyceride levels, either prediabetes or T2D. Slumber apnea Anxiety, depression, and eating problems abnormal bleeding in the uterus Endometrial cancer, as seen in Figure 3 is a malignancy of the uterine lining. Obesity is closely linked to PCOS and can worsen the condition’s symptoms worse. [19]

Types:
There are described into 4 major types based on the reason behind their occurrence. Insulin resistance PCOS is the common type in which PCOS is caused due to Insulin Resistance in the body, other types include Adrenal PCOS, Inflammatory PCOS, and Post - pill PCOS as shown in figure 4.
Factors associated with PCOS:
Several variables contribute to the development of PCOS, including hereditary and non-genetic factors. Non-genetic causes include radiations, pollutants, insertional mutagenesis by proviral mutation insertion, and so on.

Non-genetic factors
Many environmental variables, including pollution, alcohol, infections, smoking, obesity, and so on, have been linked to PCOS. Some of the factors are shown in Figure 5.

Genetic factors
PCOS is a very complex and varied disorder. The genetic foundation of PCOS varies within and within families, however, it is linked to a common mechanism. Due to the complexity and variability of the human genome, single genes or related genes within a single family have not been reported. An overview of PCOS' genetic landscape is shown in Figure 6. An in-depth discussion is given on these collections of related genes and how PCOS is affected by them.

Angiotensin Converting Enzyme (ACE):
The ACE gene is found on the long arm (q arm) of chromosome 17 (17q23.3) in the human genome. as shown in Figure 7.

Structure and function of an ACE gene:
The ACE gene has a length of 21 kilobases (kb) (21, 310 bp), 24 introns, and 26 exons, with sizes ranging from 88 to 481 base pairs. The ACE gene encodes the instructions for producing angiotensin-converting enzymes. This enzyme is capable of cutting (cleaving) proteins. ACE is also associated with various gene and lead to multiple diseases. ACE association with other genes is shown in Figure 8. Both endothelial and epithelial cells have the zinc metallopeptidase angiotensin-converting enzyme (ACE) on their surfaces. Two physiological processes, one of which results in the generation of angiotensin II and the other in the breakdown of bradykinin, both depend on the angiotensin-converting enzyme (ACE). [24]

Figure 5: The figure represents the non-genetic factors that can cause PCOS

Figure 6: Represents the summary of various genes involved in PCOS
Angiotensin II (Ang II or Ang 1 - 8), the main active component of the renin - angiotensin system, is produced when ACE transforms the inactive decapeptide angiotensin I (Ang I or Ang 1–10) into the active octapeptide (RAS) [25] which controls blood pressure and fluid and salt balance in the body.

Juxtaglomerular cells in the kidneys generate renin as a result of salts, volume loss, or sympathetic activity. Angiotensin I, a vasoactive protein, is created when it cleaves the inactive peptide angiotensinogen, which is made by the liver. Angiotensin converting enzyme then converts angiotensin I to angiotensin II. Angiotensin II is a powerful vasodilator. It also stimulates the adrenal cortex, prompting the secretion of aldosterone, which activates kidney tubules, allowing them to reabsorb more salt and water from the urine. [26] These actions immediately operate to increase the quantity of fluid in the circulation, compensate for volume loss, and toise blood pressure. Angiotensin II also stimulates different cytokines and growth factors, hence mediating cell growth and proliferation. [27] Angiotensin II may also cause endothelial dysfunction by decreasing nitric oxide bioavailability. [28]

This enzyme additionally plays a role in fertility through its ability to cleave and release GPI - anchored membrane proteins in spermatozoa. Has also a glycosidase activity that releases GPI - anchored proteins from the membrane by cleaving the mannose linkage in the GPI moiety. [29]

**ALU element:**

ALU elements are a special type of transposable element (TE) or "jumping gene" that are only present in primates. Like other TEs, they are unique DNA sequences that move about the genome, or "jump," sometimes inserting copies of themselves directly into the middle of protein - coding genes. ALU components play a significant role in human evolution and are useful tools for forensic and molecular genetic investigations.

ALU elements are SINEs (short interspersed elements), which are a type of "nonautonomous" retrotransposon in and of themselves. They are highly repetitive DNA sequences. (Retrotransposons are transposable elements that travel throughout the genome via an RNA intermediate.) An ALU element is turned into messenger RNA by RNA polymerase, and then reverse transcriptase turns that messenger RNA into a double - stranded DNA molecule. [30]

**Structure of ALU element:**

The elements have an estimated copy number of 1.1 million and are presently retrotransposing in the genome of humans. [31] The complete length ALU element has a dimeric structure and is 300 bp long. Because both the left and right monomers are produced from the 7SL RNA gene, they have a high level of sequence similarity. There is a poly (A) tail at the 3' end of the 5' region as well as an internal RNA polymerase III promoter (A and B boxes). Due to the absence of a transcription terminator, the ALU element's transcription is started by an internal RNA polymerase III promoter and terminated at a nearby chromosomal location with a TTTT terminator [32] as shown in **figure 9**.

**Figure 8:** Schematic representation Of ACE association with other genes (Source: Gene Mania)
Function of ALU element:
The chromosomal location and sequence properties of ALUs affect their functional potential. The human genome’s ALU distribution is unique in that it is tilted toward gene-rich regions. This is most likely because brief ALU insertions (300 bp) may be tolerated when placed in gene-rich locations. [33]

Because of their distinctive core sequences, ALUs have a significant potential for gene regulation. For instance, CpG dinucleotides, which are prone to methylation at the C of CpGs, are rich in ALU elements. In this instance, ALU elements might be actively implicated in gene expression control by introducing methylation at the DNA level when placed near gene bodies. Furthermore, ALU elements have several splice donor and acceptor sites, the majority of which are on the antisense strand. [34]

ALU sequences can introduce an unique splicing site selection when they are inserted into introns and co-transcribed with host genes, leading to a broader range of mRNA isoforms. [35] Finally, transcribed ALU sequences can contribute novel cis-regulatory elements like polyadenylation [p (A) ] signals [36] or adenine and uracil rich elements (AREs) [37], which are typically engaged in alternative polyadenylation or mRNA degradation.

The development of secondary structures is related to the regulatory actions of ALUs. Single ALU sequences have the ability to produce distinct secondary structures that control translation initiation when they are individually or in conjunction with other RNAs transcribed. [38]

ACE and PCOS:
The development of the corpus luteum, ovulation, body homeostasis, and steroidogenesis all depend on the Renin-Angiotensin System (RAS). Many tissues, including the ovary, contain it (Bayram et al., 2011). Peptidyl dipeptidase A, often known as ACE or kininase II, is the main rate-limiting element of the RAS system. It is encoded on chromosome 17 by the ACE gene. Among other physiological processes, steroidogenesis is aided by the ACE product angiotensin II (Ang II) (Bayram et al., 2011; Bernstein et al., 2013). Furthermore, it is believed that excessive levels contribute to the genesis of PCOS, obesity, inflammation, oxidative stress, and other diseases (Ramalingam et al., 2017).

Figure 9: Figure representing the Sequence features of consensus ALU elements

Figure 10: Represents the Hypothetical pathway of PCOS by ACE.
ACE, on the other hand, has been linked to hormonal instability in a few studies. The ACE gene has an insertion-deletion polymorphism (I/D polymorphism), based on the insertion of a 287 bp region, which is associated with increased plasma ACE levels. It disrupts the normal RAS function, which upregulates the RAS and aids in the development of PCOS (PALUmbo et al., 2016). Determining how ACE contributes to the pathophysiology of PCOS is therefore a topic of interest for researchers. Numerous investigations have discovered that high levels of ACE cause insulin resistance (IR) in tissues via releasing reactive oxygen species (ROS) (Manucha et al., 2015; Ramalingam et al., 2017).

Hyperandrogenism, a typical PCOS phenotypic expression, is brought on by IR. ROS - driven low - grade inflammation is brought on by the ACE gene's I/D polymorphism. The metabolic risk factors for the deadly quartet (obesity, diabetes mellitus, etc.) include IR and hyperandrogenism, which are connected to PCOS pathogenesis (Barrea et al., 2018). In the past, we looked at the connections between a number of genes and the pathogenic reasons of PCOS (Lone et al., 2020 a, b). Figure 10, which depicts the steroidogenesis process, was used to examine the relationship between the ACE gene's I/D polymorphism and the risk of polycystic ovarian syndrome.

**ALU ACE Insertion/deletion Polymorphism**

A polymorphic variant in intron 16 that consists of an insertion (I) or deletion (D) of a 287 - noncoding base pair ALU repeat sequence has been linked to altered ACE concentration. [39]

The Angiotensin I - converting enzyme (ACE) gene has been identified as a candidate gene for hypertension and related diseases, including diabetic nephropathy. It also helps to regulate vascular tone by inactivating the vasodilator bradykinin. The ACE gene in humans is located on chromosome 17 at position q23, spans 21 kb, and contains 26 exons. ALU ACE is a polymorphic intragenic AM insertion in the ACE gene that serves as a marker for population structure analyses. The absence of insertion in the Lq ACE ALU insertion polymorphism appears to be associated with several disease phenotypes. Its elevated ACE levels in plasma. As a result of disrupting normal steroidogenesis, it upregulates the RAS and leads to PCOS development. [40]

The DD ACE genotype is linked to the highest serum levels of the enzyme, the DI genotype to the intermediate levels, and the II genotype to the lowest levels. [41] Several studies have been conducted to date to investigate the relationship between ACE I/D polymorphism and PCOS. However, the findings of these studies were inconclusive and underpowered. The current meta - analysis was carried out to obtain a more precise estimate of the relationship between I/D polymorphism of the ACE gene and PCOS risk. [42]

2. Conclusion

The study's findings were beneficial in aiding comprehension of the intricacy of PCOS development. This component is crucial for comprehending the genetic underpinnings of illness and has proven to be an effective way for treating PCOS.

The studies suggest that the pathophysiology of PCOS was not directly linked to the I/D polymorphisms in the ACE gene. Studies show that the genotype DD and allele D were much more common in the PCOS group. The genotypes I and II of alleles were found more frequently in controls than DD. High percentages of patients with the DD genotype also had PCOS and hyperandrogenism. [43]

The Variants, however, were connected to ovarian steroidogenesis. This shows that, while not being the primary etiological cause, the I/D polymorphisms in the ACE gene may be linked to the worsened clinical signs of PCOS. Understanding how this polymorphism affects distinct ethnic groups is important since they may provide varying PCOS risks to different populations and serve as biomarkers for PCOS prevention. Therefore, as the conclusion, the study aims to investigate the intricate genetic process in the pathogenesis of PCOS and the genotyping analysis revealed that patients are more likely than controls to have the DD genotype. In controls, the ID and II genotypes predominate.

References


syndrome: the complete task force report. Fertility and sterility, 91(2), 456-488.


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