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The Molecular Changes and Genetic Pathways of the Endometrial Precancers

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ABSTRACT

Background: Endometrial hyperplasia (EH) is considered as precursor lesion to endometrioid endometrial cancer. The recently updated 2020 World Health Organization (WHO) distinguishes between atypical hyperplasia / endometrioid intraepithelial neoplasia (AH/EIN) and endometrial hyperplasia without atypia. AH/EIN is with higher risk for progression to EC than EH without atypia. The progression of atypical endometrial hyperplasia to endometrial cancer is driven by a series of molecular and genetic alterations. Recent studies focused on genetic association between AH/EIN and EC, especially in the context of molecular classification. The most common genetic mutations that occur in AH/EIN and EC are MSI, PTEN, CTNNB1, ARID1A, PIK3CA, KRAS, and PAX2.

Aim: The work aimed to give an overview on the molecular changes and genetic pathways of the endometrial precancers and the role of it in progression and diagnosis of EC.

Conclusion and Future directions: Our knowledge of endometrial carcinoma and associated precancers has greatly improved as a result of the notable advancements in genomic, molecular, and biomarker research. The development of diagnostic schemas during the previous 20 years reflects this progress. The incorporation of biomarkers into our daily clinical practice has been a gradual but steady process, leading to the updated diagnostic criteria in WHO 2020. There are genetic association between AH/EIN and EC, especially in the context of molecular classification. The most common genetic mutations that occur in AH/EIN and EC are MSI, PTEN, CTNNB1, ARID1A, PIK3CA, KRAS, and PAX2. Rapid advancements in our knowledge of the molecular pathways and abnormalities that define early endometrial cancers, precancers, and precursors should be used consistently to improve risk stratification and diagnostic approaches for this prevalent premalignancy in women. However, problems still exist and need to be investigated further in subsequent research.

Keywords: Endometrial hyperplasia, atypical hyperplasia / endometrioid intraepithelial neoplasia, genetic mutations

INTRODUCTION

Definition of endometrial hyperplasia:

Endometrial hyperplasia (EH) is a heterogeneous set of pathologic lesions that range from mild, reversible glandular proliferations to direct cancer precursors **[1].** It is considered as precursor lesion to endometrioid endometrial cancer(type 1 EC) **[2].**

Incidence of endometrial hyperplasia:

Its incidence has been estimated to be thrice the number of cases of endometrial cancer in the United States **[3] .** So earlier and more accurate diagnosis of EH represents an outstanding opportunity for prevention and improved patient management of this EC **[4].**

Risk factors of endometrial hyperplasia:

Hormonal Imbalance:

One of the most critical drivers of EH and its progression to EC is unopposed estrogen exposure, where the endometrium is subjected to prolonged estrogenic stimulation without the protective effects of progesterone **[5].**

Many factors cause these hormonal imbalances. The main factors are Obesity, polycystic ovarian syndrome (PCOS), perimenopause, functional tumors as granulosa cell tumor, and iatrogenic (estrogen only replacement hormonal therapy) **(Figure 1) [2]**.

Genetic Predisposition:

Lynch syndrome: Lynch syndrome is a genetic disease of autosomal dominant inheritance caused by mutation of one or more of the genes of the DNA mismatch repair system (MSH2, MLH1, MSH6, and PMS2), leading to microsatellite instability, which confers a markedly elevated risk for several types of cancers, particularly colon and endometrium. Patients with hereditary nonpolyposis colorectal cancer have a lifetime risk of 40% to 60% for the development of endometrial cancer **[6].** Recent studies have recommended screening patients diagnosed with atypical endometrial hyperplasia or endometrial cancer for microsatellite instability **[7].**

Familial Cancer Syndromes: Other less common familial cancer syndromes may also predispose women to EC, including Cowden syndrome (associated with mutations in the PTEN gene), which can increase the risk of both breast and EC **[8].** These genetic predispositions underscore the importance of genetic testing and counseling for women with a family history of cancer **[9]**.

Lifestyle and Other Risk Factors:

Several lifestyle-associated factors also contribute to the development and progression of atypical endometrial hyperplasia such as:

Sedentary Lifestyle: A lack of regular physical activity that causes obesity, insulin resistance, and hormonal imbalances, all of which elevate the risk of developing atypical hyperplasia and EC**[10].**

Diabetes: Diabetic women have an increased risk of developing EC, even independent of obesity **[11]**. Hyperinsulinemia and insulin resistance, common in type 2 diabetes, may promote endometrial proliferation and cancer progression through various mechanisms, including increased levels of insulin-like growth factors, which have mitogenic effects on endometrial cells **[12].**

Hypertension: Hypertension is often part of the metabolic syndrome, which is closely associated with obesity and diabetes **[13].** The relationship between hypertension and EC remains unclear , but hypertension may act as a marker for the constellation of metabolic risk factors, including obesity and insulin resistance, that raise cancer risk **[14].**

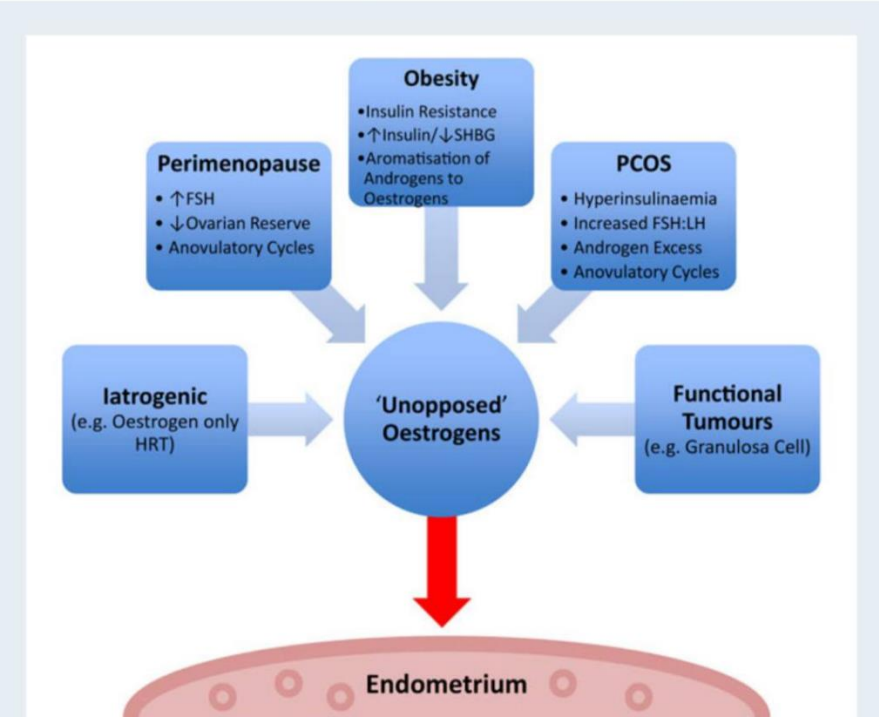

Figure 1. Factors contributing to 'unopposed' estrogen exposure of the endometrium **[2].**

Clinical Presentation of endometrial hyperplasia:

Abnormal uterine bleeding (AUB) is the most frequent presenting symptom of endometrial hyperplasia according to the International Federation of Gynecology and Obstetrics (FIGO) systems for nomenclature of symptoms of normal and abnormal uterine bleeding (AUB) in the reproductive years (FIGO AUB System 1) and for classification of causes of AUB (FIGO AUB System 2; PALM-COEIN) that were first published together in 2011 **[15].** This includes menorrhagia, intermenstrual bleeding, postmenopausal bleeding, and irregular bleeding on hormone replacement therapy or tamoxifen. Endometrial hyperplasia affects both premenopausal and postmenopausal women, accounting for approximately 15% of cases of women presenting with postmenopausal bleeding **[16]**.

Endometrial hyperplasia can also be asymptomatic and may, in some cases, regress spontaneously without ever being detected **[17].** Confirmation of diagnosis of endometrial hyperplasia requires histological analysis of endometrial tissue **[18].**

Histological Classifications of Endometrial Hyperplasia:

In 1994-1999, World Health Organization (WHO) classification had categorized endometrial hyperplasia based on the complexity of glandular architecture and the presence of cytologic atypia, identifying four categories: simple hyperplasia (SH), complex hyperplasia (CH), simple atypical hyperplasia (SAH), and complex atypical hyperplasia (CAH) **[2, 19]**. However, several studies demonstrated that endometrial hyperplasia has a dual nature, including benign proliferations reactive to unopposed action of estrogens, as well as precancerous lesions **[20, 21]**.

An additional categorization system called the endometrial intraepithelial neoplasia (EIN) system has been created in order to differentiate between benign hyperplasia and EIN based on three histomorphologic parameters: glandular crowding, lesion diameter >1 mm, and cytology distinct from neighboring endometrium **[22]**.

The 2014 WHO system has accepted the EIN system, recognizing the presence of only two categories of endometrial hyperplasia: endometrial hyperplasia without atypia (benign) or atypical hyperplasia (AH, premalignant) **(Figure2) [23] .**

The 2014 WHO classification has proven to have a more strong prognostic power, better reproducibility, and alignment with therapeutic options **[24]**. So, this classification was also maintained in the most recent WHO classification version of 2020, which, for the first time, recommended the inclusion of immunohistochemical biomarkers into the diagnostic workup for AH/EIN [25]. It states that "loss of immunoreactivity for Paired-box2 (Pax2), Phosphatase and Tensin Homolog (Pten) is desirable" in the diagnosis of AH/EIN. However, how numerous markers should be used in AH/EIN diagnosis has not yet been the objective of a thorough analysis or if other recently described markers of AH/EIN as B-Catenin would have diagnostic benefit **[26, 27].**

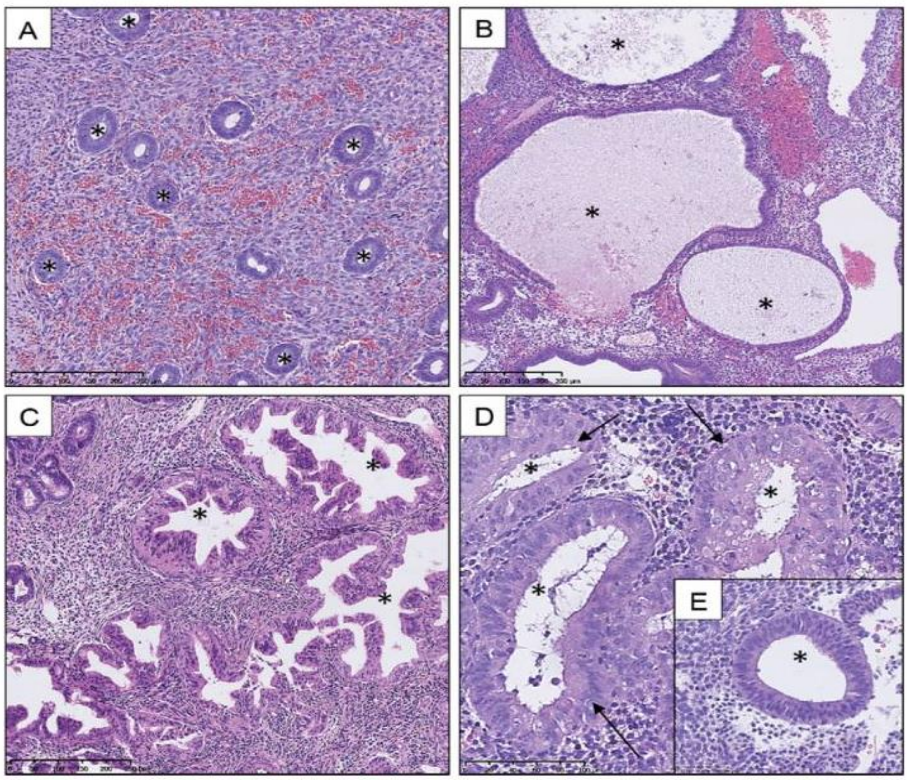

Figure.2 Hematoxylin and eosin (H&E) stained sections demonstrating variation in size and shape of endometrial glands within a spectrum of endometrial hyperplasia (EH) lesions compared to proliferative endometrium (PE). Selection of glands marked by * in lumen. (A) PE, (B) hyperplasia without atypia: large cystically dilated glands, (C) endometrial intraepithelial neoplasia (EIN): varied and irregular gland morphology, (D) high-power EIN lesion: cytological atypia within glands (arrow) and (E) excerpt of a phenotypically 'normal' gland cytology within the same section as D for comparison. Varying magnifications: see scale bars **[2].**

The risk of progression of Endometrial hyperplasia to Endometrial cancer:

It is well-established that progression to endometrial cancer (EC) is higher in women with atypical compared with non-atypical hyperplasia **[28]** and it is also well established that endometrial hyperplasia and type 1 EC are driven by estrogenic stimulation **[29].** But Other studies propose that AH/EIN is a neoplastic process that arises in NAH, a physiologic process **[30].**

Atypical endometrial hyperplasia bears a markedly elevated risk of carcinoma, with up to one-third of patients receiving a carcinoma diagnosis within a year **[31]**. Studies suggest that approximately 20–50% of untreated cases of AEH progress to EC, specifically type I endometrioid adenocarcinoma **[32, 33].** The wide range in risk estimates is likely due to differences in patient populations, risk factors, and study methodologies **[34]**.

Importance of early diagnosis of atypical endometrial hyperplasia:

The clinical importance of a diagnosis of EH relates to the long-term risk of progression to endometrioid EC. So, the early and accurate detection of AH/EIN offers an opportunity for treatment before progression to endometrial cancer. This could therefore result in a decrease in the prevalence of endometrial cancer and lower healthcare costs associated with its treatment **[34].**

Genetic characteristics of AH/EIN and its association with endometrial cancer:

The progression of atypical endometrial hyperplasia to endometrial cancer is driven by a series of molecular and genetic alterations. Recent studies focused on genetic association between AH/EIN and EC, especially in the context of molecular classification. The most common genetic mutations that occur in AH/EIN and EC are microsatellite instability (MSI), phosphatase and tensin homolog (PTEN), CTNNB1, AT-rich interaction domain 1A(ARID1A), PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha), Kirsten rat sarcoma viral oncogene homolog (KRAS), and Paired box2 (PAX2) **[35-40].** While the majority of AH/EIN cases fall into the NSMP group, a small percentage would be categorized within the POLEmut, MMRd, and p53abn groups. Immunohistochemistry (IHC) studies on AH/EIN further confirm that a minority of cases exhibit defective MMR and mutant-type p53 expression. Thus, AH/EIN likely serves as the precancer of endometrial carcinoma within the first three molecular groups and at least a fraction of the p53abn group as depicted in **(Figure 3) [41].**

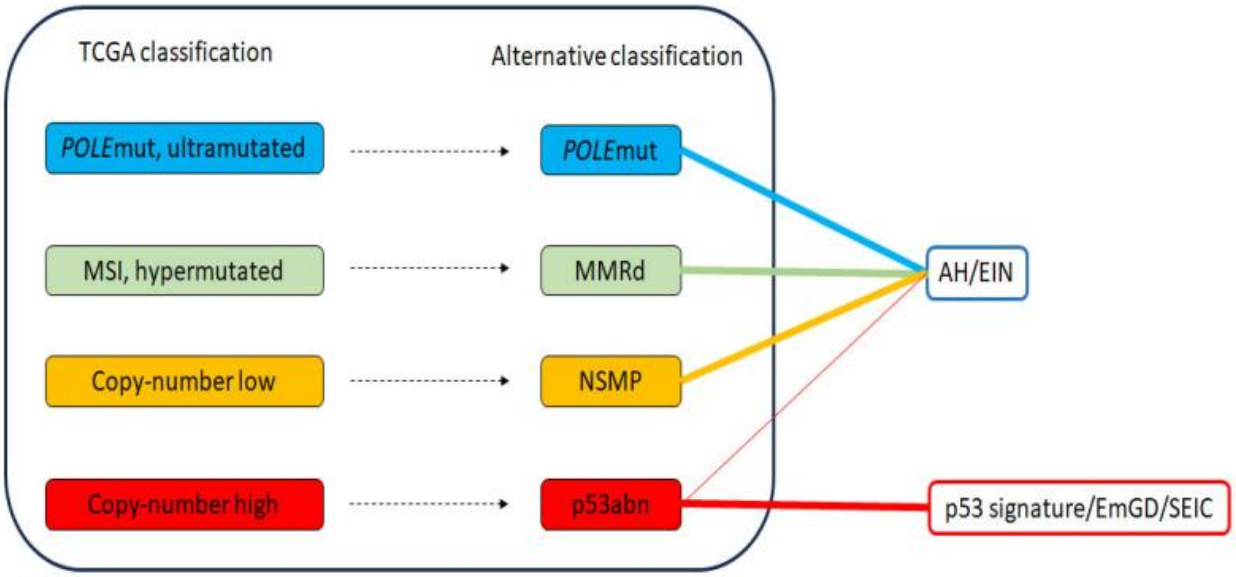

Figure.3 Relationship between TCGA molecular classification of endometrial carcinomas, alternative classification, and histopathologic variants of endometrial carcinoma precancers, along with the likely main pathway in the case of serous carcinoma. Dashed lines depict the approximate correlation between TCGA molecular classification and alternative classification groups of endometrial carcinomas. The thickness of the solid-colored lines indicates the strength of association between endometrial carcinoma groups and their corresponding precancers; thicker lines represent stronger associations, while thinner lines indicate weaker associations. MSI—microsatellite instability; MMRd—mismatch repair deficient; NSMP—no specific molecular profile; abn—abnormal; mut—mutated; EmGD—endometrial glandular dysplasia; SEIC—serous endometrial intraepithelial carcinoma **[41].**

Microsatellite instability (MSI)

MSI is a form of genetic hypermutability resulting from impaired DNA mismatch repair**[42].** MSI occurs in many types of tumors, such as colorectal, small bowel, endometrial, and gastric cancers **[43, 44]**. It is observed in a subset of atypical endometrial hyperplasia cases and is associated with an increased risk of progression to EC. MSI is also frequently observed in Lynch syndrome-associated ECs **[45, 46].**

AT-rich interaction domain 1A(ARID1A)

ARID1A acts as a tumor suppressor gene and its nuclear protein participates in forming of the SWI/SNF nucleosome-remodeling complex which included in important cellular functions as transcription modulation, DNA damage repair, DNA synthesis, and DNA methylation **[47, 48].** ARID1A was also used as a potentially useful immunohistochemical marker of AH/EIN, with loss of its expression in only 5–10% of cases [49]. It is one of the most frequently mutated genes in EC, leading to complete immunohistochemical loss of the protein in some mutant cases **[50].**

Kirsten rat sarcoma viral oncogene homolog (KRAS)

It is primarily involved in the cellular response to extracellular signals. It is strongly associated with down-regulation of mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene (PI3K/AKT) pathways **[51, 52]**. KRAS mutations have been mostly associated with type I estrogen-related EC and their frequency is estimated at around 10-30%. KRAS mutations occur at the early stages of the EC pathway **[53]**. Also, it commonly found in about 10–30% of endometrial hyperplasia cases contributing to the progression from hyperplasia to carcinoma **[54, 55].**

PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha)

Mutations of PIK3CA were discovered in multiple human cancers, including EC **[56].** It was found that PIK3CA mutations were in some cases of endometrial cancer and some of them were with PTEN mutation **[57].** Also, it was found that PIK3CA mutations in atypical endometrial hyperplasia and in endometrial carcinoma cases but in a small percentage of cases of atypical endometrial hyperplasia. It was assumed that PTEN mutations are a very early event, whereas PIK3CA mutations are important for the invasive potential **[58].**

Phosphatese and tensin homolog (PTEN)

Pten (Phosphatase and Tensin Homolog) is a tumor suppressor gene on 10q23 discovered in 1997 **[59].** Pten encodes a phosphatase with dual activity against phospholipids and proteins**[60].**

•Family & Structure:

Pten is a member of the large PTP (protein tyrosine phosphatase) family. It is a 200 kb gene located on chromosome 10q23.3. It is composed of 9 exons and 8 introns, and encodes a 403 amino acid long protein with a relative molecular mass of approximately 47 kDa **[61].** Pten also contains two PEST sequences and a PDZ motif in the carboxy-terminal (C-terminal region), and these elements were found to be dispensable for tumor suppressor function **(Figure .4)** [62]. It also has a C2 domain that is connected to the phospholipid membrane in vitro **[63].**

It is regulated by two proteins; shank-interacting protein-like 1 (SIPL1), which is a member of the NF-κB-activating linear ubiquitin chain assembly complex and protein interacting with carboxyl terminus 1 (PICT-1), which is localized to the nucleus and/or nucleolus **[64].** It is positively and negatively regulated by many transcription factors that operate at specific times and in different types of cells **[65].**

•Functions:

It has a lipid phosphatase activity, which induces cell cycle arrest, upregulates AKT-dependent pro-apoptotic mechanisms and downregulates Bcl-2-dependent anti-apoptotic mechanisms, acting in opposition to phosphatidylinositol 3-kinase (PI3K). Moreover, PTEN has 5 also a protein phosphatase activity, which is involved in the inhibition of focal adhesion formation, cell spread, and growth-factor-stimulated mitogen-activated protein kinase (MAPK) signaling**[66].**

•The role of PTEN in diagnosis of AH/EIN and EC:

It has played a major role, since PTEN loss of expression is regarded as the crucial event in endometrial carcinogenesis and occurs in an early phase **[30]** .In the 2017 European Society of Gynaecological Oncology (ESGO) guidelines (based on the 2016 European Society for Medical Oncology-ESGO-European Society for Radiotherapy & Oncology Consensus Conference), the immunohistochemical assessment of PTEN expression is recommended to recognize endometrial precancerous lesions (Atypical endometrial hyperplasia/endometrial intraepithelial neoplasia**)[67].**

Catenin beta-1(CTNNB1)

•Structure:

This gene encodes the protein β-catenin. The primary structure of B-catenin consists of three domains: a 550-amino-acid central repeat, an approximately 150-amino-acid N-terminal domain, and an approximately 100-amino-acid C-terminal domain on both sides **[68].**

•Functions:

It is involved in the establishment of body axis and orchestration of tissue and organ development during embryonic growth **[69].** Even in adult organs, it contributes significantly to processes like tissue homeostasis, organogenesis, stem cell maintenance, migration, apoptosis, proliferation, cell renewal, repair, and regeneration **[70, 71].**

•The role of CTNNB1 gene mutation in diagnosis of AH/EIN:

B-Catenin protein is normally expressed at the epithelial cell membrane where it functions in cell–cell adhesions. Mutations in exon 3 of the CTNNB1 gene or canonical Wnt pathway activation are associated with translocation of β-catenin to the nucleus, where it activates a specific transcriptional program [72, 73]**.** Wnt-b-catenin pathway is known to be involved in endometrial carcinogenesis, with specific regard to endometrioid adenocarcinoma and its precursor endometrial hyperplasia (EH)**[74, 75].**

B-catenin has been one of the most important markers studied to differentiate between premalignant EH and benign EH caused by unopposed action of estrogens **[2].**

There has been some evidence that nuclear b-catenin localization is an early event in endometrial carcinogenesis that defines AH/EIN **[76, 77].**

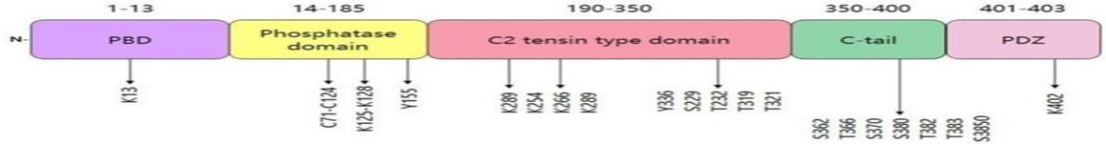

Figure (4): The structure of PTEN gene and occurrence of mutations in exons. Abbreviation: PBD: a p-hosphatidylinositol-4,5-bisphosphate (Ptdlns (4,5) P2)-binding domain) **[78].**

Paired box2(PAX2)

- **Family & Structure:**

Beginning in the late 1980s, with the advent of modern molecular biology techniques, investigators began studying a class of transcription factors that contain a "paired" DNA-binding region. Ultimately, these came to be known as the "master regulator" paired-box (PAX) proteins, due to their ability to regulate gene transcription during organismal development. These transcription factors are highly conserved that were found in vertebrates and invertebrates **[79]** .

- **Functions:**

Pax2 is one of nine Pax genes that have been described in vertebrates. Pax2 encodes a transcription factor that has a critical role in the development of the urogenital tract, the eyes, and the CNS. A mutation of PAX2 was reported in patients with optic nerve coloboma, vesicoureteric reflux, and renal anomalies **[80].**

• **The role of PAX2 in diagnosis of AH/EIN and EC:**

The loss of Pax2 expression correlates with the development of endometrial precancer and cancer. But The mechanisms of PAX2 loss in endometrium are not completely understood. Some studies have implicated epigenetic misregulation, may be due to hypermethylation of the PAX2 promoter **[81].**

Conclusion and Future directions:

Our knowledge of endometrial carcinoma and associated precancers has greatly improved as a result of the notable advancements in genomic, molecular, and biomarker research. The development of diagnostic schemas during the previous 20 years reflects this progress. The incorporation of biomarkers into our daily clinical practice has been a gradual but steady process, leading to the updated diagnostic criteria in WHO 2020.

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