ROLE OF CHALLENGING GENES IN THE DEVELOPMENT AND PROGRESSION OF OVARIAN CANCER: A REVIEW

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Abstract

Ovarian cancer incidence varies greatly across geographic areas and ethnic groups, with a high incidence in Northern Europe and the United States and a low incidence in Japan. The vast bulk of cases are sporadic, with only 5% to 10% of ovarian cancers being familial. The cause of ovarian cancer is unknown. Ovarian cancer has been linked to excessive gonadotropin and androgen stimulation. Although ovarian cancer accounts for a tiny fraction of all cases, genetics is a significant risk factor for the onset and progression of ovarian cancer. In the research of gene mutations associated with ovarian cancer, it was shown that women with no family history of the disease may nevertheless have a gene mutation associated with an elevated risk of ovarian cancer. All women diagnosed with ovarian cancer who were also found to have peritoneal cancer or fallopian tube cancer were referred for genetic counseling or testing. Ovarian cancer risk increases with increased family history of cancer. A vast number of genes in women provide hereditary susceptibility to ovarian cancer, which is commonly referred to as high-grade effective genes, Ineffective and low-grade effective genes. However, a specific predisposing gene is discovered in individuals with a suggestive personal or family history, which can alter in one of the few functioning genes, such as BRCA1, or BRCA2. A mutation in one of the uncommon, low grade effective genes such as MLH1, MSH2, MSH6, NBN, PALB2, ATM, BRIPI and EPCAM increases the risk of ovarian cancer. The identification of such genes and the development of control mechanisms may clear the way for more targeted ovarian cancer prevention.

Key words- Ovarian cancer, Genes, Risk, Protein –Protein interactions.

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Introduction

Ovarian cancer (OC) is defined as the existence of abnormal cells that begin in the ovary and then multiply uncontrollably, forming a tumor malignancy when they spread into the surrounding tissues. Ovaries are made up of three kinds of cells (oocytes, granulosa cells and thecal cell), and each cell has the potential to develop into a variety of tumors. Approximately 90% of ovarian cancers are of epithelial origin, including high-grade and low-grade serous carcinoma, clear cell endometrioid, and mucinous carcinoma, with 7% being stromal types and germ cell tumours being uncommon. There are several warning indications and signs for ovarian cancer, however the early symptoms are ambiguous and difficult to detect due to common gastrointestinal, genitourinary, and gynaecological problems. There are several obstacles to disease therapy for ovarian cancer, as well as numerous hurdles to sickness treatment. Despite early high rates of response to first chemotherapy and major surgery for approximately 70% of patients with relapses and intermediate progression-free 12- to 18-month survival and also states that long-term survival remains poorly known, with a significant opportunity of recurrence (Salima Akter *et al.*,2022).

About 25% of ovarian cancer cases are caused by an inherited genetic mutation affecting BRCA1 or BRCA2. Furthermore, healthy persons with germline BRCA1/2 mutations had a 60-70% greater likelihood of having breast cancer and a 15-40% increased risk of acquiring ovarian cancer. As a result, detecting cancer-related risk factors, particularly BRCA1 and BRCA2 gene mutations, is crucial for clinical care of high-risk women, which includes yearly screening, chemo-prevention, and preventative surgery (Alessandro Lavoro *et al*., 2022).

Since the discovery of BRCA1 and BRCA2 as breast cancer (BC) and ovarian cancer (OC) predisposing genes involved in the homologous recombination (HR) DNA repair pathway, no other major high risk gene has been identified to account for the remaining familial cancer cases found to be negative for germline pathogenic variants (PVs) in these genes.Carriers of PVs in MLH1, MSH2, MSH6, or PMS2, genes involved in the mismatch repair (MMR) pathway, have also been shown to have a substantially increased lifetime risk of getting OC, which is often linked with hereditary non-polyposis colorectal cancer syndrome families. Carriers of PVs in MMR genes, on the other hand, are exceedingly rare, accounting for fewer than 1% of sporadic OC cases, much lower than the 5-15% carrier frequency of PVs in BRCA1 and BRCA2 genes, depending on the community studied. PV carriers have been discovered in relatively new OC predisposing genes such as RAD51C, RAD51D, and BRIP1, all of which are implicated in the HR DNA repair process. PV carriers in each of these genes are expected to account for less than 2% of sporadic OC cases. PVs in other DNA repair genes, such as PALB2, CHEK2, and ATM, which have all been linked to BC risk, have lately been linked to OC, though risk has yet to be established. Other genes involved in different DNA repair pathways, such as FANCM, POLE, MRE11, RAD1, and FANCI have been suggested as candidate OC risk genes, and the frequency of PV carriers in these genes is also low in comparison to BRCA1 and BRCA2 carriers (Wejdan M. Alenezi *et al.*,2023).

Ovarian cancer is the fifth leading cause of cancer mortality in women, accounting for more fatalities than any other cancer of the female reproductive system. A woman's lifetime chance of developing ovarian cancer is about one in 78. Her lifelong risk of dying from ovarian cancer is approximately one in 108.This cancer primarily affects older people. Approximately half of all women identified with ovarian cancer are 63 or older. Ovarian cancer affects more white women than black women. Over the last 20 years, the number of women identified with ovarian cancer has gradually decreased. From 1990 to the mid-2010s, the occurrence rate fell by 1% to 2% per year and by nearly 3% per year from 2015 to 2019. This tendency is most likely due to increased oral contraceptive use in the latter half of the twentieth century and decreased menopausal hormone therapy use in the 2000s, both of which can reduce risk. Ovarian cancer mortality has decreased from 2% per year in the 2000s and early 2010s to more than 3% per year from 2016 to 2020, indicating both lower incidence and better treatment (cancer.org).

After cervical and endometrial carcinomas, ovarian cancer (OC) was the third most frequent gynaecological malignancy. OC has the highest fatality rate among gynaecological malignancies. OC was responsible for 2.5% of all cancers in women, but it was also responsible for twice as many cancer deaths.Early detection is crucial since OC has a 93% 5-year survival rate when diagnosed early. In recent decades, the number of lifetime ovulations, family history, smoking, benign gynaecological diseases, parity, and oral contraceptive use have all been identified as risk factors for OC. The combination of the aforementioned characteristics and genetic changes increases OC detection (Jia Hu, Zhe Xu *et al.*,2022).

According to research, nearly 20% of ovarian cancer patients have a hereditary genetic mutation that is the probable source of their illness. This malignancy has one of the largest rates of inherited mutations. The most prevalent variants are BRCA 1 and 2, but there are other genetic abnormalities as well. Genetic testing is important because if women have a genetic characteristic that increases their risk of ovarian or other gynecologic cancer, there are numerous things they may take to lower their risk (Ovarian cancer research alliance (ocrahope.org).

The 36 genes tested for ovarian cancer were APC, ATM, AXIN2, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM, GREM1, HOXB13, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLE, PTEN, RAD51C, RAD51D,and somatic tumor testing involved 11 genes: ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD51C, and RAD51D with microsatellite instability testing for 6–13 markers (Frank G. Lawton *et al*.,2022).

Table 1: Ovarian Cancer Classification

origin	Follopian tube epithelium	Endometriosis	Endometriosis	Follopian tube epithelium	unknown	Taken from Provinicial health services authority (PHSA) (gov.bc.ca)
% of all ovarian carcinomas	70%	10%	10%	<5%	<5%	
Precursor lesions	Serious tubal intra epithelial carcinoma(STIC)	Clear cell Boarder line tumor	Endometroid boarderline tumor	Serous boarderline tumor	Mucisinous Tumor	
Common mutations and molecular abbrevations	TP53 BRCA1/2,Herediatary Breast ovarian cancer	ARID1A PIK3CA CTNNB1 PPP2R1A MSI	PTEN CTNNB1 ARID1A PPPR2R1A MSI	KRAS BRAF	KRAS HER2 Amplication	
Potential molecular therapies	PARP Inhibitots,Immune check point inhibitors	Tyrosine kinase inhibitors	mTOR inhibitors	MEK1/2 Inhibtors	Trastuzumab	

(Table-1 taken from phsacomm@phsa.ca)

This article provides an overview of recently found genes linked to ovarian cancer risk. The purpose of this research is to highlight current findings in the genetic susceptibility of ovarian cancer revealed using candidate gene approaches of genes implicated in double strand break repair (DSB), DNA mismatch repair association studies.

Table2:Study of ovarian cancer genes according to impact on ovarian cancer

HEREDIATARY GENES	**DNAREPAIR GENES**	**MMR GENES**	**Ovarian Cancer Associated Genes**
BRCA1	PTEN	MLH1	ARIDIA
BRCA2	TP53	MSH2	HOXB13
	RAD50	MSH3	PPP2R1A
		MSH6	KRAS
		PMS2	CTNNB1

Herediatary ovarian cancer

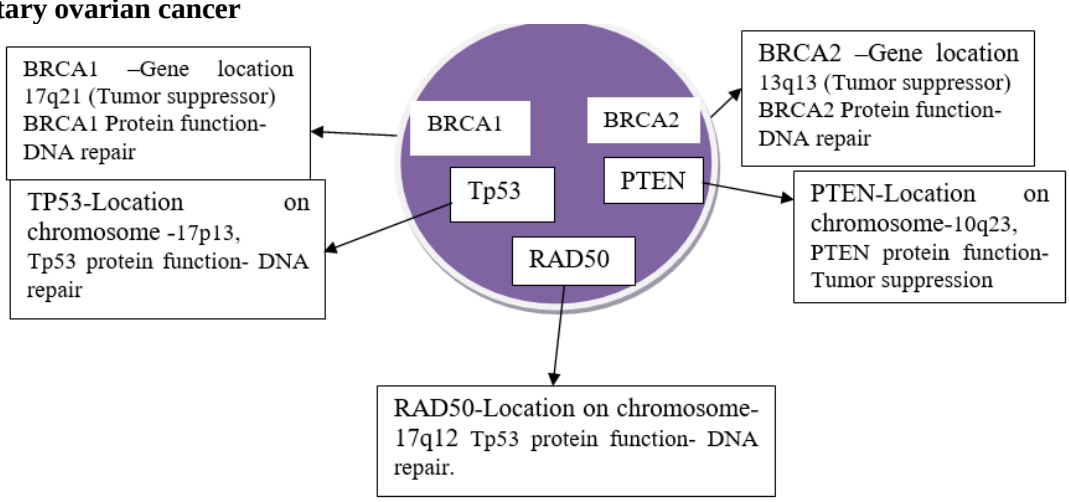


Figure 1-Indicates ovarian cancer genes chromosomal location and their proteins functional properties

Damaged DNA cannot be repaired when the BRCA1 and BRCA2 genes are mutated, leading in protein mistakes that lead to cancer. Ovarian cancer affects around 1.3% of women in the general population, but the risk is substantially higher for those with a damaging BRCA mutation. Women who carry a BRCA1 mutation have a 35% to 70% lifetime risk of ovarian cancer. Women who carry a BRCA2 mutation have a 10% to 30% lifetime risk of having ovarian cancer before the age of 70. Those with BRCA mutations are also far more likely to develop breast cancer and ovarian cancer at a younger age than those without BRCA mutations. Though BRCA mutations are most typically associated with an elevated risk of breast and ovarian cancer in women, males, as well as transgender men, are at a higher risk of developing male breast cancer. People who have BRCA genes are also more prone to acquire certain malignancies, including prostate cancer, pancreatic cancer, and melanoma (ocrahope.org).

Pathogenic genetic mutations in BRCA1 or BRCA2 are the most important heritable risk factors for ovarian cancer (OC). Women harboring pathogenic variants in either gene have a substantially elevated risk of OC ranging from 17% to 44% by age 80, based on the gene involved, whereas the general population's lifelong risk of OC is assessed to be 1.2% by age 80. Carriers of pathogenic BRCA1 or BRCA2 variants have been identified in 40-85% of OC with a family history of breast cancer (BC) and/or OC (i.e., hereditary breast and ovarian cancer (HBOC) syndrome families) and 10-15% of all epithelial OC, regardless of cancer family history. Over 20,000 BRCA1 and BRCA2 variants have been documented in the literature or Sources that are freely available in the context of hereditary BC and/or OC cases. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, approximately 15% of all reported variants were classified as pathogenic or likely pathogenic, with over 90% of these variants being of the nonsense, frameshift, or exon-intron splice junction type, resulting in a purported loss of gene function **(**Wejdan M. Alenezi *et al*.,2022).

And also, due to the possible risks of surgical involvement, oral contraceptives (OCs) have been studied as a chemoprevention strategy. Several observational studies, as well as a meta-analysis released in 2013 by Moorman et al., found that using OCs is linked with a lower risk of ovarian cancer while increasing the risk of breast cancer significantly. Based on earlier research, OCs have been recommended in some schools as a temporary or alternative means of ovarian cancer protection in BRCA mutation bearers. In women with no knowledge of BRCA mutations, the use of OCs was substantially linked with an increased chance of breast cancer (Junli Park *et al*.,2022).

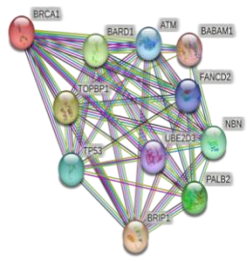
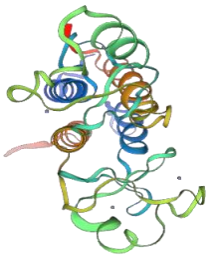
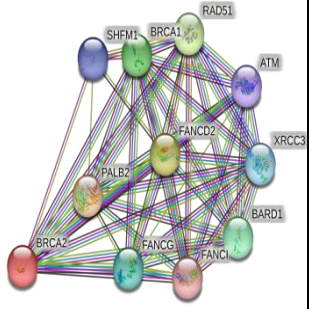
A) BRCA1	B) BRCA1 3D STRUCTURE	C) BRCA1 Functional properties
		E3 ubiquitin-protein ligase that selectively regulates the synthesis of 'Lys-6'-linked polyubiquitin chains and plays a critical role in DNA repair by enhancing cellular responses to DNA damage. It's unknown whether it also helps other forms of polyubiquitin chains develop. Its tumour suppressor action is dependent on E3 ubiquitin-protein ligase activity. To preserve genomic integrity, the BRCA1-BARD1 heterodimer coordinates a wide range of biological mechanisms such as DNA damage repair, ubiquitination, and transcriptionnal control.
D) BRCA2	E) BRCA2 3D STRUCTURE	F) BRCA2 Functional properties
		- BRCA2 is a protein that participates in double-strand break repair and/or homologous recombination, as well as binding RAD51 and promoting RAD51 assembly onto single-stranded DNA, hence increasing recombinational DNA repair. (ssDNA). BRCA2 functions by directing RAD51 to ssDNA rather than double-stranded DNA, allowing RAD51 to remove replication protein A (RPA) from ssDNA and stabilising RAD51-ssDNA strands by ATP inhibition. A PALB2-scaffolded HR complex component that contains RAD51C and is considered to have a role in HR-mediated DNA repair. Checkpoint triggering is conceivable during the S phase.

Figure2: An overview of BRCA1 Protein complex

1)a,d -BRCA1 and BRCA2 Protein network structure (The BRCA1 ,BRCA2genes generated proteins interactions with a variety of proteins involved in ovary cancer)

2) b,e BRCA1and BRCA2 protein 3D structure displaying pattern for ovary cancer function3)C,f Functional properties of BRCA1,BRCA2 protein (a, b, c ,d,e,f Taken from string.org) DNA repairing

genes In mammalian cells, DSB repair is regulated by two distinct pathways: homologous recombination (HR) and non-homologous end-joining (NEJ) or(NHEJ). In HR, the broken strand is mended using the homologous chromosome or sister chromatid as a template, whereas in NHEJ, the fractured strands are bluntly joined together at a location of microhomology. Homologous recombination is a high-fidelity mechanism, where as NHEJ frequently results in small deletions at the location of fusing and is error-prone. HR-related genes include PTEN, TP53, RAD50. To repair DSB DNA MRE11, RAD50, and NBS1 protein products produce a multi-unit complex that binds to DNA DSBs, signalling and collecting components from the HR and NHEJ processes (Annika Auranen *et al*.,2005).

PTEN

PTEN tum our suppressor gene mutations are important in the aetiology of ovarian cancer. It is unclear how it affects the development of ovarian cancer cells. PTEN was supposed to prevent ovarian cancer by boosting the expression of P21, however it was observed that the expression of TRIM39 was significantly decreased in human ovarian cancer. The expression of TRIM39, which targets P21 and prevents P21 degradation, was substantially increased in SKOV3 cells treated with naringin (Xiaoping Ke et al.,2021).PTEN is important not only in causing cell cycle halt and encoding apoptosis, but also in other areas of cell physiology, such as the control of cell adhesion, migration, and differentiation. PTEN includes a protein tyrosine phosphatase (PTP) region with properties similar to "dual-specificity" phosphatases (DSPs), which can dephosphorylate both tyrosine and serine/threonine residues. The fact that most missense mutations in PTEN identified in primary tumors and cell lines are limited to exon 5, which encodes this domain, emphasises its functional significance. PTEN is an inefficient protein phosphatase in vitro, despite its similarity with dual-specificity phosphatases; however, it is very active on extremely acidic substrates. This result indicated that PTEN's substrates may not be proteins (Antonio Di Cristofano.DF *et al*.,2000).

Phosphatase and tensin homologue (PTEN) is a powerful cancer suppressor best known for inhibiting the phosphoinositide-3 kinase (PI3K) pathway. By phosphatase-dependent and phosphatase-independent actions, PTEN controls cell growth, migration, survival, genomic integrity, and metabolism. PTEN deletion was associated with immunoresistance and poorer response to programmed cell death protein 1 (PD-1) inhibitors in experimental melanoma mouse models through lowering T cell trafficking into tumours and T cell-mediated cell death in the malignancy. PTEN mutation has been identified as a cause in endometrioid and clear cell subgroups of ovarian cancer. PTEN loss is found in 6% of HGSOC11, and PTEN loss-of-function mutations allow for accelerated tumor growth in mouse and in vitro models of HGSOC. PTEN loss is common in HGSOC using bioinformatics and image analysis methods that corrected for cellularity in gene expression signatures from The Cancer Genome Atlas. PTEN and AR gene expression were found to be highly linked and to have a favourable impact on survival (Filipe Correia Martins *et al*.,2020).

Tp53

Tp53 is a nuclear transcriptional regulator that is involved in a variety of biological functions. p53 regulates the activation of hundreds of target genes by binding to DNA in order to preserve balance and genome integrity. When DNA is damaged, p53 can trigger DNA repair proteins, halt cell development by holding the cell cycle at the G1/S transition, enabling DNA repair, and start apoptosis if DNA damage is irreversible. An N-terminal transcriptional activation domain, a central sequence-specific DNA binding domain, a tetramerization domain, and a C-terminal regulation domain comprise the p53 protein. In addition to transcriptional activation, p53 has been linked to transcriptional suppression, though binding locations in its down-regulated target genes are less well understood. New research found that activating the expression of SLC7A11, a significant component of the cystine/glutamate antiporter, causes ferroptosis, a form of cell death caused by reactive oxygen species. As a result, p53's anti-tumor activities in cells are carried out via regulatory activity. These cellular anti-tumor activities of p53 could be used to create anticancer therapies (Yu Zhang *et al*.,2016).Ovarian cancer is a fatal cancerous tumor of the female reproductive system. The most prevalent form of ovarian cancer is high-grade serous ovarian cancer (HGSOC), which has TP53 mutation as a sine qua non. P53 (encoded by TP53) is essential for regulating the G1/S checkpoint, whose mutation leaves cells reliant on a working G2/M checkpoint for DNA repair, in which WEE1 kinase plays an important part. Targeting WEE1 to break the G2 barrier thus increases cellular development, resulting in mitotic catastrophe and cell death. AZD1775, a specific WEE1 kinase inhibitor, has shown encouraging antitumor action in patients with platinum-resistant ovarian cancer, particularly those with TP53 mutations. However, mechanistic insights into its

effectiveness and tolerance in ovarian cancer must be investigated further (Rourou Xiao *et al*., 2022). Mutations in the TP53 locus have been found in more than 90% of HGSOC patients. Previous research has shown that TP53 mutations can be identified in ctDNA from patients with advanced stage HGSOC and that changes in ctDNA levels associated with clinical response and outperformed CA-125. However, TP53 mutations in HGSOC are randomly dispersed in all coding regions, and chemotherapy has been shown to induce clonal evolution of TP53 mutations, posing a problem for patient monitoring during treatment. As a result, ctDNA analysis in HGSOC is expected to necessitate the use of next generation sequencing (NGS) methods (Leslie Calapre *et al*.,2023).

RAD50

Misfunction of the MRE11-RAD50-NBS1 (MRN) complex has been linked to a variety of diseases, including inherited and sporadic cancers including ovarian cancer. MRE11 abnormally degraded nascent DNA in tumour suppressor BRCA1/2-deficient cells, and MRE11 activity is related to PARP (Poly ADP ribose polymerase) inhibitor resilience in cancer treatment. At the molecular level, human MRN and yeast Mre11-Rad50-Xrs2 (MRX) promote DNA double-strand break (DSB) repair via NHEJ and HR via DNA tethering, activation of downstream pathway components, and ATP-dependent resection of the 5′-terminated strands at DSB. The MRN/X complex also triggers the ATM/Tel1(Apical kinase) DNA damage checkpoint kinase, which phosphorylates targets to coordinate cell cycle arrest and DNA repair. Furthermore, MRN/X and ATM/Tel1 help to maintain typical telomere length (Vera M. Kissling *et al.*,2022).

The MRN (MRE11-RAD50-NBS1) and KU70/ KU80 complexes can detect double-stranded breaks (DSBs). The first complex's binding prepares the breaks for HR repair, whereas the second complex's binding results in NHEJ. The MRN complex, which is made up of two MRE11 subunits, two RAD50 subunits, and two NBS1 subunits, is involved in both DSB recognition and repair in ovarian cancer. MRN is recruited to DNA damage sites through interactions with several proteins, including H2AX and RAD17. MRE11 is a critical component of the MRN complex, displaying endonuclease and exonuclease activity from 3′-5′. The proteins UBQLN4, C1QBP, p97/VCP, and GRB2 control MRE11 nuclease activity by stopping MRE11 from binding to DNA or by inhibiting MRE11 activity (Alejandro Belmonte-Fernández .*et al.*,2023).

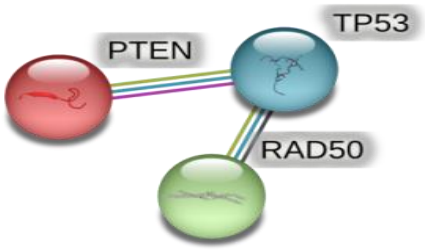


Figure3: protein network structure of DSB repairing genes

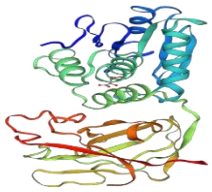
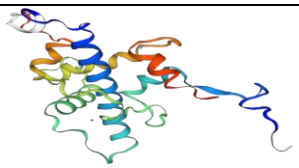
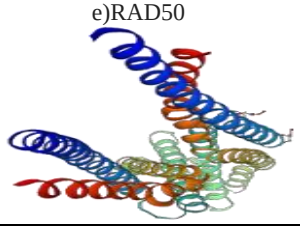
a)3D structsdure of PTEN 	b) Phosphatase and tensin ortholog; tumour inhibitor. As a dual-specificity protein phosphatase, it dephosphorylates tyrosine-, serine-, and threonine-phosphorylated proteins. It also acts as a lipid phosphatase in vitro, removing the phosphate from the D3 position of the inositol ring in phosphatidylinositol 3,4,5-trisphosphate, phosphatidylinositol 3,4-diphosphate, phosphatidylinositol 3-phosphate, and inositol 1,3,4,5-tetrakisphosphate. PtdIns(1,3,4,5)P3 > PtdIns(3,4,5)P2 > PtdIns3P > Ins(1,3,4,5)P4. Its tumour suppressive function is based on the activity of its lipid phosphatase.
 c)TP53	d) Cellular tumour antigen p53; acts as a tumour suppressor in a variety of tumour forms; triggers growth arrest or apoptosis depending on physiological conditions and cell type. As a trans-activator involved in cell cycle regulation, it operates to negatively restrict cell division by regulating a group of genes essential for this process. One of the active genes is a cyclin-dependent kinase inhibitor. Induction of apoptosis appears to be achieved by either activation of BAX and FAS antigen expression or suppression of Bcl-2 expression.
e)RAD50 	f) RAD50 is a DNA repair protein that is part of the MRN complex and is required for DSB repair, DNA rearrangement, telomere integrity preservation, and meiosis. MRE11 supplies the complex with single-strand endonuclease activity as well as double-strand-specific 3'-5' exonuclease activity. RAD50 may be required to bind and retain DNA ends close together. This might make it simpler to find short or long sequence homology regions when recombining DNA templates, as well as increase the activity of DNA ligases and/or restrict the activity of nucleases.

Figure4: 1)a,c,e 3D structures of PTEN,TP53,RAD50 Protein network structure (**PTEN,TP53,RAD50** genes generated proteins interactions with a variety of proteins involved in ovary cancer)
2) b,d,f functional property of **PTEN,TP53,RAD50**C,f) (a, b, c ,d,e,f Taken from string.org)

Everyone inherits two copies of each of the Lynch Syndrome alleles, one from their mother and one from their father. Even if an individual gets a Lynch syndrome gene mutation, they still have a normal copy of the gene from the other parent. Cancer develops when a second mutation effects the typical functioning duplicate of the gene, resulting in the individual no longer having a functional copy of the gene. Unlike the hereditary Lynch syndrome mutation, the second mutation would only be present in cancer cells and would not be present throughout the person's body. However, not everyone who has Lynch syndrome develops cancer (centers disease control and prevention).

Table 3: Mismatch repair genes involved in ovary cancer

	Chromosomal location	Protein	Protein function	Tumor suppressor/ Oncogene	Syndrome associated
MLH1	3	• MutL protein homolog 1	Mismatch repair	Tumor supressor	Lynch syndrome
MSH2	2p21-p16.3	MutS homolog 2	Mismatch repair	Tumor supressor	Lynch syndrome
MSH3	14q24.3	mutL homolog 3	Mismatch repair	Tumor supressor	Lynch syndrome
MSH6	2	mutS homolog 6	Mismatch repair	Tumor supressor	Lynch syndrome
PMS2	7p22	PMS1 protein homolog 2	Mismatch repair	Tumor supressor	hereditary nonpolyposis colorectal cancer,

MLSH1 GENE

The MLH1 gene codes for a protein that serves an important part in DNA repair. This protein aids in the correction of mistakes produced during DNA replication in readiness for cell division. The MLH1 protein interacts with another protein named PMS2 (which is produced by the PMS2 gene) to create a two-protein complex known as a dimer. This complex regulates the actions of other proteins that repair DNA replication errors. The repairs are performed by removing an error-ridden segment of DNA and substituting it with a rectified DNA pattern. The MLH1 gene is a member of the mismatch repair (MMR) gene family (https://www.nlm.nih.gov/).

Mutations in MLH1 in the sperm cells cause the cancer risk condition hereditary nonpolyposis colorectal cancer (HNPCC). Rodents with a null mutant in the Mlh1 gene were created. mice homozygous for the Mlh1 gene are prone to having gastrointestinal (GI) tract tumors, lymphomas, and a variety of other tumor forms. The researchers investigated the function of adenomatous polyposis coli gene (Apc) gene mutations in the GI tumors of Mlh1 mutant mice using various techniques and discovered that the GI tumors of Mlh1 mice express little or no adenomatous polyposis coli protein. When an Apc DNA variant was introduced into Mlh1 mutant mice, the frequency of GI tumors rose 40-100-fold. Mutations were discovered in the wild-type Apc gene in these tumors. These findings demonstrate that created two rodent models for human HNPCC and that the processes of tumor formation in these mice's GI tract involve loss of Apc gene function in a fashion very similar to that seen in HNPCC GI tumors (Winfried Edelmann.*et al*.,1999)

MLH1 promoter methylation was also discovered to be a constitutive occurrence in individuals with LS and no other MMR mutations. MLH1 methylation imparts an increased risk of CRC (colorectal cancer) and other typical LS cancers by acting like a traditional 'first strike' mutation on genomic DNA. The precise incidence of this occurrence has not been determined, but it ranges between 3% and 9% in probable LS patients with no germline MMR mutation, MSI-H, and immune histochemical loss of MLH1. These patients typically have serious LS-related cancer phenotypes in terms of tumour location, age of cancer start, and molecular pathology (Giulia Cini *et al*.,2015)

In eukaryotes, MutL is necessary for MMR function, whereas MutL and MutL play only a minor role in MMR1. In S. cerevisiae, Mlh1-Mlh2 are recruited to the mispair site and facilitate the MMR reaction in specific circumstances, whereas Mlh1-Mlh3 operate predominantly during meiosis, aiding the resolution of recombination intermediates. MLH proteins are homologs of the E. coli MutL MMR protein and have a similar structure that includes an N-terminal domain with ATPase activity, a disordered linker, and a dimerization-required C-terminal region. MLH su NTDs may also dimerize, forming a ring-like structure that may envelop DNA. Importantly, the MutL and MutL CTDs, but not MutL, contain en, which allows these complexes to nick DNA (Gloria X. Reyes 2020 *et al*.,2020).

MLH2

Lynch syndrome, also known as "hereditary nonpolyposis colorectal cancer," was first

identified in 1967 by American surgeon Henry Lynch, MD.In 1993, scientists found that abnormalities in the MSH2 gene were linked to Lynch syndrome. A gene mutation that produces Lynch syndrome affects approximately 1 in 440 individuals in the United States. In addition to MSH2, researchers have discovered four other gene changes related to the disease. MSH2 gene abnormalities account for approximately 40% of Lynch syndrome instances caused by a gene mutation. Muir-Torre syndrome is a type of Lynch syndrome caused by abnormalities in the MSH2 locus. People with this disease are more likely to acquire colorectal cancer and uncommon cutaneous tumors. The MSH2 gene codes for the MSH2 protein, which aids in the repair of mistakes produced when DNA is copied prior to cell division. MSH2 creates a protein complex with one of two additional proteins, MSH6 or MSH3. which is vital for the prevention of ovarian cancer This complex searches for DNA mistakes that happened during replication . The mistakes are then repaired by another set of proteins known as the MLH1-PMS2 complex.MSH2 is a member of the mismatch repair (MMR) gene family (Julie Lynn Marks *et al*.,2022).

A person with an MSH2 DNA variation can benefit his family members. It can also assist a person in better understanding his cancer risk.Men and women who have an MSH2 mutation are 52 to 82 percent more likely to develop colon or rectal cancer during their lifetime. Women who have the mutation have a 25 to 60% lifetime risk of endometrial cancer and a 4 to 13% lifetime risk of ovarian cancer. If a person has an MSH2 mutation, he has a 50/50 probability of passing it on to his kids (Julie Lynn Marks *et al.*,2022).

A new research using single-molecule imaging by atomic force microscopy revealed that the discrimination between specific and non-specific MutS binding is significantly greater than previously described results based on bulk measurements. Furthermore, the binding affinities are discovered to be contingent on the sort of mismatch, as well as the local sequence context. The G.T mismatch is the most efficiently recognised and mended of all the mispaired bases, whereas the C.C mismatch is the least efficiently healed by MutS.MutS, with the help of MutL, starts mismatch repair by triggering MutH, which nicks the freshly synthesized, unmethylated GATC tract in an ATP hydrolysis-dependent way. This is followed by a coordinated action of the helicase, exonuclease, polymerase, and ligase functions, which returns the original sequence.

Using the E. coli system as a model, apply the same to the recently found eukaryotic MMR. Several studies have tackled the following MutS-related problems. Hopefully it answers How does the system accomplish particular identification of mismatches and oligomeric state of MutS when bound to the mismatch site and when bound to the homoduplex length of DNA adjacent to the mismatch site, signal of mismatch identification conveyed to a remote landmark site, the GATC tract, so that the downstream components, MutH-UvrD proteins, are triggered to achieve strand-specific correction (Nabanita Nag *et al*.,2007).

The MSH2 gene codes for a protein that serves an important part in DNA repair. This protein aids in the correction of mistakes produced during DNA replication in readiness for cell division. MSH2 combines with one of two other proteins, MSH6 or MSH3 (each produced by a separate gene), to create a two-protein structure known as a dimer. This complex recognises places on the DNA where mistakes occurred during replication. The MLH1-PMS2 dimer then attaches to the MSH2 dimer and corrects the mistakes by removing the mismatched DNA and duplicating a new section. MSH2 is one of a group of genes known as mismatch repair (MMR) genes (https://www .nlm.nih.gov/).

MSH3

The MSH3 gene is frequently mutated (43-52%) in MMR-deficient CRCs(colorectal cancers); however, germline variants in MSH3 have not been found. MSH3 mutations were found in 40% of hypermutated tumours investigated as part of the Cancer Genome Atlas study, with three quarters showing MSI. MSH3 protein production is lost as a result of a biallelic frameshift mutation at the 8 coding mononucleotide repeat in MSH3 exon 7. The MSH3 gene, found on chromosome 5q11-q12 , produces the MSH3 protein, which functions in a partly redundant manner with MSH6. MSH3-deficient animals produce MSI-positive gastrointestinal cancer at a late stage, implying that MSH3 loss can contribute to tumour initiation. MSH3 appears to play a part in the development of CRC, but its capacity to regulate chemosensitivity is unknown. Recent evidence suggests that MSH3 plays a role in the healing of oxaliplatin-induced DNA ICLs and co-localizes with DSB lesions caused by laser therapy or a cancer. Histone deacetylase (HDAC) enzymes are essential for HR correction of DSBs. HDAC inhibitors, such as phenyl hydroxamic acid (PCI-24781), have evolved as a family of anti-tumor therapeutic drugs. Recent evidence that HDAC (Histone de acetalase) inhibitors synergize with ionising radiation and other DNA-damaging substances suggests that HDAC inhibitors may work in part by

inhibiting DNA repair (Jae Myung Park *et al.*, 2013).

The protein encoded by this gene forms a heterodimer with MSH2 to form MutS beta, part of the post-replicative DNA mismatch repair system. MutS beta initiates mismatch repair by binding to a mismatch and then forming a complex with MutL alpha heterodimer. This gene contains a polymorphic 9 bp tandem repeat sequence in the first exon. The repeat is present 6 times in the reference genome sequence and 3-7 repeats have been reported. Defects in this gene are a cause of susceptibility to endometrial cancer. MSH3 (MutS Homolog 3) is a Protein Coding gene. Diseases associated with MSH3 include Familial Adenomatous Polyposis and Endometrial Cancer. Among its related pathways are DNA repair pathways, full network and homologous DNA Pairing and Strand Exchange. Gene Ontology (GO) annotations related to this gene include protein homodimerization activity and single-stranded DNA binding. An important paralog of this gene is MSH6 (www.genecards.org).The MSH3 gene, which is found on chromosome 5q11-13, was discovered in 1989. MSH3 and MSH6 function overlap and do not appear to play a major part in MMR when compared to the other genes (Hui-Kai Miao *et al.*, 2015).

MSH6 gene

The MSH6 gene is one of the DNA mismatch repair genes implicated in the formation of hereditary cancers, most notably colorectal and endometrial cancers. Researchers investigate on MSH6 family, as well as pathological and clinical findings from the proband's ovarian cancer. Studies shows that MSH6 gene mutations linked with colorectal and endometrial cancer, late-onset endometrioid ovarian cancer can be a characteristic of families with MSH6 germline variants (J. Suchy *et al* 2002).

The MSH6 gene codes for a protein that serves an important part in DNA repair. This protein aids in the correction of mistakes produced during DNA replication in readiness for cell division. The MSH6 protein interacts with another protein named MSH2 (which is produced by the MSH2 gene) to create a two-protein complex known as a dimer. This complex recognises places on the DNA where mistakes occurred during replication. Additional proteins, such as the MLH1-PMS2 dimer, then fix the mistakes by removing the mismatched DNA and duplicating a new section. The MSH6 gene belongs to a group of genes known as mismatch repair (MMR) genes (https://www.nlm.nih.gov/).

This gene encodes a member of the DNA mismatch repair MutS family. In E. coli, the MutS protein helps in the recognition of mismatched nucleotides prior to their repair. A highly conserved region of approximately 150 aa, called the Walker-A adenine nucleotide binding motif, exists in MutS homologs. The encoded protein heterodimerizes with MSH2 to form a mismatch recognition complex that functions as a bidirectional molecular switch that exchanges ADP and ATP as DNA mismatches are bound and dissociated. Mutations in this gene may be associated with hereditary nonpolyposis colon cancer, colorectal cancer, and endometrial cancer. Transcripts variants encoding different isoforms have been described (www.genecards org).

The 1358 aa long MSH6 protein was found to be a component of the mismatch repair complex, and mutations in the MSH6 gene were found in some tumor cell lines and cell lines chosen for resilience to alkylating agents. In contrast to the strong wide spectrum repeat instability found in Msh2, Mlh1, and Pms2 mutant cell lines, MSH6 mutant cell lines had weak microsatellite instability at mononucleotide repeats and little if any dinucleotide repeat instability. The exact function of Gtbp/Msh6 mutations in the start and development of cancer has not been established because these cell lines had mutations in other genes. To better comprehend the function of MSH6, cloned and characterised the rodent Msh6 gene and used gene targeting to create mice with a null mutation in this gene. The findings given here demonstrate that MSH6-deficient mice are viable, but homozygous mutant cells exhibit a single nucleotide mismatch repair defect. Most intriguingly, these rodents have a substantially shorter life span and acquire lymphomas, gastrointestinal (GI) tumors, and a variety of other kinds of tumors in tissues such as the liver, lung, skin, and soft tissues. Studies indicate that MSH6 mutations cause cancer vulnerability and that mutations in this gene may be implicated in hereditary cancer predisposition syndromes as well as some sporadic tumors that do not exhibit microsatellite instability (Winfred edlmann *et a*l.,1997).

PMS2

The PMS2 gene belongs to a group of genes known as mismatch repair (MMR) genes.The PMS2 gene codes for a protein that serves an important part in DNA repair. This protein aids in the correction of mistakes produced during DNA replication in readiness for cell division. The PMS2 protein interacts with another protein named MLH1 (which is produced by the MLH1 gene) to create a

two-protein complex known as a dimer. This complex regulates the actions of other proteins that repair DNA replication errors. Repairs are made by removing the erroneous portion of DNA and substituting it with a rectified DNA pattern. Variants in the PMS2 gene have been found in approximately 6% of families with Lynch syndrome who have a known genome change. Lynch syndrome raises the chance of many cancers, especially colon cancer. Cancers of the endometrium (uterine lining), ovaries, stomach, small intestine, liver, bile ducts, upper urinary system, and brain are also more common in people with Lynch syndrome. With a PMS2 gene variant, the chance of getting one of these cancers is 30% for women and 25% for males by the age of 75 (https://www.nlm.nih.gov/).

PMS2 hereditary heterozygous variants account for less than 5% of LS cases, and PMS2-related cancers are also uncommon when compared to other LS-associated MMR genes. Even the biggest single institution LSAOC cohort research did not find a single instance of a PMS2 heterozygous mutation. Given the rarity of LSAOC with PMS2 mutations, it is critical to discuss the critical clinicopathological features of such cases in order to make clear findings and better the prognosis of this subgroup of patients. Carrying PMS2 genetic variants (c.943C>T) increases the risk of developing LS-associated malignancies. Close clinical surveillance and prophylactic surgery are thus strongly advised to help decrease the incidence and fatality of LS-associated cancers (Xiaoqing Guo *et al*.,2019).

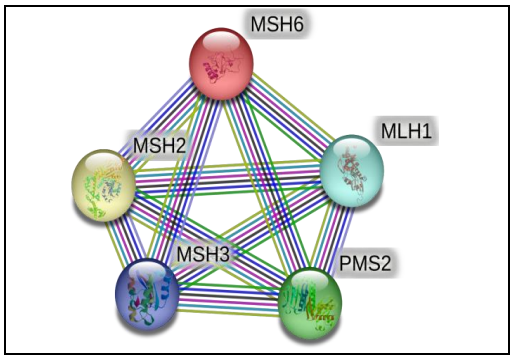
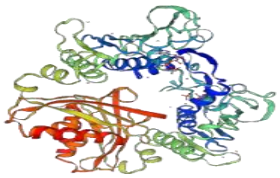
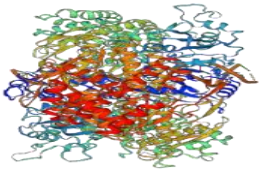
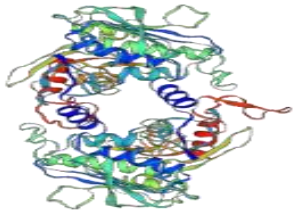
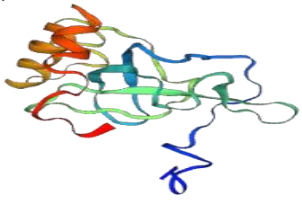


Figure 5: Shows the network structure of protein complex of MMR genes

a) MLH1 	f) Mlh1 is a DNA mismatch repair protein that forms a heterodimer with PMS2 to form MutL alpha, a component of the post-replicative DNA mismatch repair pathway. (MMR). MutS alpha (MSH2-MSH6) or MutS beta (MSH2-MSH6) attaches to a dsDNA misalignment, and MutL alpha is linked to the heteroduplex. In the presence of RFC and PCNA, the MutL-MutS- heteroduplex ternary complex is sufficient to begin PMS2 endonuclease activity.
b) MSH2 	g) Msh2 is a post-replicative DNA mismatch repair system component. (MMR). MutS alpha (MSH2-MSH6 heterodimer) and MutS beta (MSH2-MSH3 heterodimer) create heterodimers that bind to DNA mismatches and start heterodimers that bind to DNA mismatches and begin DNA repair. When heterodimers are coupled, they bend the DNA helix and protect about 20 base pairs. MutS alpha identifies single base mistakes as well as dinucleotide insertion-deletion loops (IDL) in DNA. MutS beta can identify longer insertion-deletion sequences ranging up to 13 nucleotides in length.
c) MSH3 	h) DNA mismatch repair protein Msh3 is a component of the post-replicative DNA mismatch repair mechanism (MMR). Heterodimerizes with MSH2 to create MutS beta, which binds to DNA mismatches and initiates DNA repair. When coupled, the MutS beta heterodimer bends the DNA helix and protects roughly 20 base pairs. MutS beta recognises big insertion-deletion loops (IDL) up to 13 nucleotides long. After mismatch binding, forms a ternary complex with the MutL alpha heterodimer, which is assumed to be in charge of guiding downstream MMR activities such as strand discrimination and excision.
d) MSH6 	I) DNA mismatch correction enzyme Msh6 is a component of the post-replicative DNA mismatch repair mechanism. (MMR). MutS alpha forms a heterodimer with MSH2 to form MutS, which binds to DNA mismatches and begins DNA repair. When connected, MutS alpha identifies single base mismatches and dinucleotide insertion-deletion loops (IDL) in the DNA and bends the DNA helix to protect around 20 base pairs. After binding to a mismatch, it forms a ternary complex with the MutL alpha heterodimer, which is thought to be in charge of driving downstream MMR events such as strand discrimination, excision, and translocation.
e) PMS2	j) PMS1 ortholog 2; Mismatch repair endonuclease; Mismatch repair system component PMS2 is a component of the post-replicative DNA mismatch repair mechanism. (MMR). MutL alpha is created by heterodimerization with MLH1. MutL alpha is attracted to the

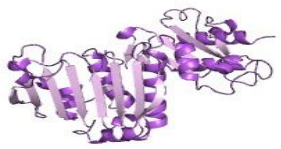
	heteroduplex after MutS alpha (MSH2-MSH6) or MutS beta (MSH2-MSH6) attaches to a dsDNA mismatch. The MutL-MutS-heteroduplex ternary complex is sufficient to induce PMS2 endonuclease activity in the presence of RFC and PCNA.

Figure6: An overview of mismatch DNA repair Protein complex

1) a,d,c,d,e–MLH1,MMSH2,,MSH3,,MSH6,,PMS2 Protein network structure (generated proteins interactions with a variety of proteins involved in ovary cancer)
2)f,g,h,I,j functional properties of proteins- MLH1,MMSH2,,MSH3,,MSH6,,PMS2 (a, b, c ,d,e,f,I,j Taken from string.org) complex.

Table 4 : Ovarian cancer associated genes

	Chromosomal location	Protein	Mode of action	Protein function	Tumor suppressor/Oncogene	Syndrome associated
AXIN2	17q23-q24	axis inhibition protein 2	Negatively controlled Wnt signaling pathway,	Reduces apoptosis	Tumor suppressor	Oligodontia-Colorectal Cancer Syndrome
HOXB13	17q21-22	Transcription factor	Activating mTOR pathway	Regulating transcription	Tumor suppressor	Increased risk of prostate cancer
NBN	8q21	nibrin	MRE11/RAD50	Involves in cell prolifiration	Tumor suppressor	Nijemen breakage syndrome
KRAS	12p	K-Ras	By turned on and off by the GTP and GDP molecules	Regulation of cell division	Oncogene	Cardiofaciocutaneous syndrome
CTNNB1	3p22.1	beta-catenin	transporting extracellular signals for nuclear programming	involved in regulation and coordination of cell–cell adhesion and gene transcription.	Oncogene	severe neurodevelopmental disorder

Ovarian cancer associated genes

ARIDIA

ARID1A is found on chromosome 1p36.11 and encodes ARID1A, a SWI/SNF complex core component. ARID1A is recognised as a cancer-inhibiting gene whose mutation may be implicated in the onset and progression of numerous malignancies due to its involvement in carcinogenesis. Next-generation sequencers have allowed genome-wide studies, and the first report of ARID1A mutation in ovarian clear cell carcinoma and ovarian endometrioid carcinoma was in 2010. Ovary clear cell cancer has a rate of 46-57%, ovarian endometrioid adenocarcinoma has a rate of 30%, and uterine endometrioid adenocarcinoma has a rate of 40%. . The mjority of these ARID1A variants are frame shift mutations. Loss of ARID1A expression is more common in endometriosis-associated ovarian clear cell carcinomas than in non-endometriosis-associated ovarian clear cell carcinomas, with loss of ARID1A in 61% of cystic ovarian clear cell carcinomas compared to 43% of adenofibromatous ovarian clear cell carcinomas. Ovarian clear cell carcinomas are classified as cystic or adenofibromatous, with cystic ovarian clear cell carcinoma being more closely linked with endometriosis and having a better outlook. Several studies have found that ARID1A mutations appear in the early stages of cancer, from endometriosis to ovarian cancer. Yamamoto et al discovered that ovarian cancer and endometriosis were linked with loss of ARID1A protein expression; that is, endometrial lesions contiguous to ARID1A-deficient ovarian carcinomas were ARID1A-deficient in 86-100% of cases. Recent research has shown that ARID1A mutations play a role in cancer via a variety of pathways, including the phosphatidylinositol-3-kinase (PI3K)/AKT pathway. Activation of this pathway promotes several processes that lead to cancer development, including cancer cell proliferation and suppression of apoptosis. These processes are primarily mediated by tyrosine kinase receptor activation and somatic mutation of specific signal transduction components, such as loss of phosphatase and tensin homolog (PTEN), a cancer-suppressor gene, and activation of mutation of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit (PIK3CA) (Takashi Takeda *et al*.,2016).

Although several other SWI/SNF subunit genes, including SMARCA4 and ARID1B, are also mutated, the ARID1A gene, which produces the BAF250A/ARID1A protein, is the most commonly mutated in OCCC. ARID1A mutations,

the majority of which are deleterious, are found in approximately 50% of OCCCs, and loss of the BAF250A/ARID1A protein, which acts as a regulatory subunit of the SWI/SNF complex, is found at a comparable frequency. Interestingly, BAF250A/ARID1A protein production is lost not only in homozygous mutants but also in heterozygous mutants. A prior research found that ARID1A mutations had post-transcriptional/ translational effects. Several studies have found that knocking out the ARID1A gene impairs transcriptional and DNA repair processes within cells; thus, the SWI/SNF complex function is (at least partly) lost in half of OCCC cases (Kazuaki Takahashi *et al*.,2021).

A smaller set of tumors (933 ENOC and 480 CCOC) were evaluated for CD8+ TILs inside the tumour epithelium, with ARID1A deletion associated with statistically significant increased CD8+ TILs in ENOC but not in CCOC, despite a tendency towards greater CD8+ TILs. ENOC patients with increased CD8+ TILs demonstrated a slight but statistically significant overall survival benefit. No comparable pattern was discovered in CCOC (clear cell odontogenic carcinoma). MMR deficiency (MMRd) was substantially associated with CD8+ TILs in ENOC and CCOC cancers, with a total incidence of MMRd of 13% of ENOC tumours and 5% of CCOC tumours.ARID1A deficiency is linked with increased CD8+ TILs in ENOC and intra-tumor CD8+ immune cells, implying a potential function for immunotherapy. Initial therapeutic studies in relapsed ovarian cancer revealed low reaction rates. However, when compared to other epithelial ovarian cancers, CCOC has shown better response rates, with the best response rate of 15.8% to pembrolizumab in the phase II trial (Saira Khalique *et al* 2022).

HOXB13

Deregulated expression of HOXB13 in a subgroup of oestrogen receptor-positive breast cancer patients treated with tamoxifen monotherapy is linked with an aggressive clinical course and horrific prognosis. Because the ovary is another hormone-responsive organ, HOXB13 plays a part in ovarian cancer development. Studies indicate that HOXB13 is expressed in numerous human ovarian cancer cell lines and tumors, and that RNA interference knockdown of endogenous HOXB13 in human ovarian cancer cell lines is linked with decreased cell proliferation (Jiangyong Miao.,*et al* 2007).HOX genes contain transcription factors that help to set fundamental body patterns during embryogenesis and keep particular organs functioning in adults. Recent research has shown that HOX genes play a role in the development of a variety of cancers. An expression profile of HOX genes was determined utilizing ovarian derived materials from surgical samples and epithelial ovarian cancer cells produced from five separate cell lines in order to establish whether HOX genes contribute to ovarian carcinogenesis (Tsuyoshi Yamashita *et al* ., 2006).

The homeobox group of transcription regulators includes the HOX gene family. The p53 promoter contains HOX consensus binding sites. In 50% of bladder cancer cases, a cell cycle abnormality and mutations in the TP53 gene were found. A TP53 DNA mutation causes the p53 protein to be overexpressed, increasing the chance of tumour development. The HOXB13 gene is found on chromosome 17q, which has been linked to renal, breast, ovary, colon, and some haematological cancers due to lack of heterozygozity. HOX and homeobox genes control many processes, including cell growth, differentiation, angiogenesis, receptor signaling, apoptosis, and the transcription of target androgen receptor genes. Abnormalities in HOX gene expression have been linked to aberrant growth and malignant neoplasms of the breast, leukemia, prostate, cervix, ovary, bladder, kidney, neuroblastoma, lung, and esophageal squamous cell carcinoma. HOX genes exhibited pro-angiogenic characteristics via increased expression of CXCL1, FGF2, IL8, and VEGFA, implying an involvement in tumour development (Elżbieta Złowocka-Perłowska *et al.*,2022).

PPP2R1A gene

The scaffolding component of the serine/threonine protein phosphatase 2A (PP2A) holoenzyme is encoded by PPP2R1A. This possible cancer suppressor complex participates in development and survival pathways. Research studies shows that somatic missense variants in 40.8% (20/49) of high-grade serous endometrial tumours and 5.0% (3/60) of uterine endometrioid carcinomas using targeted sequencing of PPP2R1A. Lower rates of mutations were found in ovarian tumors: 12.2% (5/41) of endometrioid and 4.1% (2/49) of clear cell carcinomas. In 50 high-grade and 12 low-grade serous carcinomas, no alterations were identified. PPP2R1A mutations are a common and possibly treatable characteristic of endometrial high-grade serous carcinomas. The discovery of common PPP2R1A mutations in high-grade serous endometrial cancer but not in high-grade serous ovarian carcinoma offers unambiguous genetic proof that these are separate diseases (Melissa K McConechy *et al*.,2011)

PPP2R1A, which encodes a scaffolding component of serine/threonine protein phosphatase 2A (PP2A), has lately been linked to a variety of gynaecological neoplasias. To further investigate this discovery, researchers examined the incidence of PPP2R1A mutations in some of the most prevalent histological subtypes of type I and type II ovarian cancer. A mutational study of PPP2R1A (exons 5 and 6) was performed on 88 primary ovarian carcinomas, which comprised mucinous, clear cell, high-grade serous, and high-grade endometrioid ovarian carcinoma.Exons 9 and 20 of Phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA), exon 1 of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), and exon 15 of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) were also read and analysed. Finally, mortality analysis was conducted to establish whether these mutations had any prognostic relevance. PPP2R1A mutations were found in 4.5% (1/22) of clear cell ovarian cancer, 4.5% (1/22) of high-grade serous ovarian carcinoma, and 6.7% (1/15) of high-grade endometrioid ovarian carcinoma (Munmun Rahman *et al*.,2013).

The most severe cell-cycle abnormalities produced by the PPP2R1A missense mutant were an ATRi-induced decrease in active S phase and premature mitotic entrance. ATRi treatment elevated 53BP1 bodies, a biomarker of leftover DNA damage in mitosis, in PPP2R1A mutants.

Following ATRi exposure, phospho-proteomic profiling of PPP2R1A mutant OCCC cells showed a selective increase in phosphorylation of Lysine Deficient Protein Kinase 1 (WNK1), as well as higher phosphorylation of WNK1 substrate Oxidative Stress Response Kinase 1 (OSR1). WNK1 depletion restored ATRi sensitivity and S phase abnormalities in PPP2R1A mutant cells, indicating a new function for this kinase (J.Stewart *et al*.,2022).

KRAS

Phosphoinositide 3-kinases (PI3Ks) are a lipid kinase family that plays an important part in intracellular signaling, regulating many physiological activities and cellular processes. In human tumors, the PI3K pathway is frequently mutated, resulting in dysregulated cell division, growth, survival, motility, and metabolism. Early PI3K inhibitors, so-called pan-PI3K inhibitors that target all isoforms, were tried in clinical trials due to promising therapeutic benefits in preclinical studies, but have proven to be less than ideal due to substantial toxicities and possible acquired resistance. Important signals are transduced by PI3Ks from different upstream sources such as receptor tyrosine kinases (RTKs) or G-protein coupled receptors (GPCRs). Blocking PI3K activity in cells changed by activated receptors is frequently enough to stop cell development. Despite the fact that oncogenic RAS mutants communicate in part through PI3K, PI3K inhibition has been found to be ineffectual in RAS transformed cells, and KRAS mutation has been discovered to be a prevalent resistance mechanism for PI3K inhibition. The RAS signalling pathway, like the PI3K pathway, is a ubiquitous method for controlling a wide range of cellular functions such as cell proliferation, differentiation, survival, motility, and metabolism in reaction to various extracellular stimuli. Notably, PI3K and RAS actively interact with one another to control one another and co-regulate downstream processes. By blocking only one route, compensatory signalling is induced in the other, ultimately leading to therapy failure and relapse (Min Ju Kim *et al*.,2020).

KRAS is a GTPase with a size of 21 kD that is involved in cell viability, growth, and differentiation. It is naturally expressed but only active when linked to GTP. KRAS has a comparatively brief and inducible GTP-bound life when it is operating normally. RAS protein mutations are identified in roughly one-third of all human cancers, with KRAS being the most commonly mutated variant.Single point mutations in the KRAS gene prevent intrinsic GTP hydrolysis, rendering the protein permanently active. KRAS gene mutation has been found as a transforming oncogenic event, creating an unstable environment that allows for more mutational selection and progressively violent illness. Greater KRAS activity in human tumours is caused by gene duplication, overexpression, or greater upstream activation in the absence of a mutation. KRAS genomic amplification, in particular, is linked to metastasis and a bad outcome in hormone-related malignancies such as ovarian cancer (Alexandra Maria Psaras *et al.*,2022)

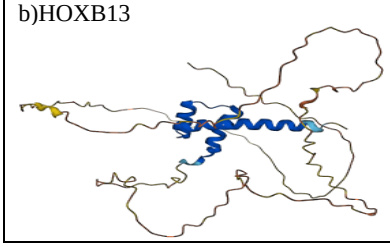
The KRAS gene codes for a protein named K-Ras, which is part of a signaling system known as the RAS/MAPK pathway. The protein sends messages from the outside world to the nucleus of the cell. These signals tell the cell whether it should expand and divide (proliferate) or mature and take on specialised tasks. The K-Ras protein is a GTPase, which means it transforms one substance, GTP, into another, GDP. In this way, the K-Ras protein functions as a switch that is activated and deactivated by the GTP and GDP molecules. To send messages, it must be activated by connecting (binding) to a GTP molecule. When GTP is converted to GDP, the K-Ras protein is switched

off (inactivated). When bound to GDP, the protein does not send messages to the cell's nucleus.
The KRAS gene is an oncogene, which is a type of gene that causes cancer. Oncogenes, when mutated, have the ability to cause regular cells to become cancerous. The KRAS gene belongs to the Ras oncogene family, which also contains the HRAS and NRAS genes. These proteins serve critical functions in cell reproduction, differentiation, and cell self-destruction (apoptosis)(https://www.nlm.nih.gov/).

CTNNB1

The CTNNB1 gene codes for the production of a protein known as beta-catenin. This protein is located in a variety of cells and tissues, mainly at junctions that link neighbouring cells. (adherens junctions). Beta-catenin is involved in both the binding of cells and the transmission of cells.
As an important component of the Wnt signalling system, the beta-catenin protein is also implicated in cell signalling. Certain proteins in this pathway bond to beta-catenin, triggering a multistep process that enables the protein to enter the cell nucleus. Once in the nucleus, beta-catenin works with other proteins to regulate gene function (expression). The Wnt signalling system promotes cell growth and division (proliferation) and assists in the selection of specific activities for cells. Wnt signalling is thought to play a role in several aspects of prenatal development. This pathway is important in the maintenance and renewal of adult stem cells, (whereby cells aid in tissue repair and can give birth to other types of cells). Beta-catenin appears to be crucial in the normal working of hair follicles, which are specialised structures in the skin where hair development occurs. This protein is involved in cells that make up the matrix of the hair shaft. These cells proliferate and mature to create the various components of the hair shaft and follicle. The hair shaft is forced upward and beyond the epidermis as matrix cells divide (https://www.nlm.nih.gov/)

Endometrial cancer has recently been discovered to have mutations in the catenin gene (CTNNB 1), resulting in abnormal nuclear -catenin accumulation (EC). It is unclear how they are related to microsatellite instability (MI). The genes for matrix metalloproteinase-7 (MMP-7) and cyclin D1 (cD) have been suggested as possibilities for -catenin stimulation. DNA was taken from cancer and normal tissue from 73 EC patients. (59 endometrioid and 14 nonendometrioid). CTNNB 1 variations in exon 3 were discovered using single-strand conformation polymorphism and DNA sequencing. Immunohistochemistry for -catenin, MMP-7, and cD confirmed the results.
The purpose of this study was to assess the extent of clinical heterogeneity caused by CTNNB1 P/LP variants by analysing clinical and genetic data from a previously unpublished cohort of 52 individuals combined with individuals previously described in the literature and clinical-genetic databases. TOPFlash was used to demonstrate loss of -catenin dependent transcriptional activity and thus understand the pathogenicity of missense variations. Together, measurement of CTNNB1 related trait rates and better understanding of variant effects provide a foundation for exact diagnosis and counseling (Sayaka Kayumi *et al*.,2022).

a)ARIDIA 	f) AT-rich interactive domain-containing protein 1A; Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Binds DNA non-specifically. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex).
b)HOXB13 	g) Hox-B13 is a homeobox protein that is part of a developmental regulatory system that provides cells with distinct anterior-posterior positional identities. HOXL subtypes include homeoboxes.

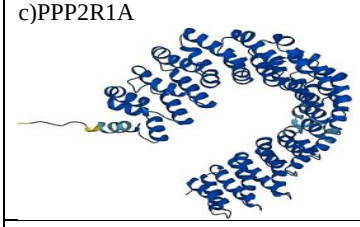
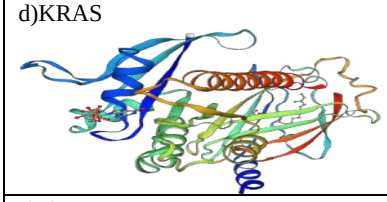
c)PPP2R1A 	h) Serine/threonine-protein phosphatase 2A regulatory subunit of 65 kDa The PR65 subunit of protein phosphatase 2A acts as a scaffolding molecule to coordinate the assembly of the catalytic subunit and a changeable regulatory B subunit. When it interacts with GNA12, it stimulates the dephosphorylation of the microtubule related protein TAU/MAPT. SGO1 centromeric location and correct chromosomal segregation are required during mitosis.
d)KRAS 	i) Ras proteins bind GDP/GTP and have GTPase activity on their own. It is essential for the control of cell growth. In colorectal cancer (CRC) cells, it promotes oncogenic processes by inducing transcriptional silence of tumour suppressor genes (TSGs) in a ZNF304-dependent manner; it belongs to the small GTPase superfamily.
e) CTNNB1 	k) Catenin beta-1 is a key secondary component of the Wnt signalling cascade. In the absence of Wnt, forms a complex with AXIN1, AXIN2, APC, CSNK1A1 and GSK3B that enables phosphorylation on N-terminal Ser and Thr residues as well as ubiquitination of CTNNB1 through BTRC and subsequent proteasome destruction. CTNNB1 is not ubiquitinated in the presence of Wnt ligand and accumulates in the nucleus, where it serves as a coactivator for transcription factors of the TCF/LEF family.

Figure7: An overview of Ovarian cancer associated genes Protein complex

1)a,d,c,d,e– ARIDIA HOXB13, PPP2R1A, KRAS CTNNB1 protein network structure (generated proteins interactions with a variety of proteins involved in ovary cancer)
2) f,g,h,I,j functional properties of proteins-ARIDIA HOXB13, PPP2R1A, KRAS CTNNB1 protein complex (a, b, c ,d,e,f Taken from string.org).

Table 5: Overview of ovarian cancer

Ovarian Cancer	**Description**	**References**
Types of ovarian cancer	1) Epithelial ovarian cancer--the most prevalent form. There are several forms of serous carcinoma and mucinous carcinoma. 2) Stromal tumours-These uncommon tumours are typically detected at an early stage than other types of ovarian cancer. 3) Germ cell tumours-These uncommon ovarian malignancies prefer to strike at a younger age**.**	https://www.cancer.net/cancer-types/breast-cancer; https://old-prod.asco.org/practice-patients/guidelines/breast-cancer https://www.cancer.org/cancer/breast-cancer/about.html mayo clinic taken from cancer.org
causes	Although it is unknown what causes ovarian cancer, doctors have found factors that may raise the chance of the disease. Ovarian cancer develops when cells in or near the ovaries undergo alterations (mutations) in their DNA. The DNA of a cell holds the instructions that inform the organism what to do. The mutations instruct the cells to expand and proliferate rapidly, resulting in a mass (tumor) of cancer cells. When good cells perish, cancer cells continue to live. They have the ability to invade adjacent tissues and break away from an original tumour in order to spread (metastasize) to other areas of the **body.**	
Genetic factors that causes breast cancer	a) Inherited mutated genes (10%) (BRCA1, BRCA2, etc.. genes) b) Acquired mutated genes (90%)	
Factors that affect a person's risk of developing Ovarian cancer	Older age, Inherited gene changes, Family history of ovarian cancer, Being overweight or obese, Postmenopausal hormonere placement therapy,Age when menstruation started and ended, Endometriosis,Never having been pregnant,Age when menstruation started and ended	
Symptoms	When ovarian cancer first appears, there may be no visible signs. When symptoms of ovarian cancer appear, they are typically attributed to other, more prevalent diseases. Ovarian cancer symptoms and signs may include: Bloating or thickening in the abdomen,When consuming, I quickly feel satisfied. Loss of weight, vaginal discomfort,Fatigue,Back ache,Constipation and other changes in digestive patternsUrge to pee frequently	

Early detection	1) Regular women's health exams 2) Screening tests for ovarian cancer a) TVUS (transvaginal ultrasound) b) CA-125 blood test c) Screening tests for germ cell tumors/stromal tumors	
Risk factor	1) Taking hormone therapy after menopause 2) Having a family history of ovarian cancer, breast cancer, or colorectal cancer 3) Having a family cancer syndrome	
Diagnosis	1**)**Consider taking birth control pills 2)Approaching genetic counselor 3) Pelvic exam. 4) Imaging tests 5) Blood tests 6) Surgery	

Conclusion

Ovarian cancer genes include BRCA1, BRCA2, PTEN, TP53, RAD50, MLH1, MSH2, MSH3, MSH6, PMS2, ARIDIA, HOXB13, PPP2R1A, KRAS, and CTNNB1. Genes also interact with other proteins in regulating strategies. However, ovarian cancer can be controlled with early detection, genetic counselling, surgery, and medication.

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