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HEREDITARY CANCER SYNDROMES AND GASTRIC CANCER: CURRENT PERSPECTIVES

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Abstract:
Hereditary cancer syndromes play a significant role in the pathogenesis of various forms of gastric cancer beyond sporadic cases. Unlike sporadic gastric cancers, which often have a multifactorial etiology, these syndromes are driven by germline mutations in tumor suppressor genes or DNA mismatch repair genes. The identification of these mutations allows for early diagnosis, risk assessment in family members, and implementation of preventive strategies, including endoscopic surveillance and prophylactic surgeries. Among these, Lynch syndrome, associated with germline mutations in **MLH1, MSH2, MSH6, PMS2, and EPCAM,** increases the risk of gastric adenocarcinoma, particularly in the proximal stomach. Familial adenomatous polyposis (FAP), and its gastric variant, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) are linked to mutations in the **APC** gene and contribute to diffuse-type and fundic gland polyposis-associated gastric cancers. Peutz-Jeghers syndrome, caused by mutations in **STK11,** and juvenile polyposis syndrome, related to mutations in **SMAD4** and **BMPR1A,** also predispose individuals to gastrointestinal malignancies, including gastric carcinoma. Understanding these genetic syndromes is crucial for early detection, surveillance, and management of at-risk individuals.
Key words: Lynch syndrome, gastric cancer, GAPPS, Peutz-Jeghers syndrome, Juvenile polyposis syndrome.

INTRODUCTION

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide, with a particularly high burden in East Asia and parts of South America. While environmental factors such as Helicobacter pylori infection, dietary influences, and smoking are well-established contributors, a subset of gastric cancers arises due to inherited genetic predispositions[1]. These hereditary gastric cancers, though relatively rare, are clinically significant due to their early onset, aggressive behavior, and the potential for targeted surveillance and intervention in at-risk individuals. Among the hereditary cancer syndromes, several are known to increase the risk of gastric cancer either as a primary or secondary malignancy [2]. Notably, syndromes such as Lynch syndrome, Familial adenomatous polyposis and its variant gastric adenocarcinoma and proximal polyposis of the stomach, Peutz-Jeghers syndrome (PJS), and Juvenile polyposis syndrome (JPS) are associated with distinct genetic mutations and characteristic gastric pathology[3]. Each of these syndromes has unique mechanisms and clinical features, yet they converge in their predisposition to gastric malignancy, often through precursor lesions such as polyps or mucosal abnormalities. Understanding these syndromes is crucial not only for gastroenterologists and oncologists but also for genetic counselors and primary care providers who play a key role in family history assessment and referral for genetic testing.

S.No	Syndrome	Gene(s) Involved	Gastric Cancer Subtype	Precursor Lesion(s)
1	Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Intestinal/diffuse gastric cancer	None well-defined

S.No	Syndrome	Gene(s) Involved	Gastric Cancer Subtype	Precursor Lesion(s)
2	FAP	APC	Intestinal-type adenocarcinoma	Fundic gland polyps (FGPs)
3	GAPPS	APC (promoter IB)	Proximal gastric adenocarcinoma	FGPs with dysplasia, HPAPs
4	PJS	STK11	Various (adenocarcinoma)	Hamartomatous polyps
5	JPS	SMAD4, BMPR1A	Various (adenocarcinoma)	Juvenile (hamartomatous) polyps

Lynch syndrome:

Lynch syndrome, an autosomal dominant disorder, is caused by germline pathogenic variations in DNA mismatch repair genes. Surveillance and preventative measures can reduce cancer risk and mortality by 4-6%. The US Department of Health and Human Services has designated identifying individuals with Lynch syndrome pathogenic variants as a priority genomics. Colorectal cancer (CRC) is the third most common cancer, accounting for 9.8% of all cases and 9.2% of cancer-related deaths. About 10% of cases have a genetic component, with Lynch syndrome-associated CRC being the most common type Lynch syndrome, affecting 3% of all colorectal cancer cases, affects 1 in 279 people. First-degree relatives (FDRs) are 50% more likely to share pathogenic genes with Lynch syndrome-associated colorectal cancer patients, leading to increased risk of developing Lynch syndrome-associated cancer, including endometrial, colorectal, stomach and urinary tract neoplasms.Lynch syndrome (LS) is a hereditary disorder caused by mutations in genes affecting EPCAM or DNA mismatch repair (MMR), a mechanism that identifies and repairs erroneous DNA base sequences and types of damage. Implicated are MLH1 (15–40%), MSH2 (20–40%), MSH6 (12–35%), PMS2 (5–25%), and EPCAM (<10%)[5].

Lynch syndrome, a 2-4% frequency genetic cause of colorectal cancer, is caused by a germline mutation in DNA mismatch repair genes, altering the length of short microsatellites.Lynch syndrome's phenotypic manifestation is influenced by the affected genes, with the inactivation of MSH2, MLH1, or PMS2 leading to high-level microsatellite instability, which affects mononucleotide, dinucleotide, and short tandem repeats. Inactivation of MSH6 is primarily due to mononucleotide repeat instability[6].Lynch syndrome, the most common genetic form of endometrial cancer, is a condition that increases the accumulation of DNA polymerase mutations, accounting for 2-6% of all endometrial tumours[7].This study presents a case of concurrent endometrial and colorectal adenocarcinomas in a 56-year-old woman, highlighting the increased risk of various gastrointestinal tract cancers, ovarian cancers, genitourinary tract cancers, central nervous system cancers, and sebaceous adenomas. It also highlights the potential for ovarian cancers and sebaceous adenomas.

Germ-line pathogenic variants (PVs) in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2, and 3 prime[8]. Lynch syndrome (LS) is caused by deletions of the gene EPCAM, which is located immediately above MSH2. It has been shown that the risk of cancer is dependent on the gene that is affected. The most familiar MLH1 and MSH2 are linked to an increased risk of colorectal cancer. MSH2 was linked to an increased risk of extracolonic cancers and female carriers of MSH6 may have the greatest risk of endometrial cancer[9]. Although the range of tumors characteristics of the LS has been widely described to encompass colon, endometrial, ovarian, stomach, small bowel, hepatobiliary tract, ureter/renal pelvis, pancreas, brain, and sebaceous neoplasms, the risks of other cancer types such as breast, prostate, and adrenocortical[10].The MMR pathway operates to fix single-base pair mismatches and small (usually 1-6 bases) insertions or deletions that arise during replication of small repeat sequences by DNA polymerase. MMR deficiency screening assays at the molecular level commonly involve microsatellite instability and immunohistochemistry on colorectal and endometrial tumours to diagnose patients with LS.1 Pathogenic variants in the MMR genes cause errors in DNA repair, which generate a high mutation load in the MMR-deficient cells[11].

Clinical reports on the risk of breast cancer in women with LS have been varied with some reporting an up to fourfold increase in breast cancer risk and others finding no excess breast cancer risk. Results could be bias by ascertaintement. many past LS studies that evaluated breast cancer did so by ascertaining their stratify study cohorts on criteria with a strong bias to colorectal cancer[12]. Consequently, several study groups were composed of MLH1 and MSH2 carriers

alone although others contained MSH6 as well. Few studies have had all four MMR genes, but reported a single combined breast cancer risk, possibly because there were few MSH6 and PMS2 carriers. Therefore, the absence of a regular correlation of breast

The fact that cancer and LS in past studies could be due to the genetic makeup of the cohorts. Although it has been hypothesized that the breast cancer risk in LS can be different by gene, no single study has addressed gene- and age-specific breast cancer risks across all four MMR genes. Our study intended to describe the risks of breast cancer according to every MMR gene in our cohort of women who were detected to have a PV through germ-line hereditary cancer panel testing due to numerous cancer-related indications[13].

1. MLH1

The gene MLH1 which participates in mismatch repair DNA (MMR) path, is found in the chromosome 3p,22.2, and it is a crucial one. The protein MLH1 heterodimerises with PMS2 generating the MutL often thought to be a key switchpoint in the repair of mismatched bases generated during DNA replication. This complex works together with other MMR proteins to recognize and remove the wrong nucleotides hence preserving the integrity of the genome[14].This repair process is impaired when there are mutulations or the loss of functions in the MLH1 gene effectively inactivating the MMR pathway. This leads to buildup of errors in replicating DNA, especially in repetitive DNA sequences termed as microsatellites resulting in what is termed as microsatellite instability (MSI). The genomic instability is also a very great predisposing factor to raising the risk of many kinds of cancer, especially colorectal cancer, endometrial and gastric cancer among others[15].[15].

2. MSH2

The MSH2 gene is found in the chromosome 2 p 2 1-p 16 and is found to be essential to DNA mismatch repair (MMR) pathway. It has a protein encoding which is involved in the heterodimer formation with other proteins in MMR. In particular, MSH2 in combination with MSH6 installs MutSa association complex, which is mainly involved in the recognition of the single base mismatch and small loop of insertions and deletions. Also it is able to complex with MSH3, called MutSb, specialised in the detection of larger insertion/deletion loops. On the recognition of DNA mismatches, the existence of these MutS complexes are coordinates with MLH1-PMS2(MutLalpha)[16] complex so as to initiate and complete the process of repair and consequently to preserve genomic stability.Gene mutations of MSH2 cause loss of mismatch recognition in turn leading to accumulation of replication errors. It is a severe impairment which poses a high risk of cancers of different types. Albeit MSH2 mutations have been best-known to be related to Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC), they are also commonly connected with extracolonial malignancies such as endometrial, ovarian, and urinary tract cancers. The reversion of MSH2 therefore impairs the structural integrity of the genome and even exposes anyone to a wider range of inherited cancers[17].

3. MSH6

The MSH6 gene mapping is on chromosome 2p16 that is significant in the DNA mismatch repair (MMR) procedure. It is associated with MSH2 to form a heterodimer (MutSalpha) that mainly identifies and initiates repair of base-base mismatches as well as small insertion-deletion loops (IDLs) that arise during replication of DNA.The MSH6 gene mutations have a less serious form of Lynch syndrome (or hereditary nonpolyposis colorectal cancer, or HNPCC). Patients with mutations of MSH6 have later onset of tumors, usually involving the colorectum or endometrium and are less penetrant than mutations in MLH1 or MSH2. This implies that the risk of contracting cancer is lower and the symptoms tend to develop at a later age[18-20].

4. **PMS2 (Postmeiotic Segregation Increased 2)**

PMS2 (Postmeiotic Segregation Increased 2) is found on chromosome 7 p 22. PMS2 is important in DNA mismatch repair (MMR) system used to maintain genomic stability by correcting replication errors.PMS2 achieves its functionality by becoming a heterodimer with MLH1, which forms MutL alpha complex. It is a scaffold complex, as well as an endonuclease[21-23]. It aids in the removal of the mismatched DNA bits as well as aids in recruiting other proteins in the repair effort so that there is proper duplication of the DNA.

PMS2 gene mutations have been linked to Lynch syndrome but they are of lower penetration and usually lead to later development of cancer than MLH1 or MSH2 gene mutations. Nevertheless, PMS2 mutations remain to play a role in hereditary nonpolyposis colorectal cancer (HNPCC), and they are clinically important when determining the genetic analysis of Lynch syndrome.

5. EPCAM (Epithelial Cell Adhesion Molecule)

EPCAM (Epithelial Cell Adhesion Molecule) is situated on chromosome 2p21, immediately next to the gene of MSH2. EPCAM is not a mismatch repair (MMR) gene, but the effects of its deletions, especially when deletions are at the 3 end, can be important downstream effects on MMR; moreover, it has been found that EPCAM is frequently deleted in endometriosis, with 3 end deletions commonest. Such deletions may cause epigenetic silencing of the MSH2 promoter by hypermethylation. This results in the loss of expression of the MSH2 gene resulting in deficient MMR pathway. This MSH2 loss dysfunctionalizes the DNA repair mechanism and enhances the possibilities of the occurrence of mutations in the genome[24].

An abnormal transmission of EPCAM, as a result of mutations or deletions, consequently results in the second inactor state of MSH2, resembling the Lynch disorder in terms of clinical details. Patients carrying this EPCAM deletion have a Lynch syndrome phenotype and they mostly develop colorectal and endometrial cancers. Although not itself the direct object of the MMR, EPCAM only renders itself noteworthy to hereditary cancer syndromes by contributing to epigenetic regulation of MSH2[25].

Familial adenomatous polyposis (FAP)/gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS):

Familial adenomatous polyposis (FAP) represents an autosomal dominant inherited disease, which occurs due to a germline mutation in the adenomatous polyposis coli (APC) gene. The incidence rate of FAP is 1: 8.300 births, and this condition is evenly distributed among sexes. The condition is marked by the development of hundreds and thousands of colorectal adenomas, which usually begins during teenage years. Most patients are diagnosed at young age because of a positive family history of FAP but a quarter of the patients has a de novo APC mutation and they present with symptoms and often advanced disease.An expected, multifocal adenoma-carcinoma sequence is characteristic of FAP and it requires 15 20 years before polyps develop into cancer, just like the sporadic adenomas.

In absence of treatment, the probability of developing colorectal cancer (CRC) is nearly 100 percent at young age with a median of 3545 years[31]. Thus, young age is the indication to prophylactic colorectal surgery.Lifelong endoscopic surveillance is still of importance after colectomy as adenomas will occur and develop within the remaining rectum or ileal pouch. There are also various extra colonic manifestations that can occur in patients with FAP.

Duodenal polyps occur in virtually all patients with FAP and must be monitored endoscopically in an attempt to avoid duodenal surgery and duodenal cancer[32]. Gastric adenomas and gastric cancer The diagnosis and management of gastric adenomas and gastric cancer has recently become an increasing concern The most problematic extra-gastrointestinal manifestation of FAP is desmoid tumours, which are benign myofibroblastic proliferations that can lead to significant morbidity and even death particularly when they occur in the mesentery.

Children and adolescents with at least one first-degree relative with classical or a-FAP or those at high risk of developing FAP or attenuated (a)-FAP should have regular monitoring. Retrospective research fails to capture the true course of illness, so it is recommended that patients with classical familial adenomatous polyposis (FAP) start surveillance at age 12[33]. A type of FAP called a-FAP, which develops later, has been referred to as a-FAP in the past.

GAPPS is an autosomal dominant hereditary gastric cancer syndrome with incomplete penetrance, first identified in 2012. It is caused by germline point mutations in the promoter 1B of the APC gene. GAPPS distinguishes itself from a-FAP by its gastric cancer and widespread fundic gland polyposis[34]. There is no information on colorectal cancer risk, so doctors should rule out polyposis in other gastrointestinal tracts and use proton pump inhibitors before diagnosing GAPPS. Genetic testing can confirm diagnosis, but not all gene panels have the 1B promoter. It is distinguished by a greater involvement of the stomach's fundus and body, with fundic gland polyps preserving the antrum, as well as a reduced curvature and a higher risk of developing gastric cancer[35]. To rule out the potential of (attenuated) FAP, the use of proton pump inhibitors and the presence of polyposis elsewhere in the GI tract should be checked out in order to contemplate a diagnosis of GAPPS. Japan, Europe, North America, and Australia have all been shown to have GAPPS families. The beginning age of stomach adenocarcinoma might vary from 22 to 75 years of age.

GAPPS is a condition with reduced curvature, increased risk of gastric cancer, and greater involvement of the stomach's fundus and body[36]. It's associated with proton pump inhibitors and polyposis in the GI tract. GAPPS families exist in Australia, North America, Europe, and Japan. Stomach adenocarcinoma can start between 22 and 75 years old. Studies show a significant overall risk of stomach cancer in GAPPS, with an estimated incidence of 12% to 25%. However, due to ascertainment bias, the actual risk may be lower. GAPPS and Helicobacter pylori infection are inversely related, and dysplasia can be identified as early as age 10. GAPPS has microscopic characteristics such as gastric-type adenomas, adenocarcinomas, FGPs, HPAPs, and hyperplastic polyps. GAPPS patients have a wide onset age, influenced by genetics, lifestyle, and environment. Upper-GI endoscopy is recommended for all affected patients, as the absence of FGPs in the antrum distinguishes it from other GI polyposis syndromes. Biopsy collection is necessary for proper diagnosis of lesions histopathologically[35].

Pathogenesis:

1. Familial Adenomatous Polyposis (FAP)

Familial Adenomatous Polyposis (FAP) is an autosomal dominant disorder of cancer predisposition that has germline mutations in the APC gene (Adenomatous Polyposis Coli). The gene is in chromosome 5q2122 and is important in controlling cell growth and apoptosis in intestinal epithelia.The inheritance pattern is autosomal dominant, implying that it is only necessary to have one copy of the defective gene, the APC to result in the occurrence of the condition. People who have FAP usually develop hundreds or thousands of adenomatous polyps in their colon and rectum, but this can start happening as early as adolescence age.The loss of APC protein function is the main pathogenesis of FAP

that plays a role in negative regulation of Wnt/beta-catenin signalling pathway pediatrics. In health, APC is a component of a destruction complex that facilitates the breakdown of β-catenin thus inhibiting the unregulated division of cells. When however, APC is mutated losing its functionality, there is an amassing of β-catenin in the nucleus, a condition that pervades in the proliferation of cell genes. This deregulated Wnt signalling is a central epithelial dysplasia and tumorigenesis agent in the gastrointestinal tract[37].

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach is a rare autosomal severe hereditary syndrome that is associated with the occurrence of a large number of polyps in proximal (upper) stomach, specifically in the fundus and the body of the stomach, but not antrum. It is autosomal dominant in its pattern of inheritance, which implies that only a single copy of a gene responsible could trigger the condition.GAPPS occurs due to particular point mutation in 1B promoter area of APC gene. These mutations do not cause inactivation of APC protein altogether but change the expression of the protein in a tissue specific manner mainly in the gastric epithelium. Consequently, the affected persons GAPPS are characterized by redundant multiplication of the gastric mucosa, which consequently results in numerous polyps that further develop to gastric adenocarcinoma.In contrast to familial Adenomatous Polyposis (FAP), GAPPS patients never develop the classical colonic polyposis, or in case of its development, only to a minor degree. The difference is significant in diagnosis and in clinical treatment, since GAPPS needs special attention with monitoring of the stomach and not of the colon. It is necessary to identify the impact early before the gastric polyps go through malignant metamorphosis[38].

Peutz-Jeghers syndrome (PJS):

Peutz-Jeghers syndrome (PJS) is a hereditary disease, which is characterized by mucocutaneous pigmentations and gastrointestinal hamartomas. ThePJS pathogenesis is related to loss-of-function germline mutations in the STK11 gene that encodes the serine/threonine kinase liver kinase B1 (LKB1). The TSHSUi002-A iPSC line that carries a heterozygous STK11mutation, is a useful cell model to study the disease and drug screening, which enhances our knowledge on PJS pathogenesis and possible treatment measures. Peutz Jeghers syndrome (PJS) is an uncommon autosomal dominant genetical disorder, which causes the hamartomatous polyps to grow in the gastrointestinal tube, mucocutaneous pigmentation, and a high likelihood of malignancy in several organ systems[31] .PJS is a condition that occurs because of mutations in the STK11 gene on chromosome 19 (Bennett et al. 2021). STK11 is a key regulator of cellular metabolism, cell polarity and DNA damage response. STK11, as a tumour suppressor, acts in a variety of ways but mainly by inhibiting the mammalian target of rapamycin (mTOR) signalling pathway via AMP-activated protein kinase (AMPK) activation.

Malignant lesions of the small bowel comprise 2 % 5 % of all primary gastrointestinal malignancies. One of them is the Peutz-Jeghers syndrome least recorded risk factors in development of small intestinal cancers Peutz-Jeghers syndrome (PJS) is a rare, autosomal dominant disorder, which is manifested by gastrointestinal polyps. hamartomatous and mucocutaneous pigmentation, PJS Hamartomatous polyps are most common in the small intestine. (duodenum, ileum and jejunum, respectively in that order of predominance). They may arise in the stomach, large bowel and in rare cases, extraintestinal sites, the bronchus, renal pelvis and urinary Bladder. It occurs in one per 8300 to 200,000 live births. PJS patients are nine times more likely to die it and their probability of mortality due to gastrointestinal cancer is 1315 times greater in comparison to the general population The most common ones are colorectal, breast, gastric, small intestine, and pancreatic cancer[32]. Other cancers include biliary tree and gallbladder, esophagus, lungs, thyroid gland, ovary and cervix in females, and testes in males Histological diagnosis of a The diagnosis of PJS necessitates Peutz-Jeghers polyp. Histologically, in which the smooth muscle arborization is in the lamina characterized propria linked with a prolonged epithelial part and cystic gland dilatation In the present work we describe a case of this uncommon organ with specific histological aspects in a young man who occurred a poorly differentiated adenocarcinoma of the jejunum with perforation. This case report has been reported according to the SCARE Criteria[30-34].

Pathogenesis

1. Overview of Peutz-Jeghers Syndrome (PJS):

The Peutz-Jeghers syndrome (PJS) is a very uncommon autosomal dominant inherited disease characterized by a reflection of both peculiar clinical findings and an increased possibility of cancer. The other characteristic in PJS is the formation of numerous hamartomatous polyps in the gastrointestinal (GI) tract, although, there is a tendency of having this polyps in the small intestines, however, the stomach, colon and the other GI tract may be affected as well. These are benign growths, which are polyps made up of abnormal combination of the tissue components normally found at the location.Beside GI polyps, PJS is also distinguished by mucocutaneous pigmentation that can generally be observed as dark blue to brown patches on the lips, oral mucosa, fingers and toes, etc. The presence of these pigmented macules can be very important in the diagnosis although they tend to clear up with age and tend to occur in childhood.Notably, patients with PJS are at the high increased risk of lifetime complications with extra-gastrointestinal and gastrointestinal cancer. This is with an increased risk of gastric, pancreatic, small intestine, colorectal cancers and breast, ovary, cervix, and testicle malignancies. This high genetic predisposition to cancer

necessitates the necessity of early diagnosis, genetic counseling, and also frequent surveillance of cancer in patients of PJS being an important scope in clinical management.

2. Genetic Cause:

Peutz-Jeghers Syndrome (PJS) occurs as a result of an abnormality in the STK11 gene which is LKB1. This is an autosomal dominant gene on chromosome 19p13.3 that one deficient copy is needed to manifest the syndrome. The mutation that causes PJS is usually inherited by the affected individuals through an affected parent; however, there are incidences whereby de novo mutations do occur.STK11 gene produces a serine/threonine kinase, which is the central enzyme that regulates a number of the cells processes. It plays a pivotal role in a number of signaling pathways that regulate cell polarity, energy metabolism, growth arrest and programmed cell death (apoptosis). STK11 functions as a tumor suppressor, which is able to prevent the progress of uncontrolled cell growth and appearance of neoplasms.The regulation of the STK11 gene is lost when that gene is damaged, resulting in the change of the tissue structure and cell growth[34]. It is a genetic error that is the cause of the development of hamartomatous polyps in all parts of the gastrointestinal tract in patients with PJS as well as a major factor in the predisposition to developing both gastrointestinal and extra-gastrointestinal cancer.

Juvenile polyposis syndrome (JPS):

About 2-5 percent of all colorectal cancer (CRC) cases occur within the syndrome that is genetically determined. The majority of the predisposing germline variants are primarily found in the adenomatous polyposis coli (APC), MUTYH and DNA mismatch repair genes, or may alter other, less common predisposing genes. Although they are hardly encountered, early identification of these syndromes holds vital clinical significance as it dictates the most desirable form of management not only of the affected patients but also of their family members[36]. In addition to the historically famous familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), Lynch syndrome, and Peutz-Jeghers syndrome (PJS), only a few syndromes are left in the niche of specialized doctors.

Juvenile polyposis syndrome (JPS) is an uncommon precancerous syndrome, which predisposes individuals to the risk of gastrointestinal malignancies. The inheritance is autosomal dominant. JPS is clinically suspected when the other hamartomatous polyposis syndromes are not observed (i.e., Peutz-Jeghers and Cowden), and when it is present of many juvenile polyps in the colorectum or elsewhere in the GI tract. The term juvenile denotes the histological sub-type of polyp and should not be used to devastate clinicians into thinking that the age of onset of These polyps predict other more aggressive syndromes, most of all FAP. The majority of patients with JPS start to develop colonic polyps at age 20 years. Individuals can also have only a small number of polyps in their lifetime (i.e. <10) but others can progress to a clinical phenotype that can be indistinguishable to major polyposis with 100 polyps[35].

The cumulative risk of colorectal cancer in subjects with JPS is 68 percent at age 60 years. The genetic test is obligatory in both in the instance of clinical suspicion or in families known to be affected.SMAD4 and BMPR1A genes are causative genes of JPS[37]. Similar to the suggested handling of any cancer predisposing condition, post-test counselling ought to arrange a suitable cancer screening and follow-up. The present global communities, that is, European Society of Gastrointestinal Endoscopy and American College of Gastroenterology guideline recommendations, propose an initial endoscopic screening at the age 1215 years, in order to alter the survival expectancy of the JPS patients and families. The purpose of this narrative review is to summarise the evidence and recommendations regarding JPS, paying attention to the diagnosis, the genetic assessment, and the endoscopic monitoring[38-39].

Pathogenesis

1. Overview of Juvenile Polyposis Syndrome (JPS):

Juvenile Polyposis Syndrome (JPS) is a very uncommon hereditary disorder and is autosomal dominant in nature i.e. it takes only a single copy of the defective gene to develop the condition. It is mainly a condition that is adopted by the growth of multiple hamartomatous polyps in the gastrointestinal tract which mostly occur in colon, although it also appeals in stomach and small intestine.They are non-cancerous polyps that entail disorganized elements of tissue characteristically found in the gastrointestinal mucosa. Although they are not categorized as neoplastic, they have the risk of malignant transformation in long term. Consequently, the JPS patients are at a much higher lifetime risk of getting any of the gastrointestinal cancers, especially the colorectal, gastric, and (less commonly) pancreatic cancer.It is worth noting that the word juvenile in Juvenile Polyposis Syndrome is not depicting the age of onset but the histology of appearance of the polyps. The characteristic features of such polyps include cystic dilation of the glands and inflammatory stroma, which are typical and differentiate them with other kinds of polyps of the gastrointestinal tract. Timely identification and monitoring are very vital in the control of JPS and mitigation of cancer.

2. Genetic Cause:

The most frequent cause of Juvenile Polyposis Syndrome (JPS) occurrence is germline mutations in tumor suppressor genes (SMAD4 and BMPR1A most of the time). These mutations have an autosomal dominant pattern of inheritance and thus individuals with JPS possess a pathogenic variant on a single gene copy.On chromosome 18q21.1, a high-priority regulator of the intracellular signaling SMAD4 gene is coded. BMPR1A is coded on chromosome 10q23.2, the receptor triggers the signaling cascades. Both the genes are constituent parts of Transforming Growth Factor-TGF- o (beta)- i signaling pathway, which has a pivotal role in the preservation of normal tissue homeostasis through

the control of cell proliferation, differentiation and apoptosis.Mutation in SMAD4 or BMPR1A will disrupt the TGF - pathway resulting in uncontrolled cell proliferation and hamartomatous polyps formation. These gene defects do not only cause the occurrence of polyps but they also lead to the high incidence of gastrointestinal malignancies that come hand in hand with JPS. Molecular tests are important in establishing the diagnosis and ability to conduct early surveillance and offer counseling to family members who are also likely to develop the condition[40].

DISCUSSION

Hereditary cancer syndromes represent a distinct and clinically significant subset of gastric cancer etiology. While sporadic gastric cancers are largely influenced by environmental and infectious factors, hereditary syndromes such as Lynch syndrome, Familial adenomatous polyposis (FAP) and its variant GAPPS, Peutz-Jeghers syndrome (PJS), and Juvenile polyposis syndrome (JPS) are driven by inherited mutations in key tumor suppressor or mismatch repair genes [41-42]. These germline mutations not only increase the lifetime risk of developing gastric cancer but also shape the pattern of disease presentation, often at younger ages and with characteristic precursor lesions, such as fundic gland or hamartomatous polyps.A common thread across these syndromes is the potential for early detection and intervention, which significantly alters disease outcomes. For example, while Lynch syndrome-associated gastric cancers often lack a defined precursor, individuals carrying MLH1, MSH2, MSH6, PMS2, or EPCAM mutations benefit from risk-based surveillance strategies[43]. In contrast, syndromes like FAP/GAPPS and JPS, which present with identifiable gastric polyposis, offer clearer windows for endoscopic monitoring and timely surgical or prophylactic management[44]. Understanding the molecular genetics underlying these syndromes enables personalized medicine approaches — guiding not only diagnosis and surveillance protocols, but also family-based genetic counseling and cascade testing to identify at-risk relatives. Furthermore, emerging insights into the unique molecular pathways of these syndromes may pave the way for targeted therapies and chemopreventive strategies [45-47.]

CONCLUSION

Hereditary gastric cancer syndromes account for a minority of overall gastric cancer cases; their clinical impact is profound. Continued efforts in genetic research, awareness, and multidisciplinary management are essential to reduce morbidity and mortality associated with these inherited conditions. Greater integration of genomic medicine into routine clinical practice will be key to achieving earlier diagnosis, improving outcomes, and offering precision care to affected individuals and their families. Despite significant progress in identifying the mutations and assessing the clinical risks, hereditary gastric cancer syndromes remain an evolving field with several unmet challenges. Future research must focus on risk stratification, surveillance, prevention, and therapeutic strategies that can minimize morbidity and improve the quality of life.

REFERENCES

1. Allemani C, Matsuda T, Di Carlo V, et al.: Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 391 (10125): 1023-1075, 2018.
2. Sung H, Ferlay J, Siegel RL, et al.: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71 (3): 209-249, 2021.
3. American Cancer Society: Cancer Facts and Figures 2025. American Cancer Society, January 16, 2025.
4. Uson PLS, Kunze KL, Golafshar MA, et al.: Germline Cancer Testing in Unselected Patients with Gastric and Esophageal Cancers: A Multi-center Prospective Study. Dig Dis Sci 67 (11): 5107-5115, 2022.
5. Ku GY, Kemel Y, Maron SB, et al.: Prevalence of Germline Alterations on Targeted Tumor-Normal Sequencing of Esophagogastric Cancer. JAMA Netw Open 4 (7): e2114753, 2021.
6. Møller P, Seppälä TT, Bernstein I, et al.: Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 67 (7): 1306-1316, 2018.
7. Abraham SC, Nobukawa B, Giardiello FM, et al.: Fundic gland polyps in familial adenomatous polyposis: neoplasms with frequent somatic adenomatous polyposis coli gene alterations. Am J Pathol 157 (3): 747-54, 2000.
8. Giardiello FM, Brensinger JD, Tersmette AC, et al.: Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 119 (6): 1447-53, 2000.
9. Correa P, Haenszel W, Cuello C, et al.: A model for gastric cancer epidemiology. Lancet 2 (7924): 58-60, 1975.
10. Hooi JKY, Lai WY, Ng WK, et al.: Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology 153 (2): 420-429, 2017.
11. Lott PC, Carvajal-Carmona LG. Resolving gastric cancer aetiology: an update in genetic predisposition. Lancet Gastroenterol Hepatol. 2018;3(12):874–883.

12. 2 Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263.
13. Toal TW, Estrada-Florez AP, Polanco-Echeverry GM, et al. Multiregional sequencing analysis reveals extensive genetic heterogeneity in gastric tumors from Latinos. Cancer Res Commun. 2022;2(11): 1487–1496.
14. Klapheke AK, Carvajal-Carmona LG, Cress RD. Racial/ethnic differences in survival among gastric cancer patients in California. Cancer Causes Control. 2019;30(7):687–696.
15. Carneiro F. Familial and hereditary gastric cancer, an overview. Best Pract Res Clin Gastroenterol. 2022;58–59:101800.
16. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020;21(8): e386–e397.
17. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. JAMA Oncol. 2015;1(1):23–32.
18. Lobo S, Benusiglio PR, Coulet F, et al. Cancer predisposition and germline CTNNA1 variants. Eur J Med Genet. 2021;64(10):104316.
19. A. Ueki, A. Hirasawa, Molecular Features and Clinical Management of Hereditary Gynecological Cancers, Int. J. Mol. Sci. 21 (24) (2020) E9504.
20. Hereditary cancer syndromes and risk assessment: ACOG committee opinion summary, number 793, Obstet. Gynecol. 134 (6) (2019) 1366–1367.
21. S.H. Chung, N. Woldenberg, A.R. Roth, R. Masamed, W. Conlon, J.G. Cohen, et al., BRCA and beyond: comprehensive image-rich review of hereditary breast and gynecologic cancer syndromes, Radiogr. Rev. Publ. Radiol. Soc. N. Am. Inc. 40 (2) (2020) 306–325.
22. ACOG Practice Bulletin No. 103, Hereditary breast and ovarian cancer syndrome, Obstet. Gynecol. 113 (4) (2009) 957–966.
23. Lindberg LJ, Wegen-Haitsma W, Ladelund S, et al. Risk of multiple colorectal cancer development depends on age and subgroup in individuals with hereditary predisposition. Fam Cancer. 2019;18(2):183–191.
24. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut. 2011;60(7):950–957.
25. Eikenboom EL, Moen S, van Leerdam ME, et al. Metachronous colorectal cancer risk according to Lynch syndrome pathogenic variant after extensive versus partial colectomy in the Netherlands: a retrospective cohort study. Lancet Gastroenterol Hepatol. 2023;8(12):1106–1117.
26. Nakatsu G, Li X, Zhou H, et al. Gut mucosal microbiome across stages of colorectal carcinogenesis. Nat Commun. 2015;6:8727.
27. Iyadorai T, Mariappan V, Vellasamy KM, et al. Prevalence and association of pks+ Escherichia coli with colorectal cancer in patients at the University Malaya Medical Centre, Malaysia. PLoS One. 2020;15(1):e0228217.
28. Zhou Y, He H, Xu H, et al. Association of oncogenic bacteria with colorectal cancer in South China. Oncotarget. 2016;7(49):80794–80802.
29. Mima K, Sukawa Y, Nishihara R, et al. Fusobacterium nucleatum and T cells in colorectal carcinoma. JAMA Oncol. 2015;1(5):653–661.
30. Joo JE, Chu YL, Georgeson P, et al. Intratumoral presence of the genotoxic gut bacteria pks(+) E. coli, Enterotoxigenic Bacteroides fragilis, and Fusobacterium nucleatum and their association with clinicopathological and molecular features of colorectal cancer. Br J Cancer. 2024;130(5):728–740.
31. Newcomb PA, Baron J, Cotterchio M, et al. Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev. 2007;16(11):2331–2343.
32. Jenkins MA, Win AK, Templeton AS, et al. Cohort profile: the colon cancer family registry cohort (CCFRC). Int J Epidemiol. 2018;47(2):387– 388.
33. Milne RL, Fletcher AS, MacInnis RJ, et al. Cohort profile: the Melbourne collaborative cohort study (Health 2020). Int J Epidemiol. 2017;46(6):1757.
34. Genta RM, Schuler CM, Robiou CI, Lash RH. No association between gastric fundic gland polyps and gastrointestinal neoplasia in a study of over 100,000 patients. Clin Gastroenterol Hepatol 2009;7(8):849e54.
35. Kadiyska TK, Todorov TP, Bichev SN, Vazharova RV, Nossikoff AV, Savov AS, Mitev VI. APC promoter 1B deletion in familial polyposis–implications for mutation-negative families. Clin Genet 2014;85(5):4527.
36. Thrift AP, El-Serag HB. Burden of gastric cancer. Clin Gastroenterol Hepatol 2020;18(3):534-42.
37. Bornschein J, Rokkas T, SelgradM,MalfertheinerP.Gastric cancer: clinical aspects, epidemiology and molecular background. Helicobacter 2011;16:45-52.
38. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, Graham DY. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 2016;150(5):1113-24.
39. P. Higham, F. Alawi, E.T. Stoopler, Medical management update: PeutzJeghers syndrome, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 109 (1) (2010) 5–11.

40. Beggs, A. D., Latchford, A. R., Vasen, H. F., Moslein, G., Alonso, A., Aretz, S., … Hodgson, S. V. (2010). Peutz–Jeghers syndrome: a systematic review and recommendations for management. Gut, 59(7), 975–986.
41. Seevaratnam R, Coburn N, Cardoso R, Dixon M, Bocicariu A, Helyer L. A systematic review of the indications for genetic testing and prophylactic gastrectomy among patients with hereditary diffuse gastric cancer. Gastric Cancer. 2012 Sep;15 Suppl 1:S153
42. **Suriano G, Huntsman DG, Carneiro F, Grady WM, Lynch HT, et al.** Hereditary diffuse gastric cancer: prophylactic surgical oncology implications. Surg Clin North Am. 2008 Aug;88(4):671–702.
43. **Lassandro F, Masone S, Izzo F, et al.** Gastric polyposis and risk of gastric cancer in patients with familial adenomatous polyposis. Am J Gastroenterol. 2022 Aug;117(8):1246–1254.
44. **Mankaney G, Leone P, Cruise M, LaGuardia L, O'Malley M, Church J, Burke CA.** Gastric cancer in FAP: a concerning rise in incidence. Fam Cancer. 2017 Jul;16(3):371–6.
45. Marimuthu MMC, Balamurugan BS, Sundaram VA, Anbalagan S, Chopra H. Cytokine-based immunotherapy for gastric cancer: targeting inflammation for tumor control. Explor Target Antitumor Ther. 2025 Apr 26;6:1002312
46. Sakthi Sanjana D, Elizabeth Rani E, Madhumitha S, Yuvaraj M, Karthikeyan E Precision oncology in head and neck cancers: From molecular mechanisms to novel therapeutic strategies, Oral Oncology Reports,2024;12:100669
47. Pandi, K., Binoy Varghese Cheriyan, Vishali Ramesh, Sowparnika Murugavel, & Jaya Surya Venkatesan. (2025). Overcoming chemoresistance in mucinous adenocarcinoma: the impact of tumor microenvironment and genetic alterations. Journal of Applied Pharmaceutical Research, 13(3), 76-93.