Genetic alternation in Peutz-Jeghers Syndrome (PJS) and its Diagnostic Method

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ABSTRACT

Peutz-Jeghers Syndrome (PJS) autosomal dominant disorder characterized by melanin spots, colon polyps and increased risk of cancer, especially due to mucosal skin pigmentation of the red edges of the lips, and gastrointestinal hematogenous polyposis. PJS was first reported in 1895. PJS can be caused with or without mutation. Polyps have also been seen in the ureter, airway body system, and gastrointestinal system. The most common location is jejunum. DBE is an enteroscopy technique that enables the evaluation and treatment of the small bowel. Cancers of the colon, stomach, small intestine, pancreas, breast, and other organs are more common in PJS patients. PJS has a strong link with several malignancies like adenoma malignum (ADM) and a rare ovary tumor called sex cord tumor with annular tubules (SCTATs) in female PJS patients.

Key words: Peutz-Jeghers Syndrome; intraoperative enteroscopy; dual-balloon enteroscopy

1. INTRODUCTION

PJS is a rare autosomal dominant disorder (hereditary syndrome) indicated by melanin spots, and colon polyps, most of which are found in the large intestine (50-64%) and the small intestine (60-90%). It is marked as a significant risk of malignancy, particularly mucosal skin pigmentation of red borders of the lips and gastrointestinal hematogenous polyposis. PJS was first described in a pair of identical twins with melanotic macules (MM), illustrated by Connor and Hutchinson in 1895 and 1896 respectively. The history of PJS is listed in table 1. This is caused by a mutation in the STK11 gene (serine-threonine kinase 11) and the LKB1 gene (liver kinase B1) on chromosome 19p13.3. The LKB1 / STK11 gene is located in 9 exons, which is approximately 1.3 Lkb1 which encodes an amino acid protein that is 433. Mutations in this gene result in aberrant protein truncation, transcriptional splicing problems, and kinase activity loss. Some researchers believe that the STK11 gene act as a tumor suppressor. Hypoxia is able to produce factor cell polarity. 1-alpha and AMP-kinase-mediated hypoxia pathway activation might all be affected if STK11 activity is lost. Skin pigmentation or consequences such as intussusception, minor intestinal hemorrhage, and blockage caused by hamartomatous polyps can be seen in this condition, which is commonly detected in early childhood. It has been observed that people with PJS are more likely to develop malignant tumors in the gastrointestinal and extraintestinal tracts, including the reproductive organs, pancreas, and breast. PJS have a risk of cancer about 9-18 times higher than the persons who are not afflicted.
TABLE 1: History of PJS

<table>
<thead>
<tr>
<th>Time period</th>
<th>Statement and work done</th>
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| 1895        | • Stated by connorin and illustrated by Hutchinson.³  
• (MMs) Melanotic macuole first reported in identical twins.³  
• After puberty , one patient died by intussusception at the age of 20 another died at age 52 from cancer in breast.⁹,¹⁰ |
| 1921        | • Stated by Johannes Peutz.  
• Two boys of one family suffered from intestine polyps and (MMs) Melanotic Macuole.¹¹ |
| 1949        | • Stated by Harold jegers and others..  
• Reported 10 cases from different family.⁹ |
| 1957        | • PJS was stamp out at Mayo clinic.¹² |
| 1974        | • JAMA editorial claim 2-3% cancer risk in intestine.¹³,¹⁴ |
| 1997        | • The loss of heterozygosity investigations and focused linkage study locus of pjs were found in 19P13.3 using comparative genomic hybridization.¹⁵ |
| 1998        | • Lkb1 gene mutation identified.¹⁶,¹⁷  
• Mutation of LKB1 found to be about 75% in PJS patient. |

1.1 STK11/LKB1 genetic function

The STK11/LKB1 gene, which codes for a serine/threonine kinase member, is important for cell polarity, energy balance, and tumor suppression. STK11 is a protein that is encoded by a gene. PJS and Testicular Germ Cell Tumor are two diseases linked to STK11. STK11 is found in a variety of tissues.¹⁸ In humans, the STK11 gene has ten exons, of which 9 code for 433 amino-acid proteins and 1 non-coding exon.¹⁹ In STK11 protein, there are 3 primary domains including catalytic kinase domain, N-terminal noncatalytic domain, and C-terminal noncatalytic regulatory domain by exons 8 and 9.

1.2 Mutation in STK11 gene

PJS mutations are most commonly found in the catalytic domain and result in kinase activity problems, which causes STK11 expression and function to be disrupted.²⁰ STK11 is hypothesized to be a tumour suppressor gene. As a result, polyps in PJS have lost heterozygosity, resulting in the loss of STK11 biallelic function. This gene is also known to aid biological processes by interacting with many proteins, such as triggering through p21 cell cycle arrest is achieved and participates in the p53-dependent programmed cell death pathway (apoptosis).¹⁹,²¹ STK11 play role in energy balance, cell polarity, and also cell metabolism, among other things.²,²¹ Homeostatic imbalance between cell growth and cell death is a reason for the cancer cause. Tumor cells may proliferate in the absence of environmental cues, avoiding apoptosis. The tumor suppressor gene p53 has the capacity to limit cell growth and initiate programmed cell death, which is one of its most significant functions (apoptosis). As a result of the lack of function of STK11 in PJS, intestinal epithelial cells are programmed to die.¹⁸

Yoon et al. discovered a variety of variants in the STK11 gene, including nonsense, splice site, and frameshift alterations.²¹

1.2.1 Nonsense

In Chinese individuals with PJS, a new STK11 gene mutation has been discovered.

a) Mutation at codon 240 (exon 5), which changes TCG to TAG, results in a shortened protein with kinase activity defects.

b) A change in the STK11 protein's catalytic kinase domain. At exon 5, the nucleotide C is replaced with the nucleotide T, results in a shortened protein. More stomach polyps appeared in this patient.¹,⁴

1.2.2 Frameshift

Frameshift may be generally caused by the following:

- In contrast to the usual 433-acid protein, a single base (A) addition between nucleotides 574 and 575 in exon 4 results in a frameshift at codon K191, leading to 73 unique amino acids and prematurely termination of a 265-residue protein.⁶
- A frameshift following codon R301 occurs when one nucleotide (903G) in exon 7 is deleted, resulting in 33 new amino acids and the premature end of a 335-amino-acid protein.⁶

1.2.3 Splicing site

At the donor location of the LKB1 gene in intron 5, G is replaced with A at nucleotide +5. This mutation results in splicing that is abnormal and a shortened protein because G is the favored nucleotide at the splicing site's position +5. No cancer was reported in this patient.⁶ A heterozygous de novo mutation in which
substitution of nucleotide G by A at intron 6 caused a splice site mutation.

Different types and locations of STK11 gene mutations are linked to different consequences, such as cancer, surgical therapy, and an increase in the number of polyps. Patients who had more surgical therapy and had more gastrointestinal polyps were discovered to have frameshift mutations, according to Huang et al. Exon 3 mutations were linked to a higher risk of cancer.

1.3 Clinical features of PJS

An early symptom of PJS patients is pigmented mucocutaneous cell lesions (which occur in 95% of cases) that appear during early childhood syndromes are present with lentigines, lesions that usually appear during infancy and occur near the nostrils, mouth, volar and dorsal sides of the hands and feet, toes, fingers, and perianal area and Skin pigmentation near the face might diminish after puberty, but it tends to stay in the buccal mucosa. These symptoms diminish during puberty, but the buccal mucosa remains. Polyps are seen in the colon (50 percent-64 percent) and the gastrointestinal tract (60 percent-90 percent) of PJS patients show as late symptoms. Polyps cause blockage in the small bowel, abdominal discomfort, intussusception, anemia, and rectal blood loss, as well as cervix tumors (ADM), ovary tumors (SCTATs), and rectal blood loss, all of these leads to a high risk of laparotomy.

2. PATHOGENESIS

2.1 PJS patients with mutation

STK11 gene mutation, which suppresses phosphorylation of AMP-activated protein kinase. STK11’s direct substrate is thought to be the cause of many hamartomas in PJS patients. The loss of heterozygosity reported in PJS polyps causes biallelic loss of STK11 expression or function, according to the authors. Another research anticipated that a STK11 gene mutation will result in a shorter or truncated protein, resulting in activity loss, functional loss, and kinase domain disruption. In PJS patients, loss of serine/threonine kinase catalytic activity can lead to cancer predisposition syndrome. Another study found that in somatic cells, the deletion of the second functional allele might cause a range of illness symptoms. The production of polyps was shown to be caused by hapolinsufficiency in an experimental mouse with a heterozygous STK11 mutation. Majority of PJS patients, STK11 gene mutation resulted in the total deletion of the protein product. The kinase domain has been found to be functionally disrupted. As a result of somatic inactivation of the wild-type STK11 allele in PJS patients, tumor and hamartoma development occur. In PJS patients, this deficiency might be the primary cause of benign hamartoma production and a high risk of malignant change.

2.2 PJS patients with no identifiable lkbl mutations

Only 25% of PJS patients have LKB1 mutations that can be detected. Patients with familial cancer symptoms who do not have mutations discovered by sequencing often have large rearrangements. MLPA will be able to identify the bulk of them, but few will not. Although conversion technology has improved the detection rate of mutations in familial cancer syndromes, there have been no reports of conversion being used to find LKB1 mutations yet. There are 3 lines of evidence that support the assumption that there is a second PJS locus in addition to LKB1. First, 3 PJS families with no connection to the LKB1 gene have been described, as well as linkage to 19p13.4 in 1 PJS family. Second, Only 75% of individuals with PJS had a mutation in the LKB1 gene, according to LKB1 sequencing. Finally, translocation of the chromosome at the already defined 19p13.4 locus was studied in PJS polyp which is taken by 6-day baby who is suffering from PJS. Despite these findings, a second PJS locus has yet to be discovered, and no mutations have been discovered in any of the genes studied. There are some protein parts of genes that affect LKB1 activity like STRAD25, MO25, BRG1, and LIP, as well as due to LKB1, protein shows higher activity.

3. POLYPS SITES AND POLYP TYPES IN PJS

The ureter, respiratory system, and tonsils are the region where polyops are also found. Polyops can be found all over the gastrointestinal system in PJS patients. The most common location is the jejunum following esophagus, stomach, duodenum, ileum, colon, appendix, rectum. Thousands of tiny polyps may carpet the small intestine in some people, whereas just a few polyops may appear in others. Polyop growth is unpredictable, according to the authors’ and anecdotal experience with polyops is some polyops may remain as it is, some may autoamputate so that they remove on their own. PJS-type poly pathology and monitoring regimes are explored simultaneously is cancer surveillance, Pathology, and Small bowel polyop.

In the Danish polyposis registry(1994), The First isolated intestine polyp is in the measurement of 1.5cm. According to new sources, the cut-off range has been widened to between 1.0 and 1.5 cm. The 1.5 cm stoppage is suitable for the writers' experience. There are some procedures created by the author for the treatment of PJS polyops especially in the small bowel example are Double balloon endoscopy, laparoscopic intraoperative endoscopy polypectomy, and extended endoscopy. Using extended endoscopy, dual-balloon enteroscopy (DBE), and laparoscopic intraoperative endoscopic polypectomy, the authors created a regimen for the therapy of PJS small intestinal polyops.

According to the authors, the age risk of cumulative intussusception is different 10 years old person 15% risk, 20-year-
old person has a 50% risk. The risk of malignancy is higher in PJS patients, especially after 20-21 years. For GI cancer risk elevate to 70%.34

4. DIAGNOSIS AND COMPARISON OF IOE AND DBE.

All individuals with PJS should be screened for potential malignancies regularly (CT, Investigation of pancreas from MR/ultrasound, mammogram, Inspection of pelvic in women from ultrasound, Investigation of testis in men, upper endoscopy, colonoscopy). MRI enteroclysis can precisely estimate the size of larger polyps and for the detection of small polyps, capsule enteroscopy is highly effective.

DBE is an enteroscopy technique that helps in the treatment and evaluation of the ileum and jejunum. DBE endoscopist doctors should be aware of polypectomy as well as endoscopy. Before 2003, intraoperative enteroscopy (IOE) was used for inspection of the small bowel. This was the sole endoscopic therapy option for PJS patients. In table 2 advantages and disadvantages of DBE and IOE are discussed. After 2003 DBE began and replaced IOE for most reasons. The significant advantage of IOE is that the surgeon may cure severe arterial bleeding following polypectomy or perforation right away. As a result, the endoscopist is less stressed during polypectomy in IOE.35

In the author’s study, IOE was implemented on seven patients (4 female and 3 male) from 1999 to 2006. From 1999 to 2006 polyps were removed by IOE 3 by the surgeon and 179 by the endoscopist. Per sessions, 6 to 75 PJS patient’s polyps were separated. The largest hamartomatous polyp had a diameter of 4 cm and patients’ ages varied from 20 years to 50 years. DBEs in ten PJS patients after 2006 (7 female, 3 male). A total of 205 polyps were eliminated in their DBE group. Per sessions 1 to 37 PJS patient polyps were separated. The largest hamartomatous polyp had a diameter of 6 cm and patients’ ages varied from 12 years to 48 years. In both the IOE and DBE groups, there were no significant problems.35

5. PJS PATIENTS WITH CANCER RISK

In PJS patients, cancer is common found in the following organs examples are breast, stomach, small bowel, colon, pancreas, and many more organs. According to the author’s study, at age 70 cancer risk was seen to be 85% in PJS patients.36

PJS has a strong link to several malignancies including adenoma malignum (ADM) cervix tumor and sex cord tumor with annular tubules in female PJS patients (SCTATs). Sertoli cell testicular tumors are the tumors that correlate to SCTATs in male PJS patients. Sometimes SCTATs and ADM have been observed.37

5.1 Adenoma Malignum (ADM)

ADM develops in a small percentage of female PJS patients, possibly less than 5%.38 PJS affects about 10% of people with ADM.39 Common symptoms of ADM in females are watery or bleeding vaginal discharge. This makes challenging to ADM diagnosis. When the cervix has a firm or nodular look or resembles a polypoid mass on examination, it is classified as normal. A Pap test or a cervix biopsy can also be diagnosed in certain cases, but not all. Multiple cervical cysts have been discovered using imaging examinations. ADM is sometimes referred to as a minimal deviation adenocarcinoma since it closely resembles normal endocervical glands histologically.40,41 Histological indications for diagnosis of ADM are nuclear atypia, desmoplastic response, and undifferentiated adenocarcinoma. According to the author, we can distinguish mucous in the endocervical gland from the normal endocervical gland with the help of the staining method. For this staining, we have to take the HIK1803 monoclonal antibody and Alcian blue periodic acid Schiff.42,43 An annual gynecological checkup with pelvic ultrasound and Pap test should be included in ADM surveillance. On confirmation of ADM, patient suppose to meet with the surgeon of gynecologic oncology. The five-year survival rate in the most recent group of ADM patients was 60%.44

5.2 Sex Cord Tumors with Annular Tubules (SCTATs)

Female PJS patients have a chance of ovarian cyst at reproductive age. The average number of physiological cysts and steady cysts is uncertain. According to the authors, surgeons are required for 10% of females who diagnose with SCTATs. PJS affects around one-third of individuals with SCTATs.45 SCTATs are characterized by simple or complex tubules lined by cells with outer positioned nuclei that adjoin a hyaline-filled lumen on histological examination. SCTATs correlated with PJS are multifocal, bilaterally, and involve localized calcifications. SCTATs linked to PJS have a low risk of cancer and a favorable prognosis. In PJS patients, there have only been two recorded examples of malignant SCTATs.46,47 Patients with PJS who have SCTATs frequently have an asymptomatic adnexal cyst or tumor that can be detected with cancer monitoring tests. SCTATs can generate oestrogen, which can lead to early puberty. The majority of PJS patients with SCTATs are in their early twenties. A cautious approach is advocated, to preserve fertility and avoid surgical menopause.38

5.3 Sertoli Cell Testicular Tumors
Male patients suffers from PJS would exhibit bilateral multifocal testicular calcifications on testicular ultrasonography, which is compatible with asymptomatic Sertoli cell testicular neoplasia, according to the authors’ experience. Only six occurrences of ILCST have been recorded in PJS patients, and these lesions seldom proceed to invasive big calcifying Sertoli cell tumors (ILCST). Children with testicular hypertrophy or prepubertal gynecomastony are the most common ILCST patients (ages ranging between 1 to 14 years). (Aromatase, which converts testosterone to an estrogen precursor and causes prepubertal gynecomastony, is expressed in Sertoli cells.) ILCST should be monitored with testicular ultrasonography once a year. Asymptomatic PJS patients with microcalcifications on testicular ultrasonography should not have a standard testicular biopsy, according to the authors. Orchiectomy has been the traditional therapy, however, given the benign nature of these tumors in PJS patients, careful surveillance of asymptomatic non-large calcifying tumors is advocated, much as it is with SCTATs. A single case of effective therapy with the aromatase inhibitor anastrozole, as well as the use of inhibin-alpha as a tumor marker, has been reported.50

**TABLE 2: Summary of IOE and DBE on basis of advantages and disadvantages.**35

<table>
<thead>
<tr>
<th>Method</th>
<th>IOE</th>
<th>DBE</th>
</tr>
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<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>-All of the polyps were removed in a single surgery.</td>
<td>-Invasiveness is reduced.</td>
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<tr>
<td></td>
<td>-Collaboration with a surgeon.</td>
<td>-Sick leave should be shorter.</td>
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<td></td>
<td>-Endoscopists have less time to spend.</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantage</strong></td>
<td>-Laparotomy is required.</td>
<td>-Several procedures are frequently necessary.</td>
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<tr>
<td></td>
<td>-Adhesion formation possibilities.</td>
<td>-In certain patients, this is not possible (because of adhesion).</td>
</tr>
<tr>
<td></td>
<td>-Convalescence lasts longer.</td>
<td>-Operation will take longer.</td>
</tr>
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</table>

### 6. EPIGENETICS INVESTIGATION

The study of inherited changes in the expression of genes that take place during mitosis and meiosis without a change in the nucleotide sequence of the genome or chromatin. This process is influenced by cell-cell communication between adjacent cells, which is influenced by flexible and dynamic responses to intracellular and extracellular stimuli, physiology, and environmental exposure. Hormone levels, growth factors, neurotrophic factors, cytokines, and stress response could all be affected by environmental factors.52

Some influences may be beneficial to behavior and health, while others may be detrimental and impede the human mind and body, resulting in homeostatic disruption or imbalance, which can lead to sickness or psychiatric disorders. These elements are classified as follows:

- Alternative medicine, microbiome (beneficial gut microorganisms), and exercise are all useful.
- Toxic chemical exposure and drug misuse are both harmful.
- Dependent on the unique influences: illness exposure, food, medicinal medications, psychological state, seasonal changes, social contacts, and financial situation, it may be useful or detrimental.

Different epigenetic processes affecting DNA, RNA, and proteins might be triggered by a variety of chemical alterations. DNA methylation, chromatin remodeling factors, histone modifications (phosphorylation, ubiquitylation, and SUMOylation), and noncoding RNAs are examples of these alterations.51,53

#### 6.1 Methylation of DNA

The covalent attachment of a (-CH₃) methyl group at position 5 on the pyrimidine ring of cytosine is known as DNA methylation. Protein transcription takes place at CpG, which is a cytosine nucleotide next to a guanine nucleotide linked by phosphate. CpG islands are formed by short sequences of CpGs, of which 60–80 percent are methylated in the human genome. By catalyzing the transfer of a (-CH₃) methyl group to position 5 of a cytosine, DNA methyltransferases, produce 5-methylcytosine (5mc). This is accomplished by one or more DNMT activities and needs the cofactor S-adenosylmethionine (AdoMet).54 Hypermethylated gene promoter regions have a function in the inhibition of gene expression which commonly affects changes in cancer, and it results in extensive or wide-spectrum aberrant gene expression.51 Hypermethylation of DNA leads to silencing of anti-oncogene and chromatin condensation. Hypomethylation of DNA promotes oncogenes, causes chromosomal instability, and activates transposons.54

#### 6.2 Histone modification

Histones are the proteins that makes chromatin complexes. Histones serve as a structural framework around which DNA is wrapped at regular intervals to form chromatin. Histones compact and organize DNA into nucleosomes, the chromatin’s building blocks. Each nucleosome is said to be made up of two subunits.
H2A, H3, H2B, and H4 are the four core histones. Histones impact transcriptional activity and transcriptional suppression via regulating DNA packing. Histone modifications are Post-translational alterations that occur at histone tails, which are composed of flexible lengths of either C or N terminal residues that extend from the globular histone octamer. This change is split into two sections:

a. Acetylation of histones

Histone acetyltransferases are enzymes that carry out this activity (HATs). HATs are responsible for promoting transcription by adding acetyl groups to histone tail lysine residues.

b. Deacetylation of histones

Histone deacetylases (HDACs) are the active enzymes, which remove acetyl groups from acetylated lysines, causing chromatin compaction and hence transcription inactivation.

6.2.1 Histone methylation

The charge of the changed residues of the histone protein is unaffected by histone methylation. As a result, it is less likely to directly disrupt nucleosomal connections essential for chromatin folding, and depending on its position, it might either inhibit or trigger transcription. It's mostly found on the lysine and arginine side chains. Histone (H3 and H4) arginine methylation promotes transcription of genes or groups of genes, whereas histone H3 and H4 lysine methylation can stimulate or restrict transcription depending on the methylation location. Histone methyltransferases are divided into two categories: lysine-specific and arginine-specific histone methyltransferases.

6.2.2 Histone phosphorylation

Tyrosines, serines, and threonines are the most often modified amino acids. The tails of the histone N-terminus are not the only place where phosphorylation occurs. Phosphatases and kinases add and remove modifications to determine the modification amount. Histone kinases influence chromatin structure and impart a significant negative charge to histones by phosphate group from ATP transferring to a hydroxyl group in the focused chain of amino-acid.

6.2.3 Histone ubiquitylation

The covalent modification caused by ubiquitylation is substantially bigger than that caused by other kinds of histone modification. The 76 amino acids polypeptide ubiquitin is linked to histone lysines by the following enzymes: Activating E1, conjugating E2, and ligating enzymes E3. These enzymes determine the degree of ubiquitylation and substrate selectivity. This alteration, however, can be undone by the activity of de-ubiquitin enzymes, which are isopeptidases. This action is said to be crucial for gene silencing and activity.

6.2.4 Histone sumoylation

Sumoylation is linked to ubiquitylation and needs tiny modifier molecules comparable to ubiquitin that can bind to histone lysines through E1, E2, and E3 enzyme processes. Four essential histones are thought to work by opposing acetylation and ubiquitylation, both of these amino acids are found on the same side chain on lysine. As a result, additional study is required to understand the molecular process.

6.2.5 RNA silencing

This is a change in a gene that occurs after it has been translated. Small tracts of non-coding RNA called small interfering RNAs (siRNA) and microRNAs (miRNA) are used to contain or repress the expression of one or more genes in RNA silencing. Both miRNA and siRNA inhibit translation, albeit in distinct ways; both are connected with the RNA-induced silencing complex (RISC), a ribonucleoprotein complex. The RISC proteins incorporate siRNA, keeping it as a single antisense strand that binds to mRNA in a sequence-specific way. The mRNA is then cut at the central binding region by a slicer, a protein component of the RISC. The cell recognizes this mRNA cut as aberrant and consequently targets it for destruction.

A microRNA-induced silencing complex (miRISC) linked to mature miRNA is the miRNA mechanism. This complex binds to mRNA and prevents it from being translated.

7. EPIGENETICS IN PJS

Promoter hypermethylation is another inactivation mechanism that acts on tumor suppressor genes in PJS. The most prevalent epigenetic alteration in humans is methylation. Changes in methylation patterns play an important part in the carcinogenesis process. Hypermethylation of unmethylated CG site in the promoter area of various DNA repair genes and tumor suppressors, including p16, p15, and hMLH1, has been linked to expression loss in primary tumors and cancer lines.

STK11 deactivation, according to Esteller et al., is caused by particular patterns of 5' hypermethylation of the CG site, resulting in epigenetic inactivation of the STK11 tumor suppressor gene. In sporadic cancers, this alternate route was discovered. Finally, Esteller et al. discovered inactivation of the STK11 gene associated with hypermethylation was identified in a fraction of primary tumors and cancer-derived cell lines, as well as in PJS patients.
8. CONCLUSION

PJS patient’s common symptoms are polyps, skin pigmentation, etc. They have a high risk of cancer. This is generally caused by a mutation in the LKB1 and STK11 genes. The First PJS patient was diagnosed in 1895, since 19s all PJS patients were diagnosed with DBE and IOE. PJS can see in both males and females with different malignancies like ADM, SCTATs, and Sertoli cell testicular tumors.

Declaration of interest

The authors report no declarations of interest.

REFERENCES


