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# A Review on Peutz-Jeghers Syndrome

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**ABSTRACT**

Peutz-Jeghers Syndrome (PJS) is a rare inherited autosomal dominant genetic disorder which mainly affects the gastrointestinal tract. The clinical features of PJS include the gastrointestinal polyposis, mucocutaneous melanocyte macules and risk of cancer. For the diagnosis of the Peutz-Jeghers Syndrome, the clinical findings are necessary. Serine/Threonine Kinase 11 (STK 11) is a heterozygous pathogenic variant which plays an important role for identifying the individuals at risk to develop PJS. Endoscopic monitoring with polypectomy can reduce the number of urgent abdominal incision and loss of bowel due to intestinal obstruction (intussusception). Imaging of the small intestine, balloon assisted and intraoperative enteroscopy are useful for removing the deep & large distal polyps within the small bowel. There are different approaches for small intestinal imaging such as video capsule endoscopy (VCE), CT enterography and magnetic resonance enterography. Standard treatment is required for the management of intestinal obstruction and tumours. On the basis of family history and the other clinical features, the prophylaxis for reducing the risk of breast cancer can include mastectomy. Monitoring of the children and adolescents at the age of 8 years or if negative, at the age of 18 years is essential by using the colonoscopic and upper endoscopic imaging. Repeat the screening for every 1 to 3 years, if there is any presence of polyps identified based on the size, frequency and histo-pathological aspects of the polyps. Genetic counselling involves the process of providing information to the family members or to the individuals regarding the nature of disease, inheritance and association of the genetic disorders which can benefit them to take their personal and the remedial decisions. Predictive testing can be helpful for the individuals at risk without symptoms among the family members. In individuals at risk, there is a necessity to undergo the evaluation of the cancer risk with or without genetic testing for understanding the remedial, psychosocial and ethical consequences. DNA banking will beneficial for further understanding of the genes, alleles and the diseases even though the probands have no confirmation in the aspect of molecular assessment and genetic alteration.



## Introduction

Peutz-Jeghers Syndrome (PJS) is a rare inherited autosomal dominant genetic disorder which mainly affects the gastrointestinal tract. The other terms used for this syndrome are polyp and spots syndrome, Hutchinson Weber-Peutz syndrome, perioral lentiginosis or inherited hamartomatous polyps associated with hyper-pigmented macules. According to Tchekmedyian et al. (2013), the prevalence of this syndrome can be estimated from the range of 1:25000 to 1:280000. Peutz-Jegher's syndrome can occur in any human race or lineage [1,2].

## Clinical features

The clinical features of PJS include the gastrointestinal polyposis, mucocutaneous melanocyte macules and risk of cancer. Polyps are non-cancerous hamartoma which can be observed in the small intestinal areas such as jejunum, ileum and duodenum. These polyps can also be observed in other parts of the gastrointestinal tract such as stomach, large intestine and outside of the gastrointestinal tract such as airways, gall bladder, renal pelvis, ureter and the urinary bladder. The gastrointestinal (GI) polyps can lead to persistent haemorrhage, anaemia and frequent obstruction. Dark blue to dark brownish macules can be present during the childhood affecting the areas like external nares, mouth, anorectal, periorbital regions and mucosa of the buccal cavity. Fingers are most frequently observed with discoloured macules. During the age of puberty and adulthood these macules may disappear. Denovo pathogenic variant can sometimes be associated with various clinical characteristics, which can be a dermatological or gastrointestinal signs and symptoms.

Patients with PJS are having the higher chance to develop various epithelial cancers such as gastrointestinal, pancreatic, colorectal, breast and the ovarian cancers. Gonadal tumours can be observed in both the genders. Women are having the tendency to

get ovarian and cervical cancers. Men can develop tumour in testes involving the Sertoli cells, which can result in gynecomastia due to abnormal oestrogen secretion leading to short stature and the extreme bone aging which arises due to lack of the medical treatment [3].

## Diagnosis

For the diagnosis of the Peutz-Jeghers Syndrome, the clinical findings are necessary. Serine/Threonine Kinase 11 (STK 11) is a heterozygous pathogenic variant which plays an important role for identifying the individuals at risk to develop PJS. It includes the molecular genetic level testing which is essential for the confirmatory diagnosis of this syndrome. Single gene testing, multi-gene panel and comprehensive genomic testing are the different perspectives of molecular genetic testing which depends on the phenotype of an individual. For establishing the diagnosis of this syndrome two or more histological confirmations, frequency of PJS type polyps, muco-cutaneous melanocyte pigmentation and family history plays a crucial role.

## Differential Diagnosis

The other autosomal dominant genetic cancer syndromes such as Juvenile polyposis syndrome (JPS), Hereditary mixed polyposis syndrome (HMPS), PTEN (Phosphatase and tensin homolog) hamartoma tumour syndrome (PHTS), Carney complex, Familial adenomatous polyposis and Lynch syndrome shows the clinical signs and symptoms that can coincide with the Peutz-Jeghers syndrome [4,5].

## Molecular Pathogenesis

A multi-tasking tumour suppressor STK 11 referred as serine/threonine-protein kinase plays an important role in programmed cell death, halt of cell cycle, proliferation of the cell, polarity of the cell and metabolic pathways of the energy production. In individuals with PJS, greater than 300 STK 11 pathogenic variants have been described [1].

## Management strategies

Endoscopic monitoring with polypectomy can reduce the number of urgent abdominal incision and loss of bowel due to intestinal obstruction (intussusception). Imaging of the small intestine, balloon assisted and intraoperative enteroscopy are useful for removing the deep & large distal polyps within the small bowel. There are different approaches for small intestinal imaging such as video capsule endoscopy (VCE), CT enterography and magnetic resonance enterography. Standard treatment is required for the management of intestinal obstruction and tumours.

On the basis of family history and the other clinical features, the prophylaxis for reducing the risk of breast cancer can include mastectomy (surgical removal of the breast). But there are no particular studies or evidences in the aspect of both breast or gynaecologic prophylactic surgeries related to the PJS patients.

Monitoring of the children and adolescents at the age of 8 years or if negative, at the age of 18 years is essential by using the colonoscopic and upper endoscopic imaging. Repeat the screening for every 1 to 3 years, if there is any presence of polyps identified based on the size, frequency and histopathological aspects of the polyps.

For monitoring of PJS in adults, the screening should be done by using the colonoscopy, upper endoscopic and small bowel imaging techniques for every 2 to 3 years. At the initial age of the 18-20 years, the females should undergo pap smear test and pelvic region examination. At the starting age of 30 years, females should undergo breast examination for every 6 months which can include MRI of the breast and the mammogram. At the age of 30-35 years, endoscopic ultrasound or MRI screening for identifying any pancreatic disorders should be done every year.

Evaluation of the individuals at risk of PJS based on the familial history is required for the further monitoring or prophylactic management. Molecular genetic testing will be helpful if the family history shows the known pathogenic variant for PJS. Diagnosis at the initial stages, following prophylactic measures and prevention of the disease by monitoring may be possible by reducing the risk of morbidity & mortality in the individuals at risk. In some aspects, the pathogenic variant for PJS is unknown. Then, the individuals at risk should be subjected to further clinical assessments and diagnostic evaluations that can be helpful for the early management and effective monitoring of the disease. As there is risk of developing various cancers like cervical, lung and

pancreatic cancers, smoking cessation is crucial for the persons with pathogenic variants SKT 11 [6-9].

## Aspects of genetic counselling

Genetic counselling involves the process of providing information to the family members or to the individuals regarding the nature of disease, inheritance and association of the genetic disorders which can benefit them to take their personal and the remedial decisions. This process involves in the various aspects such as evaluation of risk related to the genetic disorders, familial history and genetic level testing [10].

## Conclusion

As Peutz-Jeghers Syndrome is an inherited autosomal dominant genetic disorder, most of the individuals assessed with this disease can be observed with affected parent in the family history. There is a probability of 50% inheritance among the siblings who have an affected parent of the proband with presence of the pathogenic variant STK 11, which is transmissible to next generation. If family history or proband is once reported with pathogenic variant STK 11 there is a requirement of antenatal or pre-implantation genetic testing before pregnancy. Predictive testing can be helpful for the individuals at risk without symptoms among the family members. In individuals at risk, there is a necessity to undergo the evaluation of the cancer risk with or without genetic testing for understanding the remedial, psychosocial and ethical consequences. DNA banking will beneficial for further understanding of the genes, alleles and the diseases even though the probands have no confirmation in the aspect of molecular assessment and genetic alteration.

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