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Peutz-Jeghers syndrome: clinicopathology and molecular alterations

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Abstract. Peutz-Jeghers syndrome (PJS, OMIM 175200) is an unusual inherited intestinal polyposis syndrome associated with distinct peri-oral blue/black freckling [1–9]. Variable penetrance and clinical heterogeneity make it difficult to determine the exact frequency of PJS [4]. PJS is a cancer predisposition syndrome. Affected individuals are at high risk for intestinal and extra-intestinal cancers. In 1997, linkage studies mapped PJS to chromosome 19p [10, 11], and subsequently a serine/threonine kinase gene defect (LKB1) was noted in a majority of PJS cases [12, 13]. A phenotypically similar syndrome has been produced in an LKB1 mouse knockout model [14–18]. Several PJS kindred without LKB1 mutations have been described, suggesting other PJS loci [19–22]. The management of PJS is complex and evolving. New endoscopic technologies may improve management of intestinal polyposis. Identification of specific genetic mutations and their targets will more accurately assess the clinical course, and help gage the magnitude of cancer risk for affected individuals.

Keywords. Peutz-Jeghers, polyposis, cancer predisposition, LKB1.

Historical perspective

In 1896, the renowned London physician Jonathan Hutchinson illustrated a case of twin sisters with 'unique ink-black pigmentation of the lips and mouth.' The 12-year-old girls were otherwise well, and the distinct peri-oral pigmentation was dismissed as a dermatologic curiosity [23] (Fig. 1). However, a follow-up of the Hutchinson twins noted that one sister died of intestinal blockage at age 20, and the second twin died of breast cancer at age 52 years [24, 25].

In 1921, the Dutch physician Peutz, from the Hague, reported a family with intestinal polyposis and mucocutaneous pigmentation [26]. The definitive description of the syndrome was published by Jeghers, McKusick and Katz in 1949 [25] after Jeghers' initial description of two patients in 1944 [27]. The authors recognized the syndrome as gene linked and due to a 'single pleiotrophic gene responsible for both characteristics, the polyps and the spots' [25]. The syndrome has been called by several names, including the Hutchinson-Weber-Peutz syndrome, the inherited hamartomatous polyps in association with mucocutaneous melanocytic macules, and the polyps and spots syndrome among others. The name Peutz-Jeghers syndrome (PJS) was coined by Bruwer et al. from the Mayo Clinic in 1954 [28].

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Figure 1. The 'Hutchinson twins' (1896) illustrate the characteristic ink-black perioral and buccal mucosal pigmentation of PJS.

Clinicopathology

Hutchinson described the typical skin findings of PJS of 'black pigmented spots on the lips, and inside of the mouth' [23]. The term 'peri-orificele' was coined by Touraine and Couder, who described the localization of pigmented macules around the mouth, eyes, nostrils and peri-anal area and also on the digits [29]. Jeghers initially described the clinical course of a 14-year-old girl on the medical service of the Boston City Hospital in 1939. 'A distinctive type of melanin pigmentation of the oral mucosa, lips and digits with intestinal polyposis. Twice in 1933, she had been operated upon at another hospital for intussusception and intestinal obstruction. On the second occasion, a portion of the ileum was resected. Polyps of the stomach, ileum and sigmoid were found at that time' [25].

A working definition of PJS was developed by Giardello et al. [30]. For individuals with a histologically confirmed hamartoma, a 'definite' diagnosis of PJS was made when two of the following clinical criteria were present: (i) family history of PJS; (ii) mucocutaneous hyperpigmentation and (iii) small bowel polyposis. A 'probable' diagnosis of PJS was made on individuals who did not have confirmed histology but had two of three clinical parameters present. This working definition of PJS is helpful for clinicians. However, in the future an increasing number of 'molecular' diagnoses of PJS with variable clinical expression especially in sporadic cases can be expected.

Gastrointestinal (GI) polyposis syndromes are grouped according to the predominant type of polyp present, either hamartomatous or adenomatous. Adenomatous polyposis syndromes include familial adenomatous polyposis, hereditary non-polyposis, colorectal cancer/their subtypes and the newly described MYH mutation associated polyposis [4, 7, 8, 9, 31]. The hamartomatous syndromes are characterized by an overgrowth of cells native to the organ in which they arise, including ectodermal, mesodermal and endodermal cell types. The hamartomatous polyposis syndromes occur at approximately 1/10 the frequency of the adenomatous polyposis syndromes. There are seven autosomal dominant inherited hamartomatous polyposis syndromes. These include juvenile polyposis syndrome (the most common), followed by PJS and Cowden's syndrome [9]. Although rare, proper identification of these syndromes has major clinical implications for the affected individual and family members, as these are cancer predisposition syndromes with high malignant potential. Polyps in PJS predominate throughout the GI tract but have also been described in the gallbladder, nares, lung and urogenital tract [2, 6, 26, 32]. Gastrointestinal polyposis occurs early in life, with over one-third of patients developing symptoms within the first decade of life, and 60% before age 20 years [33]. In a review of 75 PJS patients, the average age of diagnosis was 22 years of age without gender differences [34]. The median time of polypectomy in a more recent study of 51 patients was 13 year of age [35].

Polyps in PJS predominate in the small intestine, and are more common in the jejunum than the ileum, followed by the duodenum. Polyps of the large intestine and stomach are also quite common. In a large series of 182 cases reported from the Mayo Clinic, 6% of patients had small bowel polyps, 51% had colorectal polyps and 24% stomach polyps [36]. In a Japanese series, equal distribution was noted in polyps in the small bowel compared with the large bowel and stomach [37].

PJS hamartomatous polyps have a characteristic arborizing pattern of growth of the muscularis mucosa, producing a long stalk which predisposes these lesions to intestinal intussusception [38]. Polyps typically appear in the first decade of life, and mechanical problems due to polyp size dominate the clinical picture in the first 2 decades of life for patients with this syndrome. Major symptoms due to gastrointestinal polyps include abdominal pain, GI bleeding with anemia and intestinal blockage secondary to intussusception. These polyps can grow to a large size and typically have a long thick stalk (Fig. 2). This results in a need for repeated surgeries with bowel loss, which can lead to short bowel syndrome and malabsorption. Recently, a more proactive approach with endoscopic surveillance with polypectomy has been advocated to reduce the recurrent morbid presentation of patients with untreated polyposis [39–42]. Routine surveillance by small bowel enteroscopy and colonoscopy with polypectomy have become standard recommendations [1, 4–9, 43] (Table 1). To view the more distal small bowel polyps, barium x-rays with small bowel follow-through have been advocated every 2 years. Laparotomy with per-operative enteroscopy for small bowel polyp removal for polyps greater than 1.5 cm in diameter, or patients presenting with abdominal pain and known polyposis, has been recommended. Controlled trials of surveillance endoscopy have not been done in PJS. There is some evidence in

Figure 2. Intraoperative picture of a young male with PJS with multiple large pedunculated small bowel polyps, which can result in bleeding, pain and intestinal obstruction.

Table 1. Screening recommendations for PJS.

Screened cancer	Age to begin screening	interval	Diagnostic tests
Colon	25	2	colonoscopy
Proximal GI tract/small intestine	10	2	upper endoscopy UGI w/SBFT [1, 2]
Pancreas	30	1–2	endoscopic ultrasound
Transabdominal ultrasound			
Breast	20	2	mammography
		1	breast self-exam
Uterus	20	1	transvaginal ultrasound
Endometrial biopsy			
Cervix	20	1	pap smear
Testicular	10	1	physical exam ultrasound if clinically indicated

Adapted with modification [6].

[1] Depending on local availability, capsule endoscopy may replace small bowel follow-through contrast radiographic studies.
[2] Consider intra-operative endoscopy to remove polyps >1.5 cm. Depending on local availability, double-balloon enteroscopy might replace the need for laparotomy and intraoperative endoscopy.

the literature to suggest a decreased need for emergency surgeries and reduction in bowel loss with surveillance endoscopy and polypectomy [39–42].

Management of distal small bowel polyps is problematic in that they may be outside the reach of conventional endoscopy. Also, barium contrast studies lack the sensitivity to identify polyps in many patients. Several advances have been made recently and include wireless capsule endoscopy and double-balloon endoscopy (DBE). Capsule endoscopy is a vitamin pill-sized video capsule which includes a lens and light source which transfers images captured on a waist recorder. Capsule endoscopy allows for a more accurate visualization of the duodenum, jejunum and ileum [44–47]. Although the published literature is limited, it appears that capsule endoscopy has better sensitivity than contrast barium studies for the identification of small bowel polyp and polyposis syndromes [46, 47]. DBE is a new technique where one balloon is at-

tached to the tip of 200-cm working-length endoscope, and the second balloon is attached to the distal end of a soft over tube [48–50]. Using a series of techniques of balloon insufflations and deflations, 'unchartered' areas of the small bowel can be visualized. A newer, larger-channel DBE allows for polypectomy. In one study of nine polyposis patients, DBE detected a larger number of polyps than capsule endoscopy, and detected polyps in three patients in whom capsule endoscopy failed to detect any polyps [49]. Currently these two procedures are reviewed as being complementary, and would be used in sequential fashion. Taken together, capsule endoscopy and DBE have the potential to replace small bowel radiography, enteroscopy and intra-operative endoscopy for PJS patients with small bowel polyps. These techniques appear to have greater sensitivity and less morbidity for the identification and removal of small bowel polyps.

With advancing age, intestinal cancer becomes a major clinical concern of intestinal polyposis [1–9, 30, 37, 51]. In a Japanese series comprising 222 PJS patients, 43% of deaths before age 30 were secondary to GI polyps, whereas 60% of deaths over the age of 30 years were due to malignancy [37]. Hamartomatous polyps are non-dysplastic with normal overlying epithelium. The coexistence of adenomatous tissue within PJS hamartomas of the stomach, small bowel and colorectum has been demonstrated [52–55] Malignant transformation via adenomatous change of hamartomas has been suggested as the mechanism for malignant transformation and has been referred to as the hamartoma-adenoma-carcinoma sequence [1, 52–55]. Alternatively, PJS may have a greater predisposition toward the development of premalignant adenomas, particularly in the large intestine [personal observations]. The literature is replete with case reports and case series of GI adenomas noted in young PJS individuals clearly distinct from what is encountered in the general population. However, the existence of a hamartoma-carcinoma sequence and an earlier occurrence of adenoma in PJS is unproven. Thus, a sound biological basis for proper surveillance is lacking.

Patients with PJS are at increased risk of intestinal and extra-intestinal malignancies, and these cancers include colorectal, small bowel, stomach, breast, ovarian, uterine, cervix and pancreas. Although historically the cancer potential of PJS was debated, it is clearly recognized that the risk is real and alarmingly high [2, 5, 30, 45–51, 56–64]. PJS patients are at risk for developing common cancers at a younger age. The Japanese series includes three teenagers with gastric cancer [37]. In a meta-analysis of 210 PJS patients, relative risk of stomach, small bowel and large bowel cancer was 235, 279 and 98, respectively, compared with the general population [62]. In a review by Spigelman et al. [59], the relative risk of developing GI malignancy in 72 patients was 13 compared with the general population, with three-fourths of GI malignancies occurring before the age of 50 years. PJS patients are also at increased risk for development of extra-intestinal malignancies, specifically breast and pancreas. The risk of developing breast cancer in PJS female patients approaches that of known breast cancer predisposition mutations BRCA 1 and 2. Early onset and bilateral breast cancer have been reported in PJS patients. And a 32% chance of developing breast cancer by age 60 in PJS patients has been reported [57–63]. A survey of the Johns Hopkins PJS registry by Giardella et al. reported a 93% cumulative risk of developing cancer by age 65 years [62]. An issue with many of these studies has been that they relied upon patients evaluated at referral cancer centers, and there may therefore be biases associated with better follow-up of diseased patients. However, Boardman et al. [51] identified 34 patients that had been ascertained at the Mayo Clinic between 1945 and 1994. The patients were systematically recontacted to estimate cancer risks. In this series, the relative risk for breast and gynecological cancers was 20-fold increased over population risks, and the overall relative risk for cancer was 18.5. In men, the relative risk of cancer was increased 6.2-fold over population risk. The incidence of cancer was recently reported in 240 patients, with documented germine mutations in STK 11. The risk of cancer at age 20, 30, 40, 50, 60 and 70 years was 1%, 3%, 19%, 13%, 63% and 81%, respectively [62]. No gender difference in cancer risk has been demonstrated. The magnitude and multitude of organs at risk for cancer development translates into an aggressive and cumbersome surveillance strategy for PJS patients (Table 1).

In addition, affected PJS individuals are at risk for distinctive genital tract, neoplastic and non-neoplastic tumor [65–73]. Female patients with PJS are at risk for ovarian sex cord tumors with annular tubules (SCTATs), mucinous tumors of the ovary and fallopian tubes and a well-differentiated adenocarcinoma of the uterine cervix/adenoma malignum. Adenoma malignum or minimum deviation endocarcinoma is an unusual subtype of mucinous adenocarcinoma of the uterine cervix. Due to a high degree of glandular differentiation, it is almost impossible to differentiate these from normal endocervical glands obtained from punch biopsy [72]. Typically, patients present young with this highly aggressive form of cancer. In a series of 11 cases of adenoma malignum associated with PJS, 8 patients presented in their 20s and 30s, and there was a poor prognosis [72]. SCTATs were initially described by Scully in 1970 [65]. The clinical presentation and course of SCTAT in PJS patients is distinct compared with sporadic tumors that occur in the general population, which tend to be large, unilateral and associated with a 20% cancer risk. In contrast SCTATs in PJS patients are bilateral, multi-focal and usually only cause modest ovarian enlargement (less than 3 cm). SCTAT in PJS females is not believed to be a premalignant condition but rather

developmental alteration or hematoma [6]. Clinically, women present with menstrual irregularity, hyperestrogenemia with sexual precocity and infertility. Screening for gynecologic malignancies in PGJ females include regular pelvic exams and transvaginal ultrasounds beginning at age 20 years (Table 1).

Males with PJS are at risk for development of testicular tumors referred to as large cell calcifying sertoli cell tumors or testicular tumors resembling SCTATs [66, 67, 70]. Similarly, these tumors are multi-focal, usually small in size and bilateral. Males with this condition present with gynecomastia, rapid growth and advanced bone age secondary to increased estrogen production as a result of increased aromatase activity. Management must be individualized. The majority of these patients are treated medically, avoiding orchiectomy. In contradistinction to sporadic Sertoli cell tissue, malignant degeneration of these testicular tumors in PJS is unusual.

Genetics and molecular biology of PJS

The genetic locus responsible for PJS was mapped to chromosome 19p13.3 [10, 11]; subsequently, a mutation in a novel serine/threonine protein kinase, LKB1, was identified [12, 13]. The human LKB1 gene is 3.1 kb on Northern blot, consisting of 10 exons, 9 of which are coding, resulting in a 433-amino acid product [12, 13] (Fig. 3). An early study of LKB1 noted nonsense mutations in 23 familial and two sporadic cases of PJS. All mutations were predicted to lead to synthesis of a truncated protein, resulting in disruption and loss of function of the kinase domain and activity. This discovery was unique in that PJS is the first cancer predisposition syndrome that is the result of loss of catalytic activity of a serine/threonine kinase, and some of the disease manifestations are believed to be triggered by the subsequent loss of the second functional allele in somatic cells [12]. Predictive gene testing in conjunction with genetic counseling should be offered for confirmation of individuals with a clinical diagnosis of PJS and at-risk family members. The effect of haploinsufficiency versus loss of function from both alleles in polyp development has yet to be fully resolved. Analysis of a mouse model that was heterozygotic for an LKB1 mutation strongly suggested haploinsufficiency is sufficient to cause polyp formation [16]. In addition, immunohistochemical staining of polyps from PJS patients showed that the majority of hamartomatous polyps retained STK11 staining [74]. This study was not definitive because the antibody used was in the extreme 5′ region of the gene. Loss-of-heterozygosity [75] studies show a minority of polyps with loss of heterozygosity for 19p13 (15/39) compared with loss of heterozygosity in all carcinomas studied (5/5).

A few PJS families have been identified with mutations in the C-terminal non-catalytic region [76]. Subsequent testing of extended PJS families found LKB1 mutations in approximately 50% of cases and less in sporadic cases [11, 19–22]. For example, Boardman et al. evaluated 10 familial PJS kindreds and 23 individuals with sporadic PJS for LKB1 mutations with confirmation-sensitive gel electrophoresis followed by direct sequencing and detection of large deletions by large-range polymerase chain reaction (PCR). Mutations were found in only 2 of the 10 PJS families and 4 of the 23 sporadic cases [21]. Similarly, LKB1 mutations were found in only 50% of 14 Australian families [22]. Taken together, these studies might suggest the existence of another susceptibility locus for PJS. A recent study indicated that deletions of LKB1, which cannot be detected by sequence analysis, commonly occur in patients that have PJS and do not show mutations [77]. Among the patients that met criteria for PJS, 64% were found to have point mutations, and deletions were found using a multiple-ligand-dependent probe assay in an ad-

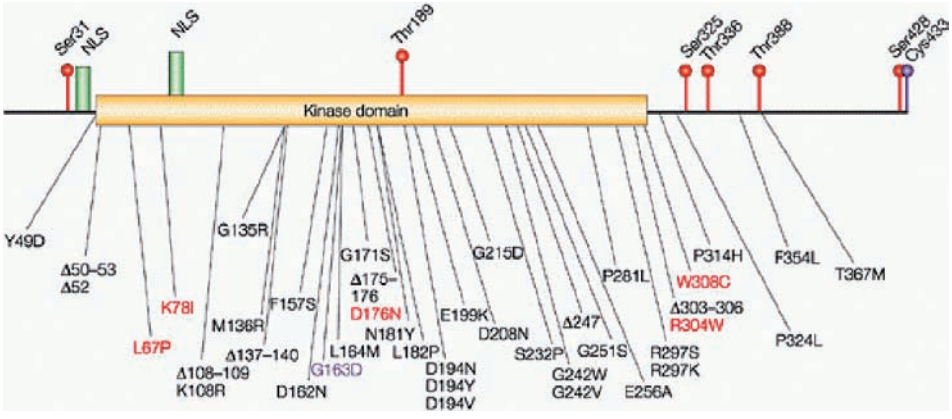

Figure 3. Schematic diagram of the *LKB1* gene. Two putative nuclear localization signals (NLS) are indicated in green, phosphorylation sites are indicated in red and a prenylation site is indicated in purple. Small deletions (Δ) or point mutations of *LKB1* that have been detected in PJS patients are in black. Mutants that have been tested and shown to lack autophosphorylation activity are in red, and a mutant (G163D) that has reduced autophosphorylation activity is in blue. Reproduced with permission from [82].

ditional 30% of patients. Thus, in this series, only 6% of patients were not found to have LKB1 mutations.

A few studies have suggested the existence of additional loci causing PJS beyond LKB1. Linkage analysis of 32 families identified 29 linked to chromosome 19p13.3 and 3 that were not linked to this region [19]. One family has been noted to show strong evidence for linkage to 19g13.4, but this family was found to have a translocation of 19g13.4. Analysis of candidate genes mean this breakpoint in PJS patients who did not have LKB1 mutations did not identify any mutations in this loci [78]. Genetic studies seeking to identify mutations in candidate genes that interact with STK11 have not yet yielded additional mutations [79]. An alternative explanation for a lack of molecular diagnosis, noted especially in sporadic cases, may be due to clinical misdiagnosis of individuals suspected of having PJS.

LKB1 is expressed ubiquitously in adult and fetal tissue [12, 13, 18, 80–82], particularly pancreas, liver, testes and skeletal muscle. Overexpression of LKB1 in fetal small bowel and stomach tissue was noted, compared with adult, suggesting a role for LKB1 in gastrointestinal development. Functional LKB1 is required for normal mouse embryogenesis [18]; LKB1–/– mouse embryos showed a striking decrease in vascularization with increased vascular endothelial growth factor expression [81].

Since its discovery 8 years ago, the pathogenic mechanism of LKB1 in PJS polyps and cancers is an evolving story. LKB1 has a nuclear localization signal at its amino-terminal but is also found in the cytoplasm [83]. LKB1 associates with p53 and regulates p53-dependent apoptotic pathways [82, 84]. LKB1 is found to translocate to the mitochondria during apoptosis. A bimodal distribution of LKB1 protein expression in the small intestines has been demonstrated, with a predominance in basal crypt cells and also at the villous tips, which is the site of apoptosis. LKB1 staining is particularly strong in pyknotic intestinal cells [82].

The role of LKB1 as a tumor suppressor gene was established early in its discovery. LKB1's role in suppressing cell proliferation through GI cell-cycle arrest was documented when functional LKB1 was introduced into cells lacking LKB1, whereas the introduction of LKB1 with a defective kinase had no such activity [82, 85–89]. LKB1's role in inhibition of cellular proliferation may be through the induction of WAF1, a cyclin-dependent kinase inhibitor [89–92]. LKB1 mutations interfere with its kinase activity and also its cellular localization. LKB1 is mainly localized in the nucleus but also, less so, in the cytoplasm and cell membrane [93]. LKB1 mutations affected phosphorylation of β-catenin and regulation of the WNT signaling pathway. In addition, mutation in the C-terminal non-catalytic protein of LKB1 decreased mediation of AMP-activated protein kinase (AMPK) and cell polarity [76, 86]. Mutation of the LKB1 homologue in *Caenorhabditis elegans* resulted in altered cellular polarity [94]. The role of LKB1 in maintaining proper cellular polarity may account for hamartomatous polyp formation in PJS, where there is an architectural disarray and overgrowth of differentiated cells indigenous to that organ. LKB1 and its downstream target AMPK have been shown to regulate activity of the tuberous sclerosis complex and particularly TSC2 [95], particularly in low-growth-potential situations. TSC2 controls expression of mTOR (mammalian target of rapamycin), and loss of either TSC2 or LKB1 expression therefore leads to a loss of growth-regulation control [96]. Rapamycin is a down regulator of TOR, which has been shown in early clinical trials to decrease the growth of astrocytomas in patients affected with tuberous sclerosis [97]. The multifunctional roles of LKB1, including apoptosis, cellular proliferation and polarity, may account for the multitude and aggressiveness of tumors that plague individuals with PJS [98, 99]. Available data would not suggest a major role for LKB1 mutations in sporadic cancer. The exception may be lung adenocarcinoma, where LKB1 mutations were noted in one-third of cases [100, 101]. Further studies will be necessary to unravel LKB1's downstream signaling pathways and targets.

Cowden's syndrome, or the multiple hamartoma syndrome, is another unusual autosomal dominant syndrome, where affected individuals develop mesodermal, ectodermal and endodermal hamartomatous polyps [3, 4, 7, 9]. Approximately 60% of Cowden's patients have GI polyposis. Recent studies have shown that LKB1 interacts with the tumor suppressor PTEN, which is mutated in approximately 80% of Cowden's patients. Normally the interaction of PTEN and LKB1 leads to the relocalization of LKB1 to the cytoplasm, which was disrupted with LKB1 mutation [102]. Furthermore, while LKB1 regulates mTOR during low-nutrient conditions to control cell growth, PTEN downregulates TSC2 in response to mitogenic stimuli [95]. Thus, there is a functional link between these two genes, which accounts for the majority of cases presenting with these two unusual hamartomatous polyposis syndromes. This genetic interaction may account for some clinical overlap between these two syndromes.

The hope of increasing our knowledge of the genetic alterations responsible for the pathogenesis of PJS is to develop new therapies to improve the lives of affected people. Cyclooxygenase-2 (COX-2) overexpression has been demonstrated not only in the animal model of PJS but also in PJS polyps and cancers [14, 74, 103–107]. Selective COX-2 overexpression has also been demonstrated in sporadic colorectal cancers and other malignancies. Prostaglandins and other reactive species formed a covalent adduct with LKB1 and attenuated downstream signals of the LKB1 AMPk pathway [108]. These observations identified COX-2 as a potential target for chemo-

prevention in PJS patients. In an LKB1 knockout model of hamartomatous polyposis, treatment with the selective COX-2 inhibitor celecoxib led to a dramatic reduction in tumor burden [107]. In a pilot study, two of six PJS polyps treated with 400 mg of celecoxib per day showed a dramatic decrease as noted by serial endoscopies. Unfortunately, two recent studies of selective COX-2 inhibitors as chemopreventive agents against premalignant colorectal adenomas were ended early because of an increased risk of cardiovascular and cerebrovascular events [109, 110]. The recent observation that low-level rapamycin treatment decreased growth of astrocytomas in patients with tuberous sclerosis [97] raises the hope that rapamycin treatment may similarly decrease polyp growth in PJS patients, but clinical trials have not yet been performed in humans or mice. Because LKB1 is upstream of TSC2, rapamycin treatment may not be as effective as it has been for patients with tuberous sclerosis [97].

Key points: the role of LKB1 in PJS

- PJS is the first cancer predisposition syndrome due to loss of function of the catalytic activity of a serine/threonine kinase.
- LKB1 is ubiquitously expressed in adult and moreso in fetal tissue. LKB1 is necessary for normal embryogenesis.
- LKB1 regulates p53-mediated apoptotic pathways and is preferentially expressed in the villous tips and pyknotic cells of the small intestine.
- LKB1 regulates cell proliferation via G1 cell-cycle arrest and WAF1 signaling. LKB1 mutations alter cell polarity. These effects may account for the formation of hamartomatous polyps, a hallmark feature of PJS.
- Overexpression of COX-2 has been noted in animal models and human PJS polyps and cancers, and may provide a target for chemoprevention.

Conclusions

PJS is an autosomal-dominant syndrome most commonly caused by a truncating mutation in the LKB1 gene, found on chromosome 19. The effects of this gene mutation lead to an array of clinical conditions, including gastrointestinal hamartomatous polyposis, mucocutaneous pigmentation and cancer predisposition, both intestinal and extra-intestinal. Strict endoscopic and cancer surveillance is recommended for all PJS individuals. Heightened awareness, development of optimal screening and therapeutic options will decrease the incidence and mortality of cancer of PJS. The molecular genetics of this unusual syndrome have only recently been elucidated. However, the downstream targets and mechanisms of germline LKB1 mutations are complex and diverse. This knowledge will hopefully translate soon into pharmacologic treatment that is based on molecular targeting. Until that day, the PJS community deserves our support, counsel and close observation.

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