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Peutz-Jeghers Syndrome

[*PJS*]

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Summary

Disease characteristics. Peutz-Jeghers syndrome (PJS) is characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. Peutz-Jeghers-type hamartomatous polyps are most common in the small intestine (in order of prevalence: in the jejenum, ileum, and duodenum) but can also occur in the stomach and large bowel. Gastrointestinal polyps can result in chronic bleeding and anemia and cause recurrent obstruction and intussusception requiring repeated laparotomies and bowel resections. Mucocutaneous hyperpigmentation presents in childhood as dark blue to dark brown macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. Hyperpigmented macules on the fingers are common. The macules may fade in puberty and adulthood. Individuals with Peutz-Jeghers syndrome are at increased risk for malignancies (colorectal, gastric, pancreatic, breast, and ovarian cancers). Females are at risk for sex cord tumors with annular tubules (SCTAT), a benign neoplasm of the ovaries, and adenoma malignum of the cervix, a rare aggressive cancer. Males occasionally develop calcifying Sertoli cell tumors of the testes, which secrete estrogen and can lead to gynecomastia.

Diagnosis/testing. The diagnosis of Peutz-Jeghers syndrome is based on clinical findings. In individuals with a clinical diagnosis of PJS, molecular genetic testing of the *STK11(LKB1)* gene reveals disease-causing mutations in approximately 100% of individuals who have a positive family history and approximately 90% of individuals who have no family history of PJS. Such testing is available clinically.

Management. *Treatment of manifestations:* routine endoscopic and intraoperative enteroscopy with polypectomy to decrease the frequency of emergency laparotomy and bowel loss resulting from intussusception; consider using wireless capsule endoscopy to diagnose small-bowel polyps and double-balloon ("push and pull") enteroscopy to eradicate small-bowel polyps without laparotomy; treatment of malignancies in a standard manner; conservative

management of gonadal tumors in males and females. *Surveillance:* Protocols have been suggested for monitoring stomach, small and large bowel, breasts, testicles, ovaries, uterus, and pancreas by various procedures as early as age eight years and as frequently as once a year. *Testing of relatives at risk:* If the family mutation is known, offer molecular genetic testing to at-risk relatives so that morbidity and mortality can be reduced in those with the family-specific mutation by early diagnosis and treatment and appropriate surveillance; if the family mutation not known, offer clinical diagnostic evaluations to identify those family members who will benefit from early treatment and appropriate surveillance. *Other:* Although not studied in individuals with PJS, prophylactic hysterectomy and bilateral salpingo-oophrectomy to prevent gynecologic malignancy in women after age 35 years or after child-bearing has been completed could be considered.

Genetic counseling. Peutz-Jeghers syndrome is inherited in an autosomal dominant manner. About 50% of probands have an affected parent and about 50% have no family history of PJS, but the proportion of cases caused by *de novo* gene mutations is unknown as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic data are insufficient. Parents of affected individuals with no known family history of PJS should be evaluated clinically, and with molecular genetic testing if a disease-causing *STK11* mutation has been identified in the proband. The risk to the offspring of a proband with a positive family history is 50%. The risk to offspring of a proband with a negative family history is 50% if the proband tests positive for a pathogenic *STK11* mutation. The risk to offspring of a proband with no family history of PJS who tests negative for an *STK11* mutation remains unknown. Prenatal testing is possible for pregnancies at increased risk if the disease-causing mutation in the family is known. Requests for prenatal diagnosis of (typically) adult-onset diseases, however, are uncommon and require careful genetic counseling.

Diagnosis

Clinical Diagnosis

The *sine qua non* of the diagnosis of Peutz-Jeghers syndrome (PJS) is the hamartomatous gastrointestinal polyp characterized histopathologically by the unique finding of mucosa with interdigitating smooth muscle bundles in a characteristic branching tree appearance [Buck et al 1992]. Epithelial misplacement that can occur in PJS small-bowel polyps appears as "pseudocarcinomatous" invasion, i.e., benign polyp epithelium surrounded by smooth muscle bundles that extend into the submucosa, muscularis propria, and even the bowel wall [Petersen et al 2000].

A working definition of PJS has been suggested by Giardiello et al (1987):

- For individuals **with a histopathologically confirmed hamartoma, a definite diagnosis** of PJS requires two of the following three findings:
  - Family history consistent with autosomal dominant inheritance
  - Mucocutaneous hyperpigmentation
  - Small-bowel polyposis
- For individuals **without histopathologic verification of hamartomatous polyps, a probable diagnosis** of PJS can be made based on the presence of two of the three clinical criteria above.
- For individuals **without a family history of PJS**, diagnosis depends upon the presence of two or more histologically verified Peutz-Jeghers-type hamartomatous polyps [Tomlinson & Houlston 1997].

- For individuals **with a first-degree relative with PJS**, presence of mucocutaneous hyperpigmentation is sufficient for presumptive diagnosis.

Note: Individuals with PJS also develop many other polyps; polyps showing adenomatous changes frequently arise in the colon, and may cause confusion with familial adenomatous polyposis.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. Currently only mutations in the gene *STK11(LKB1*) have been identified as a cause for Peutz-Jeghers syndrome (PJS) [Hemminki et al 1998, Jenne et al 1998].

Other loci. Although one child with a PJS hamartoma had a translocation of 19q13.4, no mutations in candidate genes mapping to this breakpoint were identified [Hearle et al 2004].

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis and deletion/duplication studies.** In a study of 56 individuals with a clinical diagnosis of PJS in which a combination of sequence analysis to detect point mutations and multiple ligand-dependent probe assay (MLPA) to detect large *STK11* deletions was used, *STK11* mutation detection rate was 94% [Aretz et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Peutz-Jeghers Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1, 2]		Test Availability
		Positive Family History	Negative Family History	
Sequence analysis	*STK11* coding region sequence variants	100%	91%	Clinical Testing
Deletion/ duplication analysis	Large *STK11* deletions			

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method
2. Aretz et al 2005

Interpretation of test results

- For general issues to consider in interpretation of sequence analysis results, click here.
- Of the mutations in *STK11* that have been detected, 65% affect the protein structure and are likely to abrogate protein function. The significance of missense mutations identified in 35% of individuals/families is more difficult to interpret; the existence of a deduced protein structure [Swiss-Prot, Mehenni et al 1998] may facilitate the evaluation of their significance.

- Clinical misdiagnoses of PJS could account for a decreased mutation detection rate, particularly in simplex cases.

Testing Strategy

Burt & Neklason (2005) recommended genetic testing of anyone with a PJS polyp or typical perioral pigmentation.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *STK11*.

Clinical Description

Natural History

Peutz-Jeghers syndrome (PJS) is characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. The risk for gastrointestinal and extra-intestinal malignancies is increased. Distinct benign and malignant gonadal and gynecologic tumors can also be seen. Variable expressivity is common; for example, some affected individuals in families with PJS may have only polyps or perioral pigmentation.

Gastrointestinal polyposis. Peutz-Jeghers-type hamartomatous polyps are most prevalent in the small intestine. The density of polyps is greatest in the jejenum, followed by the ileum, then the duodenum. Polyps can occur elsewhere in the GI tract, including the stomach and large bowel. In a series of 182 affected individuals from the Mayo Clinic, polyps occurred in the small bowel (96%), colon (27%), rectum (24%), and stomach (24%) [Bartholomew et al 1957, Bartholomew et al 1962].

Adenomas also appear with increased prevalence throughout the gastrointestinal tract.

Peutz-Jeghers-type hamartomatous polyps can cause intussusception and bleeding with secondary anemia. Mucinous cysts of the bowel can cause bowel obstruction.

The age at onset for symptoms from polyps is variable, with some individuals developing symptoms within the first few years of life. Significant interfamilial variability is observed in the age at which polyps are first observed, suggesting that the natural history of polyps in a family may be a predictor of severity for offspring. In studies from MD Anderson Cancer Center, the median age at first GI symptoms was ten years, while the median age at first polypectomy was age 13 years [Amos et al 2004]. A report from Korea indicated a mean age of onset for GI symptoms of 12.5 years [Choi et al 2000]. In a review of 32 kindreds with PJS, laparotomy for bowel obstruction was performed in 30% of individuals by age ten years and in 68% by age 18 years [Hinds et al 2004].

Mucocutaneous pigmentation. Hyperpigmented macules are rarely present at birth; they become pronounced in most individuals before the fifth year, but then may fade in puberty and adulthood. Children often present with dark blue to dark brown mucocutaneous macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa [Finan & Ray 1989]. In addition, hyperpigmented macules on the fingers are common.

Histologically, increased melanocytes are observed at the epidermal-dermal junction, with increased melanin in the basal cells.

Gonadal tumors. Females with PJS are at risk for ovarian sex cord tumors with annular tubules (SCTAT) and mucinous tumors of the ovaries and fallopian tubes. Symptoms include irregular or heavy menstrual periods and, occasionally, precocious puberty. SCTATs in PJS

are bilateral, multifocal, small tumors with a typically benign course [Young 2005]. In contrast, in the general population, SCTAT tumors are large, unilateral, and associated with a 20% cancer risk.

Males occasionally develop calcifying Sertoli cell tumors of the testes that secrete estrogen and can lead to gynecomastia [Young et al 1995].

Malignancy. Individuals with PJS are at increased risk for intestinal and extraintestinal malignancies.

Boardman et al (1998) found that individuals with PJS had a 9.9-fold increased relative risk for cancer; relative risks (RR) were highest for gastrointestinal cancer (RR=151) and breast cancer (RR=20.3). The age of onset for many PJS cancers was very young.

Choi et al (2000) found a similar relative risk of 11.1 overall for cancer among individuals with PJS and also noted that this increased risk results from higher risks for cancer among young individuals compared with the low risks in the general population. However, the natural history of cancer development in families and its correlation to offspring is unclear.

Lim et al (2003) found that 37% of individuals with PJS developed cancer by age 65 years, yielding a relative risk of 9.9 for all cancers. In 240 individuals with PJS with *STK11* mutations, the risk of cancer at age 20 years, 40 years, 60 years, and 70 years was 1%, 19%, 63%, and 81%, respectively [Lim et al 2004]. No gender difference in cancer risk was noted. Similar figures were reported in a series of 419 individuals with PJS, of whom 297 had documented *STK11* mutations [Hearle et al 2006a].

Although Giardiello et al (2000) observed a 93% cumulative lifetime risk of cancer in a large collected series from registries, the risks reported by Boardman et al (1998) and Lim et al (2003) are more reliable.

Colorectal and gastric cancers can arise from adenomas that are commonly found in individuals with PJS.

The risk for pancreatic cancer is greatly increased over the population risk [Giardiello et al 1987], although the absolute risk is much lower than for the other cancers common in Peutz-Jeghers syndrome.

Breast cancer and ovarian cancers can occur at early ages in Peutz-Jeghers syndrome, although data describing the age-specific risks for these cancers are not available. Some families with PJS report relatives with early-onset breast cancer, suggesting that some family members with a disease-causing mutation may on occasion develop breast or other cancers without having symptoms from the hamartomatous polyps. Lim et al (2004), reported that 8% and 32% of women with PJS developed breast cancer by age 40 years and 60 years, respectively.

Females can also present with adenoma malignum of the cervix.

Genotype-Phenotype Correlations

Genotype-phenotype information related to *STK11* mutations is lacking. Further analysis of pooled registry data is needed to better characterize genotype-phenotype correlations and confirm malignancy risks.

In a study of 297 individuals with PJS, the type or site of the *STK11* mutation did not influence cancer risk [Hearle et al 2006a].

In contrast, Amos et al (2003) found that individuals with truncating mutations in *STK11* or who tested negative for mutations had similar ages of onset for first reported polyps or polypectomy and that individuals with missense mutations had later onset for these symptoms.

Among 240 individuals with germline mutations in *STK11*, Lim et al (2004) identified similar cancer risks in individuals with missense and truncating mutations. However, this study did provide some evidence that exon 3 mutations resulted in a higher cancer risk than mutations elsewhere in *STK11*.

The risk of small-bowel intussusception was not influenced by *STK11* mutation status [Hearle et al 2006b].

The observations of Olschwang et al (2001) suggest that in addition to *STK11*, another genetic locus may predispose to the clinical features of PJS.

Anticipation

Anticipation is not observed.

Nomenclature

The term Peutz-Jeghers syndrome was introduced by Bruwer et al (1954).

The following terms have also been used for PJS:

- Polyp and spots syndrome
- Inherited hamartomatous polyps in association with mucocutaneous melanocyte macules
- Hutchinson Weber-Peutz syndrome

Prevalence

Estimates of birth prevalence range widely from 1:25,000 to 1:280,000, but these have not been reliably established.

PJS can occur in any racial or ethnic group.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

For the differential diagnosis of hamartomatous syndromes, see Table 2.

Juvenile polyposis syndrome (JPS) is characterized by predisposition for hamartomatous polyps in the gastrointestinal (GI) tract, specifically in the stomach, small intestine, colon, and rectum. The term "juvenile" refers to the type of polyp, not the age of onset of polyps. Juvenile polyps are hamartomas that show a normal epithelium with a dense stroma, an inflammatory infiltrate, and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria. Most individuals with JPS have some polyps by age 20 years. The number of polyps is highly variable. Most are benign. The risk of developing GI cancers in families with JPS ranges from 9% to 50%. Although most of this increased risk is attributed to colon cancer, cancers of the stomach, upper GI tract, and pancreas have been reported. JPS is distinguished from PJS by the lack of lentigines and the histology of polyps. Approximately 20% of individuals with JPS have mutations in *SMAD4* [Howe et al 1998] (previously called *MADH4*); about 25% have mutations in *BMPR1A*. JPS is inherited in an autosomal dominant manner.

Mixed hereditary polyposis syndrome. Individuals with mixed hereditary polyposis syndrome have polyps with the morphologic characteristics of both juvenile polyposis coli and adenomas and are at increased risk for colon cancer [Heiss et al 1993]. Some families with mixed hereditary polyposis syndrome have *SMAD4* mutations.

***PTEN* hamartoma tumor syndrome (PHTS),** an autosomal dominant cancer syndrome caused by mutations in *PTEN*, includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and a Proteus-like syndrome. The features of Cowden syndrome that distinguish it from PJS include facial trichilemmomas, mucosal papillomas, acral keratoses, macrocephaly, and tumors of the thyroid, breast, and endometrium. The distinguishing features of Bannayan-Riley-Ruvalcaba syndrome include macrocephaly, intestinal polyposis, and lipomas. Proteus-like syndrome is undefined but refers to individuals with significant clinical features of Proteus syndrome who do not meet the diagnostic criteria for Proteus syndrome.

Unexplained hamartomatous mixed polyposis. In a study of 49 unrelated persons with unexplained hamartomatous mixed polyposis, Sweet et al (2005) determined that 22% had various germline mutations.

- Of 14 individuals with juvenile-type polyposis, two had mutations in *ENG* (encoding endoglin), a gene associated with hereditary hemorrhagic telangiectasia; one had a hemizygous deletion encompassing *PTEN* and *BMPRIA*; and one had a *SMAD4* mutation.
- Of 23 individuals with hyperplastic/mixed polyposis, two had *PTEN* mutations.
- Of nine individuals with unknown hamartomatous polyposis, mutations were seen in *STK11* (4), *BMPRIA* (2), and *SMAD4* (1).

Carney complex (also known as NAME or LAMB syndrome) is an autosomal dominant disorder characterized by skin pigmentary abnormalities, myxomas of the skin, heart, and breast, endocrine tumors/overactivity, and schwannomas. Pale brown to black lentigines are the most common presenting feature of Carney complex and typically increase in number at puberty. The endocrine tumors that develop include primary pigmented nodular adrenocortical disease (PPNAD), which may cause Cushing syndrome, growth hormone-producing pituitary adenomas, large-cell calcifying Sertoli cell tumors (LCCSCT), thyroid adenoma or carcinoma (papillary or follicular), or multiple thyroid nodules [Carney et al 1986, Stratakis et al 1997]. PJS-type polyps do not occur in Carney complex. Despite some clinical overlap between Carney complex and Peutz-Jeghers syndrome, no individuals with Carney complex have been found to have mutations in *STK11*. About 40%-50% of individuals have mutations in *PRKAR1A*. Families with Carney complex have been linked to 2p16 as well [Stratakis et al 1996].

Table 2. Syndromes Showing Signs and Symptoms that Overlap with PJS

Syndrome	Gene Symbol	Pigmentation	GI Tumors	Sertoli Cell Tumors	Cancers	Other
PJS	*STK11*	Facial++ Mucosal +++	Adenoma+ Hamartoma+++	+/-	Colon, gastric, cervical, ovarian, breast, pancreatic	Hyper-estrogenism
JPC	*SMAD4*	-	Adenoma+ Hamartoma+++	-	Colon	Heart defects?
Cowden syndrome	*PTEN*	Axillary+ Inguinal + Facial+	Adenoma+ Hamartoma+++	-	Breast, brain	Trichilemmoma, skin hamartoma, hyperplastic polyps, macrocephaly, breast fibrosis
Carney complex	*PRKAR1A*	Facial+ Mucosal+	-	++	Thyroid	Myxomas of skin and heart
FAP	*APC*	-	Adenoma+++	-	Colon, brain	Desmoid tumors, osteomas, CHRPE
HNPCC	*MLH1*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, *PMS2*		Adenoma+	-	Endometrial, gastric, renal pelvis and ureter, ovarian	Sebaceous adenoma

+ indicates presence of symptom with number of +'s indicating relative frequency of sign or symptom for the condition
+/- indicates an occasional or rare symptom
? indicates anecdotal association
JPC=juvenile polyposis coli
FAP=familial adenomatous polyposis
CHRPE=congenital hypertrophy of the retinal pigment epithelium
HNPCC=hereditary non-polyposis colorectal cancer

The differential diagnosis of oral pigmented lesions includes the following:

- The Langier-Hunziker syndrome: the presence of perioral lentiginosis (small, well-demarcated; dark-brown to blue-black in color); it occurs in one in 8,300 to 29,000 births. The term perioral lentiginosis is sometimes used inappropriately as a synonym for PJS.
- A fixed drug reaction
- A normal variant, especially in African-Americans [Bishop et al 2004]

The differential diagnosis of some of the rare cancers observed in PJS includes:

- Sex cord tumors with annular tubules (SCTAT): 50% are associated with Peutz-Jeghers syndrome; the remainder may occur as an isolated finding.
- Calcifying Sertoli tumors of the testes and adenoma malignum of the cervix in women may also occur as an isolated finding or in other disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Peutz-Jeghers syndrome (PJS), the following evaluations are recommended:

- Upper and lower endoscopy (preferably wireless capsule endoscopy) plus radiographic examination of the small bowel beginning at age eight years or when symptoms occur
- Women: gynecologic and breast examinations and, if over age 20 years, mammogram

- Men: testicular examination and testicular ultrasound examination, if clinically indicated

Treatment of Manifestations

Polyps. Routine endoscopic and intraoperative enteroscopy with polypectomy decreases the frequency of emergency laparotomy and bowel loss resulting from intussusception [Pennazio & Rossini 2000, Edwards et al 2003, Oncel et al 2004].

Laparotomy and intraoperative endoscopy are appropriate for removal of polyps larger than 1.5 cm.

Distal small-bowel polyps that are beyond the reach of conventional endoscopy have been difficult to manage. Until recently, barium contrast upper gastrointestinal series with a small-bowel follow-through has been recommended. However, two recent advances allow better diagnosis and eradication of small-bowel polyps, oftentimes without laparotomy:

- Wireless capsule endoscopy allows for better visualization of the small-bowel polyps [Parsi & Burke 2004, Burke et al 2005, Mata et al 2005, Schulmann et al 2005].
- Double-balloon, or "push and pull," enteroscopy can remove distal small-bowel polyps without laparotomy [Ohmiya et al 2005].

Intussusception should be treated in a standard manner.

Malignancies should be treated in a standard manner. Conservative management of gonadal tumors in males and females is appropriate.

Prevention of Primary Manifestations

Although not studied in PJS, prophylactic hysterectomy and bilateral salpingo-oophrectomy to prevent gynecologic malignancy in women after age 35 years or after child-bearing has been completed should be considered. In other high-risk disorders, such as HNPCC, evidence supports this strategy [Schmeler et al 2006].

Surveillance

The surveillance program for the multiple organs at risk for cancer is outlined in Table 3; however, the effect of such surveillance on morbidity and mortality has not been evaluated in controlled trials.

Table 3. Screening and Surveillance Guidelines for Peutz-Jeghers Syndrome

Site	Procedure	Onset (yr)	Interval (yr)
Stomach, small and large bowel	Upper and lower endoscopy	8 [1]	2
	Small bowel follow-through [2]	8 [1]	2 [3]
	Colonoscopy	25	2
Breast	Breast examination	20	1
	Mammography	20	2-3
Testicle	Testicular examination	10	1
Ovary, uterus	Pelvic examination	20	1
	Pelvic ultrasound	20	1
Pancreas	Endoscopic ultrasound [4] (if available) or abdominal ultrasound	30	1-2

Adapted from Boardman 2002 and McGarrity & Amos 2006

1. In a review of 32 kindreds with PJS, laparotomy for bowel obstruction was performed in 30% of individuals by age ten years and in 68% by age 18 years [Hinds et al 2004]. For this reason, screening of asymptomatic at-risk children by age eight years was recommended by the authors.
2. Depending on local availability, wireless capsule endoscopy may replace small-bowel follow-through radiographs.
3. Consider laparotomy and intraoperative endoscopy to remove polyps >1.5 cm.
4. Canto et al 2004

Testing of Relatives at Risk

Family mutation known. If the disease-causing mutation has been identified, it is appropriate to offer molecular genetic testing to at-risk relatives. Morbidity and mortality can be reduced in those individuals identified to have the family-specific mutation by means of:

- Early diagnosis and treatment;
- Surveillance as outlined in Surveillance.

Family mutation not known. If the disease-causing mutation in the family is not known, it is appropriate to offer:

- Clinical diagnostic evaluations to identify those family members who will benefit from early treatment;
- Surveillance as outlined in Surveillance to all first-degree relatives whether or not they meet diagnostic criteria.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

No chemopreventive agent to decrease polyp formation or cancer risk has been tested in individuals with PJS.

Several animal models of PJS have been generated using *STK11* gene knockout mice [Karuman et al 2001, Bardeesy et al 2002, Miyoshi et al 2002, Nakau et al 2002]. Gastrointestinal hamartomatous polyposis developed with STK11 haploinsufficiency. In these animal models, up-regulation of Cyclooxygenase-2 (COX-2) in polyp tissue was noted [Rossi et al 2002]. Overexpression of COX-2 in human PJS hamartomatous and PJS-associated cancers has also been detected [McGarrity et al 2003, Wei et al 2003]. Selective COX-2 inhibitors have been approved for the prevention of colorectal polyps in familial adenomatous polyposis. Whether selective COX-2 inhibition in individuals with PJS will decrease polyp formation and cancer risk remains to be studied. Currently, no clinical trials in the US are studying efficacy of COX-2 inhibitors in reducing polyp formation in individuals with PJS. Increased cardiovascular and cerebrovascular adverse events with selective COX-2 inhibitors limit their use.

Low-dose rapamycin, which inhibits mTOR, has been shown to decrease the growth of astrocytomas in tuberous sclerosis [Franz et al 2006]. Whether rapamycin would decrease PJS polyp growth is unknown.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as

information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Peutz-Jeghers syndrome (PJS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 50% of probands have an affected parent and about 50% appear to be simplex cases (i.e., PJS in a single family member).
- Of the simplex cases, many appear to be caused by *de novo* mutations in *STK11*. The proportion of cases caused by *de novo* gene mutations is unknown as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic data are insufficient. It is appropriate to evaluate the parents of a proband clinically, and with molecular genetic testing if a disease-causing *STK11* mutation has been identified in the proband.
- Recommendations for the evaluation of parents of a proband with Peutz-Jeghers syndrome and no known family history of PJS include: examination of the buccal mucosa and skin of the digits and genital area for hyperpigmented macules; upper and lower gastrointestinal endoscopy; mammography; bimanual pelvic examination and ovarian ultrasound examination (females), and testicular examination (males).

Note: Family history may appear to be negative because of failure to recognize the disorder in family members or early death of the parent (and other relatives) before the onset of symptoms. In addition, the cause of Peutz-Jeghers syndrome in families with only one affected member may be heterogeneous, so that some cases may not be the result of autosomal dominant inheritance of a disease susceptibility locus.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the parents.
- If one parent is affected, the risk to sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of the either parent, two possible explanations are germline mosaicism in a parent or

a *de novo* mutation in the proband [Hernan et al 2004]. No instances of germline mosaicism have yet been reported.

Offspring of a proband

- Every child of an individual with Peutz-Jeghers syndrome with a positive family history and/or a mutation identified in *STK11* has a 50% chance of inheriting the mutation.
- The risk to the offspring of a proband with a negative family history and no identified *STK11* mutation is unknown. Since the cause of Peutz-Jeghers syndrome in one family member only could be heterogeneous, risk assessment for offspring of individuals without an identified *STK11* mutation is difficult.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Genetic heterogeneity. PJS occurring in individuals who do not have a family history of PJS may be caused by mutations in genes other than *STK11* and could have been inherited in a different manner from PJS caused by *STK11* mutations.

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see:

- Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors
- Elements of Cancer Genetics Risk Assessment and Counseling (part of PDQ®, National Cancer Institute)

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for Peutz-Jeghers syndrome is available after the disease-causing *STK11* mutation has been identified in an affected family member. Such testing may provide some insight concerning age of onset, as Amos et al (2004) found that onset was later in individuals with missense mutations than in those with protein-truncating mutations. However, only six different missense mutations were present in individuals in the Amos et al study; therefore, there may be heterogeneity in presentation of disease, depending upon the effect of the missense mutation upon the STK11 protein structure or function. Lim et al (2003) showed higher risks for cancer among individuals with PJS who have a *STK11* mutation.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek molecular genetic testing in order to make personal decisions regarding medical surveillance, reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of Peutz-Jeghers syndrome, and the possible impact of positive and negative test results are discussed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and evaluations.

Testing of at-risk individuals during childhood. Testing of at-risk individuals during childhood for Peutz-Jeghers syndrome is available after the disease-causing *STK11* mutation has been identified in an affected family member.

Because early detection of at-risk individuals who have an *STK11* mutation affects medical management, particularly surveillance (see Table 3), testing of at-risk individuals during childhood is beneficial [ASCO Policy Statement 2003]. This testing may also provide some insight concerning age of onset for disease, as individuals with missense mutations of *STK11* had a later onset than individuals with truncating mutations [Amos et al 2004], but the age of onset distribution is highly variable among individuals.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations, including alternate paternity or undisclosed adoption, could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of PJS are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal diagnosis for conditions such as Peutz-Jeghers syndrome that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate. To date, there are no reports of prenatal testing for Peutz-Jeghers syndrome, although it is technically possible in families with known mutations.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Peutz-Jeghers Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
STK11	19p13.3	Serine/threonine-protein kinase 11

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Peutz-Jeghers Syndrome

175200	PEUTZ-JEGHERS SYNDROME; PJS
602216	SERINE/THREONINE PROTEIN KINASE 11; STK11

Table C. Genomic Databases for Peutz-Jeghers Syndrome

Gene Symbol	Entrez Gene	HGMD
STK11	6794 (MIM No. 602216)	STK11

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Dysregulation of mTOR may be a common molecular pathway for hamartoma syndromes [Inoki et al 2005]. Tuberous sclerosis complex, an autosomal dominant disorder with multiple hamartomas noted in the skin, brain, kidneys, and heart, results from mutations in either *TSC1* or *TSC2* [Cheadle et al 2000]. *STK11* acts as a suppressor by activating *TSC2* through the AMP-depended protein kinase [Corradetti & Guan 2006] leading to accumulation of mTOR, which is critical for protein translation. *PTEN* also effects *TSC2* and mTOR pathway via AKT, a potent pro-survival protein.

Normal allelic variants: The normal structure includes ten exons, of which nine are translated.

Pathologic allelic variants: Of the 102 mutations reported to the Human Genome Mutation Database as of August 5, 2003 (HGMD), 52 were deletions, insertions or other mutations affecting the normal nucleotide sequence, 12 were splicing variants, and 38 were missense mutations. No known hotspots for recurrent mutation have been identified. No variants are associated with any particular ethnicity [Hastings et al 2005, Schumacher et al 2005].

Normal gene product: This serine/threonine-protein kinase has a prenylation motif suggesting that it is involved in protein-protein interactions and membrane binding [Collins et al 2000]. The predicted protein structure also shows an autophosphorylation domain [Mehenni et al 1998], along with a cyclic AMP-dependent protein kinase phosphorylation site. STK11 expression was shown to cause apoptosis in epithelial cells [Karuman et al 2001]. The transport of STK11 to the mitochondria appears to be an early step in apoptosis. STK11 colocalizes with p53 during apoptosis. The ability of STK11 to induce apoptosis also depends upon p53. These results suggest that signaling through STK11 may be an early event leading to apoptosis through p53 pathways. Tiainen et al (2002) showed that STK11 affects G1 cell cycle arrest and that growth suppression by STK11 is mediated through signaling of cytoplasmic STK11. Inhibition of cellular proliferation by *STK11* may occur through induction of WAF1, a cyclin-dependent kinase inhibition [Tiainen et al 2002, Spicer et al 2003]. More recently, the role of *STK11* on cell polarity has been established. Mutations in the C-terminal non-catalytic region decreased mediation of AMP-activated kinase and cell polarity [Boudeau et al 2003, Spicer & Ashworth 2004, Forcet et al 2005].

Abnormal gene product: Nezu et al (1999) suggest that truncating mutations prior to amino acid 311 abrogate the kinase activity of STK11. Tiainen et al (2002) demonstrated that kinase-

deficient mutants predominantly display nuclear immunostaining, suggesting aberrant signal transduction for such mutants. Mehenni et al (1998) discussed the potential impact that several missense mutations which they detected may have upon the protein structure. Hemminki et al (1998) found nonsense mutations predicted to lead to a truncated protein and loss of kinase activity in all 23 familial cases and two simplex cases (i.e., single occurrence in a family) studied. More recently, a few individuals with PJS with mutations in the C-terminal non-catalytic region have been identified [Forcet et al 2005].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Genetics of Breast and Ovarian Cancer (PDQ)
A service of the National Cancer Institute
Peutz-Jeghers syndrome

National Library of Medicine Genetics Home Reference
Peutz-Jeghers syndrome

Hereditary Colon Cancer Association (HCCA)
3601 N 4th Ave Suite 201
Sioux Falls SD 57104
Phone: 800-264-6783; 605-373-2067
Fax: 605-336-6699
Email: info@hereditarycc.org
www.hereditarycc.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Clinical Oncology. Statement on genetic testing for cancer susceptibility . 2003

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Chapter Notes

Author Notes

Drs. Amos and Frazier hold a grant from the American Cancer Society investigating the molecular genetics of Peutz-Jeghers syndrome. Dr. McGarrity is a gastroenterologist who partially specializes in the diagnosis and treatment of Peutz-Jeghers syndrome.

Revision History

- 15 May 2007 (me) Comprehensive update posted to live Web site
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- 26 November 2003 (me) Comprehensive update posted to live Web site
- 23 February 2001 (me) Review posted to live Web site
- 11 July 2000 (ca) Original submission