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The differential diagnosis of familial lentiginosis syndromes

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Abstract

Cutaneous markers of systemic disease are vital for clinicians to recognize. This chapter outlines familial lentiginosis syndromes that include Peutz-Jeghers syndrome, Carney Complex, the PTEN hamartomatous syndromes, and LEOPARD/Noonan syndrome. The inheritance of these syndromes is autosomal dominant; they also share characteristic skin findings that offer a clue to their recognition and treatment. We will discuss the clinical presentation of these disorders, with a focus on the dermatological manifestations, and will provide an update on the molecular mechanisms involved. Recognition of cutaneous markers associated with these rare familial cancer syndromes provides the opportunity to pursue early surveillance for malignancies, as well as genetic counseling.

Keywords

hamartoma; lentigines; mamallian target of rapamycin; tumor suppressor

Introduction

Malignancies may occur in a number of inherited conditions with associated dermatologic manifestations. In this review, we discuss the clinical presentation of disorders associated with lentigines and provide an update on the molecular mechanisms involved. The common feature of lentigines in these familial syndromes is not only a clinical feature but represents an underlying convergence of related signaling pathways. It is now known that most of these disorders (but not all) are caused by mutations in components of the rat sarcoma - mitogen-actived protein kinase (Ras-MAP kinase) and the mammalian target of rapamycin (mTOR) signaling pathway. The presence of lentigines therefore provides a window to underlying cellular mechanisms that control embryonic development and neural crest differentiation.

Lentigines (from the Latin *lentigo*, 'small lentil') consist of flat-pigmented macules on the skin and mucosa. Lentigines are characterized by their small size (< 0.5 cm), irregular borders, and discrete markings of different shades of brown and black. Familial lentiginosis syndromes are associated with an increased incidence of neural, endocrine, and mesenchymal tumors [1]. Histological examination of lentigines reveals prominent epidermal thickening and basal cell hyperpigmentation associated with melanocyte hyperplasia. This feature is distinct from the histological appearance of freckles which contain a normal number of melanocytes and are pigmented due to increased melanin in basal keratinocytes (Figure 1) [1]. While freckles are found almost exclusively on sun-exposed areas of the body, lentigines may occur on all parts of the body and typically do not darken with sun exposure

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(as compared to freckles). Specific sites of pigmentation, such as the labia majora, palms and soles, conjunctivae, and vermillion border of the lips, are characteristic locations for lentigines that provide important clues to the presence of an underlying syndrome and associated systemic disease. Peutz-Jeghers syndrome (PJS) is the most well known of the lentiginoses. A number of related disorders are also associated with lentigines and may be confused with PJS, including Carney Complex (CNC), Laugier-Hunziker syndrome (LHS), Ruvalcaba-Myhre-Smith, Bannayan-Zonnana syndrome (BRRS), Cowden disease (CD), and LEOPARD/Noonan syndrome (Table 1) [2]. Most of these syndromes are inherited in an autosomal dominant manner, have a relatively high rate of *de novo* cases, and predispose to a variety of neoplasms [3]. An algorithm for the approach of patients presenting with the three most prevalent syndromes associated with lentigines is presented in Figure 2. The downstream signaling pathways involved in these disorders regulate protein kinase A (PKA), Ras-MAP kinase, and the mammalian target of rapamycin (mTOR) [4]. These pathways converge to the regulation of growth, proliferation, and differentiation of many cell types. Mutations affecting these signaling pathways may include conditions ranging from benign lentigines to aggressive malignancies.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is a dominantly inherited syndrome that incurs an increased risk of malignancy. The association of lentigines with intestinal polyposis in ten cases from different families was named for Drs. Peutz and Jeghers [5, 6]. PJS is characterized by an increased susceptibility to tumors, including benign ovarian sex cord tumors, calcifying Sertoli tumors of the testis, cervical cancer, breast cancer, gastrointestinal cancer, pancreatic cancer, and endometrial cancer [7, 8]. Thyroid cancer has been associated with PJS, and differentiated thyroid cancer may occur earlier in life and behave more aggressively in patients with PJS[9–11]. However, the association between PJS and thyroid cancer is not strong enough to warrant routine screening without clinical suspicion. Key diagnostic features of PJS include hamartomatous polyps and mucosal hyperpigmentation. The characteristic pigmentation in PJS consists of dark brown-blue macules, but other lesions are not uncommon. The typical brown-blue macules are commonly found on the border of the lips (Figure 3) and oral and bowel mucosa, as well as on the palms and soles, eyes, nares, and peri-anal region [12]. The pigmented macules are first visible in early childhood, and tend to fade in late adulthood [12]. The fact that pigmentation may become less prominent over time can contribute to the difficulty in diagnosis of PJS [13]. Other syndromes may mimic the pigmentation of PJS and are outlined later in this chapter. Malignant melanoma is not a general feature of Peutz-Jeghers syndrome and has only been reported in a few cases [14, 15]. The origin of the lentigines in PJS remains poorly understood. One theory is that the lentigines are benign neoplasms of melanocytes with limited growth potential [16]. The most recent surveillance recommendations for PJS patients do not include dermatologic evaluation and these lesions are rarely biopsied [17]. Individuals with PJS may desire cosmetic removal of lentigines, which may be successfully treated with laser therapies [18].

Epidemiology

The estimated prevalence of PJS is 2.2 individuals per 100,000. Estimates have included 1 in 8,500 to 23,000 live births[19], 1 in 50,000 to 1 in 100,000 in Finland[20]

Molecular Mechanism

The majority of cases of PJS are due to heterozygous mutations in the serine-threonine kinase *STK11/LKB1* tumor suppressor gene located on chromosome 19p13.3 [21, 22]. To date mutations in *LKB1* can be found in only up to 80% of patients; linkage to other loci, including 19q13.4 has also been reported but the causative gene(s) have not been

identified [13, 23]. Alhopuro et al identified a mutation in the *MYH11* gene in 1 of 33 PJS patients who did not have *STK11* mutations, and the mutation was not identified in 1,015 controls [24]. In most cases, elimination of the kinase activity of STK11 underlies the molecular cause of the phenotype [25]. *STK11* is a classic tumor suppressor gene, as evidenced by loss of heterozygosity (LOH) of markers in hamartomas and adenocarcinomas from patients with PJS; gastrointestinal polyps in PJS patients develop via germ line mutations in *LKB1/STK11* in combination with somatic mutation or LOH of the normal allele [26]. Patients with PJS are not known to have an excess of malignant skin tumors; however, the lentigines of PJS patients likely represent small, benign tumors [16, 27]. Somatic mutations in *LKB1/STK11* were identified in cell lines and tumor samples from 35 patients with sporadic malignant melanoma [16].

PJS is caused by dysregulated signaling in the pathway upstream of mTOR, as loss of function mutations in *LKB1/STK11* inhibit AMP-activated protein kinase (AMPK) that signals downstream to inhibit mTOR [28]. Many of the regulatory components of this pathway have been elucidated and are outlined in Figure 3. mTOR is a member of the phosphoinositide-3-kinase-related family, and serves as a critical mediator of cell growth and proliferation, responsible for stimulating cell growth and controlling cellular energy levels [2930]. mTOR is highly conserved throughout evolution and regulates ribosomal biogenesis, protein translation, and formation of the actin cytoskeleton [31].

Carney complex (CNC)

Carney complex is a dominantly inherited multiple endocrine neoplasia syndrome first described in 1985 that is characterized by spotty skin pigmentation (lentiginosis), cardiac and peripheral myxomas, schwannomas, and endocrine overactivity [32, 33]. The most common cutaneous features of CNC include lentigines, freckling, café-au-lait spots, and blue nevi [34, 35]. Typical lentigines of the inner canthi and genital mucosa are presented in Figure 4. The endocrine tumors associated with Carney complex include primary pigmented nodular adrenal cortical disease (PPNAD), growth hormone secreting pituitary adenomas, large-cell calcifying Sertoli cell tumors, Leydig cell tumors, and thyroid neoplasms [36–38]. PPNAD, or primary pigmented nodular adrenocortical disease, is a rare cause of corticotrophin (ACTH)-independent Cushing syndrome. Historically, cardiac myxomas have been reported to be responsible for more than 50% of the disease-specific mortality among CNC patients [35]. Therefore, identification of affected patients and family members is crucial in order to screen for other features of Carney complex, namely potentially critical cardiac myxomas that require surgical removal [39].

Epidemiology

More than 500 patients are known world-wide. In a recent analysis, a total of 353 patients with CNC from 185 families were described[35, 40] The majority of patients (68%) had a family history consistent with CNC, whereas 113 cases (32%) had no known affected relatives and were classified as sporadic. A total of 221 patients (63%) were female. The median age of diagnosis was 20 years, although at least 5 patients were identified at birth[35, 41]

Molecular Mechanism

The molecular cause of disease in most patients with CNC (and isolated PPNAD) has been identified as mutations within the gene *PRKAR1A* on chromosome 17q22–24 [42]. *PRKAR1A* encodes the regulatory subunit type 1-α of Protein Kinase A, a key regulator of the cyclic-AMP-dependent signaling pathway that has been implicated in endocrine tumor formation [43]. Inactivating mutations of *PRKAR1A* have been reported in 45–80% of

families with CNC [44, 45]. Over 100 pathogenic variants in *PRKAR1A* have been detected, most leading to R1α haploinsufficiency [46]. Loss of R1α leads to increased cAMP-stimulated total kinase activity, however the link to increased tumor formation is still under investigation [42, 47]. A number of pathways are involved, but one that links this disease to others covered by this review is that of the mitogen-activated protein kinase (MAPK) ERK 1/2 signaling: lymphocytes isolated from CNC patients with known *PRKAR1A* mutations showed altered PKA activity and increased ERK 1/2 phosphorylation [48].

Overall *PRKAR1A* appears to serve as a tumor suppressor gene in which loss of activity is associated with loss of PKA-mediated inhibition of downstream pathways resulting in increased cell proliferation [48]. Loss of expression of PRKAR1A has been shown in pigmented epithelioid melanocytoma but not in melanoma or other melanocytic lesions [49]. The lentigines in CNC are typically benign; despite the high number of lesions, so far only one case of malignant melanoma in association with CNC has been reported [50], making this tumor incidence among CNC patients lower than that in the general population. On the other hand, high expression (and not loss) of PRKAR1A has been seen in association with increased proliferation of human melanoma cells in vitro [51].

Laugier-Hunziker Syndrome (LHS)

Laugier-Hunziker syndrome (LHS) is a rare, sporadic disorder, originally described in 1970, that is often confused for PJS due to similar appearance and distribution of hyperpigmented cutaneous and mucocutaneous lesions [52]. Only 100 cases have been reported thus far in the medical literature [53]. However, unlike PJS, LHS is an acquired, benign condition characterized by hyperpigmentation of the nails, palms and soles, and lips and oral mucosa without polyposis [54]. Lentigines in LHS typically appear later in life than in those individuals with PJS [52]. Interestingly, approximately 50–60% of patients with LHS have longitudinal melanonychia, brown or black pigmentation of the nail unit [55]. In LHS there is increased pigmentation in the basal keratinocytes and increased numbers of macrophages, however, the number of melanocytes is not affected[55].

Benign lentiginoses

Two separate syndromes, patterned lentiginosis and centrofacial neurodysraphic lentiginosis, are both benign lentiginoses conditions that are inherited in an autosomal dominant manner without systemic involvement [56–58]. Patterned lentiginosis was first reported in 1989 by O'Neil et al., who described 10 African-American patients with autosomal dominant transmission of lentigines distributed on the face, lips, extremity, buttock, and palms and soles. None of the patients had lesions of the oral mucosa or internal organ system abnormalities [56]. A separate syndrome, centrofacial neurodysraphic lentiginosis, consisting of facial lentigines associated with mental retardation and autosomal dominant inheritance has also been described.[58] None of the genes involved in either of these benign lentiginoses syndromes are known to date.

Ruvalcaba-Myhre-Smith or Bannayan-Zonnana syndrome (BRRS), and Cowden disease (CD): *PTEN* gene-related disorders

BRRS and CD are part of a group of inherited disorders that have been previously been classified as familial hamartoma syndromes. With the discovery of mutations in the tumor suppressor gene *PTEN* (10q22-q23) in up to 80% of CD patients and up to 60% of BRRS patients, it has been suggested that these conditions should be all listed under the heading "PTEN hamartoma tumor syndromes" (PHTS) [59–67]. Approximately 500 individuals with germline pathogenic *PTEN* mutations have been reported to date.[68]

Patients with *PTEN* mutations have an increased risk of developing multiple hamartomas in various organ systems such as the breast, skin, thyroid, central nervous system, and the GI tract [69]. BRRS is characterized by delayed motor development, macrocephaly, lipomatosis, as well as the presence of lentigines on the glans penis beginning in childhood [69]. Diagnostic criteria for CD include skin findings such as gingival papillomas and acral keratoses. Patients are susceptible to breast cancer, follicular thyroid cancer, and endometrial carcinoma [70]. Major criteria include breast cancer, thyroid cancer, macrocephaly, and Lhermitte-Duclos disease (hamartomatous growths of the cerebellum with associated ataxia). Minor criteria include thyroid disease (adenoma and goiter), gastrointestinal hamartomas, lipomas, fibromas, genitourinary tumors, fibrocystic breast disease, and developmental delay [71]. Up to 10 percent of patients with CD develop follicular carcinoma, and 50–75% will manifest benign thyroid disease [72, 73]. Lentigines develop by age 20 in 90% of patients with CD. In order to diagnose CD patients must have one major and three minor criteria. Most of the cutaneous lesions in CD are benign, however, the association of squamous cell carcinoma with CD has been reported [74–76]

Molecular Mechanism

PTEN hamartoma tumor syndromes, including BRRS and CD, all represent additional disorders associated with loss-of-function mutations in a tumor suppressor gene leading to constitutive mTOR activation. A recent overview of the PTEN hamartoma tumor syndromes as well as a newly developed clinical scoring system to guide selection of patients for PTEN testing provide excellent resources for clinicians[68, 77]. Approximately 80 percent of patients with CD are found to have associated mutations in the phosphate and tensin gene *(PTEN)* on chromosome 10q23.31, which codes for a neuroendocrine developmental regulator protein [70, 78]. PTEN plays a key role in cell growth, apoptosis, differentiation, membrane trafficking, cellular interactions and cellular motility [67, 79, 80]. Loss of PTEN activity leads to constitutive activation of the cytosolic signaling protein AKT [81]. One of the key downstream targets of AKT is the tuberin-hamartin complex (*TSC1/TSC2*), mutations of which are associated with the hamartomatous syndrome tuberous sclerosis (TS) [82]. In TS, loss of PTEN function results in the constitutive activation of AKT, down regulation of tuberin/T*SC2* and mTOR and subsequent promotion of cell-cycle progression and suppression of apoptosis. The discovery of this pathway therefore links the pathogenesis of tumor formation in hamartomatous tumor syndromes as outlined in Figure 5 [83]. Loss of PTEN may have a critical role in the pathogenesis of melanoma, as widespread PTEN loss has been demonstrated in primary cutaneous melanomas [84]. Recent developments have shown PTEN as a key tumor suppressor for the development of basal cell carcinoma, squamous cell carcinoma, and melanoma [74].

LEOPARD syndrome

LEOPARD is an acronym that also describes the pattern of pigmentation found in this familial multiple lentigines syndrome. The manifestations of this syndrome include Lentigines, Electrocardiographic conduction defects, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness [85]. The diagnosis is established if multiple lentigines are present in association with at least two other features; if lentigines are absent, a first-degree relative affected with LEOPARD syndrome and three of the other six features are needed for diagnosis [86, 87].

Lentigines are often the first clinical manifestation of in LEOPARD syndrome, and they are found primarily on the face and upper trunk, although rarely involve the oral mucosa, extremities, genitalia or conjunctiva [88]. Lentigines in LEOPARD syndrome do not cross the vermilion border of the lips, a characteristic that distinguishes this disorder from CNC and PJS [4]. It is unknown whether pigmented lesions in LEOPARD syndrome progress to

malignancy; to date, only one case of LEOPARD syndrome associated with malignant melanoma has been reported [89].

Facial dysmorphism in LEOPARD syndrome includes low-set ears, hypertelorism and palpebral ptosis. These features, combined with an increased incidence of pulmonic stenosis, show significant phenotypic overlap with Noonan syndrome, which goes along with molecular evidence that these two disorders share the same allele [90]. Morbidity and mortality associated with LEOPARD syndrome are dependent on the extent of cardiac disease. Multiple congenital heart defects have been reported to include not only pulmonic stenosis (present in 40% of patients) but also subaortic and subpulmonic stenosis, and hypertrophic obstructive cardiomyopathy [88].

Molecular Mechanism

LEOPARD syndrome is caused by mutations in genes that regulate the mTOR signaling pathway [91]. LEOPARD syndrome can be caused by mutations in the *PTPN11* gene on chromosome 12q24.1 This is the identical allele implicated in Noonan syndrome, and explains the phenotypic overlap between the two conditions. A distinct form of LEOPARD syndrome is caused by RAF1 defects (chromosome 3p25); this form is strongly associated with hypertrophic cardiomyopathy [92, 93].

PTPN11 encodes SHP2, a positive regulator of RAS-MAPK signaling The *PTPN11* mutations that have been described in both NS and LEOPARD are believed to be gain-of-function mutations leading to dysregulated phosphatase activity with subsequent increased inhibition of GTPase which in turn leads to increased Ras activity [90].

The lentiginoses and the mTOR Pathway

The genetic defects of most of the disorders associated with lentigines are linked directly or indirectly to a common oncogenic pathway, that of the mammalian target of rapamycin (mTOR). mTOR is a highly conserved serine/threonine kinase that mediates cellular growth, and is also thought to play key roles in cancer, diabetes and ageing [83, 94]. Dysregulated activation of mTOR is hypothesized to be the unifying underlying mechanism responsible for the formation of lentigines and neoplasia in PJS and related conditions. Activation of mTOR is strongly associated with malignant melanocytic lesions in vivo, suggesting that mTOR inhibition may have clinical benefit in patients with melanoma and/or other malignant lesions associated with the lentiginoses [95]. Rapamycin inhibits mTOR and results in decreased expression of mRNAs necessary for cell cycle progression and arresting cells in the G1 phase of the cell cycle [96]. A clinical trial using the mTOR inhibitor *Everolimus* was initiated in 2008 as a pilot-open label phase II study for patients with PJS and gastrointestinal polyps (clinical trials.gov identifier NCT00811590). As dysregulation of mTOR has been demonstrated in several types of cancers, inhibition of mTOR may be of benefit to these patients. Targeting of the mTOR pathway with rapamycin together with the RAF inhibitor *Sorafenib* as been investigated in melanoma cell lines in vitro [97]. A clinical trial investigating the use of *Sorafenib* and *Temsirolimus* (an analog of rapamycin) in treating patients with metastatic, recurrent, or unresectable melanoma is currently underway (clinical trials.gov identifier NCT00349206).

Conclusions

Familial lentiginosis syndromes represent a large phenotypic spectrum ranging from a benign inherited predisposition to develop lentigines alone, to associations with several syndromes that carry an elevated risk of neoplasia. The etiologic molecular pathways have been defined over the past 20 years, including the PKA pathway in CNC the Ras/Erk MAP

kinase pathway in LEOPARD/Noonan syndromes, and mTOR in both Peutz-Jeghers syndrome and the diseases caused by PTEN mutations. Patients presenting with lentigines that may be associated with syndromes linked to increased risk of malignancy should be evaluated to confirm the suspected diagnosis. This will allow the patient to be appropriately screened for malignancy and other disease associated sequellae.

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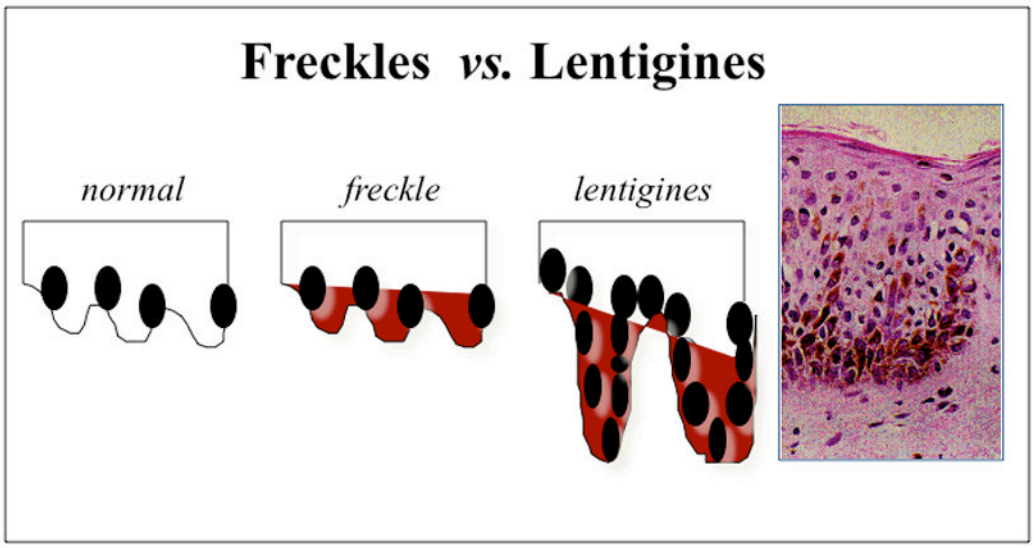


Figure 1.
Histological appearance of freckles vs lenigines Magnification of the lentigen showing melanocytic hyperplasia, characteristic of the lesion (x 200). This differs from common freckles, in which the number of melanocytes is normal but the amount of melanin is increased.

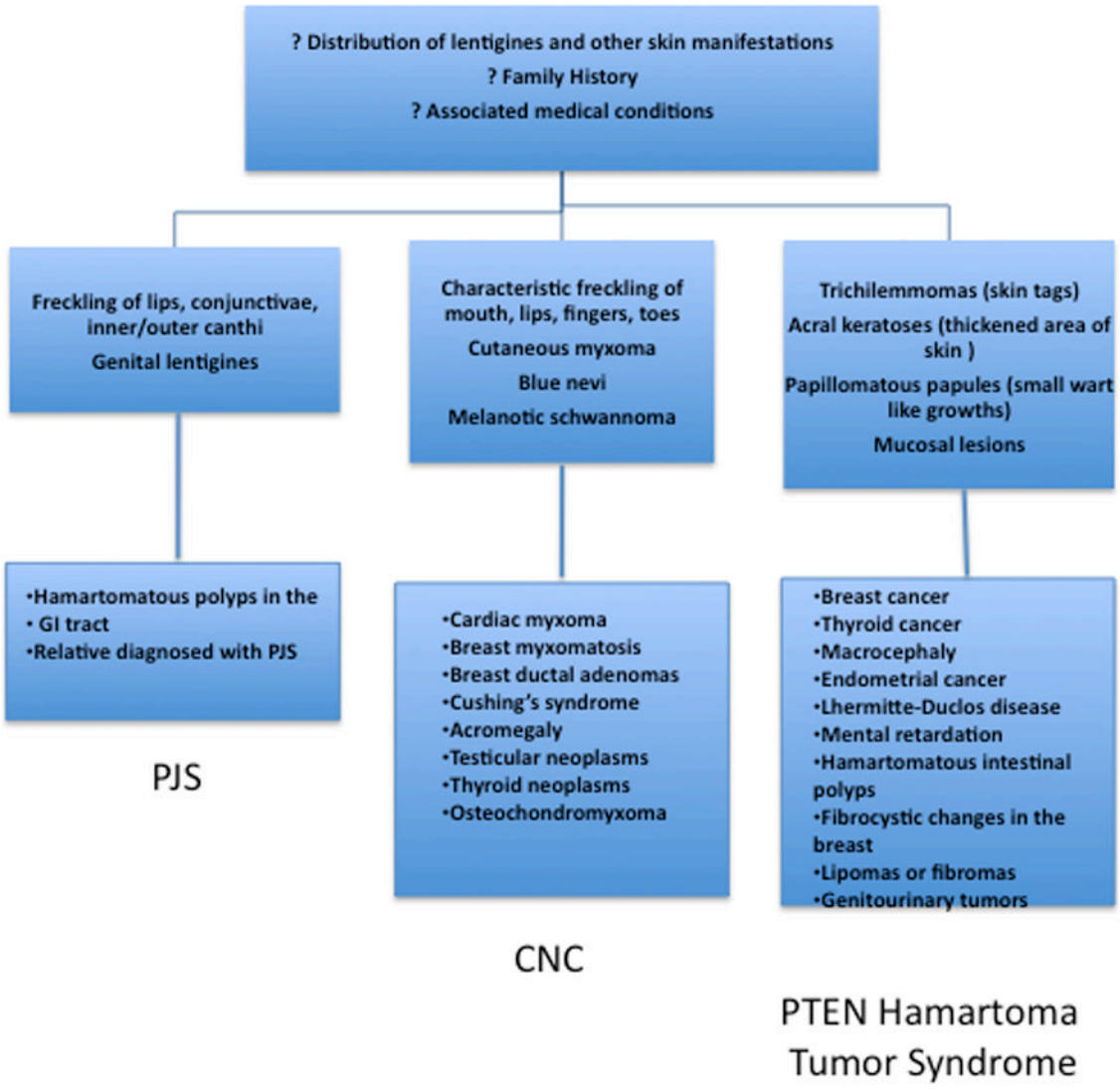


Figure 2.
Algorithm of approach to patients presenting with lentigines (includes the three most prevalent lentigines outlined in this review).

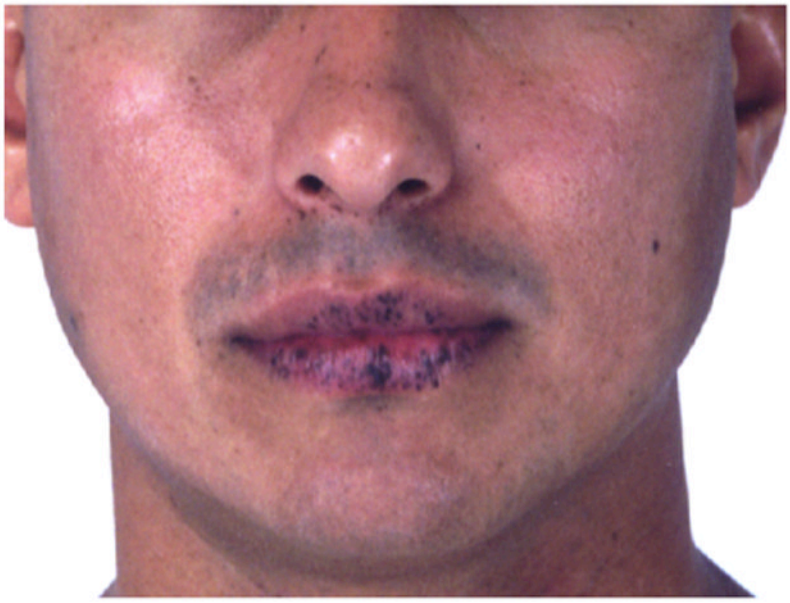
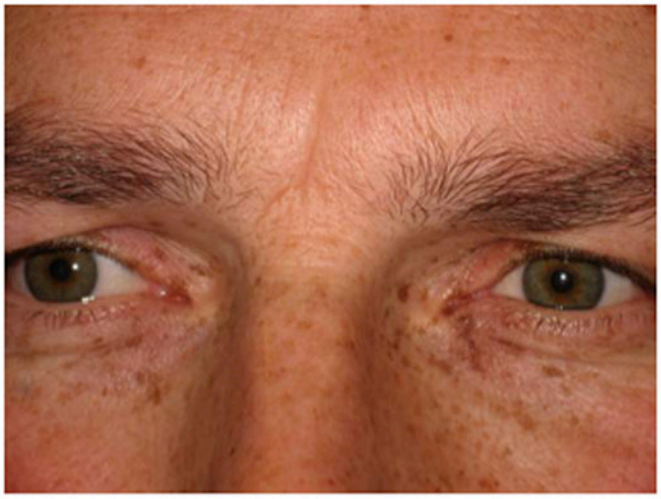


Figure 3.
Typical oral pigmentation of a patient with PJS.



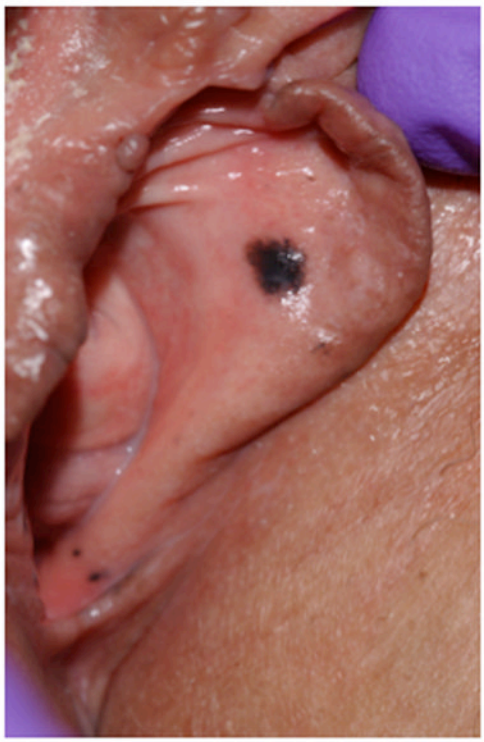


Figure 4.
Cutaneous manifestations in CNC: pigmentation at (a) inner canthi; *and* (b) vaginal mucosa.

Figure 5.

The tumor-suppressor genes *LKB1*, *PTEN*, *PRKAR1A* exert inhibitory effects on signaling through the TSC complex that inactivates mTOR, while SHP2 gain-of-function mutations also lead to downstream mTOR activation. Each of genes is mutated in distinct syndromes that are characterized by the development of lentigines and other skin lesions. *Abbreviations*: LKB1, serine/threonine kinase 11; AMPK, AMP-activated protein kinase; PTEN, phosphatase and tensin homolog; P13K, 1-phosphatidylinositol 3-kinase; AKT, protein kinase B; NF1; neurofibromatosis type 1MEK, mitogen activated protein kinase kinase; ERK, extracellular signal-regulated kinase; TSC1; tuberous sclerosis 1; TSC2; tuberous sclerosis 2; mTOR, mammalian target of rapamycin.

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Table 1

Disease	MIM	Clinical Manifestations	Inheritance	Locus	Gene	Prevalence
Peutz-Jeghers Syndrome	175200	lentigines, GI polyps, neoplasia (GI tract, pancreas, breast, ovary, uterus)	AD	19p13.3	*LKB1*/*STK11*	2.2/100,000
Carney Complex	160980	lentigines, PPNAD cardiac and skin myxoma schwannomas, acromegaly, breast and testicular tumors	AD	17q22–24	*PRKAR1A*	>500cases described
Lentiginoses	151001 151000	lentigines (centrofacial palmoplantar, trunk), As above in addition to mental retardation	AD AD/sporadic	unknown unknown	unknown unknown	unknown
PTEN Hamartoma Tumor Syndrome (BRRS + Cowden Disease)	153480 158350	macrocephaly, lipomatosis, pigmentation of the glans penis, mental retardation, vascular malformations	AD	10q23.31	*PTEN*	>500 cases described
LEOPARD Syndrome	151100 611554	lentigines, cardiac conduction abnormalities, aneurysms, pulmonic stenosis, cephalo-facial dysmorphism, short stature, sensorineural deafness, mental retardation, skeletal abnormalities	AD AD	12q24.1 3p25	*PTPN11* *RAF1*	200 cases described