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GENETICS OF CARNEY COMPLEX AND RELATED FAMILIAL LENTIGINOSES, AND OTHER MULTIPLE TUMOR SYNDROMES

Constantine A. Stratakis

Unit on Genetics and Endocrinology, Developmental Endocrinology Branch, National Institute of Child Health & Human Development (NICHD), National Institutes of Health (NIH), Building 10, Room 10N262, Bethesda, MD 20892-1862

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1. ABSTRACT

Carney complex is a multiple endocrine neoplasia (MEN) syndrome that affects the adrenal cortex, the pituitary and thyroid glands, and the gonads. The complex is also associated with skin and mucosa pigmentation abnormalities and myxoid and other neoplasms of mesenchymal and neural crest origin. Thus, this syndrome also belongs to another group of genetic disorders, the lentiginoses (or lentigenoses), which include the Peutz-Jeghers, LEOPARD, arterial dissections and lentiginosis, and Laugier-Hunziker syndromes, Cowden disease and Ruvalcaba-Myhre-Smith (Bannayan-Zonana) syndrome and the centrofacial, benign patterned and segmental lentiginoses, all of which can be associated with a variety of developmental defects. The inheritance of Carney complex, just like that of the other MENs and the lentiginoses, is autosomal dominant. Genetic loci or genes have been identified for Carney complex, Peutz-Jeghers and Ruvalcaba-Myhre-Smith syndromes, but not for other lentiginoses. Elucidation of the molecular defects responsible for these disorders is expected to shed light on aspects of early neural crest differentiation, the regulation of pigmentation, the development of autonomous endocrine function, and endocrine and nonendocrine tumorigenesis.

2. INTRODUCTION

In recent years, a number of proto-oncogenes and genes with tumor-suppression or developmental functions have been implicated in endocrine and nonendocrine tumorigenesis and skin disorders (1). The tumors and cafe-au-lait spots (CALS) of the McCune-Albright syndrome (MAS) are caused by gain-of-function mutations of the *gsp* oncogene, the α-subunit of the guanine nucleotide-binding proteins (Gsα) (2). The multiple endocrine neoplasia (MEN) syndromes, which have been associated with several cutaneous abnormalities, are caused by two distinct genes: MEN 1 is associated with mutations in a recently identified tumor-suppressor gene on chromosome 11q13 which codes for *menin* (3), while the MEN 2A and 2B (the latter also known as MEN 3) syndromes are caused by mutations of the *RET* proto-oncogene, an important regulator of neural crest development and the receptor of glia-derived neurotrophic factor (*GDNF*) (4). A variety of other disorders with multiple endocrine and nonendocrine tumors and skin pigmentation anomalies have been elucidated at the molecular level: The neurofibromatosis type I and II syndromes are due to mutations of the tumor-suppressor genes coding for *neurofibromin* and *schwannomin*, respectively, both expressed early in cells derived from the neural crest (5). Cowden disease, associated with thyroid tumors and various hamartomas and skin anomalies, is caused by mutations in the *PTEN* gene, which codes for a neuroendocrine developmental regulator protein (6). Other developmental genes involved in oncogenesis and skin differentiation include the human homologue of the fruit fly *patched* gene, which is responsible for inherited nevoid basal cell carcinoma (Gorlin syndrome) (7), and the *PAX-3* gene, responsible for Waardenburg syndrome and pediatric alveolar rhabdomyosarcoma (8).

The familial lentiginoses are less well known syndromes associated with numerous skin lesions and an increased predisposition toward neoplasms. Although the first of these conditions-the Peutz-Jeghers syndrome (PJS)-was fully described as early as in 1949 (9), the responsible

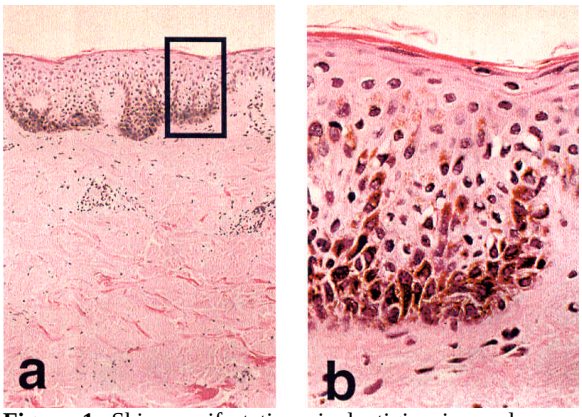

Figure 1. Skin manifestations in lentiginosis syndromes. Epidermis from a patient with Carney complex, including a lentigen (in the box) (x 40) (panel a). Magnification of the lentigen showing melanocytic hyperplasia, characteristic of the lesion (x 200) (panel b). This differs from common freckles, in which the number of melanocytes is normal but the amount of melanin is increased. This type of skin lesion is present in all lentiginosis syndromes.

genetic defect or defects remain elusive. Recently, the genetic loci for the "syndrome of spotty skin pigmentation, myxomas and endocrine overactivity" or Carney complex and PJS were identified (10, 11). Another familial lentiginosis, Ruvalcaba-Myhre-Smith or Bannayan-Zonana syndrome was recently found to be caused by mutations in the *PTEN* gene (12). *PTEN* is also involved in the pathogenesis of Cowden disease (6), underlining the substantial clinical and molecular overlap between disorders associated with multiple tumors and pigmentation defects.

The genes responsible for the lentiginoses are expected to shed light on important aspects of endocrine and nonendocrine tumorigenesis, neuroendocrine differentiation and the regulation of skin pigmentation. In this article, we provide an overview of the lentiginosis syndromes and their genetics, as they relate to Carney complex and other developmental defects.

3. FAMILIAL LENTIGINOSIS SYNDROMES

The familial lentiginosis syndromes have in common the presence of pigmented spots on the skin, called *lentigines* (from the Latin *lentigo*, "small lentil"), and share with the MENs and phacomatoses an increased incidence of endocrine and mesenchymal tumors. Lentigines are flat, poorly circumscribed, slightly variegated, pinpoint-to-6 mm, brown-to-black macules. On histologic examination, lentigines show prominent rete ridges and basal cell layer hyperpigmentation associated with an increased number of melanocytes (13). Thus, they differ from common freckles, or ephelides, in that they represent true melanocytic hyperplasia (Figure 1). Indeed, common freckles contain a normal number of melanocytes and are pigmented because of melanin donation to adjacent keratinocytes. In addition, lentigines are present in early childhood and occur preferentially, but not exclusively, on sun exposed skin, whereas freckles are smaller (2 to 4 mm) and usually lighter macules that are found almost exclusively on sun-exposed skin areas, particularly in lightly pigmented persons. Lentigines can be deeply pigmented in certain anatomic sites, such as the mucosae of the vermilion border of the lips, the labia majora of the vulva, and the inner and outer canthi of the conjunctivae. This fact is of particular clinical significance, since the presence of lentigines in these areas almost always suggests an association with one of the familial lentiginosis syndromes (Table 1).

4. CARNEY COMPLEX

The first report of the syndrome in 1985 described 39 patients. It stemmed from earlier observations on patients with pituitary-independent Cushing syndrome and an unusual adrenal pathology characterized by multiple, small, pigmented, adrenocortical nodules and internodular cortical atrophy (14-16). This condition, which proved to be primary and bilateral, is now commonly referred to as primary pigmented nodular adrenal disease (PPNAD). By 1981, 23 cases of PPNAD (4 from the Mayo Clinic and 19 from the world literature) were available for study; 6 of them involved siblings from two families, one from Cuba and another from Switzerland (17). By 1984, 40 cases were identified, with various combinations of myxomas affecting multiple organs (heart, skin, and breast), spotty skin pigmentation (lentigines and blue nevi), and tumors of three endocrine organs (adrenal, pituitary, and testis) (18). The group had five sets of siblings, adding to the suspicion that the disorder was familial. Shortly afterward, the syndrome, apparently transmitted in a manner consistent with dominant inheritance (18,19), was identified in three generations of a family. Soon, it was realized that "Carney complex" described a clinical syndrome that included a number of associations reported earlier. Thus, the characteristic pathology of PPNAD had been described in children and young adults with Cushing syndrome as early as 1949 and in a number of case reports thereafter (19). It appears likely that PPNAD caused hypercortisolism in one of the patients included in the report by Dr. H. Cushing on the condition that now bears his name (19). Accordingly, several familial cases of cutaneous and cardiac myxomas associated with lentigines and blue nevi of the skin and mucosae had been described under the acronyms NAME (for nevi, atrial myxoma, myxoid neurofibromata, and ephelides) and LAMB (for lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) syndromes (20, 21).

4.1. Clinical Manifestations of Carney Complex

When compared to their sporadic counterparts, virtually all of the individual components of the Carney complex are unusual (Table 2). For example, the usual cardiac myxoma is a single tumor in the left atrium of an older, usually female, patient; in Carney complex, the tumor is often multiple, affects any or all cardiac chambers, occurs at a relatively young age, and is equally distributed between the sexes (22). The cutaneous myxomas have a predilection for the eyelids and external ear canals, although they may affect any part of the skin (23, 24). Mammary myxoid fibroadenoma is usually an isolated finding in an

Table 1. Familial Lentiginoses : Clinical Manifestations, Genetics and Overlapping Syndromes

Disease	Main Manifestations	Genetics	Overlap Syndromes	References
Carney complex	Lentigines, myxomas, endocrine overactivity, other	AD, chr. 2p16 and 17q22-24 loci	Peutz-Jeghers, LEOPARD MEN-I, phakomatoses, MAS	10,13-42,86,87, 91-94, 98-101
Peutz- Jeghers	Lentigines, polyps, neoplasias	AD, *STK11/LKB1* gene and chr. 19q13 locus	Carney complex, familial polyposis, other	11, 13, 43-52, 95, 102-108
LEOPARD	Lentigines, cardiac, endocrine, and mental deficiencies, deafnes	AD	Developmental defects, Watson and Noonan syndromes109	13, 42, 58-66, -111, 117
Arterial Dissections and Lentiginosis	Dissecting aneurysms of aorta, renal, and carotid arteries	AR or AD	Lentiginoses, connective tissue defects(Marfan syndrome)	67
Laugier- Hunziker d.	Lentigines, other pigmented lesions	Unknown	Lentiginoses	13, 72, 73
Lentiginosis	Familial, benign; lentigines only	AD	Lentiginoses	68
Ruvalcaba- Myhre-Smith s.	Lentigines, developmental defects	AD	Lentiginoses, hamartomatoses(Cowden disease), Sotos syndrome	12, 54-57
Centrofacial lentiginosis	Lentigines	AD	Lentiginoses, skeletal and nervous system defects	13, 69,70
Segmental lentiginosis	Lentigines	Unknown	Lentiginoses	13, 70
Agminated lentigenes	Lentigines, other segmental defects	Unknown	Lentiginoses	13, 71
P. vascularis	Lentigines, other	Unknown	Lentiginoses, dev. defects	75
Dowling-Degos	Skin tumors, other	Unknown	Hamartoses. lentiginoses	13, 76-78

AD = autosomal dominant; AR = autosomal recessive; LEOPARD = lentigenes, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retardation, deafness; MEN = multiple endocrine neoplasia; MAS = McCune-Albright syndrome.

Table 2. Clinical and Pathological Components of Carney Complex

Condition	Features
Spotty skin pigmentation	Hypermelanosis, lentigines, blue nevi (usual and epithelioid types), combined nevi
Myxomas	Heart, skin, breast, tongue, palate
Endocrine tumors	Primary pigmented nodular adrenal disease (Cushing syndrome), testicular large-cell calcifying Sertoli cell tumor (sexual precocity), pituitary adenoma (acromegaly), thyroid tumors, ovarian cysts
Psammomatous melanotic schwannoma	Sympathetic nerve chain, upper gastrointestinal tract (stomach and esophagus)
Other tumors	Breast ductal adenoma

otherwise normal breast (25). In the complex, the tumor is often multiple and bilateral, and the non-tumorous breast commonly shows microscopic foci of nonneoplastic myxomatous change between the masses (25,26).

The classic facies of Carney complex are characterized by relative hypertelorism and centrofacial spotty pigmentation that involves the vermilion border of the lips and the conjunctiva (Figure 2). The pigmented spots may be either (a) tan, irregularly shaped and poorly outlined, several millimeters in diameter, and freckle-like or (b) small, sharply delineated, and dark brown to black. The conjunctival pigmentation typically affects the lacrimal caruncle and the conjunctival semilunar fold and may involve the sclera. Commonly, one or more eyelid masses (myxomas) are present (Figure 2c). The combination of facial, labial, and conjunctival spotty pigmentation and eyelid tumors presents a diagnostic picture that should precipitate investigation for cardiac myxoma or myxomas. Indeed, 5% to 10% of patients with Carney complex have one or more intraoral pigmented spots, and the female external genitalia are commonly heavily pigmented (Figure 2d).

Skin pigmentation in Carney complex is of multiple pathologic types (Table 2). Most of the lesions are lentigines or represent other examples of hypermelanosis (increased melanin in basal cells and throughout the thickness of the epidermis). Blue nevi (the usual type, as well as the exceptionally rare epithelioid type); combined and common junctional, dermal, and compound nevi; and CALS also occur in the syndrome (27,28) (Figure 3a).

Cushing syndrome, which appears to be the most common endocrine manifestation of Carney complex and

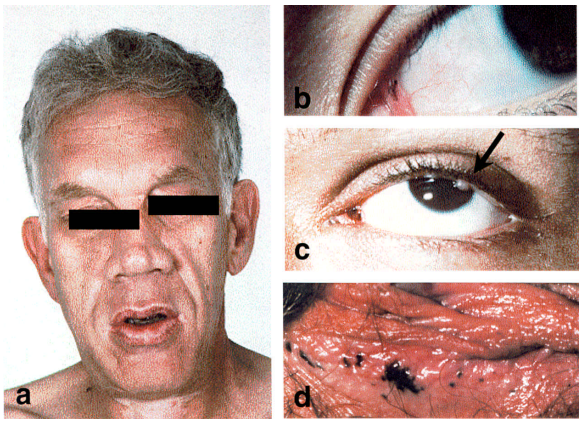

Figure 2. Typical features of Carney complex. The characteristic spotty skin pigmentation visible on the vermilion border of the lips in a patient with acromegaly is shown in panel a. Conjunctival pigmentation (outer canthus) is shown in panel b. Conjunctival inner canthal pigmentation and an eyelid myxoma (arrow) are shown in panel c. Pigmentation of the labia majora of the vulva is shown in panel d.

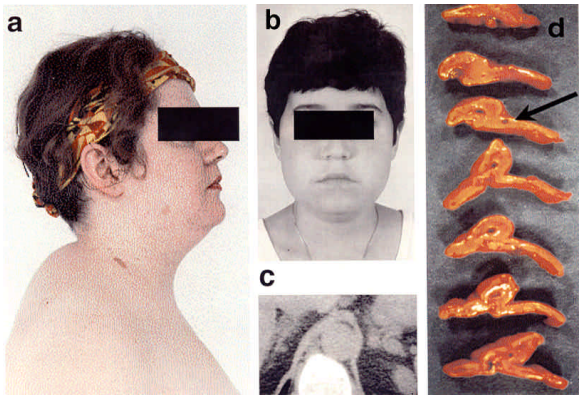

Figure 3. Adrenal manifestations of Carney complex. A woman with Cushing syndrome is shown in panel a; in addition to lentigenes, other pigmented skin lesions on the face and the trunk are present. A young boy with periodic Cushing syndrome (see also reference 35) appears in panel b. The irregular contour of adrenal glands with PPNAD is shown in panel c using computed tomography scanning (see also references 29 and 34). Sections of a left adrenal gland with primary pigmented nodular adrenocortical disease appear in panel d; an arrow points to one of the characteristic multiple pigmented nodules.

affects about one-third of the patients, is caused by a distinct adrenal lesion, PPNAD, which is uniquely associated with the complex and only rarely occurs as an isolated, sporadic lesion. In this disorder, the glands are most commonly normal-sized or small and peppered with black or brown nodules set in a cortex that is usually atrophic (Figure 3d). This atrophy is pathognomonic and reflects the autonomous function of these nodules and the suppressed levels of pituitary ACTH. Despite their small size (less than 6 mm), the nodules are visible with computed tomography or magnetic resonance imaging of the adrenal glands, most likely because of the surrounding atrophy (29). The combination of atrophy and nodularity gives the glands an irregular contour, which is distinctly abnormal and diagnostic, especially in younger patients with Cushing syndrome (Figure 3c). Occasionally, one or both of the glands may be larger and harbor adenomas with a calcified center, while macronodules larger than 10mm may be present in older patients.

Patients with Carney complex often present with a variant of Cushing syndrome called “atypical” (ACS) (30), which is characterized by an asthenic, rather than obese, body habitus caused by severe osteoporosis, short stature, and muscle and skin wasting. ACS was recognized as early as 1956 and has since been described in several cases of patients with Cushing syndrome (30-33); only recently, however, was this condition associated with Carney complex (34,35). A recent review of the literature indicated that almost all the reported cases of ACS could be attributed to PPNAD, including that of a patient who presented 27 years after unilateral adrenalectomy (34). Patients with ACS tend to have normal or near-normal 24-hour cortisol production, but this is characterized by the absence of the normal circadian rhythmicity of this hormone (30-34). Occasionally normal cortisol production is interrupted by days or weeks of hypercortisolism, which gives rise to a yet another variant called “periodic Cushing syndrome” (PCS). PCS is frequently found in children with the complex (35).

About 10% of patients with Carney complex have a GH-secreting pituitary adenoma that results in acromegaly (10,19) (Figure 2a). Although most of the known patients with this condition had macroadenomas, a number of recently investigated cases show that abnormal 24-hour GH secretion can precede the development of a pituitary tumor in Carney complex (Stratakis et al. manuscript in preparation). The disorder, therefore, provides the unusual opportunity for prospective screening of affected patients without clinical acromegaly. In one such case, serial measurements of GH or somatomedin C, or both, became progressively abnormal over several years, but a possible pituitary mass was identified on computed tomography examination only recently; partial hypophysectomy revealed minute foci of a GH-producing adenoma.

Endocrine involvement in Carney complex also includes three types of testicular tumors: large-cell calcifying Sertoli cell tumor (among the rarest of testicular neoplasms), adrenocortical rests, and Leydig cell tumor (36) (Figure 4a and b). About one-third of affected male patients have these masses. The large-cell calcifying Sertoli cell tumor, a bilateral, multicentric, and benign neoplasm, may secrete estrogens and cause precocious puberty, gynecomastia, or both (19,36).

Since 1985, the number of identified patients with Carney complex has more than quadrupled. Information derived from these cases has resulted in a reordering of the frequency of occurrence of the components of Carney complex, with spotty skin pigmentation currently the most frequent component (10). In addition, three new components of the syndrome have

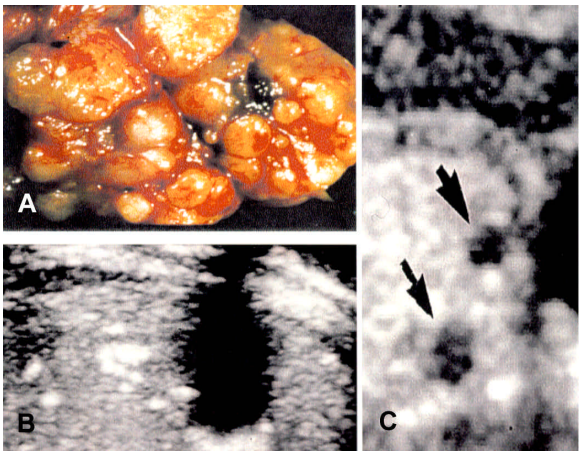

Figure 4. Testicular and thyroid manifestations in Carney complex. Panel a shows a large-cell, calcifying Sertoli cell tumor (LCCST); panel b, sonographic imaging of the testis showing the characteristic calcifications of LCCST (36); panel c, sonographic appearance of the left lobe of the thyroid gland (two hypoechoic lesions are indicated by the arrows) (Picture 4a was given to us by Dr. Carney).

been identified: psammomatous melanotic schwannoma, epithelioid blue nevus, and ductal adenoma of the breast (26, 37-39). Because thyroid follicular neoplasms, both benign and malignant, have been found in a number of patients, it is possible that thyroid involvement will prove to be a component of the syndrome (40) (Figure 4c). Thus far, although a number of patients with the complex have had large ovarian cysts, no specific ovarian involvement has been found (10).

4.2. Overlap Between Carney Complex and Other Syndromes

The clinical and inheritance aspects of Carney complex have been characterized well enough that questions about its nosology may be entertained. It is evident that the syndrome shares components (lentiginosis, Cushing syndrome, acromegaly, thyroid and gonadal tumors) (10,19), a transmission pattern (autosomal dominant inheritance with possible parent of origin effects) (41), and a pattern of organ involvement (bilateral and multifocal involvement in the case of paired organs) with other syndromes (42). Among these, two that feature spotty skin pigmentation, the Peutz-Jeghers and LEOPARD syndromes, have components in common with Carney complex. Multiple intramuscular myxomas occasionally occur in MAS, a disorder that manifests CALS and may feature acromegaly and Cushing syndrome, the latter arising from adrenal cortical hyperplasia rather than PPNAD, however (2). Finally, there are similarities between the MEN syndromes and Carney complex: Lesions are often bilateral and multifocal; somatotropinomas, lipomas and other benign skin lesions are common to both MEN 1 and the complex; and adrenal pathology is present in both conditions (10,19,42). In addition, the distribution of the facial lesions in MEN 2B and the Carney complex has a curious and remarkable anatomical symmetry: the eyelids, lips, tongue, and ears are affected in both syndromes.

5. PEUTZ-JEGHERS SYNDROME (PJS) AND DISORDERS ASSOCIATED WITH POLYPOSIS AND PIGMENTATION ABNORMALITIES

PJS is an autosomal dominant condition characterized by lentigines of the skin and mucosae; gastrointestinal hamartomas and other tumors, as well as polyps of the respiratory and renal collecting systems; and thyroid, breast, testicular and ovarian neoplasms. It was first described by Peutz (1921) and Jeghers (1949) (9) and appears to be found in all ethnic groups, although its incidence is unknown. Lentigines in this syndrome can be indistinguishable from those in Carney complex, and their presence, particularly in the mucosae, serves to screen affected families (43). These lesions are not present at birth, but rather appear in infancy or early childhood, most commonly on the lips and buccal mucosa and, less commonly, on the eyelids and dorsa of the fingers. While the pigmentation on the lips may fade with time, that on the buccal mucosa does not (44).

Although hamartomas are not generally regarded as premalignant lesions (45), patients with PJS demonstrate gastrointestinal and other malignancies in excessive numbers (44,46). A 49-year follow-up of the “Harrisburg family”, the kindred originally described by Jeghers *et al.*, revealed that PJS is a premalignant condition associated with significant morbidity and increased mortality (47). Among the 12 affected family members, 10 underwent 75 polypectomies, and 2 developed gastric cancer and duodenal carcinoma, respectively. In another report, cancer developed in 15 of 31 patients from 13 unrelated families; the overall incidence of carcinoma in patients with PJS varies from 20% to 50%, and it appears at a relatively early age (47,48).

Among the nongastrointestinal neoplasms associated with PJS, endocrine tumors including thyroid cancer and ovarian and Sertoli cell tumors are the most frequent (48-50). Testicular tumors in this syndrome can produce estradiol, which may lead to precocious puberty or gynecomastia (51). The only other familial condition in which large cell, often calcifying, Sertoli cell tumors are seen is Carney complex (36). The two syndromes also share an increased incidence of ovarian and thyroid tumors and, it is interesting to note that one patient with Carney complex and intestinal polyposis and another with pancreatic adenocarcinoma have been reported (10).

In addition to Carney complex and LEOPARD syndrome, PJS shares clinical manifestations with several developmental defects. Cronkhite-Canada syndrome is characterized by a diffuse pattern of hyperpigmentation (rather than lentigines), multiple gastrointestinal polyps, and a variety of ectodermal defects, including alopecia (52). Cowden disease is associated with hamartomas and tumors of ecto-, meso- and endodermal origin affecting multiple organs (53). Thyroid and breast masses, hamartomatous polyps, and mucocutaneous lesions (oral papillomatosis, acral keratosis, and multiple fibromas) occur consistently in this syndrome, which is also associated with anomalies of the skeletal and nervous

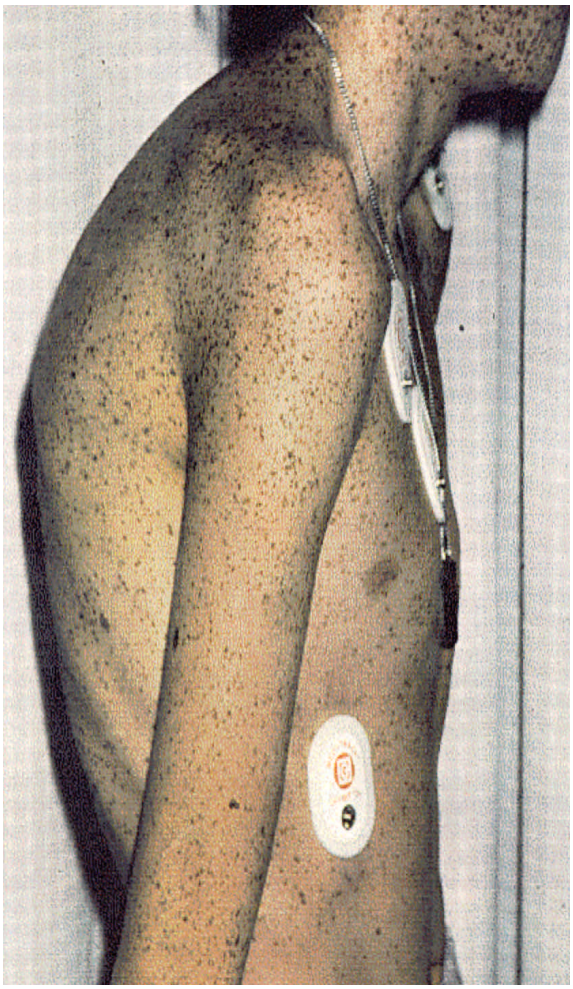

Figure 5. A patient with LEOPARD syndrome. Multiple lentigines and other skin pigmented lesions are shown in association with skeletal deformities. The lentigines are indistinguishable from those of the other lentiginoses, (courtesy of Dr. Turner, NCI, NIH).

systems (6,53). Ruvalcaba-Myhre-Smith, Bannayan-Zonana or Bannayan-Riley-Ruvalcaba syndrome is also associated with hamartomatous intestinal polyposis; in addition, these patients have characteristic lentiginosis of the genitalia and developmental defects (macrocephaly, eye and skeletal anomalies) and myopathy (12, 54-57). A form of polyposis known as "juvenile polyposis of infancy" is frequently associated with ectodermal changes (like those in Cronkhite-Canada syndrome), pigmented lesions and a variety of anomalies of the skeletal and nervous systems (46,54).

6. LEOPARD SYNDROME AND ITS VARIANTS

LEOPARD syndrome is also known as the "multiple lentigines syndrome" (Figure 5). First suggested by Gorlin et al. in 1969, the acronym describes the association of lentigines, (multiple, darkly pigmented and present on the lips, but absent from other mucosal sites) electrocardiographic abnormalities, ocular hypertelorism (with other dysmorphic features), pulmonary stenosis, abnormalities of the genitalia (hypogonadism), (mental) retardation, and deafness (sensorineural) (58). This condition was also referred to as "cardiocutaneous syndrome" in older reports, which had not recognized the pleomorphy of the phenotype (59,60). Watson syndrome, characterized by lentigines, CALS, pulmonic stenosis, and mental retardation, as well as the association of heart defects, pigmented lesions, and deafness in other patients could represent variant forms of the LEOPARD syndrome (61). LEOPARD syndrome and its variants are inherited in an autosomal dominant manner. Variable expression within the same family, a feature of all the lentiginosis syndromes, is frequently seen. This is best exemplified by a kindred where the propositus, an 11-year-old boy, had many lentigines and severe heart problems. His father and five out of six siblings with generalized lentiginosis had no other abnormalities, and nine other relatives from three generations who had lentigines were otherwise healthy (60).

Among the lentiginosis syndromes, LEOPARD and its variants are also the most suggestive of an association with various developmental defects. Almost all the patients have low intelligence and other delays, and various skeletal abnormalities (62). In addition, neural tube defects have been described in association with LEOPARD syndrome, and the facies of many patients are reminiscent of other conditions that include heart or skeletal defects, or both , such as Noonan syndrome (63,64). The patients can also have other pigmented lesions (Figure 5), including dark CALS, junctional nevi, and abnormal pigmentation of the iris and retina (59,60,64,65). Neoplasms, although uncommon, are also present LEOPARD syndrome and include rhabdomyosarcoma and granular cell myoblastoma (66).

7. ARTERIAL DISSECTIONS AND LENTIGINOSIS SYNDROME

The arterial dissections and lentiginosis (ADL) syndrome was recently described in two sets of siblings from a series of 240 patients with arterial dissections seen at the Mayo Clinic (67). Six additional sporadic cases were reported, all with lentigines of the trunk and the extremities, particularly the lower legs. There were no other pigmented lesions, and the mucosae were most likely not affected. This disease shares with Marfan syndrome and other connective tissue disorders a predisposition to dissections of the aorta, renal artery, and extracranial internal carotid artery. The inheritance of ADL syndrome is not clear, although it was suggested to be autosomal recessive (67).

8. OTHER LENTIGINOSIS AND/OR HYPERPIGMENTATION SYNDROMES

Benign, patterned inherited lentiginosis has been described in individual patients and two African-American families without any associated internal anomalies (68). This syndrome may be the most frequent form of familial lentiginosis, especially among persons with dark skin, but its incidence is currently unknown. The lentigines are

identical to those seen in Carney complex, PJS, and LEOPARD syndrome and are present on the face, the vermilion border of the lips, the trunk, and the extremities. The mucosae are spared, although blue nevi are occasionally present. The inheritance of this condition appears to be autosomal dominant.

Centrofacial lentiginosis is also inherited in an autosomal dominant manner and characterized by lentigines restricted to a horizontal band across the central face (69). It is associated with a number of developmental anomalies, such as skeletal, midline and neural tube defects; mental retardation; and endocrine disorders, including thyroid nodules and abnormal urinary 17-corticosteroid excretion and calcium metabolism (69).

A number of patients with local (segmental) lentiginosis, often congenital and present on various sites, have also been described. It is interesting to note that the affected sites overlap with those involved in the familial lentiginoses, and include the penis, vulva, conjunctiva, and oral mucosa. Although partial unilateral lentiginosis with lesions that do not cross the midline has been reported, it probably represents a variant of the segmental form (70). Agminated lentigines is a distinct form of congenital or early childhood-appearing segmental lentiginosis, also known as "zosteriform lentiginous nevus" (71). These lesions can be associated with other segmental anomalies, such as epidermal nevus, rigid cavus foot, and cardiac anomalies.

Localized (but not patterned) lentiginosis is a feature of the Laugier-Hunziker syndrome (72). Here, the oral, anal, and vaginal mucosae are involved, while classic lentigenes are present on the lips, fingers, toes, and eyelids. Nail involvement is characteristic and consists of longitudinal bands of pigment that vary in width and intensity (73). Although pigmented nails have also been reported in PJS, it is rare in this condition and has not been reported in patients with Carney complex or LEOPARD syndrome.

Pigmented macules on the lips occur in patients with MAS and NF (74), conditions that, as discussed above, share many similarities with the lentiginoses. They can be present in the other phacomatoses, in Noonan syndrome, and in various developmental defects (13). Segmental hyperpigmented lesions are a feature of phacomatosis pigmentovascularis, a condition representative of a mixture of melanocytic and vascular dysplasia (75). The melanocytic component consists of ocular melanosis, aberrant mongolian spots, nevi, lentigines, and other pigmented macules, whereas the vascular part is usually a nevus flammeus. This disorder has been associated with anomalies of the skeletal and nervous systems, and is characteristic of a group of diseases, that like ADL syndrome, affect skin pigmentation as well as the vascular and other systems.

Dowling-Degos disease features pigmented lesions similar to those in LEOPARD syndrome (lentigines and perioral pigmented pits) and is associated with the formation of multiple epidermoid cysts and pilonidal sinus (76). It shares clinical signs with other disorders, such as Haber syndrome (facial telangiectasias and follicular papules), Kitamura's acropigmentatio reticularis (hyperpigmentation of the extensor surfaces of the hands and feet and milia-sized keratotic papules) and pigmentatio reticularis faciei and colli with epithelial cystomatosis (facial pigmented macules and epit helial cysts of the trunk) (77). It is noteworthy that epidermal cysts and other skin fibromas or papules occur frequently in patients with Carney complex and MEN 1; patients with possible PJS and hemangiomas of the small intestine have also been described (78).

Individual families with lentigines and other defects have also been reported (79, 80); however, it is uncertain whether these conditions represent distinct clinical syndromes, because they have not been reported in other patients. One such example is that of a French Canadian family with mutliple lentigines and CALS associated with hiatal hernia and gastric ulcer, hypertelorism and myopia (79) The disease was inherited in an autosomal dominant manner and had a variable expression (79). Another proposed syndrome, inherited in an autosomal recessive manner, is that reported in three siblings with lentigines and vitiligo, multiple other pigmented spots and premature graying associated with hypertelorism and other facial features and progressive spastic paraparesis (80).

Familial multiple blue nevi with no other skin changes or tumors have been reported in two unrelated families (81, 82). A syndrome of multiple pigmented nevi, including both intradermal and compound types, vaginal leiomyomas and (non-pigmented) schwannomas was recently reported as a disorder affecting seven members of a family and inherited in an autosomal dominant or X-linked manner; interestingly, at least one family member had an endocrine tumor (a thyroid adenoma) but there were no other tumors similar to those encountered in Carney complex (83). A similar condition, albeit associated with predisposition to malignant tumors (melanoma, astrocytoma, schwannoma, neurofibroma and meningioma) was reported in French families (84). These conditions are associated with pigmentary changes and, perhaps, will end up being related molecularly to the familial lentiginoses.

9. GENETICS OF CARNEY COMPLEX AND THE OTHER LENTIGINOSIS SYNDROMES

9.1. Carney complex

Like the MENs and the phacomatoses, the familial lentiginosis syndromes are inherited in an autosomal dominant manner. On the basis of a report of two affected siblings in a consanguinous family, the ADL syndrome might be an exception to the rule; however, the inbreeding coefficient in this kindred was only 1/512 (67), and it is possible that the mode of inheritance for this disease was also autosomal dominant.

Sporadic cases constitute approximately half of the known patients with Carney complex, PJS and LEOPARD syndrome (10,19). The inheritance of the first two also satisfies the criteria set up for familial neoplasia syndromes: that is the disease is more severe in sporadic vs.

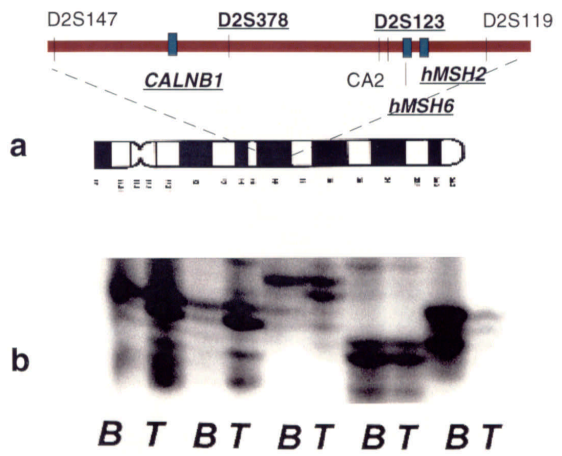

Figure 6. Panel a shows a diagram of the short arm of chromosome 2; the cytogenetic band 2p16 and the polymorphic markers (underlined) that flank the Carney complex region are shown, and genes in the area are indicated. Panel b shows the results of molecular genetic analysis of DNA from patients with Carney complex (B = peripheral blood) and their tumors (T = tumor) with an anonymous polymorphic marker on chromosome 4p (D4S392): Multiple replication defects (gain and loss of heterozygosity, microsatellite instability) are seen (see also reference 86).

familial cases; multiple generations within a family are affected with various types of tumors, which are often bilateral; and the disease appears at younger ages and with increased severity in the affected offsprings of transmitting parents (anticipation). In Carney complex, like the MEN 2 syndromes (85), parent-of-origin effects in the inheritance of the disease have been observed (41).

The genetic defects responsible for the lentiginosis syndromes remain unknown. Two genetic loci have been determined for Carney complex by linkage analysis of polymorphic markers from likely areas of the genome (10, 86). Initially, positive lod scores were obtained for nine markers on the short arm of chromosome 2, identifying an approximately 4 centiMorgan (cM)-long area in the cytogenetic band 2p16 (*CNC* locus), which was likely to contain the gene(s) responsible for the complex (87) (Figure 6a). This region includes the *D2S123* locus, where another genetic syndrome, hereditary nonpolyposis colorectal cancer (HNPCC), had been mapped (88). The gene for HNPCC (*hMSH2*) codes for a protein that plays a direct role in DNA mismatch repair, increasing microsatellite stability and enhancing mutation avoidance in human cells (89). Linkage analysis excluded this gene from being a candidate for the complex (19, 87). Another recently identified gene, the *hMSH6* (90), also involved in DNA stability, is adjacent to *hMSH2*, but outside the defined region on 2p16 (87).

The fact that one of the Carney complex loci resides where genes responsible for regulating DNA stability reside is of particular interest, since several lines of evidence indicate that chromosomal instability may be a feature of the tumor cell lines established from patients with the lentiginosis syndromes. Indeed, the formation of telomeric associations and dicentric chromosomes is a frequent feature of fibroblasts derived from the myxoid tumors excised from patients with Carney complex (91-93). Also, a recent study found similar features in cultured in vitro adrenocortical cells derived from PPNAD nodules (94). Earlier investigations had found chromosomal instability in cultured skin fibroblasts, peripheral blood lymphocytes and adenomatous polyp cells established from patients with familial polyposis coli and PJS (95-97). In these studies, no specific chromosomal breaks or exchange points were revealed, although several sites were involved in three or more rearrangements.

Microsatellite analysis of the tumors excised from patients with Carney complex confirmed the significant genomic instability that accompanies tumorigenesis in this syndrome (94) (Figure 6b). Numerous areas of loss or gain of heterozygosity, and/or deletions, involving all 22 autosomal chromosomes were found. These changes did not include the *CNC* locus on chromosome 2p16, a finding that suggests that alterations of the heterozygosity of the responsible gene(s) are not necessary for oncogenesis in this condition; rather, a gain-of-function mutation is more likely. Although mutations of the *gsp* proto-oncogene were not present in Carney complex tumors (98), and the locations of several genes that code for components of the guanine nucleotide-binding proteins (G-proteins) were excluded by linkage analysis (10, 99), it seems likely that the gene or genes responsible for this condition participate in G-protein -controlled or -related signaling systems.

The identification of the 2p16 locus for Carney complex was followed by the description of a family that did not map to chromosome 2 (100). This finding was then confirmed in another large kindred that had a number of recombinant genotypes with the first locus (101). Genetic heterogeneity was confirmed in this syndrome when a second locus on 17q22-24 was identified (86). So far, no chromosome 17 abnormalities have been seen in tumors from patients with the complex (unpublished information).

9.2. Peutz-Jeghers syndrome

One of the first reports on the genetics of PJS, was that of a patient with the syndrome and a pericentric inversion of chromosome 6 (102). However, other patients with similar chromosomal changes do not manifest symptoms of the disease. More recently, three families with PJS were studied by linkage analysis and were mapped to the short arm of chromosome 1 (1p) (103); however, the finding ended up being spurious (most likely due to the small number of patients investigated) and was not confirmed in a more recent investigation of 12 kindreds with the syndrome (11). Instead, linkage was demonstrated between the syndrome and a chromosome 19p locus (microsatellite repeat D19S886), which was also deleted in the tumors from the investigated patients (11), suggesting a gene with tumor suppression function. Indeed, *STK11* or *LKB1*, a gene with serine threonine kinase activity was cloned from that area and was found to harbor mutations in patients with PJS in the heterozygous state; in tumors from

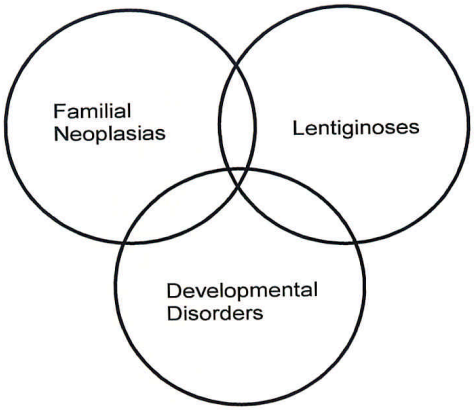

Figure 7. A Venn diagram of the familial neoplasias, lentiginoses, and developmental syndromes, which overlap in many of their clinical manifestations: It is suggested that the genetic defects leading to these disorders may participate in the same or similar pathways of cellular differentiation, growth, and proliferation.

patients with the syndrome, the normal allele of *STK11*/*LKB1* was lost (104, 105).Genetic heterogeneity, like in Carney complex, is possible in PJS; in ours and other laboratories, kindreds with this syndrome have been found that either do not link to the reported locus or do not have *STK11/LKB1* mutations (106, 107). Another locus for PJS has been proposed on the long arm of chromosome 19 (19q13) (106). Despite the clinical similarities between Carney complex and PJS loss-of-heterozygosity of the 19p *STK11/LKB1* locus was not present in tumors from patients with the complex (108).

9.3. Other lentiginoses

There is little information available about the genetics of the other lentiginoses, with the exception of Ruvalcaba-Myhre-Smith syndrome. Kindreds with LEOPARD syndrome and those with Noonan syndrome and pigmented lesions have been tested for linkage to the NF-1 locus on chromosome 17q11.2 (109, 110); indeed, a patient with NF-1 and lentigines had mutations in the NF-1 gene (111). Kindreds with the lentiginosis Ruvalcaba-Myhre-Smith or Bannayan-Zonana syndrome were found to have mutations in the *PTEN* gene (12), which encodes a phosphatase with tensin-like homology and is responsible for Cowden disease, a hamartomatosis syndrome associated with frequent thyroid tumors. With the exception of a few isolated case reports (112), no chromosomal studies or other information is available for the other lentiginoses, despite the early observation that "freckling is the outstanding trait in body-built [genetic] linkage" (113). The genetic component of pigmented skin lesions independent of associated conditions has been confirmed in the general population in large epidemiologic studies (114, 115), but surprisingly few studies have investigated the skin or other lesions excised from patients with the lentiginosis syndromes; two such examples are referenced here (116, 117).

10. PERSPECTIVE

The lentiginoses constitute a group of diseases that share melanocytic hyperplasia as their feature and affect a variety of organs of the cardiovascular, endocrine, and gastrointestinal systems (42). They represent overlap syndromes with the familial neoplasias and certain, diverse developmental defects (Figure 7). Although the genetic defects responsible for the lentiginoses remain unknown, several lines of evidence point to their nature: Like the multiple neoplasia syndromes, the lentiginoses affect many organs and systems. The associated lesions are genetically transmissible and multicentric, often bilateral in paired organs, and originate from cells of mesenchymal (myxomas, certain endocrine tumors) or neural crest origin (melanocytes, arterial media, endocrine tumors). Despite the apparent differences between the main types of familial lentiginoses, they share many clinical manifestations. This finding is further supported by a number of patients with lentigines who have features that could fit under any of the mentioned syndromes: One example is a kindred with lentiginosis and vascular malformations of the gastrointestinal system, and another is patients with lentigines, myxomas, and intestinal polyps (10, 42, 78).

Thus, the genetic defects leading to Carney complex, PJS, and LEOPARD and ADL syndromes and the other forms of lentiginoses may be allelic, or located in homologous genes that belong to similar biochemical pathways participating in the early development, growth and proliferation of neural crest and mesenchymal cells. Alternatively, the genes responsible for the lentiginoses may belong to the same network of genetic determinants of melanocytic function and, hence, human pigmentation, but may also have other functions in various tissues (118-120). Recent studies have pointed to a number of candidate genes that are involved in controlling the cell cycle and in tumor suppression, as well as the differentiation and function of neural crest and mesenchymal cells (121-123), analogous to the pluripotent effects of the *RET* proto-oncogene (124). Clinical variability in syndromes caused by *PTEN* mutations support the multiple potentials of the lentiginosis genes in being associated with various inherited syndromes, as well as sporadic tumors (125-127). As with the phacomatoses genes (5), the identification of the genetic defects that lead to lentiginosis and associated anomalies is expected to shed light on important aspects of endocrine and non-endocrine tumorigenesis and developmental regulation.

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Send correspondence to: Dr. Stratakis: Chief, Unit on Genetics and Endocrinology, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Building 10, Room 10N262, 10 Center Drive, MSC 1862, Bethesda, MD 20892-1862, Tel: 301-4021998, Fax: 301-4020574, E-mail: stratakc@cc1.nichd.nih.gov

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