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The Hamartomatous Polyposis Syndromes: A Clinical and Molecular Review

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Inherited forms of gastrointestinal cancer have been a major focus of study and advancement over the past decade. Familial adenomatous polyposis and hereditary nonpolyposis colon cancer are the two most common heritable colon cancer syndromes. Inherited polyposis syndromes are characterized by the dominant type of polyp (whether adenomatous or hamartomatous) present and by the polyp's location within the gastrointestinal tract. The hamartomatous polyposis syndromes are characterized by an overgrowth of cells native to the area in which they normally occur. They represent a small but appreciable number of the gastrointestinal inherited cancer predisposition syndromes; it is now known that many of these syndromes carry a substantial risk for developing colon cancer as well as other gastrointestinal and pancreatic cancers. Patients afflicted with these syndromes are also at significant risk for extraintestinal malignancies. Seven inherited hamartomatous polyposis syndromes have been described: familial juvenile polyposis syndrome, Cowden's syndrome, Bannayan-Ruvalcaba-Riley syndrome, Peutz-Jeghers syndrome, basal cell nevus syndrome, neurofibromatosis 1, and multiple endocrine neoplasia syndrome 2B. Hereditary mixed polyposis syndrome is a variant of juvenile polyposis characterized by both hamartomatous and adenomatous polyps. The hamartomatous syndromes occur at approximately 1/10th the frequency of the adenomatous syndromes and account for <1% of colorectal cancer in Northern America. While the diagnosis of these inherited syndromes is primarily clinical, genetic testing is now available for all six syndromes. However, there are a significant number of spontaneous mutations seen in each of the syndromes. The management of these patients necessitates a coordinated multidisciplinary approach. The purpose of this review is to characterize the clinical and pathological features of these syndromes and to review the targets of cancer surveillance. The molecular alterations responsible for the inherited hamartomatous polyposis syndromes will also be discussed.

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INTRODUCTION

Inherited forms of gastrointestinal cancer have been a major focus of study and advancement in the past decade. Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC) are the two most common diseases of inherited colon cancer and together account for approximately 5% of the total number of colorectal cancers. Insight into the genetic basis of these disorders has greatly increased our understanding of the genesis of sporadic colorectal cancer. FAP is caused by germline mutations in the adenomatous polyposis coli (APC) gene located in the short arm of chromosome 5 (5q21) whereas HNPCC is caused by a mutation in any of several different mismatch repair genes including hMSH2, hMLH1, hMSH6, and PMS2, which have been identified on chromosomes 2, 3, and 7 (1–9).

The adenomatous polyposis syndromes are part of a larger family of inherited gastrointestinal polyposis syndromes. These polyposis syndromes are characterized by the dominant type of polyp (whether adenomatous or hamartomatous) present. The hamartomatous syndromes are characterized by an overgrowth of cells native to the area in which they normally occur, i.e., mesenchymal, stromal, endodermal, and ectodermal elements. They represent a small but appreciable number of the inherited gastrointestinal cancer predisposition syndromes. It is now known that many of these syndromes carry a substantial risk for developing colon cancer as well as other gastrointestinal and pancreatic cancers (10).

These inherited hamartomatous syndromes occur at approximately 1/10th the frequency of the adenomatous syndromes and account for <1% of colorectal cancer in Northern America (7–10). However, proper identification has major importance for the affected individual and at-risk family members as the malignant potential in these autosomal dominant syndromes is quite high. Although the inherited hamartomatous polyposis syndromes are less common and

less well characterized than the adenomatous polyposis syndromes, major advances in the molecular understanding and genetic basis of these syndromes have similarly occurred. The proper identification of affected patients points to the need for genetic counseling prior to predictive gene testing for the individual and at-risk family members. Potentially, as our understanding of these novel genes accumulates, our ability to diagnose, classify, treat, and hopefully prevent polyp formation and malignant transformation will improve.

Seven inherited hamartomatous polyposis have been described: familial juvenile polyposis syndrome, Cowden's disease, Bannayan-Ruvalcaba-Riley syndrome, Peutz-Jeghers syndrome, basal cell nevus syndrome, neurofibromatosis 1, and multiple endocrine neoplasia syndrome 2B. The newly identified hereditary mixed polyposis syndrome is a variant of juvenile polyposis; it is characterized by both hamartomatous and adenomatous polyps. All of these syndromes are inherited in an autosomal dominant fashion. A significant number of patients have no family history and developed spontaneous, *de novo* gene mutations. Thus, the diagnosis of these syndromes remains primarily a clinical process. The endoscopic findings, extraintestinal (especially dermatologic) features, and family history alert the clinician to a specific hamartomatous polyposis syndrome. The identification of the major susceptibility genes underlying hamartomatous syndromes has led to a period of reclassification. For instance, now that mutations in the phosphatase and tensin homolog (PTEN) gene have been observed to occur in both Cowden's syndrome and Bannayan-Ruvalcaba-Riley syndrome, some authors have reclassified them as a single entity: the PTEN hamartoma syndrome (11).

The care and management of these patients necessitate a coordinated multidisciplinary approach involving gastroenterology, dermatology, surgery, oncology and genetics. The purpose of this review is to characterize the clinical and pathological features that alert the clinician that a patient may harbor an inherited hamartomatous polyposis syndrome and to review the targets of cancer surveillance. In addition, the molecular alterations responsible for the hamartomatous polyposis syndromes will be discussed.

FAMILIAL JUVENILE POLYPOSIS SYNDROME

Clinical Pathology

Familial juvenile polyposis syndrome (JPS; OMIM 174900) is a rare disorder occurring with an incidence of approximately 1 per 100,000 births. It is the most common of the hamartomatous syndromes and characterized by multiple, hamartomatous polyps affecting the colon and rectum (7, 8). Unlike sporadic juvenile polyps (the most common form of polyp in the pediatric population—occurring in 2% of the pediatric population), the polyps of JPS are more numerous and may affect the proximal GI tract (9). On endoscopic view, these polyps have a smooth, shiny, and translucent

Figure 1. Gross view of the colon after total abdominal colectomy in a 56-yr-old female with Juvenile Polyposis Syndrome. She had a strong family history of colon cancer and was noted to have numerous polyps during screening colonoscopy. Note the large polyp located at the ileocecal valve. Courtesy of Dr. Walter Koltun, Division of Colorectal Surgery, The Milton S. Hershey Medical Center, Penn State University, Hershey, PA.

appearance (Fig. 1). On histology, the polyps exhibit markedly dilated mucus-filled glands with extensive edema and inflammation in the lamina propria with plasma cell and lymphocytic infiltration. There is no proliferation of smooth muscle; the underlying smooth muscle layer is attenuated by inflammation (9, 12). There are no histological differences between sporadic juvenile polyps and the polyps of JPS. A family history of JPS together with the number and location of polyps present suggests the diagnosis as discussed in detail below.

As with the other hamartomatous syndromes described, there is an increased risk of colon cancer as well as gastric, small intestinal, and pancreatic cancer. These cancers arise from adenomatous components present in the juvenile polyps (13–15). The incidence of colon cancer is 17–22% by age 35 yr and approaches 68% by age 60 yr. The incidence of gastric adenocarcinomas is 21% in those patients afflicted with this syndrome who have gastric polyps (7, 16). Unfortunately, because JPS is a rare disease, clinical experience is limited. There are no comparative studies to demonstrate the benefit of aggressive screening for gastrointestinal malignancies. Current guidelines recommend colonoscopy every 1–2 yr beginning at ages 15–18 yr. Frequency can be lengthened once the patient reaches 35 yr, provided that no new or dysplastic polyps are detected. Upper endoscopy is recommended every 1–2 yr beginning at age 25 yr (17). Diffuse polyposis may require colectomy or gastrectomy. The development of invasive colorectal carcinoma mandates definitive surgery with or without ileorectal anastamosis depending upon the degree of rectal involvement (10). The current screening guidelines for JPS are summarized in Table 1.

A new potential tool for the surveillance and diagnosis of JPS is capsule endoscopy. Costamagna *et al*. published an article in 2002 (18) comparing clinical outcomes of small bowel radiographs with the wireless capsule endoscopy. Although only 20 patients were compared, capsule endoscopy was found to be superior to small bowel radiograph for evaluation of small bowel diseases. Further studies are needed before this procedure can be recommended for JPS, or any of the other hamartomatous syndromes, on a routine basis.

Table 1. Screening Recommendations for JPS

Screened Cancer	Age to Begin Screening*	Interval‡	Diagnostic Tests
Colon	15	2 years†	Colonoscopy
Proximal GI tract/small tract/intestine	15	2 years†	Upper endoscopy UGI w/SBFT
Breast§	21	Monthly 6–12 months	Self breast exam Clinical exam
Thyroid§	Adolescence	Annual	Clinical exam plus baseline U/S

*Earlier if symptomatic.
†Annually if polyps are noted.
‡Screening intervals can be extended at age 35 in at-risk patients; gene carriers, and affected cases should be kept under similar surveillance.
§Especially if a PTEN mutation has been identified; annual mammography beginning at age 30 is recommended.
Adapted from Boardman 2002, Burt 2002, Dunlop 2002 (8, 9, 17).

Clinical Diagnosis of JPS

The diagnosis of JPS is made when any of the following three criteria are met (16):

1. Multiple (3–10) colonic hamartomatous polyps
2. Any number of hamartomatous polyps in a patient with a family history of JP
3. Extracolonic hamartomatous polyps

Clinically, JPS may often be silent. Obstruction, intussusception, and gastrointestinal bleeding may be presenting complaints (19). Anemia, diarrhea, and protein-losing enteropathy may also result from the polyposis (9). These clinical manifestations are age dependent. In infancy, intussusception, protein-losing enteropathy, and either acute or chronic gastrointestinal bleeding are common. The older patient typically presents with either acute or chronic gastrointestinal bleeding alone (10). The risk of having an associated malignancy also increases with age as described above.

JPS may also co-occur with hereditary hemorrhagic telangectasia (Osler-Weber-Rendu syndrome), which carries a significant risk for aortic aneurysm and pulmonary thrombosis. Therefore, patients should also be checked for digital telangectasias, and findings of arterio-venous malformations or digital clubbing require evaluation for HHT (15, 20–22) (Tables 2 and 3).

Genetics of JPS

The disorder follows an autosomal dominant pattern of inheritance. At the present time, two genes have been identified: (1) MADH4 (Mothers Against Decapentaplegic Homolog 4, also known as SMAD4) and (2) BMPR1A (Bone Morphogenetic Protein Receptor Type IA).

MADH4, located on the chromosome 18q21.1, was identified in approximately 15% of patients with JPS (22). This gene is part of a larger family (MADH) that was initially identified in members of the Drosophila species with "defects in midgut morphogenesis, imaginal disc development and embryonic dorsal-ventral patterning" (23). Homologous genes were identified in the C. elegans and termed "sma" genes. Xenopus, mouse, and human have all been shown to have homologous genes as well. To unify the nomenclature, the designation SMAD has been offered to refer to the vertebrate homologues of these genes (23). However, the current bulk of the GI literature primarily refers to the MADH4 gene. MADH4 encodes a protein involved in mediation of cellular responses (cell growth, apoptosis, arrested growth, etc.) to transforming growth factor beta (TGF-β). Following activation by TGF-β, several members of the SMAD family are activated and then form heteromeric complexes with MADH4. These heteromeric complexes are then transported to the nucleus where they likely lead to growth inhibition. MADH4 mutations prevent formation of these complexes

Table 2. Extraintestinal Manifestations of the Hamartomatous Polyposis Syndromes—Part I

Juvenile polyposis syndrome	Other	Pulmonary arterio-venous malformations Digital clubbing
Cowden's syndrome	Dermatologic	Papillomatous papules Acral/plantar keratoses Trichilemommas
	Endocrinologic	Malignant thyroid tumors
	Gonadal	Endometrial cancer Benign fibroids
	Head and neck	Brain tumors Macrocephaly Dolicocephaly
	Other	Malignant breast cancer Renal cell carcinoma
Bannayan-Ruvalcaba-Riley syndrome	Dermatologic	Lipomas Pigmented macules of the glans penis
	Head and neck	Macrocephaly
	Musculoskeletal	Myopathy in proximal muscles Joint hyperextensibility Pectus excavatum Scoliosis
	Neurologic	Developmental delay Mental deficiency
	Other	Large birth weight
Peutz-Jeghers syndrome	Dermatologic	Hyperpigmentation • Dark blue to dark brown macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. • Hyperpigmented macules of the finger
	Endocrinologic	Thyroid cancer
	Gonadal	Sex cord tumors with annular tubules (SCTAT) Sertoli cell tumors of the testes Gynecomastia Adenoma malignum of the cervix Ovarian cancer Ovarian cysts
	Pulmonary	Bronchial polyps Lung cancer
	Urologic	Ureteral polyps Bladder polyps
	Other	Pancreatic cancer Breast cancer

Adapted from Attard and Lynch, Wirtzfield, *et al*., Eng, McGarrity, *et al*., Schwarz, *et al*., Guttman, and Morrison and Nevin (7, 10, 36, 61, 79, 88, 100).

Table 3. Extraintestinal Manifestations of the Hamartomatous Polyposis Syndromes—Part II

Basal cell nevus syndrome	Dermatologic	Coarse facial features Basal cell carcinomas
	Head and neck	Jaw keratocysts Macrocephaly Bossing of the forehead Facial milia Medulloblastoma
	Other	Cardiac and ovarian fibromas
Neurofibromatosis	Dermatologic	Café-au-lait spots Cutaneous neurofibromas Axillary freckling
	Head and neck	Lisch nodules (iris hamartomas) Optic gliomas Other CNS neoplasms—e.g., astrocytomas, brainstem gliomas
	Musculoskeletal	Pseudoarthrosis Bone dysplasia Scoliosis Short stature
	Neurologic	Cognitive deficits and learning disabilities Seizures Macrocephaly
	Oncologic	Chronic myeloid leukemias of childhood Neurofibrosarcoma Pheochromocytoma
Multiple endocrine neoplasia syndrome 2B	Head and neck	Mucosal neuromas of the lips and tongue Distinctive facies with enlarged lips Thickened corneal nerves,
	Endocrine	Medullary thyroid carcinoma Pheochromocytoma
	Other	"Marfanoid" body habitus

Adapted from Attard and Lynch, Wirtzfield *et al*., Eng, McGarrity *et al*., Schwarz *et al*., Guttman, and Morrison and Nevin (7, 10, 36, 61, 79, 88, 100).

with subsequent cellular proliferation and development of neoplasia (24–26).

BMPR1A, located on chromosome 10q22.3, is a member of the transforming growth factor beta superfamily. It is a serine threonine kinase. With MADH4, it is involved in mediating bone morphoenetic protein intracellular signaling (8). It has been identified in about 25% of familial cases (22).

Friedl *et al*. observed that patients with a mutation in the MADH4 gene were more likely to be affected with massive gastric polyposis than those with a mutation in the BMPR1A gene (27). Sayed *et al*. confirmed this observation. This marked the first genotype-phenotype correlation of JPS (22). Therefore, the presence of gastric polyposis suggests that the underlying gene mutation is MADH4.

Certain patients labeled with JPS were also noted to have a mutation in the PTEN gene (phosphatase and tensin homolog). Five percent of familial JPS cases have a PTEN mutation (8). However, upon further review, these patients, in fact, had the Cowden's syndrome, which will be discussed below. Thus, it is possible that JPS patients with a PTEN mutation may in fact be afflicted with the Cowden's syndrome (28–31). Until this point is further examined, it is reasonable to conclude that JPS may also be caused by mutations in

this third gene. If a PTEN mutation is identified in a patient diagnosed with JPS, then screening for breast and thyroid neoplasms should be undertaken given the high prevalence of these cancers in patients with Cowden's syndrome as discussed below.

Molecular genetic testing has a sensitivity of approximately 40–60% with a cost of $1,200. It is recommended that ordering of these tests be performed in a sequential fashion with MADH4 and BMPR1A mutations checked for initially, followed by PTEN mutations (7). (Tables 4 and 5) Approximately 25% of newly diagnosed patients with JP are sporadic *de novo* mutations, with 75% exhibiting a family history (11).

COWDEN'S SYNDROME

Clinical Pathology

Cowden's syndrome (CS, OMIM 158350) or the multiple hamartoma syndrome is a disease that must be differentiated from JPS. Cowden's syndrome is rarer than JPS with a prevalence of 1 per 200,000 as opposed to 1 per 100,000. Cowden's syndrome, like JPS, is inherited in an autosomal dominant fashion with variable expressitivity (9). It is characterized by multiple hamartomatous tumors of ectodermal, mesodermal, and endodermal origin. Its manifestations are most striking in the skin, intestine, breast, and thyroid gland. The hamartomatous polyps of Cowden's can be indistinguishable from the JPS polyp and are seen throughout the gastrointestinal tract. Ganglioneuromas, lipomatous, and inflammatory polyps may also be seen. Starinck's review of seven families documented that 60% of patients had gastrointestinal polyps (33, 34). The esophagus may exhibit glycogenic acanthosis in patients with Cowden's disease (35).

As opposed to JPS, numerous extraintestinal manifestations are seen in patients with Cowden's syndrome. These manifestations are quite distinctive but can also be subtle and not detected if the clinician is not aware of them. If identified correctly, they can serve to alert the clinician that this disease in present. The disease is likely underdiagnosed and the 1 in 200,000 prevalence mentioned above is likely an underestimation. The most striking of these are the mucocutaneous lesions: facial trichilemmomas (benign tumors of the hair shaft), acral keratosis, subcutaneous lipomas, palmarplantar keratoses, oral cobblestoning, and oral papillomas. Indeed, up to 80% of Cowden's patients will have some dermatologic manifestation (33) (Fig. 2).

Progressive macrocephaly, high arched palate, hypoplastic mandible and maxilla, and microstomia may affect the head and neck. The chest may be affected with supernumerary nipples and pectus excavatum. Hemangiomas, neuromas, ovarian cysts, and uterine leiomyomas may also occur (9).

The benign mucocutaneous manifestations of Cowden's nearly always manifest in early childhood before the more severe neoplastic processes develop. Recognizing these benign disease manifestations is crucial for early diagnosis and initiating appropriate cancer screening (Tables 2 and 3) (34). However, we have described a man with Cowden's who was not afflicted with cutaneous manifestations with a PTEN germline mutation (35).

Patients afflicted with Cowden's syndrome are at particularly high risk for developing breast and thyroid cancers. Benign lesions of these glands such as nontoxic multinodular thyroid goiter, thryoglossal duct cysts, and fibrocystic breast disease may also develop. Breast cancer is the most serious complication of Cowden's syndrome and affects 36% of the patients (33). Furthermore, up to 50% of Cowden's patients exhibit some type of breast abnormality—benign or malignant (34). The lifetime risk for developing thyroid cancer is 10% (36). Cowden's patients are also at risk for ovarian and cervical cancer, uterine adenocarcinomas, transitional cell carcinomas of the bladder, and meningiomas (7).

While the increased risk for breast and thyroid neoplasias is well documented, it is unclear if patients with Cowden's are at increased risk for intestinal cancer as was previously believed. The hamartomatous polyps in the intestinal tract are not felt to increase the risk for colorectal cancer. Starink *et al.* found no increased risk for gastrointestinal cancers (34). Furthermore, Carlson's review also questioned the association of Cowden's syndrome with gastrointestinal cancer (37). Hamby *et al*. did describe one case of identifying gastric carcinoma *in situ* (38). The Japanese national registry found a high incidence of colon cancer, 9%, in patients afflicted with this syndrome (39). Until further information becomes available, we recommend a vigorous screening protocol for gastrointestinal, thyroid, and breast cancers in patients afflicted with Cowden's syndrome and at-risk patients (Table 6). A minority of patients with Cowden's syndrome will not exhibit cutaneous findings; these patients would be clinically indistinguishable from JPS patients. For this reason, patients labeled with JPS should also undergo thyroid and breast screening (Table 1).

Clinical Diagnosis

The diagnosis of Cowden's syndrome was initially proposed by Salem and Steck (33). They divided the clinical manifestations into major and minor criteria. A diagnosis was made when a specific combination of major and minor criteria was met. The most recent consensus for making the diagnosis uses a similar system as shown in Table 7 (40).

The diagnosis may be made when an individual meets any of the four criteria:

1. Pathognomic mucocutaneous lesions alone provided that there are
   - Six or more facial papules, of which three or more must be trichilemmomas OR
   - Cutaneous facial papules and oral mucosal papillomatosis OR
   - Oral mucosal papillomatosis and acral keratoses OR
   - Six or more palmoplantar keratoses
2. Two major criteria (one must be either macrocephaly or LDD)

Table 4. Genetics of The Hamartomatous Polyposis Syndromes—Part I

Syndrome/ OMIM ID	Gene Symbol Location	Product	Testing Availability	Sensitivity (Cost)
Juvenile Polyposis syndrome 174900	MADH4 (SMAD4) 18q21.1	Mothers against decapentaplegic homolog 4	Ohio State University, Molecular Pathology Laboratory Columbus, OH	40–60%† ($1,400.00)
	BMPR1A 10q22.3	Bone morpho-genetic protein receptor type IA		
Cowden's syndrome 158350	PTEN 10q23.31	Dual-specificity phosphatase PTEN	1. GeneDx, Inc, Gaithersburg, MD 2. Northwick & St Mark's Park Hospitals, Kennedy-Galton Centre, NW Thames Regional Genetics Service, Harrow, United Kingdom 3. Ohio State University, Molecular Pathology Laboratory Columbus, OH	81%* ($1,400.00 for new pt; $350.00 for testing of relative with a known mutation)
Bannayan-Ruvalcaba-Riley syndrome 153480	PTEN 10q23.31	Dual-specificity phosphatase PTEN	1. GeneDx, Inc, Gaithersburg, MD 2. Northwick & St Mark's Park Hospitals, Kennedy-Galton Centre, NW Thames Regional Genetics Service, Harrow, United Kingdom 3. Ohio State University, Molecular Pathology Laboratory, Columbus, OH	60%* ($1,400.00 for new pt; $350.00 for testing of relative with a known mutation)
Peutz-Jeghers syndrome 175200	STK11 (LKB1) 19p13.3	Serine/threonine-protein kinase 11	1. GeneDx, Inc, Gaithersburg, MD 2. Northwick & St Mark's Park Hospitals, Kennedy-Galton Centre, NW Thames Regional Genetics Service, Harrow, United Kingdom 3. Ohio State University, Molecular Pathology Laboratory, Columbus, OH	50–100%* ($1,400.00 for new pt; $350.00 for testing of relative with a known mutation)

Adapted from GeneTests Website, OMIM Website (11, 86).
*Information from GeneDx Website (32)
†Information from Attard and Lynch (7).

3. One major and three minor criteria
4. Four minor criteria (40)

When a proband has been identified in a family, other relatives are considered to have the diagnosis of CS if they meet any of the following three criteria:

1. Pathognomonic mucocutaneous lesion
2. Any major criterion with or without minor criteria
3. Two minor criteria (40)

Genetics

Approximately 80% of Cowden's patients were noted to carry germline mutations in the PTEN (phosphatase and tensin homolog) tumor suppressor gene located on chromosome 10q23 (41). PTEN inhibits growth by acting as a check on the cell growth potentiated by the protein tyrosine kinase (35). To date, no mutations in other genes have been identified. The majority of newly diagnosed patients is isolated with no family history of disease. One early study reported that only 10–15% have an affected parent (37). As the disease is likely underdiagnosed, the true proportion of sporadic and familial cases cannot be accurately reported (42, 43) (Tables 4 and 5).

BANNAYAN-RUVALCABA-RILEY SYNDROME

Clinical Pathology

Another hamartomatous polyp syndrome is the Bannayan-Ruvalcaba-Riley syndrome (BRR, OMIM 153480). This disease encompasses three previously described disorders: Bannayan-Zonana syndrome, Riley-Smith syndrome, and Ruvalcaba-Myhre-Smith syndrome. In 1960, Riley and Smith noted an autosomal dominant condition in which macrocephaly with slowed psychomotor development, pseudopapilledema, and multiple hamangiomas were observed (44). In 1971, Bannayan noted the congenital combination of macrocephaly with multiple subcutaneous and visceral lipomas as well as hemangiomas (45). Then in 1980, Ruvalcaba described two males with macrocephaly, hamartomatous intestinal polyposis, and pigmentary spotting of the penis. Other cases were soon reported thereafter (46–48). Given the clinical similarities between the conditions and the autosomal dominant pattern of inheritance, geneticists began to accept the notion of combining the disorders into a single entity before a defined biochemical basis for the disease was identified (49).

Intestinal polyposis affects up to 45% of these patients. Usually multiple hamartomatous polyps are identified with the majority limited to the distal ileum and colon, though

Table 5. Genetics of The Hamartomatous Polyposis Syndromes—Part II

Syndrome/ OMIM ID	Gene Symbol Location	Product	Testing Availability	Sensitivity (Cost)
Basal Cell Nevus syndrome 109400	PTCH 9q22.3	Patched Protein Homolog 1	1. GeneDx, Inc, Gaithersburg, MD 2. Yale University School of Medicine, DNA Diagnostics Laboratory, New Haven, CT	N/A
Hereditary Mixed Polyposis syndrome 601228	HMPS/CRAC1 15q13-q14	N/A	N/A	N/A
Neurofibromatosis 1 162200	NF1 17q11	Neurofibromin	1. Univeristy of Alabama at Birmingham 2. London Health Sciences Center, London, Ontario, Canada	80–90%* ($1,400)
Multiple Endocrine Neoplasia syndrome 2B 162300	RET 10q11.2	Proto-oncogene tyrosine-protein kinase receptor RET	GeneDx, Inc, Gaithersburg, MD	>95%* ($500.00 for new pt; $350.00 for testing of relative with a known mutation)

Adapted from GeneTests Website, OMIM Website (11, 86).
*Information from GeneDx Website (32).
†Information from Attard and Lynch (7).

they may be seen throughout the GI tract. Histologically they appear similar to the JPS-type polyp (49) (Tables 2 and 3).

Genetics

Germline mutations in the PTEN gene have been identified in the Bannayan-Ruvalcaba-Riley syndrome. Marsh *et al*. noted in one study that 60% of patients with Bannayan-Ruvalcaba-Riley had a PTEN mutation (50). See Tables 4 and 5. This raises the intriguing possibility that Cowden's syndrome and Bannayan-Ruvalcaba-Riley may be allelic and "might even be one and the same syndrome along a broad spectrum" (51). Over 90% of families with CS-BRR overlap were found to

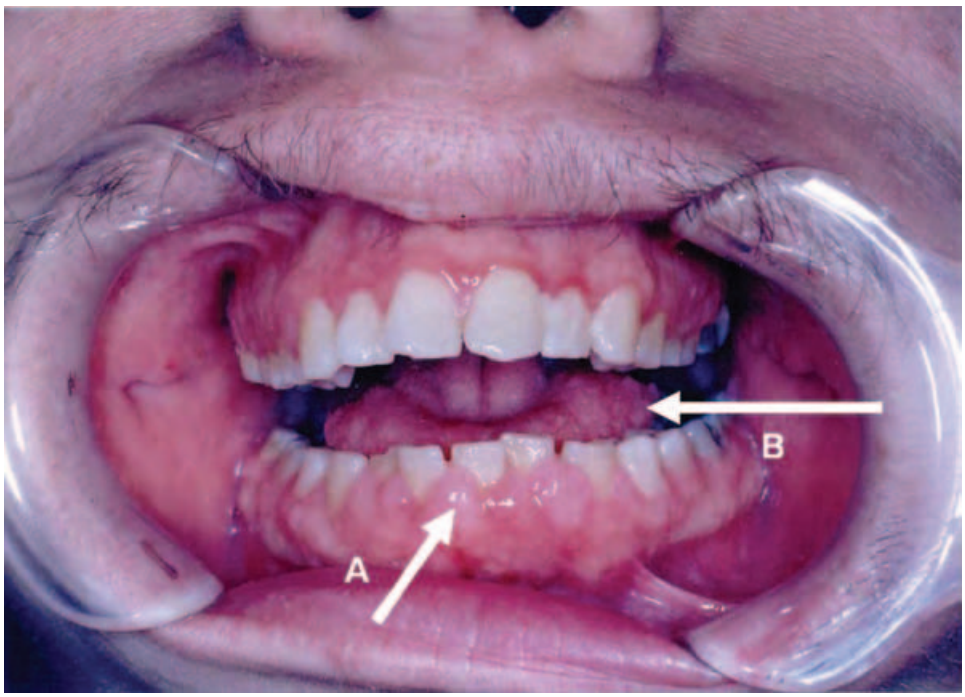

Figure 2. Oral cavity of a 38-yr-old female with Cowden's syndrome. Note the multiple papillomas along the gum-line (*A*) and the lateral portions of the patient's tongue (*B*). Courtesy of Dr. Maria Baker, Division of Genetics, The Milton S. Hershey Medical Center, Penn State University, Hershey, PA.

Table 6. Screening Recommendations for Cowden's Syndrome

Screened Cancer	Age to Begin Screening*	Interval†	Diagnostic Tests‡
Colon§	15	2 years‡	Colonoscopy
Proximal GI tract/Small Intestine§	15	2 years	Upper Endoscopy UGI w/SBFT
Breast	21	Monthly	Self breast exam
	30	Annual	Mammography
Thyroid	Adolescence	Annual	Clinical exam plus baseline U/S

*Earlier if symptomatic.
†Annually if polyps are noted.
‡Screening intervals can be extended at age 35 in at-risk patients; gene carriers and affected cases should be kept under similar surveillance.
§A definitive consensus has not been reached.
Adapted from Attard, 2003, Boardman 2002, Burt 2002, McGarrity 2003 (7–9, 35).

have germline PTEN mutations. Marsh *et al*. also noted that the presence of *PTEN* mutations in BRR was associated with the development of lipomas and tumors of the breast (50). Several BRR patients do not demonstrate a PTEN mutation. However, Zhou *et al*. recently demonstrated that a significant portion of these patients have germline deletions of the PTEN gene (31). Therefore, the various mutations or deletions in the different regions of the PTEN gene may confer varying risk for developing BRR *versus* Cowden's syndrome. As screening and molecular testing of these two syndromes progresses, more genotype-phenotype correlates may be revealed.

To date, there has been no reported increased risk of colorectal or other gastrointestinal malignancies described in these patients (10). However, from the discussion above, patients with BRR and PTEN mutations may have, as yet undocumented, increased extraintestinal cancer risks and should be screened accordingly. The cancer risk in those patients without a documented PTEN mutation remains unclear (50).

PEUTZ-JEGHERS SYNDROME

Clinical Pathology

Peutz-Jeghers syndrome (PJS, OMIM 175200) is an autosomal dominant hamartomatous polyposis syndrome associated with mucocutaneous hyperpigmentation (52). Its prevalence is approximately 1 in 200,000. The disease has variable penetrance—even within families; some members will only manifest with hyperpigmentation, while others may manifest with pigmentation and intestinal polyps (9). In contrast to JPS, in which the polyps occur in the colon, Peutz-Jeghers hamartomatous polyps are most prevalent in the small intestine but may also be present in the stomach and large bowel. The median time to first presentation with polyps is about 11 yr of age (53), but there is a very broad spectrum in age to onset, with exceptional cases presenting with polyposis at birth. These polyps will typically develop around the time of early adolescence (9). Clinical gastrointestinal manifestations of the disease include intussusception and bowel obstruction resulting in multiple laparotomies and bowel resections, as well as chronic bleeding and anemia. Because the polyps progress, multiple surgical procedures can be anticipated.

Extraintestinal manifestations often precede the GI manifestations, developing from birth to childhood, and include mucocutaneous hyperpigmentation presenting as dark blue to dark brown mucocutaneous macules around the mouth, eyes, nostrils, perianal area, and on the buccal mucosa. Hyperpigmented macules on the fingers are common. These macules can be distinguished from common freckles as the latter never appear in the buccal mucosa, are sparse near the lips, and absent at birth (17). The pigmented lesions may fade in puberty and adulthood. See Figure 3. Extraintestinal polyposis may develop as well. Hamartomatous polyps have also been

Table 7. The Criteria for the Diagnosis of Cowden's Syndrome-International Cowden Consortium, Ver 2000

Pathognomonic Criteria	Major Criteria	Minor Criteria
Facial trichilemmomas	Breast carcinoma	Other thyroid lesions Mental retardation,
Acral keratoses	Thyroid carcinoma (especially follicular type)	Hamartomatous intestinal Polyps
Papillomatous papules	Macrocephaly	Fibrocystic breast disease
Mucosal lesions	Lhermitte-Duclos disease*	Lipomas
	Endometrial Carcinoma	Fibromas
		GU tumors
		GU malformation

*Lhermitte-Duclos Disease (LDD) is defined by the presence of dysplastic cerebellar gangliocytoma.
Adapted from Eng, 2000 (40).

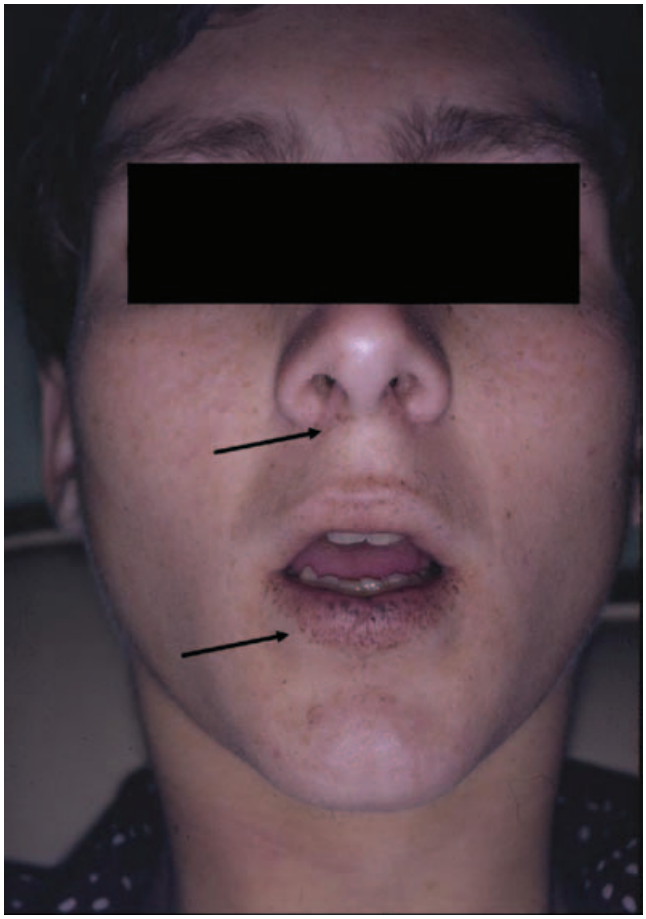

Figure 3. 16-yr-old male with Peutz-Jeghers syndrome. Note the dark brown mucocutaneous macules around the nostrils and mouth. Courtesy of Dr. Thomas McGarrity, Division of Gastroenterology and Hepatology, The Milton S. Hershey Medical Center, Penn State University, Hershey, PA.

reported in the nares, pelvis, bladder, and lungs (54, 55) (see Tables 2 and 3).

Females are at risk for sex cord tumors with annular tubules (SCTAT), a benign neoplasm of the ovaries, as well as adenoma malignum of the cervix, a rare aggressive adenocarcinoma arising from the glandular cells. Males occasionally develop calcifying Sertoli cell tumors of the testes, which secrete estrogen and can lead to gynecomastia. Patients with Peutz-Jeghers syndrome are at increased risk for intestinal and extraintestinal malignancies, including colorectal, esophageal, gastric, small intestinal, breast, ovarian, and pancreatic cancers. Indeed, in one large collected series, Giardiello *et al*. (56) estimated from a survey of the Johns Hopkins registry that the cumulative lifetime risk of cancer was 93%. Giardiello *et al*. also surveyed registry reports and found very high relative risks for some cancers compared to the general population: small intestine RR = 520, gastric RR = 213, pancreatic RR = 132, colorectal cancer RR = 84, esophageal RR = 57, ovarian RR = 27, lung cancer RR = 17, endometrial RR = 16, breast RR = 15 (57). However, the survey methodology used by Giardiello *et al*. may result in elevated risks for cancer if the registries do not systematically maintain contact with the enrollees. A more recent review by Lim *et al*. followed all patients identified by the St. Marks polyposis registry and showed that the possibility of developing any cancer by age 65 was only 37%. This risk increased slightly to 47% when analysis was limited to carriers of mutations in the LKB1/STK11 gene—see discussion below (58). A systematic study by Boardman *et al*. showed an increased risk for all cancers (RR = 9.9). The relative risk for gynecologic and breast cancers in women was 20.3; the relative risk for gastrointestinal cancers was 50.3 with women exhibiting a markedly higher RR of 150.9 (59). While these studies do show markedly increased risk for cancer among PJS-affected patients, the estimates are not as extremely high as had been reported earlier by Giardiello, likely reflecting a more systematic follow up of PJS-affected patients.

Clinical Diagnosis of PJS

The diagnosis of PJS is based upon clinical findings and the histologic appearance of the polyps. The polyps exhibit a unique morphology consisting of mucosa with interdigitating smooth muscle bundles that yield a characteristic branching tree appearance termed "arborization" (60). Polyps in PJS can displace the underlying epithelium and infiltrate the muscularis propria and appear as a pseudocarcinomatous invasion. Histological evidence of hamartomatous-adenomatous-carcinomatous evolution has been demonstrated for stomach, small bowel, and colorectal polyps in PJS. Larger hamartomas will often contain foci of adenomatous change (61).

The distinctive pathology is not pathognomonic of the syndrome. Several authors have reported solitary cases of Peutz-Jeghers-type polyps (62–65). The most recent report, by Kitaoka *et al*. described a solitary hamartomatous polyp in the duodenum of a 22-yr-old Japanese woman (66). This patient lacked any mucocutaneous findings or familial history. Histology showed "hyperplasia with a tree branch-like extension of the lamina propria derived from the muscularis mucosae," consistent with PJS. Genomic analysis revealed none of the observed mutations seen in PJS. To Kitaoka's knowledge, this was the only report in which genomic analysis was performed on these isolated cases. Based upon these case studies, we acknowledge that patients in the general population may exhibit solitary Peutz–Jeghers-type hamartomatous polyps without the true PJS. The true incidence of such isolated polyps is not currently known. Therefore, the diagnosis is not based solely upon the pathology of a single polyp as discussed below.

Giardiello *et al*. (56) defined a definite diagnosis by the presence of histopathologically confirmed hamartomatous polyps and at least two of the following clinical criteria: (1) family history, (2) hyperpigmentation, and (3) small bowel polyposis. A probable diagnosis is based on the presence of two of the three clinical criteria, without histopathological

verification of hamartomatous polyps. Genetic testing may then be used to confirm the diagnosis.

For patients without a family history of PJS, definitive diagnosis depends upon the presence of two or more histologically verified Peutz-Jeghers-type hamartomatous polyps (67). For patients with a first-degree relative with PJS, the presence of mucocutaneous hyperpigmentation is sufficient for presumptive diagnosis.

Genetics of PJS

To date, the only identifiable mutations causing PJS affect the STK11 (Serine/threonine-protein kinase 11, also known as LKB1) gene, located on chromosome 19p13.3 (68–70). STK11 encodes for a multifunctional serine-threonine kinase involved in the transduction of intracellular growth signals; it acts as a tumor suppressor gene. PJS is inherited in an autosomal dominant manner. However, up to 25% of documented cases are not familial. These sporadic cases are felt to be due to *de novo* mutations in STK11 or low penetrance variants (57).

Genetic testing for STK11 mutations is available but they have variable sensitivity. In familial cases with a known genetic linkage to STK11, testing carries a sensitivity of 70% (69, 71–73). In sporadic cases, genetic testing has sensitivity ranging from 30% to 67% (11, 74). Gene testing for STK11 mutations costs approximately $1,400 and is available from GeneDx (see Tables 4 and 5).

One recent study of 33 familial PJS families identified germline STK11 mutations in only 52% of cases (57). Another study of 34 PJS families found mutations in 70% of the probands (75). Several extended families have also been reported without disease linkage to chromosome 19p (68). Taken together, these studies suggest that a significant proportion of familial and sporadic Peutz-Jeghers cases may result from mutations in genes other than STK11 (70, 76–78).

Given the multitude of cancers that these patients are susceptible to, aggressive screening protocols are recommended. Upper and lower gastrointestinal endoscopies are indicated for any adolescent or adult suspected of having PJS. Radiographic studies should also be used to screen for distal small intestinal polyps. Pelvic ultrasound of females and gonadal examination in young men is also recommended (61).

An at-risk but unaffected relative is a first-degree relative of an individual with PJS who does not meet clinical criteria for PJS. The guidelines for surveillance of affected patients also apply to these at-risk family members. For children, the indication for invasive clinical studies is controversial unless symptoms occur (61). The current guidelines for cancer screening are summarized in Table 8.

BASAL CELL NEVUS SYNDROME

Basal cell nevus syndrome (BCNS, also know as nevoid basal cell carcinoma syndrome and Gorlin syndrome, OMIM 109400) is a rare disorder of autosomal dominant inheritance that is due to germline mutations of the human patched gene (PTCH) (see below). It is characterized by multiple basal cell carcinomas (BCCs), other cancers (such as medulloblastoma), and developmental anomalies including macrocephaly, frontal bossing, hypertelorism, bifid ribs, palmar and plantar, and bone cysts, especially in the mandible (Fig. 4). Multiple BCCs are the most common cancer in this syndrome; a diagnosis should be suspected when several of these lesions are seen before 35 yr of age (79, 80). African Americans with BCNS are at reduced risk for BCCs; light skinned individuals and those who easily burn are at much greater risk of developing multiple BCCs (11).

Heritable mutations in BCNS patients and a somatic mutation in a sporadic BCC case were identified in a human homolog of the Drosophila patched (PTC) gene. The PTCH gene encodes a transmembrane protein that is involved in controlling cell fates, patterning, and growth in numerous tissues. The gene is located on chromosome 9q22.3 (81, 82). Approximately 20–30% of cases are due to *de novo* gene mutations in the PTC gene and have no preceding familial history (11).

Schwarz has described multiple gastric hamartomatous polyps in patients afflicted with BCNS. However, the

Table 8. Screening Recommendations for Peutz-Jeghers Syndrome

Screened Cancer	Age to Begin Screening	Interval	Diagnostic Tests
Colon	25	2 yr	Colonoscopy
Proximal GI tract/small intestine	10	2 yr	Upper endoscopy
			UGI w/SBFT
Pancreas	30	1–2	Endoscopic ultrasound
			Transabdominal ultrasound
Breast	20	2	Mammography
		1	Self breast exam
Uterus	20	1	Transvaginal ultrasound
			Endometrial biopsy
Cervix	20	1	Pap smear
Testicular	10	1	Physical exam
			Ultrasound if clinically indicated

Adapted from GeneTests Website authored by McGarrity *et al*. 2003 (11).

presence of polyps is not a major characteristic of the disease. Most families with the disorder have no GI manifestations (79, 80). As this syndrome remains exceedingly rare, screening protocols for GI neoplasms are not recommended (11).

HEREDITARY MIXED POLYPOSIS SYNDROME

Hereditary mixed polyposis syndrome (HMPS, OMIM 601228) is characterized by a variety of different colorectal tumors including atypical juvenile polyps, hyperplastic polyps with areas of dysplasia (serrated adenomas), classical adenomas, and carcinomas. There is currently only one kindred described with the disorder: St. Mark's Family 96 (SM96). In analyzing this family, younger individuals presented with atypical juvenile polyps and/or hyperplastic polyps whereas the older individuals presented with carcinoma. This observation suggests that the natural history of the disease is a progression from hyperplastic polyp to serrated adenoma to carcinoma. This disease appears to affect the colon only; no other gastrointestinal or extraintestinal manifestations have currently been described (83). The HMPS locus had been previously mapped to 6q (84). However, when one family member without the putative disease-associated haplotype developed multiple colorectal adenomas by age 40, the locus was called into question. The most recent genetic analysis now maps the disease to 15q13–q14 (85, 86). Furthermore, the region containing the HMPS gene overlaps the region containing the CRAC1 (colorectal adenoma and carcinoma) gene. CRAC1 is a newly discovered colorectal cancer susceptibility gene located at 15q14–q22 (87). It is currently felt that these genes are likely to be identical (85, 86).

NEUROFIBROMATOSIS 1

Although neurofibromatosis 1 (NF1, also known as Von Recklinghausen disease and Von Recklinghausen's neurofibromatosis, OMIM 162200) is not classically considered a hamartomatous polyposis syndrome, these patients may also be affected with multiple submucosal neurofibromas that may cause dyspepsia, abdominal pain, and/or hemorrhage. Most GI involvement is usually incidental and asymptomatic (11). The disease is classically characterized by multiple café au lait spots, axillary and inguinal freckling, multiple, discrete dermal neurofibromas, and iris Lisch nodules (88).

Like the other syndromes described, NF1 is inherited in an autosomal dominant manner. However, nearly half of the affected patients have NF1 as the result of a sporadic *de novo* gene mutation (89, 90). Although the disease is caused by mutations in the NF1 gene (located on chromosome 17q11) and genetic testing is clinically available, the diagnosis can be assigned because of the specific clinical manifestations (91). The normal gene product is neurofibromin; its function is not fully understood. It appears to activate ras GTPase, thereby controlling cellular proliferation and acting as a tumor suppressor (92, 93).

In the 1980s, several authors had reported an association of NF1 with polyposis coli and neurofibromatosis (94, 95). Lynch *et al*. described one patient affected with both FAP and NF1. His father was documented to have FAP and his mother had NF1. Gene analysis showed that this patient carried both mutations (96). We performed a Medline search and did not uncover any recent articles commenting on any further associations between NF1 and FAP.

Recent data have suggested a developing relationship between NF1 and HNPCC. In 1999, Wang *et al*. described the

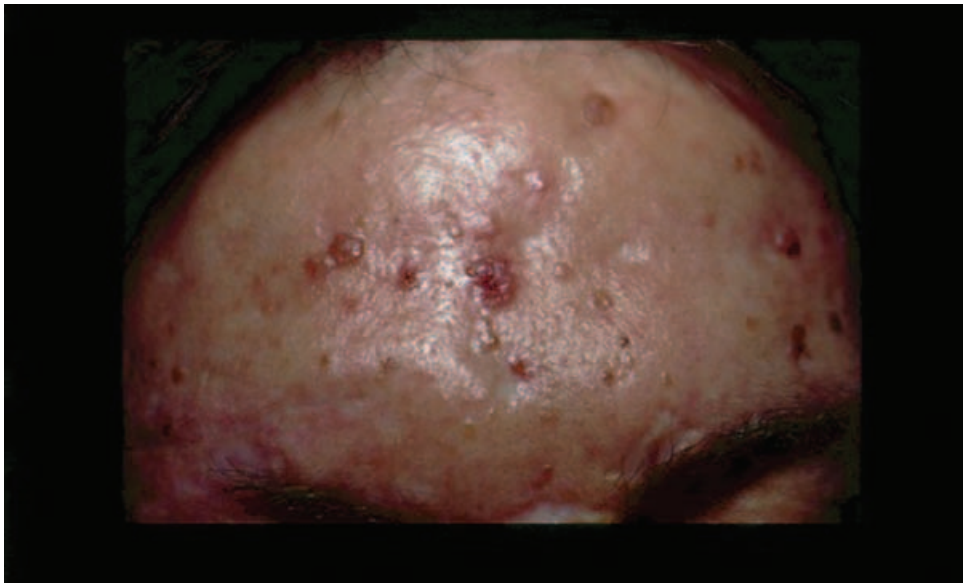

Figure 4. Forehead of a 56-yr-old male with basal cell nevus syndrome. Note the multiple basal cell carcinomas. Courtesy of Dr. Elizabeth Billingsley, Division of Dermatology, The Milton S. Hershey Medical Center, Penn State University, Hershey, PA.

first human homozygotes for the hMLH1 mismatch repair genes. These children exhibited clinical features of *de novo* NF1 and early onset of extracolonic cancers: hematologic and central nervous system malignancies (97). Curiously, Wang *et al*.'s patients did not exhibit any gastrointestinal cancers. A new family has just been identified by Gallinger *et al*. in which two homozygous siblings for the hMLH1 gene did develop early gastrointestinal cancer: malignant colon polyps in one child and metastatic duodenal adenocarcinoma in another. Both of these children had clinical features suggestive of NF1. A third sibling with homozygote deficiency in the MMR gene does not exhibit any malignancy to date but is also afflicted with clinical features suggestive of NF1 (98).

Wang *et al*. speculated that the NF1 gene is a preferential site for somatic mutations in these homozygote MMR-deficient individual cells. A case report by their group in 2003 supported this claim. NF1 mutations were seen in five of ten tumor cell lines with microsatellite instability. Conversely, MMR-proficient tumor cell lines expressed a wild-type NF1 gene. Somatic NF1 mutations were also detected in two primary tumors exhibiting an MSI phenotype. Mouse embryonic fibroblasts were also documented to have 35bp deletion in the murine NF1 coding region in homozygote mlh1-deficient cells (99). Thus, the NF1 gene is a mutational target in these hMLH1-deficient cells. Its inactivation presumably leads to the clinical phenotype and plays an important role in the malignant progression of MMR-deficient cells (99).

Multiple Endocrine Neoplasia Type 2B

Multiple endocrine neoplasia type 2B (MEN 2B, also known as mucosal neuroma syndrome and Wagenmann-Froboese syndrome, OMIM 162300) is one of three subtypes of the multiple endocrine neoplasia Type 2 syndrome (MEN 2); the other two subtypes in this disorder are MEN 2A and familial medullary thyroid carcinoma (FMTC). The prevalence of MEN 2 has been estimated to be one in 30,000. Of these cases, 5% are of the MEN 2B subtype. Gastrointestinal ganglioneuromatosis is observed in up to 40% of patients with MEN 2b. Ganglioneuromatosis is also seen in NF1 and Cowden's syndrome. Abdominal distension, megacolon, constipation, and diarrhea may all be manifestations of this polyposis. Other clinical characteristics of MEN 2B include mucosal neuromas of the lips and tongue, distinctive facies with enlarged lips, and an asthenic "Marfanoid" body habitus. Prominent thickened corneal nerves may be seen by slit lamp examination. The two most severe complications of this syndrome are (i) a high risk for development of medullary thyroid carcinoma (MTC) early in life and (ii) an increased risk for pheochromocytoma, seen in 50% of patients with MEN 2B. Patients who do not undergo thyroidectomy early in life are very likely to develop metastatic MTC with a mean survival of only 21 yr. Unlike MEN 2A, patients with MEN 2B are not typically affected with parathyroid abnormalities (100–105).

MEN 2B is inherited in an autosomal dominant fashion. Mutations in the RET gene (chromosomal locus 10q11) are identified in 95% of patients with MEN 2B. Most patients with the MEN 2B phenotype have a single-point mutation in the tyrosine kinase domain of the *RET* gene at codon 918 in exon 16, which substitutes a threonine for methionine (106, 107). However, other mutations are being detected as further studies progress (108–110). The gene product is a receptor tyrosine kinase that plays a role in signal transduction with the glial-derived neurotropic factor (GDNF) family of ligands: GDNF, neurturin, persephin, and artemin (111). Up to 50% of index cases are caused by spontaneous mutations in this gene with no preceding family history (112, 113). To date, this is the only gene noted to be associated with MEN 2B and, for that matter, the entire MEN 2 syndrome. Genetic testing is available clinically and is used to identify at-risk patients and to reduce morbidity and mortality through early intervention.

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