

# Mucocutaneous Neuromas

## An Underrecognized Manifestation of PTEN Hamartoma-Tumor Syndrome

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**Background:** The spectrum of clinical findings associated with *PTEN* tumor suppressor gene germline mutations, referred to as *PTEN* hamartoma-tumor syndrome (PHTS), includes Cowden and Bannayan-Riley-Ruvalcaba syndromes. Although the skin is the ectodermal structure most often affected by these autosomal dominant genodermatoses, abnormalities of neural tissues are frequently observed.

**Observations:** We describe a 5-year-old boy with macrocephaly, prominent corneal nerves, and progressive development of multiple painful, dome-shaped, translucent pink to skin-colored papules on the vermilion portion of the upper lip, fingers, palms, and shins. Histologic evaluation demonstrated dermal proliferation of well-demarcated nerve bundles associated with abundant mucin and surrounded by a distinct perineural sheath, find-

ings diagnostic of a nonencapsulated neuroma. Genetic analysis revealed a novel heterozygous germline nonsense mutation in *PTEN*, predicted to result in a truncated *PTEN* protein. To our knowledge, this represents the first report of multiple neuromas as the sole mucocutaneous manifestation of PHTS.

**Conclusions:** This article highlights neuromas as a cutaneous sign of PHTS, drawing attention to manifestations of PHTS in neural tissues of the skin, eye, gastrointestinal tract, and brain. Along with multiple endocrine neoplasia type 2B, PHTS should be considered in the differential diagnosis of multiple mucocutaneous neuromas, particularly those involving extrafacial sites.

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**T**HE SPECTRUM OF CLINICAL findings associated with germline mutations in the *PTEN* tumor suppressor gene, referred to as *PTEN* hamartoma-tumor syndrome (PHTS), includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), and some cases of Proteuslike syndrome.<sup>1-4</sup> Cowden syndrome and BRRS are clinically overlapping autosomal dominant genodermatoses characterized by different hamartomatous lesions involving tissues of ectodermal, mesodermal, and endodermal origin (ie, overgrowth of mature cells of types appropriate to the affected tissue).<sup>5</sup> Cowden syndrome and BRRS share several mucocutaneous features, including the tricholemmomas, oral papillomas, and acral keratoses that were initially described in patients with CS; the lipomas and vascular malformations that typify BRRS; as well as findings such as acrochordons, acanthosis nigricans, and café au lait macules.<sup>1,6,7</sup> Sclerotic fibromas represent another skin manifestation of CS,<sup>8</sup> while pigmented macules of the genitalia have a particular association with BRRS.<sup>9-11</sup> Hamartomatous gastrointestinal tract polyps are commonly found in both disorders. However, an increased incidence of

benign and malignant neoplasms (particularly of the thyroid gland, breast, and uterus) is primarily seen in CS,<sup>4</sup> and macrosomia at birth, hypotonia, and lipid storage myopathy have thus far been limited to patients with BRRS.<sup>10</sup>

Although the skin is the ectodermal structure most consistently affected by PHTS, abnormalities of neural tissues are also frequently observed. Macrocephaly (more specifically termed *megalencephaly*, as the brain itself is enlarged) is seen in one third of individuals with CS and in virtually all of those with BRRS.<sup>10-15</sup> Clinical manifestations of central nervous system involvement in PHTS range from developmental delay to seizures.<sup>10,12,15-18</sup> Lhermitte-Duclos disease (LDD), a dysplastic gangliocytoma of the cerebellum thought to represent a hamartoma rather than a true neoplasm, is another occasional component of CS.<sup>19-22</sup> In addition, patients with PHTS have an increased risk of developing meningiomas,<sup>5,20,22-24</sup> and pseudopapilledema and amblyopia have been described in individuals with BRRS.<sup>10</sup>

Abnormalities of the peripheral nervous system have not yet been firmly established as components of PHTS. However, some authors have proposed that a

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**Table 1. Mucocutaneous Neuromas in Patients With *PTEN* Hamartoma-Tumor Syndrome (PHTS)**

Source	Sex/Age at Onset, y	Location of Neuromas, No.	Other Neural Manifestations	Other Cutaneous Features	Other Systemic Features	Diagnosis	<i>PTEN</i> Mutation
Weary et al, <sup>5</sup> 1972	F/45*	Hand, 1	ND	Facial papules, oral papillomas, and acral keratoses	Thyroid carcinoma and fibrocystic breast disease	CS	ND
Gentry et al, <sup>26</sup> 1974							
Case 1	F/35*	Calf, 1†	ND	Verrucous facial papules, oral papillomas, acral keratoses, acanthosis nigricans, and vascular malformations	Thyroid adenomas, GI tract hamartomatous polyps, dental caries, and cataracts	CS	ND
Case 4	M/early childhood	Alar rim, 2	ND	Verrucous facial papules, acral keratoses, and perioral pigmented macules	Dental caries	CS	ND
Case 5	M/childhood	Cheek, 1	ND	Verrucous facial papules and oral papillomas	ND	CS	ND
Nuss et al, <sup>16</sup> 1978	M/13	Chest, 1	Macrocephaly, developmental delay, abnormal electroencephalographic pseudotumor cerebri, and retinal glioma	Acral keratoses, lipomas, and vascular malformations	ND	CS	ND
Weinstock and Kawanishi, <sup>27</sup> 1978	M/38*	Face, ≥1	ND	Facial papules, oral papillomas, acral keratoses, and lipomas	Thyroid adenomas and GI tract polyps	CS	ND
Laugier et al, <sup>28</sup> 1979	F/17*	Buccal mucosa, lips, tongue, larynx; multiple	Macrocephaly	Facial papules	Thyroid adenomas, fibrocystic breast disease, scoliosis, and dental caries	CS‡	ND
Hoshino, <sup>29</sup> 1981	F/3	Buttock, 1	Macrocephaly	Vascular malformations	GI tract lymphoid hyperplasia and hypotonia or muscle wasting	BRRS§	ND
Barax et al, <sup>30</sup> 1987	F/13	Arm, 1	Hydrocephalus	Verrucous facial papules, acral keratoses, sclerotic fibroma, lipomas, vascular malformations, and acanthosis nigricans	GI tract inflammatory polyps, thyroid adenomas, breast carcinoma, and fibrocystic breast disease	CS	ND
Bussaglia et al, <sup>31</sup> 2002, case 12.3	F/8*	Acral sites, multiple	None	Oral papillomatosis and epidermal nevus	Adenoid facies	PHTS	487-491 del A
Zambrano et al, <sup>32</sup> 2004, case 2	M/19*	Buttock, gingiva; multiple	Macrocephaly, developmental delay, and GI tract ganglioneuromas	Pigmented penile macules	GI tract inflammatory and hamartomatous polyps, thyroid adenomas, autoimmune thyroiditis, and C-cell hyperplasia	CS or BRRS	R130Q
Present report	M/5	Acral sites, shin, vermilion of the lip; 15	Macrocephaly, prominent corneal nerves	None	None	PHTS	W111X

Abbreviations: BRRS, Bannayan-Riley-Ruvalcaba syndrome; CS, Cowden syndrome; del, deletion; GI, gastrointestinal; ND, not documented.

\*Age at diagnosis (rather than onset) of neuromas.

†Diagnosis of neuroma was not confirmed histopathologically.

‡Patient was initially described by Mascaro and Kuffer<sup>33</sup> in 1966 as having multiple oral mucosal neuromas (before the development of features diagnostic of CS).

§Although the authors proposed that this represented a new syndrome, the constellation of findings is suggestive of BRRS.

||Patient had a first-degree relative with CS.

closer examination of the peripheral nervous system in patients with PHTS is warranted.<sup>25</sup> A review of the world literature (including a search of the MEDLINE database from January 1, 1966, to March 31, 2005, case series, reviews, textbooks, editorials, and the reference lists of all articles identified) revealed that cutaneous neuromas have previously been described in at least 11 patients with PHTS, 8 of whom had CS (**Table 1**).<sup>5,16,26-33</sup> These lesions had a predilection for the extremities and face, and mucosal neuromas were noted in 2 patients.<sup>28,32</sup> Despite these observations, neuromas are not mentioned as a manifestation of CS in the diagnostic criteria for the disorder,<sup>2,34</sup> in databases such as the Online Mendelian Inheritance in Man,<sup>35</sup> or in several recent review articles.<sup>4,36,37</sup>

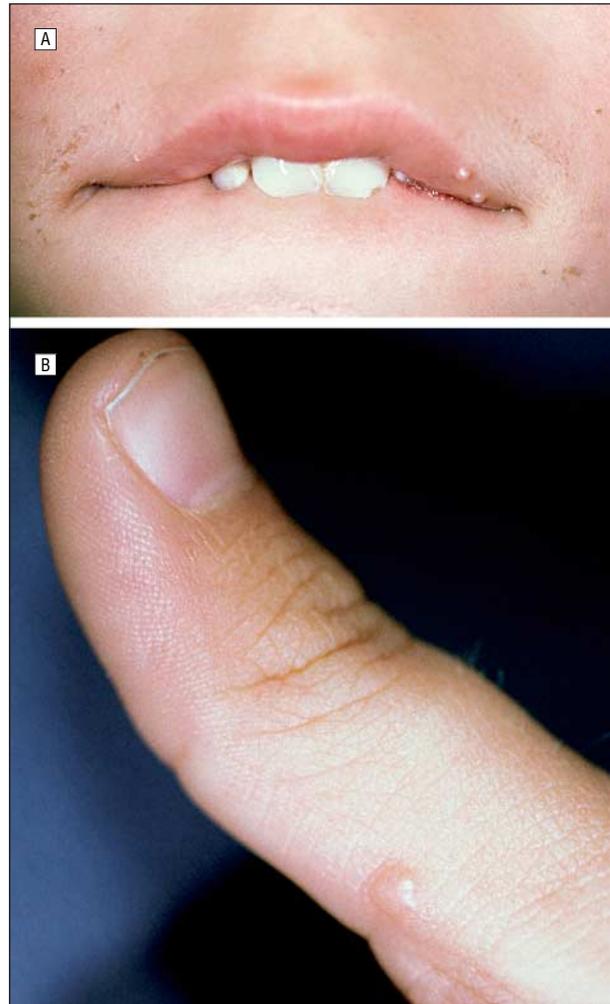
In addition to mucocutaneous neuromas, there are a few reports of solitary neurofibromas,<sup>17,31,38,39</sup> neurilemmomas,<sup>40</sup> and ganglions<sup>10</sup> in association with PHTS. Hypertrophy of cutaneous nerves is also a common incidental observation in skin biopsy specimens from patients with CS.<sup>13</sup> Furthermore, the presence of gastrointestinal tract ganglioneuromas has been documented in more than 15 individuals with PHTS.<sup>5,23,32,41-49</sup> Last, corneal nerve hypertrophy (a finding stated by some to be pathognomonic for multiple endocrine neoplasia type 2B [MEN2B])<sup>50,51</sup> has been noted in approximately one third of patients with BRRS.<sup>9,10,12</sup>

The patient described herein developed multiple mucocutaneous neuromas as a consequence of a novel heterozygous germline nonsense mutation in *PTEN*. This article highlights neuromas as a cutaneous sign of PHTS, drawing attention to manifestations of PHTS in neural tissues of the skin, eye, gastrointestinal tract, and brain.

#### REPORT OF A CASE

A 5-year-old boy was initially seen with a 6-month history of the progressive development of multiple painful papules on the vermilion portion of the upper lip, fingers, palms, and shins. The patient had been born at 36 weeks' gestational age, the product of an uncomplicated twin pregnancy. His birth weight was 3300 g (95th percentile), and his occipitofrontal head circumference was 40 cm (>99th percentile). Magnetic resonance imaging studies performed during the neonatal period to evaluate the marked macrocephaly revealed no abnormalities other than a small arachnoid cyst of the left anterior middle cranial fossa, which was stable in repeated studies at ages 6 months and 2 years. The patient's occipitofrontal head circumference remained above the 99th percentile for his age, while his height and weight were at the 50th percentile. His cognitive and motor development was normal, and he had no other significant medical problems. The patient's parents and fraternal twin were normocephalic, with no history of mucocutaneous lesions, gastrointestinal tract polyps, thyroid disorders, pheochromocytoma, or other benign or malignant neoplasms. Family history was significant for renal cancer in the patient's maternal grandfather at age 59 years and for pancreatic cancer in his maternal aunt at age 65 years.

On physical examination, the patient was macrocephalic (occipitofrontal head circumference, 60 cm [>99th

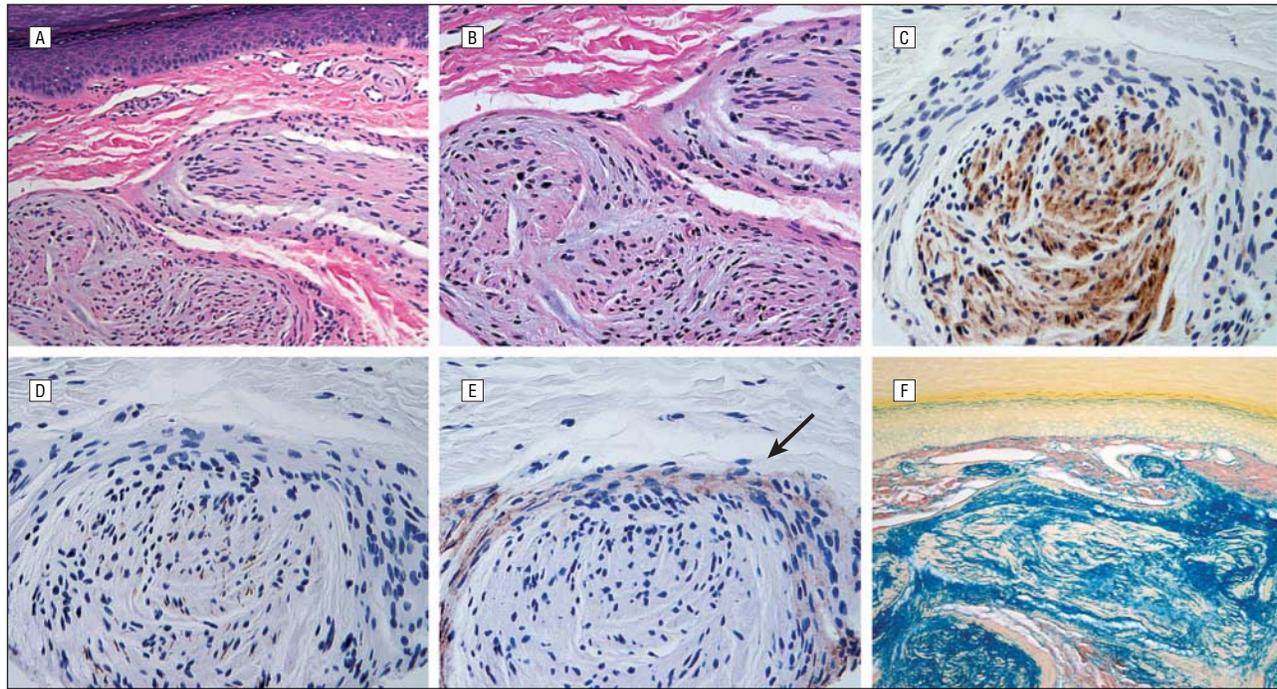


**Figure 1.** Dome-shaped, smooth, translucent skin-colored papules on the vermilion portion of the upper lip (A) and on the thumb (B).

percentile]) with dolichocephaly and mild frontal bossing. Approximately 15 dome-shaped, smooth, translucent pink to skin-colored papules measuring 2 to 6 mm in diameter were noted on the vermilion portion of the upper lip, fingers (sides and palmar surface), palms, and shins (**Figure 1**). The patient reported pain on palpation of the lesions. No verrucous papules, oral mucosal papillomas, thickening of the lips or tongue, acral or palmo-plantar keratoses, pigmented macules of the penis or perioral area, cafe au lait macules, acanthosis nigricans, acrochordons, lipomas, vascular malformations, or other significant mucocutaneous lesions were present. Muscle strength and tone were normal, joints were not hyperextensible, and no additional skeletal anomalies (eg, a high-arched palate or marfanoid habitus) were evident. The thyroid gland was not palpable.

A biopsy specimen from a papule on the thumb demonstrated a dermal proliferation of well-demarcated nerve bundles associated with abundant mucin and surrounded by a distinct perineural sheath (**Figure 2**). These findings were diagnostic of a nonencapsulated neuroma.

An ophthalmologic examination showed prominent corneal nerves bilaterally but normal Schwalbe lines. Results of laboratory studies, including a complete blood cell count,



**Figure 2.** Photomicrographs of a biopsy specimen from a papule on the thumb. A, Several discrete tumor nodules in the upper dermis are demonstrated (hematoxylin-eosin, original magnification  $\times 10$ ). B, The compact fascicles are composed of cytologically bland Schwann cells (hematoxylin-eosin, original magnification  $\times 20$ ). C, The Schwann cells show immunoreactivity for S100 protein (original magnification  $\times 40$ ). D, Numerous axons are present within the Schwann cell fascicles (neurofilament stain, original magnification  $\times 40$ ). E, Epithelial membrane antigen stain highlights perineurial cells (arrow) surrounding individual nerve fascicles (original magnification  $\times 20$ ). F, Abundant mucin is evident within the tumor stroma (colloidal iron stain, original magnification  $\times 20$ ).

thyroid function tests, serum calcium and calcitonin levels, and urinalysis, were within normal limits.

Because cutaneous neuromas have been reported in patients with CS, prominent corneal nerves have been described as a feature of BRRS, and macrocephaly represents a frequent manifestation of both of these conditions, we considered the possibility that our patient had a form of PHTS affecting predominantly neural tissues. Genetic analysis by direct sequencing of the 9 exons of *PTEN* was performed and revealed a novel heterozygous germline nonsense mutation (Trp111X) in exon 5, expected to result in a truncated *PTEN* protein. No mutations were detected on sequencing of exons 15 and 16 of the *RET* gene, excluding the possibility of an atypical form of MEN2B.

The patient subsequently experienced several episodes of crampy abdominal pain during a 2-week period. An abdominal ultrasonogram revealed enlarged pericolic lymph nodes, the results of an examination of the stool for occult blood was negative, and the pain resolved spontaneously. A baseline colonoscopy and thyroid ultrasonography were planned. *PTEN* gene analysis for the patient's parents revealed no mutations.

#### COMMENT

Recognition of the mucocutaneous manifestations of PHTS is important to establish the diagnosis and to facilitate early detection of associated systemic disease in patients and their family members. Characteristic skin findings develop in 99% of individuals with CS and in most individuals with BRRS.<sup>13,52</sup> In early series of patients with CS, neuromas were

described in as many as 5% to 10% of affected individuals.<sup>5,13,16,23,26-30</sup> More than half of the PHTS-associated neuromas reported to date first appeared during childhood (Table 1). In contrast, the classic mucocutaneous manifestations of CS often do not develop until late adolescence or early adulthood.<sup>23</sup> Therefore, as seen in our case, neuromas may represent the initial cutaneous sign of PHTS in a subset of patients.

The involvement of neural tissues in PHTS should not come as a surprise, as levels of *PTEN* expression throughout embryological development and during adult life are higher in the central and peripheral nervous systems than in any other organs.<sup>25</sup> Furthermore, the initial identification of *PTEN* in 1997 was based on the high frequency of somatic deletions involving chromosome 10q23 in glioblastomas,<sup>53,54</sup> and somatic *PTEN* mutations are frequently found in different tumors of glioneural lineage.<sup>55-57</sup> Recently, *Pten* conditional knockout mouse models provided additional insight into the role of this tumor suppressor gene in the central nervous system. Homozygous deletion of *Pten* in neural progenitor cells during murine embryogenesis led to enlarged, histologically disordered brains with increased cell proliferation, decreased cell death, and increased cell size.<sup>58</sup> Postnatal deletion of *Pten* in neuronal populations resulted in progressive macrocephaly, seizures, and ataxia associated with dramatic increases in neuronal soma size but normal proliferation; in particular, cerebellar abnormalities that closely resembled LDD histologically were identified.<sup>59,60</sup> All of these observations highlight the importance of *PTEN* as a "master regulator" in developing and mature neural tissues.<sup>61</sup>

**Table 2. Mucocutaneous Neuromas in Patients Without *PTEN* Hamartoma-Tumor Syndrome or Multiple Endocrine Neoplasia Type 2B (MEN2B)\***

Source	Sex/Age at Onset, y	Autosomal Dominant Inheritance	Location of Cutaneous Neuromas	Location of Mucosal Neuromas	Prominent Corneal Nerves	Other Features	<i>RET</i> Mutation
Thies, <sup>74</sup> 1964	F/4	No	Face, especially periorificial areas	Gingiva, hard palate, and conjunctiva	Yes	Abnormal electroencephalogram and oligomenorrhea	ND§
Holm et al, <sup>75</sup> 1973	M/66	No	Trunk and upper arms	None	ND	Enlarged thyroid gland	ND
Schnitzler et al, <sup>76</sup> 1973	M/3	No	Face, ears, soles of feet, and toes	Lips, buccal mucosa, tongue, larynx, and conjunctiva	No	Seizures	ND§
Altmeyer and Merkel, <sup>77</sup> 1981	M/28	No	Head, neck, trunk, and arms	Lips, tongue, and larynx	No	None	ND
Valentines et al, <sup>78</sup> 1984	F/7 M/16 F/38†	Yes	None	Lips and oral mucosa‡	Yes	Abdominal pain and hyperextensible joints	ND
Guillet et al, <sup>50</sup> 1987	F/50	No	Linear hyperpigmented bands on the trunk	Tongue (prominent papillae)‡	Yes	Marfanoid habitus	ND
Dennehy et al, <sup>79</sup> 1995	M/8 F/10 F/40	Yes	None	Tongue‡	Yes	None	No
Pujol et al, <sup>69</sup> 1997	F/7	No	None	Lower lip and tongue	No	Breast fibroadenoma	No
Gomez et al, <sup>80</sup> 1998	F/<10 F/39†	Yes	None	Lips and tongue‡	Yes	None	No
Truchot et al, <sup>81</sup> 2001	F/40	No	Trunk, extremities, and face	Gingiva	ND	None	No
Jashnani et al, <sup>82</sup> 2003	F/birth	No	Right side of the face	Oral	Yes	Enlarged thyroid gland and skeletal hypertrophy	ND

Abbreviation: ND, not documented.

\*Multiple laryngeal neuromas have also been described in a 73-year-old man with a persistent cough due to chronic bronchitis and with no evidence of MEN2B.<sup>83</sup>

†Age at diagnosis (rather than onset) of neuromas.

‡Diagnosis of neuroma was not confirmed histopathologically.

§A complete biochemical and endocrine evaluation to exclude MEN2B was not performed.

||Authors postulated that the patients may have had a forme fruste of MEN2B.

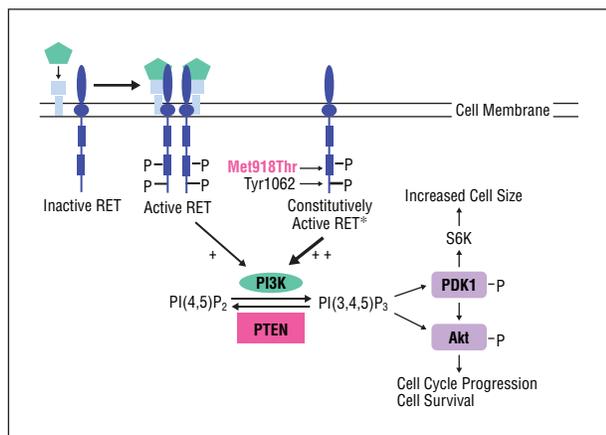
To our knowledge, this is the first reported case of multiple neuromas as the sole mucocutaneous manifestation of PHTS. The presence of macrocephaly and corneal nerve hypertrophy provided additional clues to the diagnosis. Thus far, our patient's PHTS has been found to involve only neural tissues and does not meet diagnostic criteria for CS or BRRS.<sup>1,2,10,34</sup>

The histologic features of the nonencapsulated neuromas observed in our patient and in previously reported cases of PHTS are strikingly similar to those of the neuromas seen in MEN2B, with a compact arrangement of well-delineated hypertrophic nerve bundles surrounded by a distinct perineural sheath.<sup>26,62</sup> These findings resemble those of the solitary circumscribed neuroma (also known as palisaded encapsulated neuroma), although palisaded encapsulated neuromas typically show intersecting fascicles of spindle cells forming larger nodules, with less obvious mucin than was evident in our case.<sup>62,63</sup>

The novel nonsense germline mutation detected in our patient (Trp111X) is located in exon 5 of *PTEN*, which encodes the phosphatase core motif (discussed in the penultimate paragraph of this section) and represents the site of 40% of all CS mutations reported to date.<sup>4</sup> Although

our patient's mutation has not been previously described, a nearby Gln110X mutation has been observed in individuals with phenotypic features of LDD, CS, and BRRS.<sup>4,64</sup> Perhaps the truncated proteins that result from such mutations lead to the preferential loss of a *PTEN* function that is especially critical in regulating the growth of neural cells. Staal et al<sup>65</sup> recently described a man with a germline mutation (Arg234Gln) in the 3'-encoded C2 domain of *PTEN* who developed brain tumors of multiple lineages (meningioma and glioma) but no other stigmata of PHTS. However, previous studies<sup>1,4,7,31,46,66</sup> failed to correlate particular germline *PTEN* mutations with specific phenotypic characteristics; clinical features often vary considerably within affected kindreds, and identical mutations have been described in individuals with CS and BRRS phenotypes. It is likely that modifying genes or cell type-specific RNA regulators have important effects on the types of tissues involved and the degree of severity of the manifestations (eg, hamartomas vs malignant neoplasms).<sup>67</sup>

Most cases of multiple mucocutaneous neuromas reported in the literature occurred in patients with MEN2B. Multiple mucosal neuromas represent a cardinal feature



**Figure 3.** Overlap in the signaling pathways regulated by PTEN and RET. The phosphatidylinositol 3-kinase (PI3K)/Akt cascade is negatively regulated by PTEN (a lipid phosphatase) and positively regulated by RET (a tyrosine kinase receptor that is normally activated by dimerization on the binding of soluble ligands [green pentagons] to cell surface-bound coreceptors of the glial cell line–derived neurotrophic factor receptor  $\alpha$  family [light blue squares and rectangles]). Loss-of-function *PTEN* mutations and gain-of-function *RET* mutations are associated with a highly activated PI3K pathway. The Met918Thr *RET* mutation responsible for multiple endocrine neoplasia type 2B not only results in constitutive activation of RET but also causes a change in its substrate specificity; the change in substrate specificity leads to markedly increased phosphorylation of Tyr1062, which specifically activates the PI3K cascade. PDK1 indicates phosphoinositide-dependent kinase 1. The asterisk indicates altered substrate specificity (with hyperactivation on ligand binding and dimerization); P, phosphate group; +, activation of PI3K cascade; ++, excess activation; PI(4,5)P<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate; PI(3,4,5)P<sub>3</sub>, phosphatidylinositol 3,4,5-trisphosphate; PDK1, phosphoinositide-dependent kinase 1; and S6K, ribosomal protein S6 kinase 1.

of MEN2B and have been previously considered a pathognomonic finding.<sup>51,68,69</sup> Their appearance in early childhood provides an important clue to the diagnosis of this uncommon autosomal dominant cancer predisposition syndrome. Multiple endocrine neoplasia type 2B is caused by mutations in the *RET* proto-oncogene (particularly Met918Thr) that lead to activation and altered substrate specificity of the RET tyrosine kinase receptor.<sup>70,71</sup> In addition to mucosal neuromas (typically involving the lips, tongue, and eyelids), MEN2B is characterized by aggressive medullary thyroid carcinomas, pheochromocytomas, gastrointestinal tract ganglioneuromatosis, corneal nerve hypertrophy, and a marfanoid body habitus.<sup>72</sup> Patients with MEN2B occasionally develop cutaneous neuromas, most often located in periorificial areas of the face.<sup>73</sup> However, cutaneous neuromas in acral sites or occurring in the absence of mucosal lesions have not yet been described in individuals with MEN2B.

Multiple mucosal neuromas have also been observed outside the setting of MEN2B (**Table 2**).<sup>50,69,74-83</sup> At least 6 patients had cutaneous and mucosal lesions,<sup>50,74,76,77,81,82</sup> and 11 patients were noted to have prominent corneal nerves.<sup>50,74,77-80,82</sup> In 4 affected families, genetic analysis confirmed the absence of mutations in the *RET* proto-oncogene.<sup>69,79-81</sup> We postulate that some of these patients may have actually had PHTS.

*PTEN* hamartoma-tumor syndrome and MEN2B share several clinical features, including mucocutaneous neuromas, hypertrophy of cutaneous nerves, prominent cor-

neal nerves, gastrointestinal tract ganglioneuromatosis, thyroid C-cell hyperplasia, a high-arched palate, pectus excavatum, and joint hyperextensibility.<sup>10,14,15,32,44,72,84,85</sup> On a molecular level, there is also considerable overlap in the signaling pathways regulated by PTEN and RET (**Figure 3**), especially those with important functions in controlling the growth and development of neural and neural crest–derived tissues. PTEN is a lipid phosphatase that serves as a central negative regulator of the phosphatidylinositol 3-kinase/Akt pathway, and proper PTEN signaling leads to G1 cell cycle arrest, apoptosis, or both.<sup>86,87</sup> In contrast, RET represents a positive regulator of the phosphatidylinositol 3-kinase/Akt pathway. Recently, loss-of-function *PTEN* mutations in patients with LDD and the gain-of-function Met918Thr *RET* mutation responsible for MEN2B have been associated with a highly activated phosphatidylinositol 3-kinase/Akt pathway in neural tissues (including the “dysplastic gangliocytoma” cells of LDD), implicating enhanced phosphatidylinositol 3-kinase signaling in the pathogenesis of the overlapping clinical phenotypes of these disorders.<sup>64,88,89</sup>

Because MEN2B is a potentially deadly disease with an effective intervention available (prophylactic thyroidectomy during early childhood), analysis of the *RET* gene is recommended in any patient with multiple mucosal neuromas.<sup>90</sup> We propose that PHTS also be considered in the differential diagnosis for patients with multiple mucocutaneous neuromas. Since multiple neuromas are rare in the general population and involve primarily mucosa and periorificial skin in individuals with MEN2B, their occurrence in extrafacial sites is particularly suggestive of PHTS. The presence of multiple neuromas (especially involving acral sites) may prove to be more specific for PHTS than other cutaneous findings that serve as diagnostic criteria (eg, lipomas, fibromas, and acral keratoses).<sup>2,34,91</sup> Because the exact risk of malignancy associated with forms of PHTS other than CS has not yet been determined, it is recommended that patients with PHTS be monitored following the CS guidelines.<sup>34</sup>

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Author Contributions: Dr Schaffer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Schaffer and Orlow. Acquisition of data: Schaffer, Kamino, Witkiewicz, and Orlow. Analysis and interpretation of data: Schaffer, Kamino, Witkiewicz, McNiff, and Orlow. Drafting of the manuscript: Schaffer, Kamino, and Orlow. Critical revision of the manuscript for important intellectual content: Schaffer, Kamino, Witkiewicz, McNiff, and Orlow. Administrative, technical, and material support: Schaffer, Witkiewicz, and Orlow. Study supervision: Schaffer, Kamino, McNiff, and Orlow.

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#### ARCHIVES Web Quiz Winner

Congratulations to the winner of our February quiz, Shaila N. Shah, professor and head, Department of Pathology, Medical College, Bhavnagar, Gujarat, India. The correct answer to our February challenge was *vulvar basal cell carcinoma*. For a complete discussion of this case, see the Off-Center Fold section in the March ARCHIVES (Suda T, Kakinuma H. Erosive velvety lesion on the vulva. *Arch Dermatol.* 2006;142:385-390).

Be sure to visit the *Archives of Dermatology* Web site (<http://www.archdermatol.com>) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of *The Art of JAMA II*.