

ARTICLE

# Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) syndrome is related to mosaic *PTEN* nullizygosity

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We describe two patients from distinct Cowden disease families with specific germline *PTEN* mutations whose disease differs from the usual appearance of Cowden disease. Their phenotype associates classical manifestations of Cowden disease and congenital dysmorphisms including segmental overgrowth, arteriovenous and lymphatic vascular malformations, lipomatosis and linear epidermal nevus reminiscent of the diagnosis of Proteus syndrome. We provide evidence in one of the two patients of a secondary molecular event: a loss of the *PTEN* wild-type allele, restricted to the atypical lesions that may explain an overgrowth of the affected tissues and the atypical phenotype. These data provide a new demonstration of the Happle hypothesis to explain some segmental exacerbation of autosomal-dominant disorders. They also show that a bi-allelic inactivation of *PTEN* can lead to developmental anomalies instead of malignant transformation, thus raising the question of the limitations of the tumor suppressive function in this gene. Finally, we suggest using the term 'SOLAMEN syndrome' (Segmental Overgrowth, Lipomatosis, Arteriovenous Malformation and Epidermal Nevus) in these peculiar situations to help the difficult distinction between the phenotype of our patients and Proteus syndrome.

*European Journal of Human Genetics* (2007) 15, 767–773; doi:10.1038/sj.ejhg.5201823; published online 28 March 2007

**Keywords:** Hamartoma syndrome, multiple; *PTEN*; Proteus syndrome

## Introduction

The tumor-suppressor gene *PTEN* shows somatic mutations in a wide variety of sporadic neoplasias whereas its heterozygous germline mutations are responsible for a

cancer-prone syndrome, Cowden disease (MIM 158350), and a related entity known as Bannayan-Riley-Ruvalcaba syndrome (MIM 153480). These diseases are characterized by a progressive development of numerous hypertrophic, hamartomatous and neoplastic lesions involving the skin, mucous membranes, gastrointestinal tract, thyroid, breast, brain and genitor-urinary system. Lipomas, angiomas and macrocephaly are frequently associated. The Proteus syndrome (MIM 176920), characterized by asymmetric and disproportionate overgrowth, cerebriform connective tissue nevi, the presence of an epidermal nevus and

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Received 7 November 2006; revised 17 January 2007; accepted 21 February 2007; published online 28 March 2007

dysregulated adipose tissue, was attributed to *PTEN* germline mutations by one team who referred to this entity as Proteus or Proteus-like syndromes.<sup>1</sup> However, that finding was not confirmed by others<sup>2</sup> who questioned the accuracy of the patients' phenotypic evaluations and suggested misdiagnoses of Proteus syndrome.<sup>3</sup>

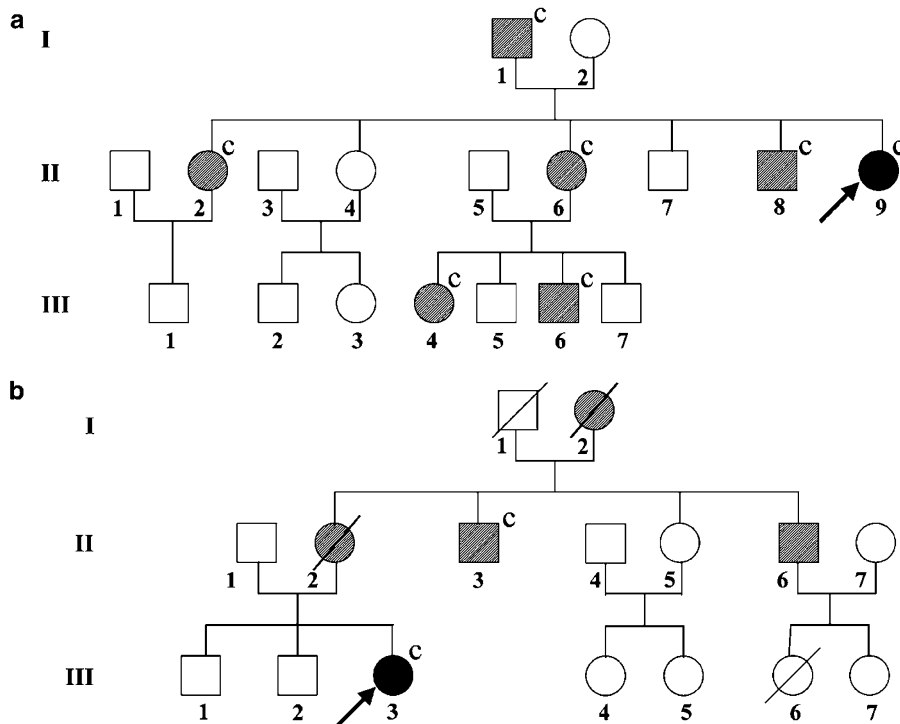
We describe two patients belonging to distinct Cowden disease families each associated with a germline *PTEN* mutation whose phenotypes mimicked Proteus syndrome. A secondary molecular event in one patient, a mosaic *PTEN* wild-type allelic loss, might explain the atypical phenotype.

## Materials and methods

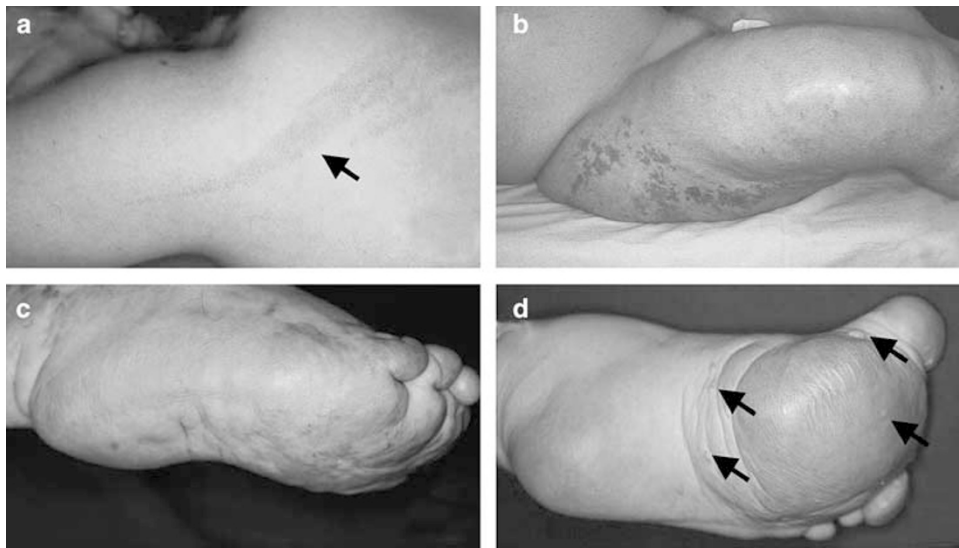
### Report of cases

In the first family, the proband (Figure 1a: II<sub>9</sub>), a 30-year-old woman, had normal skin at birth but 5 days later a lymphatic vascular malformation appeared on her legs, back and abdomen. One month later, a difference in the length of her legs became evident. At 3 years of age, physical examination revealed macrocephaly, a few subcutaneous soft masses on the chest, overgrowth of the left thigh with a large vascular malformation on its anterior face and several lymphatic vascular malformations. At

7 years, four voluminous lipomas infiltrating the chest wall and one in the xyphoid region were surgically removed. At 8 years, two large lipomas in the left femoral triangle and the left thigh under a lymphatic vascular malformation were debulked. At 14 years, a microvesicular thyroid adenoma was removed. At 23 years, a mucinous cystadenoma of the left ovary was excised. At 26 years, the patient suffered a spontaneous fracture of the left hip. She underwent hip replacement and a bulky fibrous angiolipoma under the gluteus maximus was removed during the operation. Two years later, skin examination revealed two small gingival papules and large patchy lymphatic vascular malformations on the upper right and lower left parts of the back, the latter spreading to the left flank, hip and groin. An epidermal nevus following Blaschko's lines on the middle and upper left portion of the back extended to the left shoulder (Figure 2a). Marked hypertrophy of both calves was associated with right talipes varus limiting the patient's mobility. Subcutaneous varicosities and capillaries were present on the right thigh (Figure 2b), leg and sole (Figure 2c), whereas the big toe and medial ball of the left foot were ballooned and covered with several fibrotic papules (Figure 2d). Radiographs of the legs showed enlarged and dystrophic bones, diffuse demineralization and soft tissue calcifications in the right thigh. At 30 years,



**Figure 1** Pedigree of the two families reported. (a) and (b) The respective pedigrees of families 1 and 2. Gray symbols indicate the patients with Cowden disease and solid symbols the patients with Cowden disease mimicking Proteus syndrome. (c) carriers of the germline *PTEN* mutation; a transition A > G at nucleotide 403 leading to the change of the isoleucine 135 in valine for family 1 and a deletion of one nucleotide within a stretch of adenine (487–491) leading to a frameshift with a premature stop codon at 166 in family 2.



**Figure 2** Cutaneous lesions of patient 1. An epidermal nevus (arrow) following Blaschko's lines extends from the upper left part of the back to the shoulder (a). Hypertrophy of the right thigh is associated with subcutaneous varicosities (b), deformation of the knee and a 'hillocky' appearance of the sole (c), whereas the medial ball of the left foot is ballooned (d) and covered with several fibrotic papules (arrows).

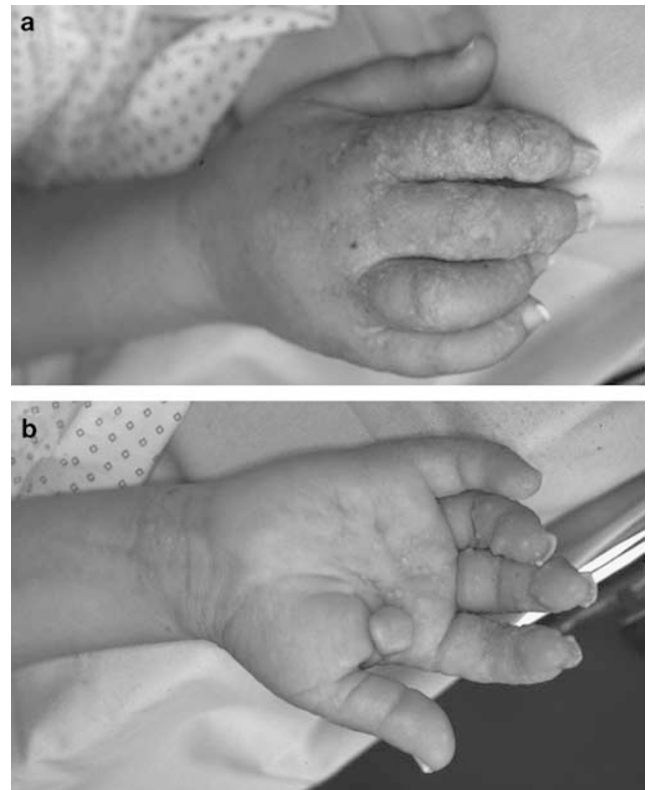
a diffuse fibrotic lipoma infiltrating the whole right calf was surgically removed in order to correct pes varus. Thyroid ultrasonography revealed multiple nodules and mammography detected fibrocystic breasts.

The other affected members of family 1 (Figure 1a: I<sub>1</sub>, II<sub>2</sub>, II<sub>6</sub>, II<sub>8</sub>, III<sub>4</sub> and III<sub>6</sub>) presented a classical Cowden disease phenotype according to International Consortium criteria.<sup>4</sup>

In the second family, the proband (Figure 1b: III<sub>3</sub>), a 45-year-old woman, had a lumbar angioma at birth. One month later, overgrowth of the back of her right hand began and subsequently progressed. At 6 years, asymmetric overgrowth of the left leg was visible. One year later, a tumor was surgically removed from her right breast. At 10 years, the extramedullary part of an extensive fibrotic lipoma in the right paravertebral groove, infiltrating T9–T12 and the thoracic spinal canal, was partially removed. Six months later, she developed flaccid paraplegia, followed by an intrathoracic angioma and angiomas of the C7 and T5 vertebrae.

At 35 years, a multiheteronodular goiter was excised. Physical examination revealed macrocephaly, overgrowth of the right hand covered by multiple papules (Figure 3a) with a voluminous palmar sclerosing fibroma (Figure 3b), a lipoma of the left groin, a subcutaneous palpable vascular malformation on the left side of the chest and mild left leg overgrowth. At 44 years, intrathoracic arteriovenous shunts responsible for high-output heart failure were embolized and excised.

The other affected family 2 members (Figure 1b: I<sub>2</sub>, II<sub>2</sub>, II<sub>3</sub> and II<sub>6</sub>) presented a classical Cowden disease phenotype.



**Figure 3** Morphological appearance of the right hand of patient 2. Hypertrophy of the right hand with macrodactyly is associated with multiple fibrotic papules (a) and a voluminous palmar storiform collagenoma (b).



### Search for allelic loss

Owing to the tendency to homozygosity observed in the three lesions in patient 1, a loss of heterozygosity (LOH) for three *PTEN*-flanking markers was sought in DNA extracted from various tissues from the first patient. A clear decrease in intensity was observed for one allele of each marker with the DNA originating from the cutaneous fibroma of the left big toe, the epidermal nevus and the fibrotic lipoma of the right calf, compared to that of the blood leukocytes (Figure 5b). In contrast, LOH was not found in DNA from

normal skin, cultured skin-lesion fibroblasts, other skin lesions or ovarian cyst. Haplotype analysis showed that LOH involved the maternal allele, that is the wild-type allele (Figure 5a). Separate searches for LOH in the epidermal sheet and the dermis of the cutaneous biopsies of the three lesions showing LOH revealed conservation of heterozygosity in the epidermis but LOH in the dermis sample (Figure 5c).

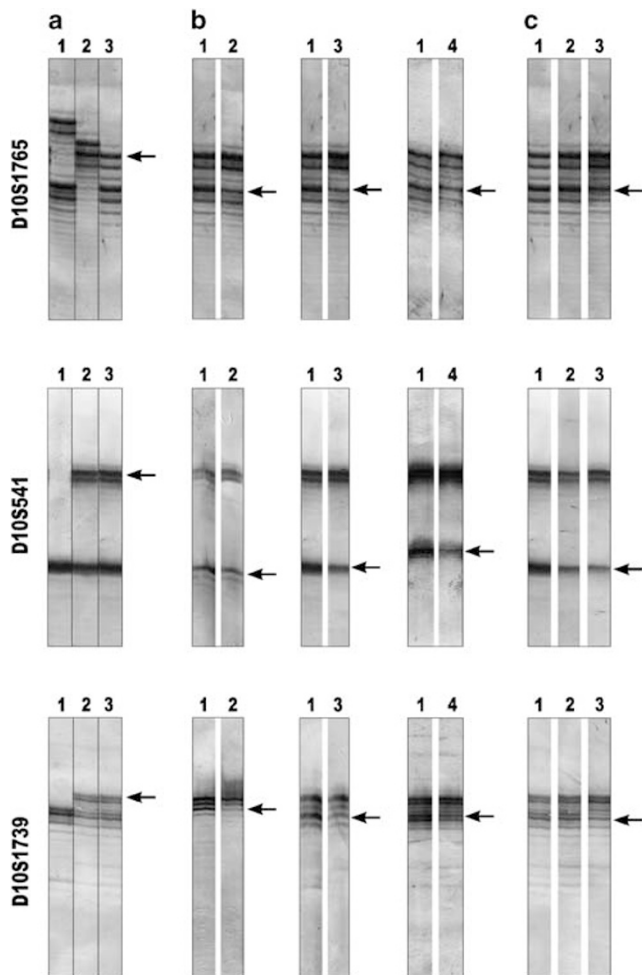
No evidence of LOH was found for DNA extracted from cutaneous fibroblast cells in culture and from a right hand lesion biopsy from patient 2.

### Discussion

We describe two families that had 12 members with manifestations of Cowden disease. The diagnosis was confirmed by genetic analysis demonstrating a *PTEN* mutation in the nine affected patients for whom blood samples were available. For family 1, the p.I135V *PTEN* variant had previously been identified in another family with Bannayan-Riley-Ruvalcaba syndrome.<sup>7</sup> To our knowledge, the functional consequence of this variant is not known, but it is probably deleterious because missense mutations of amino acids 133 and 136 were previously found to be responsible for the loss of *PTEN* lipid-phosphatase activity.<sup>8</sup> The cosegregation of the disease with the variant in the family 1 (Figure 1) is demonstrative of linkage and single nucleotide polymorphism has never been described in this codon despite extensive human *PTEN* exploration in recent years. The mutation observed in family 2 (c.491delA) was also reported in another Cowden disease family.<sup>9</sup> It causes the synthesis of a non-functional truncated protein so both these mutations are very probably responsible of the disease.

Our patients 1 and 2 had an atypical Cowden disease phenotype that could evoke Proteus syndrome. Both women had complex congenital dysmorphisms, including overgrowth of the legs, lipomatosis, vascular malformations and, in patient 1, a linear epidermal nevus and ovarian cystadenoma. However, they strictly do not meet the revised diagnostic criteria for Proteus syndrome.<sup>10–12</sup> The foot and hand hypertrophic malformations presented by both patients (Figure 2c, d and 3) are different from the cerebriform connective tissue nevi of the palm or sole observed in Proteus syndrome.<sup>12</sup> On the other hand, several findings including macrocephaly, thyroid adenoma, fibrocystic breast, gingival papules for the patient 1, and macrocephaly, multinodular goiter, multiple breast tumors for the patient 2, are suggestive of the ordinary nonsegmental Cowden disease.

To explain these additional manifestations in our patients, we looked for a second molecular event at the *PTEN* locus in lesional tissues. Three lesions in patient 1 show a tendency to homozygosity for *PTEN* mutation. This finding was confirmed by a decrease in intensity of the wild type



**Figure 5** Microsatellite typing around the *PTEN* locus (centromere – D10S1765 – *PTEN* – D10S541 – D10S1739 – telomere) showing loss of heterozygosity in tissue samples. (a): allelic typing of blood leukocyte DNA from the proband's mother (lane 1), proband's father (lane 2) and patient 1 (lane 3), showing the disease-linked allele (arrow) in family 1. (b): loss of the wild-type allele at the *PTEN* locus detected in patient 1's DNA extracted from three different lesions compared to blood leukocyte (lane 1); the cutaneous fibroma of the left big toe (lane 2); the epidermal nevus on the back (lane 3); and the fibrotic lipoma on the right calf (lane 4). (c) allelic typing of various components of the cutaneous biopsy of the lesion on the left big toe showing allelic loss restricted to the dermis: cultured fibroblasts (lane 1); and after dispase digestion of the sample, the epidermal sheet (lane 2), and the dermis (lane 3).

allele of *PTEN* flanking markers suggestive of deletion of all or part of the 10q chromosomal arm in a subset of cells of these lesions. Interestingly, the deleted allele in each lesion carries the wild type *PTEN* allele. Availability of samples did not allow us to perform FISH experiments to investigate the *PTEN* locus at the cellular level.

These data are reminiscent of two recently published observations. The first one described a patient with a 'Proteus-like' syndrome associating congenital hemihypertrophy of the right leg, macrocephaly, epidermal nevi arranged in whirls, multiple lipomas and massive arteriovenous malformations involving the muscles and bones of the right leg reported by Zhou *et al.*<sup>13</sup> That patient harbored a germline *PTEN* mutation (R335X) and a second-hit *PTEN* mutation (R130X) on the opposite allele in lesioned tissues, for example an epidermal nevus, a lipoma and an arteriovenous malformation. The second described a 3-year-old boy reported as Proteus syndrome by Loffeld *et al.*<sup>14</sup> showing an extensive epidermal nevus, macrocephaly, vascular malformation affecting both lower limbs, asymmetric hypertrophy of a leg, localized macrodactyly, and abdominal lipoma. This patient has a missense mutation of *PTEN* (p.Y68D) inherited from his mother who shows features of Cowden syndrome, as do several members of her family. Sequence analysis of the *PTEN* exon 3 from DNA extracted from curettings of the epidermal nevus shows a profile of homozygosity for the pY68D mutation evoking a *PTEN* wild-type allele loss.

The molecular data of these patients including ours showed that a heterozygous germline *PTEN* mutation, which is usually causative of Cowden disease, associated with a mosaic inactivation of the wild-type *PTEN* allele, may be associated with multiple dysmorphisms suggestive of other diseases (Proteus syndrome, Klippel-Trenaunay syndrome). These different lesions could be explained by the bi-allelic *PTEN* inactivation and a complete loss of the *PTEN* function responsible for hypertrophy of the affected tissues. The lesions in patient 2 are also probably related to a complete *PTEN* inactivation in specific tissues, even though we were unable to demonstrate a second *PTEN* alteration probably because of the small number of available samples. We indeed only tested one biopsy of the pathological skin and as we experimented for the first patient several skin samples from different areas have to be tested to demonstrate mosaicism. On the other hand, other mechanisms of inactivation like epigenetic silencing or a transcriptional defect cannot be excluded.

The same phenomenon is well known as 'Knudson's hypothesis' in malignant tumors arising in cancer-prone syndromes for which extensive demonstrations of a second hit restricted to tumoral cells was obtained.<sup>15</sup> A similar mechanism with a second hit occurring earlier during development was postulated for autosomal-dominant genodermatoses<sup>16</sup> and such a phenomenon was recently confirmed for Hailey-Hailey disease.<sup>17</sup> Cowden disease is

another example in which a germline dominant mutation can be associated with mosaic inactivation of the wild-type allele, resulting in segmental exacerbations of the disease.

However, although Cowden disease is a cancer-prone syndrome and *PTEN* a tumor-suppressor gene in accordance with Knudson's model,<sup>18,19</sup> these three observations demonstrate that the biallelic inactivation of *PTEN* does not lead systematically to malignant transformation. As malignant complications of Cowden disease are mainly of epithelial origin (breast carcinoma, thyroid carcinoma, renal cell carcinoma, endometrial carcinoma), it is likely that bi-allelic *PTEN* inactivation has different consequences depending on the cell types affected. We detected allelic loss in the dermis of the skin biopsies, not in epidermis, and in adipose and vascular tissues of the right calf fibrotic lipoma (data not shown) of patient 1. Similarly, Zhou *et al.*<sup>13</sup> demonstrated mosaic mutation in biopsies of a lipoma and a vascular malformation tissue from their patient suggestive of a mesenchymal origin. Allelic loss was not seen in the cultured cutaneous fibroblasts of our first patient and may involve other dermal cell types like adipocytes and/or endothelial cells, in which, unlike epithelial cells, *PTEN* nullizygosity might not lead to malignant transformation. If this hypothesis is correct, it is surprising that segmental exacerbation of Cowden disease is a rare phenomenon although malignant transformation is a very frequent complication of it. Epithelial cells might be more subject to genetic instability than connective tissue cells, as the high frequency of carcinoma with regard to sarcoma seems to suggest.

The first report of a *PTEN* mutation in a patient with a Proteus-like phenotype<sup>13</sup> incited others to search for germline mutations in this gene in Proteus syndrome patients. The results of those studies were contradictory. *PTEN* mutations were found in 5/14 patients diagnosed with a Proteus or Proteus-like syndrome<sup>1</sup> and in an isolated case presenting the Proteus phenotype.<sup>20</sup> Other authors were unable to confirm these findings because no *PTEN* mutation was detected in 33 patients with Proteus syndrome.<sup>11,21,22</sup> These contradictory data have generated a heated debate on the reliability of the phenotypes reported.<sup>3,11,23,24</sup> Our two patients and the case reported by Loffeld *et al.*<sup>14</sup> rekindle this controversy because, unlike the previously published cases, they are members of typical Cowden disease families with several affected members carrying the causal *PTEN* mutation. Their disease manifestations confirm that some patients with an inherited *PTEN* mutation may develop atypical lesions, such as segmental overgrowth, vascular malformations, multiple lipomas and epidermal nevus mimicking Proteus syndrome.

Our patient 2, lacking epidermal nevus indicates that such a phenotype can also show an incomplete presentation. In spite of obvious clinical overlap between these entities, some clinical findings should make it possible to distinguish them (Table 1). Epidermal nevus is common to the two diseases, whereas invasive lipomatosis and shunting arteriovenous

**Table 1** Proteus syndrome versus SOLAMEN syndrome – clinical manifestations

Phenotypic features	Proteus syndrome	SOLAMEN syndrome
Connective tissue nevus	Cerebriform connective tissue nevus with deep grooves and gyration	Thickening of the soles and increased wrinkling
Epidermal nevus	Linear epidermal nevus	Linear epidermal nevus
Asymmetric overgrowth	Progressive, disproportionate and disorganized overgrowth with hyperostosis	Segmental proportionate overgrowth with soft tissue hypertrophy and ballooning effect
Dysregulated fat	Association of lipomas and regional absence of fat	Lipomatosis with multiple lipomas, invasive lipomas, fibro and angioliipomas
Vascular malformation	Capillary, venous or lymphatic malformation	Lymphatic and shunting arteriovenous malformations
Cowden disease manifestations	No	Mucocutaneous lesions Macrocephaly Breast, thyroid hamartomas

malformation seem more specific of segmental exacerbation of Cowden disease. Conversely, cerebriform connective tissue nevus and disproportionate overgrowth with hyperostoses are more specific of Proteus syndrome.<sup>12,25</sup> In the event of segmental exacerbation of Cowden disease, the lesions observed are thickening of the sole as in our patient 1 and segmental proportionate overgrowth like the macrodactyly observed in our patient 2. Early manifestations such as macrocephaly should also point towards the diagnosis of a segmental form of Cowden disease. To clinically better distinguish between Proteus syndrome and segmental exacerbation of Cowden disease, we propose naming this latter entity the SOLAMEN syndrome with regard to the main lesions observed, that is Segmental Overgrowth, Lipomatosis, Arteriovenous Malformation and Epidermal Nevus.

### Acknowledgements

We are grateful to our patients and their families who participated in this study, and to the clinicians who care for these patients. We thank Bernadette Gastaldello and Delphine Lafon for technical assistance, and Jean-Luc Birac for his help in preparing the figures. This study was partially funded by the Comités Dordogne et Charente Maritime de la Ligue Nationale Contre le Cancer.

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