XVII^{èmes} Journées de sénologie de l'hôpital Saint-Louis

19 Septembre 2014

Quoi de neuf dans la maladie de Cowden?

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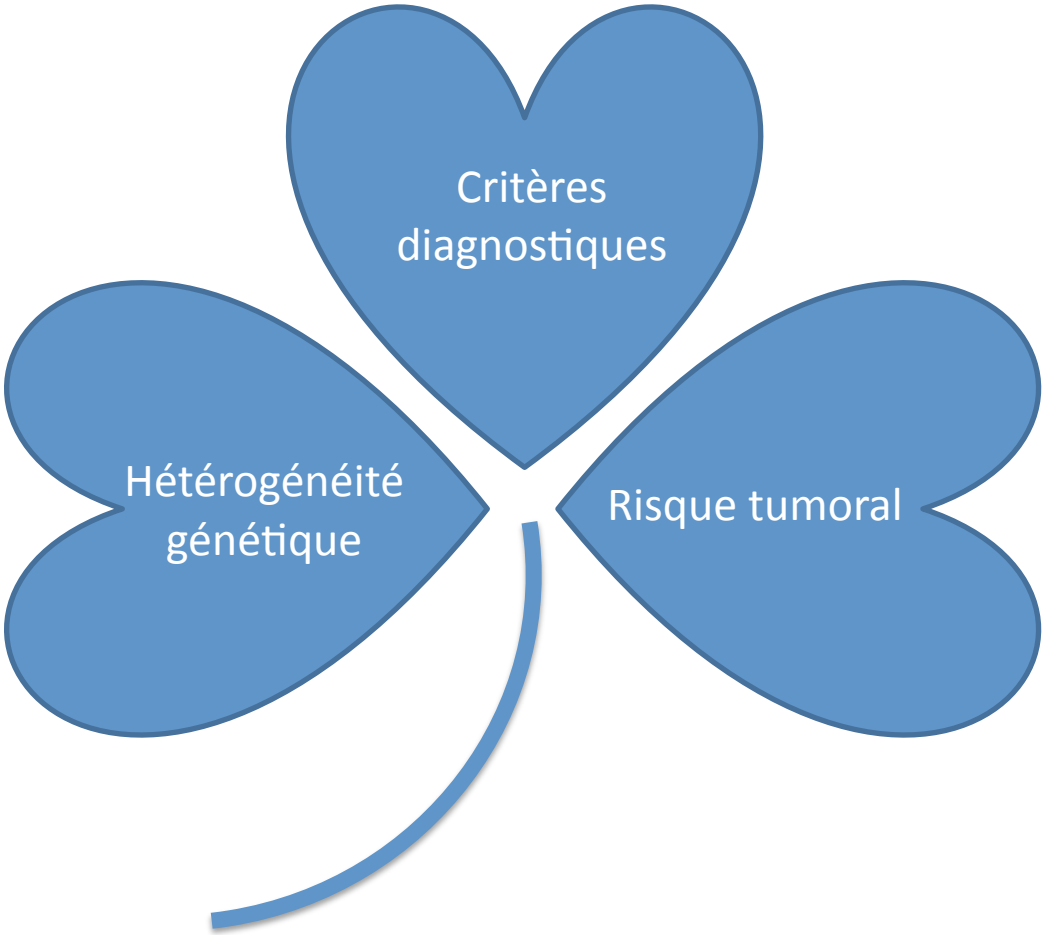
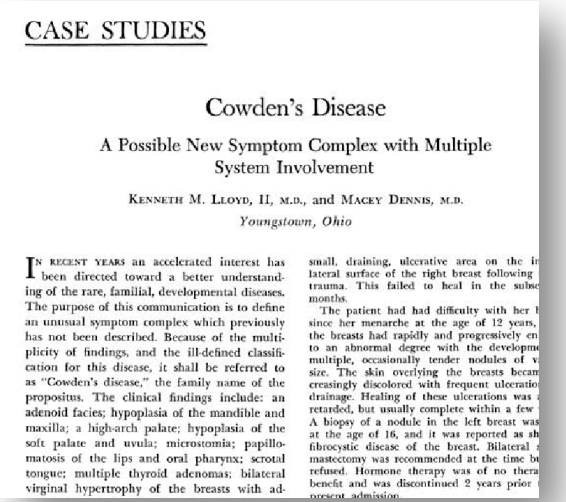


Maladie de Cowden

MIM 158350

- Bref historique
  - 1962 : Rachel Cowden
  - 1972 → 1991 : hérédité et signes cliniques
  - 1996
    - Associations phénotypiques (BRR/Cowden)
    - Cartographie du gène en 10q23
  - 1997 : clonage du gène *PTEN*
- Mutations constitutionnelles
  - Maladie de Cowden
  - PHTS, *PTEN Hamartoma Tumour Syndrome*



CASE STUDIES

Cowden's Disease

A Possible New Symptom Complex with Multiple System Involvement

KENNETH M. LLOYD, II, M.D., and MACEY DENNIS, M.D.

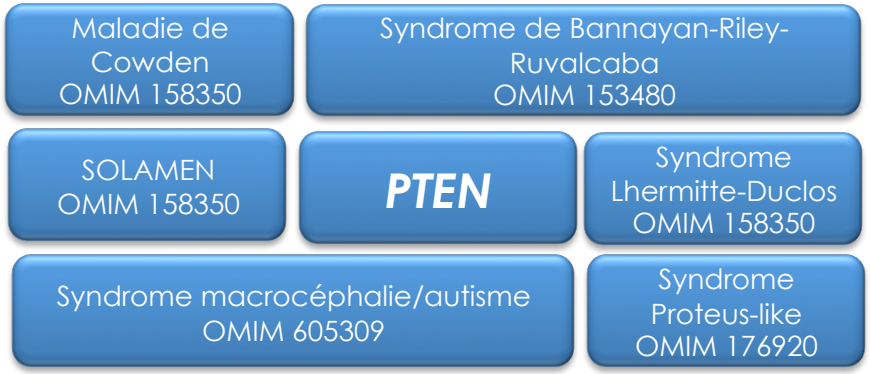
Youngstown, Ohio

IN RECENT YEARS an accelerated interest has been directed toward a better understanding of the rare, familial, developmental diseases. The purpose of this communication is to define an unusual symptom complex which previously has not been described. Because of the multiplicity of findings, and the ill-defined classification for this disease, it shall be referred to as "Cowden's disease," the family name of the propositus. The clinical findings include: an adenoid facies; hypoplasia of the mandible and maxilla; a high-arch palate; hypoplasia of the soft palate and uvula; microstomia; papillomatosis of the lips and oral pharynx; scrotal tongue; multiple thyroid adenomas; bilateral virginal hypertrophy of the breasts with ad-

small, draining, ulcerative area on the in lateral surface of the right breast following trauma. This failed to heal in the subse months.

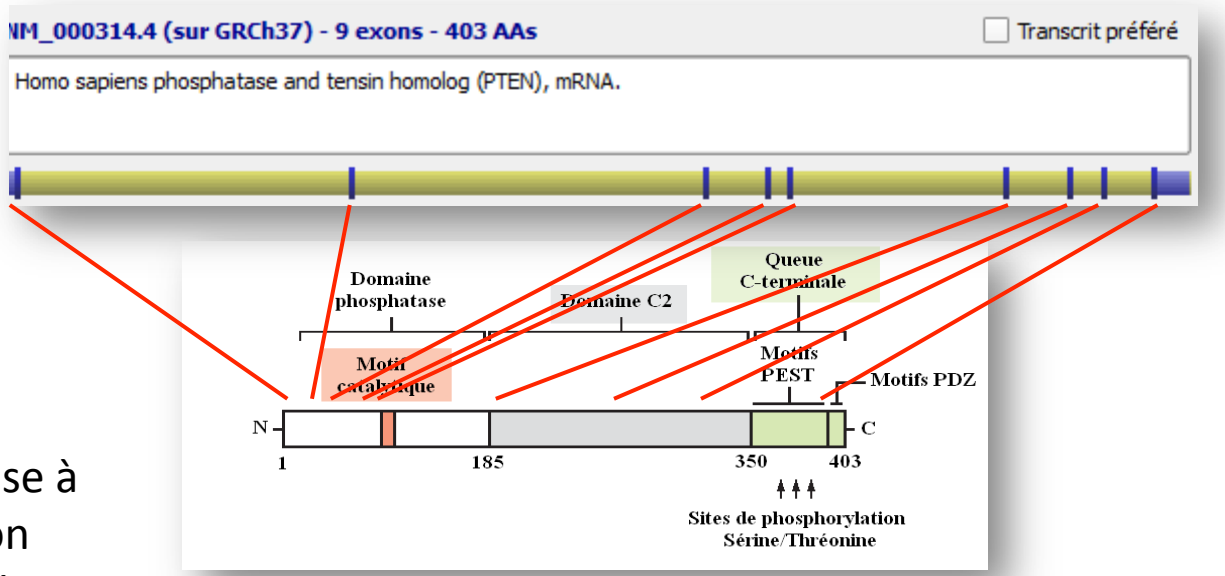
The patient had had difficulty with her b since her menarche at the age of 12 years, the breasts had rapidly and progressively en to an abnormal degree with the developme multiple, occasionally tender nodules of v size. The skin overlying the breasts becam creasingly discolored with frequent ulceratio drainage. Healing of these ulcerations was retarded, but usually complete within a few A biopsy of a nodule in the left breast was at the age of 16, and it was reported as sh fibrocystic disease of the breast. Bilateral mastectomy was recommended at the time bu refused. Hormone therapy was of no thera benefit and was discontinued 2 years prior

Lloyd KM 2nd, Dennis M (1963) Cowden's disease. A possible new symptom complex with multiple system involvement. Ann Intern Med. 58:136-42.

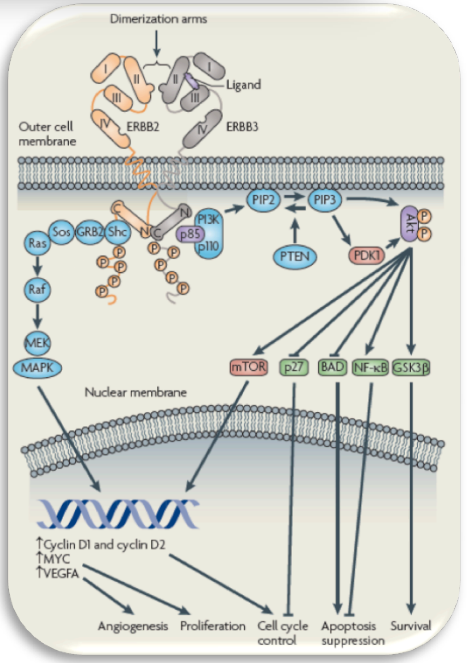


PTEN

MIM 601728



- Gène suppresseur de tumeur
  - Code une phosphatase à double spécificité non redondante impliquée dans la régulation négative de la voie de transduction du signal mitogénique impliquant la PI3Kinase
- Mutations somatiques
  - dans de nombreux types tumoraux (glioblastomes, cancers de l'endomètre)



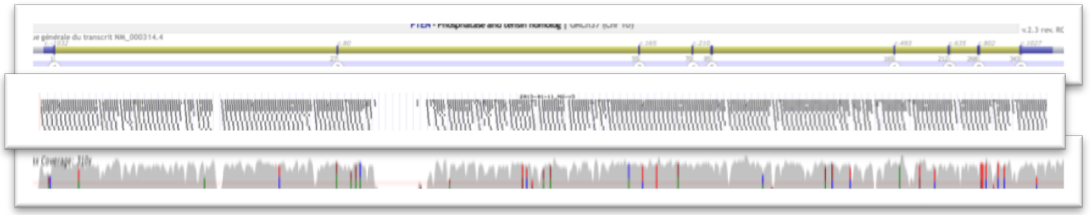
Baselga J, Swain SM (2009) Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nature Rev Cancer 9, 463-75

Étude structurelle des éléments cis-régulateurs de l'expression de PTEN

- 22 patients
  - présentant une maladie de Cowden cliniquement démontrée
  - sans mutation constitutionnelle du gène *PTEN* identifiée en phase codante
- NGS locus génomique *PTEN*

Numéro de Dossier	Interprétation Clinique	Score PTEN Predict	Score CC : Probabilité de Cowden	Série NGS
2010384	Cowden	94,40%	48,00%	3
1998101	Cowden	93,30%	100,00%	2
2006406	Cowden	93,30%	100,00%	1
2002213	Cowden	93,30%	48,00%	2
2001012	Cowden	85%	100,00%	3
2010391	Cowden	85%	85,00%	1
1999104	Cowden	85%	48,00%	3
2008207	Cowden	85%	20,00%	2
2012465	Cowden	70,80%	100,00%	1
2011128	Cowden	70,80%	100,00%	1
2010029	Cowden	65,90%	42,00%	1
2011694	Cowden	58,20%	10,00%	3
2009038	Cowden	52,70%	75,00%	1
2010148	Cowden	51,40%	42,00%	2
1997060-1*	Cowden	44,30%	100,00%	1
1998002	Cowden	34,70%	72,00%	2
1997060-2*	Cowden	34,70%	4,50%	3
1999009	Cowden	19,50%	20,00%	2
2003023	Cowden	15,30%	10,00%	2
2003007	Cowden	15,30%	3,50%	3
2008383	Cowden	15,30%	1,80%	3
2012115	LDD enfant	10,90%	100,00%	2
2008340	Cowden	9,00%	55,00%	1
2010018	SOLAMEN	4,50%	1,50%	3

Liste des 22 patients atteints de maladie de Cowden ou PHTS classés selon leur indice clinique de probabilité de détecter une mutation de PTEN



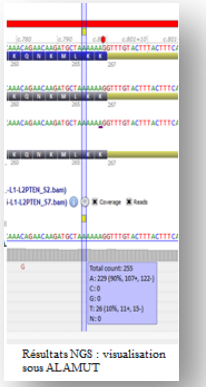
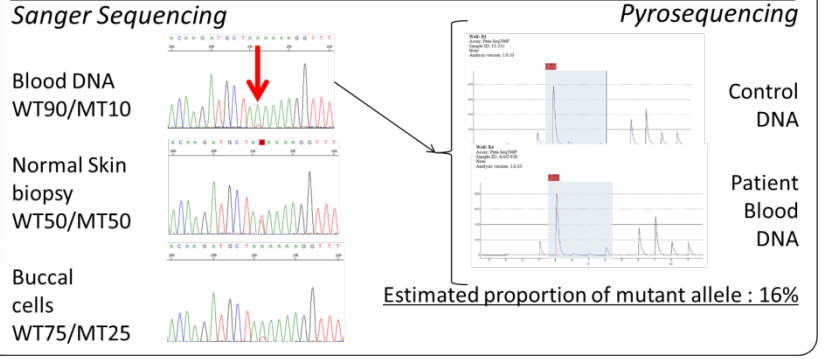


Figure 1 : Index Case 2012465 :

24 year old boy with adult-Lhermitte-Duclos disease, mucocutaneous lesions (facial trichilemmomas & cutaneous facial papules & mucosal papillomatosis), macrocephaly, mental retardation (IQ<75), GI hamartomas, lipomas. No known familial history of Cowden disease.

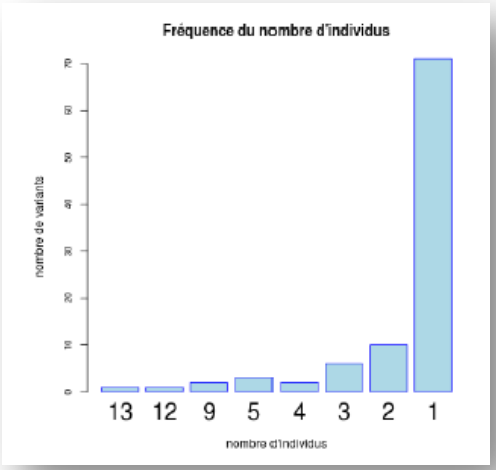
PTEN* Exon 7, c.796A>T, p.Lys266



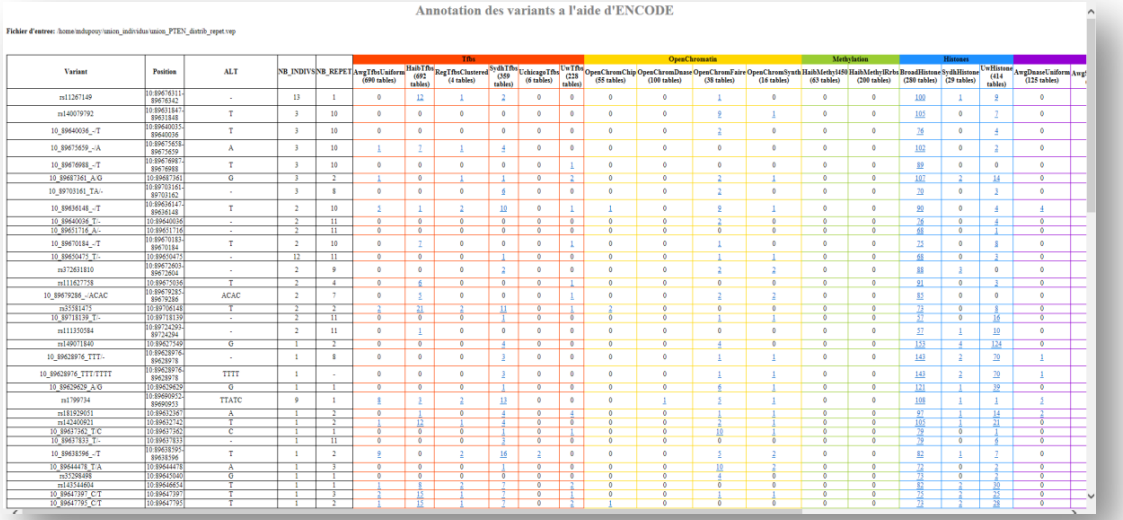
ENCyclopedia **O**f **D**NA **E**lements

ENCODE project

- Résultats
  - 96 variants uniques caractérisés, 95 introniques

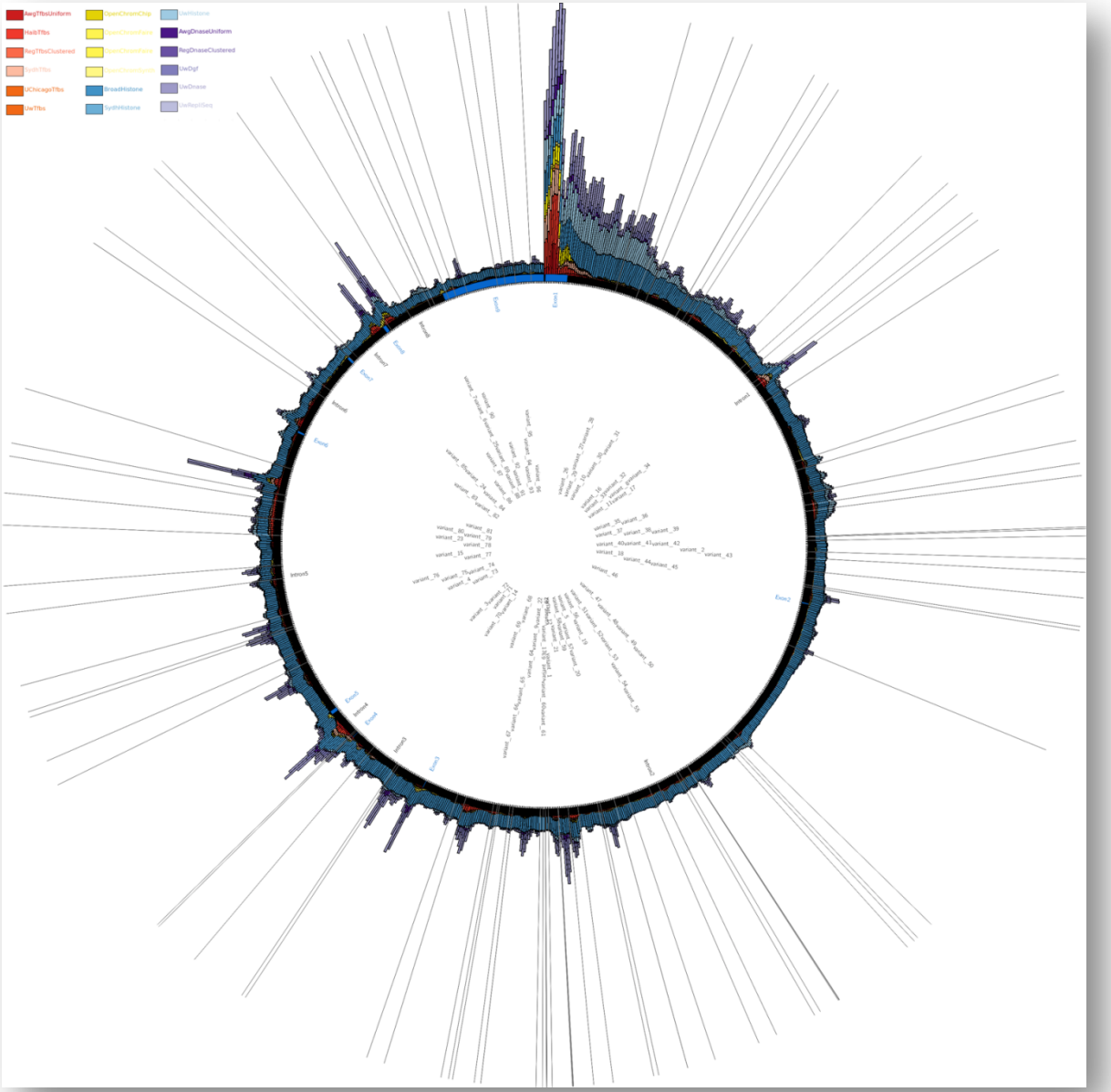


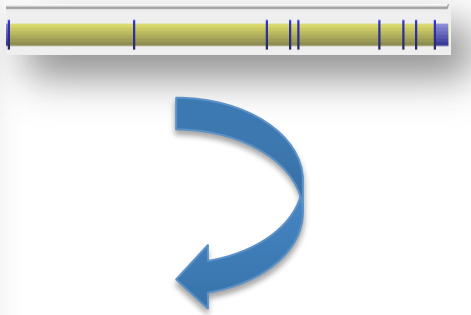
Graphe représentant le nombre de variants en fonction du nombre d'individus les portant



Capture d'écran du tableau de concordance de chaque variant caractérisé dans les méta-tables du projet ENCODE (chromatine, histones, facteurs de transcription, méthylation, autres)

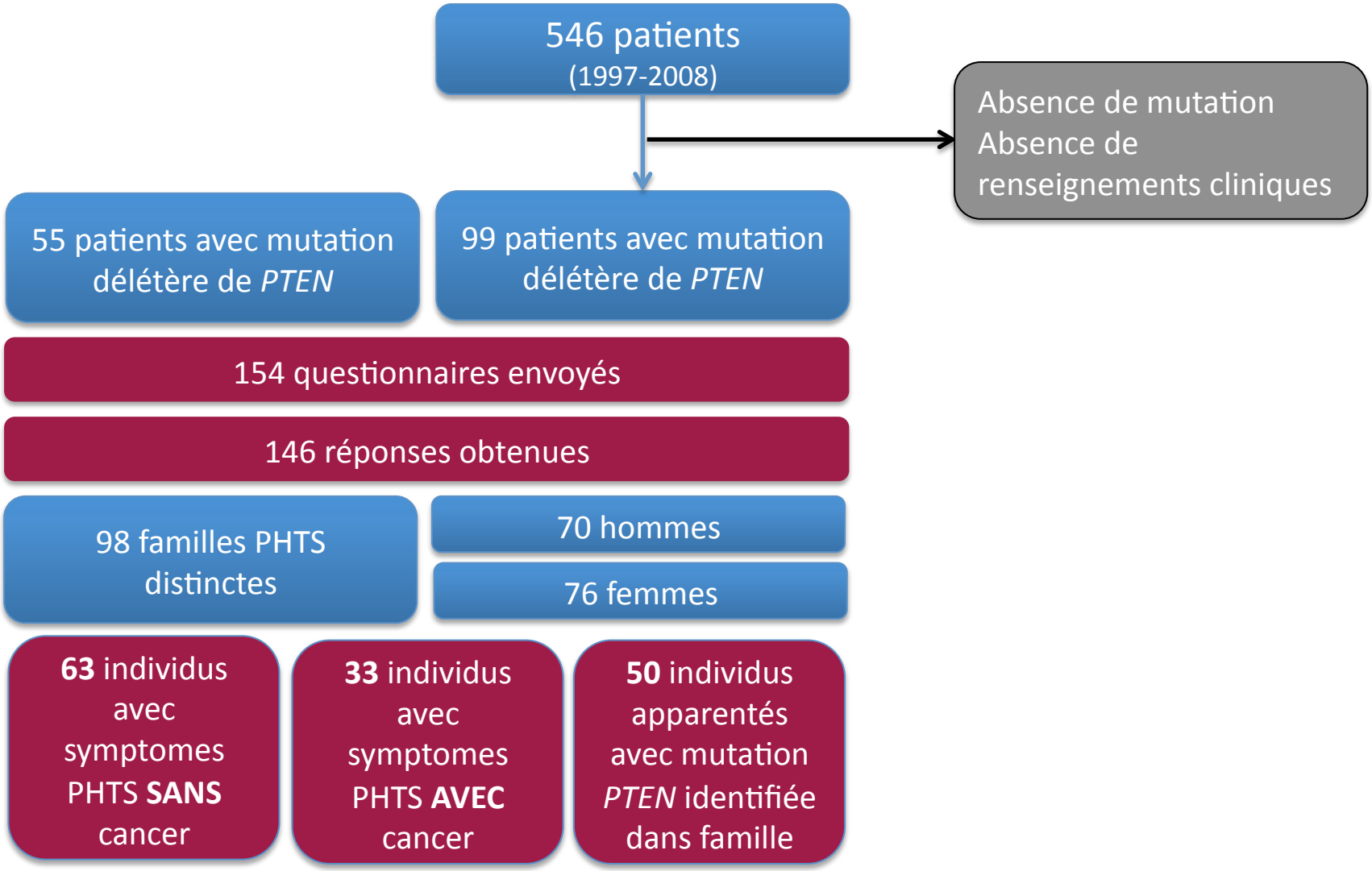
Mutations introniques profondes de *PTEN*



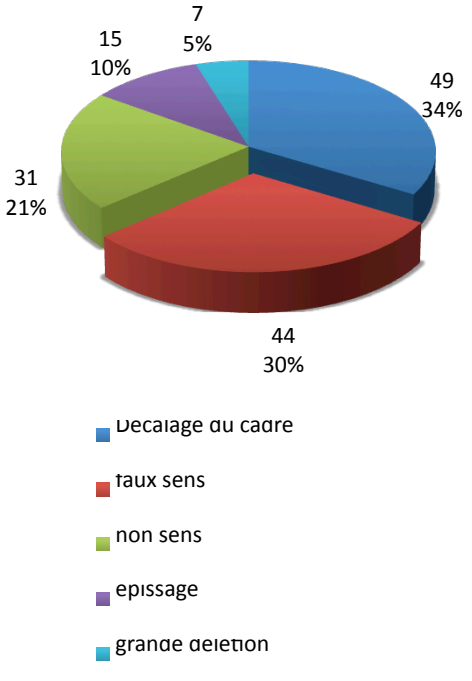


Modélisation de la répartition des zones de régulation de l'expression de PTEN et de la répartition des variants uniques détectés sur le locus génomique de PTEN. *Le résultat est présenté sous forme d'un circos plot.*

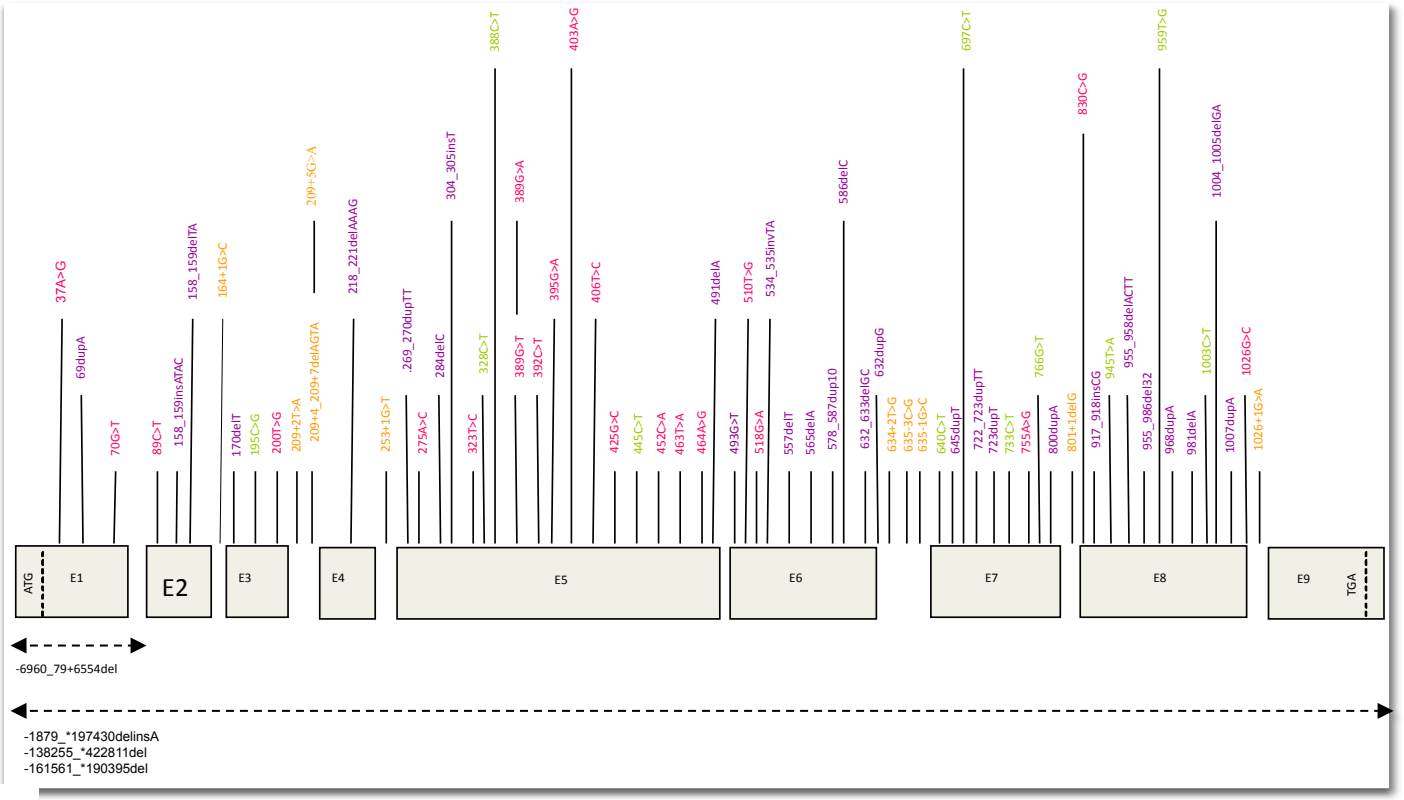
Critères diagnostiques



Mutations constitutionnelles de *PTEN*



Répartition par type des mutations caractérisées sur le gène PTEN *(tronquantes vs non troncantes)*

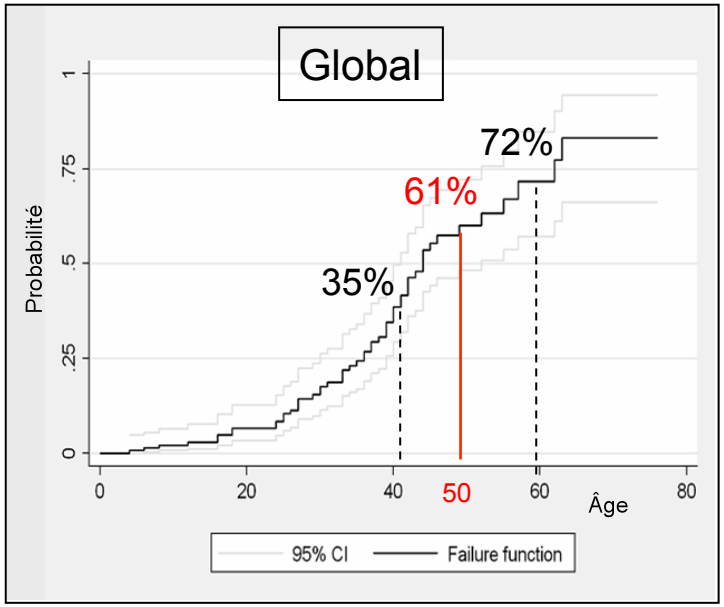


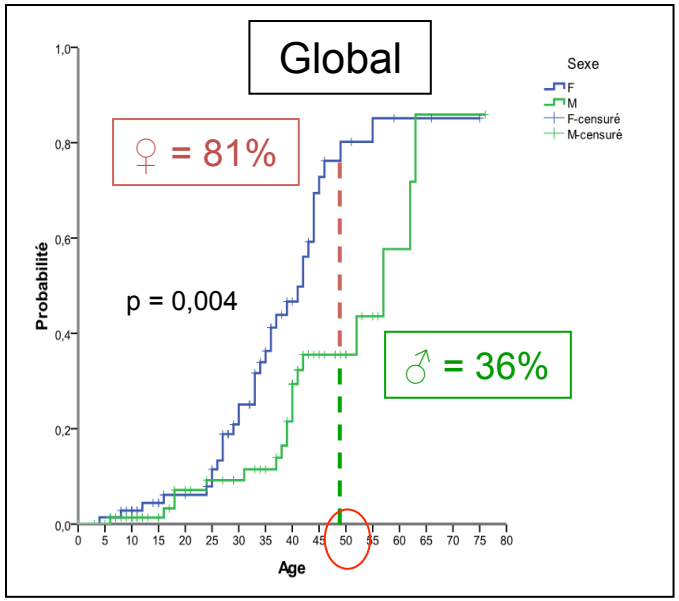
Répartition le long de la séquence codante des mutations caractérisées sur le gène PTEN

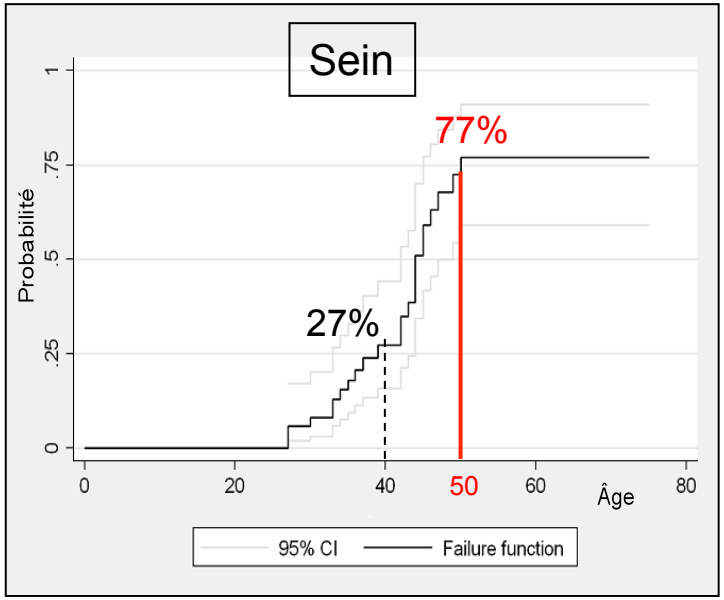
Phénotypes observés

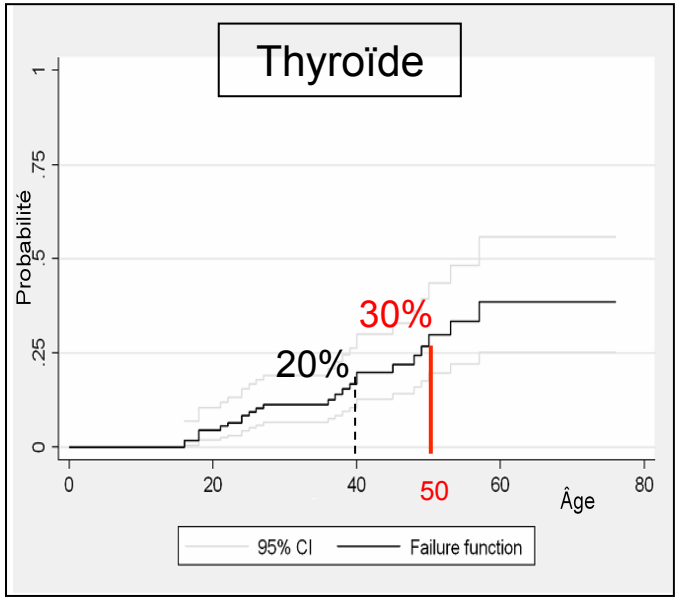
Lésions (population renseignée)	Nombre n (%)	Mutations Tronquantes	Mutations Non tronquantes	p	Domaines protéiques Phosphatasique	Domaines protéiques C2	p
Lésions dermatologiques (98)	96 ***(98%)***	-	-	-	-	-	-
Lésions thyroïdiennes							
Lésions bénignes (136)	96 ***(71%)***	70/95 *(74%)*	26/41 *(63%)*	***0,2***	56/76 *(74%)*	36/54 *(67%)*	***0,1***
Lésions mammaires							
Lésions bénignes (65)	48 ***(74%)***	32/42 *(76%)*	16/23 *(70%)*	-	30/41 *(73%)*	16/22 *(73%)*	-
Lésions digestives (80)	74 ***(93%)***	-	-	-	-	-	-
Polypes coliques (79)	67 ***(85%)***	54/61 *(88%)*	13/18 *(72%)*	***0,1*** *	38/46 *(83%)*	24/28 *(86%)*	***0,7***
Lésions lipo-vasculaires							
Lipomatose (135)	65 ***(48%)***	50/93 *(54%)*	15/42 *(36%)*	***0,2***	33/76 *(43%)*	27/53 *(51%)*	***0,2***
Lésions vasculaires (136)	48 ***(35%)***	33/94 *(35%)*	15/42 *(35%)*	***0,6***	*28/ 77 (36%)*	19/53 *(36%)*	***0,6***
Lésions neurologiques							
Macrocéphalie (122)	113 ***(93%)***	-	-	-	-	-	-
Lhermitte-Duclos (144)	19 ***(13%)***	14/102 *(14%)*	5/42 *(12%)*	-	14/81 *(17%)*	5/57 *(9%)*	-
RPM/RM/Autisme (144)	15 ***(10%)***	10/102 *(10%)*	5/42 *(12%)*	-	8/81 *(10%)*	7/57 *(12%)*	-
Lésions uro-génitales (57)							
Atteinte ♂ (52)	5 ***(9%)***	-	-	-	-	-	-
Atteinte ♀	27 ***(52%)***	-	-	-	-	-	-
Lésions cancéreuses (146)	53 ***(33%)***						
Cancer du sein (68)	23***(34%)***	**Kaplan-Meier (Test du Log rank)**					
Cancer de la thyroïde (140)	24 ***(17%)***						
Cancer du rein (146)	3 ***(2%)***	-	-	-	-	-	-
Cancer de l'endomètre (146)	3 ***(2%)***	-	-	-	-	-	-
Mélanome (146)	9 ***(6%)***	-	-	-	-	-	-
Cancer colo-rectal (146)	4 ***(3%)***	-	-	-	-	-	-
Cancer de l'ovaire (146)	4 ***(3%)***	-	-	-	-	-	-

Risque tumoral

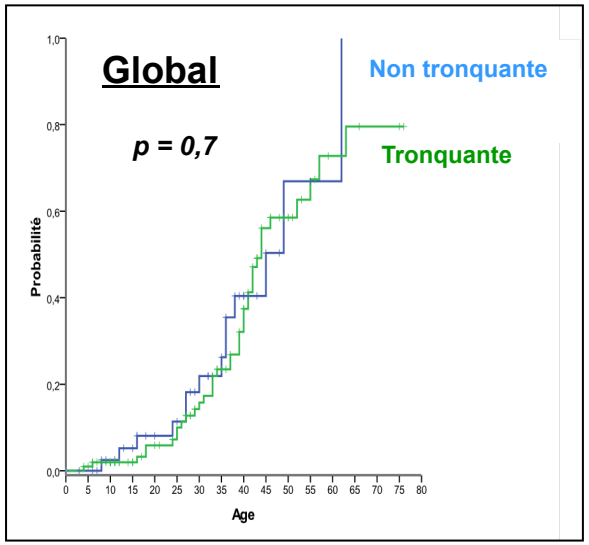


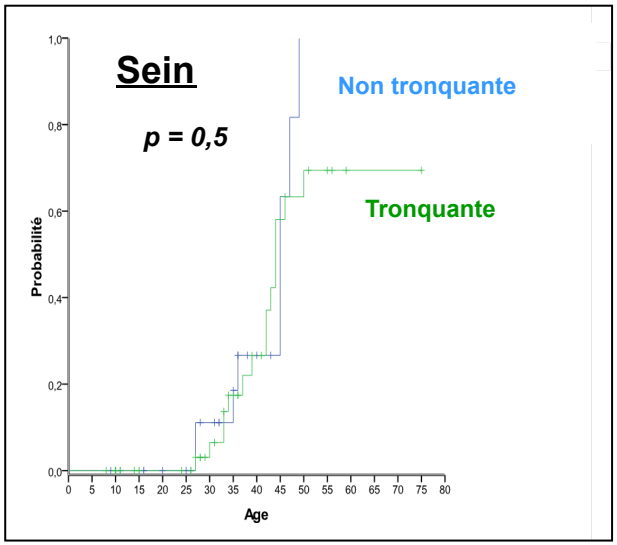


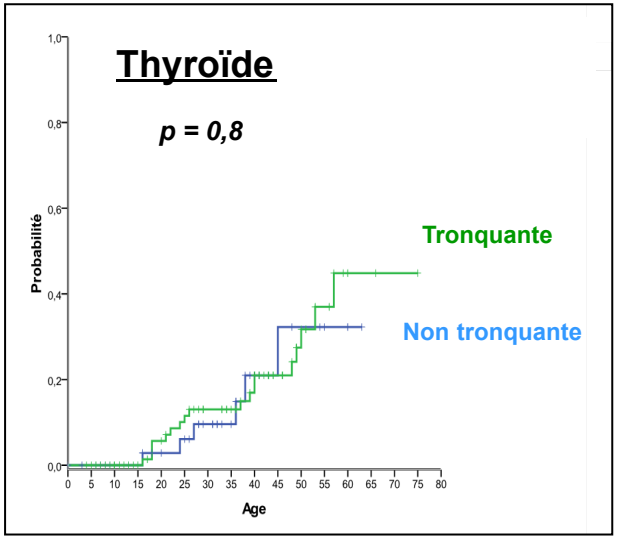


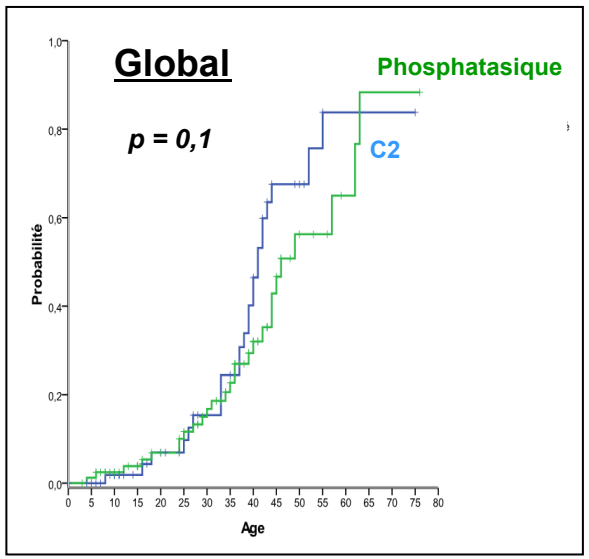


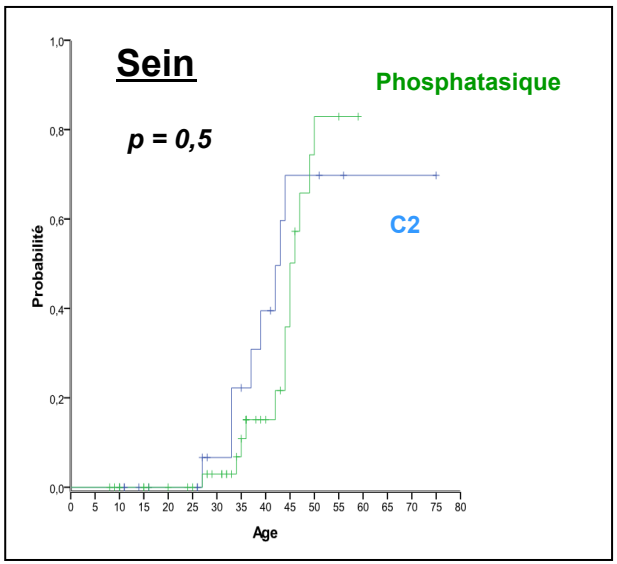
Corrélation génotype – risque tumoral

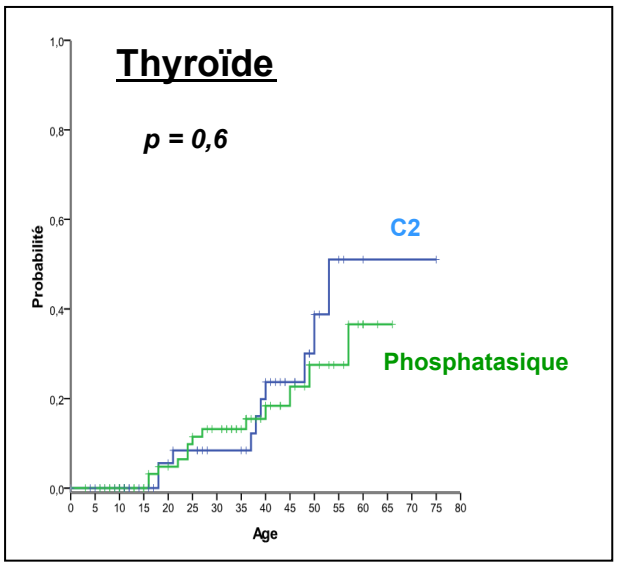












Critères diagnostiques (NCCN)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Cowden Syndrome/PHTS

NCCN Guidelines Index
Genetics Table of Contents
Discussion

REVISED PTEN HAMARTOMA TUMOR SYNDROME CLINICAL DIAGNOSTIC CRITERIA[n]

MAJOR CRITERIA:
- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (≥97 percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - Multiple trichilemmomas (≥3, at least one biopsy proven)
  - Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - Mucocutaneous neuromas (≥3)
  - Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed

MINOR CRITERIA:
- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthoses (≥3)
- Lipomas (≥3)
- Mental retardation (ie, IQ ≤75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, multinodular goiter)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

Operational diagnosis in an individual (either of the following):
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
2. Two major and three minor criteria.

Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a PTEN mutation:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

http://penrad.com/MRIPapers/NCCN_Genetics2014.pdf

Pilarski R et al (2013) Cowden syndrome and the PTEN hamartoma tumor syndrome : Systematic review and revised diagnostic criteria. JNCI 105, 1607-16.

Proposition d'un modèle de prise en charge

Dépistage/Prévention		Date de début	Périodicité
Femmes			
Si mastopathie modérée	Examen clinique mammaire +/- échographie	25 ans	1x/an
	Mammographie + IRM mammaire	30 ans (ou 5 ans avant le plus jeune cas de cancer familial)	1x/an
Si mastopathie majeure	Examen clinique + IRM mammaires	Dès 15 ans	1x/an
	Mastectomie bilatérale prophylactique	25-30 ans	
Echographie pelvienne endovaginale		35-40 ans (ou 5 ans avant le plus jeune cas de cancer familial)	1x/an

Proposition d'un modèle de prise en charge

Dépistage/Prévention		Date de début	Périodicité
Hommes & Femmes			
Examen clinique complet	Thyroïde, sein, peau ++	Au diagnostic	
	Echographie thyroïdienne de référence	10 ans	1x/an
Thyroïdectomie totale		Si nodules Si chirurgie de la thyroïde	
Endoscopie digestive		30 ans	Tous les 5 ans (tous les 3 ans en cas de polypose ou de polypes adénomateux)
Echographie rénale (ou IRM)		30 ans (si histoire familiale de cancer du rein)	2x/an (1x/an)
Education du patient		Consulter au moindre symptôme inhabituel	
Soutien psychologique +++			

Remerciements

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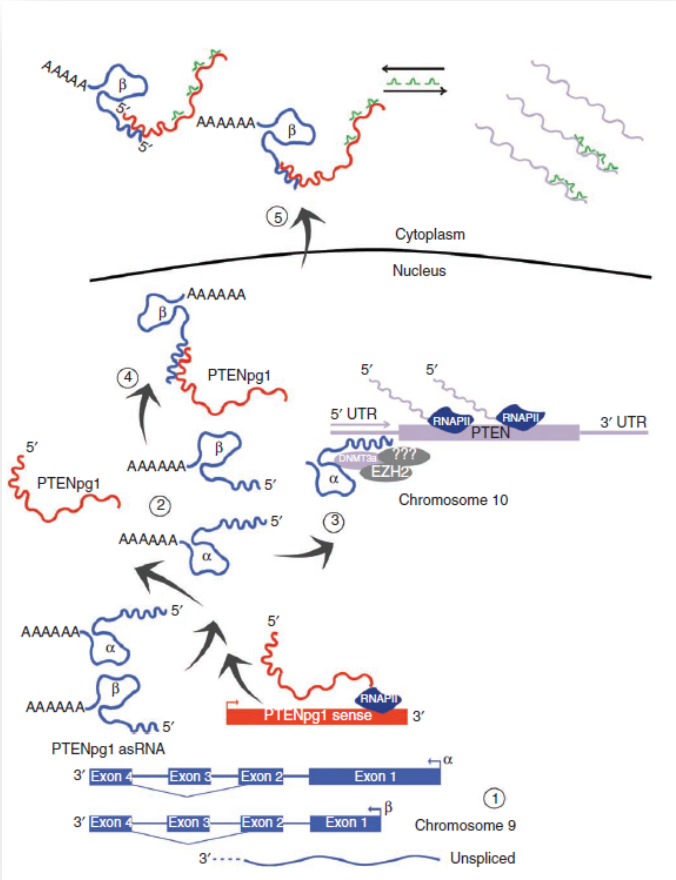
Capucine Delnatte
Liliane Demange
Catherine Dugast
Patrick Edery
François Feillet
Thierry Frebourg
Jean-Pierre Fricker
Brigitte Gilbert-Dussardier
Sophie Giraud
Irina Giurgea
Delphine Heron
Muriel Holder
Hubert Journel
Sophie Julia
Maha Kacem
Valérie Layet
Fattouma Bourguiba
Sophie Lejeune
Frédéric Leprat
Dominique Leroux,
Catherine Lok,
Alain Lortholary
Stanislas, Lyonnet
Geneviève Margueritte
Jacques Mauillon
Juliette Mazereeuw-Hautier
Sylvie Odent
Clotilde Penet
Anne Philippe,
Henri Plauchu
Ghislaine Plessis
Emmanuel Plouvier
Marie-Aleth Richard
Abdelkrim Saadi
Jean-Christophe Saurin
Julie Tinat,
Pierre Vabres
Lionel Van Maldergem
Philippe Vennin
Pierre-Jean Weiller

Données cellulaires récentes

Régulation de l'expression de *PTEN* et localisations cellulaires de PTEN



Modèle de régulation de l'expression de PTEN par son pseudogène PTENP1 et les 3 transcrits issus de PTEN-P1AS. *Johnsson et al (2013) A pseudogene long-noncoding-RNA network regulates PTEN transcription and translation in human cells. Nature structural and molecular biology 20, 440-6*

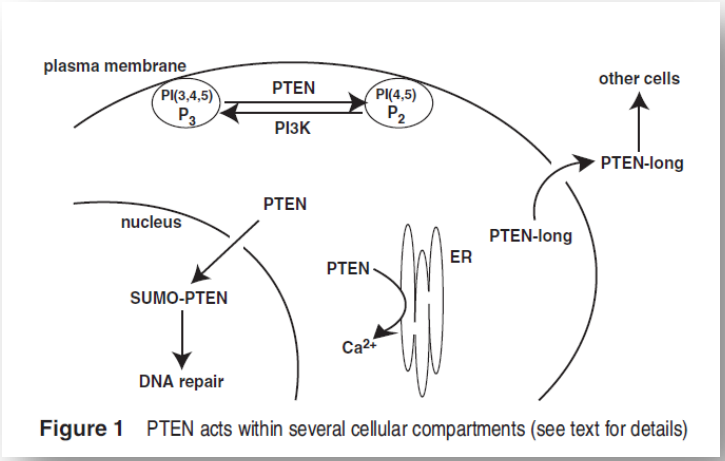
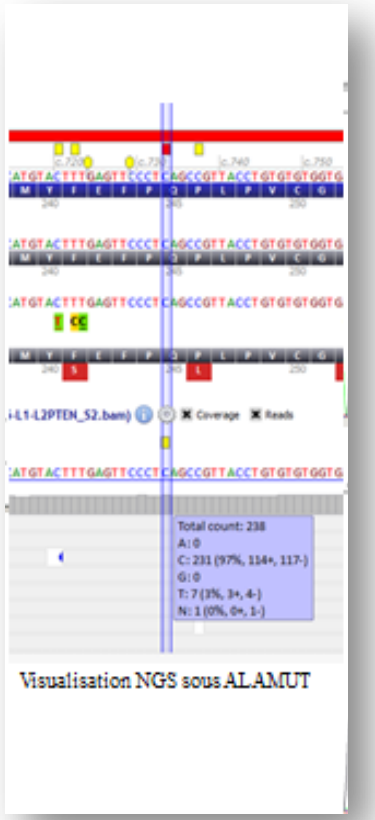


Figure 1 PTEN acts within several cellular compartments (see text for details)

Représentation schématique des activités cellulaires de PTEN *(Bassi C & Stambolic V (2013) PTEN, here, there, everywhere. Cell Death & Differentiation 20, 1595-6.*

First results

Germline *PTEN* mosaicism (low frequency variant)

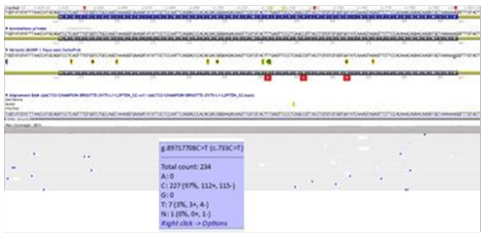


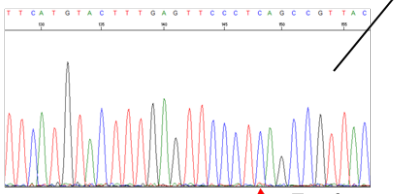
Visualisation NGS sous ALAMUT

Figure 2 : Index Case 2008340 :

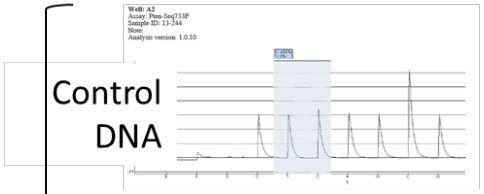
54 year old woman with adult-Lhermitte-Duclos disease, multinodular goiter, colonic polyps, breast fibroadenomas. Invasive ductal carcinoma detected at 49 yrs, HR+, SBR2. No known familial history of Cowden disease.

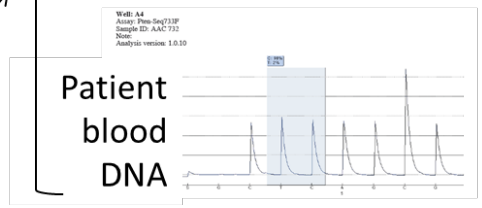
PTEN* Exon 7, c.733C>T; p.Gln245





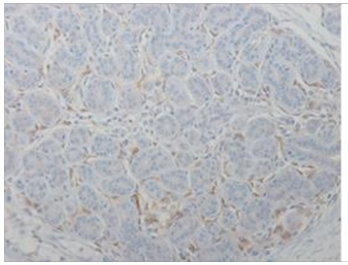
Pyrosequencing



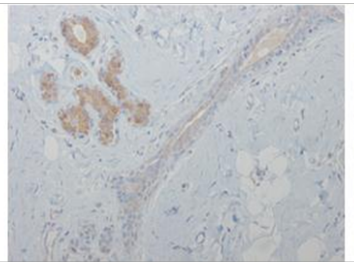


Estimated proportion of mutant allele : 2%

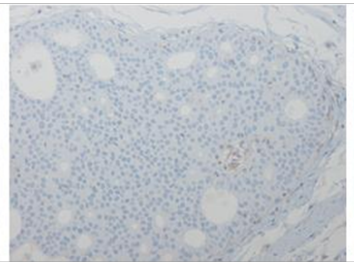
PTEN immunohistochemistry



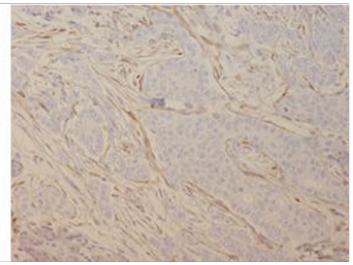
Normal lobule with loss of PTEN expression in luminal cells & normal expression of PTEN in stromal cells



Another area of the breast showing normal expression of PTEN in luminal cells



Ductal carcinoma in situ with loss of PTEN expression in carcinoma cells



Invasive breast cancer NST with loss of PTEN expression in invasive breast carcinoma cells & normal PTEN expression in stromal cells

Recommandations de suivi (NCCN)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Cowden Syndrome/PHTS

NCCN Guidelines
Genetics Table of Co
Discu

COWDEN SYNDROME/PHTS MANAGEMENT

WOMEN

- Breast awareness[1] starting at age 18 y.
- Clinical breast exam, every 6-12 mo, starting at age 25 y or 5-10 y before the earliest known breast cancer in the family.
- Annual mammography and breast MRI screening starting at age 30-35 y or individualized based on earliest age of onset in family.[2,3]
- For endometrial cancer screening,[4] encourage patient education and prompt response to symptoms. Consider annual random endometrial biopsies and/or ultrasound beginning at age 30-35 y.
- Discuss risk-reducing mastectomy and hysterectomy[5] and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.

MEN AND WOMEN

- Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.
- Annual thyroid ultrasound starting at age 18 y or 5-10 y before the earliest known thyroid cancer in the family, whichever is earlier.
- Colonoscopy, starting at age 35 y, then every 5 y or more frequently if patient is symptomatic or polyps found.
- Consider renal ultrasound starting at age 40 y, then every 1-2 y
- Dermatologic management may be indicated for some patients
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding the signs and symptoms of cancer.

RISK TO RELATIVES

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

REPRODUCTIVE OPTIONS

- For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.