Acquis et limites dans les lésions frontières

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Acquis et limites en anatamo-pathologie et biologie moléculaire

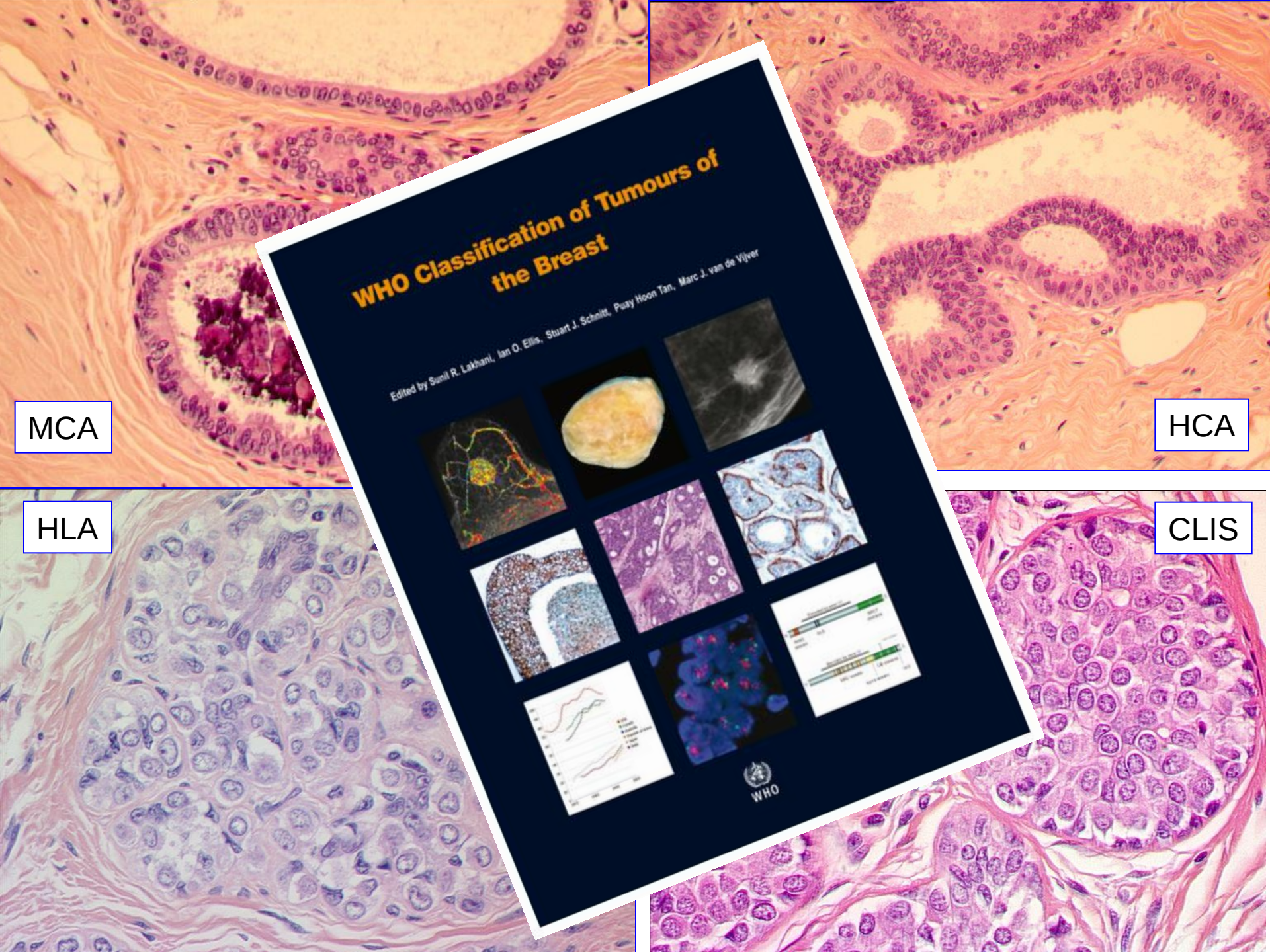
Société Française de Sénologie et de Pathologie Mammaire
15 Novembre 2012, Paris La Défense

Lésions frontières

- Entités du spectre des lésions de bas grade
  - Métaplasie cylindrique atypique (MCA)
  - Hyperplasie canalaire atypique (HCA)

  - Hyperplasie lobulaire atypique (HLA)
  - Carcinome lobulaire in situ (CLIS)

- Lésion entre épithélium normal vers lésions malignes
  - Potentiel évolutif vers des lésions malignes
    - RR X 2 à 8 - 11 de développer un carcinome
  - Sur biopsies = “sentinelles “ de lésions plus péjoratives existantes dans le sein


MCA
HCA
HLA
CLIS
WHO Classification of Tumours of the Breast
Edited by Sunil R. Lakhani, Ian O. Ellis, Stuart J. Schnitt, Puay Hoon Tan, Marc J. van de Vijver
WHO

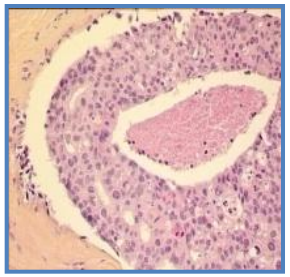
Limites communes à toutes les lésions

- Inaccessibilité épithélium mammaire et lésions frontières

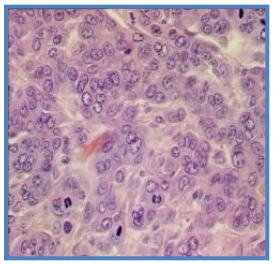
- Analyse histoire naturelle impossible

- Analyse moléculaire :
  - Complexe et peu fréquente sur matériel congelé
  - Nécessite tri du matériel tumoral // stroma // tissu normal
  - Analyse in situ
    - par hybridation in situ
    - par immunohistochimie

Précurseurs ?

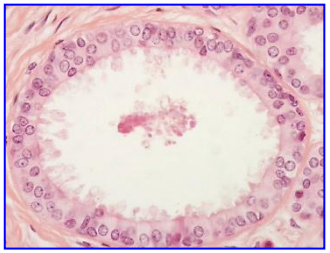


Carcinome in situ
de haut grade

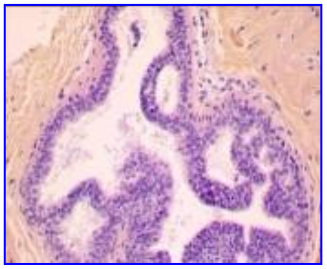


Carcinome infiltrant
de haut grade

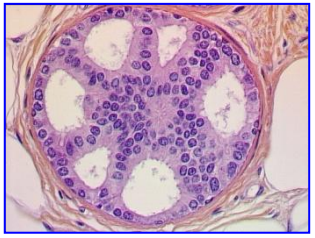
Métaplasie cylindrique
atypique



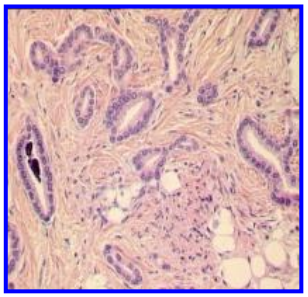
Hyperplasie canalaire
atypique



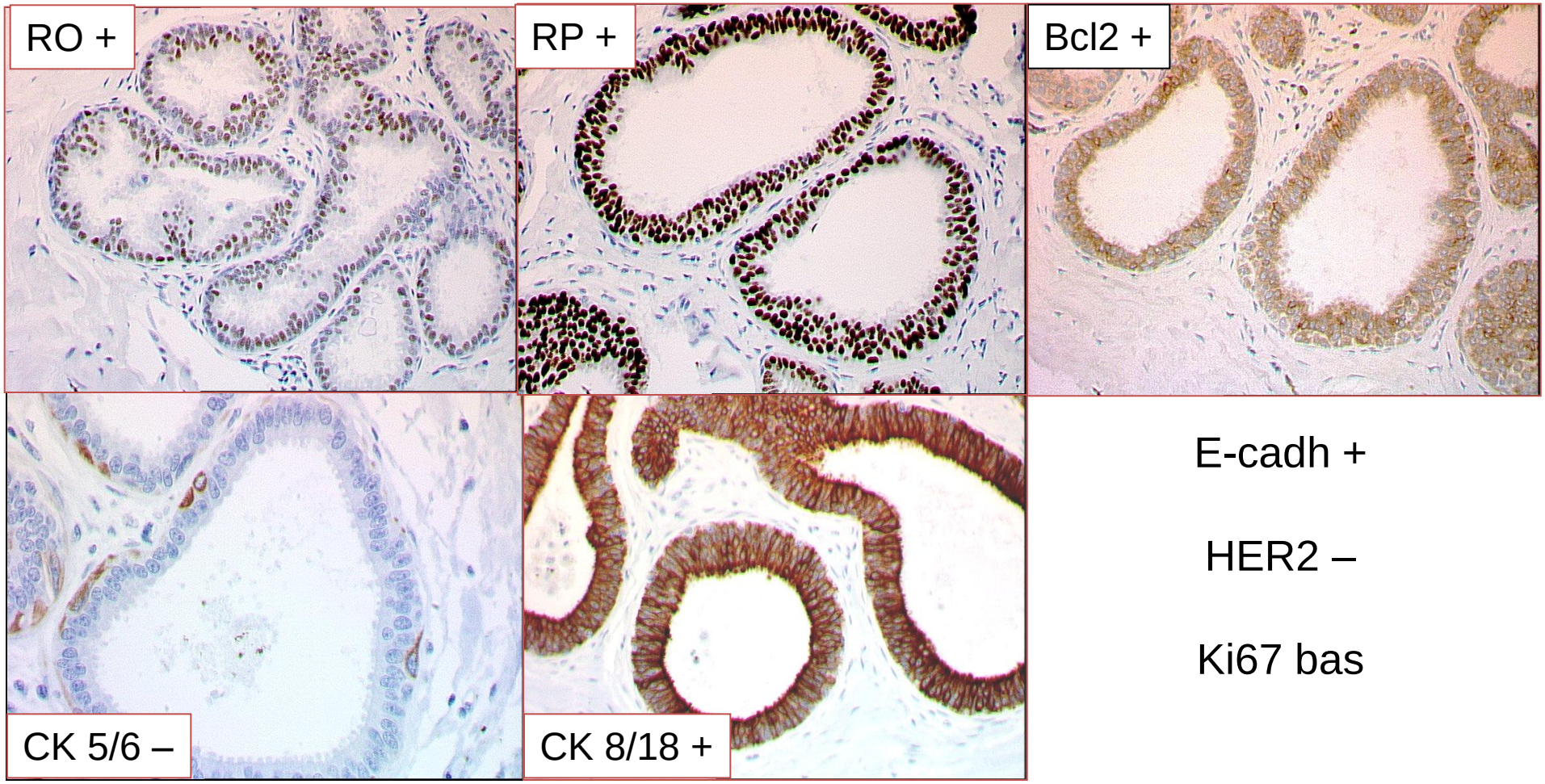
Carcinome in situ
de bas grade



Carcinome infiltrant
de bas grade



MCA, HCA et CCIS de bas grade : Phénotype identique



E-cadh +

HER2 –

Ki67 bas

Boecker, Virchows Arch A Pathol Anat Histopathol 1992
Otterbach, Histopathology, 2000
Simpson, Am J Surg Path 2005
Tremblay, Breast J, 2005
Lee, Breast Can Res , 2006

Altérations génomiques des MCA

- MCA ont les mêmes anomalies que HCA et CCIS bas grade
  - Peu d'altérations chromosomiques: 16q –
  - LOH au moins un locus dans 70% des cas
  - pertes >> gains

- Dans 1 même cas :

  Altérations communes entre MCA, CCIS et CCI

Moinfar, Cancer, 2000
Simpson, Am J Surg Path 2005
Aulmann, Am J Surg Path 2012

Pas d'altération génomique dans les lésions de métaplasie cylindrique simple

Pertes alléliques observées dans :

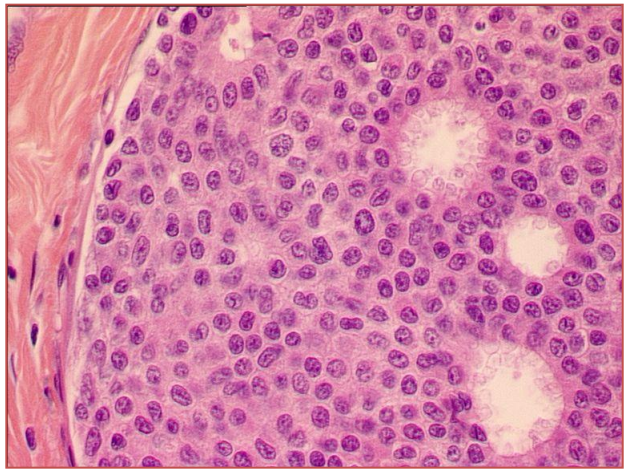
- 0 cas de métaplasie cylindrique simple (2/2 cas)
- 2/3 cas de métaplasie cylindrique avec hyperplasie
- 10/11 cas
  - MCA
  - CCIS
  - Carcinome infiltrant de bas grade

Dabbs, Mod Path, 2006

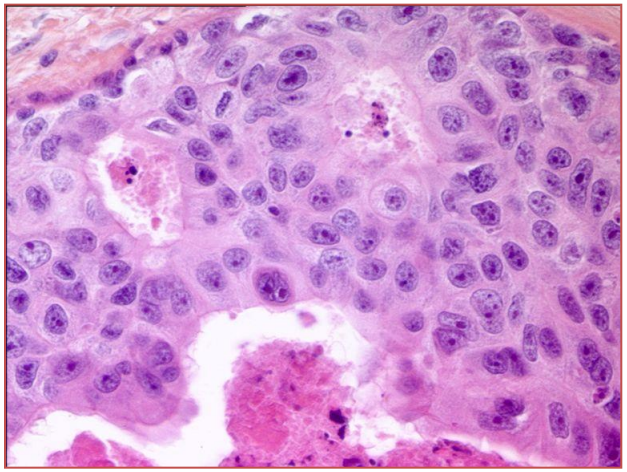
Altérations génomiques des CCIS en fonction du grade

Bas grade

Grade Intermédiaire



Haut grade



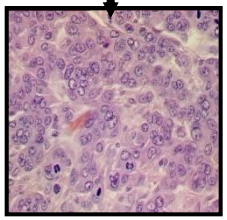
1q+, 16q-
CCND1 +
BCL2 +
Mutations *PI3KCA*

1q+, 3q+, 17q+, 8q+, 11q-, 14q-, 8p-, 13q-
Mutations *TP53*
Amplification *ERBB2*
Amplifications 8q22, 11q13, 6q22
Proliferation (Ki67)

RO -

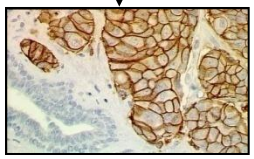
Précurseurs ?

Carcinome in situ
de haut grade triple neg



Carcinome infiltrant
de haut grade triple neg

In situ
ERBB2+
RO -



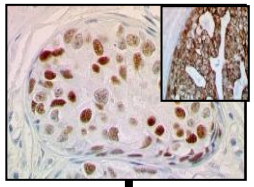
Triple neg

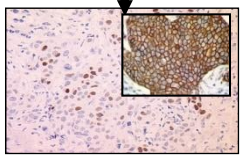
ERBB2

RO +

Précurseurs ?

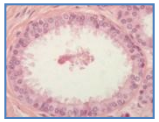
In situ
RO +
ERBB2+



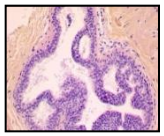


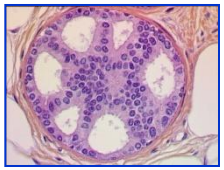
Luminal B

Métaplasie cylindrique
atypique

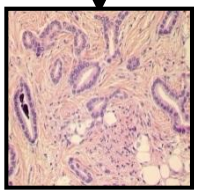


Hyperplasie canalaire
atypique





Carcinome in situ
de bas grade

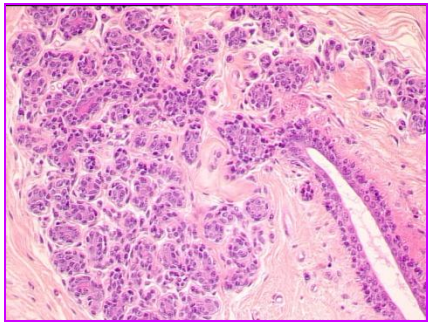


Carcinome infiltrant
de bas grade

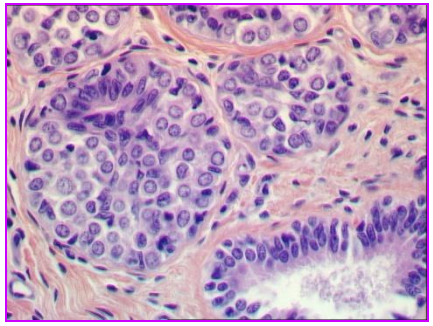
Luminal A

Lésions de néoplasie lobulaire in situ

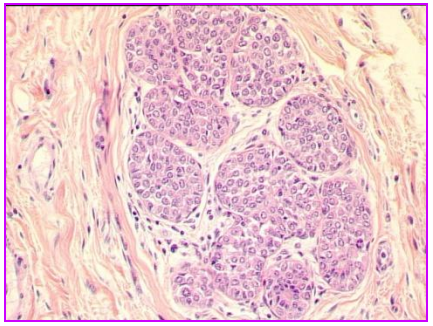
Normal



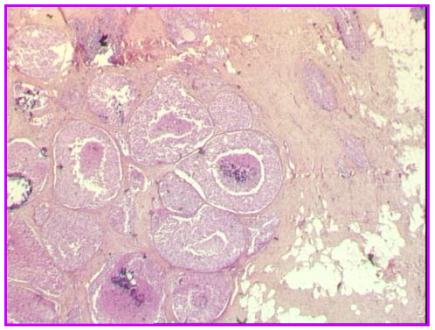
Hyperplasie lobulaire atypique

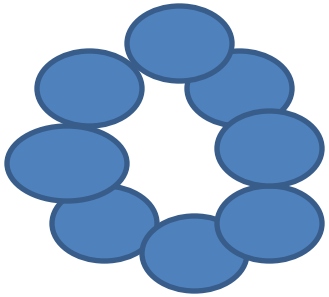


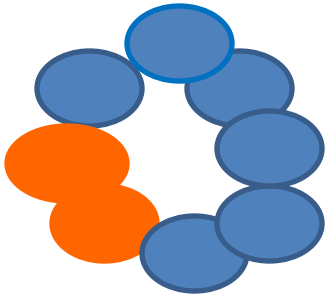
Carcinome lobulaire In situ



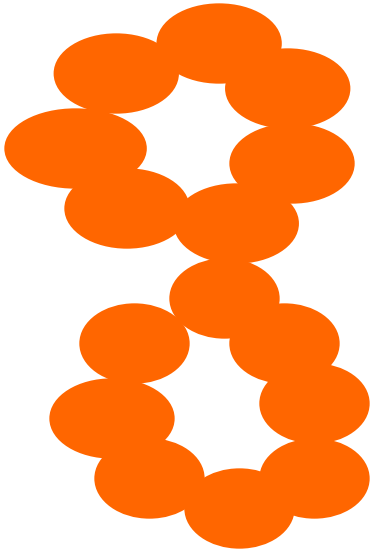
Carcinome lobulaire In situ pléomorphe
-nécrose centrale
- pléomorphisme nucléaire

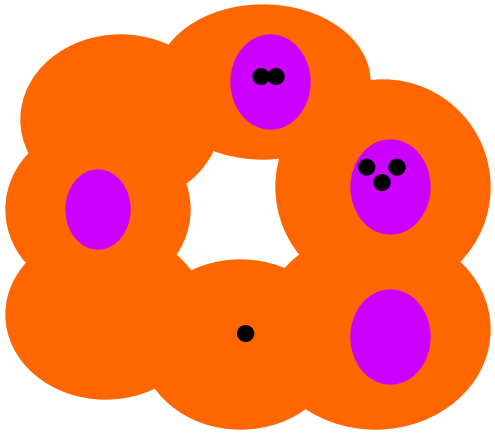






mutation E-cadhérine

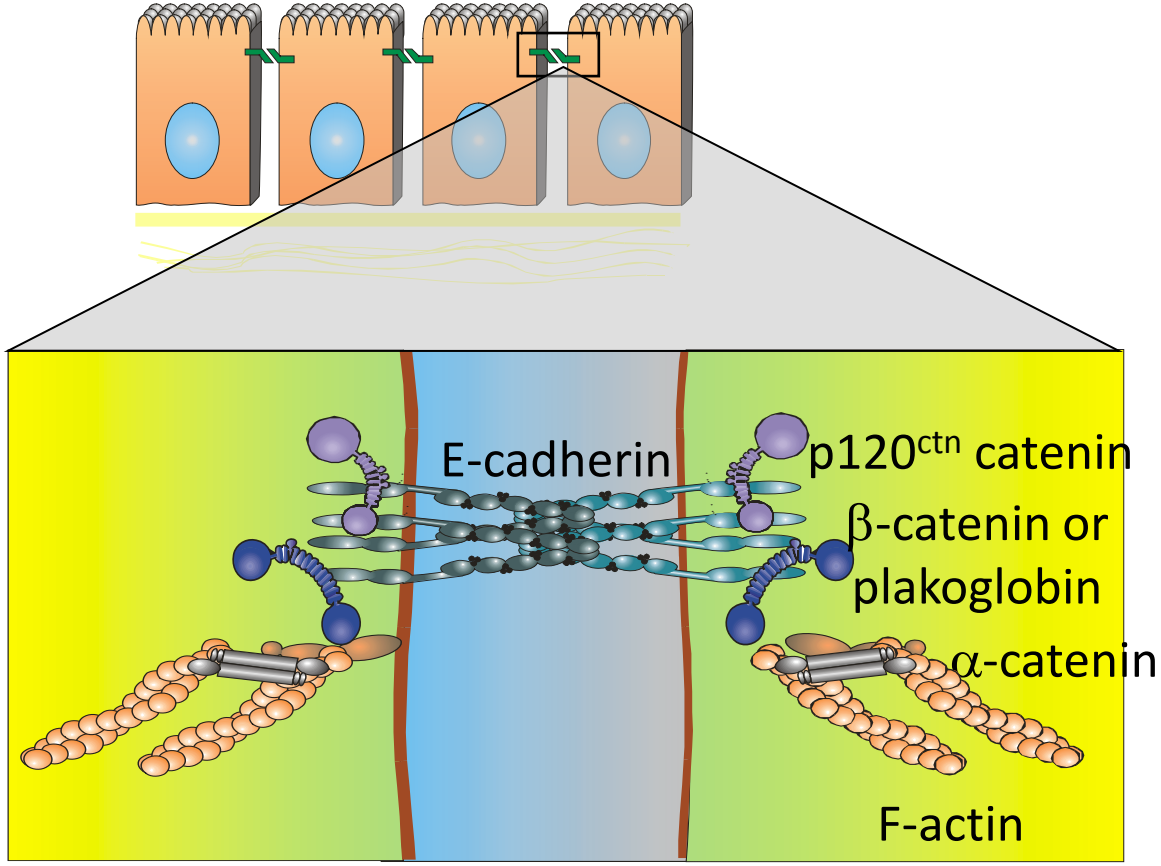




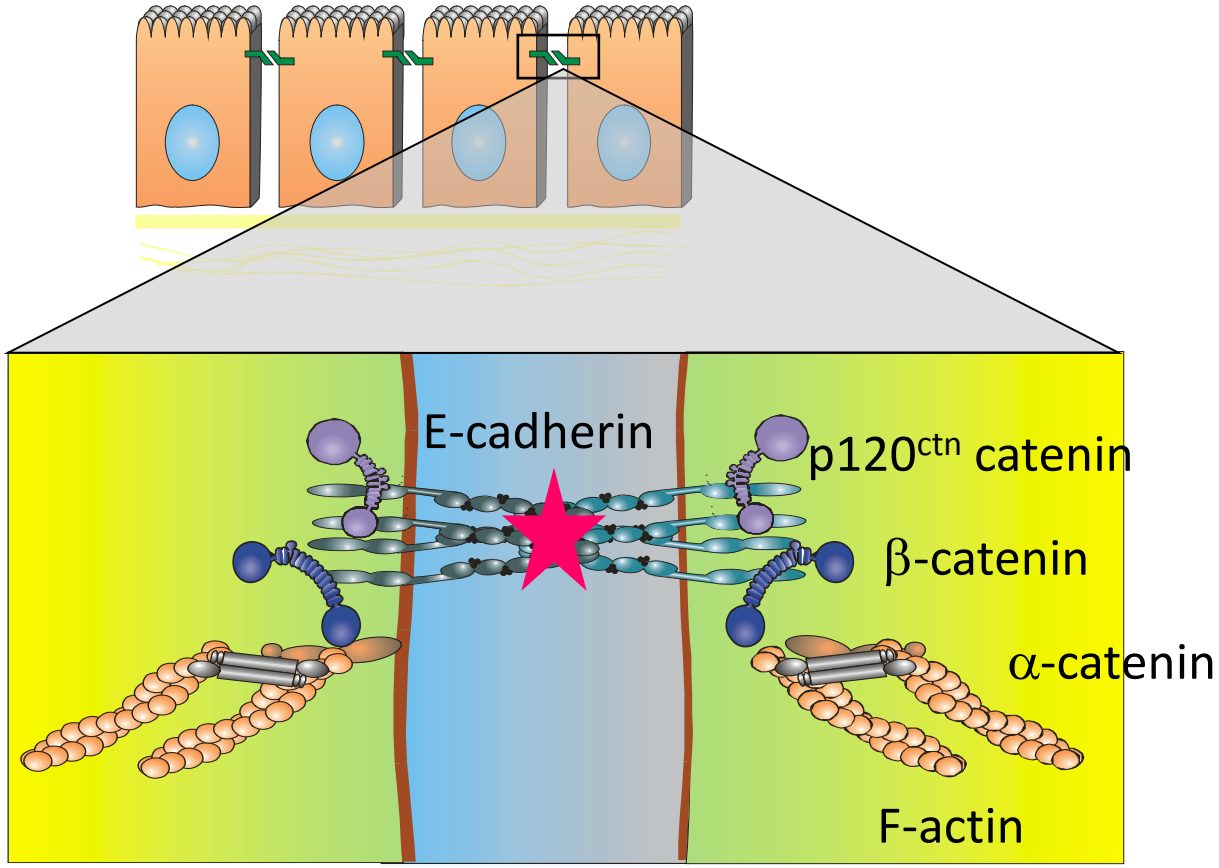
E-cadhérine

Gène: chr 16q22.1 ; gène suppresseur de tumeur

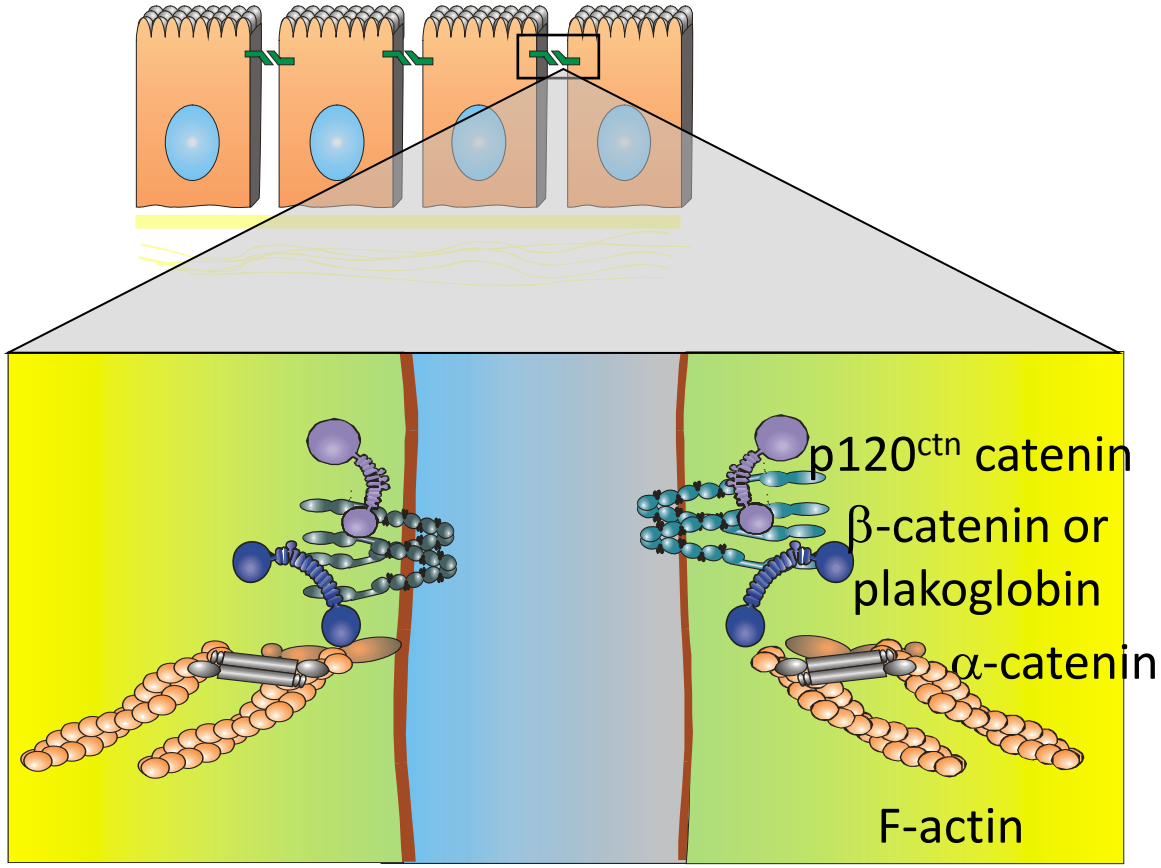
Protéine transmembranaire avec un domaine extracellulaire impliquée dans les jonctions adhérentes



Mutations dans le domaine du gène codant pour la partie extra-cellulaire de la protéine

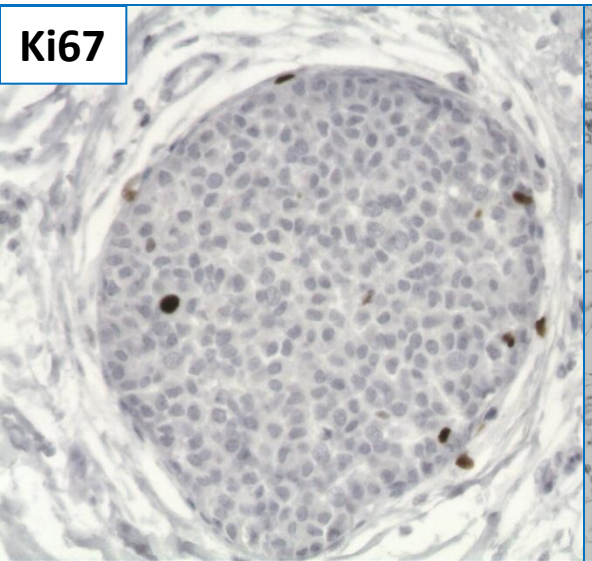


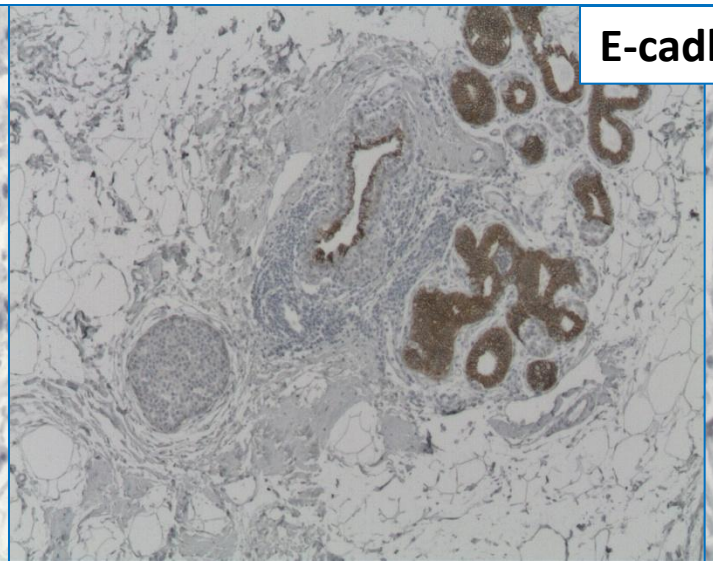
Mutations dans le domaine du gène codant pour la partie extra-cellulaire de la protéine

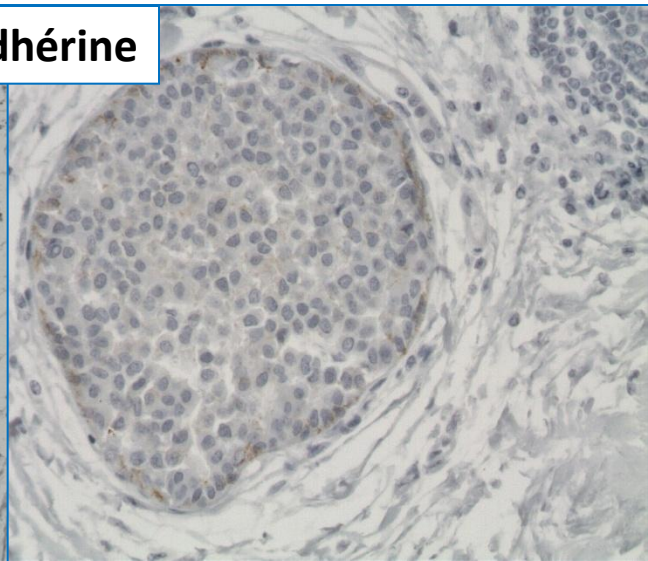


Immunophénotype

- CLIS :
  - Faible prolifération
  - RO +
  - HER2-
  - E-cadhérine (80-90%) -
- CLIS pléomorphe :
  - Prolifération ++
  - RO -/+
  - HER2-/+
  - E-cadhérine (80-90%) -







Altérations génétiques commune entre CLIS et HLA

Communes

- Altérations E-cadhérine
  - Mutation
  - Méthylation du Promoteur
- Pertes du 16q21-q22.1
- Gains du 1q, 14q (*AKT1*), 5q32 (*CSF1R*)

Spécifiques

- HLA :

  2p11+, 7q-, 22q-
- CLIS :

  20q+ and 19q-

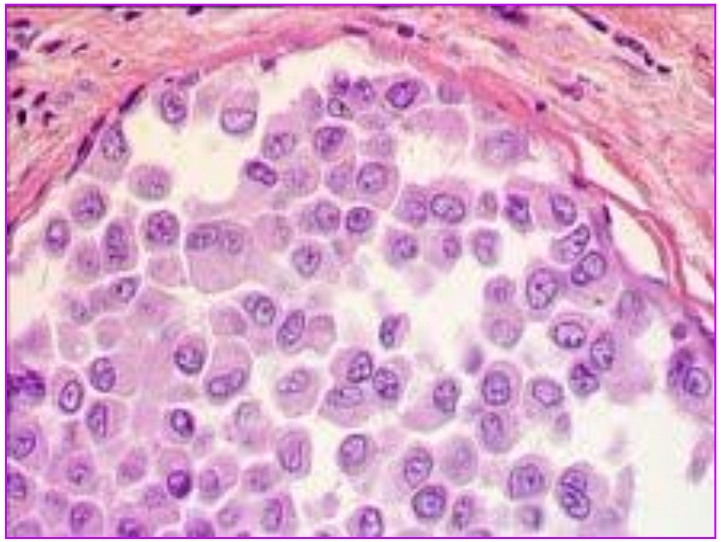
Mastracci *et al* G C &C 2006
Shelley Hwang *et al*, Cancer 2004

CLIS Pléomorphe

The American Journal of Surgical Pathology:
November 2009 - Volume 33 - Issue 11 - pp 1683-1694
doi: 10.1097/PAS.0b013e3181b18a89
Original Articles

Genetic and Phenotypic Characteristics of Pleomorphic Lobular Carcinoma In Situ of the Breast

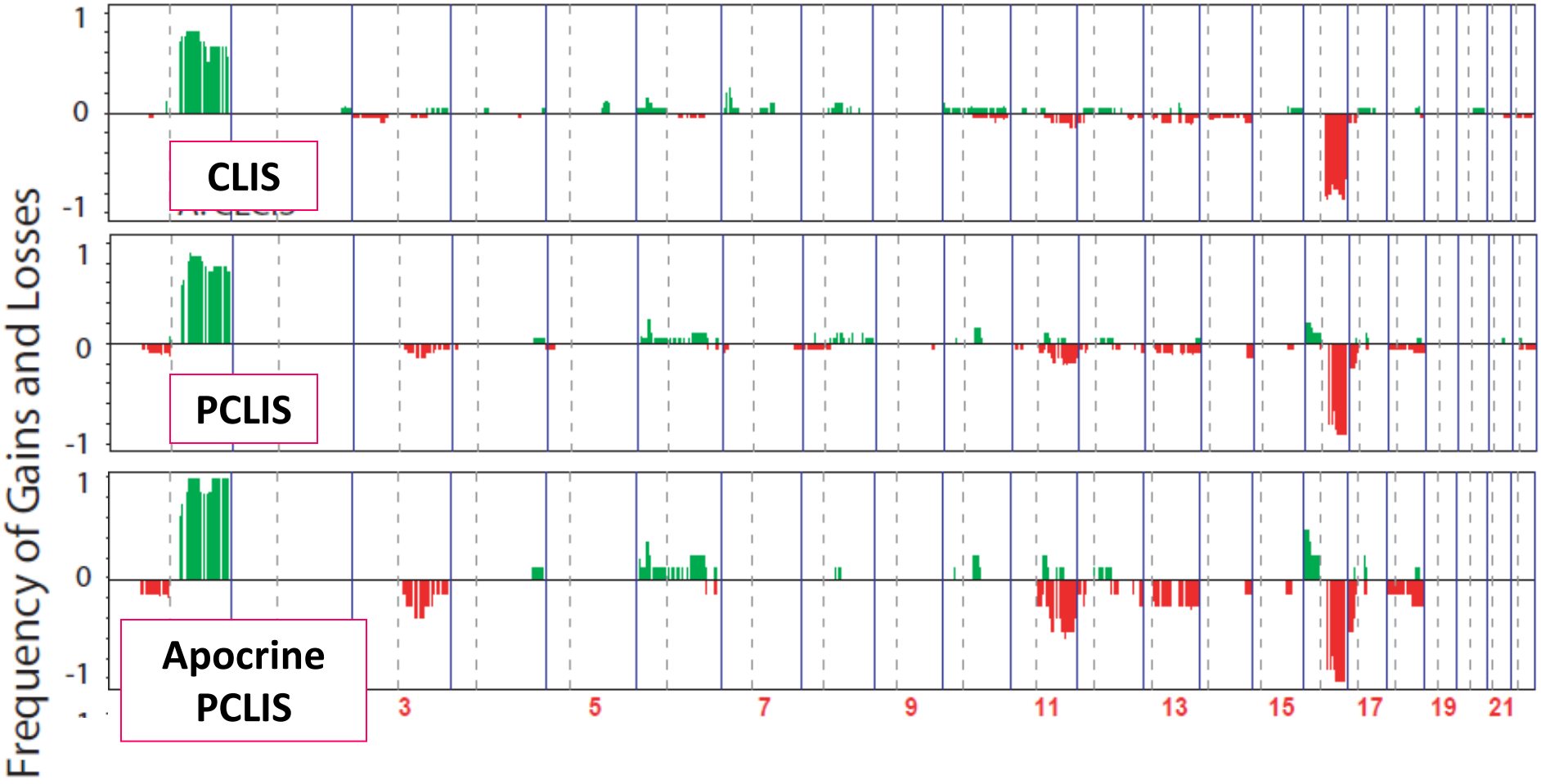
Chen, Yunn-Yi MD, PhD; Hwang, Eun-Sil Shelley MD, MPH; Roy, Ritu MA; DeVries, Sandy MS; Anderson, Joseph MD; Wa, Chrystal BA; Fitzgibbons, Patrick L. MD; Jacobs, Timothy W. MD; MacGrogan, Gaetan MD; Peterse, Hans MD; Vincent-Salomon, Anne MD, PhD; Tokuyasu, Taku PhD; Schnitt, Stuart J. MD; Waldman, Frederic M. MD, PhD



	CLIS classique	CLIS P Non apocrine	CLIS P apocrine
N	24	18	13
Age	50	51	60
Nécrose	0 (0%)	9 (50%)	13 (100%)
E-cadhérine -	21 (100%)	18 (100%)	13 (100%)
GCDFP15 +	ND	7 (50%)	13 (100%)
RO +	21 (100%)	16 (100%)	3 (23%)
RP +	21 (100%)	16 (94%)	2 (17%)
Ki-67 (median)	4.2%	9.9%	13.9%
HER2 (3+)	0 (0%)	0 (0%)	4 (31%)

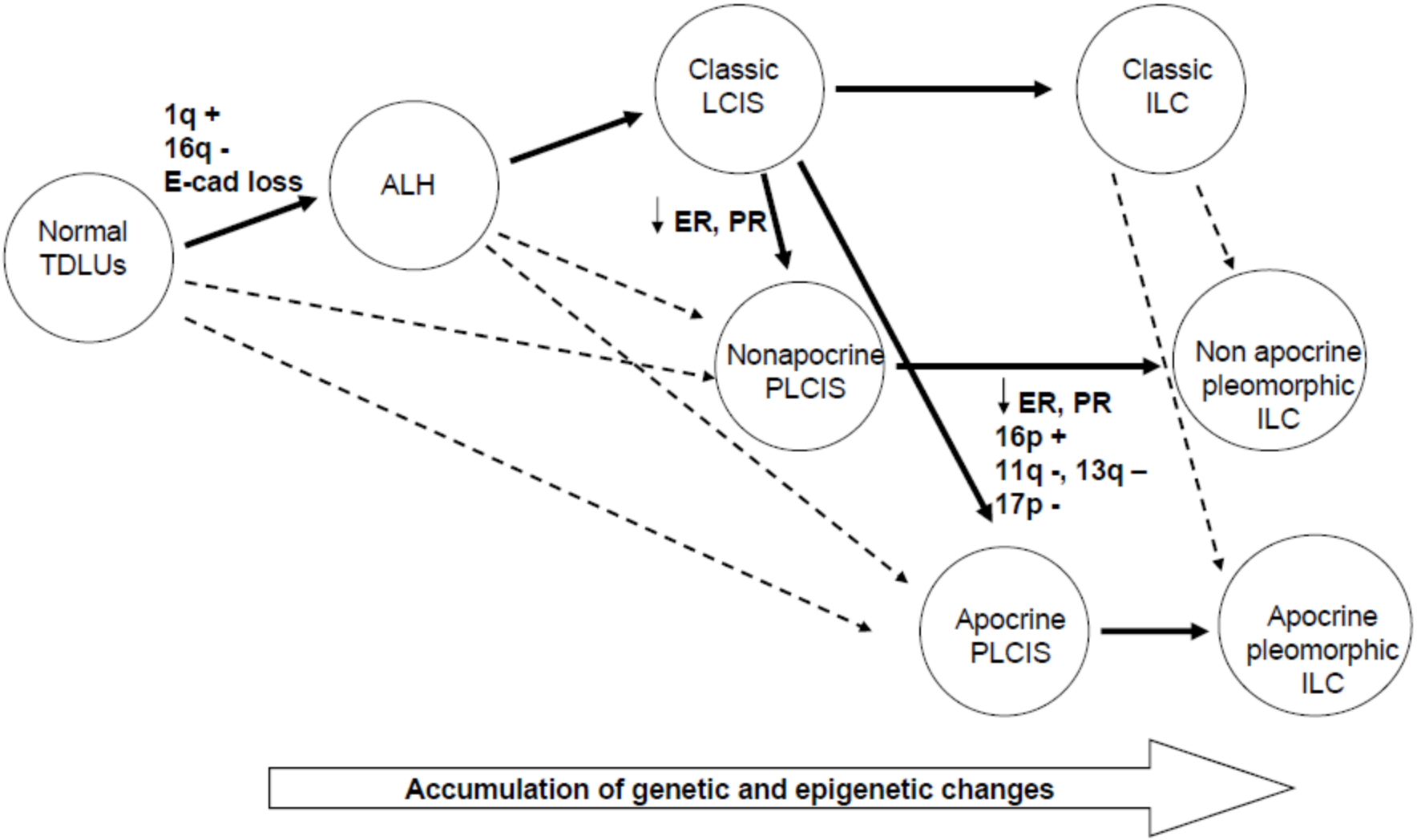
Chen *et al* Am J Surg Path 2009

Profil en CGH des CLIS



Chen *et al* Am J Surg Path 2009

Modèle de carcinogenèse des CLIS



Chen *et al* Am J Surg Path 2009

Analyse transcriptomique des CLIS

- Echantillons congelés rarissimes
- Une étude en 2008 faite sur 1 cas !!!

Validation par immunohistochimie sur 18 CLIS

- Resultats :
  - Claudin 4 “down”régulée
  - MMP9 “up”regulée

Cao *et al,* Br Can Res 2008

Limites

- Pas d'amélioration de la reproductibilité inter-observateur

  Pas de marqueur spécifique

  – HCA // CCIS

  – HLA // CLIS

- Pas d'identification des lésions qui ont un réel potentiel évolutif (CLIS +++)

Perspectives

The Breast 21 (2012) 380–383

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

High Ki67 expression is a risk marker of invasive relapse for classical lobular carcinoma *in situ* patients

Anne Vincent-Salomon [a,b,*], David Hajage [c], Alexandre Rouquette [a], Aurélie Cédenot [a], Nadège Gruel [b], Séverine Alran [d], Xavier Sastre-Garau [a], Brigitte Sigal-Zafrani [a], Alain Fourquet [e], Youlia Kirova [e]

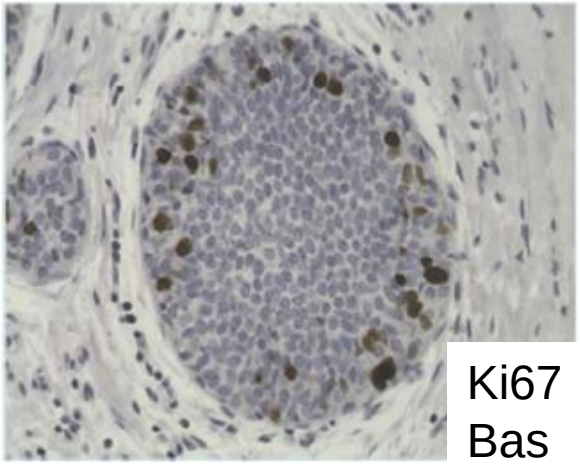
Parameters	No.	%
ER		
+	39	91
−	4	9
NA	1	
PR		
−	29	66
+	15	34
KI67		
> 10% (high)	9	20
≤ 10% (low)	35	80
EGFR		
< 10%	39	89
> 10%	5	11
LCIS sub-groups		
ER+ve KI67 low	30	70
ER+ve KI67 high	9	21
ER−ve PR−ve EGFR+ve	1	2
ER−ve PR+ve	3	7
NA	1	

- 1/34 RO+, KI67 bas
- 4/9 Ki67 haut ont récidivé :

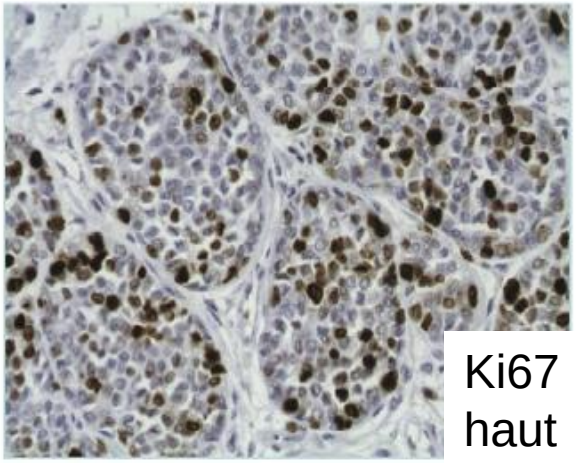
  1 CCIS, 3 infiltrants (2 CCI et 1 CLI)

  (*p = 0.0054*)

  RR= 10.42 (IC 95%: 0.67- 8.08)



Ki67 Bas



Ki67 haut

Perspectives

- Séquençage massif (all exomes)
  - Diminution quantités d'acides nucléiques nécessaires
  - ADN extrait de matériel fixé utilisable

- Analyses des polymorphismes constitutionels associés à des maladies du sein particulières
    - Grande cohorte de patientes porteuses d'HCA et de MCA
    - Consentement
    - Prise de sang
    - Suivi clinique
        - » Dans le contexte médico-économique actuel est-ce réaliste ?