La « Saga débutante » des mutations activatrices dans ESR1

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GERM le 29/01/2014

Avant d'oublier…

- Tous mes vœux pour cette nouvelle année!

nature genetics

Activating *ESR1* mutations in hormone-resistant metastatic breast cancer

Dan R Robinson[1,2,12], Yi-Mi Wu[1,2,12], Pankaj Vats[1,2], Fengyun Su[1,2], Robert J Lonigro[1,
Shanker Kalyana-Sundaram[1,2], Rui Wang[1,2], Yu Ning[1,2], Lynda Hodges[1], Amy Gursky[1,
Scott A Tomlins[1,2], Sameek Roychowdhury[5], Kenneth J Pienta[6], Scott Y Kim[7], J Scott R
Catherine H Van Poznak[9], Daniel F Hayes[9], Rashmi Chugh[9], Lakshmi P Kunju[1,2], Mosl
Anne F Schott[9] & Arul M Chinnaiyan[1–4,10,11]

nature genetics

ESR1 ligand-binding domain mutations in hormone-resistant breast cancer

Weiyi Toy[1], Yang Shen[2], Helen Won[1], Bradley Green[3], Rita A Sakr[4], Marie Will[5], Zhiqiang Li[1], Kinisha Gala[1], Sean Fanning[3], Tari A King[4], Clifford Hudis[5,6], David Chen[7], Tetiana Taran[7], Gabriel Hortobagyi[8], Geoffrey Greene[3], Michael Berger[1,9], José Baselga[1,5] & Sarat Chandarlapaty[1,5,6]

Priority Report

Cancer Research

D538G Mutation in Estrogen Receptor-α: A Novel Mechanism for Acquired Endocrine Resistance in Breast Cancer

Keren Merenbakh-Lamin[1,2], Noa Ben-Baruch[5], Adva Yeheskel[3], Addie Dvir[6], [illegible]
Rinath Jeselsohn[8], Roman Yelensky[9], Myles Brown[8], Vincent A. Miller[9], Davi[illegible]
Baruch Klein[4], Tami Rubinek[1], and Ido Wolf[1,2]

Clinical Cancer Research

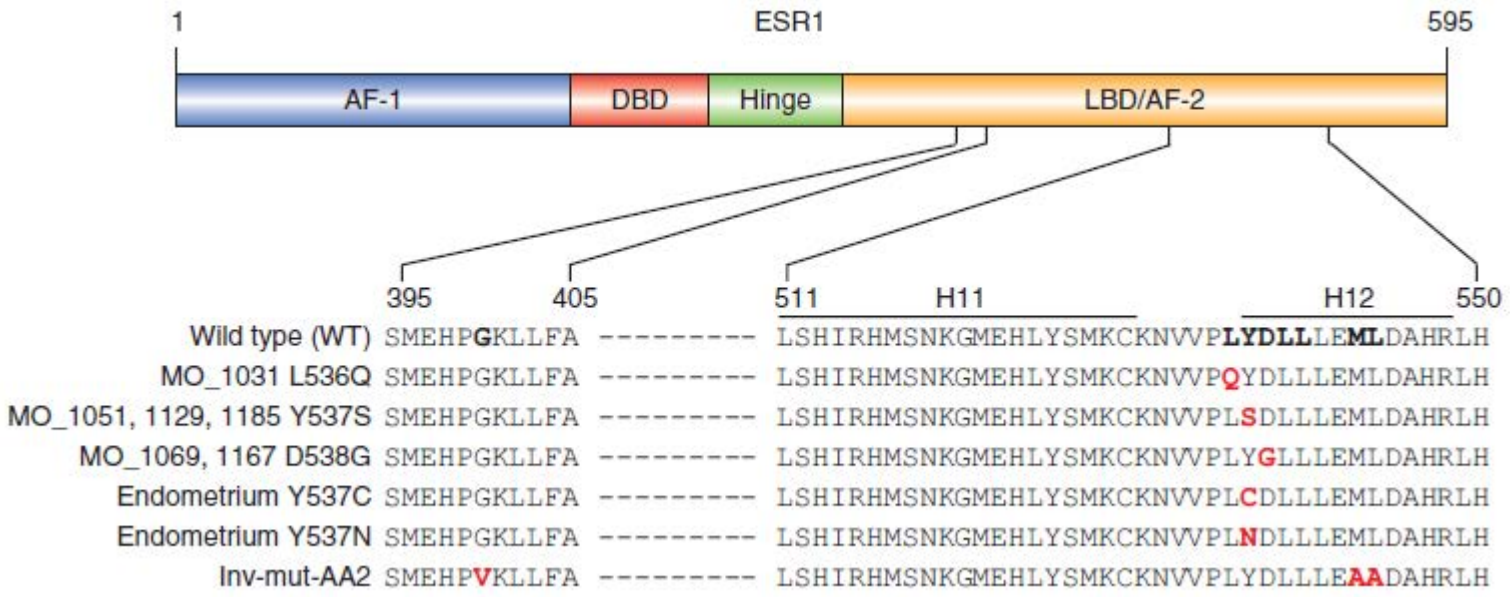
AACR

Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor positive breast cancer

Rinath Jeselsohn, Roman Yelensky, Gilles Buchwalter, et al.

Clin Cancer Res Published OnlineFirst January 7, 2014.

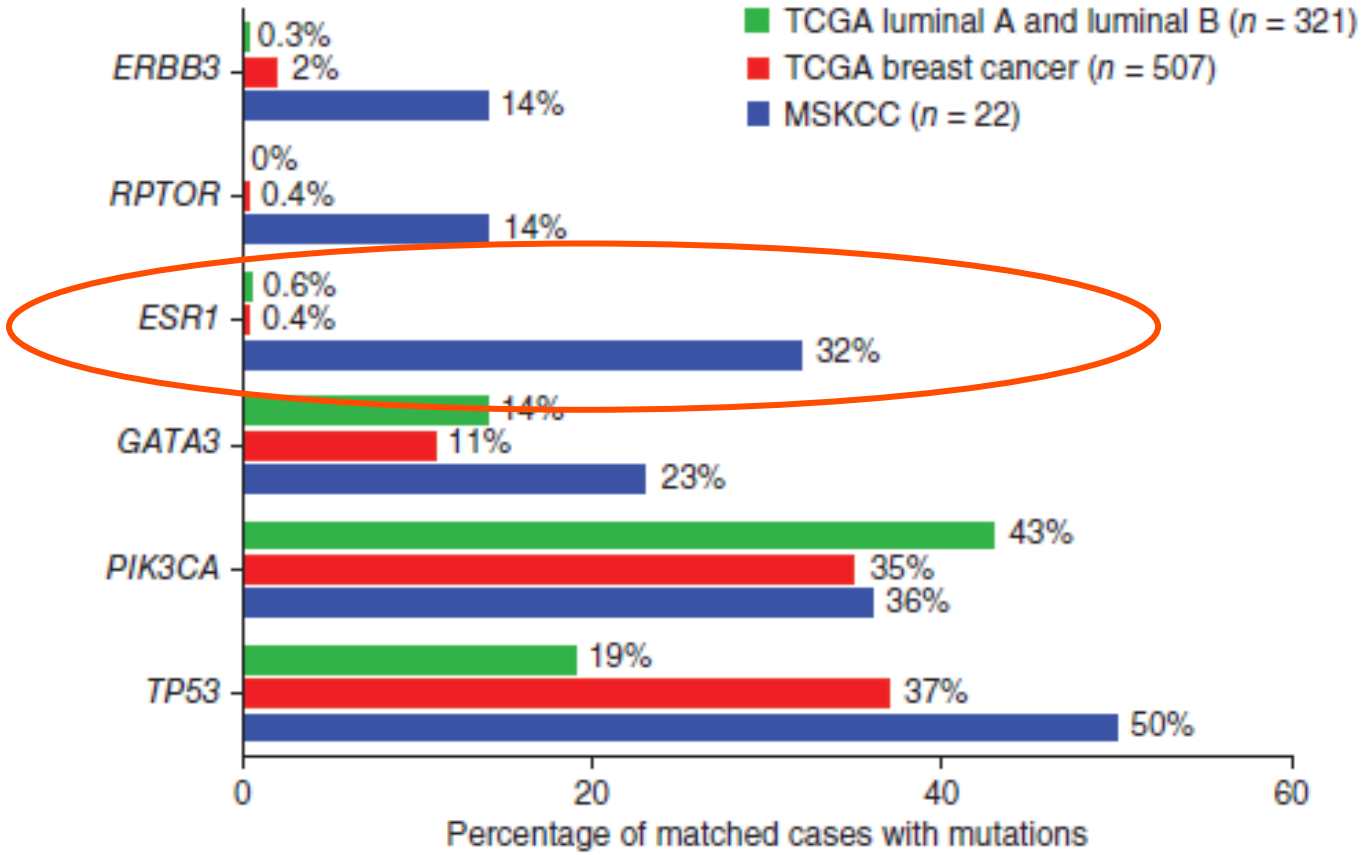
Apparition de mutations dans le gène ESR1



Mutations dans le domaine de liaison au ligand

Robinson et al, Nat Genet 2013, Toy et al, Nat Genet 2013
Merenbakh-Lamin Can Res 2013,jehelson et al , Clin Can Res 2014 sous press

Apparition sous hormonothérapie: mutations acquises

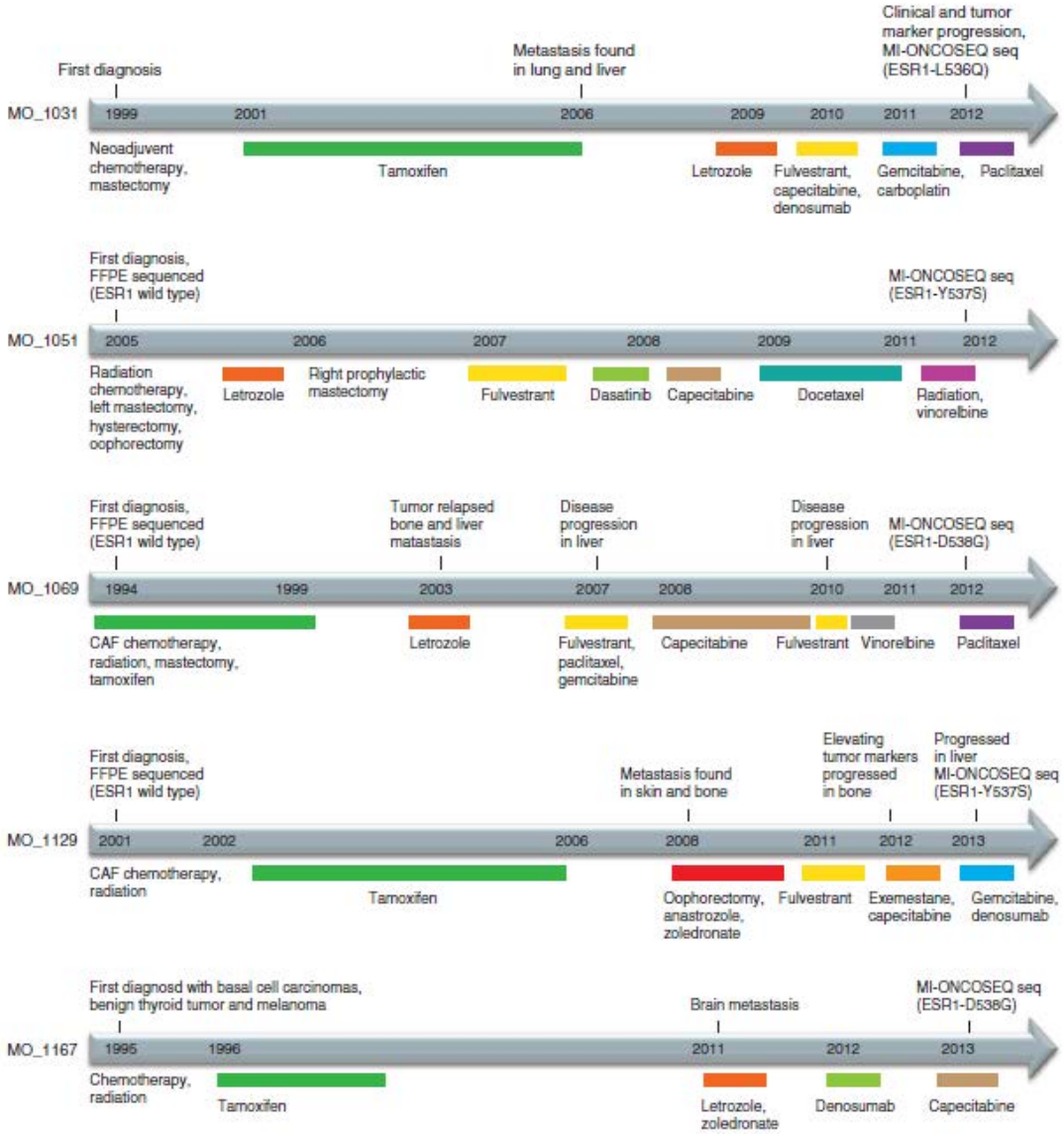


Analyses TCGA faites sur tumeurs primitives,

MSKCC sur lésions métastatiques.

Toy et al, Nat Genet 2013

Apparition sous hormonothérapie: mutations acquises



Robinson et al, Nat Genet 2013

Apparition sous hormonothérapie: Exposition prolongée

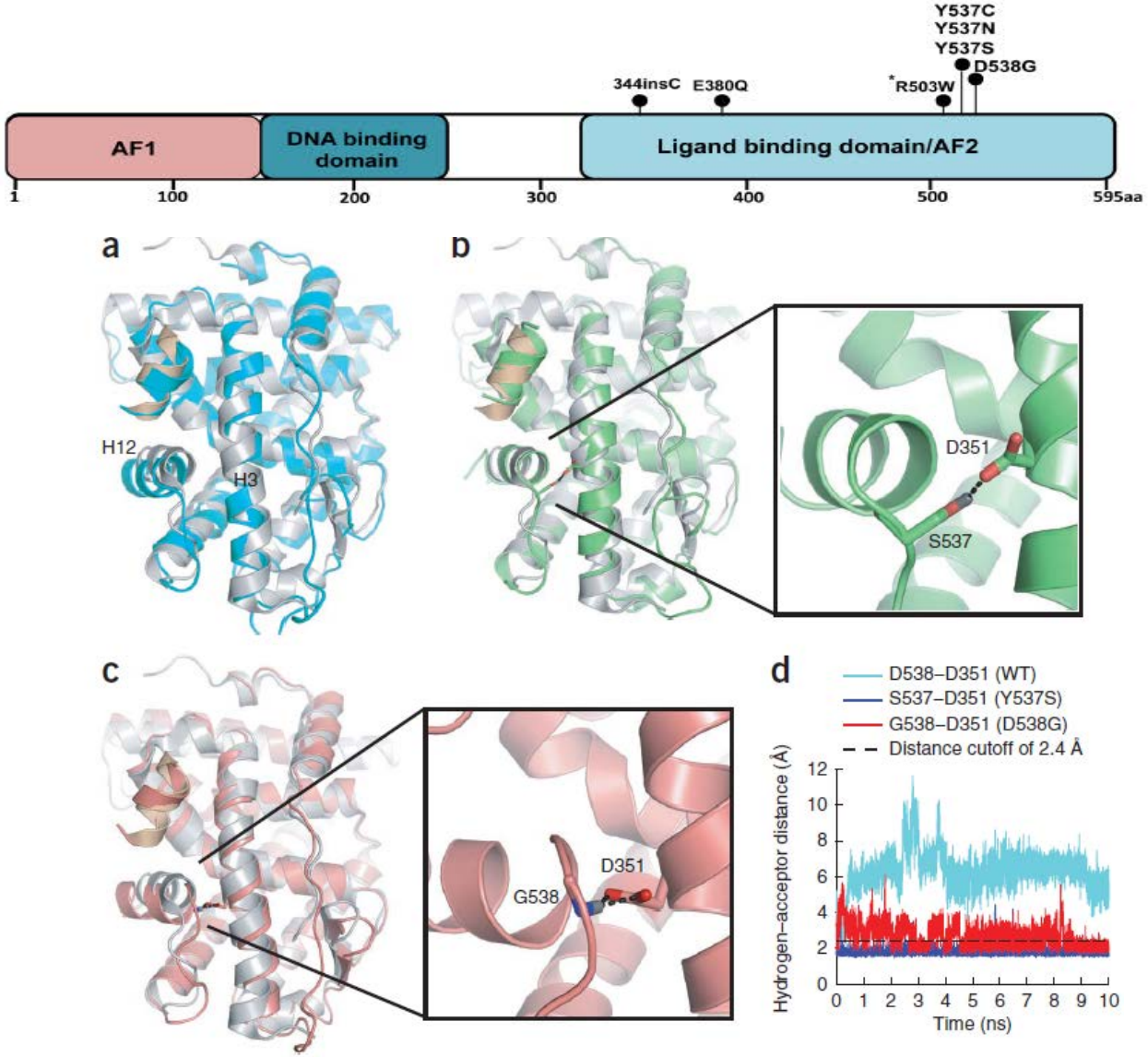
Case	*ESR1*-encoded alteration	Primary tumor	Mutation frequency	Duration of hormonal therapies (years)	Types of hormonal therapies given
1	p.Tyr537Ser	WT	0.528	2.5	AI, SERM
2	p.Asp538Gly	WT	0.285	6.5	AI, SERM
3	p.Ser463Pro/p.Asp538Gly	N/A	0.122/0.280	7.5	AI, SERM
4	p.Tyr537Ser/p.Asp538Gly	N/A	0.082/0.103	3.3	AI, SERD, SERM
5	p.Leu536Arg	N/A	0.114	10.0	AI, SERM
6	p.Val534Glu	N/A	0.056	5.5	AI, SERD
7	p.Tyr537Asn	N/A	0.839	5.5	AI, SERM
8	p.Tyr537Ser	N/A	0.253	1.5	AI, SERD
9	p.Tyr537Ser	N/A	0.265	2.0	AI, SERM, SERD

Table 2 *ESR1* mutations in metastatic samples from the BOLERO-2 clinical trial

Case	*ESR1*-encoded alteration	Mutation frequency	Duration of aromatase inhibitor therapy (years)	Affected ER domain
1	p.Ser463Pro/p.Tyr537Asn	0.18/0.10	2.0	LBD/AF-2
2	p.Pro535His	0.22	5.0	LBD/AF-2
3	p.Tyr537Cys	0.75	3.0	LBD/AF-2
4	p.Tyr537Ser	0.09	5.0	LBD/AF-2
5	p.Asp538Gly	0.13	6.0	LBD/AF-2

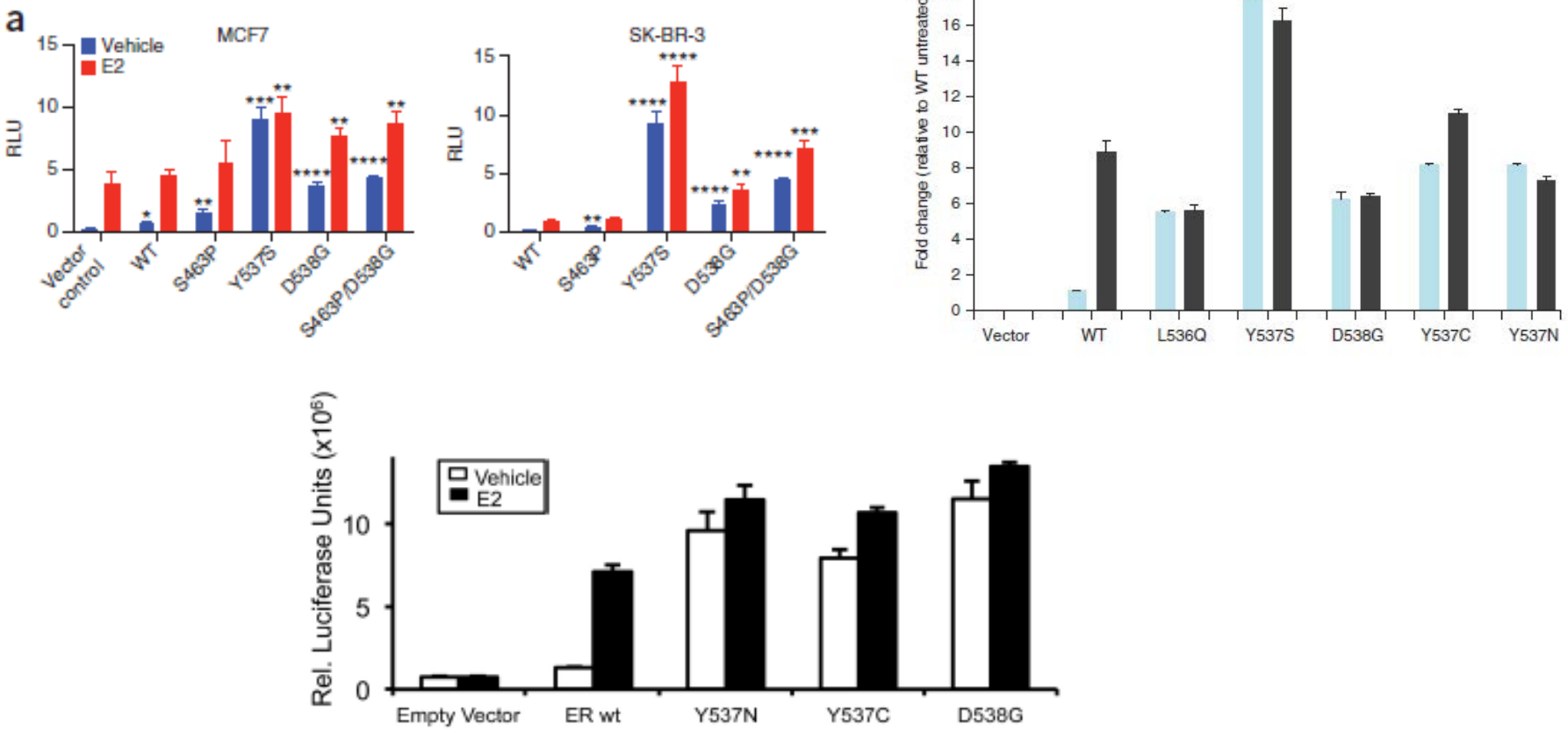
20% sur l'ensemble des deux cohortes

Modifications structurales



Toy et al, Nat Genet 2013,

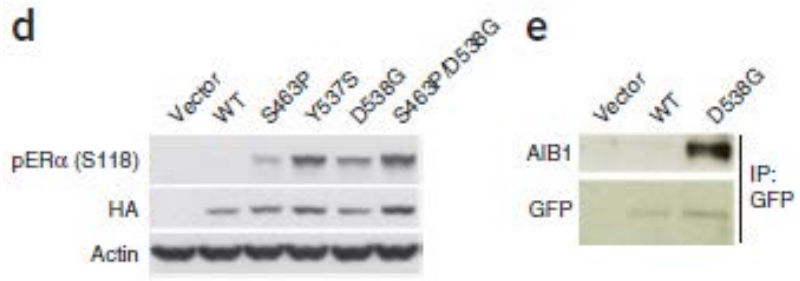
Activation indépendante du ligand ; mutation activatrice



Activité en Absence d'œstradiol

Toy et al, Roberson et al Nat Genet 2013

Activation indépendante du ligand ; mutation activatrice

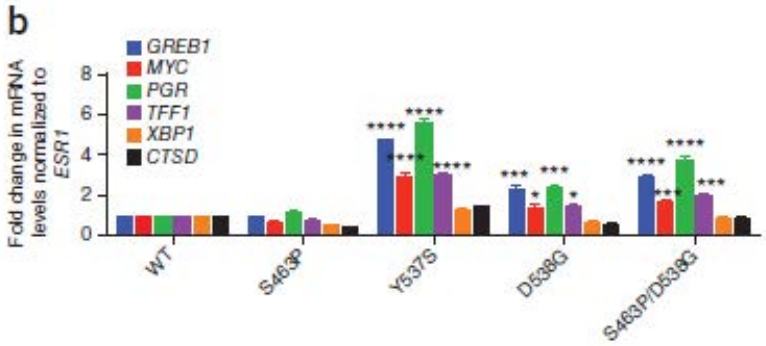


Ser118 phosphorylée IP cofacteur « assemblé »

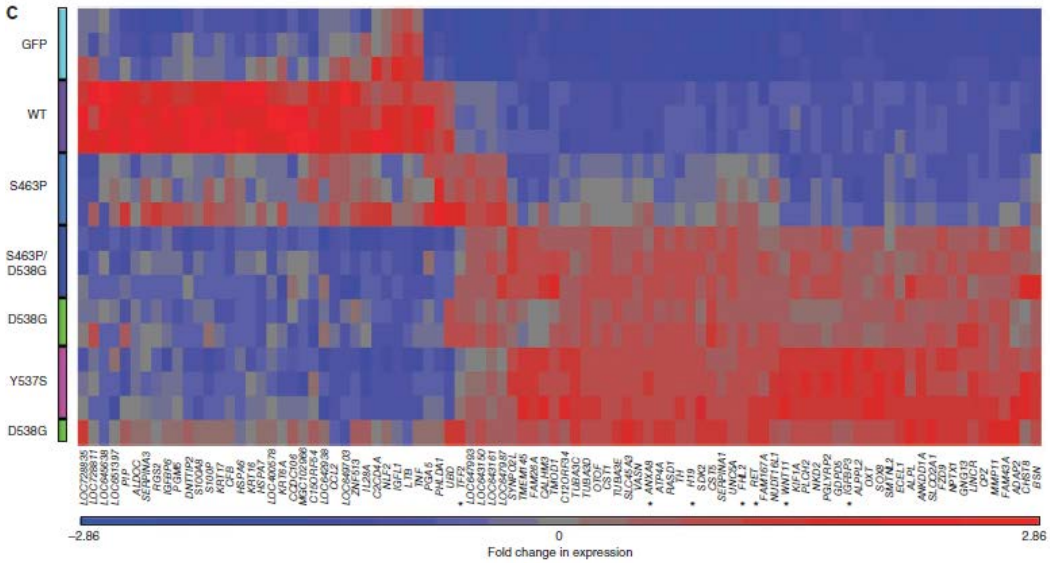
Ne nécessiterait plus de Chaperone HSP90

Toy et al, Nat Genet 2013

Activité transcriptionnelle



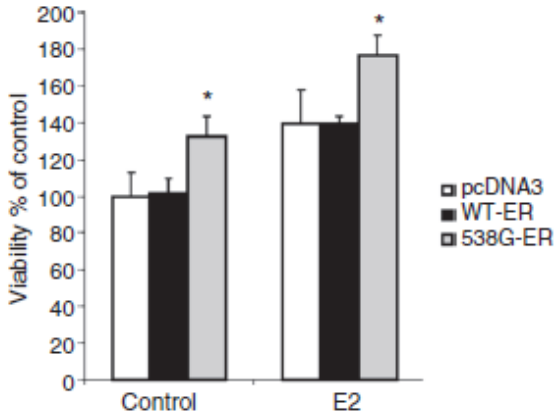
Transcription de gènes cibles ERE

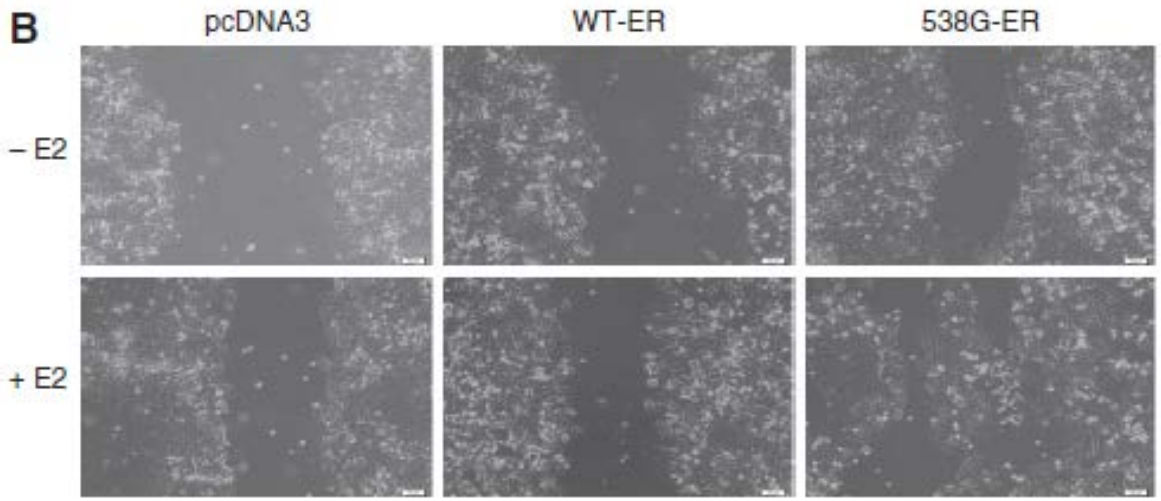


Mais pas seulement…

Toy et al, Nat Genet 2013,

Activation indépendante du ligand ; mutation activatrice

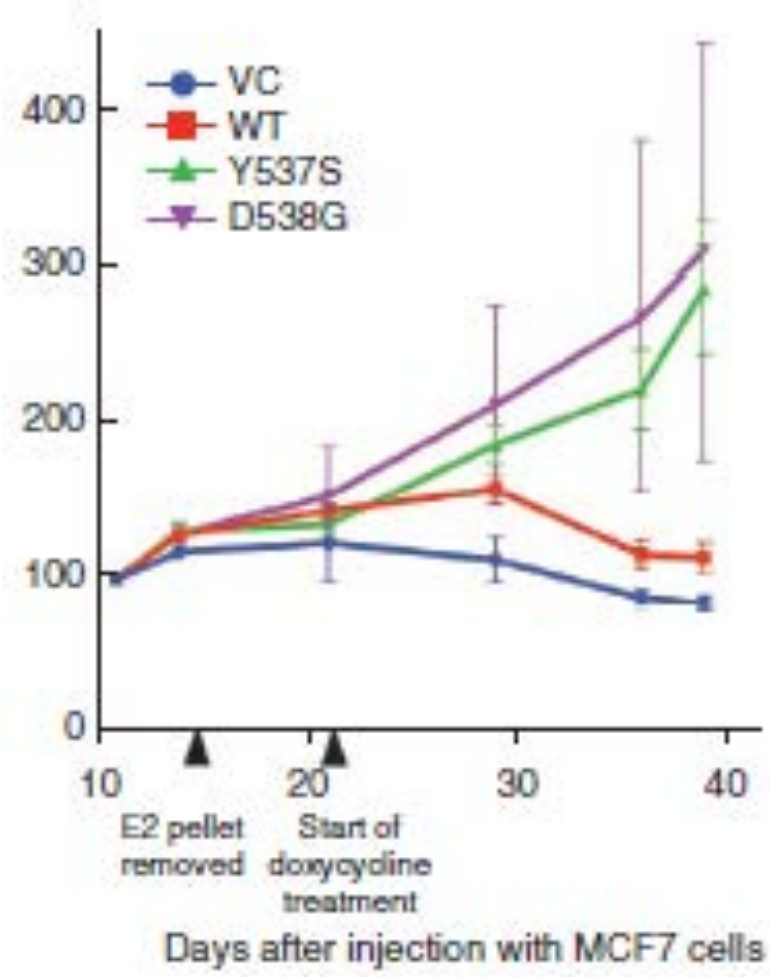




mut D538G augmente la viabilité (MTT) et la migration (scrap test) des MCF7

Merenbakh-lamin et al, Can Res 2013

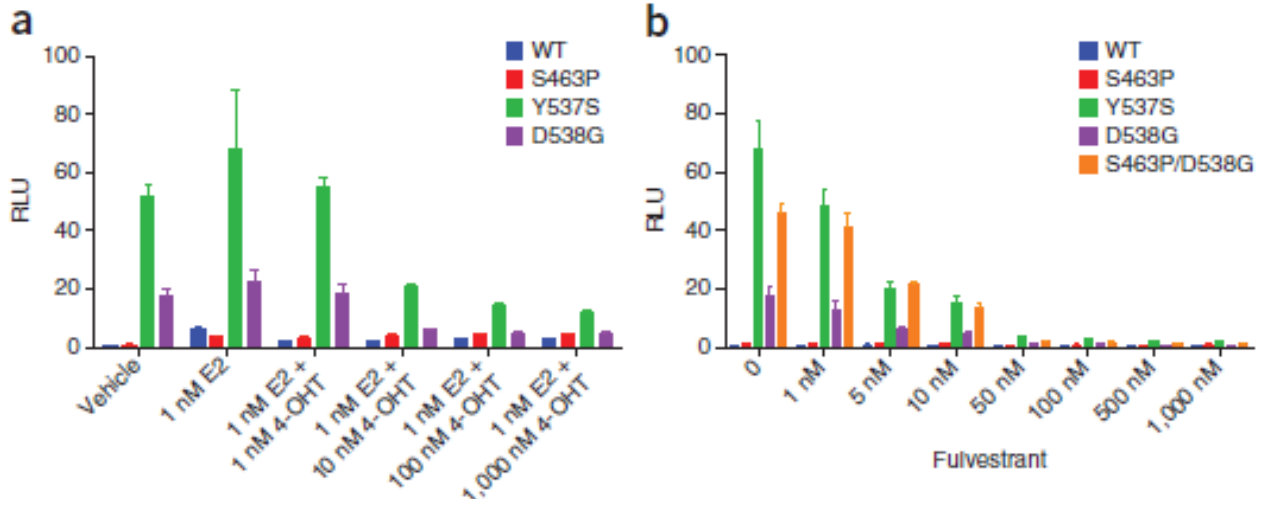
Croissance tumorale Indépendante du ligand *in vivo*

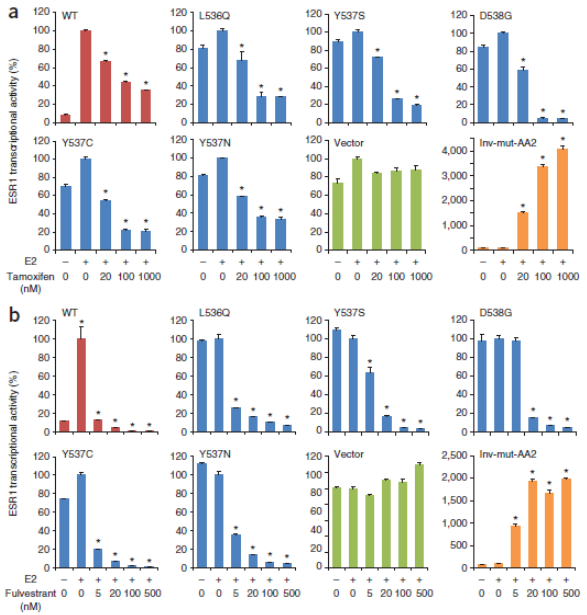


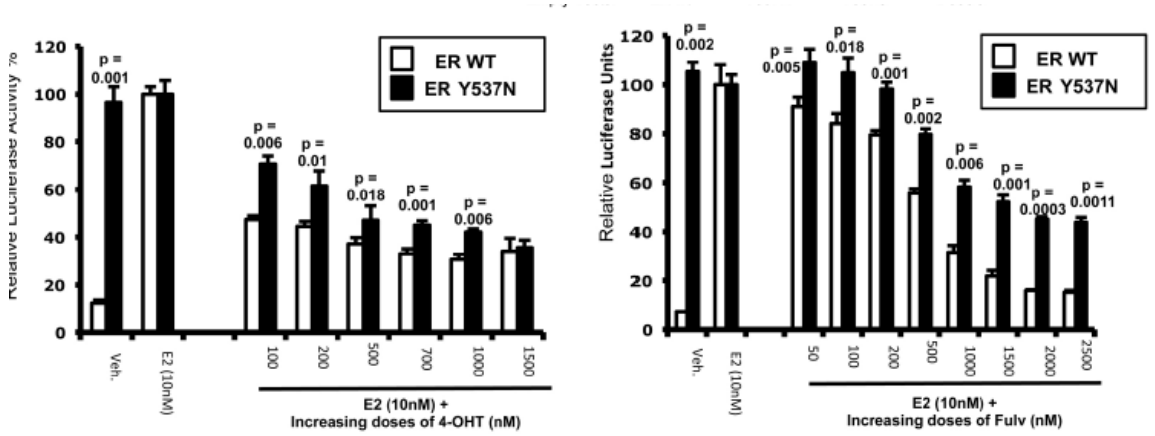
Xénogreffe modèle murin; après déprivation hormonale et mutation des récepteurs inductibles (Tet on)

Toy et al, Nat Genet 2013

Sensibilité partielle au Tamoxifène et au Fulvestrant







Toy et al, Robinson et al Nat Genet 2013
Jeselsohn clin can res 2014

Anomalies moléculaires associées

Case	Age (years)	ER/PR/ERBB2	Treatment[a]	Number of SNVs/fusions	Genetic aberration[b]
MO_1031	41	+/+/–	Tamoxifen, letrozole, fulvestrant	266/18	*ESR1* (p.Leu536Gln), gene copy gains of *FGFR1*, *FGFR2*, *CCND1* and *GNRHR*
MO_1051	31	+/–/–	Oophorectomy, letrozole, fulvestrant	248/5	*ESR1* (p.Tyr537Ser), *PIK3CA* (p.His1047Arg), *TP53* (p.Gly199Glu), *FGFR2-AFF3* fusion
MO_1069	62	+/+/–	Tamoxifen, letrozole, fulvestrant	74/9	*ESR1* (p.Asp538Gly), *ARID2* (p.Glu245*), gene copy losses of *TP53*, *BRCA1*, *RB1*, *ARID1A* and *SMARCA4*
MO_1129	44	+/+/–	Tamoxifen, oophorectomy, anastrozole, fulvestrant, exemestane	32/3	*ESR1* (p.Tyr537Ser), *PIK3CA* (p.Glu542Lys), gene copy gains of *CCND1* and *PAK1*
MO_1030	78	+/+/–	Tamoxifen (short), anastrozole, fulvestrant	26/2	*PIK3CA* (p.Glu545Ala), *TP53* copy loss
MO_1068	65	+/–/–	Tamoxifen, anastrozole	83/10	*PIK3CA* (p.His1047Arg), *TP53* (p.Glu51*), *MSH2* copy loss
MO_1090	52	+/+/–	Tamoxifen, anastrozole	28/11	No significant drivers identified
MO_1107	46	+/+/–	Tamoxifen, oophorectomy, anastrozole, fulvestrant, exemestane	63/12	*BRCA1* (c.5385_5386insC), frameshift deletions in *TP53*, *SMARCA4* and *NF1*
MO_1167	60	+/–/–	Tamoxifen, letrozole	47/3	*ESR1* (p.Asp538Gly)
MO_1185	58	+/+/–	Tamoxifen, letrozole, fulvestrant, exemestane	88/1	*ESR1* (p.Tyr537Ser), *CDH1* (p.Gln641*), *NOTCH2* (frameshift deletion), *TP53* copy loss
TP_2004[c]	52	+/–/–	Tamoxifen (short)	29/22	*MDM2* gene amplification, gene copy losses of *CDKN2A* and *CDKN2B*

En conclusion; questions ouvertes

1. Traduction en clinique?

2. Détection du Adn libre circulant?

3. Apparition de mutations (dont ESR1) après progression sous Hormonothérapie (surtout IA).
   - Qui fait quoi? (mut PI3K, Ampl FGFR1… impliqués dans l'hormonorésistance)
   - Facteur prédictif d'échec?
   - Indication à Combinaison ?
     - Hormonothérapie (plutôt Tamoxifène ou Fulvestrant) +thérapie ciblée?

Merci pour votre attention

Si vous souhaitez les articles

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