PATHOLOGIES DE LA CROISSANCE FŒTALE : ANOMALIES MOLECULAIRES DANS LES SYNDROMES DE BECKWITH WIEDEMANN ET SILVER RUSSELL

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CONTRÔLE DE LA CROISSANCE FŒTALE

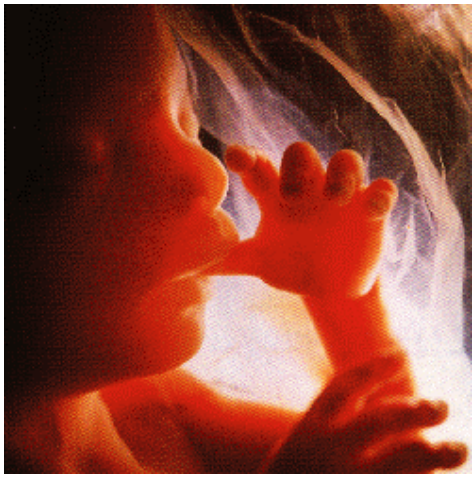
Facteurs génétiques

Facteurs environnementaux

Nutrition

Toxiques

Infections



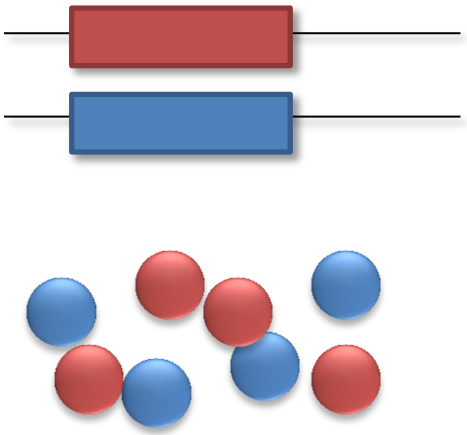
Facteurs endocriniens

Syst. des IGF

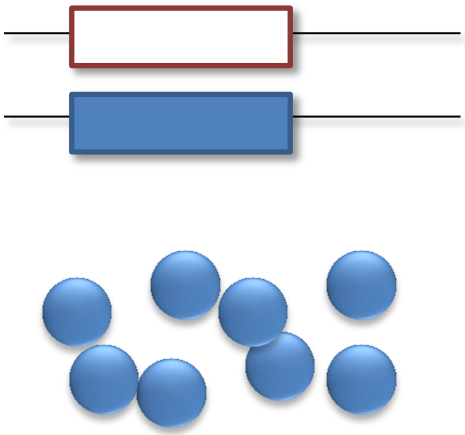
Insuline…

EMPREINTE PARENTALE : DÉFINITION

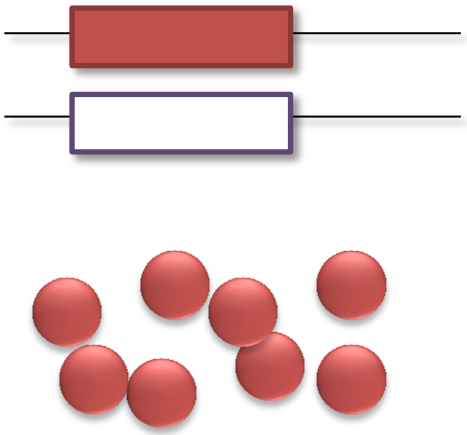
> Expression différentielle d'un gène en fonction de son origine parentale



Expression biallélique



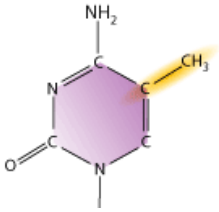
Empreinte maternelle

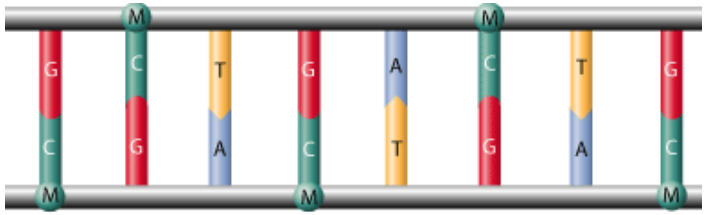


Empreinte paternelle

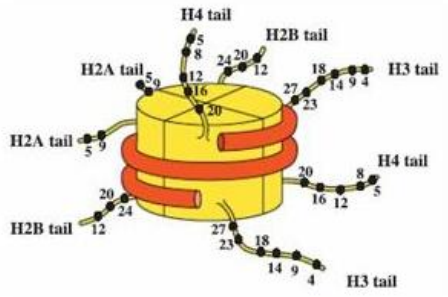
L'EMPREINTE : MODÈLE DE RÉGULATION ÉPIGÉNÉTIQUE

> Méthylation de l'ADN

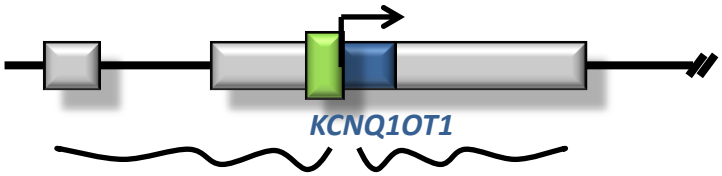




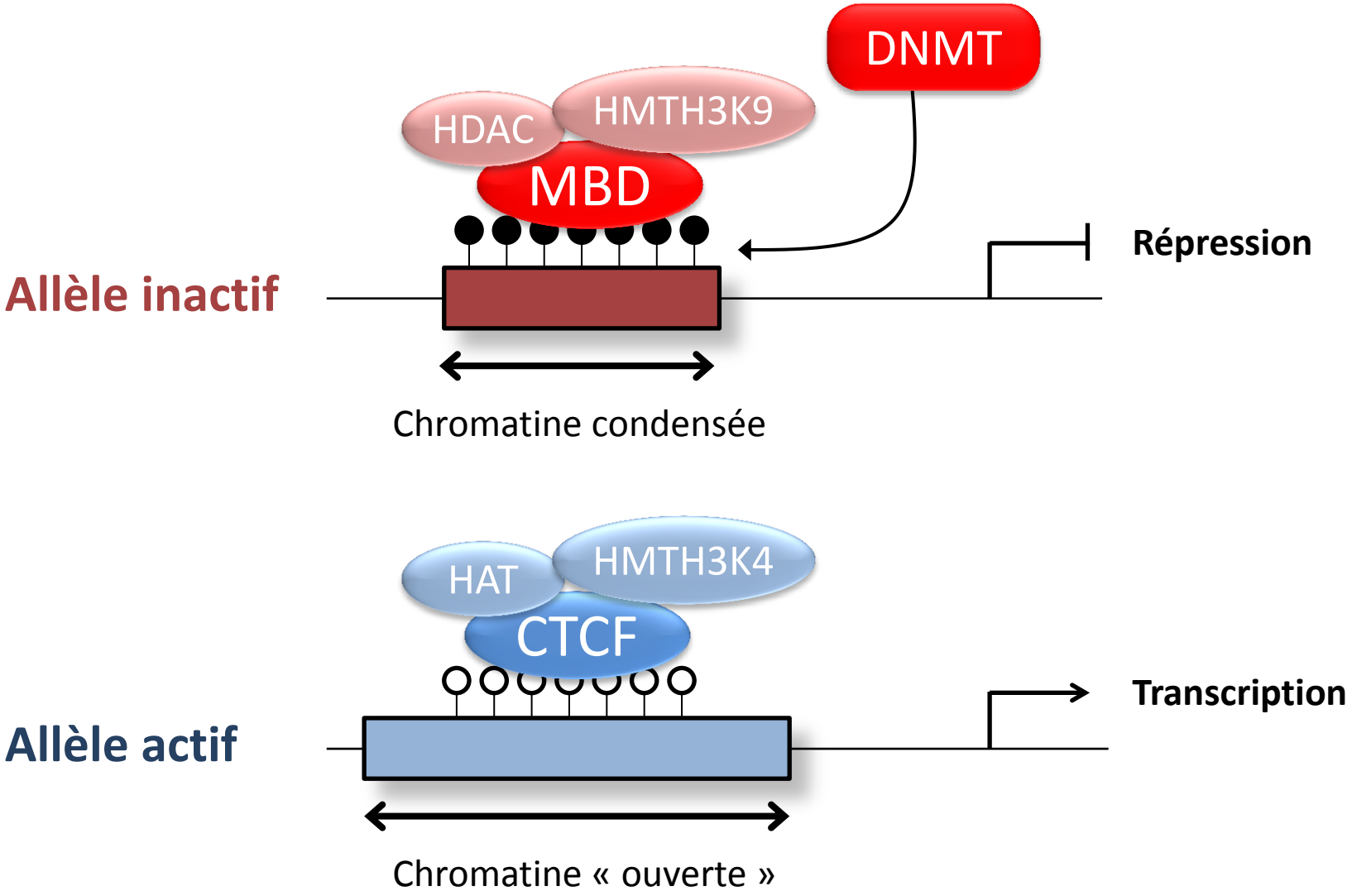
> Modification des histones



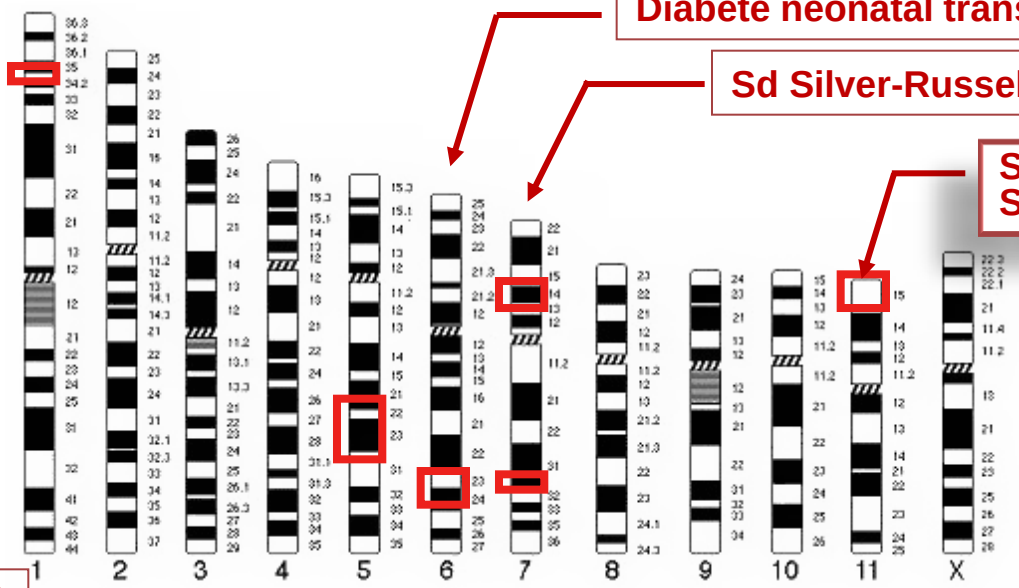
> Longs ARN non codants

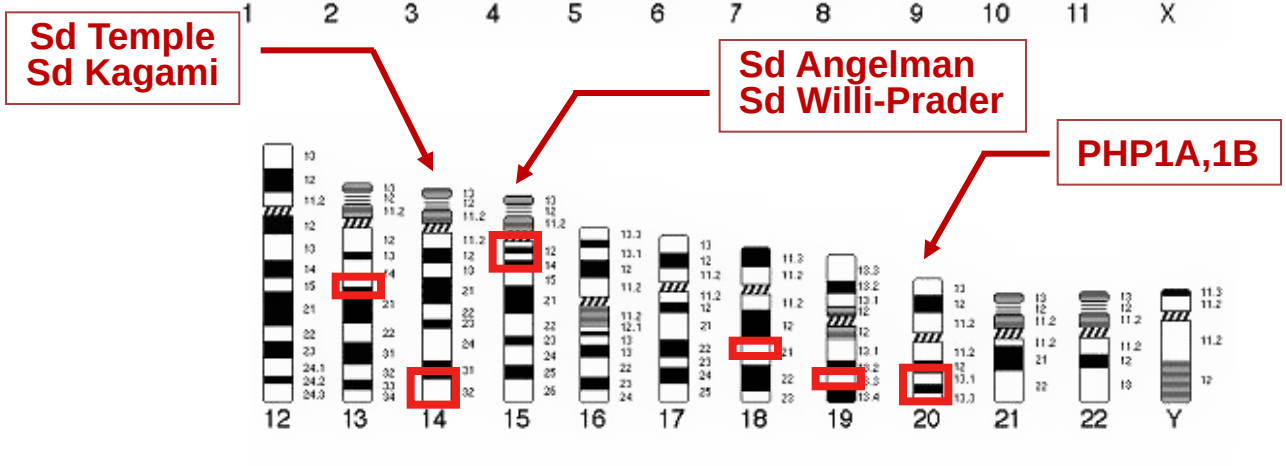


RÉGULATION ÉPIGÉNÉTIQUE DE L'EXPRESSION DES GÈNES



RÉGIONS SOUMISES À EMPREINTE

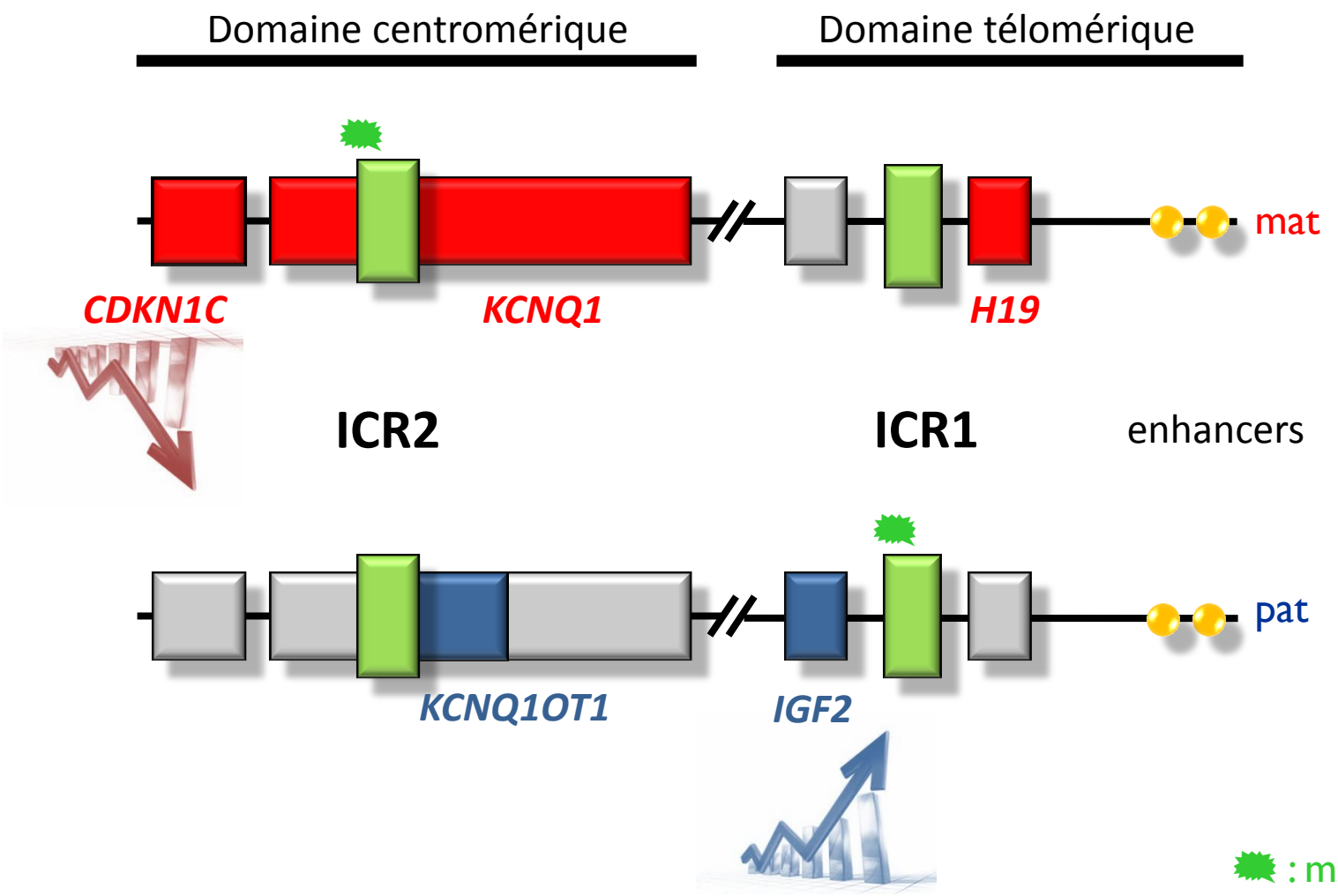




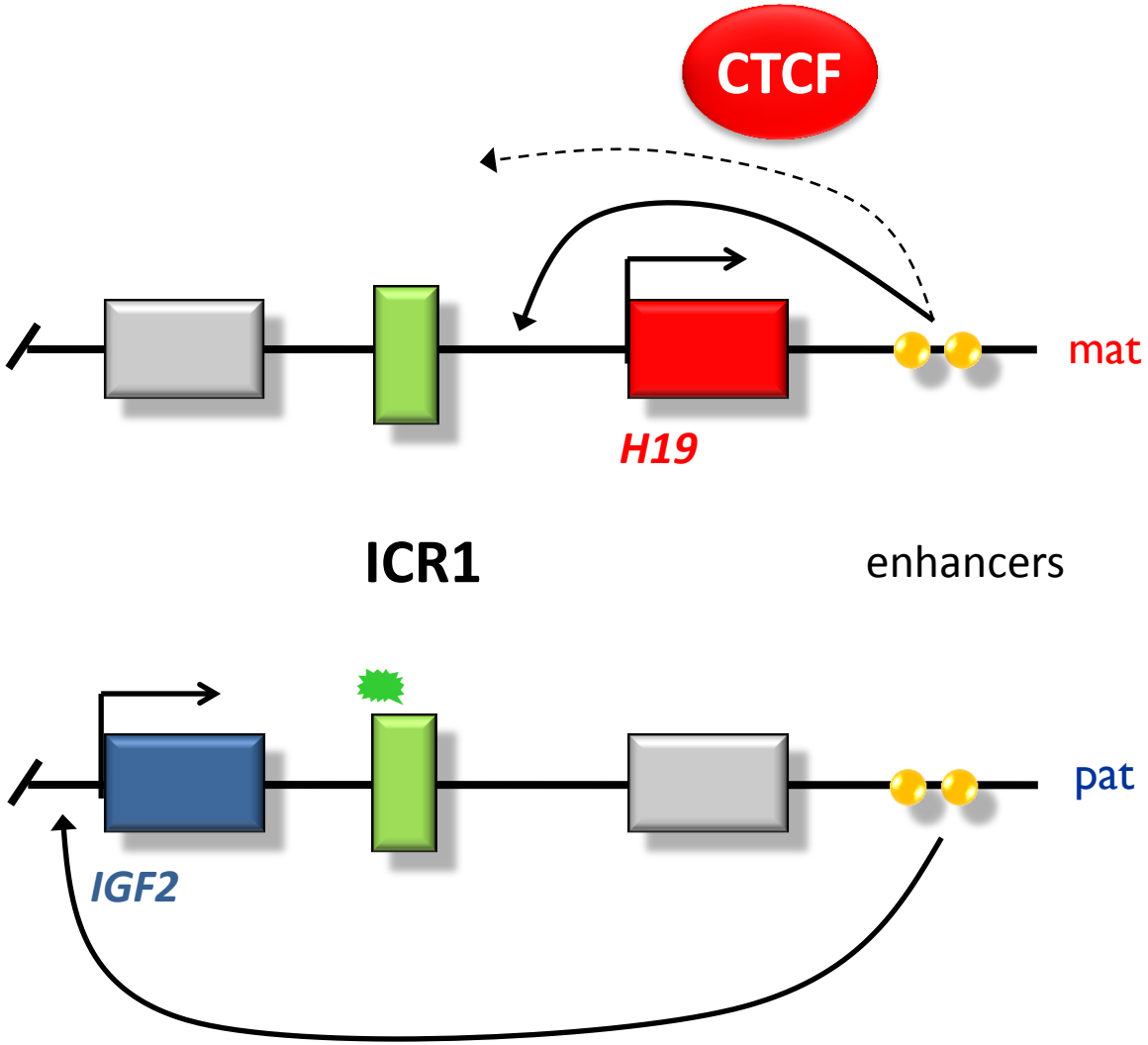
Mécanismes :

- > Duplication/délétion
- > Mutations
- > Disomies uniparentales
- > Perte/gain de méthylation

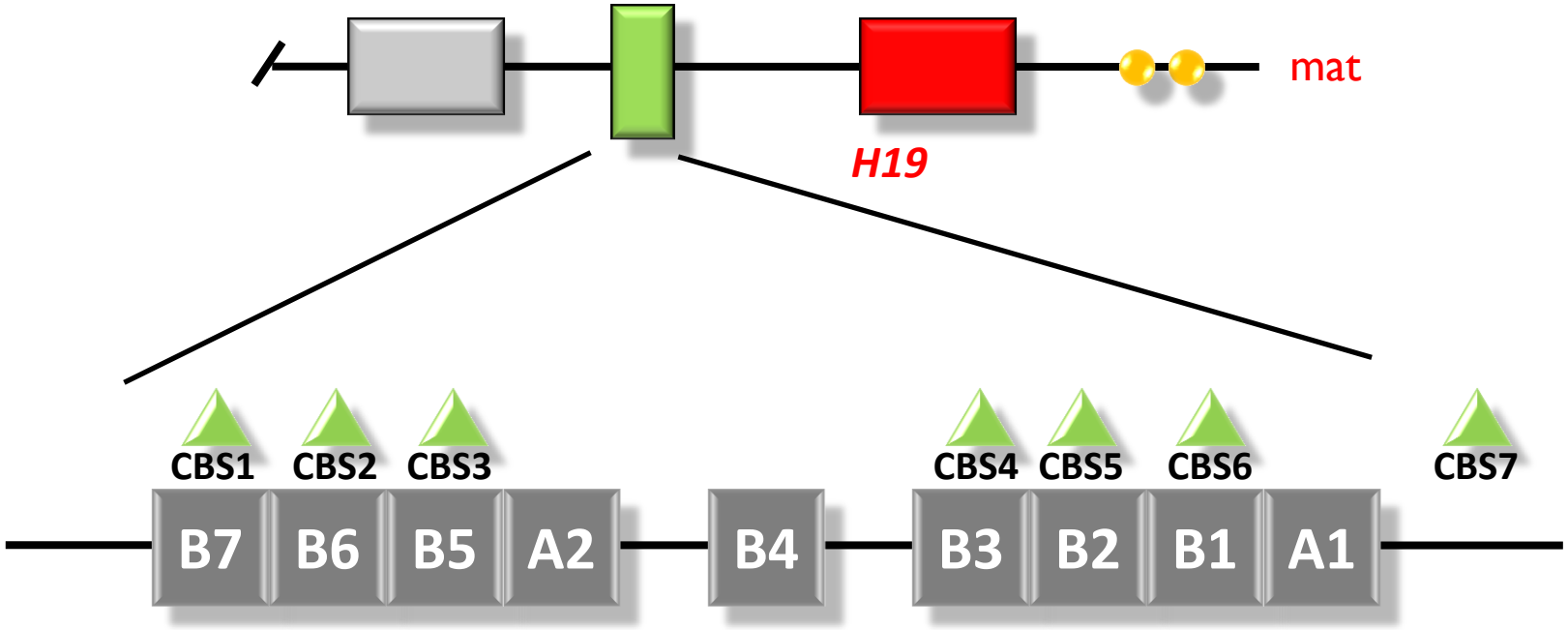
La région 11p15 contient des gènes soumis à empreinte



RÉGULATION DU DOMAINE TÉLOMÉRIQUE



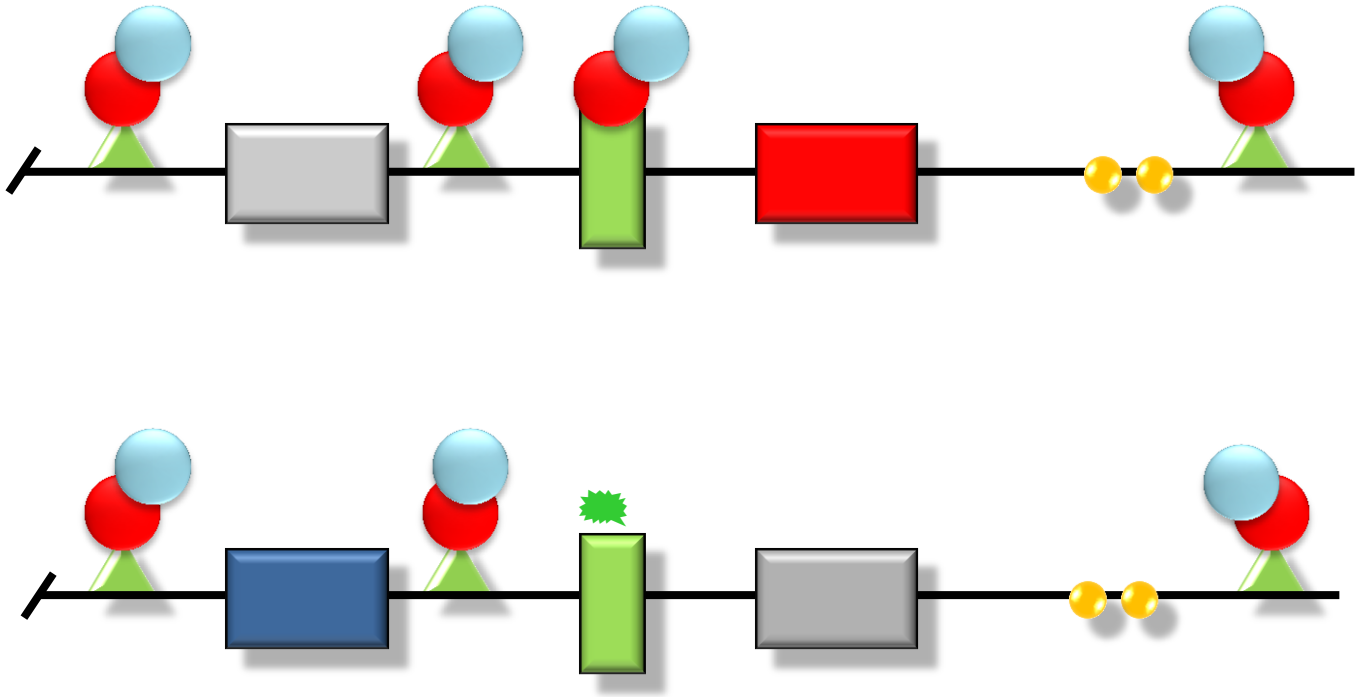
CENTRE D'EMPREINTE ICR1

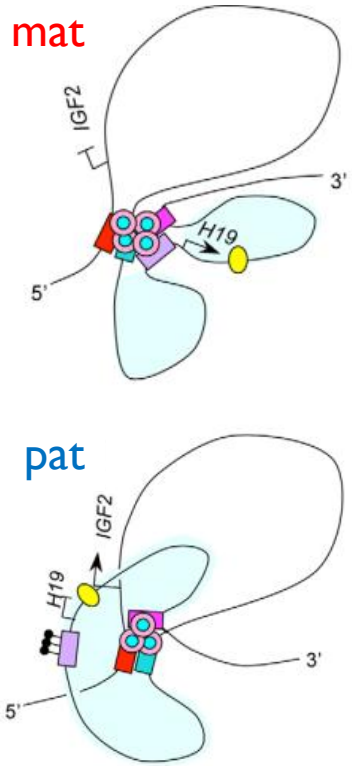


> CTCF : Protection de l'allèle maternel contre la méthylation *de novo*
(mutations des CBS → gain de méthylation sur l'allèle maternel)

CENTRE D'EMPREINTE ICR1

> Co-localisation CTCF/cohésine à l'origine de conformations allèle-spécifiques de la chromatine

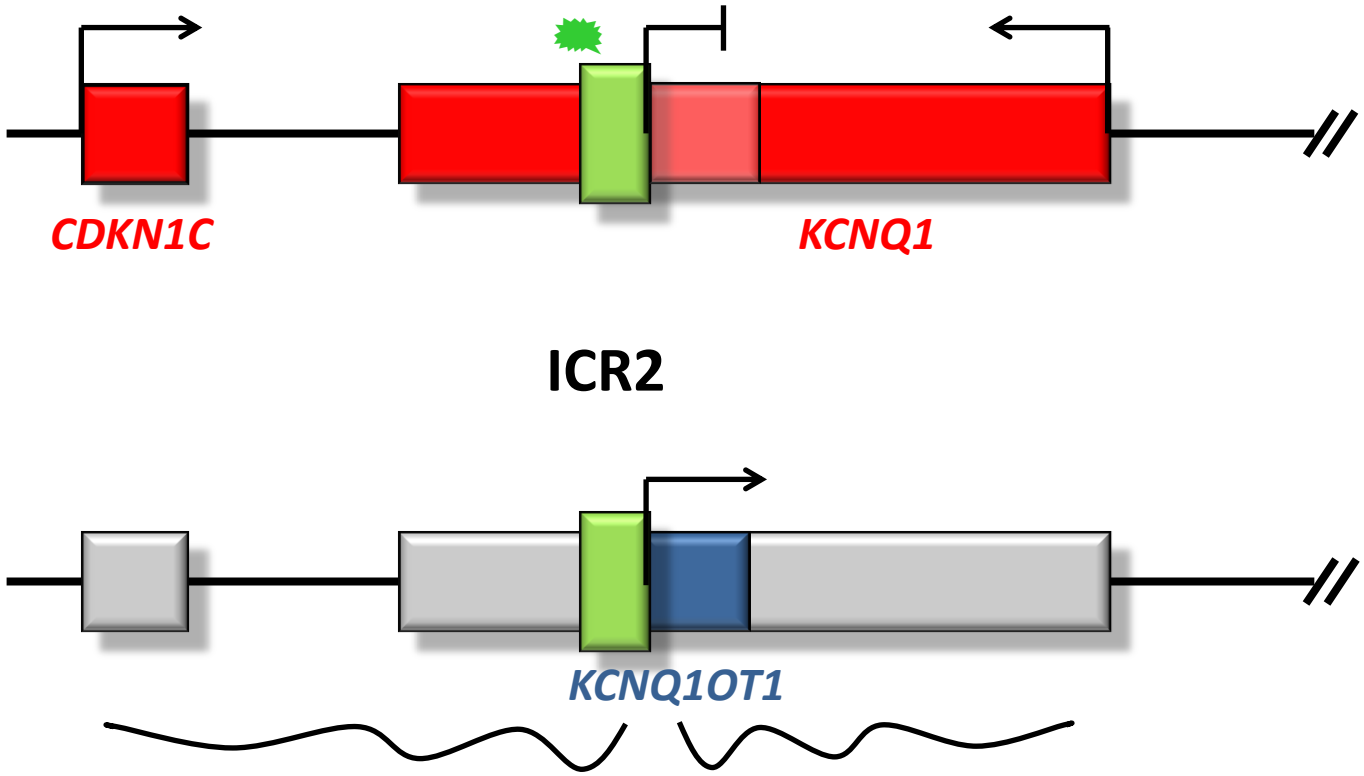




CTCF/cohésine CTCF binding site

Nativio et al., 2009

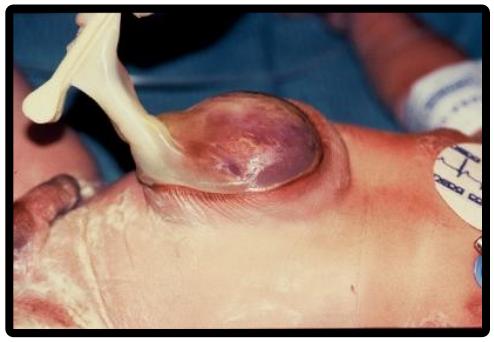
RÉGULATION DU DOMAINE CENTROMÉRIQUE

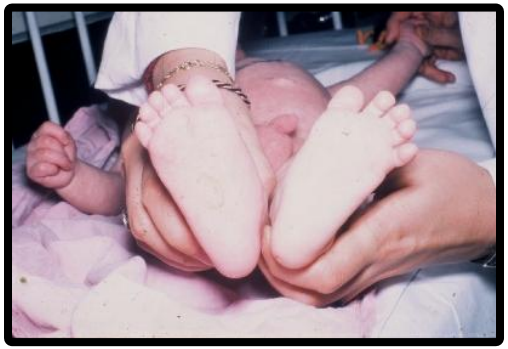


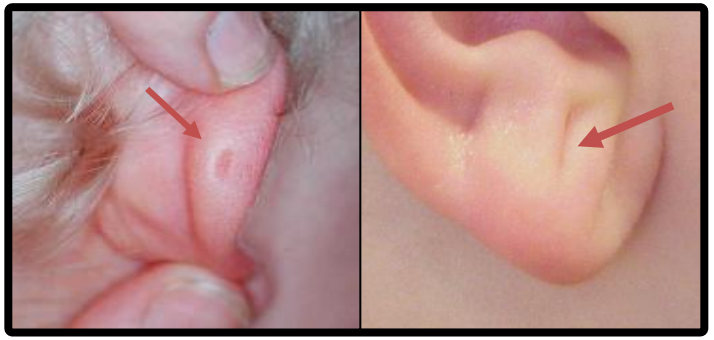
Syndrome de Beckwith-Wiedemann (BWS)

> **Syndrome de croissance excessive**

	2013*	1990s
Macroglossie	94%	95%
Macrosomie	43%	88%
Anomalies de paroi abdominale	62%	80%
Organomégalie	44%	60%
Malformations des oreilles	62%	50%
Hypoglycémies néonatales	43%	35%
Angiomes flammeus	45%	30%
Hémihypertrophie	33%	30%



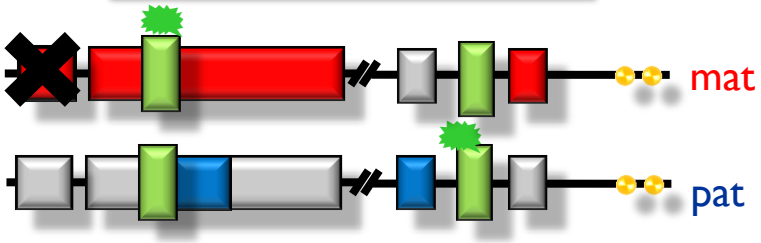




** Brioude et al., Horm Research in Paediatrics 2013 (in press)*

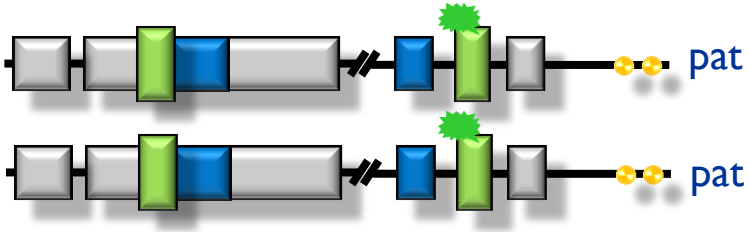
BWS : MÉCANISMES MOLÉCULAIRES

Mutations de *CDKN1C*

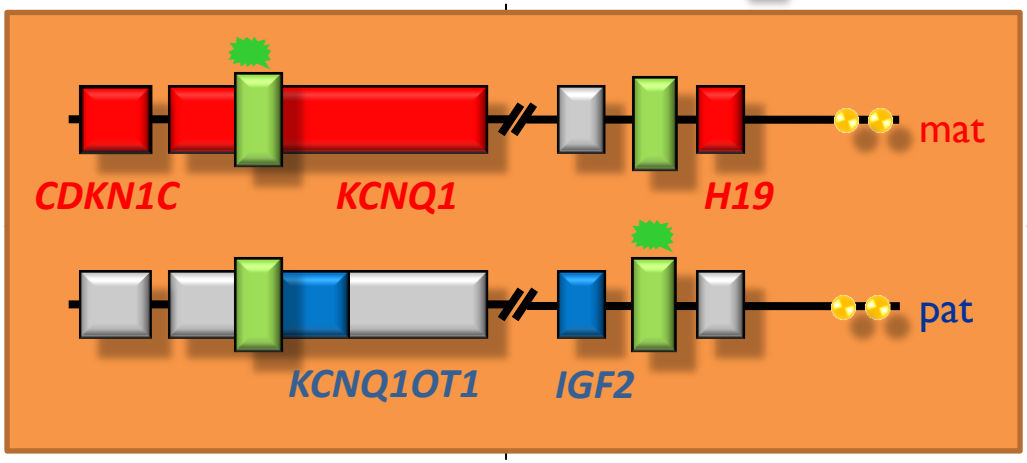


CDKN1C ↘ (activité)
IGF2 =

Isodisomies paternelles 11p15

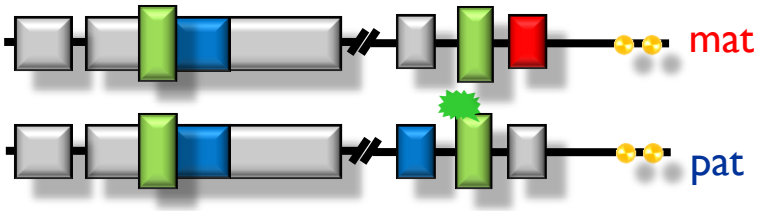


↘ CDKN1C
↗ IGF2

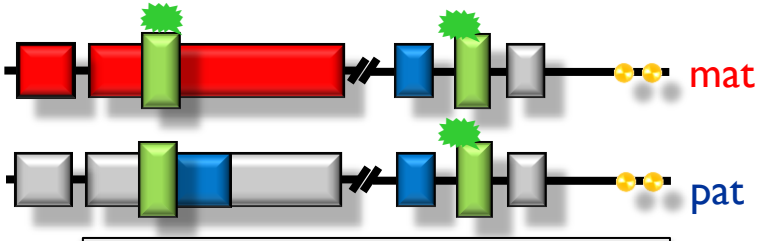


CDKN1C ↘
IGF2 =

= CDKN1C
↗ IGF2



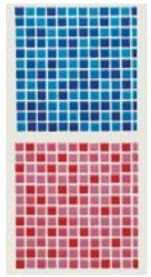
Perte de méthylation d'ICR2

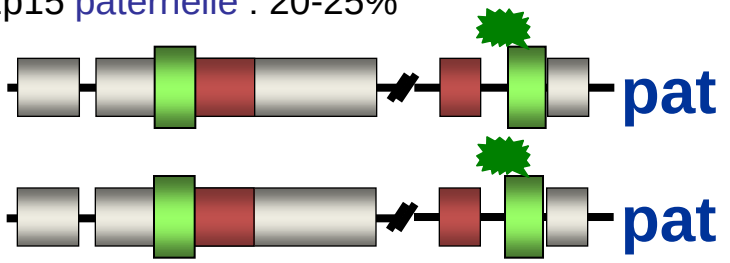


Gain de méthylation d'ICR1

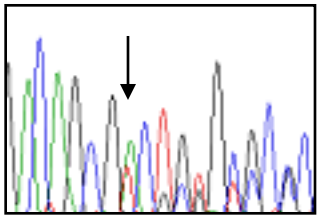
Syndrome de Wiedemann Beckwith:anomalies moléculaires

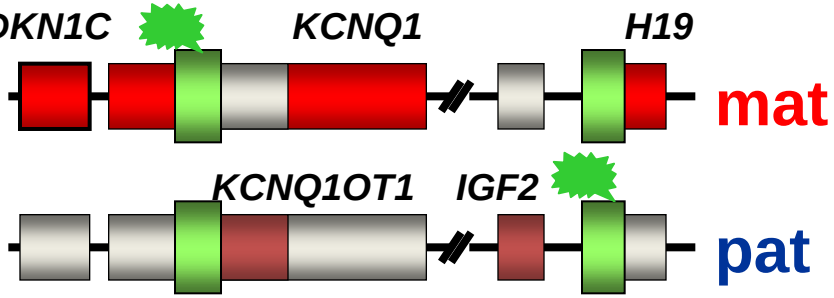
Unidisomie 11p15 paternelle : 20-25%



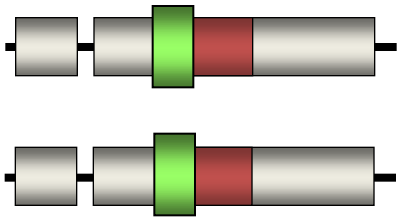


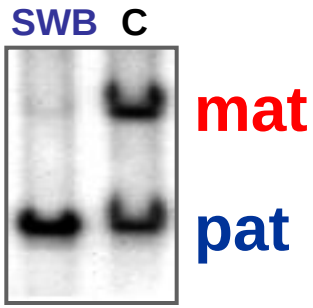
Mutation du gène *CDKN1C* d'origine maternelle: 5%

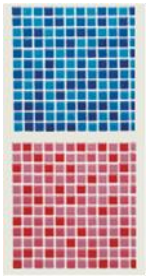


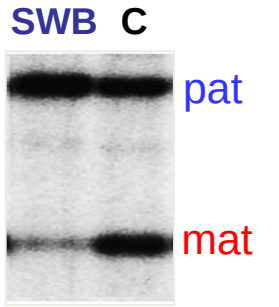


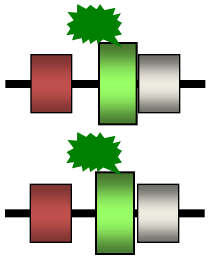
ICR2 **ICR1**











Perte de méthylation maternelle d'ICR2 : 60%

Gain de méthylation maternelle d'ICR1 10%

Syndrome de Beckwith-Wiedemann (BWS)

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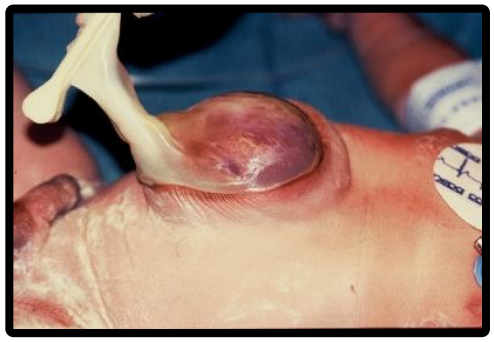
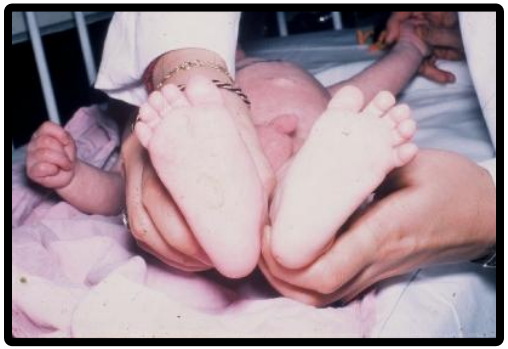
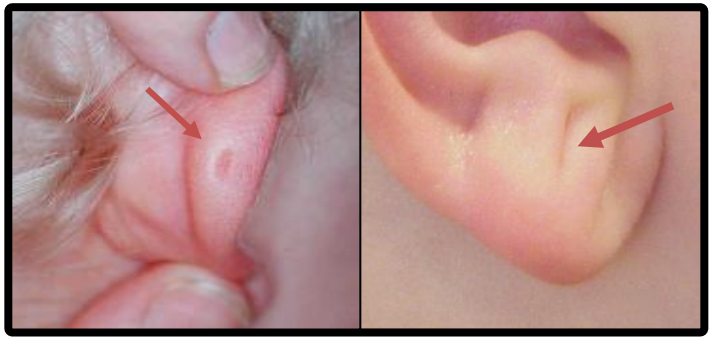
Organomégalie	44%	60%
Malformations des oreilles	62%	50%
Hypoglycémies néonatales	43%	35%
Angiomes flammeus	45%	30%
Hémihypertrophie	33%	30%
Tumeurs embryonnaires	8.6%	10%



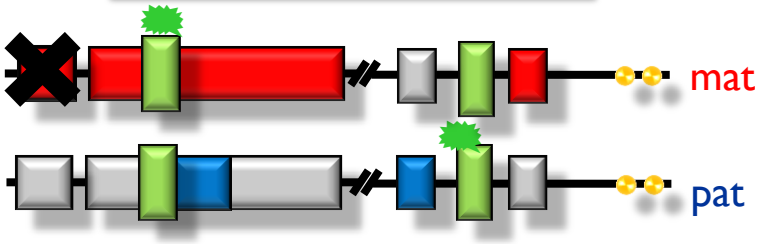




** Brioude et al., Horm Research in Paediatrics 2013 (in press)*

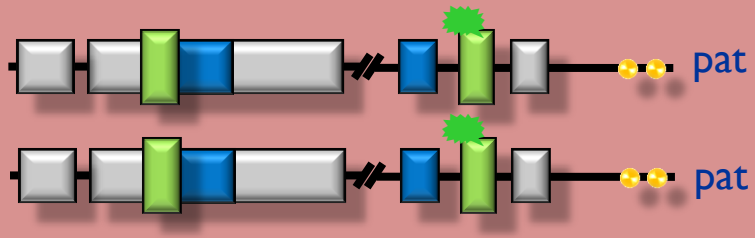
BWS : Mécanismes Moléculaires

Mutations de *CDKN1C*



CDKN1C ↘ (activité)
IGF2 =

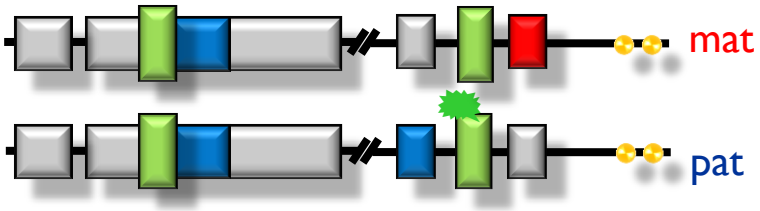
Isodisomies paternelles 11p15



↘ **CDKN1C**
↗ **IGF2**

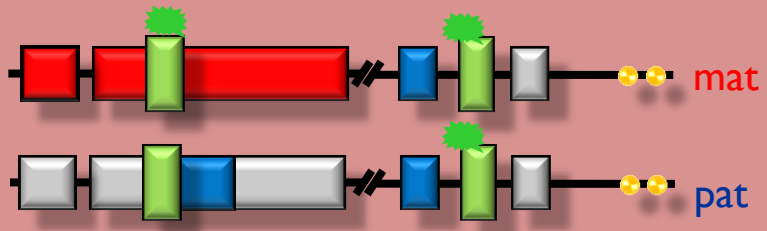
Risque tumoral +++
(Néphroblastome)

CDKN1C ↘
IGF2 =



Perte de méthylation d'ICR2

= **CDKN1C**
↗ **IGF2**



Gain de méthylation d'ICR1

SYNDROME DE SILVER-RUSSELL (SRS)

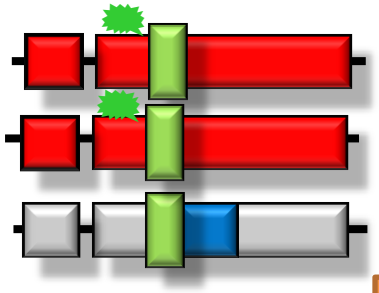
> **Syndrome de restriction de croissance**

Retard de croissance intra-utérin
Retard de croissance post-natal
Asymétrie corporelle (hémihypotrophie)
Relative macrocéphalie
Grand front bombant
Difficultés alimentaires / IMC < -2 SDS

Netchine et al., J Clin Endoc Metab 2007

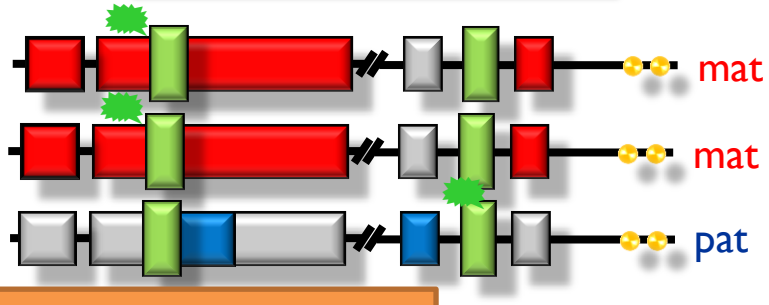
SRS : MÉCANISMES MOLÉCULAIRES

Duplications du domaine centromérique

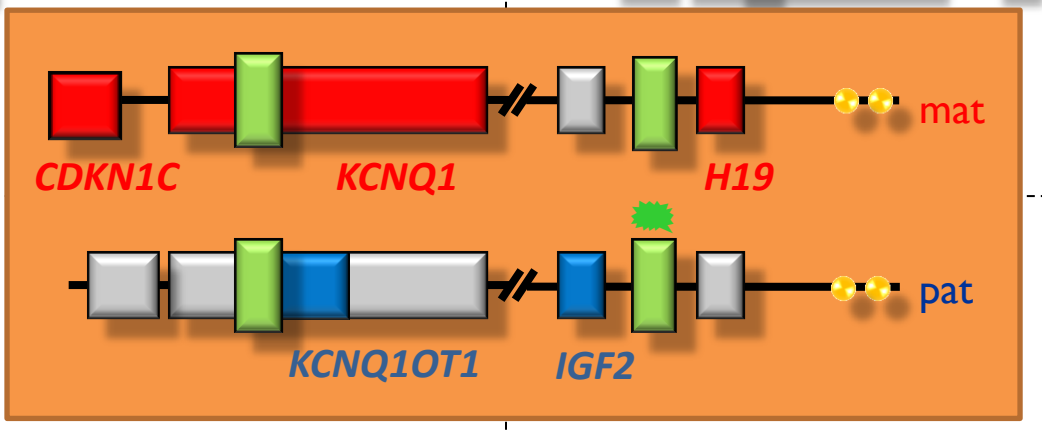


CDKN1C ↗
IGF2 =

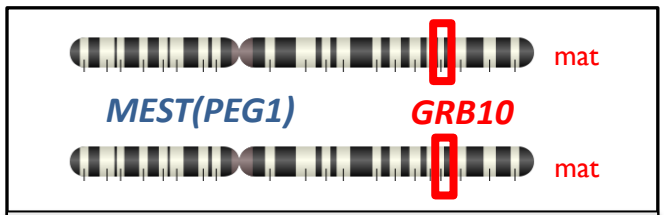
Duplications de 11p15



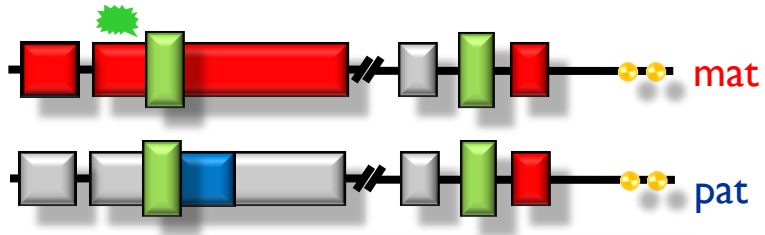
↗ CDKN1C
= IGF2



= CDKN1C
↘ IGF2



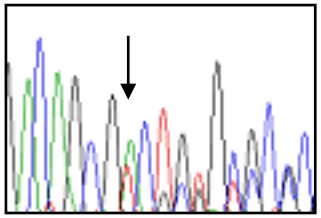
Disomies maternelles du chr. 7



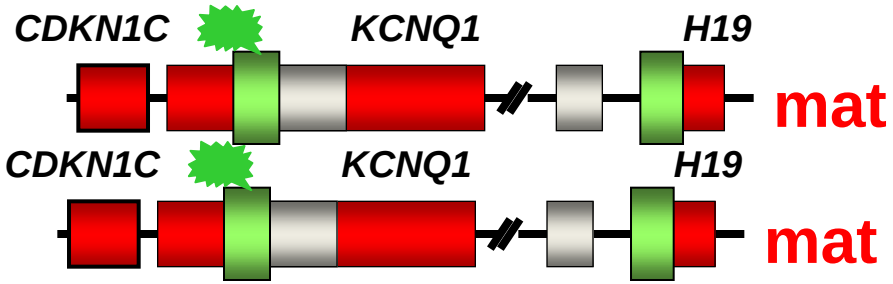
Perte de méthylation d'ICR1

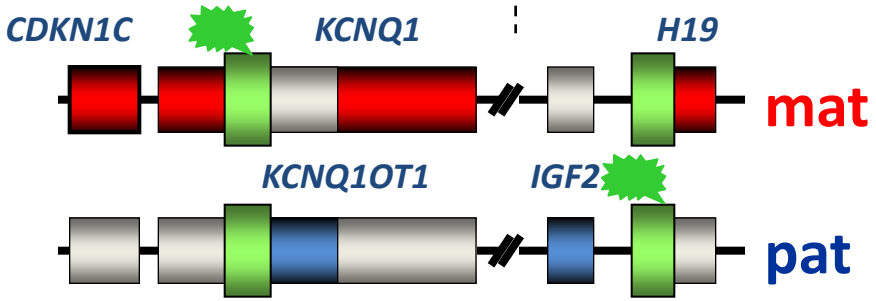
Silver Russell Syndrome: 11p15 molecular anomalies subtypes

« Activating » mutation in *CDKN1C* of maternal origin: 1%



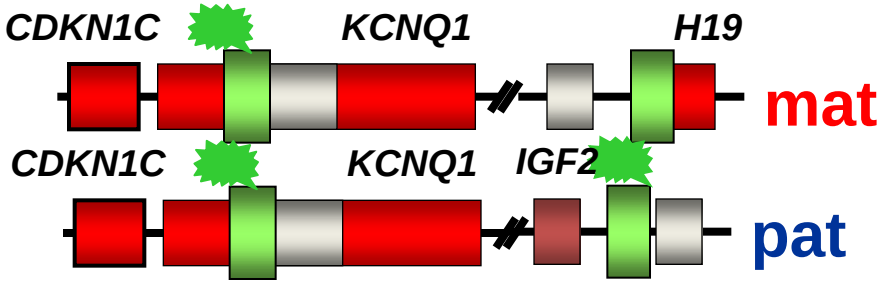
Maternal 11p15 duplication: 2-3%

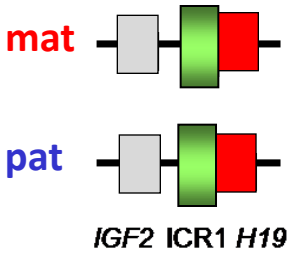




ICR2 **ICR1**

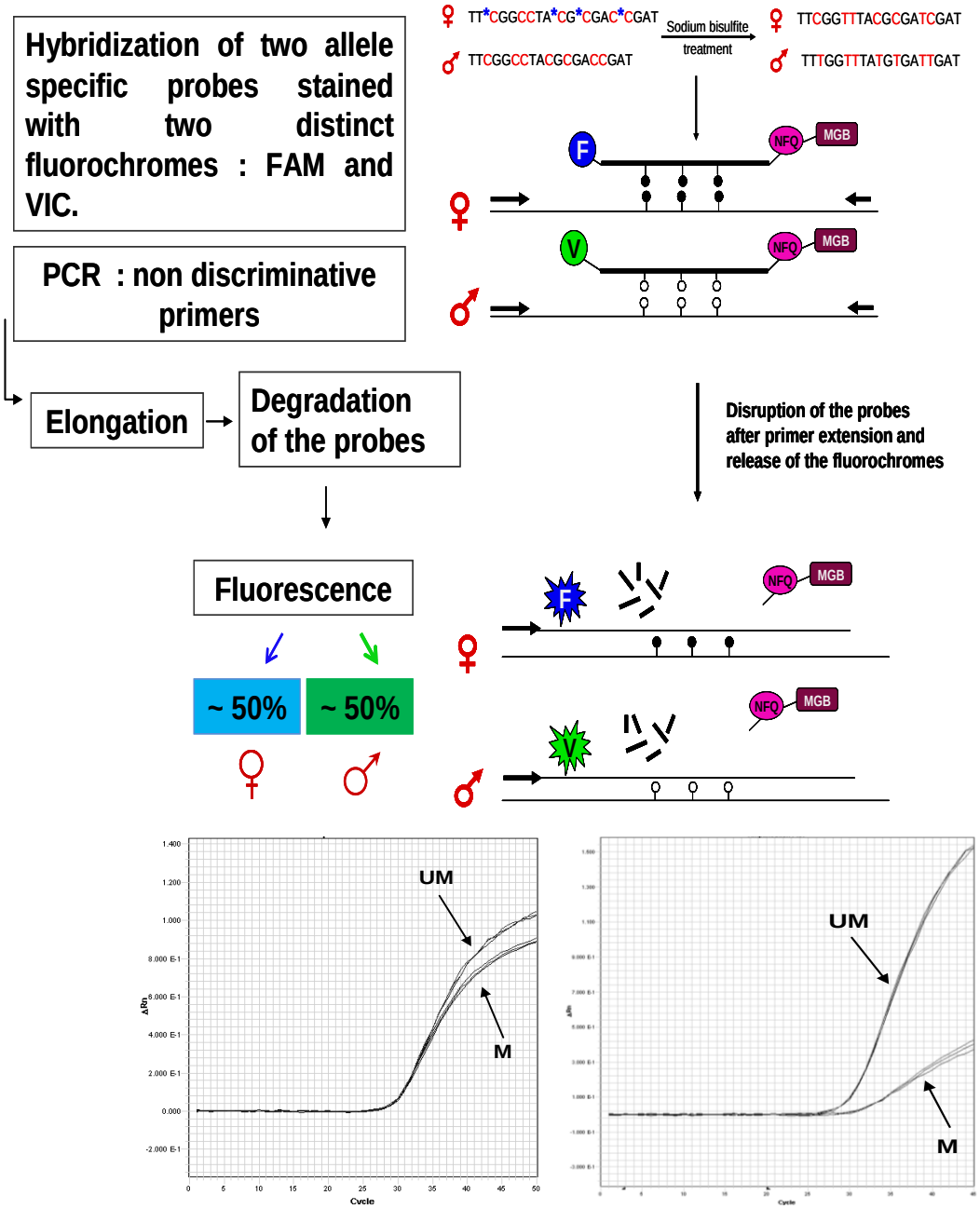
Maternal 11p15 ICR2 duplication: 1 %





Loss of methylation of the paternal ICR1 : 50-60%

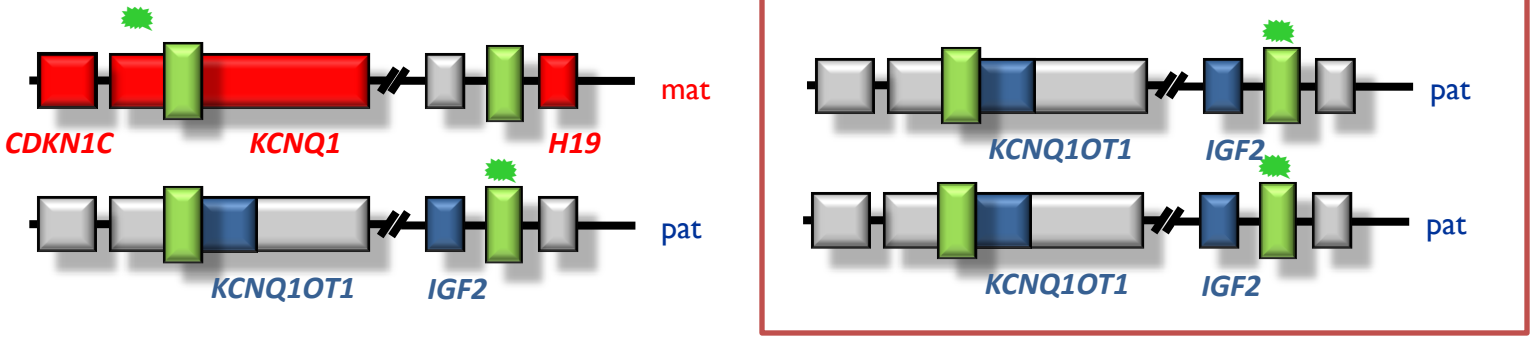
Allele Specific Methylated Multiplex RTQ-PCR: After Bisulfite Conversion



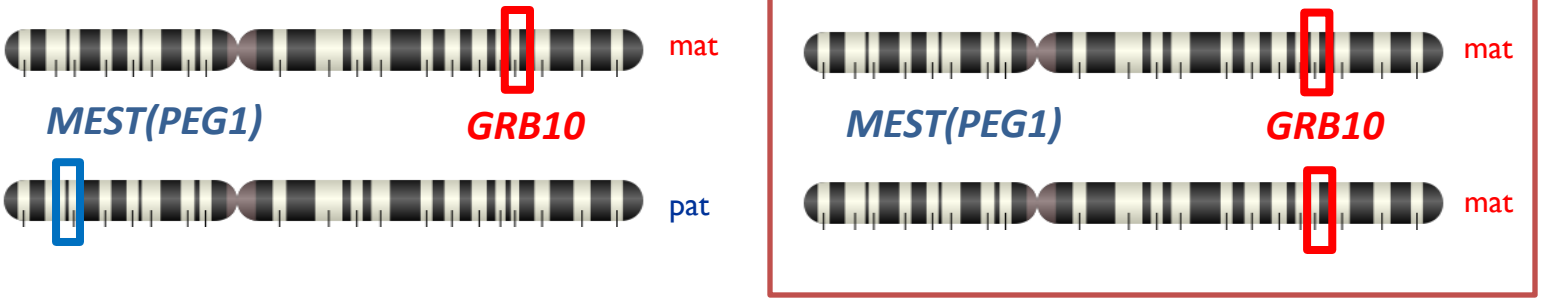
Interrogates 2 to 3 CpG
Possible with very small DNA quantity
Very rapid
Developed for many imprinted regions

Azzi *et al*, Human Mutation, 2011

BWS, SRS ET DISOMIES UNIPARENTALES



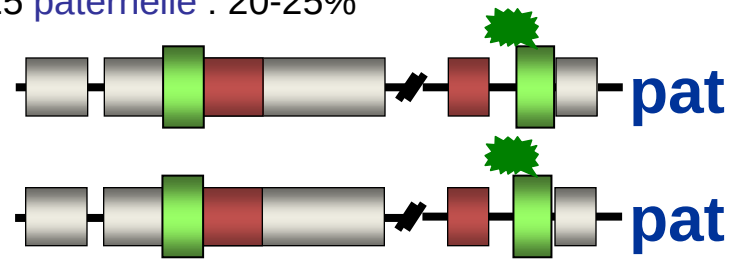
Isodisomie paternelle de 11p15

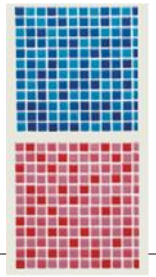


Disomie maternelle du chromosome 7

Interêt des SNP Array

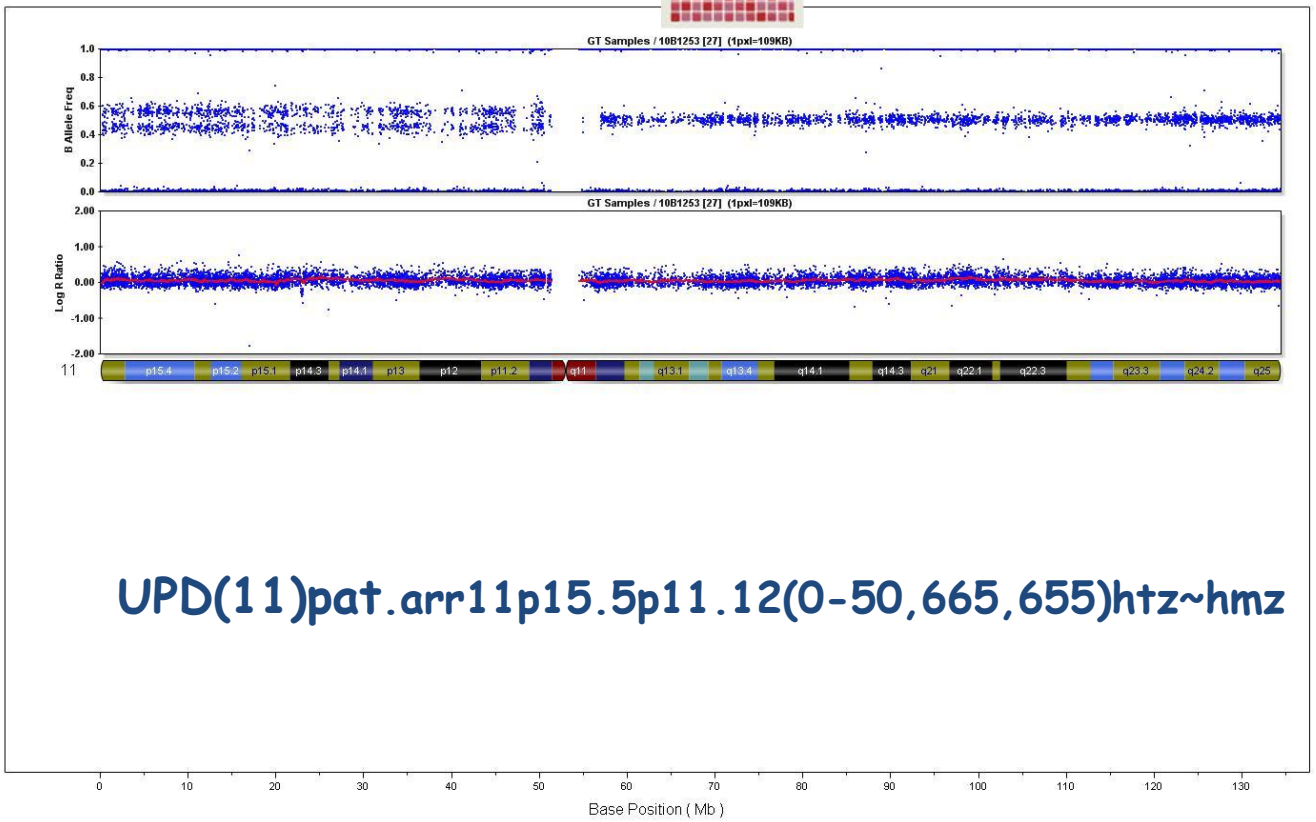
Disomie 11p15 paternelle : 20-25%





CR1=56 [46-56]
CR2=41 [41-53]

UPD ~10%



UPD(11)pat.arr11p15.5p11.12(0-50,665,655)htz~hmz

Keren, Chantot, Siffroi, communication orale samedi matin

SOMMAIRE

• Anomalies de méthylation des ICR de régions soumises à empreinte sont fréquents dans le SRS et SWB : région 11p15 où se situe *IGF2*, *H19*…

• Suivi de cohortes de patients SBW ou SRS permettra de
définir des recommandations de prise en charge thérapeutique et de suivi du risque tumoral

• Il n'y a pas d'anomalie moléculaire identifiée pour environ 40% des patients SRS et SBW.

• Bien que le mécanisme de ces anomalies d'empreinte soit non connu dans la majorité des cas, l'identification d'anomalies génétiques des centres d'empreinte va compliquer le conseil génétique

• Le diagnostic moléculaire de ces anomalies de méthylation en mosaïque est délicat. Le diagnostic prénatal devient techniquement accessible bien que nécessitant une étape encore importante de validation, est il souhaitable de le développer ?

SOMMAIRE

Si suspission de SBW ou SRS en foetopathologie:

Nous contacter si possible

Prélèvement non macérés pour étude de la méthylation

avant foeticide, prélèvement de sang en intra cardiaque

après IMG ou FCS :

si possible extraction d'ADN de plusieurs tissus

foie
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muscle
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