Epigenetic regulation of the IGF2 /H19 gene cluster. Prospects for novel therapeutic traits

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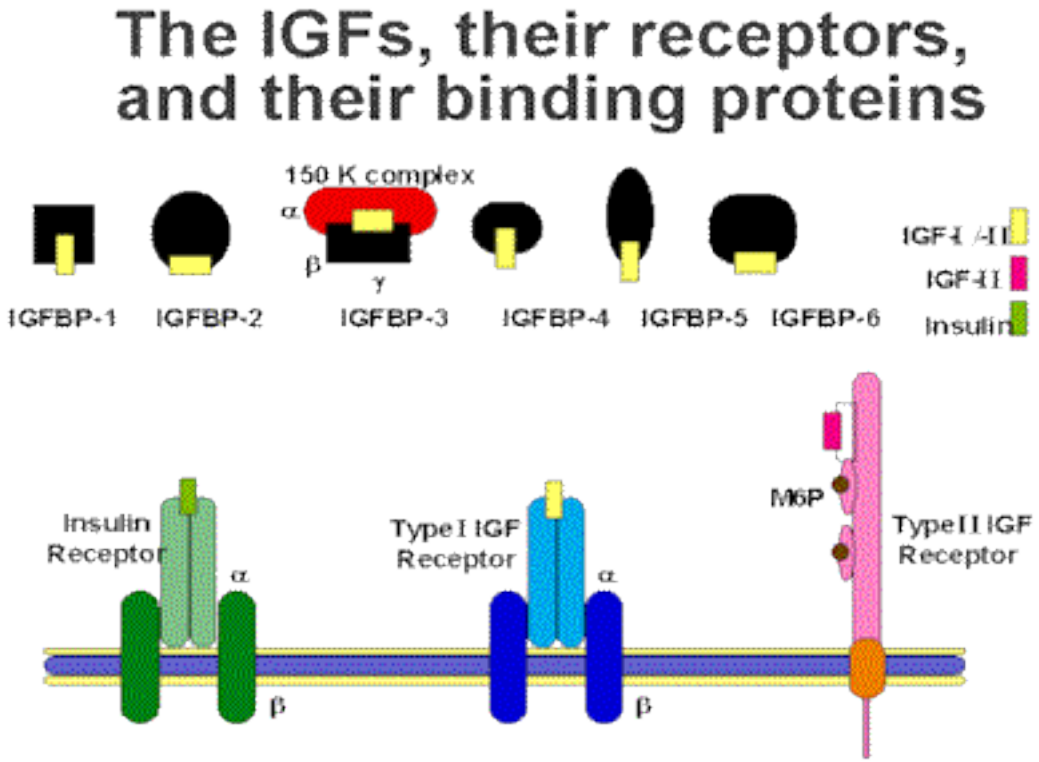
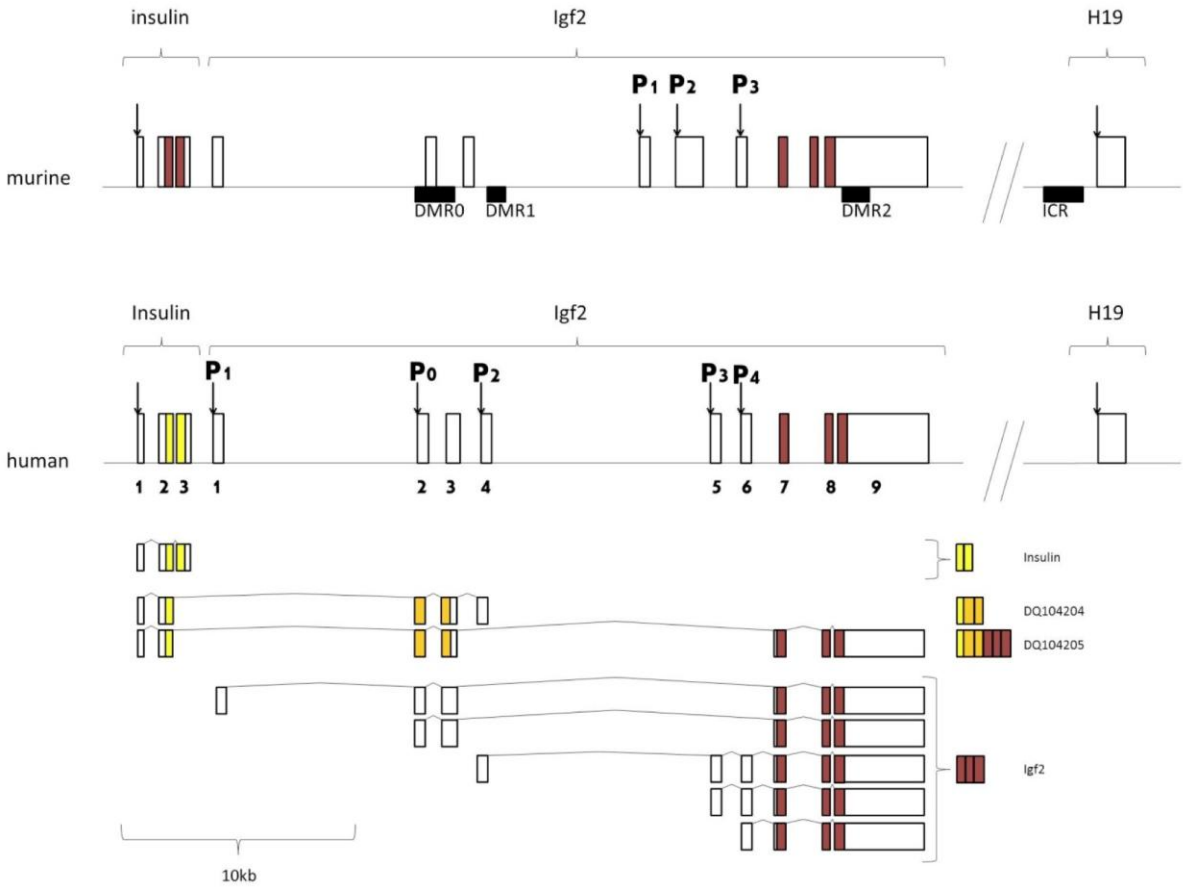
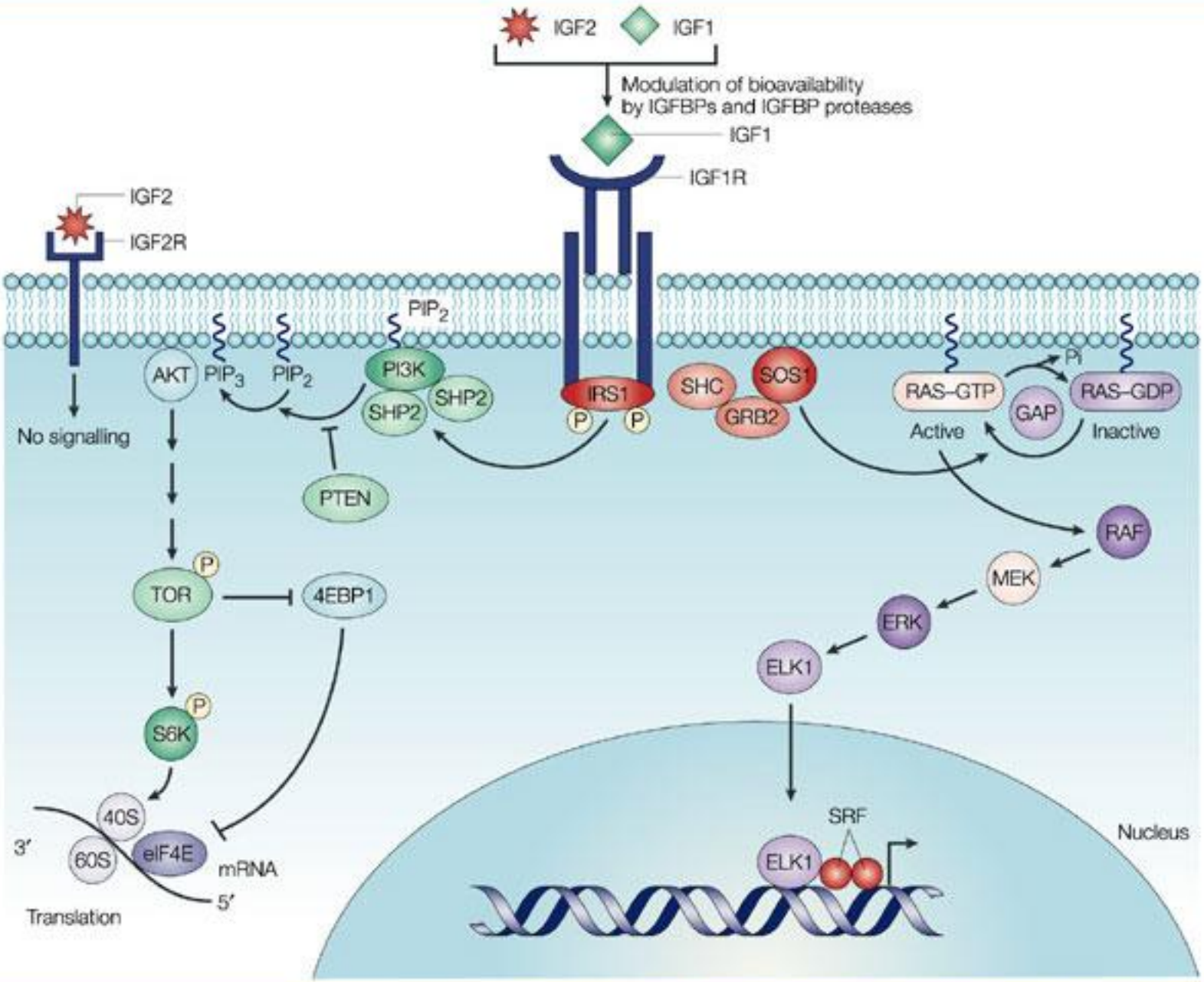
The IGF system



IGF2/H19 domain

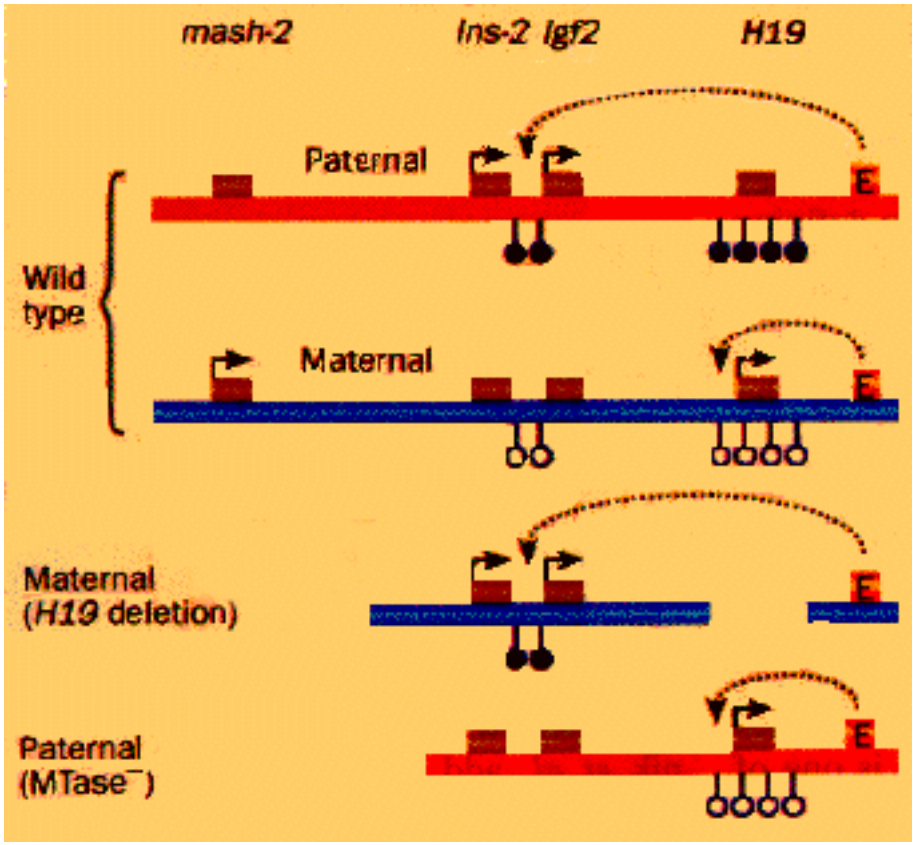



IGF2
IGF1
Modulation of bioavailability by IGFBPs and IGFBP proteases
IGF1
IGF1R
IGF2
IGF2R
PIP2
AKT
PIP3
PIP2
PI3K
SHP2
SHP2
IRS1
P
P
SHC
SOS1
GRB2
RAS–GTP
Pi
GAP
RAS–GDP
Active
Inactive
No signalling
PTEN
RAF
MEK
ERK
ELK1
TOR
P
4EBP1
S6K
P
40S
3′
60S
eIF4E
mRNA
5′
Translation
SRF
ELK1
Nucleus

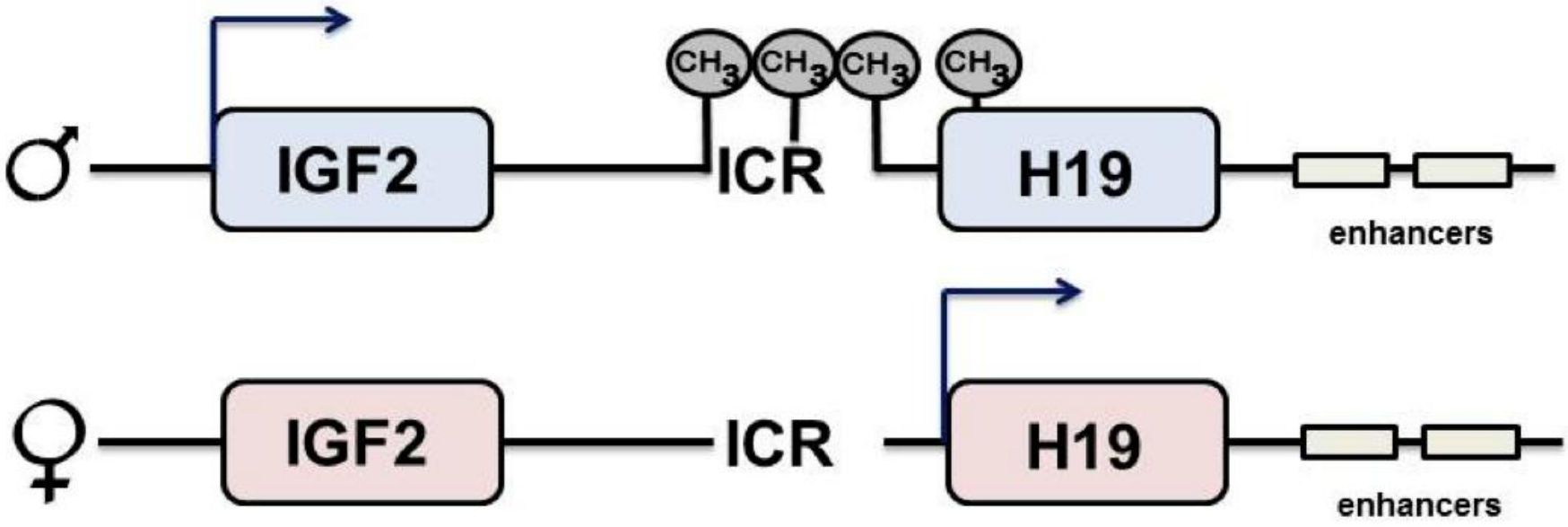
IGF2 is parentally imprinted

- Classic knockout experiments demonstrated that the IGF2 gene is expressed exclusively from the paternally inherited allele
- The gene is imprinted in a variety of mammals including humans

Epigenetic mechanisms

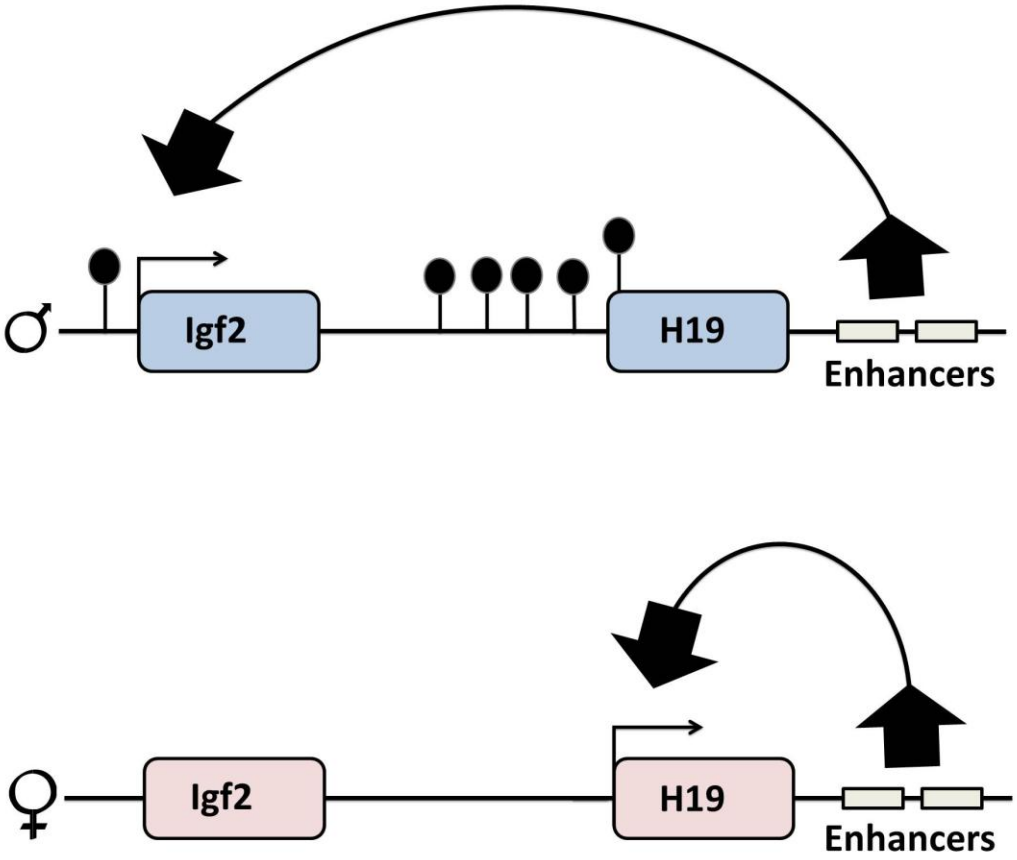


Methylation of ICR

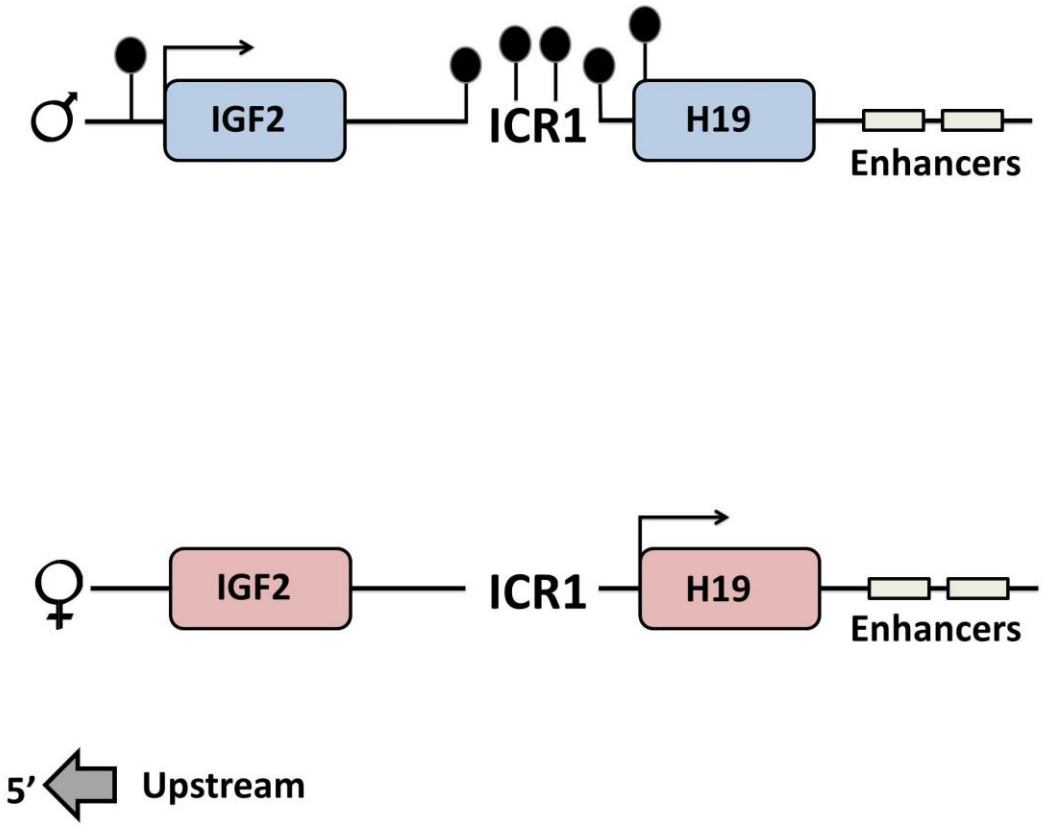


Three different concepts to explain the imprinting mechanism

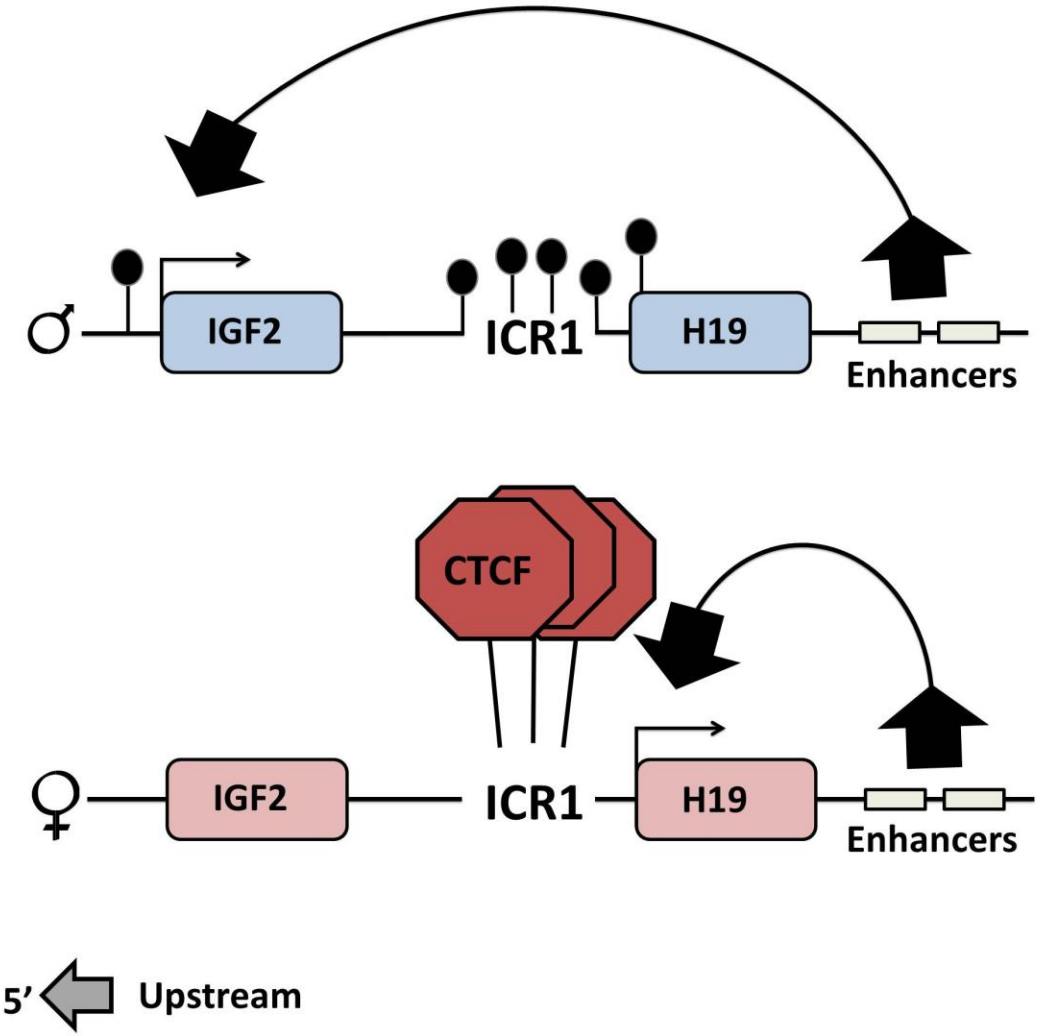
1. Enhancer competition



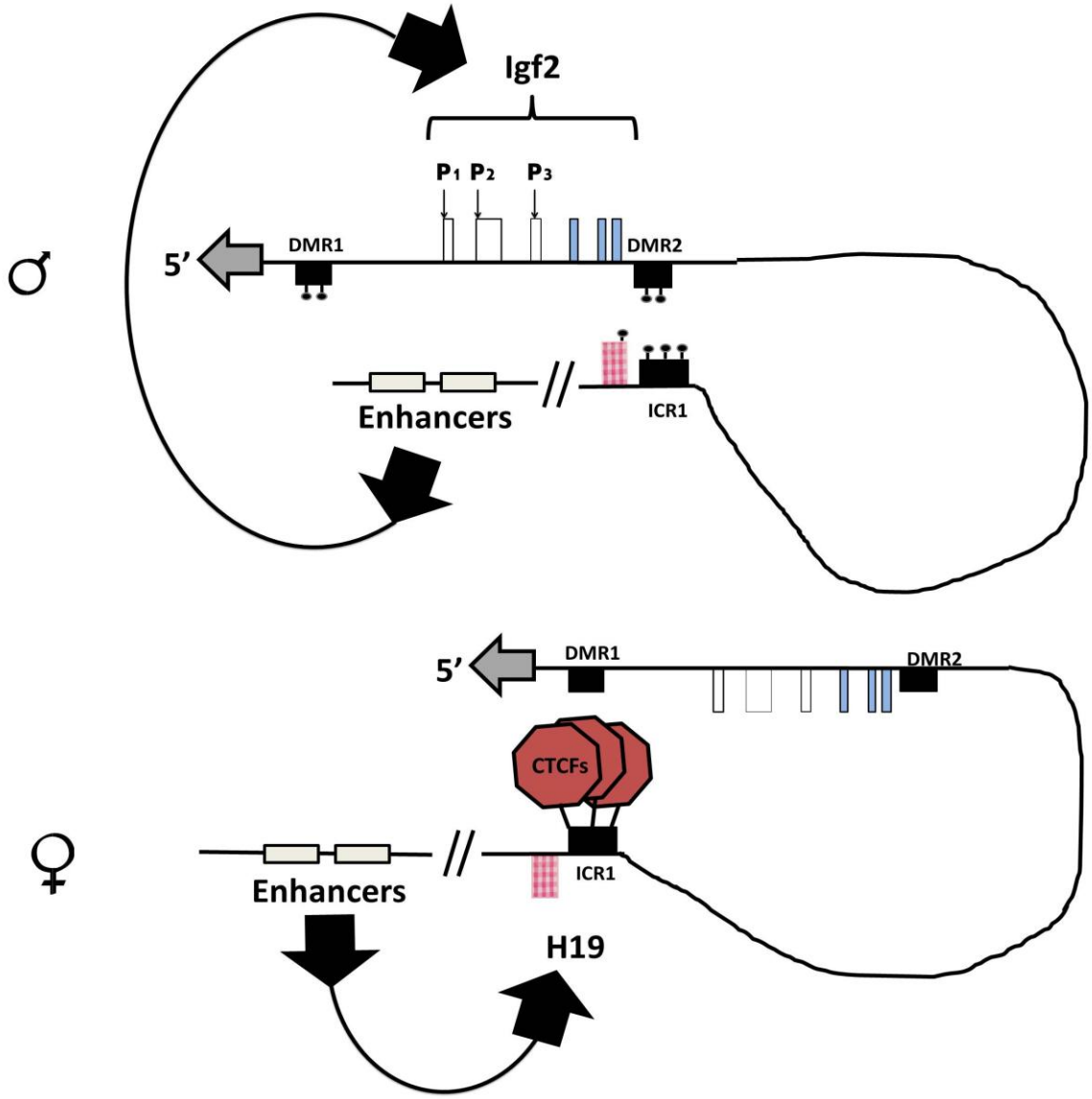
The enhancer competition model and parental specific methylation of ICR



2. Boundary model



3. Chromatin looping



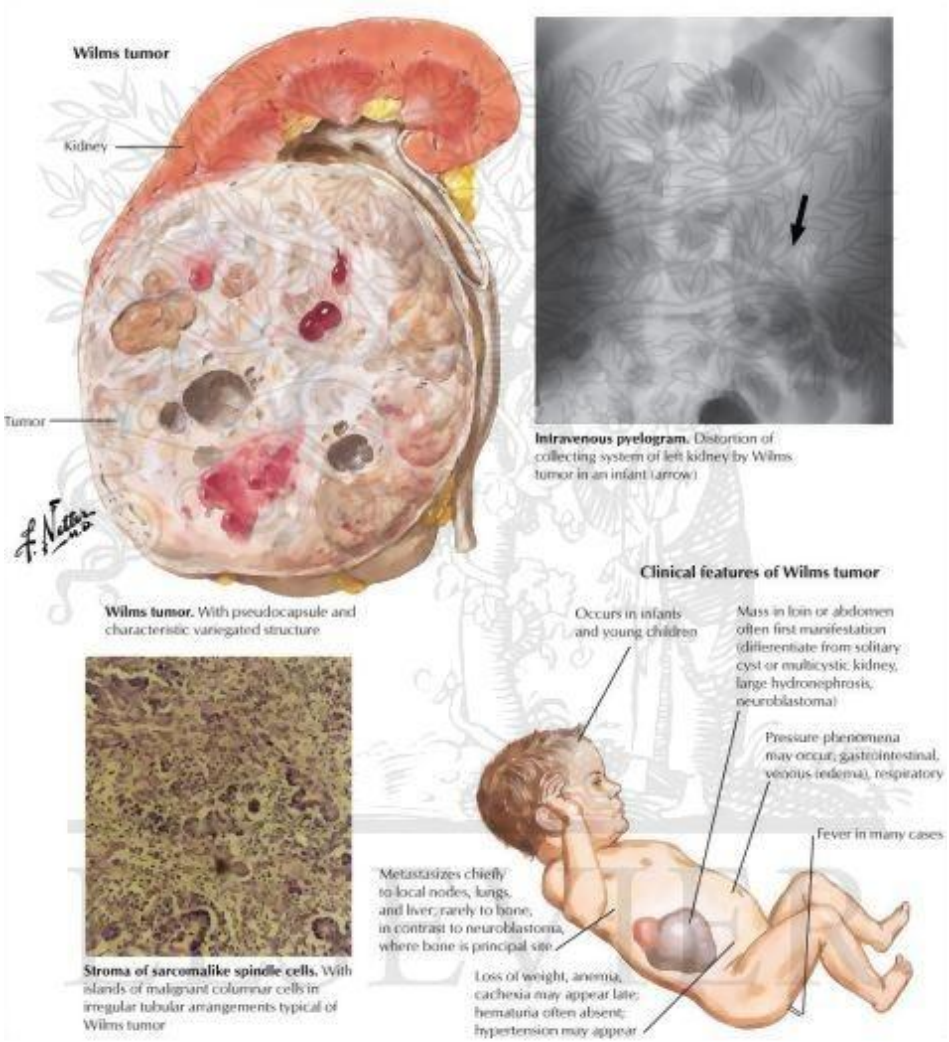
The role of imprinting in tumourigenesis

- Wilms tumour common denominator for this concept.

Wilms tumour – a puzzling story

MAX WILMS (1867 - 1918)

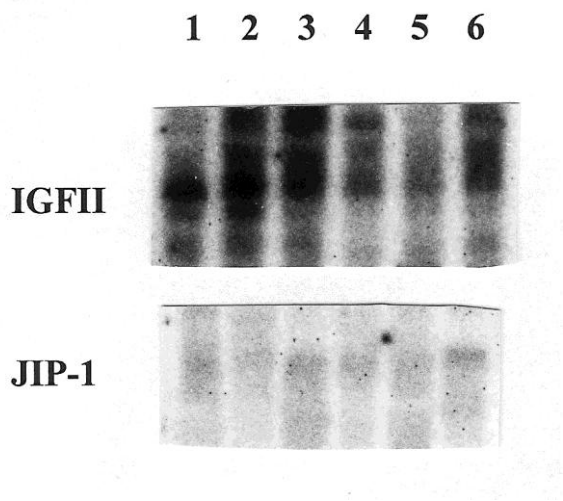
Wilms tumour



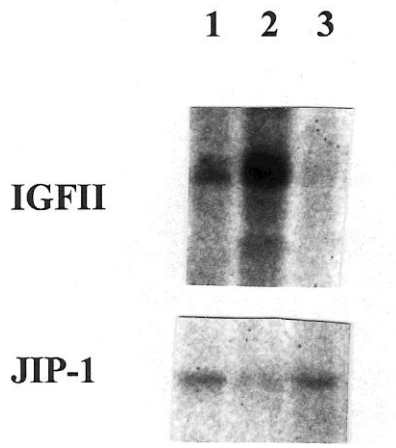
Wilms tumour and IGF2

- The IGF2 gene is overexpressed in Wilms tumour and a wide spectrum of other neoplasms
- Early data suggested that imprinting is relaxed even in non-neoplastic BWS tissues

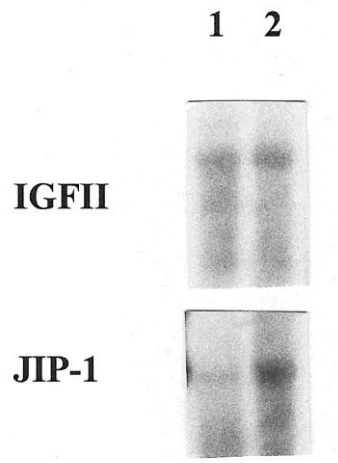
JIP-1 and IGF2 are coexpressed in Wilms tumour



The co-regulation of IGF2 and JIP-1 expression is relaxed in Wilms tumour cell lines



Exogenous IGF2 upregulates JIP-1 expression in one Wilms tumour cell line (WCCS-1)



Abrogation of IGF2 effects in human Wilms tumour cell lines

- WCCS-1
- Gawa
- GOS-4

Effects of antibodies and binding proteins on JIP-1 expression in WCCS-1

- Alpha IR-3
- IGF-BP-2

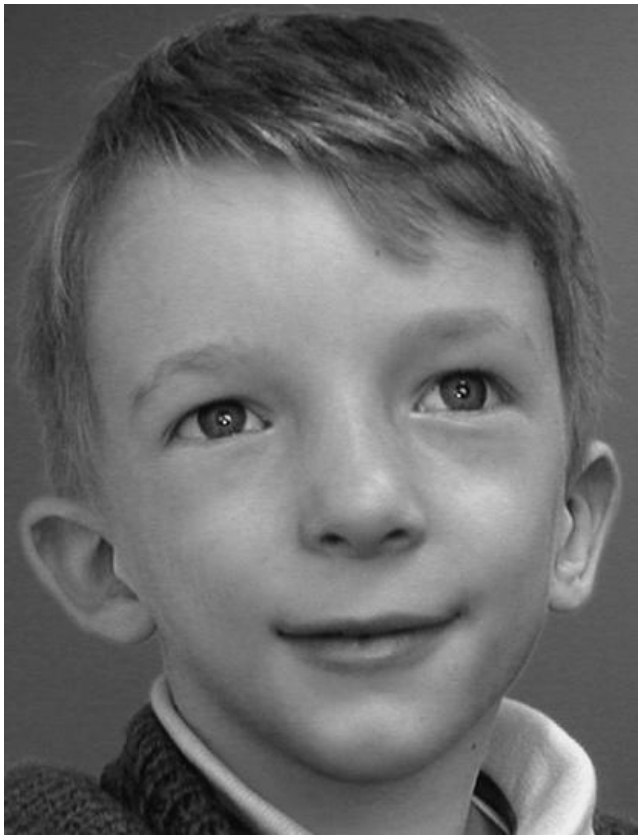
- Will restore JIP-1 expression to normal levels

Imprinting effects – 2 model diseases

- Silver Russell Syndrome
- Beckwith Wiedemann Syndrome

1. Silver Russell syndrome

S



Chromosomes 7 and 11

- Growth retardation before and after birth
- Large head compared to rest of the body
- Prominent head, narrow chin
- 5th finger clinodactyly
- hemihypoplasia

2. Beckwith Wiedemann Syndrome

- Overgrowth syndrome
- hemihypertrophy
- Increased risk of acquiring Wilms tumour

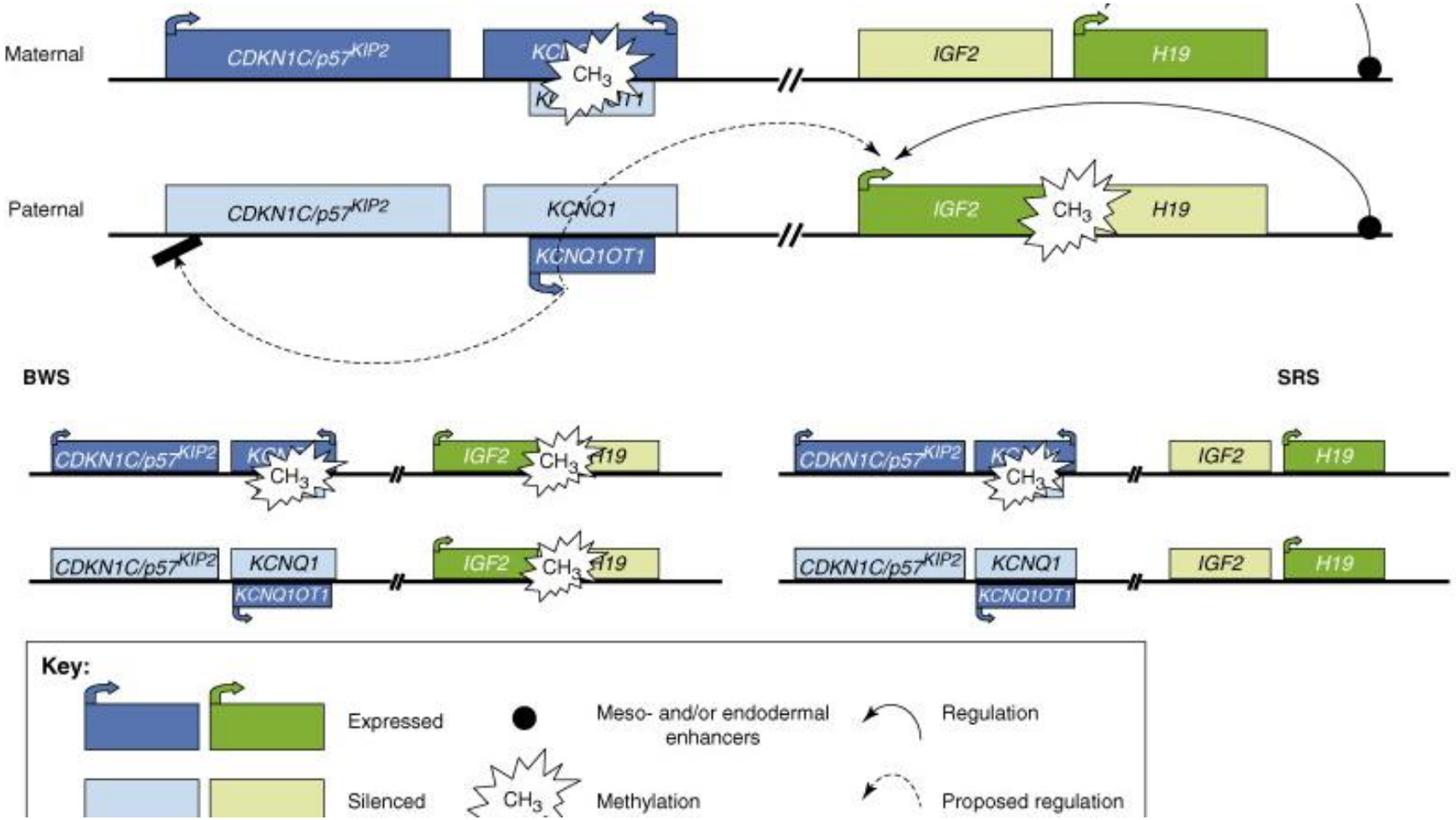
SRS vs BWS

- SRS – ICR1 hypomethylation
- BWS – a variety of mechanisms to relax IGF2 imprinting.

Complicating the picture…..
Introducing ICR2

- Deletion of H19 sequence without effect
- ICR2 regulates reciprocal expression of CDKN1C and KCNQ1
- Mutations i paternally suppressed CDKN1C accounts for 40% of BWS

SRS, BWS and imprinting control



CONCLUSIONS

- IGF2 expression is one of the most puzzling parentally imprinted genes
- Relaxation of imprinting will alter the growth factor concentration
- Imprinting control within a locus rather than in individual genes.
- Interference with imprinting an interesting basis for the development of novel treatment

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