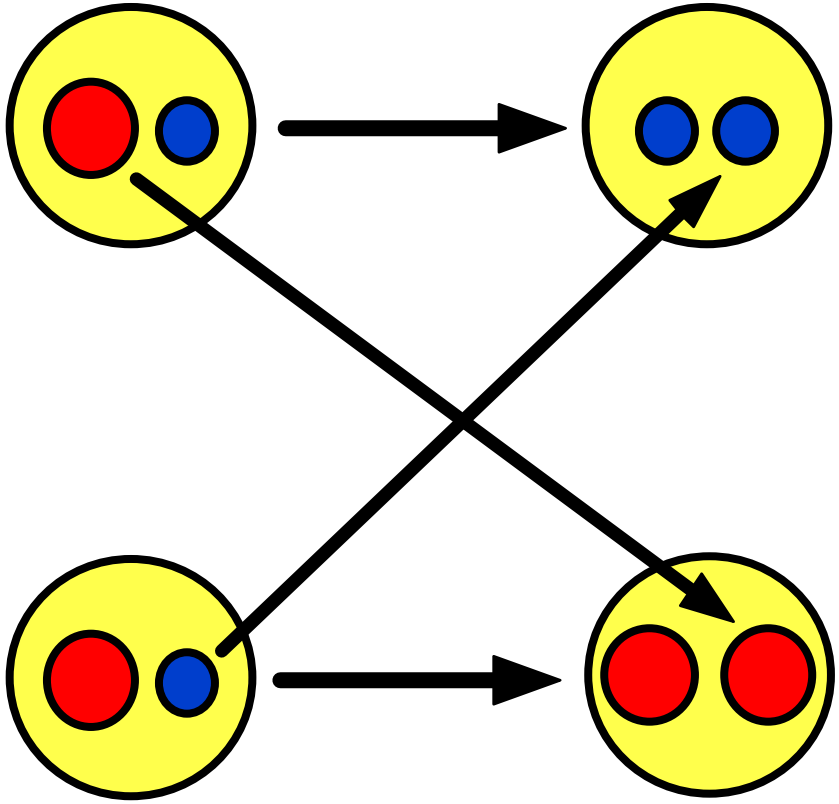
Genomic Imprinting

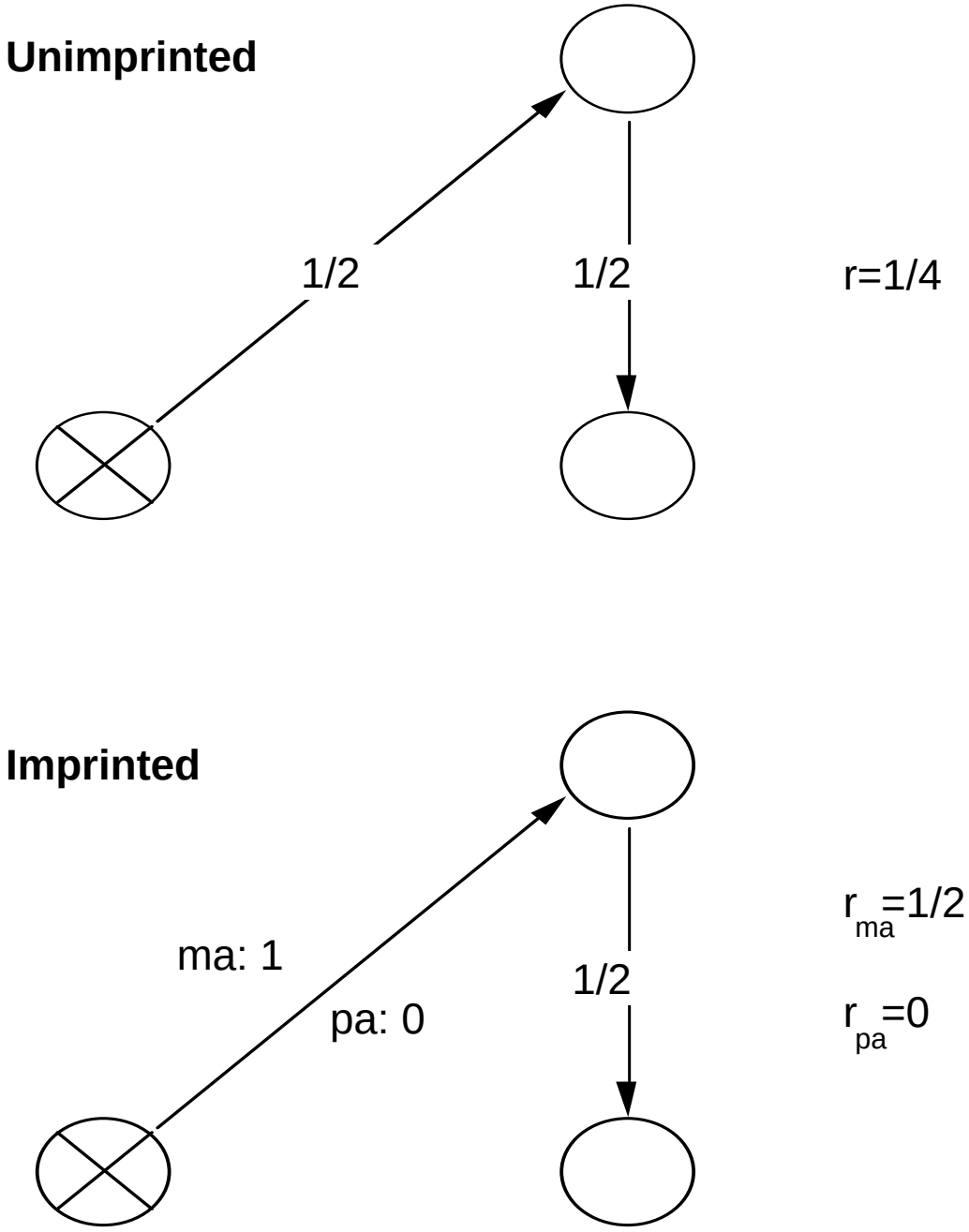
- phenomenon
- logic
- clinical manifestations
- general implications

PRONUCLEAR SUBSTITUTIONS



Oppositely imprinted genes

- Igf2 Paternally activegrowth ↑ 40%
- Igf2r Maternally active growth ↓ -30%



r's between maternal half-sibs

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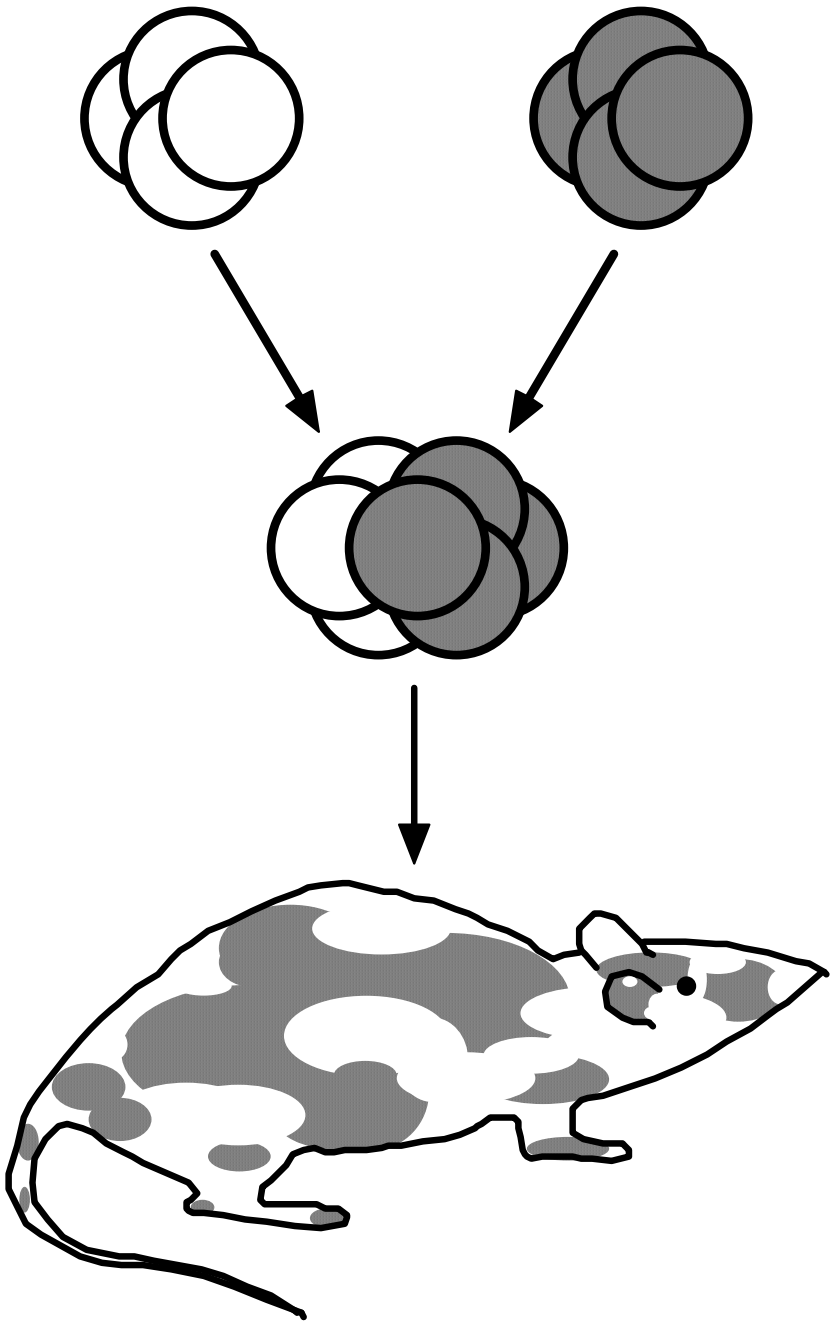
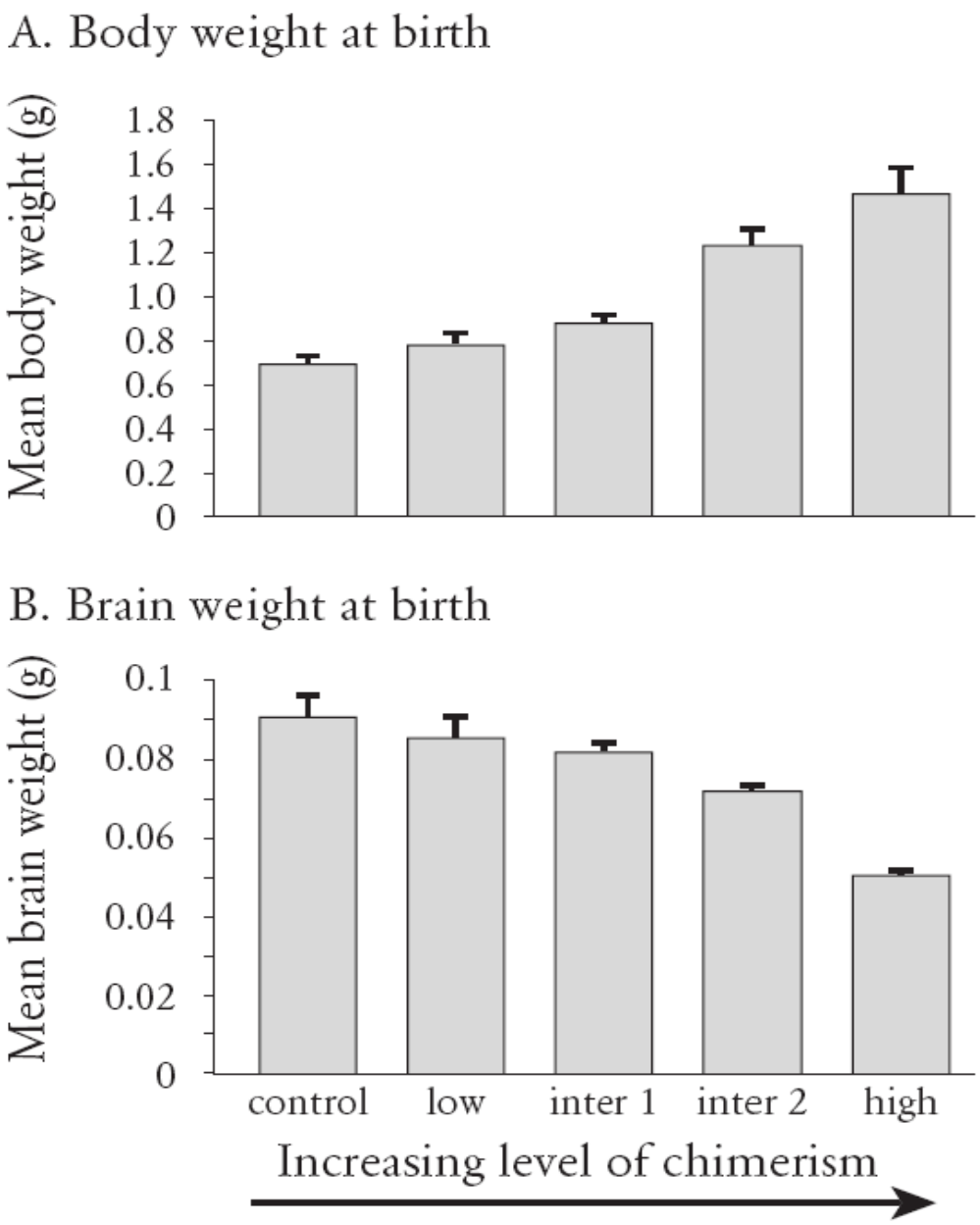




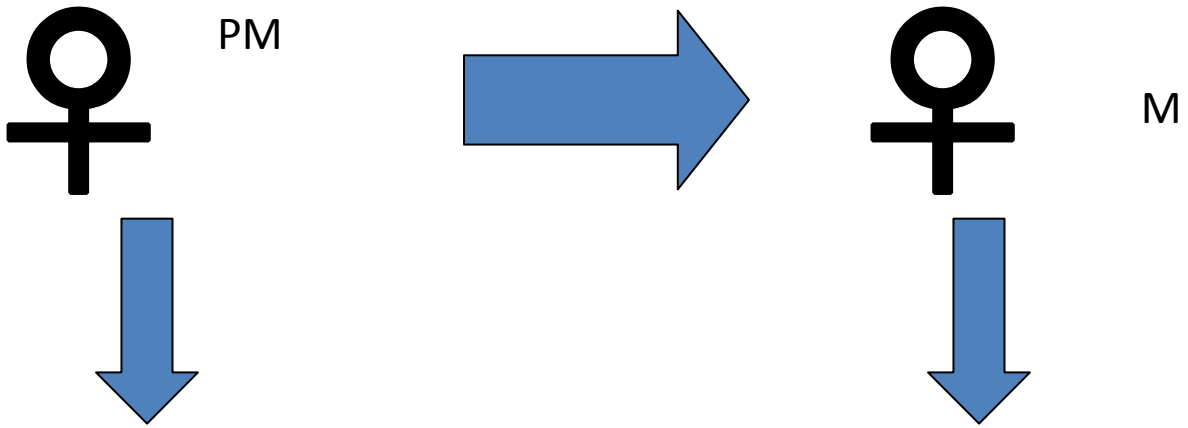
Data from Keverne et al 1996

Contribution to brains of chimeric mice

	hypothalamus	neocortex
“two mums”	—	+ + +
“two dads”	+ + +	—

Keverne et al. (1996)
Developmental Brain Research 92: 91

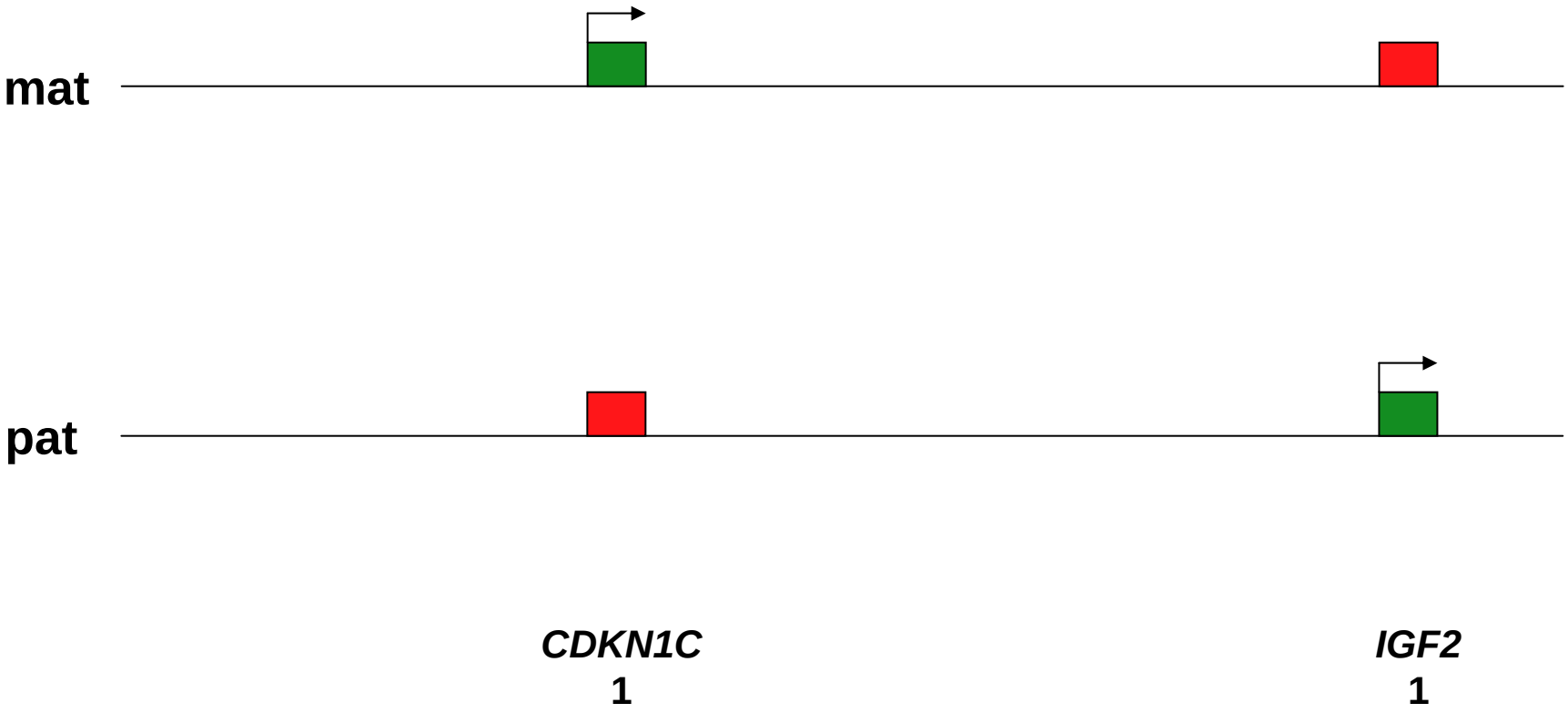
Paternal genes in female mice control **maternal** behavior



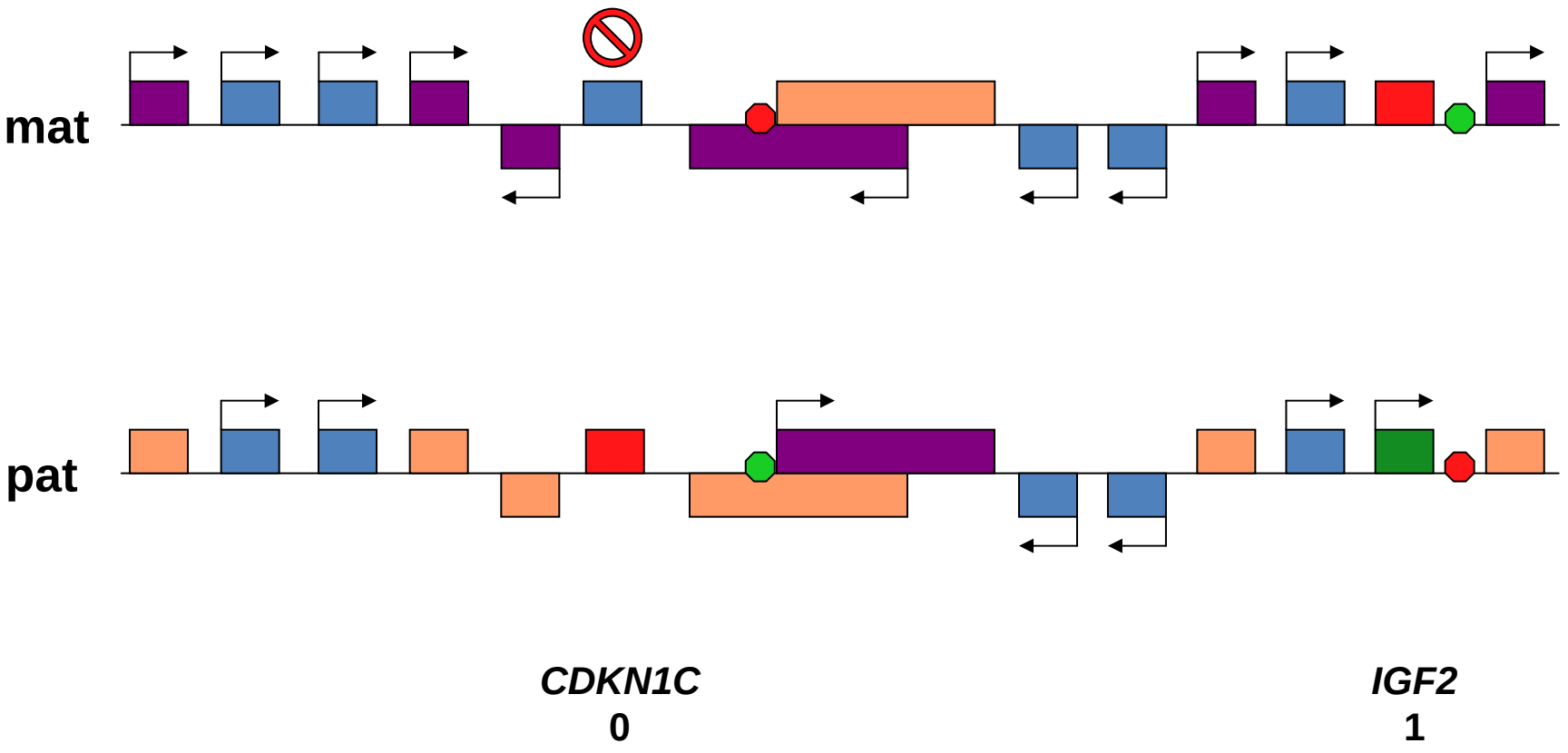
Beckwith-Wiedemann syndrome
(fetal overgrowth)

- Full term delivery
- Cesarean delivery
- 11 pounds 5 ounces (≈ 5100 grams)
- macroglossia
- umbilical hernia

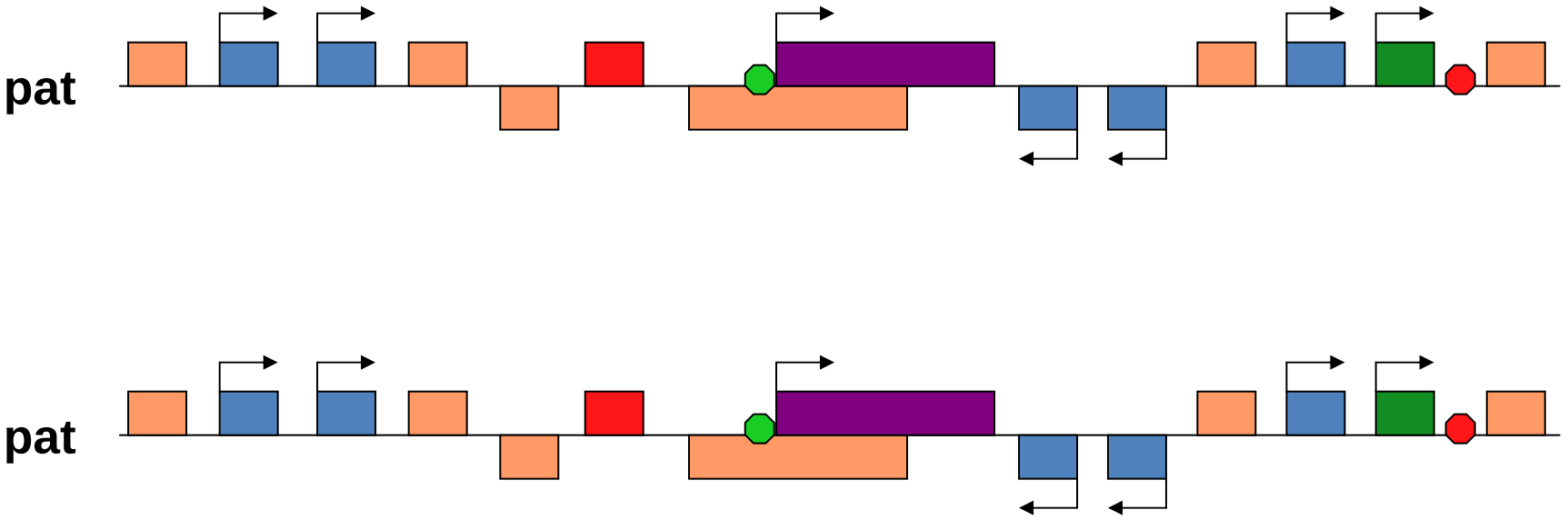
Human chromosome 11p15.5



Inactivating mutation of maternal *CDKN1C*



Paternal uniparental disomy



CDKN1C
0

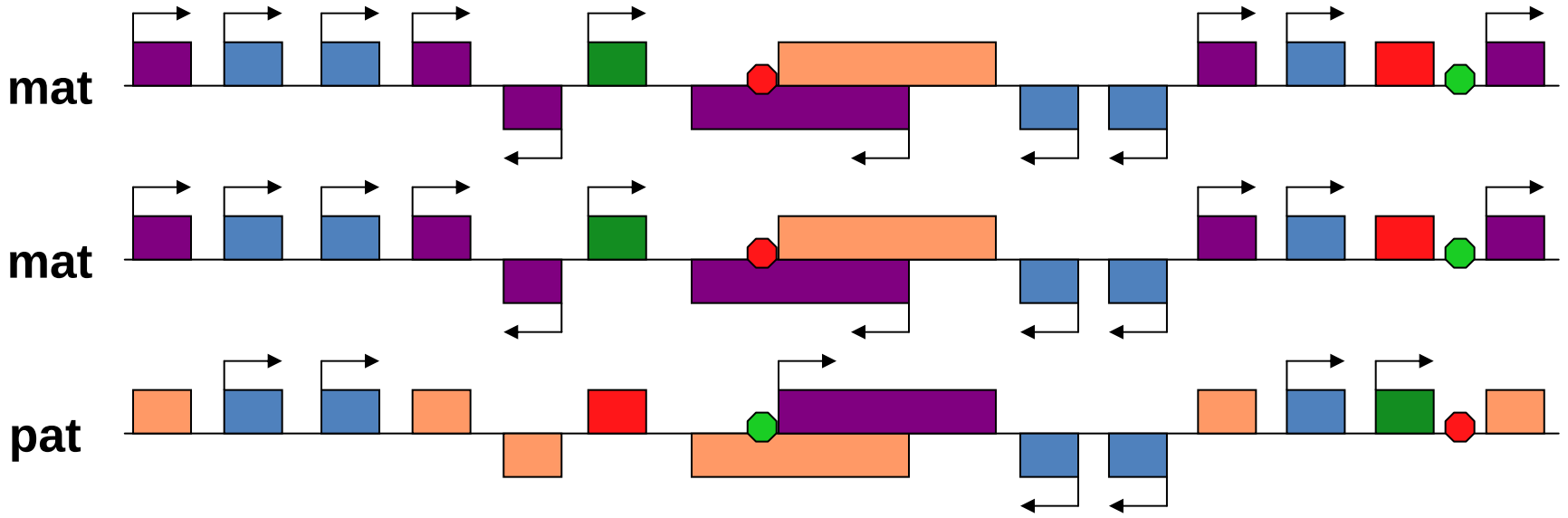
IGF2
2

high cancer risk

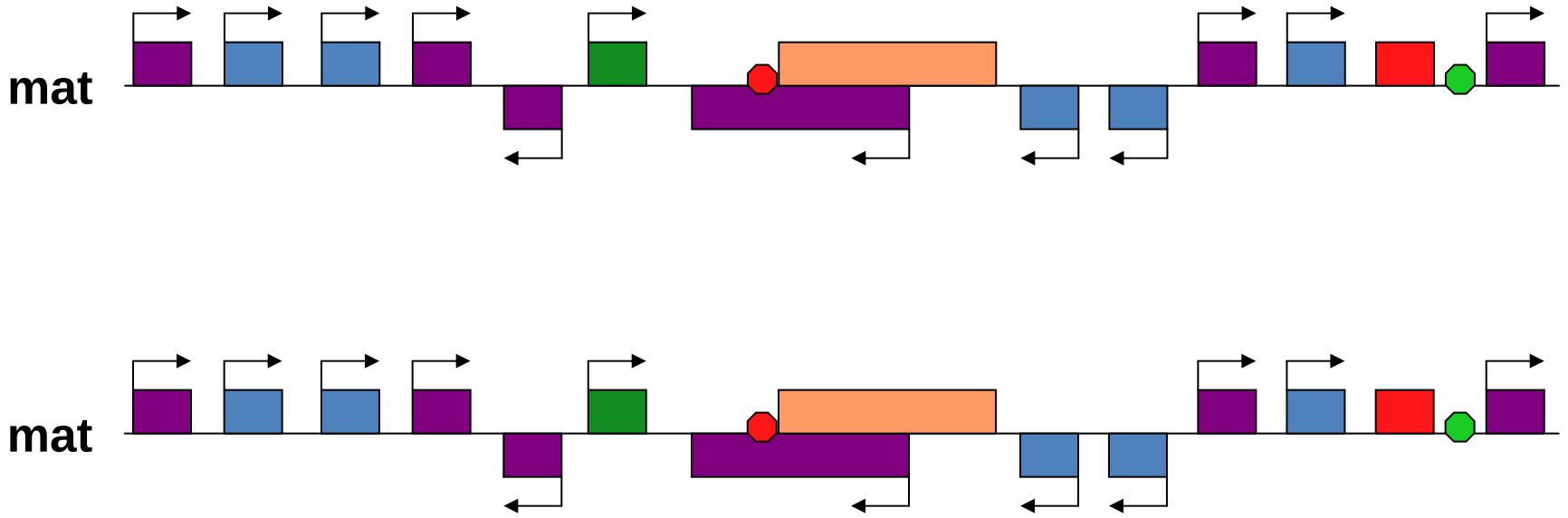
Silver-Russell syndrome

- intrauterine growth retardation
- postnatal growth retardation
- triangular face

Maternal duplication 11p15.5



Maternal uniparental disomy

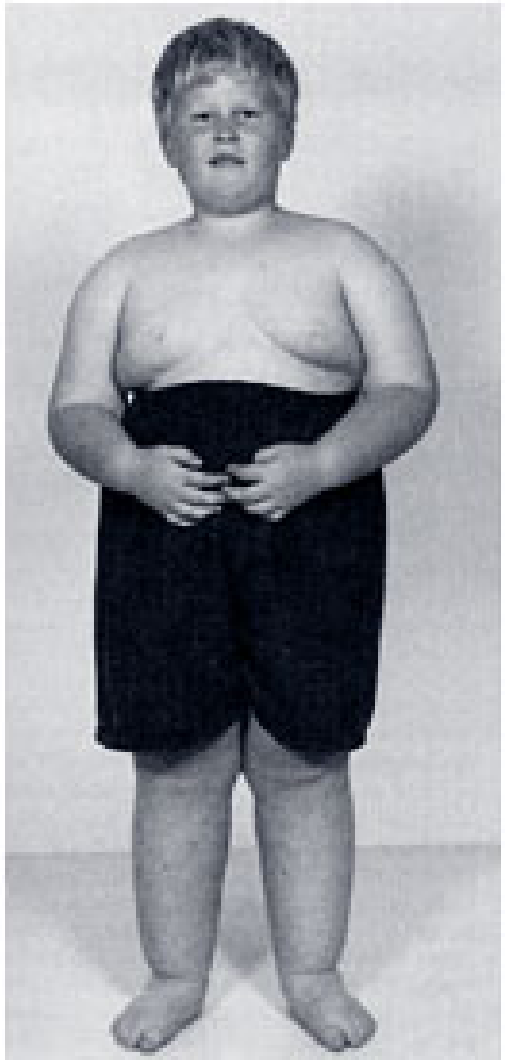


CDKN1C
2

IGF2
0

predictions

- paternally-derived genes will favor delayed maturation and late weaning
- maternally-derived genes will favor early maturation and early weaning

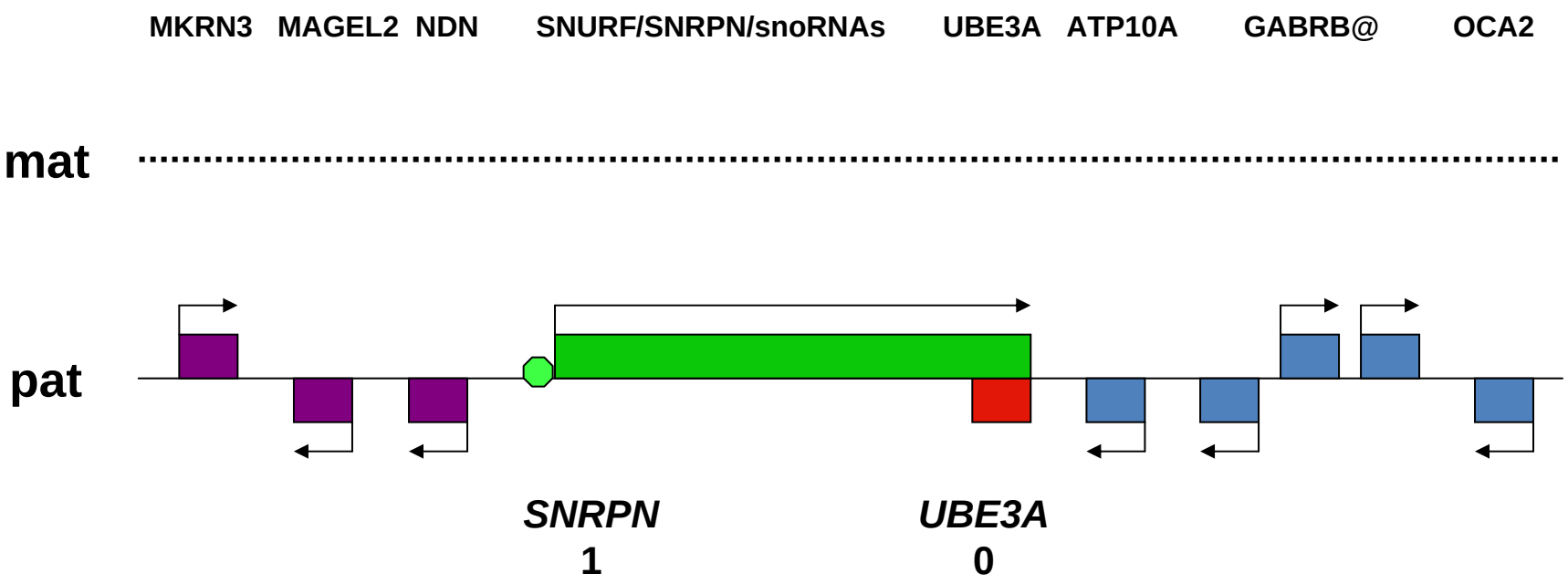


Prader-Willi

Angelman

Angelman syndrome is caused by the absence of expression of maternally-derived *UBE3A*

maternal deletion (70%)



Angelman syndrome

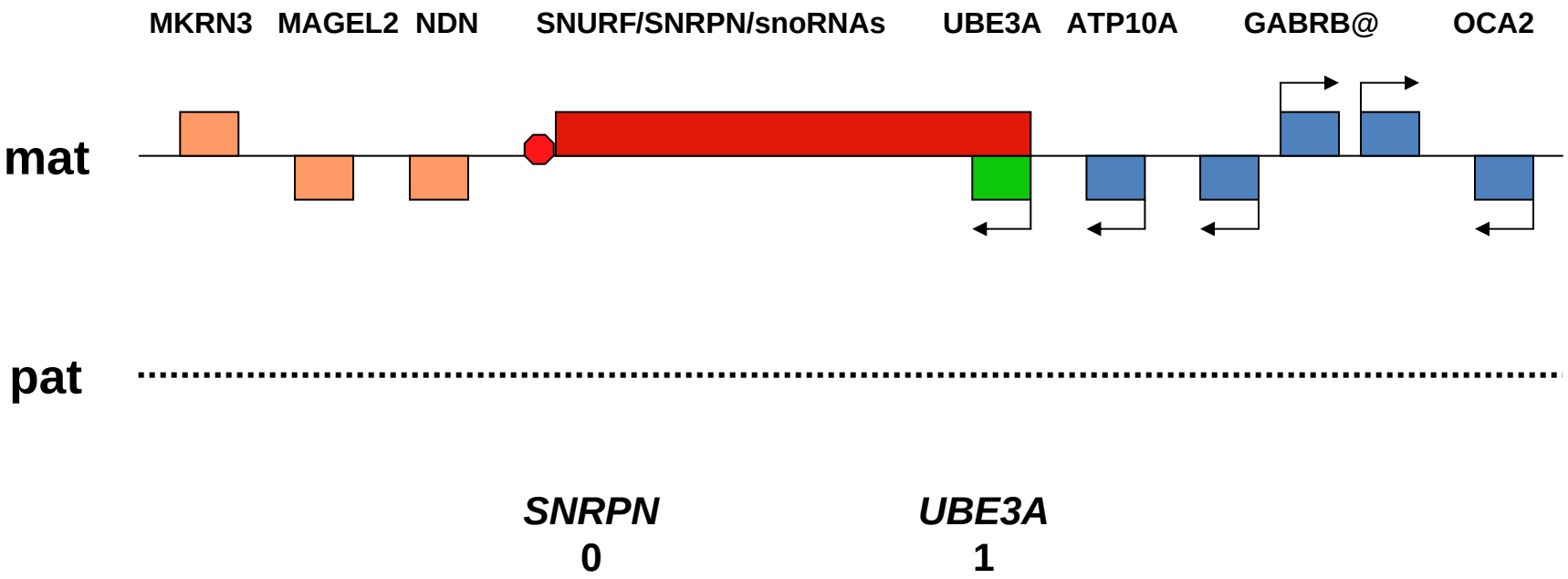
- uncoordinated suck and swallow
- tongue protrusion
- hypertonia; ataxia; hyperactivity
- epileptic seizures
- excessive wakefulness
- happy affect and frequent laughter
- speech absent

Prader-Willi syndrome

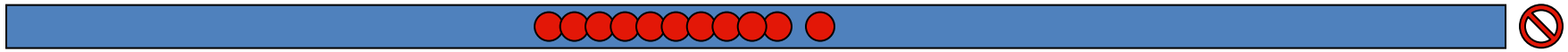
Prader-Willi syndrome
(neonatal phenotype)

- reduced fetal movements
- neonatal hypotonia
- poor suck (usually gavage fed)
- excessive sleepiness

paternal deletion

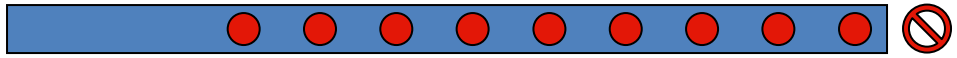


Emma



Emma started late but then produced babies rapidly

Fifi



Fifi is an outlier among female chimps

age at weaning

Orangutan	7-8 years
Gorilla	3-4 years
Chimpanzee	5 years
Human	2-3 years

Prader-Willi syndrome
(childhood phenotype)

- hyperphagia (from 2nd year)
- non-fastidious appetite
- obsession with food and 'foraging'
- massive obesity with short stature
- premature adrenarche
- delayed (or precocious) puberty

conjecture

- paternally-derived genes promote suckling
- paternally-derived genes inhibit appetite for supplemental foods
- children benefited from delayed weaning (at mother's expense) because:
  - milk is superior but more costly food
  - suckling prolonged interbirth intervals

Eugenia Martinez Vallejo

Juan Carreno de Miranda c. 1680

Jigsaw puzzles

- individuals with PWS placed twice as many puzzle pieces as controls
- individuals with PWS looked at the picture less often
- individuals with PWS were more likely to start with the borders

Dykens (2000) J. Child Psychol. Psychiatry 43: 343

Broader applications

In what species is imprinting found?

How many genes are imprinted?

Special features of the X chromosome

Can we predict the molecular mechanisms of imprinting?

What human traits are imprinted?

How many imprinted genes in mice?

1% or 5%?

MECHANISMS OF IMPRINTING IN MICE

Paternally active (N=8)

-----maternal copy (or its promoter) is silenced by methylation

-----direct and simple

Maternally active (N=5)

-----paternal copy is silenced by cis-acting anti-sense RNA

-----more complex

Why?

Former are more stable than latter because in the latter it is more likely that selection will favor conflict over the process of imprinting itself.

David Haig

Human traits

- Degree of inbreeding
- Life history traits
- Discounting functions
- Cancer