Behavioural Phenotype in Prader-Willi syndrome

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Case scenario 1

- 8yrs male 2nd born to 2nd degree consanguineous parents.
- Postnatal –floppiness/b/l undescended testis/feeding difficulties.
- O/e fair skin/almond shaped eyes/abnormal rt ear lobe/small narrow
- hands with straight ulnar border/b/l undescended testis.
- Anthropometry – Ht 123cm(50th centile), wt 36kg(97th centile)
- Behavioural problems-over eating/steals food/skin picking/stubborness/tantrums
- Methylation study for prader willi syndrome positive

Case scenario 2

- 12yr male 3rd born to 3rd deg consanguineous parents.
- Postnatal-floppiness/feeding difficulty
- o/e almond shaped eyes/straight ulnar border / micropenis /undescended testis.
- Anthropometry – wt 52kg(>97th centile) ht140cm(50th centile)
- Behavioural problems: overeating/steals food/skin picking/talks too much/stubborness/tantrums/obssesive behaviour.
- Methylation study for prader willi syndrome positive.

Case scenario 3

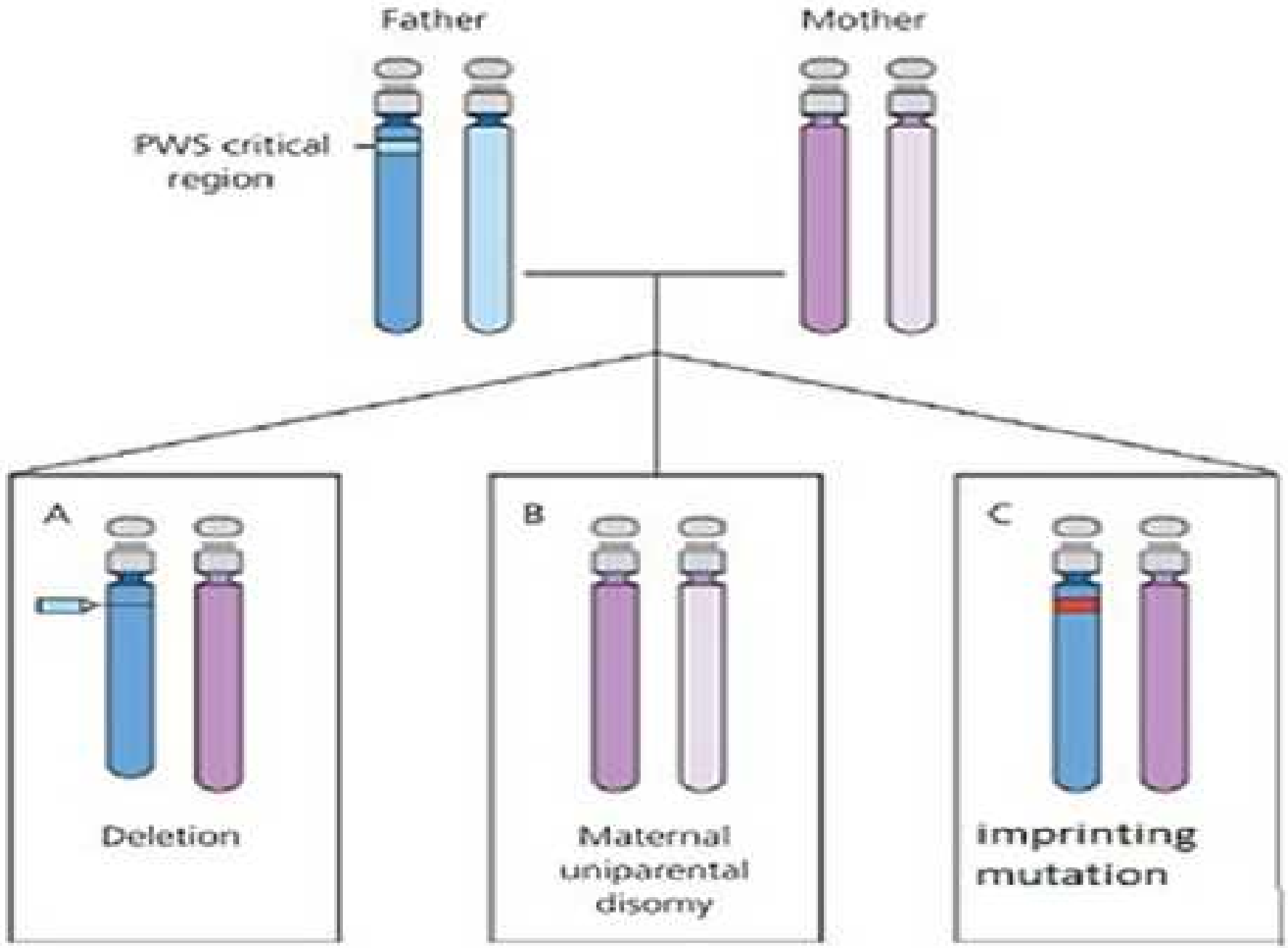
- 1yr male 1st born to 2nd degree consanguineous parents
- Antenatal - Decreased fetal movements.
- Postnatal - floppiness since birth/feeding diffculty/dev delay.
- O/e : plagiocephaly/abn ear lobes/small mouth/short philtrum/hypotonia /b/l undescended testis.
- Anthropometry – wt 7kg, ht 60cm
- FISH - Microdeletion 15q11-q13.
- Karyotyping – 46,X,inv(Y)(p11q11).

Prader Willi syndrome

- A disorder of Chromosome 15
- Occurs in 1 out of every 12,000 -15,000 births
- 1st recognised micro deletion syndrome
- 1st recognised imprinting disorder
- Most common genetic cause of obesity

Genetics

- Due to lack of paternal chromosome copy of *SNRPN* gene expression
- Located on chromosome 15q11-q13
- Molecular mechanisms
  1. del 15q11-q13 pat (~70%)
  2. Maternal uniparental disomy (~30%)
  3. Mutation of the imprinting control center (~1%)

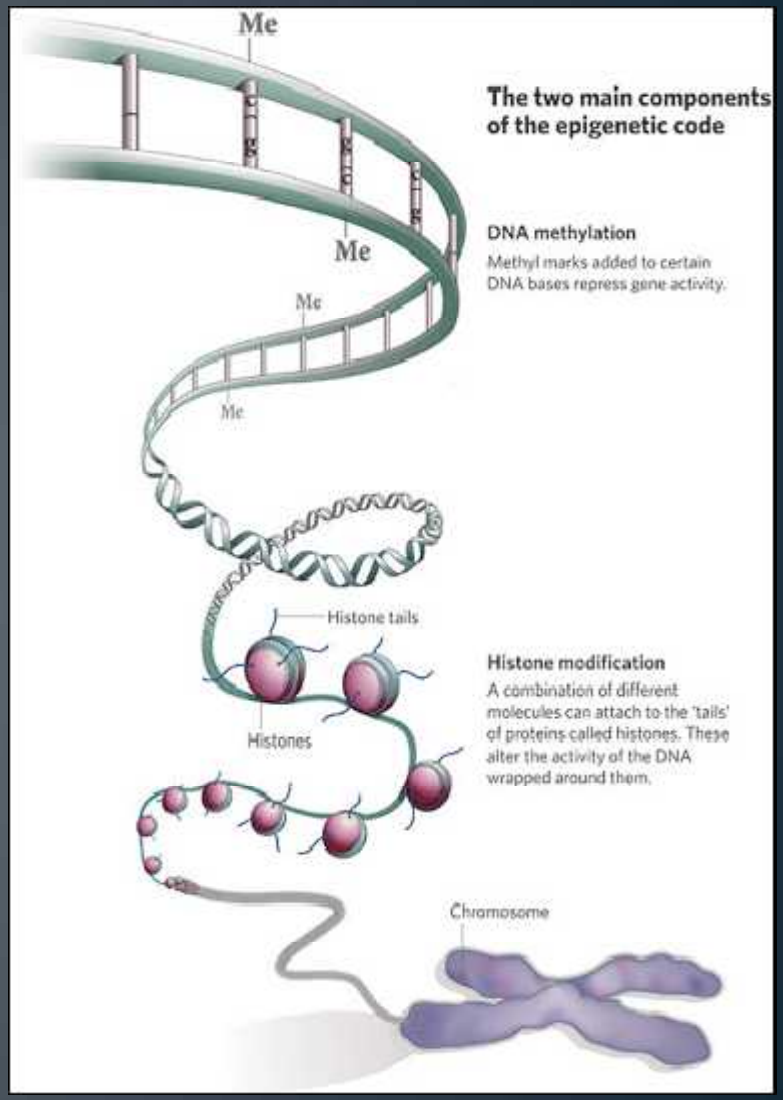

Father
Mother
PWS critical region
A
Deletion
B
Maternal uniparental disomy
C
imprinting mutation
(~ 70)
(~ 25)
(~ 1)

Imprinting and Epigenetics

- Most of our genes come in pairs with one copy inherited from each parent. Both the copies are equally important. (biallelic expression)
- In some cases, parent of origin of the gene is very important (i.e. there is monoallelic expression of the gene)
- These genes cause different diseases depending on the parent of origin.
- This parent of origin effect is known as Imprinting and the genes are known as “imprinted genes”.
- These “imprinted” genes are controlled by epigenetic phenomenon.

Common Epigenetic Mechanisms

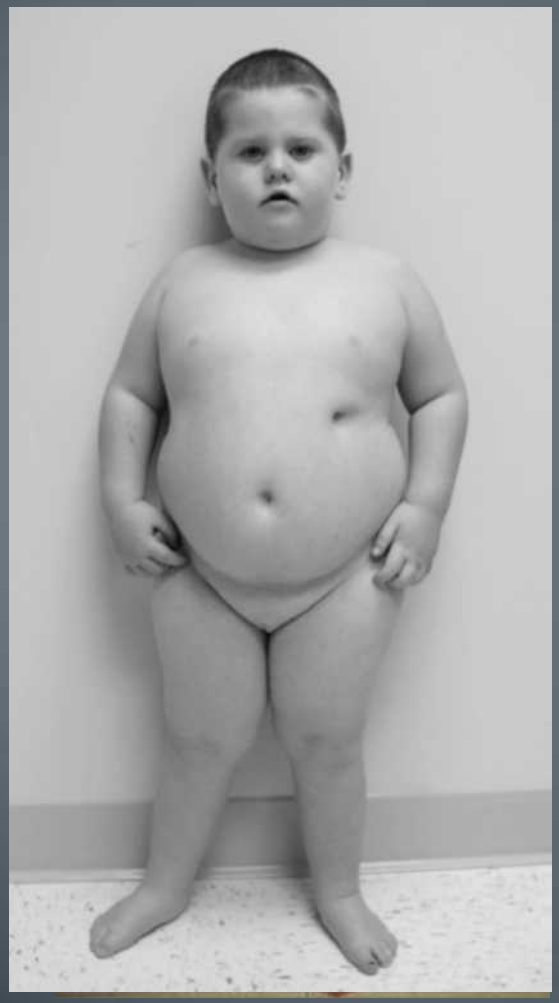
- DNA Methylation
- Histone modification
  - Acetylation and Deacetylation
- Interfereing RNA (RNAi)



Clinical features of PWS

- Floppy newborn infant (hypotonic)
- Small for gestational age
- Undescended testicles for males
- Delayed motor development
- Slow mental development
- Very small hands and feet in comparison to body
- Rapid weight gain
- Food cravings
- Almond Almond-shaped eyes
- Narrow bifrontal skull
- Morbid obesity
- Skeletal (limb) abnormalities

Body composition



- Abnormal linear growth
  - –growth hormone deficiency
- Body fat -40 to 60%
- Lean muscle mass reduced
- Resting energy expenditure reduced
  - – ~60% of predicted based on BSA
  - – caloric tolerance

BEHAVIOURAL PHENOTYPE

- Is characteristic cognitive, personality, behavioural and psychiatric pattern.
- Number of genetic syndromes have distinctive and consistent behaviour pattern.
- It may act as an important diagnostic sign.

Behavioural and psychological

- Temper tantrums (often food related)
- Obsessional thinking
- Compulsive behaviour
  - –ordering
  - –skin picking
  - –food

  Stubborn
- Anxiety
- Impulsive
- Stealing
- Lying
- True OCD and psychosis

Testing options for PWS

- Methylation analysis
  - –identifies all causes of PWS
- FISH (fluorescence in-situ hybridization)
  - –identifies deletions (~70-75% of PWS)
- UPD (uniparental disomy) studies
  - –~20% of PWS
- Imprinting center analysis
  - –~5% of PWS
  - –only cause with significant potential for recurrence

Criteria to Prompt Diagnostic Testing-PWS (Guray Aygun et al., 2001)

- Less than 2 years-Hypotonia with poor suck in NB
- 2-6 years-Hypotonia w/h/o poor suck in NB & develop delay
- 6-12 years-H/o hypotonia & Develp delay& Excessive eating with central obesity
- 13 years and older-Cognitive impairment, excessive eating with central obesity& hypothalamic hypogonadism and/or typical behavior problems

PWS-Management

- Mostly supportive
- Special feeding techniques in infancy
- Infant stimulation & special educational resources
- Obesity-appropriate nutrition,exercise &environmental controls
- Growth deficiency and abnormal body composition by Growth Hormone replacement
- Sex hormone therapy
- Behavioral problems-parental skill enhancement, behavior modification or psychotropic medication
- Treatment for abnormal saliva secretion % sleep disturbance

Conclusion

- PWS –a complex multisystem mental retardation disorder
- Caused by several genetic alterations of 15 q
- Distinctive behavioral phenotype
- Treatable genetic disorder