A Syndromic cause for Hypotonia

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History

- 40 day old term male baby
- FTND Birth Wt : 2.47 kg
- APGAR-3,4,6 at 0,5,10 min
- Hypotonic
- Poor sucking – Tube feed initiated
- Poor respiratory effort- Intubation and positive pressure ventilation

On Examination

- Dolichocephaly
- Low set ears
- Micrognathia
- Low voice volume

Investigations

- Blood counts
- CPK
- Electrolytes
- Ammonia
- Pyruvate
- Glucose

} Normal

- Karyotyping –Normal 46 XY

Course & Follow up

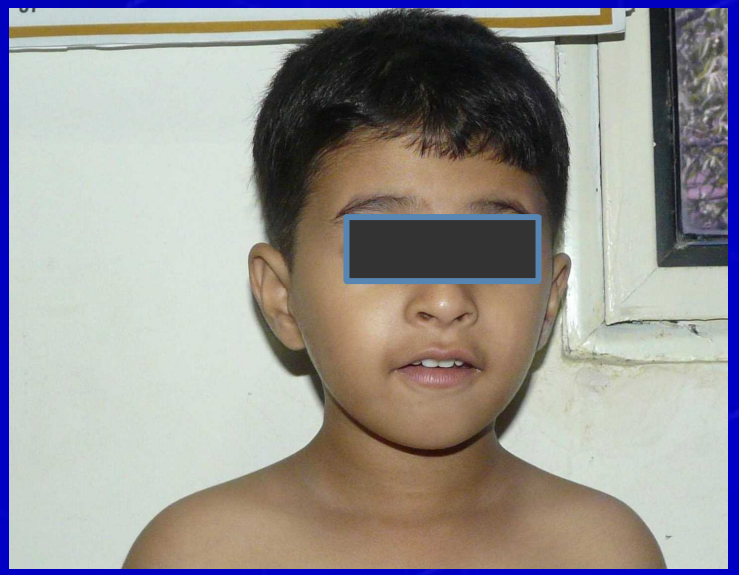
- Tone improved substantially
- Took direct breast feeds
- Discharged after 10 days of hospital stay
- Needs further work up
- Lost for follow up

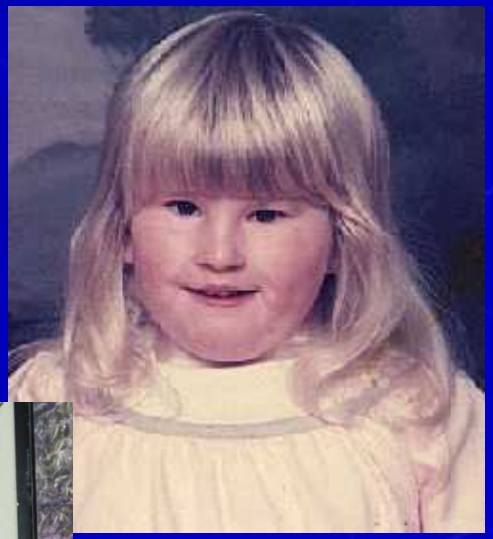
After 4 years

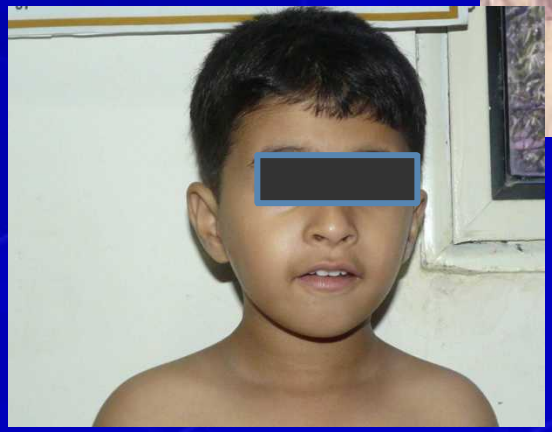
- Patient was referred again in view of cat like cry
- Rule out Cri du chat

Dysmorphism

- Narrow bifrontal diameter
- Almond-shaped palpebral fissures
- Narrow nasal bridge
- Thin upper lip
- Down-turned mouth
- Low set ears
- Hypoplastic genitalia







Diagnosis

PRADER- WILLI SYNDROME

(FISH- Deletion in 15q11-13 region)

Discussion

- Clinical presentation
  - Dysmorphism
  - Other features
- Genetics in Prader Willi Syndrome
- Multidisciplinary Approach in case management

Clinical Presentation

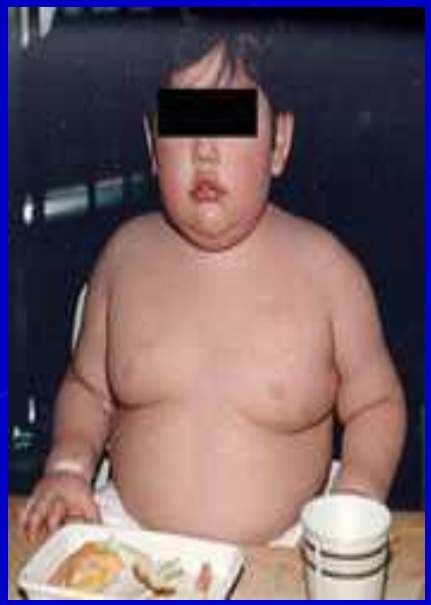
- Facial Dysmorphism
- Small hands with narrow palms with hypoplastic hypothenar eminence
- Short feet with short toes
- Fair hair & hypopigmentation of the eyes and skin (OCA 2 deletion)

Clinical features - Stage 1: Hypotonia

- Neonatal hypotonia
- Difficulty in feeding
  - Feeding gastrostomy
- Failure to thrive
- Delayed motor milestones
- Delayed speech
- Genital hypoplasia

Stage 2- Progressive hyperphagia

- Constant hunger
- Insatiable appetite
- Food seeking behaviour
- Hypothalamic dysfunction
- Short stature- GH deficiency
- Sleep apnea
- Behavioural problems
- Morbid obesity



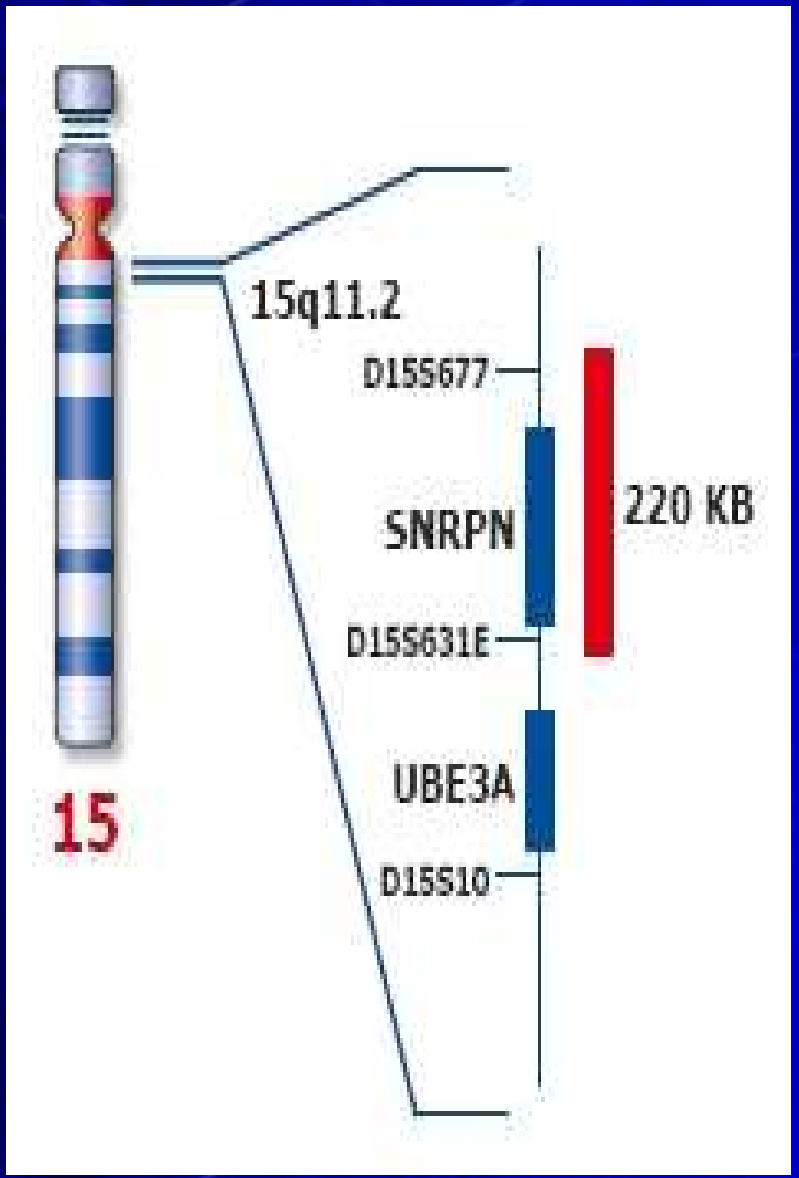
Stage 3:Adolescence and Adults

- Complications of obesity
- Hypercholesterolemia
- Type II diabetes
- Hypertension
- Osteoporosis
- Myocardial Infarction and Stroke
- Sleep apnea

Living with Prader Willi .....

People with this disorder can literally eat themselves to death because they never feel full

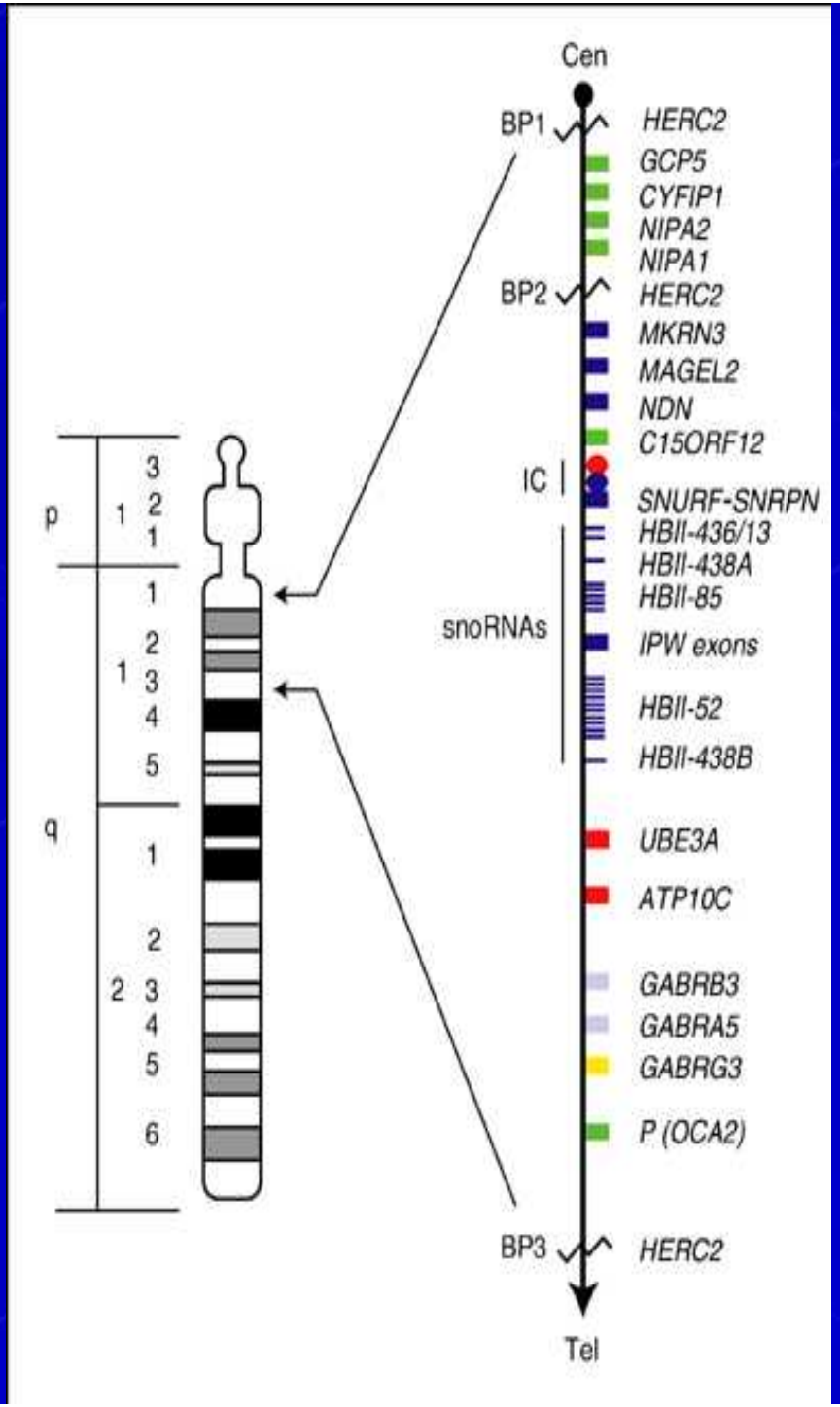
Genetics in Prader Willi Syndrome



- Complex multisystem genetic disorder
- Lack of expression of paternally inherited imprinted genes
- 15q 11-q13

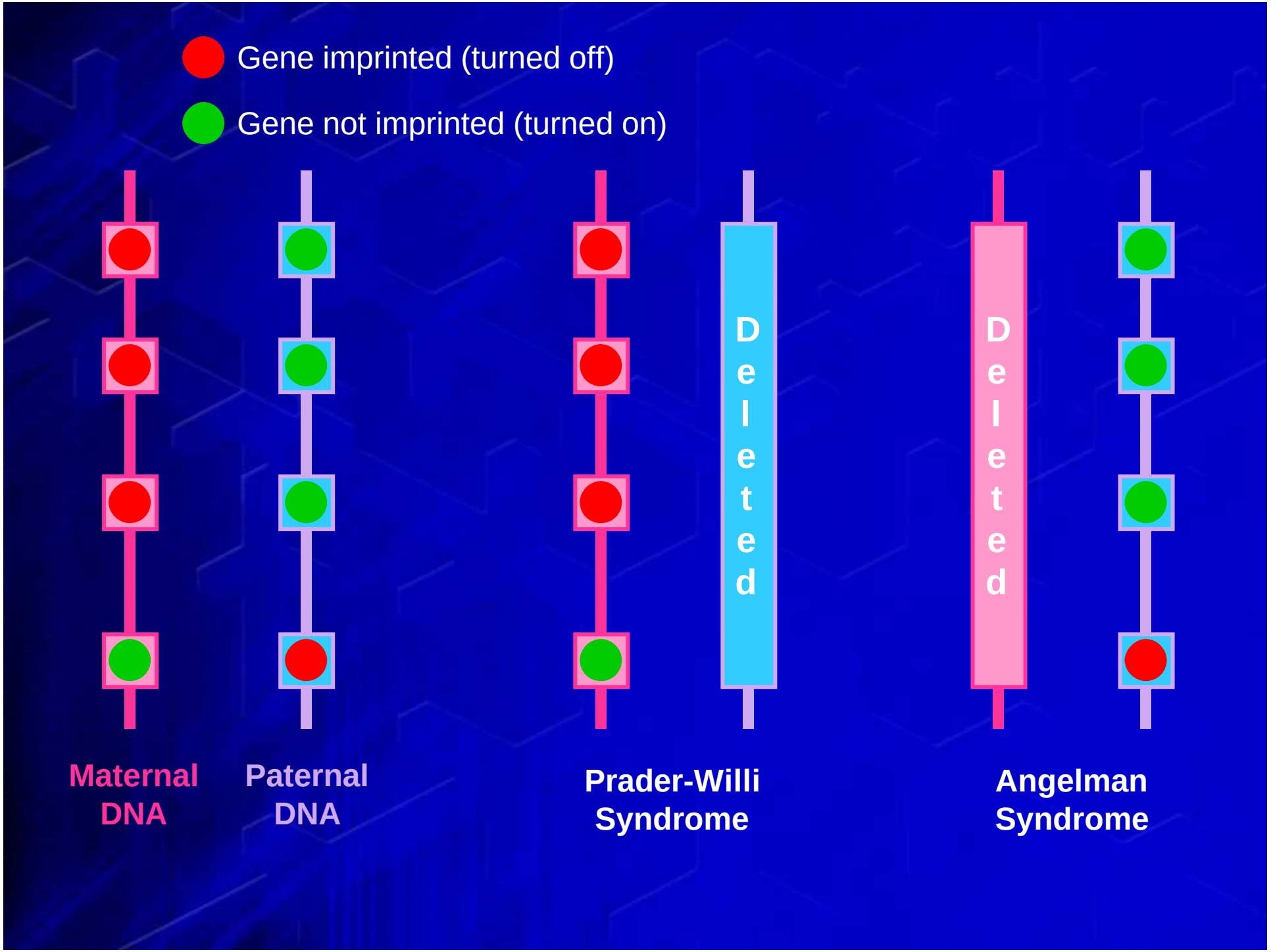
Important genes in 15q11-13

- **NDN-NECDIN :candidate gene**
- **MAGEL2 (Melanoma antigen like gene)**
- **SNURF-SNRPN**
- **MRFP**
- **PAR 5**
- **PAR 7**
- **OCA 2**



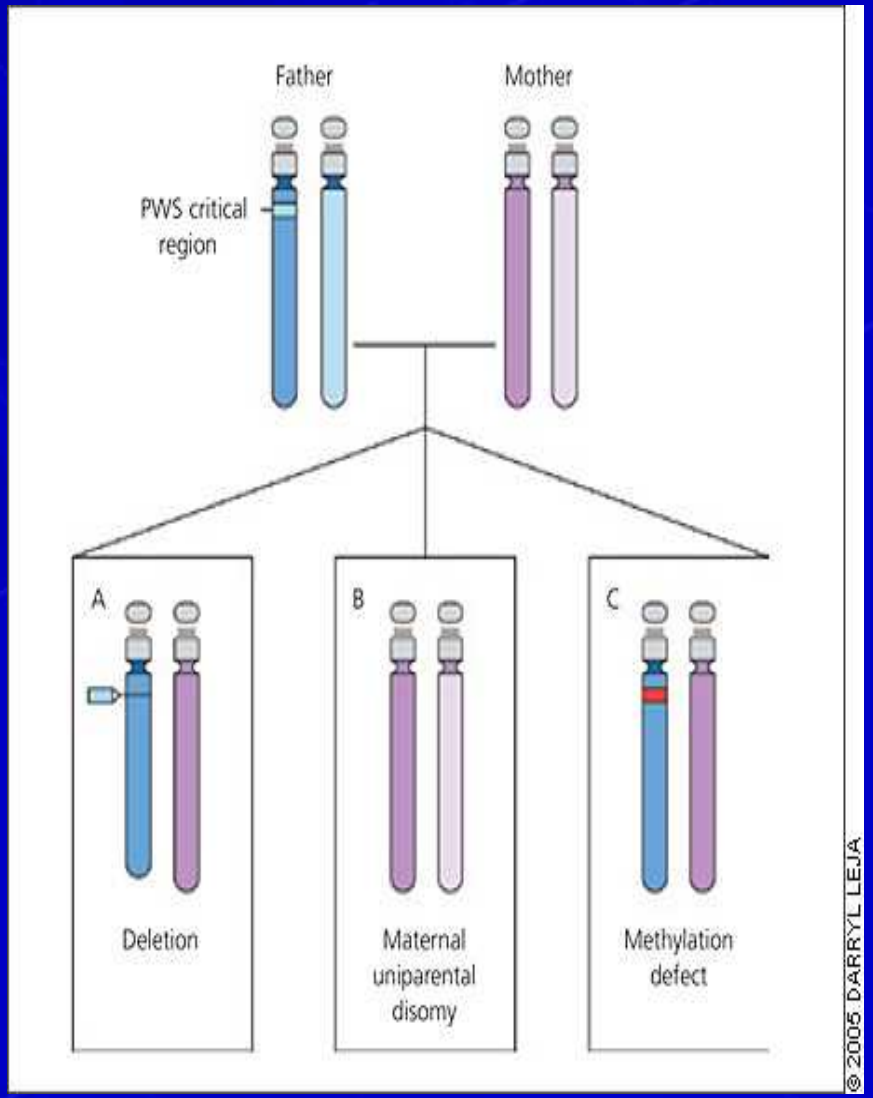
Genomic Imprinting

- Expression of a gene from only one parent's chromosome
- Silencing of the genes from the other parent's chromosome.
- In Prader Willi region
  - Paternal region is active
  - Maternal inactive


Gene imprinted (turned off)
Gene not imprinted (turned on)
Deleted
Deleted
Maternal DNA
Paternal DNA
Prader-Willi Syndrome
Angelman Syndrome

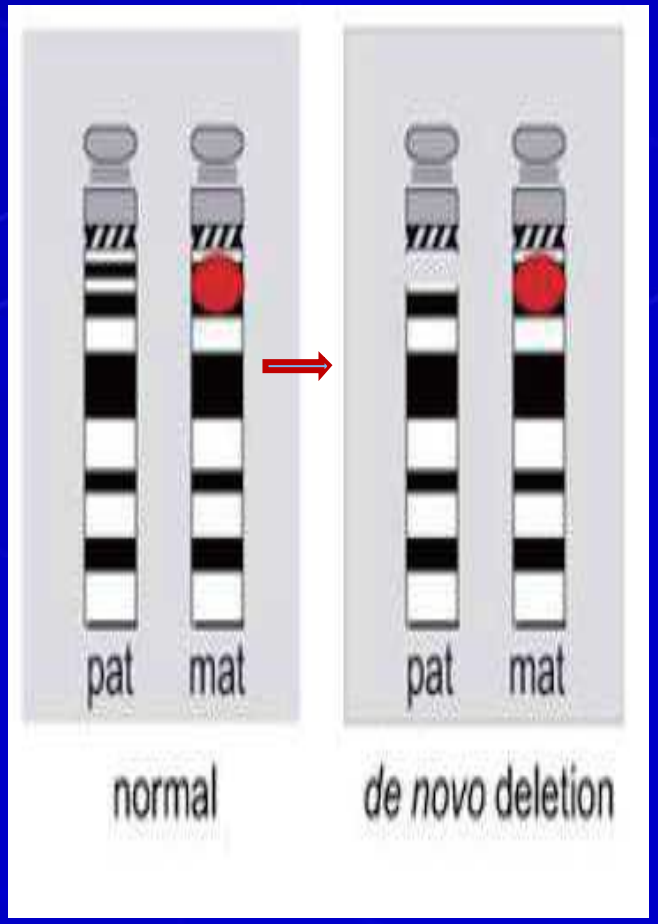
Three genetics mechanisms in Prader Willi Syndrome

1. Paternal deletion 70%
2. Maternal uniparental disomy-25%
3. Imprinting defect <5%

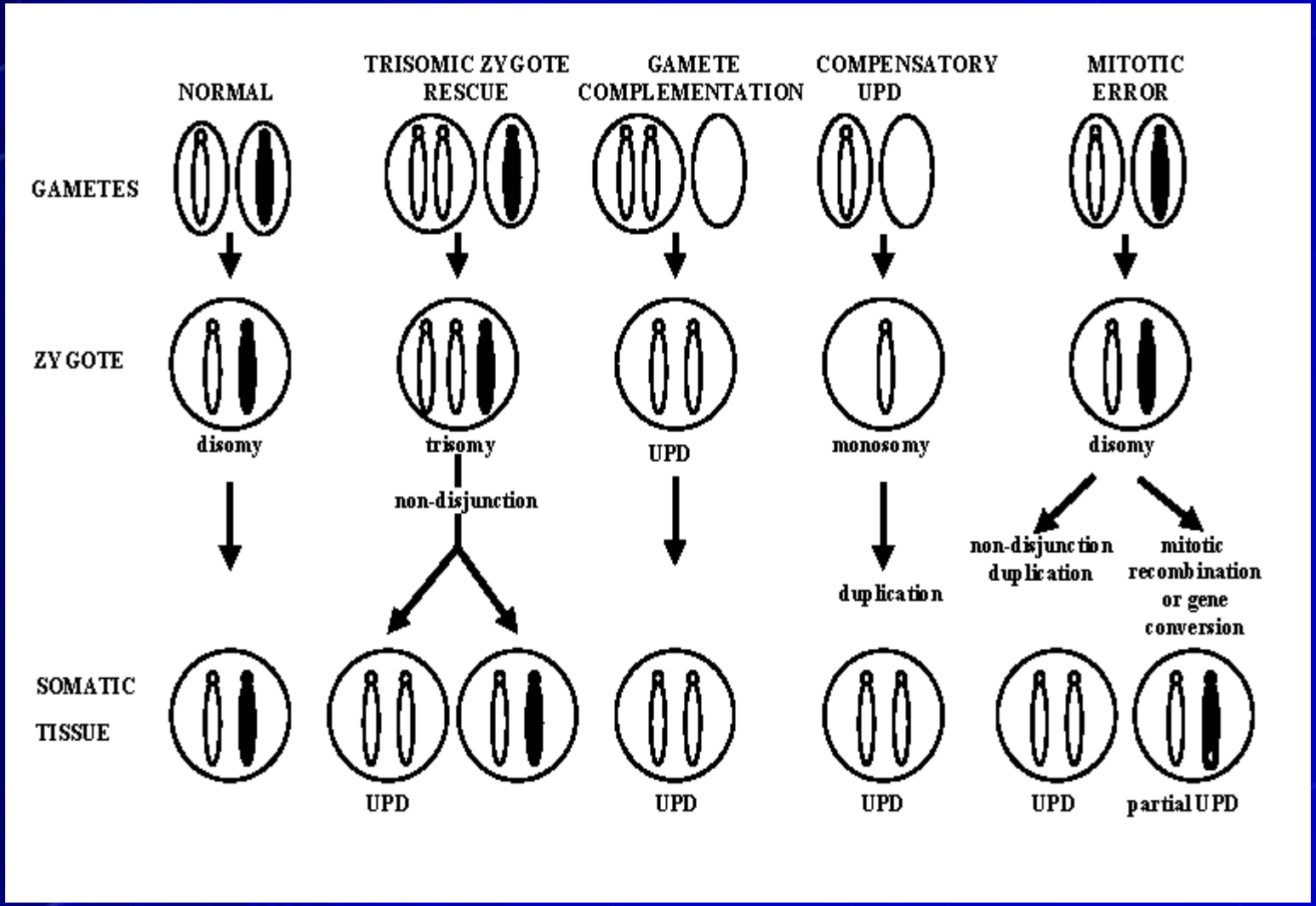


Deletion

- Constitutes 70% cases
- Etiology Unknown
- <1% chance of recurrence



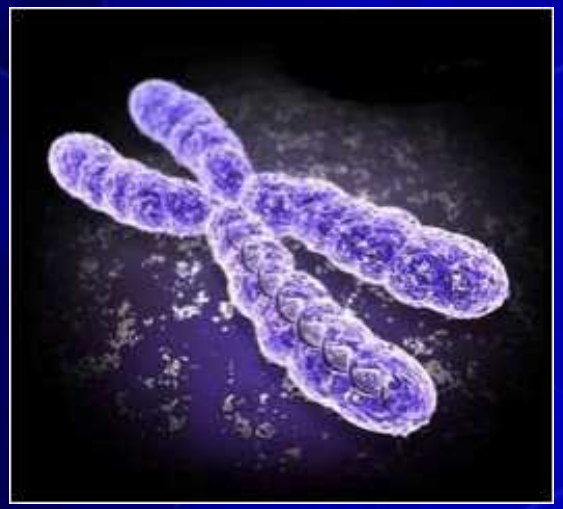
Uniparental disomy : <1%recurrence



Imprinting defects

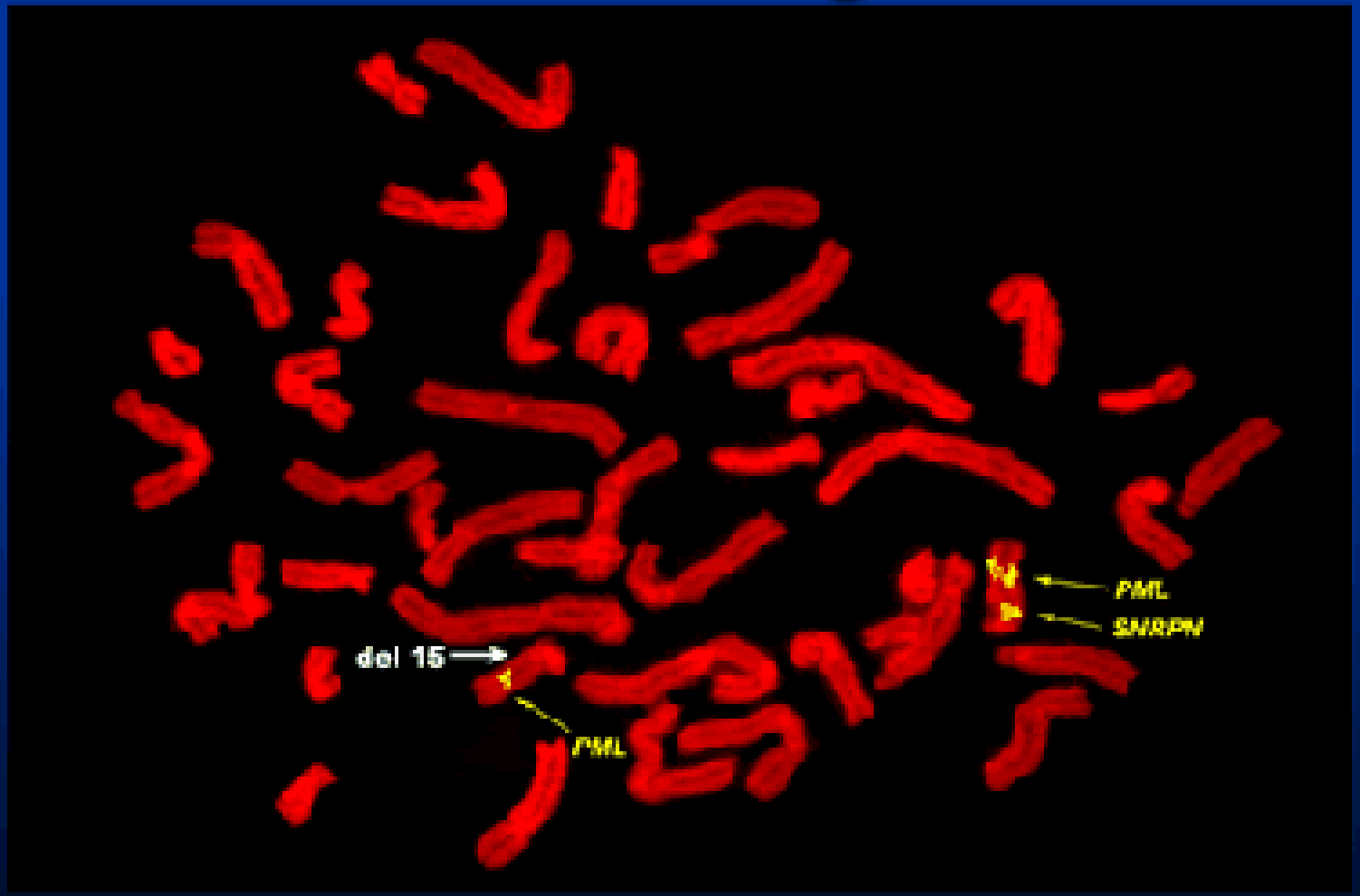
- Two Mechanism
  - Deletions in imprinting centre
  - Epigenetic mutation
- Can be identified by methylation studies
- Risk of recurrence - 50%

Genetic tests in Prader Willi Syndrome



- High resolution chromosomal analysis
- FISH
- DNA methylation studies
- DNA polymorphism studies- UPD

Prader-Willi Syndrome



Fluorescent *in situ* hybridization (FISH) demonstrating deletion (del) of *SNRPN* probe on one of the chromosomes 15s.

Follow up- Multidisciplinary Team

- Endocrinologist
  - Hypopituitarism
  - Growth hormone supplementation
  - Type 2 DM
  - ?LH supplementation
- Ophthalmologist
  - Strabismus
  - Astigmatism
  - Myopia
- ENT specialist
  - Recurrent ear infection
  - Obstructive sleep apnea

Follow up- Multidisciplinary Team

- Orthopaedician
  - Scoliosis
  - Slipped capital femoral epiphysis
  - Hip dysplasia
  - Pathological fractures
- Psychologist
  - Speech therapy
  - Binge eating
  - Temper tantrums
  - Stubbornness
  - Obsessive compulsive disorder
  - Psychosis

Follow up- Multidisciplinary Team

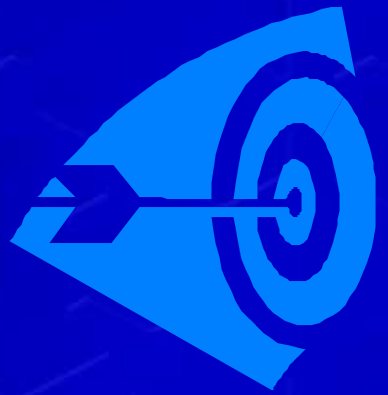
Dietician

- Most important role
- Dietary restrictions
- Calorie guidance

Family support

- Support & understanding
- Restrictions on food
- Lock food, kitchen cupboards
- Encourage exercises

Take Home Message



- Suspect Prader Willi Syndrome

  (Neonatal hypotonia,Hypogonadism,Dysmorphism)

- Confirm Prader Willi Syndrome
  - FISH
  - DNA methylation studies
  - DNA polymorphism studies- UPD
- Genetic diagnosis takes time in some cases and

  Periodic follow up with revaluation will definitely help

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