Mahidol University
Faculty of Medicine Ramathibodi Hospital

Prader-Willi syndrome: Genetics and Development

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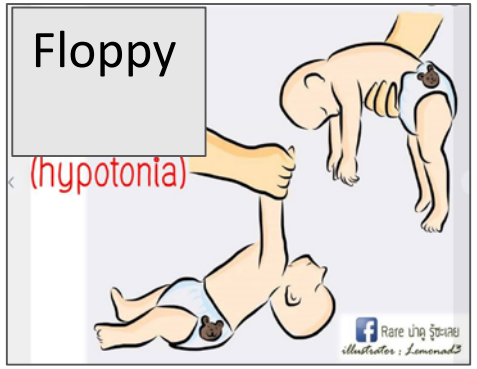
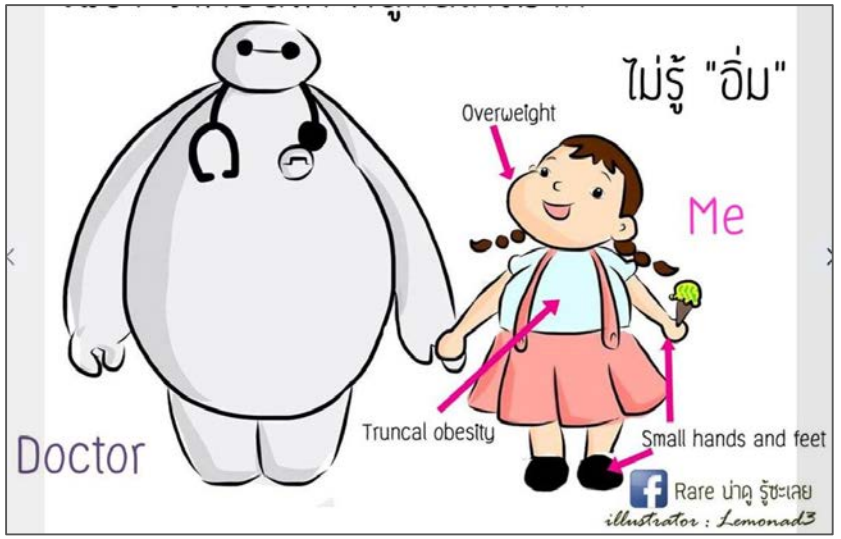
APPWS 29th Oct 2021





Early infancy

- Severe hypotonia
- Poor suck &
  Feeding difficulties
- Lethargy
- Weak cry
- Decreased movement
- Poor growth
  & Development

Childhood (if left untreated)

- Excessive eating
- Morbid obesity
- Developmental delay

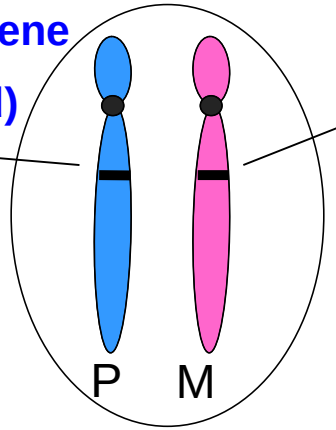
3 main molecular mechanism causing Prader-Willi syndrome

Lack of functional SNRPN

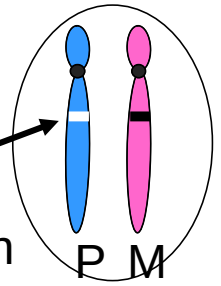
Normal
15q11-q13

SNRPN & its related gene active (unmethylated)

SNRPN & its related gene imprinted (methylated)

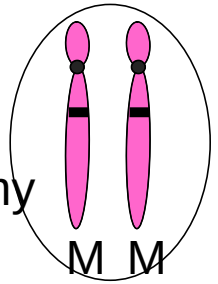


15q11 deletion



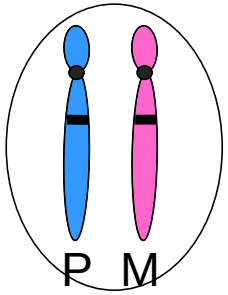
65-75%

mat disomy 15



20-30%

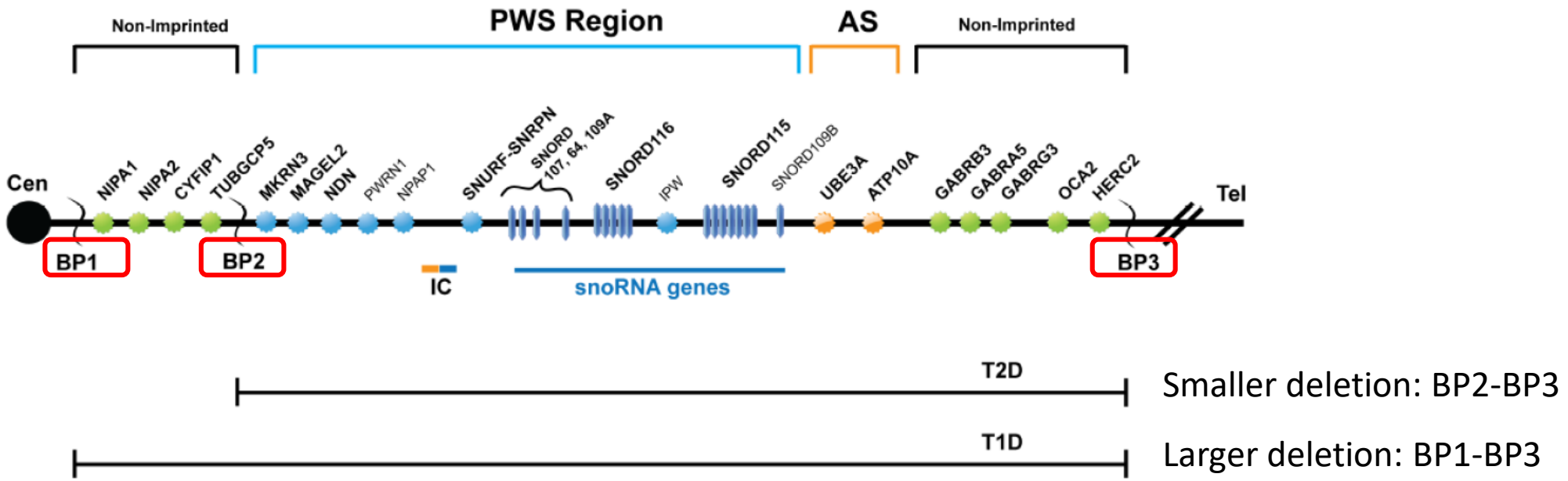
Imprinting defect



<1%

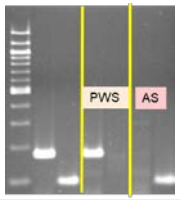
Genomic imprinting of 15q11-q13: genes to be expressed in a parent-of-origin-specific manner

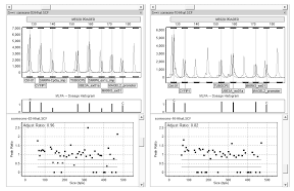
15q11.2-q13 regions and gene expressed

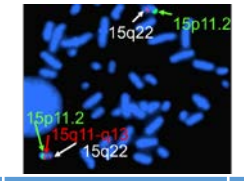


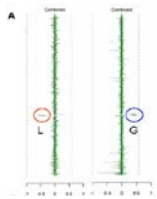
- paternal-only-expressed
- maternal-only-expressed
- Biparental-expressed (non-imprinted)

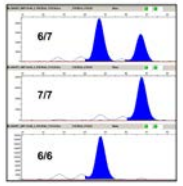
Driscoll DJ, et al. Prader-Willi Syndrome.. GeneReviews®; 1993-2021. https://www.ncbi.nlm.nih.gov/books

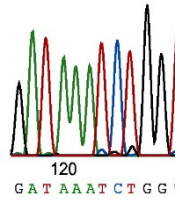


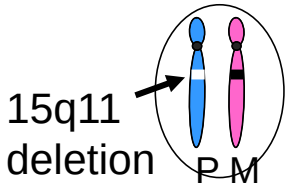


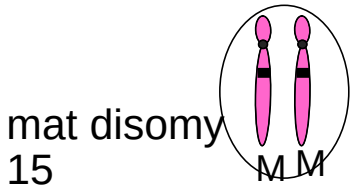


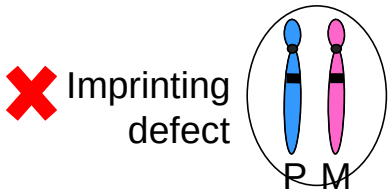












	MS (methylation)	MS-MLPA	FISH	CMA	CMA-SNP array	DNA polymorphism	sequence
15q11 deletion	✓	✓	✓	✓	✓		
mat disomy 15	✓	✓			✓	✓	
Imprinting defect	✓	✓				✓	✓
detection frequency	>99%	>99% detect size of deletion	65-75%	65-75% detect size of deletion	80-90%	20-30%	<1%

UPD = uniparental disomy
MS = Methylation-specific study
MS-MLPA = multiplex ligation-dependent probe amplification(MS-MLPA)

FISH = fluorescence in situ hybridization (along with karyotype)
CMA = chromosomal microarray
CMA-SNP array = CMA using single nucleotide polymorphism (SNP)

Comprehensive testing strategy to identify molecular defect of PWS

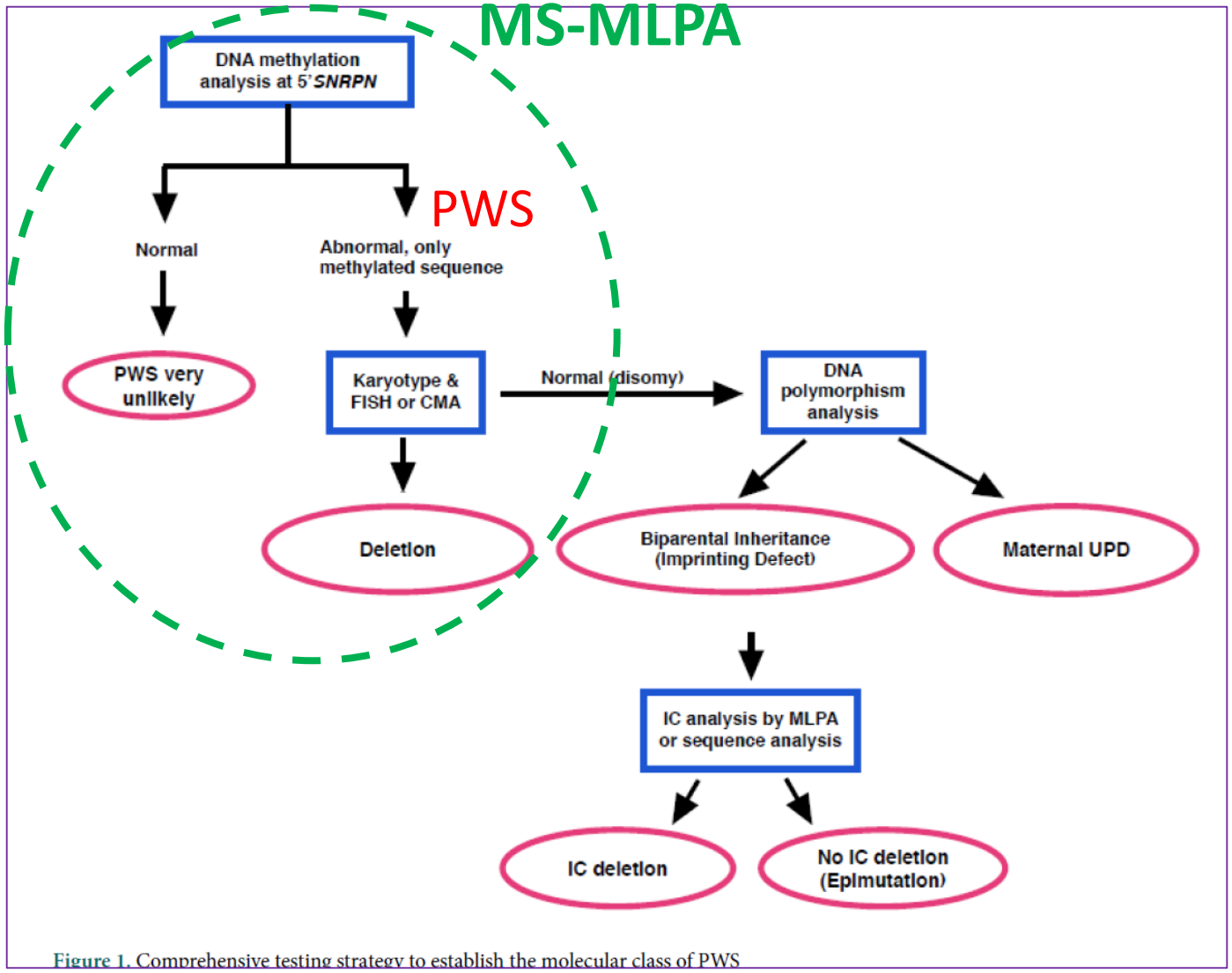


Figure 1. Comprehensive testing strategy to establish the molecular class of PWS

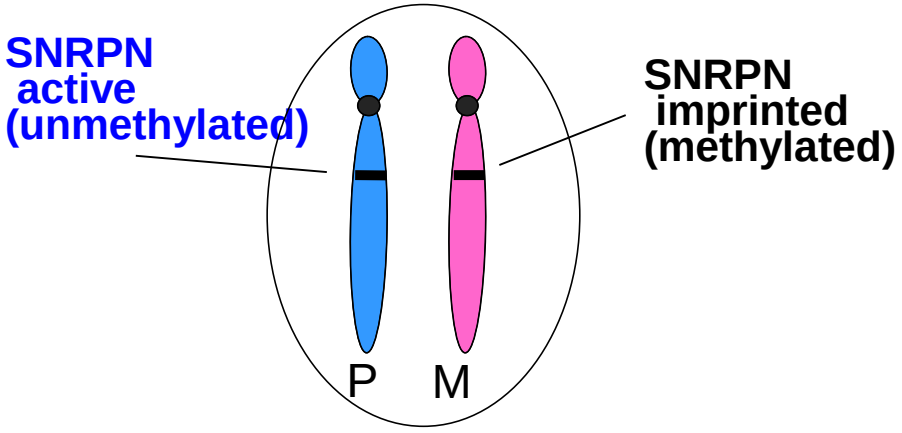
Driscoll DJ, et al. Prader-Willi Syndrome.. GeneReviews®; 1993-2021. https://www.ncbi.nlm.nih.gov/books

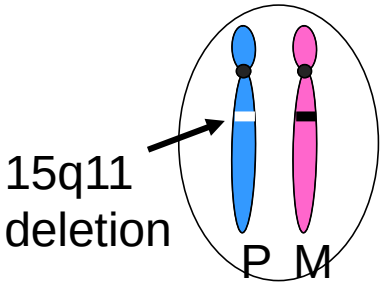
to identify genetic mechanism underlying PWS in each child?

A DNA methylation (MS) is sufficient for confirmation of PWS diagnosis, BUT NOT SUFFICIENT FOR **Genetic Counseling**

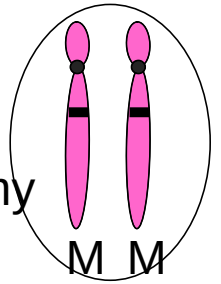
3 main molecular mechanism causing Prader-Willi syndrome

Normal
15q11-q13

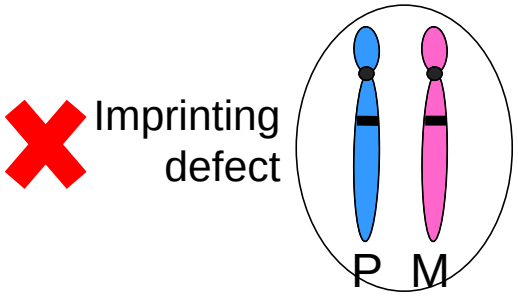




65-75%



20-30%



<1%

Genetic Counseling: Risk to Sibs

<1%

but possibly 50% in case of unbalanced chromosomal rearrangement

<1%

but could be 1-100% in rare case with parental chromosomal translocation or marker chromosome

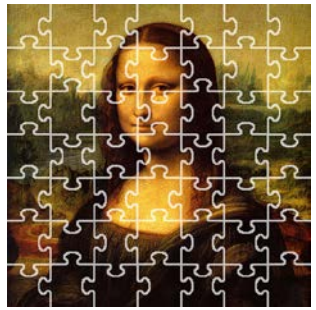
<1%

but up to 50% in case of the father having imprinting center gene defect

Genomic imprinting of 15q11-q13: genes to be expressed in a parent-of-origin-specific manner

- No exclusive correlation between clinical manifestations and type of genetic defect
  BUT there are some statistical differences in the frequency or severity of certain features

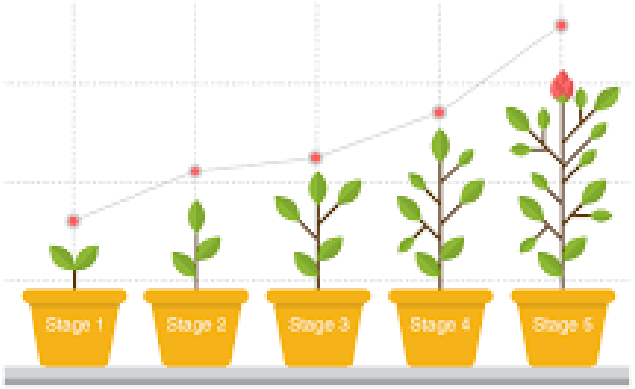
	Disomy (matUPD)	Deletion
Typical facial feature	+	++
Hypopigmentation	+	++
Jigsaw puzzle skill	+	++
Verbal IQ	higher	Speech articulation defect
Behavioral problem	milder	Larger (type 1) deletion: Poorer adaptive behavior, intellectual ability, academic performance, as compared to smaller (type 2) deletion
Risk of psychosis	higher (62%)	lower (16%)
Risk of autism spectrum disorder	++	+



- Larger studies are needed to determine whether there are significant clinical differences between the disomy vs deletion; and between the larger vs smaller deletion

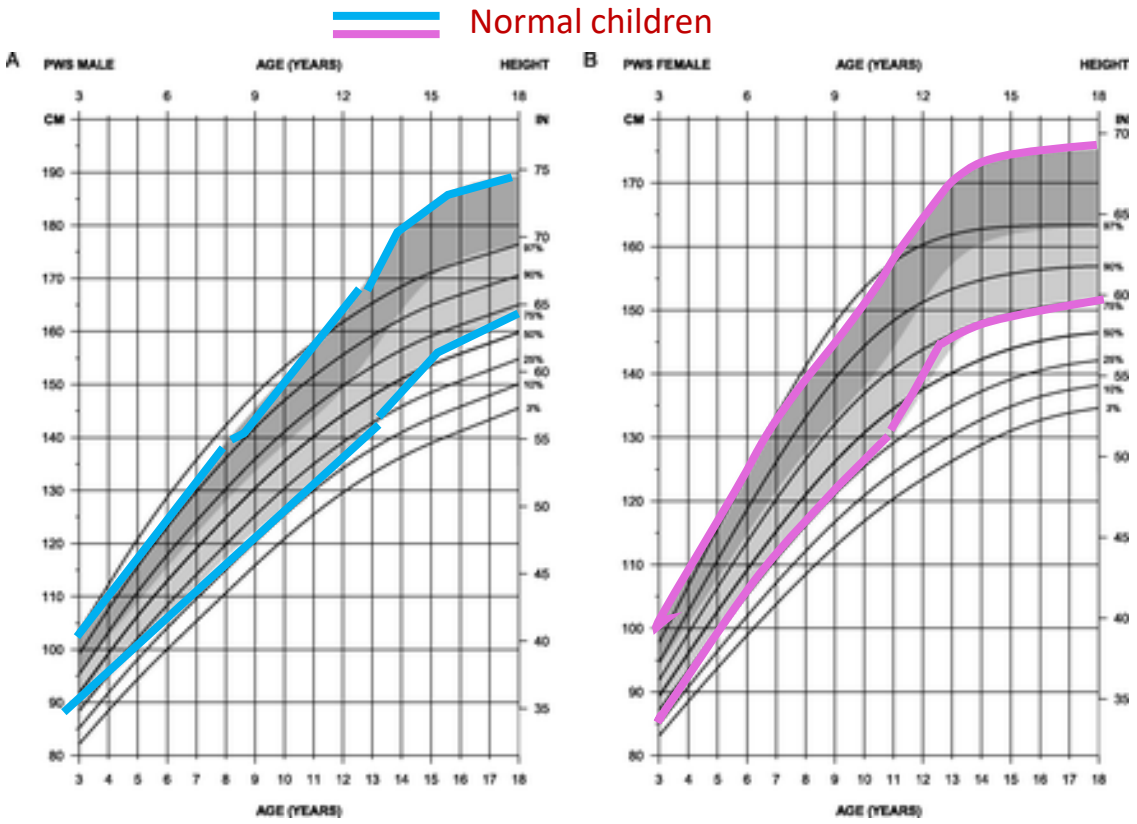
Driscoll DJ, et al. Prader-Willi Syndrome.. GeneReviews®; 1993-2021.
https://www.ncbi.nlm.nih.gov/books

Growth and Development

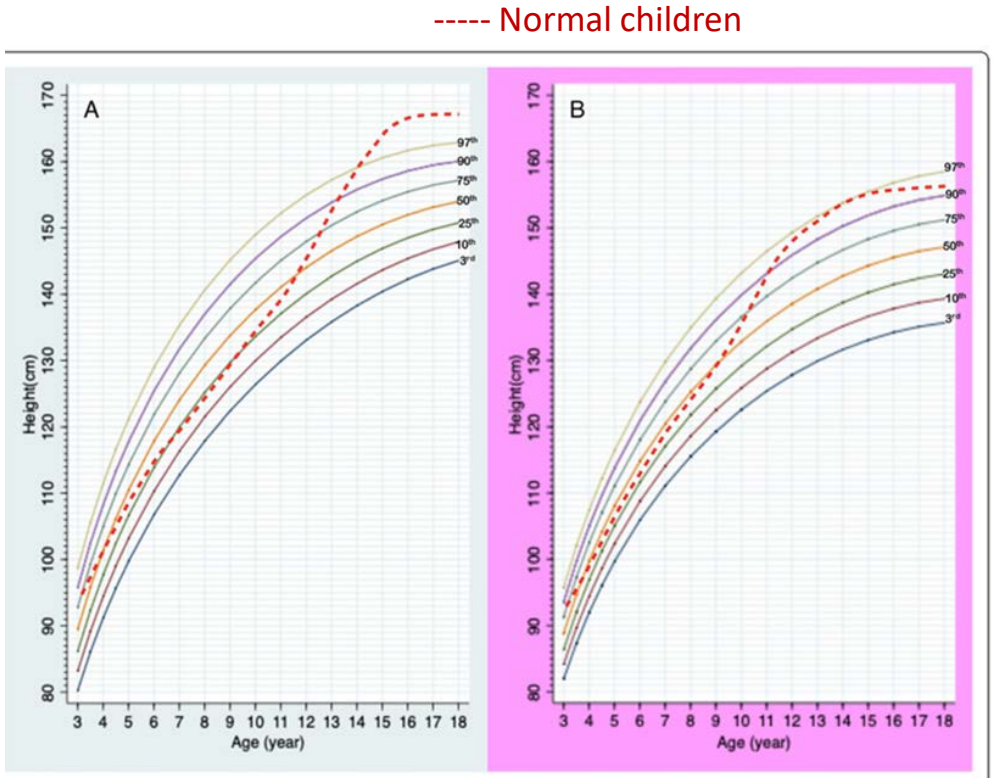


Growth in PWS

- **Short stature**, if not apparent in childhood, is almost always **present during the second decade in the absence of growth hormone** (GH) replacement
- Lack of a pubertal growth spurt - average untreated height: 155 cm for M; 148 cm for FM



Growth Charts for Non-Growth Hormone Treated Prader-Willi Syndrome.
Butler MG,et al. Pediatrics. 2015, 135 (1) e126-e135



Growth charts for Thai children with Prader-Willi syndrome aged 0–18years
Mongkollarp, N. et al. Orphanet Journal of Rare Diseases (2020) 15:111

Growth in PWS

- The hands and feet grow slowly and are generally below the 5th centile by age 10 years

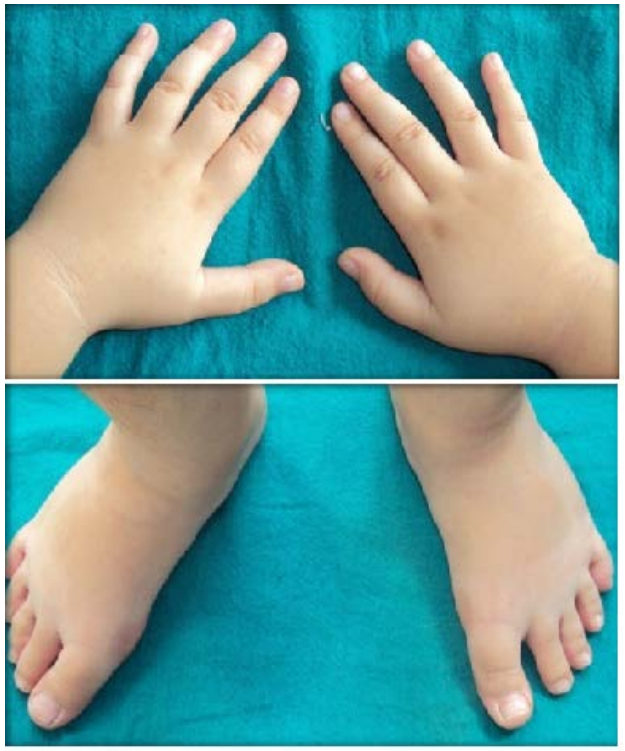
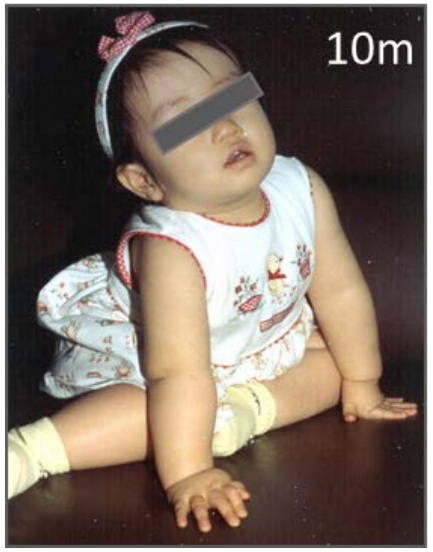


Figure 4: Small hands and feet.

Tayal, E at al. Public Health Open J. 2016; 1(1): 12-15.

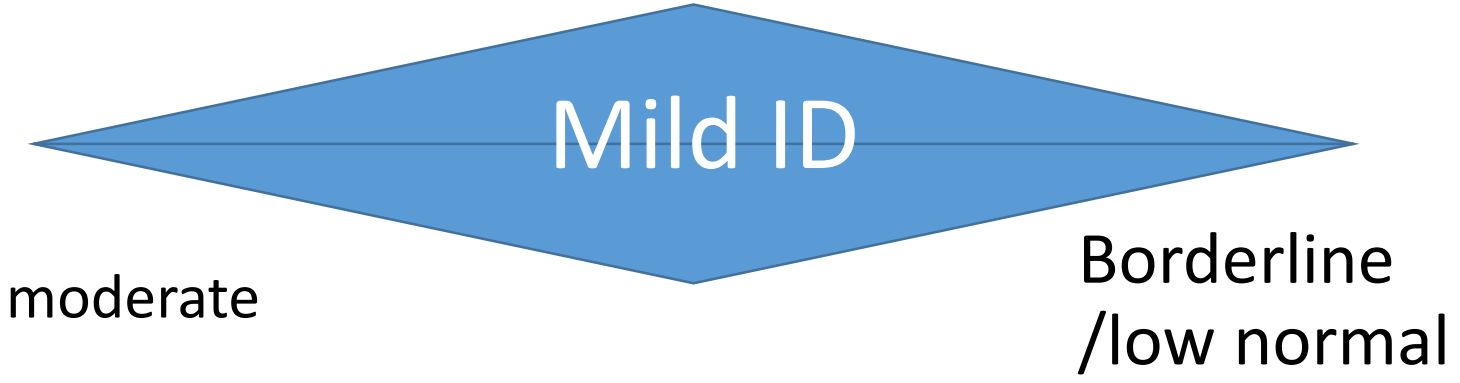
Motor Development

- Delayed motor development found in 90%-100% of children with PWS average early milestones **achieved at about double the normal age** (e.g., sitting at 12 months, walking at 24 months)



Language and Intellectual Abilities

- Language milestones are also typically delayed.
- Intellectual disabilities are generally evident by the time the child **reaches preschool age**
- Most persons with PWS - mildly intellectually disabled range - mean IQ: 60s to 70s with approximately 40% having borderline disability or low-normal intelligence and approximately 20% having moderate disability



Driscoll DJ, et al. Prader-Willi Syndrome.. GeneReviews®; 1993-2021. https://www.ncbi.nlm.nih.gov/books

- Most children with PWS have **multiple severe learning disabilities** and poor academic performance for their intellectual abilities

- Learning disabilities occur in very young children, the disorders are usually not recognized until the child reaches school age

- It is important to identify LD earlier in children with PWS – proper intervention

Learning Disabilities

Disorders that affect the ability to

- Understand or use spoken or written language (Dyslexia)
  difficulty decoding words or with phonemic awareness,
  identifying individual sounds within words

- Trouble converting their thoughts into writing or drawing (Dysgraphia),
  spelling, grammar, vocabulary, critical thinking, memory,
  difficulty with letter spacing,
  trouble thinking and writing simultaneously

- Do mathematical calculations (Dyscalculia),
  math concepts, numbers and reasoning, reading clock to tell time,
  counting money, identifying patterns, remembering math facts,
  solving mental math

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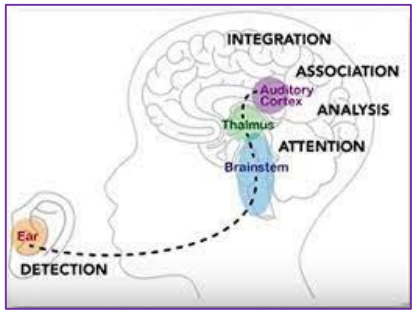
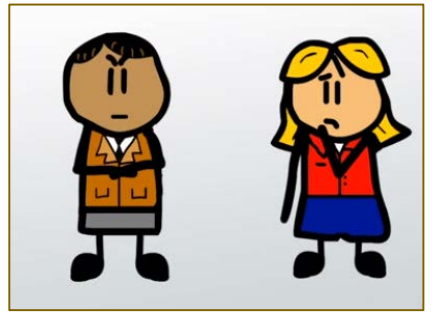
Disorders that affect the ability

- Difficulty processing sounds,
  may confuse the order of sounds or unable to filter different sound,
  like a teacher's voice vs background noise
  Brain misinterprets the information heard and processed from the ears



- Nonverbal learning disability
  difficulties in decoding/understanding and expressing body language,
  facial expression and tone of voice, nonverbal aspect of communication



- Visual motor coordination
  Poor eye-hand coordination – pencils, crayons, scissors,
  other fine motor skill (shoelace tying)

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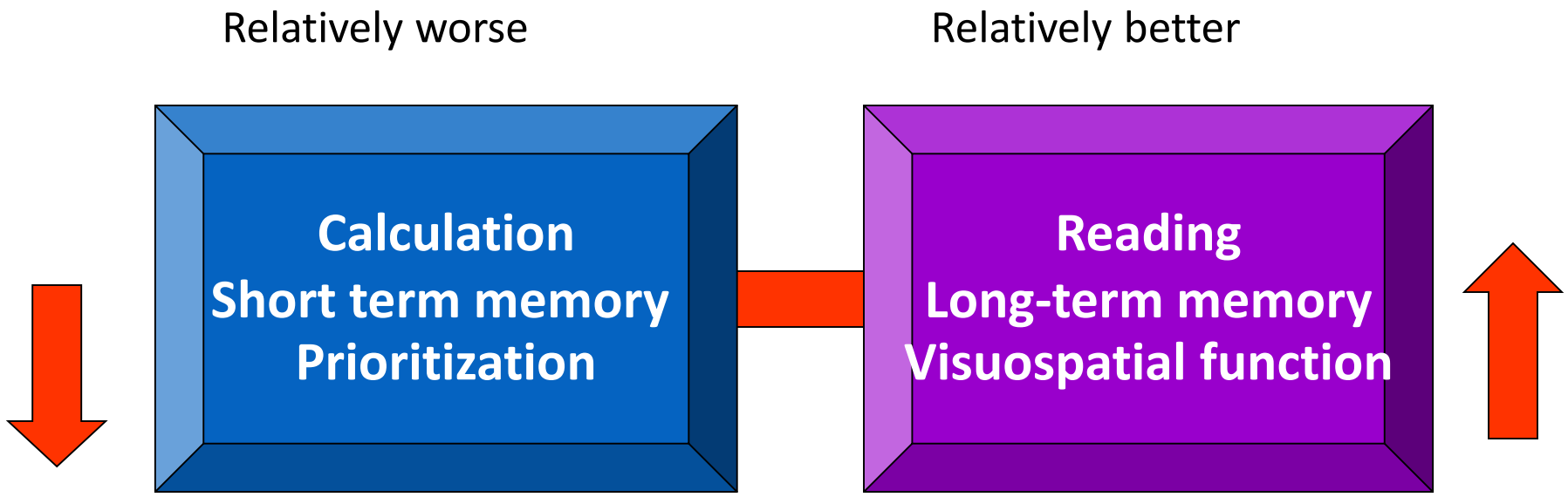

Relatively worse
Relatively better
Calculation
Short term memory
Prioritization
Reading
Long-term memory
Visuospatial function

- Although a small proportion of affected individuals have extremely impaired language development, **verbal ability is a relative strength for most.**

- Understanding LD is critical so that the parents and HCP could help the children with PWS to become more inclusive, to get the right educational support and understanding from peers and surrounding people

Driscoll DJ, et al. Prader-Willi Syndrome.. GeneReviews®; 1993-2021. https://www.ncbi.nlm.nih.gov/books

Management: Age-dependent Team approach

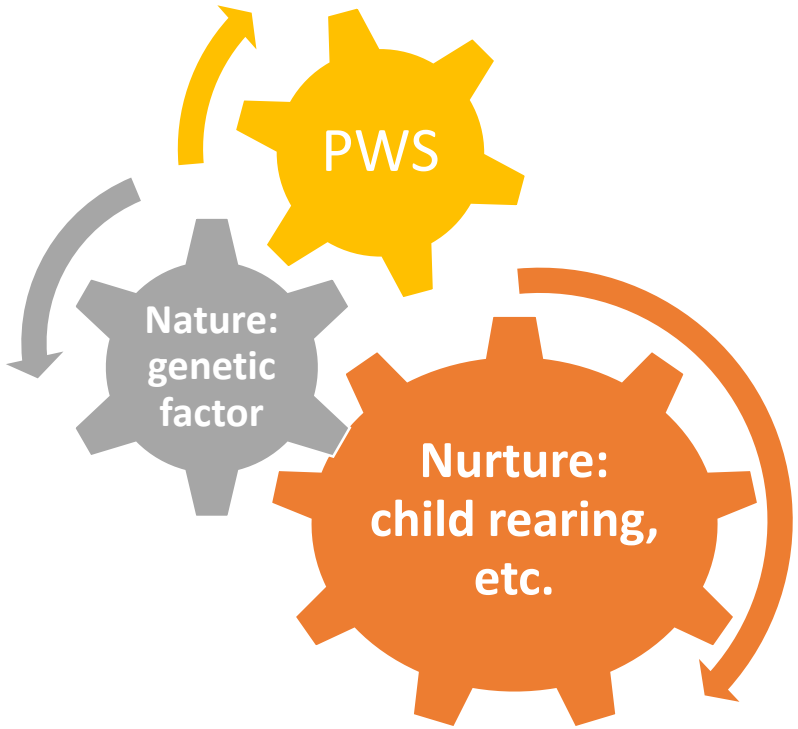
- Newborn and young infants
  – poor sucking, fail to thrive:
    special feeding techniques, gavage feeding, oromotor training,
    nutritional consultation --- adequate caloric intake & avoid poor growth
  - developmental delay: early intervention before 3yr of age – PT, OT, speech therapy

Management: Age-dependent Team approach

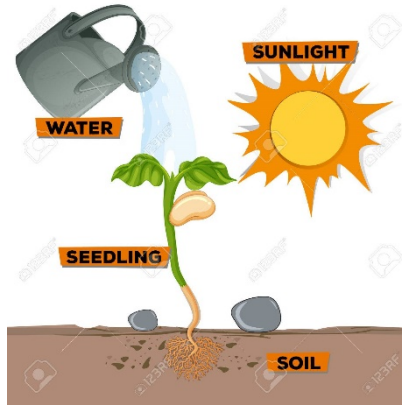
- Late infancy & Early childhood

  - balanced diet, regular exercise, close supervision to minimize food stealing
  - caloric needs: 60-80% of recommended daily allowance, dietician consultation
  - GH therapy – significant benefit on language, cognitive skill, mental speed, motor performance in treated infants
  - speech therapy
  - daily muscle training -- increase physical activity & lean body mass
  - educational development / child developmental and behavioral pediatrics specialist
  - special education – inclusive education

Factors influencing development and behaviors of a person with PWS



Attention
Understanding
Support



Thank you

Growth with love
PWS. THAILAND

มูลนิธิเพื่อผู้ป่วยโรคหายาก
Thai Rare Disease Foundation