Common genetic disorders

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เอกสารอ่านเพิ่มเติม

- ตำรากุมารเวชศาสตร์ มข. บทที่ 11-13
- E-learning KKU
- Thompson & Thompson, Genetics in medicine
- Emery and Rimoin's Principles and Practice of Medical Genetics
- Management of Genetic Syndromes
- Smith's Recognizable Patterns Of Human Malformation 6th Edition

Scope

- Common chromosomal disorders
- Common single gene disorders
- Approach to dysmorphic child

เกณฑ์ความรู้ความสามารถในการประเมินเพื่อ
รับใบอนุญาตเป็นผู้ประกอบวิชาชีพเวชกรรม พ .ศ. 2555

หมวดที่ 2. ภาวะผิดปกติจาแนกตามระบบอวัยวะ (Individual organ systems or types of disorders)

2.1 อาการ / ปัญหาสาคัญ (ICD10 ข้อ XVIII, R00 - R69)

- 2.1.4 ภาวะผิดรูป

2.2 โรค/ภาวะ/กลุ่มอาการฉุกเฉิน (รวมทุกระบบ) (ICD10 ข้อ XVIII, R00 - R69)

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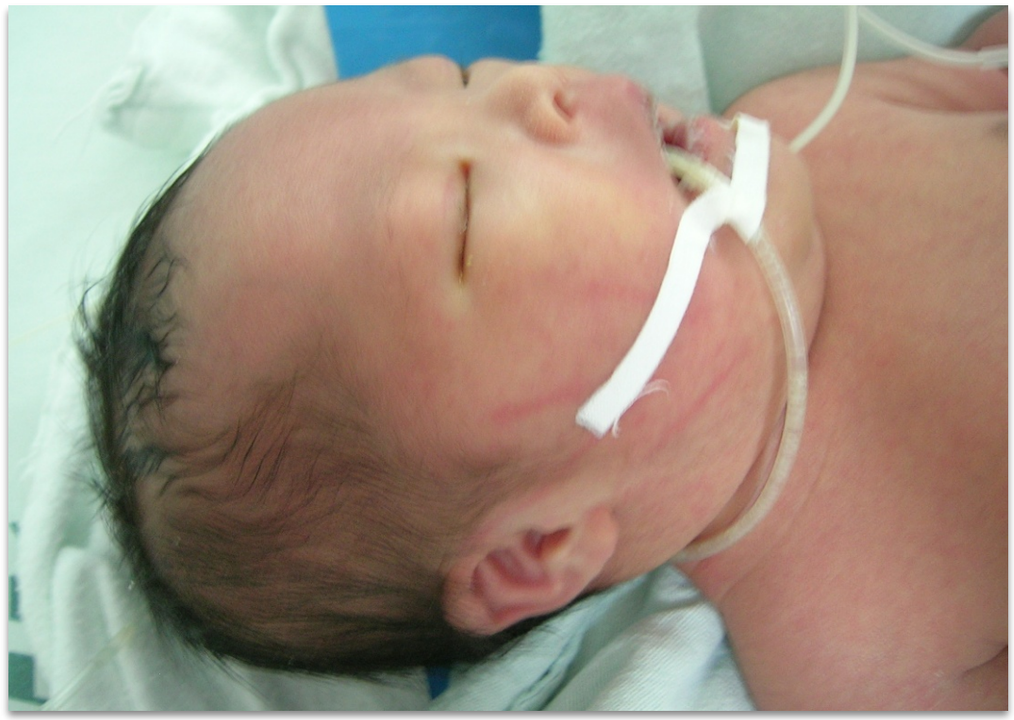
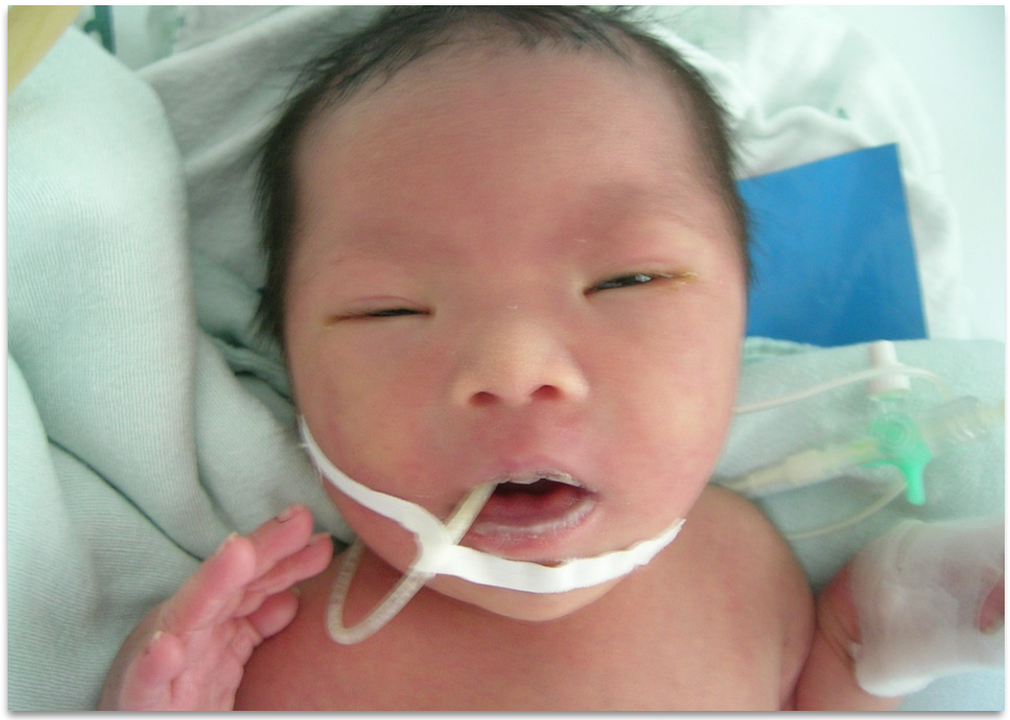
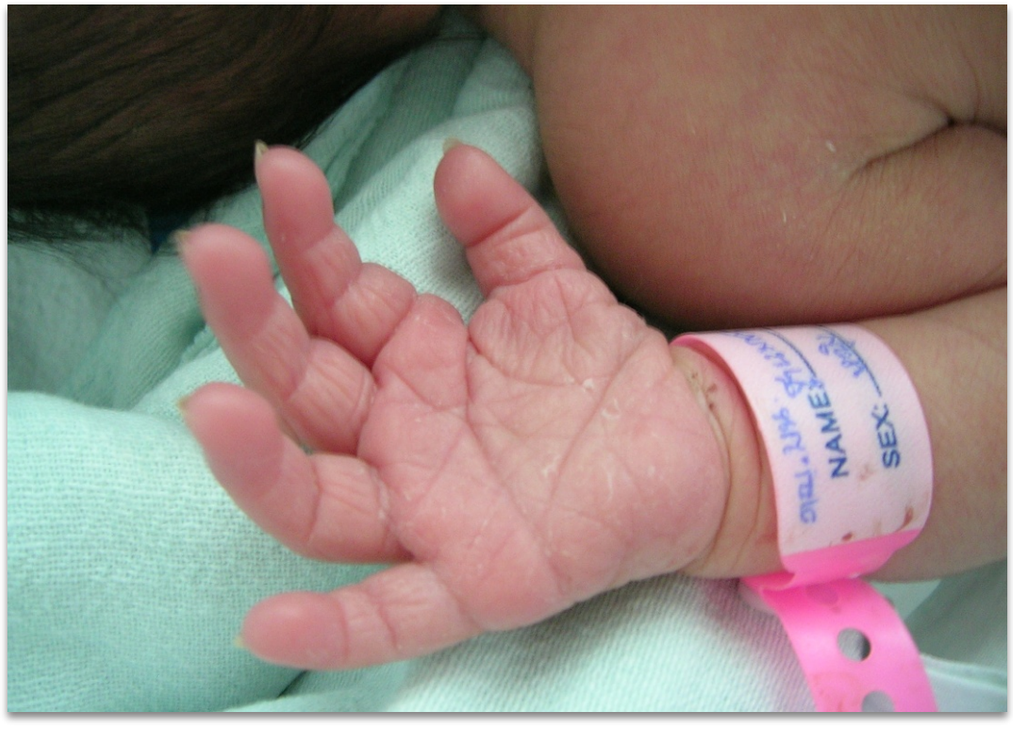
2.3 โรคตามระบบ

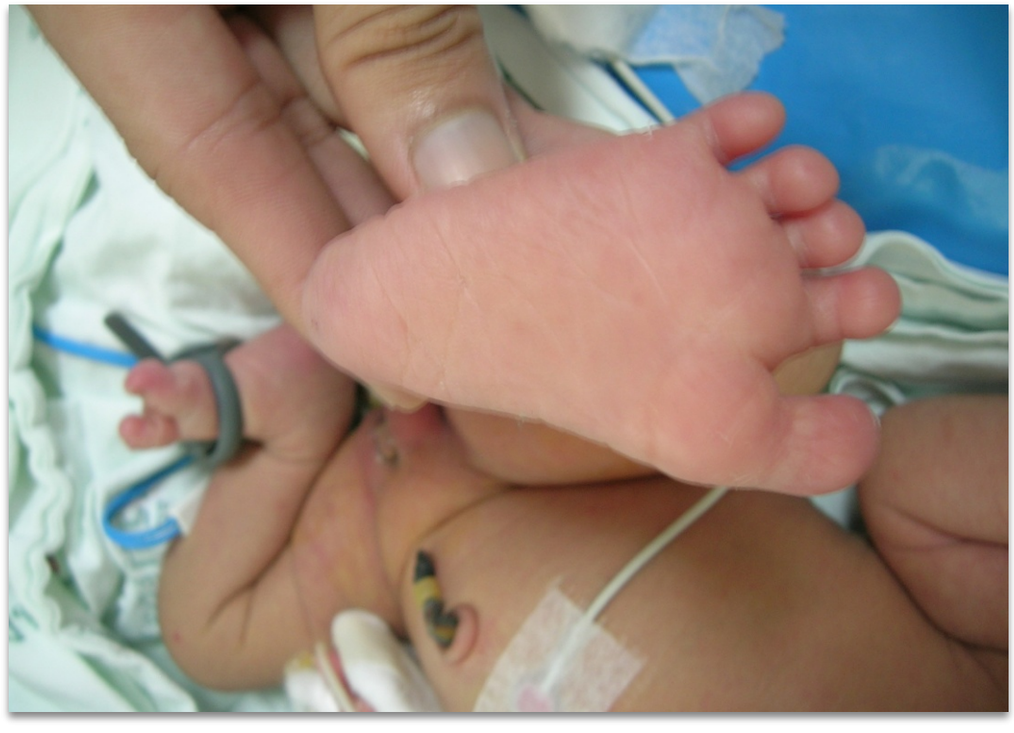
- 2.3.17 CONGENITAL MALFORMATIONS, DEFORMATIONS AND CHROMOSOMAL ABNORMALITIES (ICD 10, ข้อ XVII Q00 - Q99)
    - (14)chromosomal abnormalities (e.g., Down's syndrome, trisomy18, trisomy13) กลุ่มที่ 3 โรค/กลุ่มอาการ/ภาวะที่ต้องรู้กลไกการเกิดโรค สามารถให้การวินิจฉัยแยกโรค และรู้หลักในการดูแลรักษาผู้ป่วย การฟื้นฟูสภาพ การสร้างเสริมสุขภาพ และการป้องกันโรค แก้ไขปัญหาเฉพาะหน้า ตัดสินใจส่งผู้ป่วยต่อไปยังผู้เชี่ยวชาญ

Down syndrome









Medical problems in Down syndrome

Condition	%
Hearing problems	75
Vision problems	60
Cataracts	15
Refractive errors	50
OSA	50-75
Otitis media	50-70
Congenital heart disease	40-50
Gastrointestinal atresias	12

Condition	%
Thyroid diseases	4-18
Seizures	1-13
Hematologic problems	
Iron deficiency	10
Transient myeloproliferative disorder	10
Leukemia	1
Atlantoaxial instability	1-2
Hirschsprung disease	<1

Marilyn J. Bull, the Committee on Genetics. Health Supervision for Children With Down Syndrome. Pediatrics Aug 2011, 128 (2) 393-406; DOI: 10.1542/peds.2011-1605

Down syndrome

- Incidence ~ 1:830
- Mechanisms
  - Trisomy 21; 95%
  - Robertsonian translocation; 4%
  - Mosaicism; 1%

Down syndrome

- **Trisomy 21**
  - **Usually sporadic**
  - **Nondisjunction in meiosis I**
  - **Associated with advanced maternal age**
- **Robertsonian translocation**
  - **Unbalanced translocation between ch.21 and another acrocentric ch. (13, 14, 15, 21, 22), usually ch.14**
  - **Three-quarters of these unbalanced translocations are de novo, and the remainder result from familial balanced translocation carrier**
- **Mosaicism**
  - **A mix of 2 cell lines is present: one normal and the other with trisomy 21**
  - **Mitotic nondisjunction**

Marilyn J. Bull, the Committee on Genetics. Health Supervision for Children With Down Syndrome. Pediatrics Aug 2011, 128 (2) 393-406; DOI: 10.1542/peds.2011-1605

Health supervision in Down syndrome

Neonate to infant

- Thyroid function tests
- CBC
- Echocardiography
- Hearing screening
- Eye examination
- Developmental stimulation
- Genetic counselling

Marilyn J. Bull, the Committee on Genetics. Health Supervision for Children With Down Syndrome. Pediatrics Aug 2011, 128 (2) 393-406; DOI: 10.1542/peds.2011-1605

Health supervision in Down syndrome

Early to late childhood

- Thyroid function tests and CBC; annually
- Review the risk of hearing loss associated with serous otitis media
- Check the child's vision
- Screening for OSA
- Special education
- Genetic counselling

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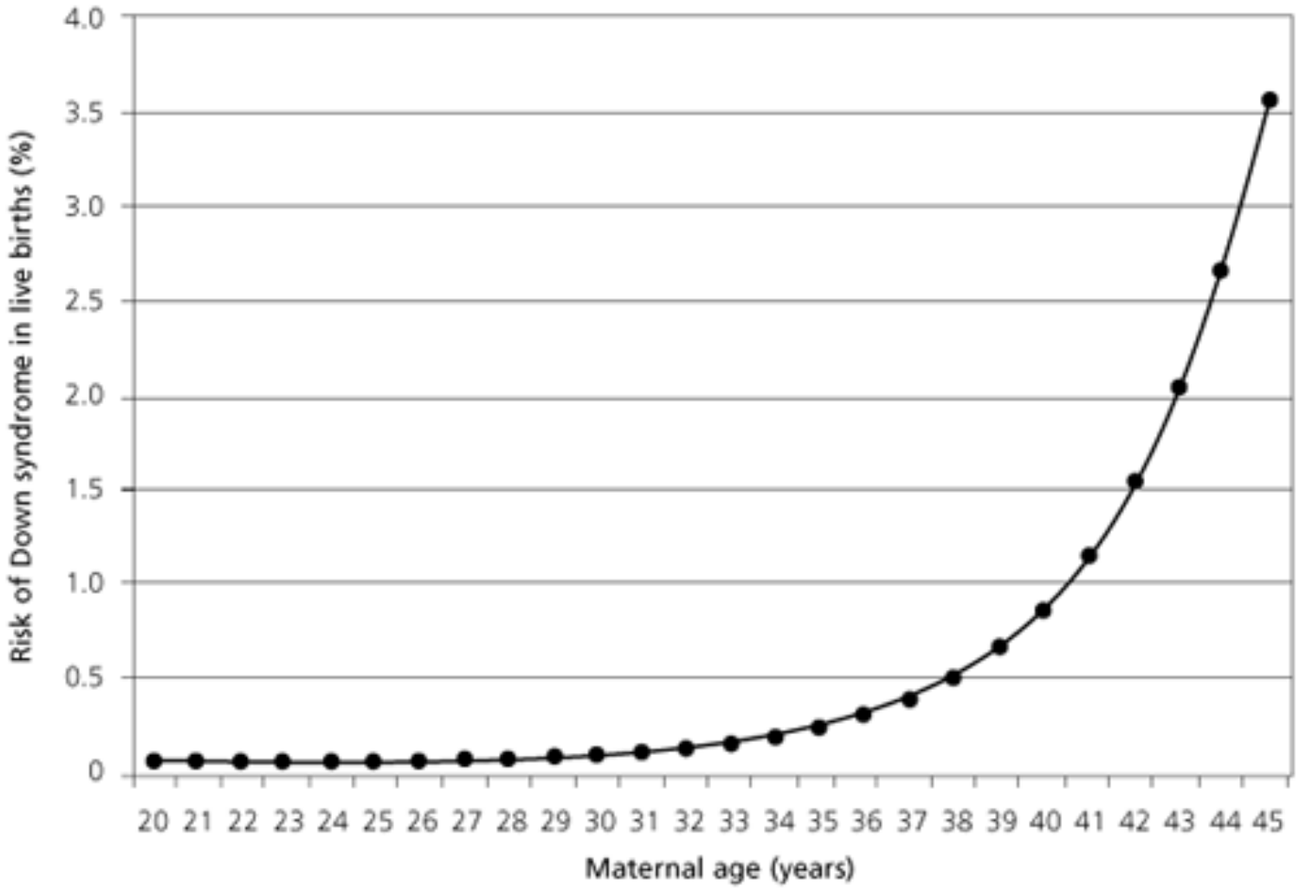
Genetic counselling in Down syndrome

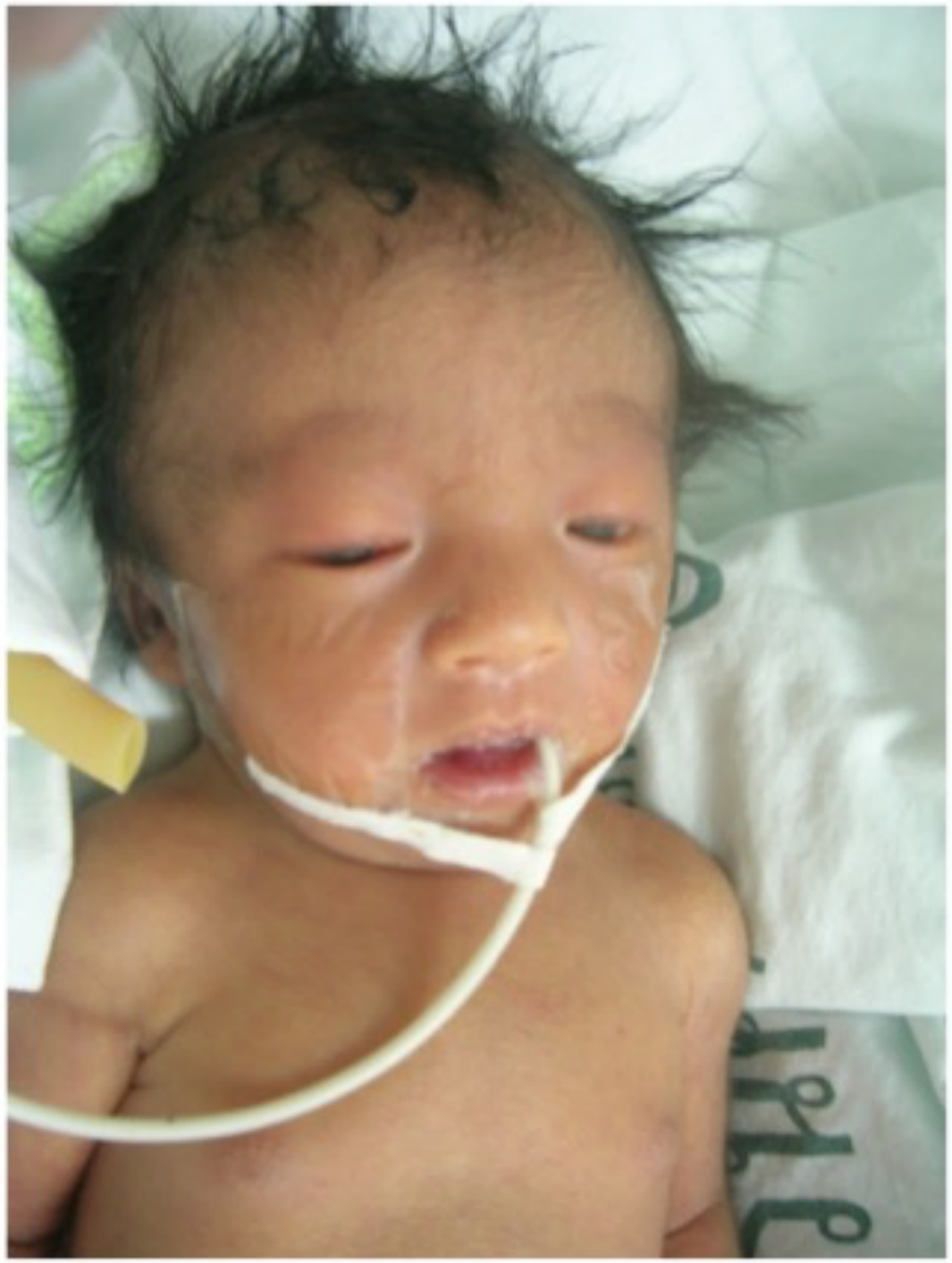


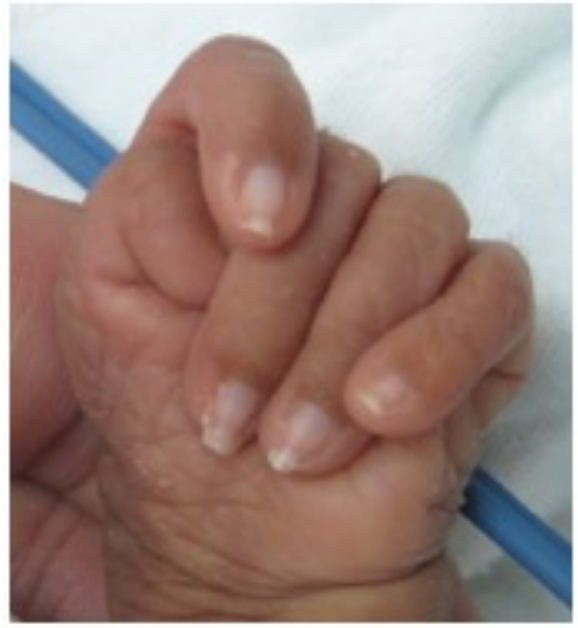
- **Trisomy 21: recurrence risk in a subsequent pregnancy increases to ~1% above the baseline risk determined by maternal age**

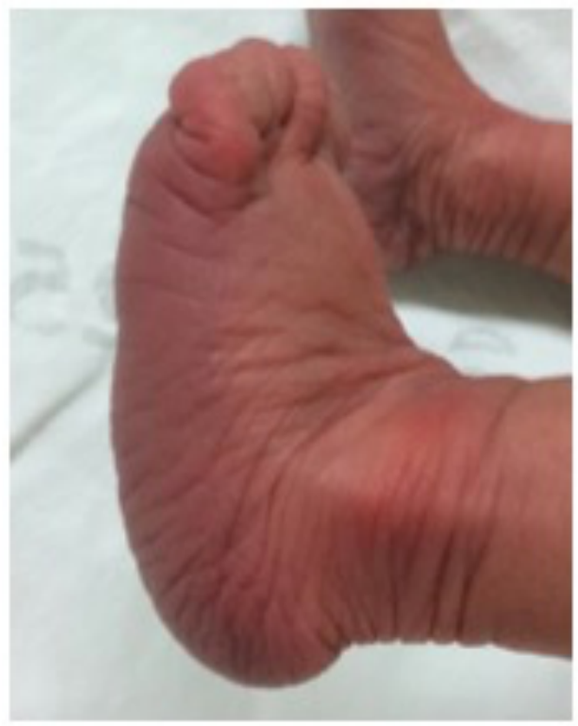
Newberger DS. Down syndrome: prenatal risk assessment and diagnosis. Am Fam Physician. 2000 Aug 15;62(4): 825-32, 837-8.

- **Robertsonian translocation:**
  - **10-15% if the mother is the translocation carrier, and ~5% if the father is the translocation carrier**
  - **Parental karyotypes is necessary to determine the recurrence risk**

Trisomy 18, Edwards syndrome



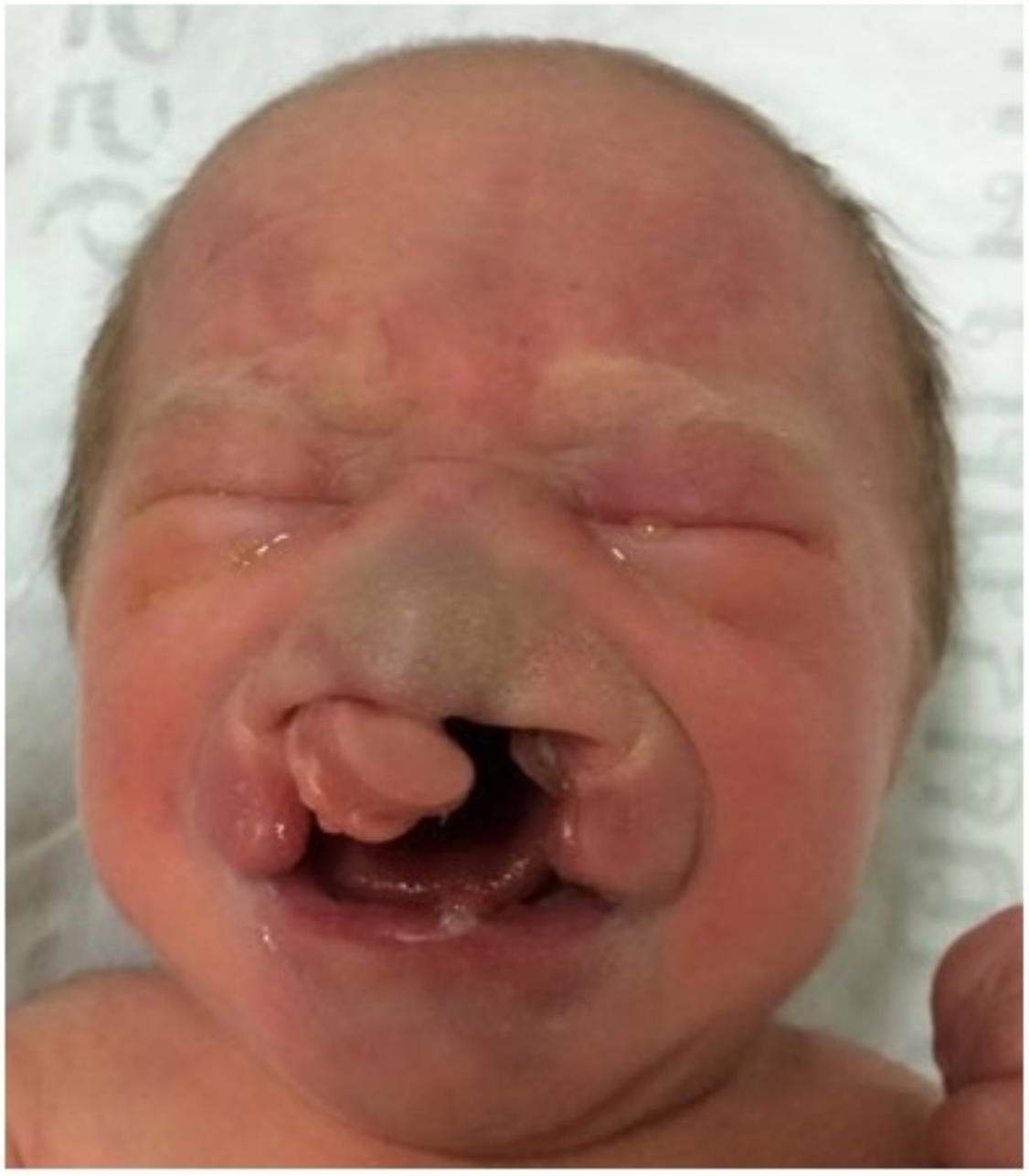


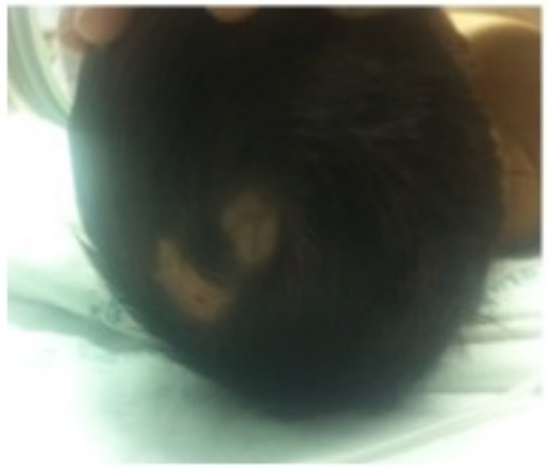


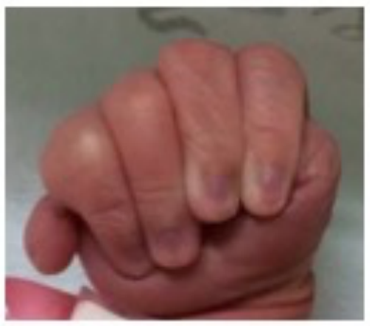
Trisomy 18, Edwards syndrome

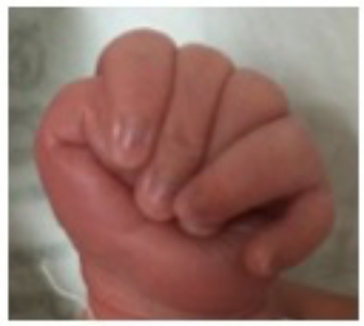
- SGA
- Prominent occiput
- Low-set and malformed ears
- Short palpebral fissure
- Small oral opening, micrognathia
- Clenched hand, absence distal crease on fifth finger
- Short sternum
- Small nipple
- Cryptorchidism
- Rocker bottom feet
- IUGR
- Maternal meiotic nondisjunction
- Congenital heart diseases 90% of case; VSD
- Short life expectancy

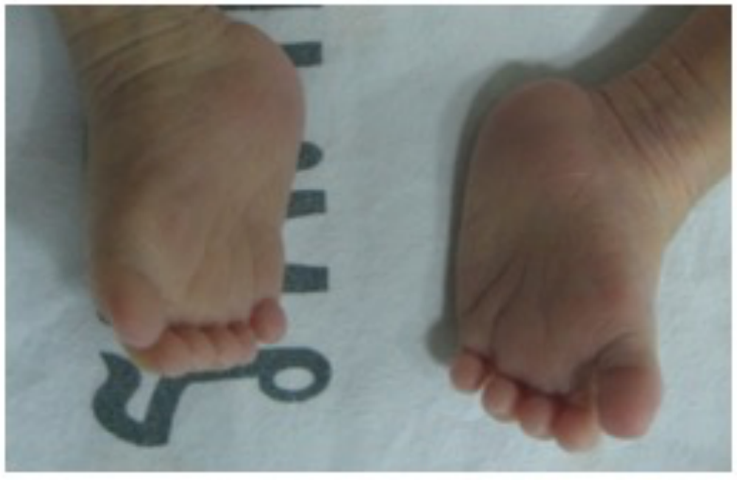
Trisomy 13, Patau syndrome











Trisomy 13, Patau syndrome

- Growth and mental retardation
- Holoprosencephaly 60-70%
- Microphthalmia 60-70%
- Cleft lip and cleft palate 60-70%
- Cutis aplasia
- Cardiac malformations 80%; ASD, VSD
- Post-axial polydactyly, limb defect
- Omphalocele
- Maternal nondisjunction
- Short life expectancy

Trisomy 13 VS trisomy 18

Trisomy 13

- Patau syndrome
- midline defect
- cleft lip/palate
- ambiguous genitalia
- polydactyly

Trisomy 18

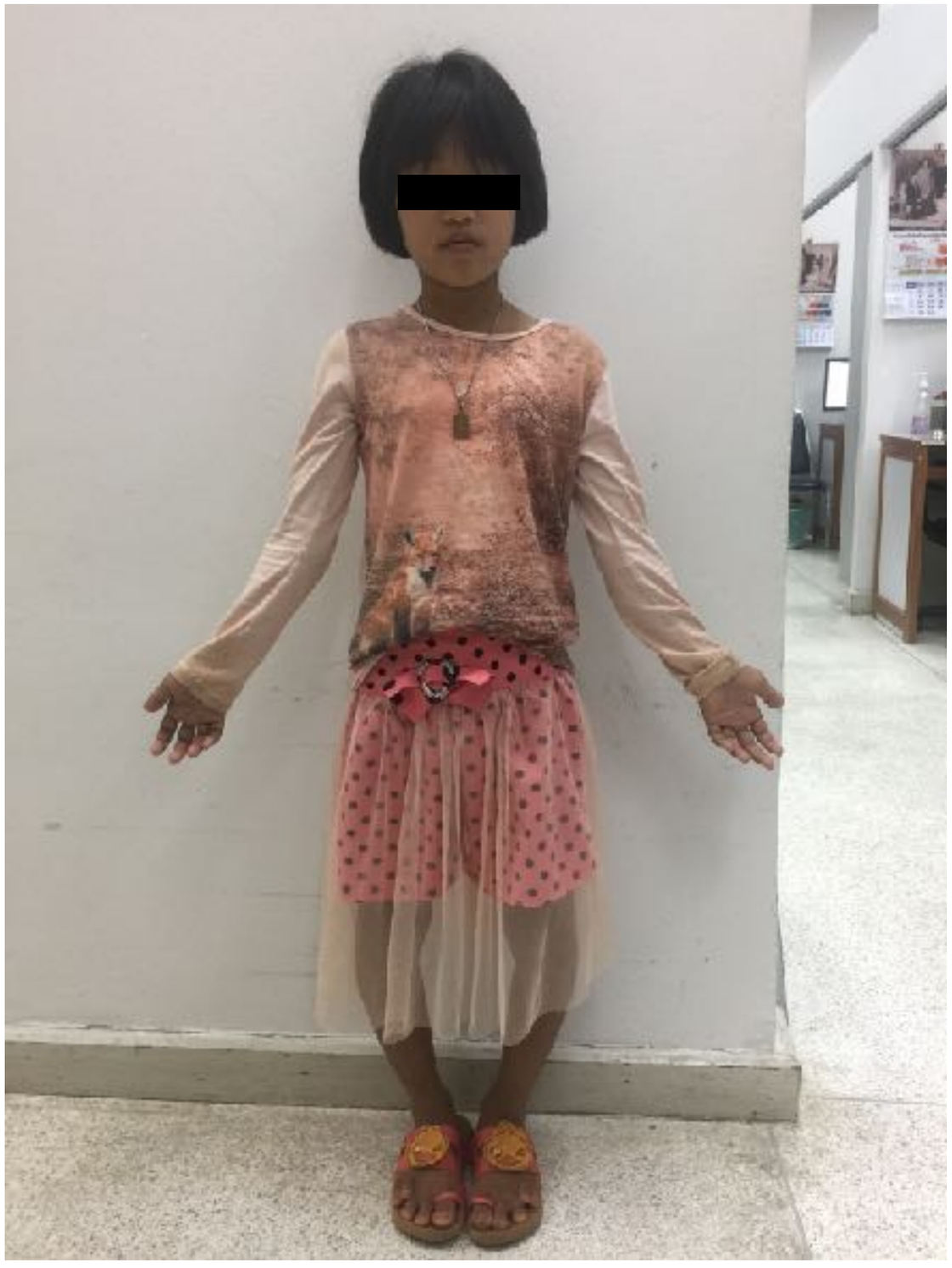
- Edwards syndrome
- syndrome of small
- prominent occiput
- clench hand
- rocker bottom feet

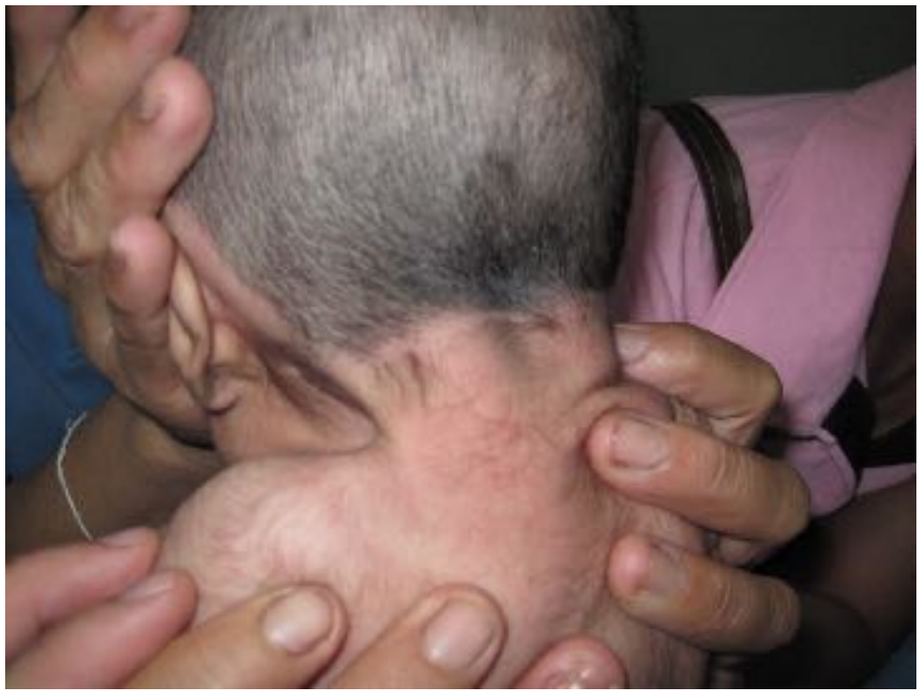
Turner syndrome

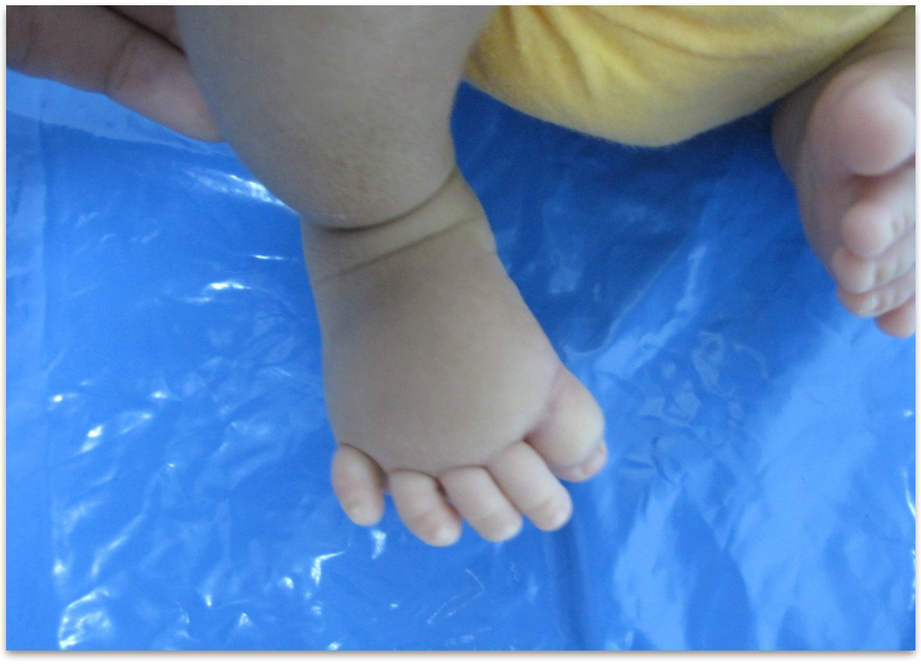
- Causes
  - 45,X (50%)
  - Structural abnormalities (25%)
  - 45,X mosaicism with other cell lines (25%)

Jaime L. Frías, Marsha L. Davenport, Committee on Genetics, Section on Endocrinology. Health Supervision for Children With Turner Syndrome. Pediatrics Mar 2003, 111 (3) 692-702; DOI: 10.1542/peds.111.3.692

Turner syndrome







Clinical abnormalities in Turner syndrome

Very frequent (50% of individuals)

- Growth deficiency
- Gonadal dysgenesis
- Lymphedema of hands and feet
- Deep set, hyperconvex nails
- Unusual shape and rotation of ears
- Narrow maxilla and dental crowding
- Micrognathia
- Low posterior hairline
- Broad chest with inverted or hypoplastic nipples
- Cubitus valgus
- Short fourth metacarpals
- Tibial exostosis
- Tendency to obesity
- Recurrent otitis media

Jaime L. Frías, Marsha L. Davenport, Committee on Genetics, Section on Endocrinology. Health Supervision for Children With Turner Syndrome. Pediatrics Mar 2003, 111 (3) 692-702; DOI: 10.1542/peds.111.3.692

Clinical abnormalities in Turner syndrome

Frequent (<50% of individuals)

- Hearing loss
- Pigmented nevi
- Webbed neck
- Renal abnormalities (1/3)
- Cardiovascular anomalies
- Hypertension
- Hypothyroidism
- Glucose intolerance
- Hyperlipidemia

Occasional (<5% of individuals)

- Scoliosis, kyphosis, lordosis
- Osteoporosis
- Gonadoblastoma
- Inflammatory bowel disease
- Colon cancer
- Neuroblastoma
- Juvenile rheumatoid arthritis
- Liver disease

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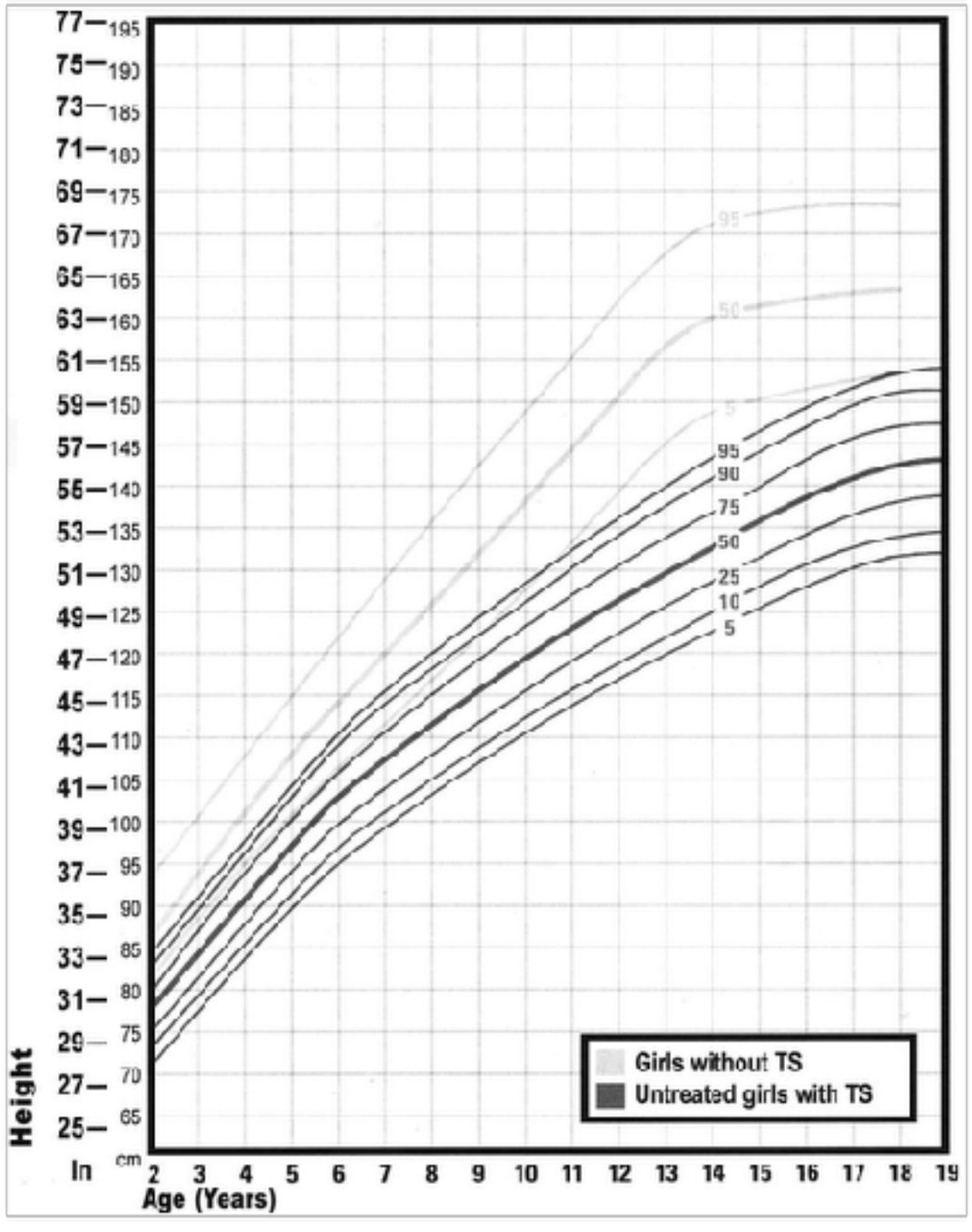
Medical treatment in Turner syndrome

- Short stature: GH therapy
- Cardiovascular abnormalities:
  - 20-40%
  - Bicuspid aortic valve
  - Coarctation of aorta
- Hearing aids
- Strabismus
- Obesity and related conditions
- UTI
- Thyroid dysfunction and autoimmune diseases
- Orthopedic problems



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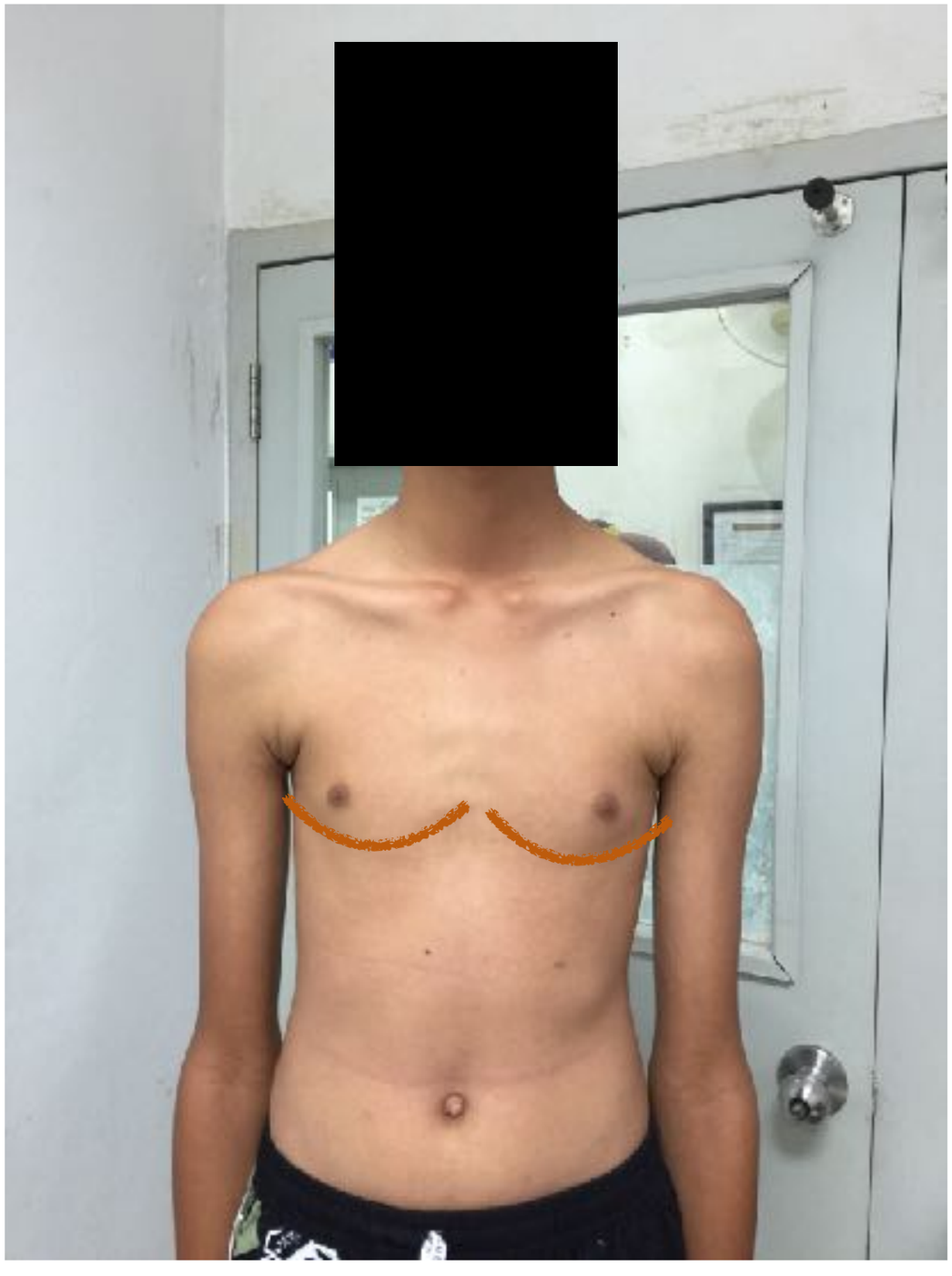
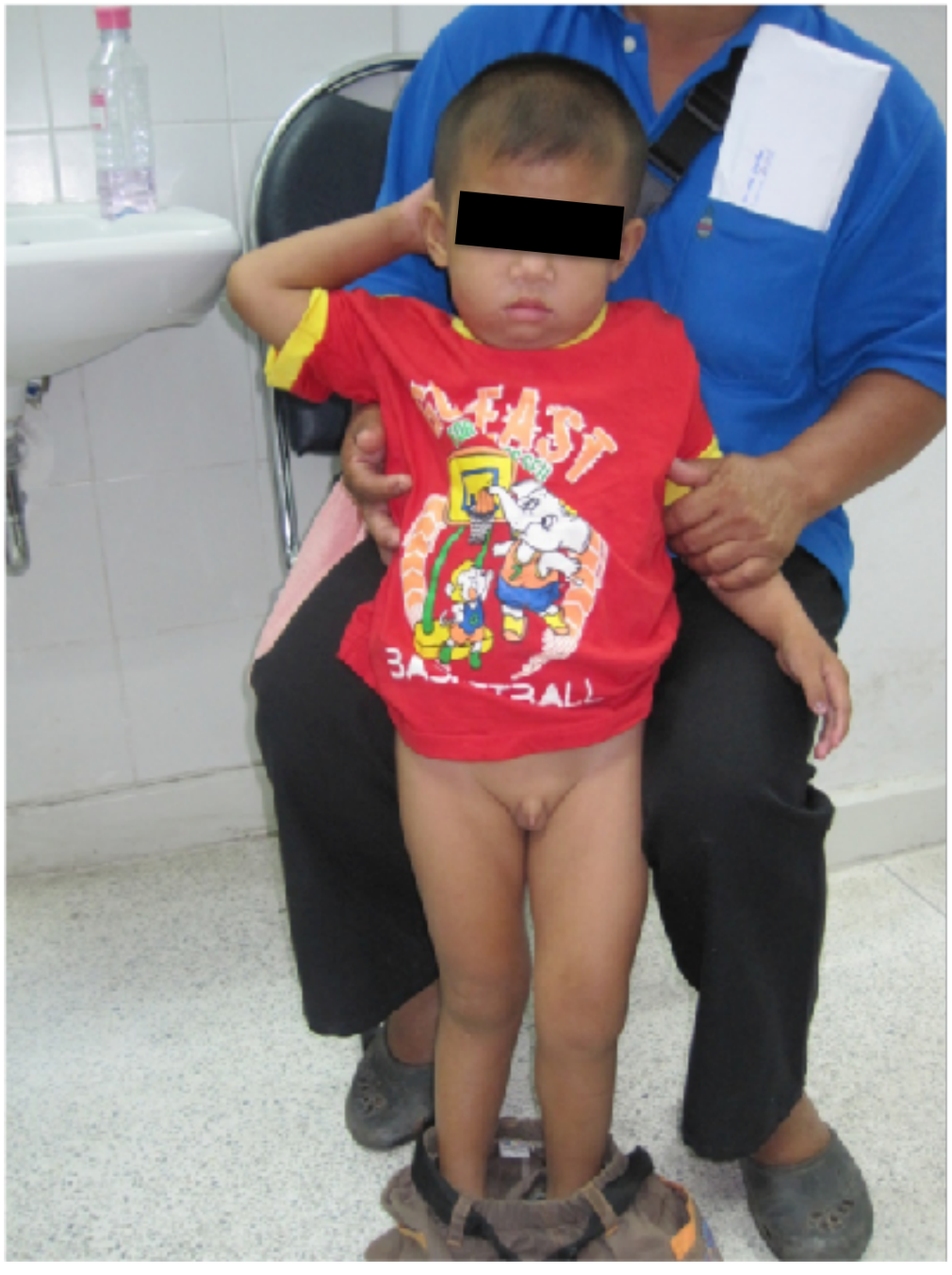
Klinefelter syndrome



Klinefelter syndrome

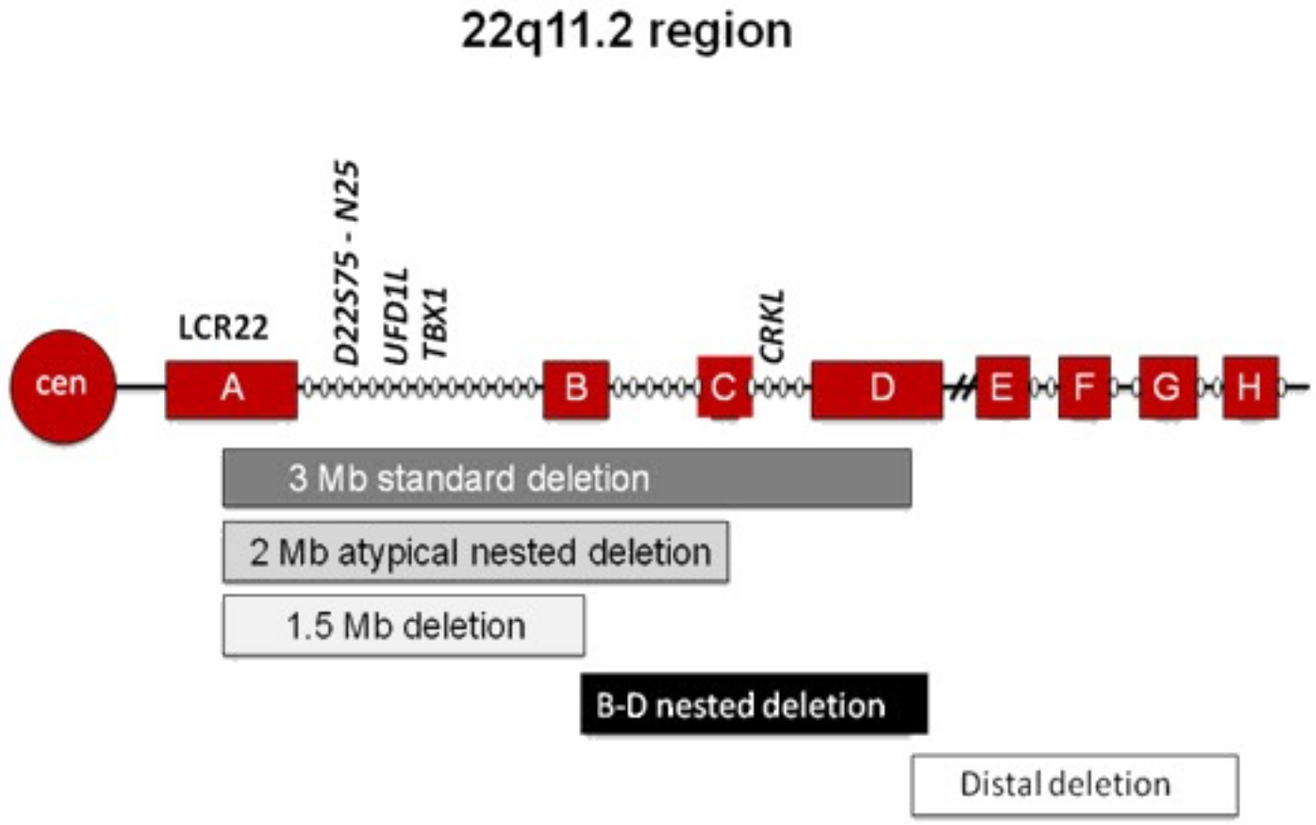
- 47,XXY
- Tall stature
- Disproportionate long arms and legs
- Small testes
- Infertile
- Gynecomastia
- IQ dullness
- Meiotic errors



22q11.2 deletion syndrome

Nomenclature

- Velo-cardio-facial syndrome
  - velopharyngeal insufficiency
  - conotruncal heart
  - facial dysmorphism
- DiGeorge syndrome
  - hypocalcemia
  - congenital heart disease
  - thymus hypoplasia



McDonald-McGinn DM, Hain HS, Emanuel BS, et al. 22q11.2 Deletion Syndrome. 1999 Sep 23 [Updated 2020 Feb 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1523/

22q11.2 deletion syndrome

- Incidence 1:4,000
- Craniofacial features (e.g., hooded eyelids, ear anomalies, prominent nasal bridge, bulbous nose, micrognathia, asymmetric crying facies, craniosynostosis)
- Congenital heart disease (60-80%); conotruncal defects
- Palatal abnormalities (~67%) including velopharyngeal insufficiency, submucosal cleft palate, bifid uvula, cleft palate, and hypernasal speech
- Laryngotracheoesophageal abnormalities including vascular ring, laryngeal web, laryngotracheomalacia, and subglottic stenosis
- Immune deficiency (~77%) and autoimmune disorders

McDonald-McGinn DM, Hain HS, Emanuel BS, et al. 22q11.2 Deletion Syndrome. 1999 Sep 23 [Updated 2020 Feb 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1523/

22q11.2 deletion syndrome

- Gastrointestinal anomalies including constipation with or without structural gastrointestinal anomalies Hearing loss (sensorineural and/or conductive)
- Developmental delay and/or learning difficulties (in 70%-90%), especially a nonverbal learning disability
- Skeletal anomalies
- Genitourinary tract anomalies
- Hypoparathyroidism and hypocalcemia (50%)
- Hypothyroidism
- Cytopenias (hemolytic anemia, neutropenia, thrombocytopenia)

McDonald-McGinn DM, Hain HS, Emanuel BS, et al. 22q11.2 Deletion Syndrome. 1999 Sep 23 [Updated 2020 Feb 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1523/

22q11.2 deletion syndrome

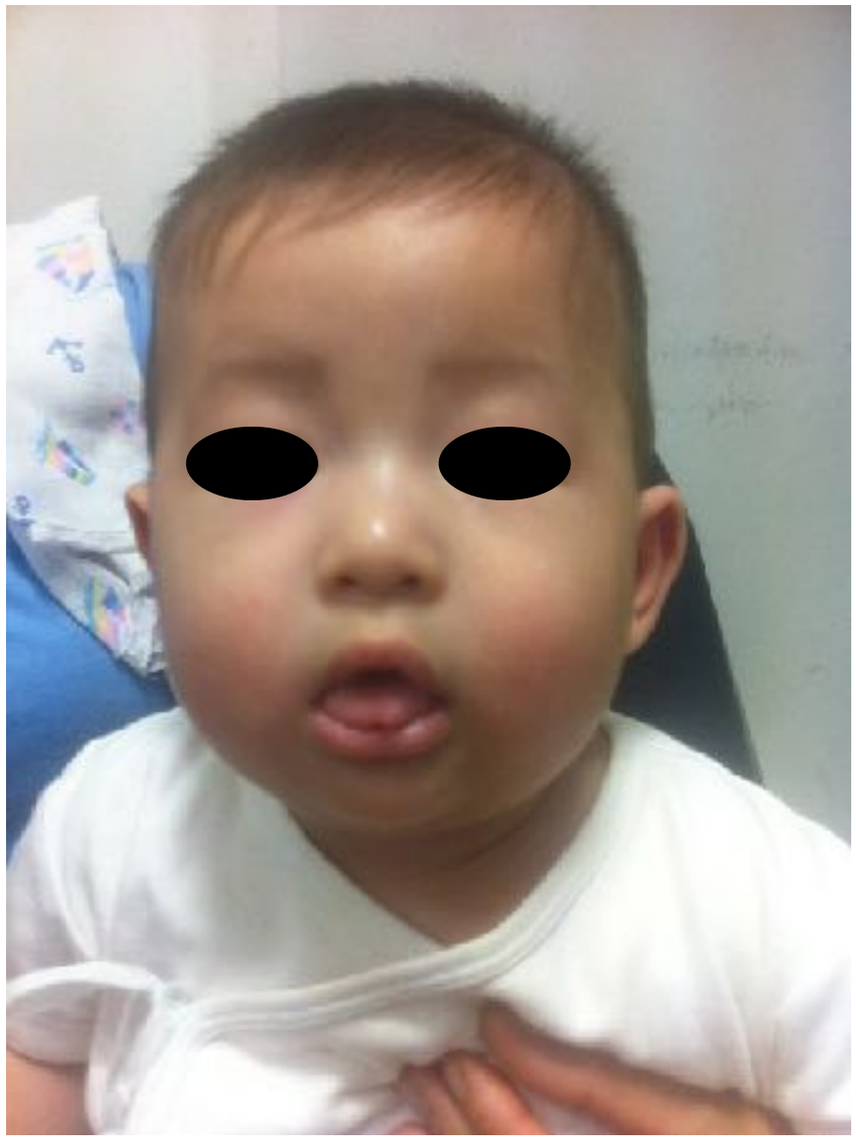
Table 1. Clinical phenotype of north-eastern Thai patients with 22q11.2 deletion syndrome and comparison with other countries (%)

Clinical phenotype	This report	McDonald-McGinn et al 1999[20]	Repetto et al 2009[22]	Kitsiou-Tzeli et al 2004[23]	Oskarsdottir et al 2005[24]	Ryan et al 1997[25]	Tan et al 2008[26]
	Thai	US	Chile	Greece	Sweden	Europe	Singapore
Number of patients	20	250	208	17	100	558	17
Dysmorphic facies	100			82	100		
Congenital heart defects	80	74	59.6	65	64	75	94.1
TOF (all)	45	20	20.2	17.6	13	17	23.5
TOF with PA	15						
VSD	20	14	12	35.3	14	14	58.8
ASD	15	3.5	2.9		1	1	35.3
TrA	5	6	2.4		10	9	5.9
DORV	5				2		
Isolated cleft palate	30	11	13	11.8	6	9	11.8
Pierre-Robin sequence	10						
Laryngeal anomalies	5				1	1	
Asymmetrical crying	5						
Indirect inguinal hernia	5				13		6.3
Polydactyly	5				1	1	
Anorectal malformation	5				5	2	

TOF = tetralogy of fallot; PA = pulmonary atresia; VSD = ventricular septal defect; ASD = atrial septal defect; TrA = truncus arteriosus; DORV = double outlet of right ventricle

Wichajarn K, Kampan J. Difference of clinical phenotypes and immunological features of 22q11.2 deletion syndrome in north-eastern Thai children compare to western countries. J Med Assoc Thai. 2014 Oct;97 Suppl 10:S59-66.

Prader-Willi syndrome



Prader-Willi syndrome

- Characteristic facial features;
  - Narrow bifrontal diameter,
  - Almond-shaped palpebral fissures,
  - Narrow nasal bridge,
  - Thin vermilion of the upper lip with down-turned corners of the mouth
- Severe hypotonia and feeding difficulties in early infancy,
- Followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity (unless eating is externally controlled)

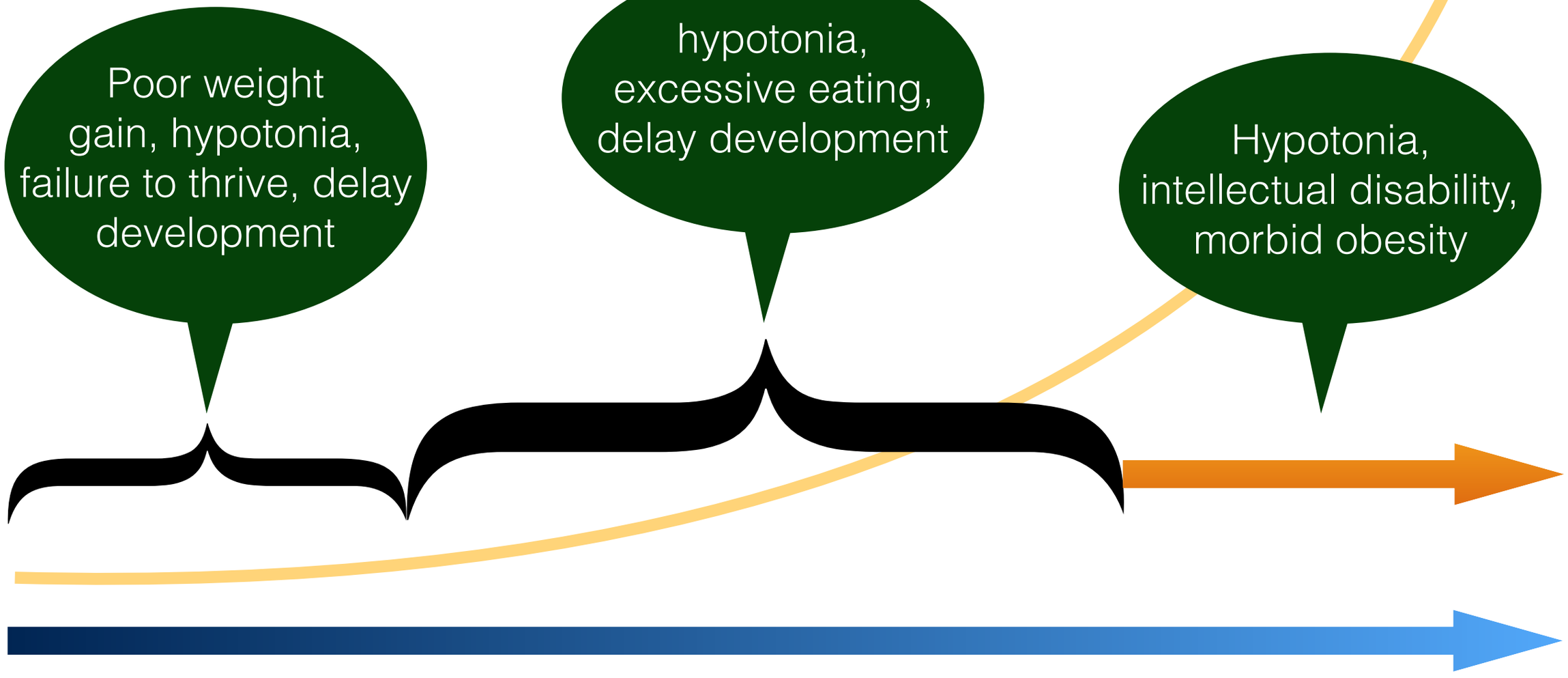
Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/

Prader-Willi syndrome

- Global developmental delayed
- A distinctive behavioral phenotype (with temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics)
- Hypogonadism
- Short stature
- Endocrine abnormalities
  - Hypothyroidism
  - Type 2 diabetes
- Sleep abnormalities

Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/

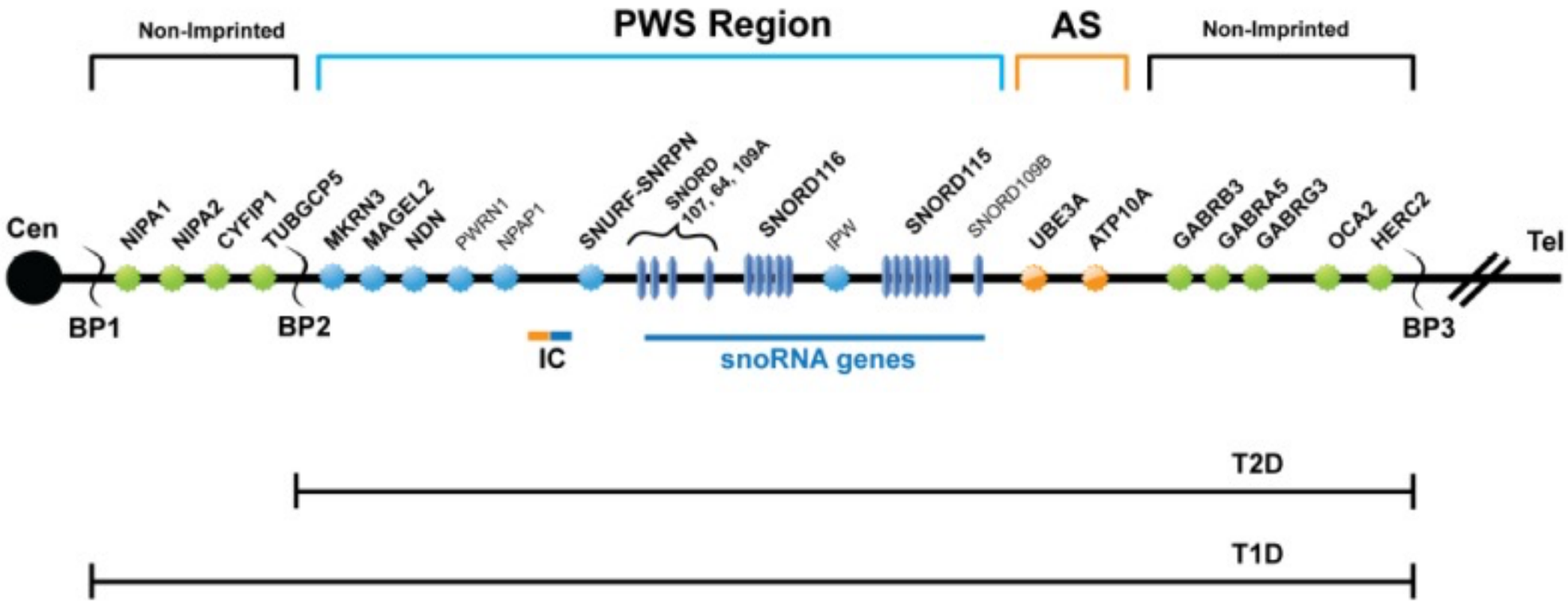
Prader-Willi syndrome



Prader-Willi syndrome

Causes

- Paternal deletion of chromosome 15q11-13: 70%
- Maternal uniparental disomy: 25%
- Imprinting defects: 5%



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Prader-Willi syndrome

Diagnosis

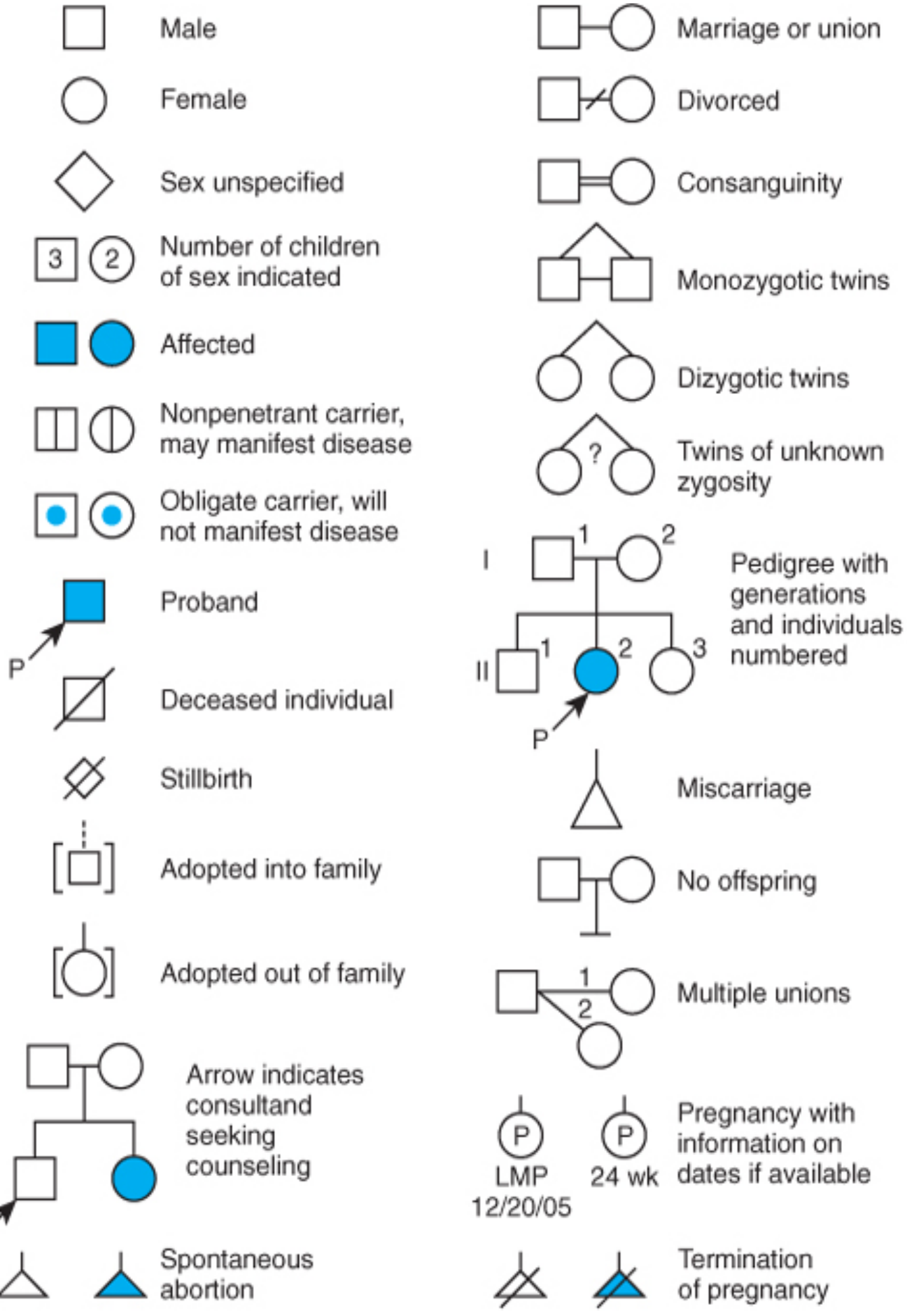
- Methylation specific PCR for *SNRPN*
- FISH for 15q11-13 (only deletion type)

Treatment

- Treatment with growth hormone

Single gene disorders

- Autosomal dominant inheritance
- Autosomal recessive inheritance
- X-linked dominant inheritance
- X-linked recessive inheritance



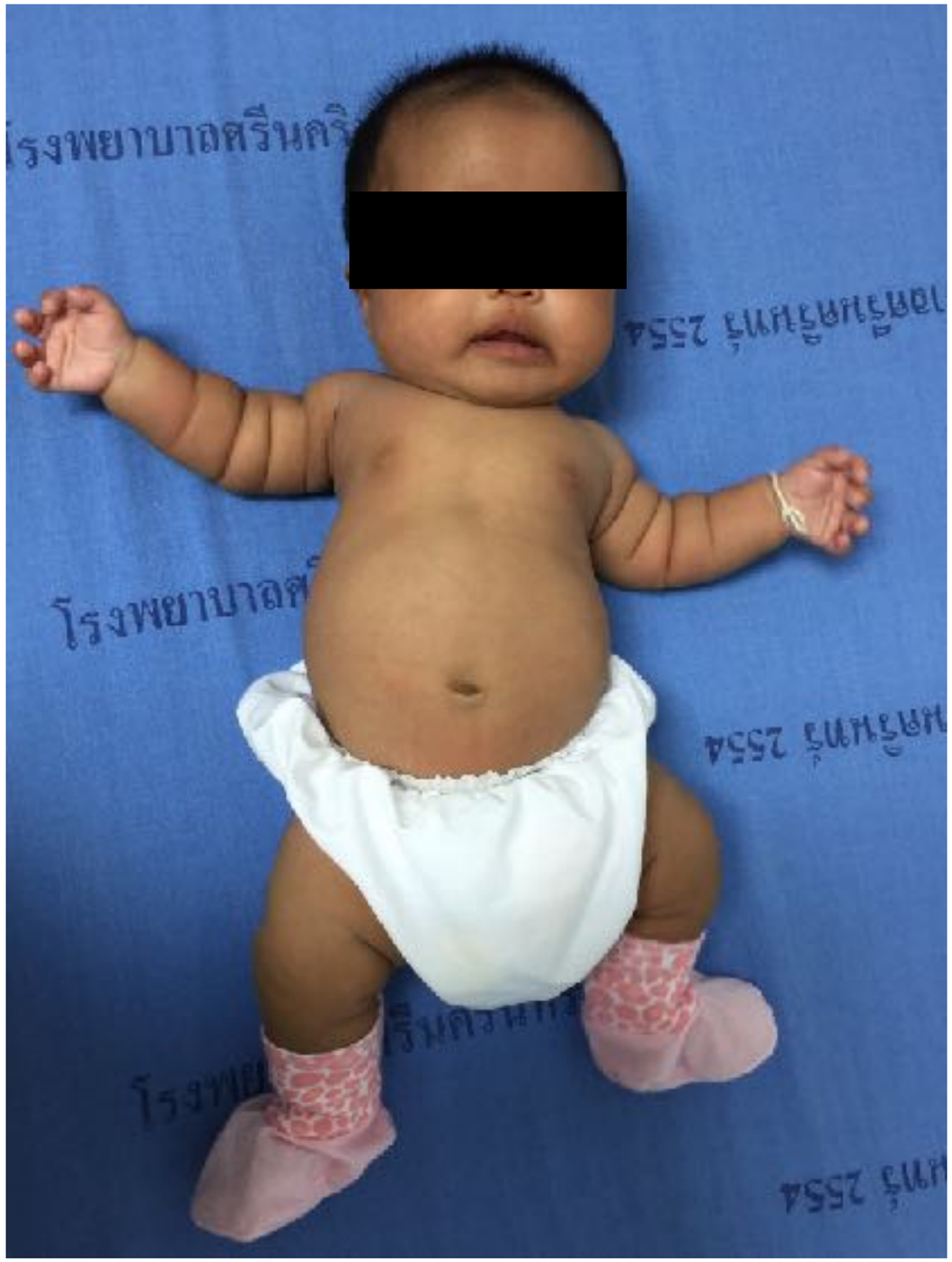
Autosomal dominant

- The phenotype usually appears in every generation except
  - New mutation
  - Nonpenetrance
- Any child of an affected parent has a 50% risk of inheriting the trait
- Males and females are equally likely to transmit the phenotype
- Male-to-male transmission can occur

Autosomal dominant

- Achondroplasia
- Osteogenesis imperfecta
- Marfan syndrome
- Neurofibromatosis type I
- etc.

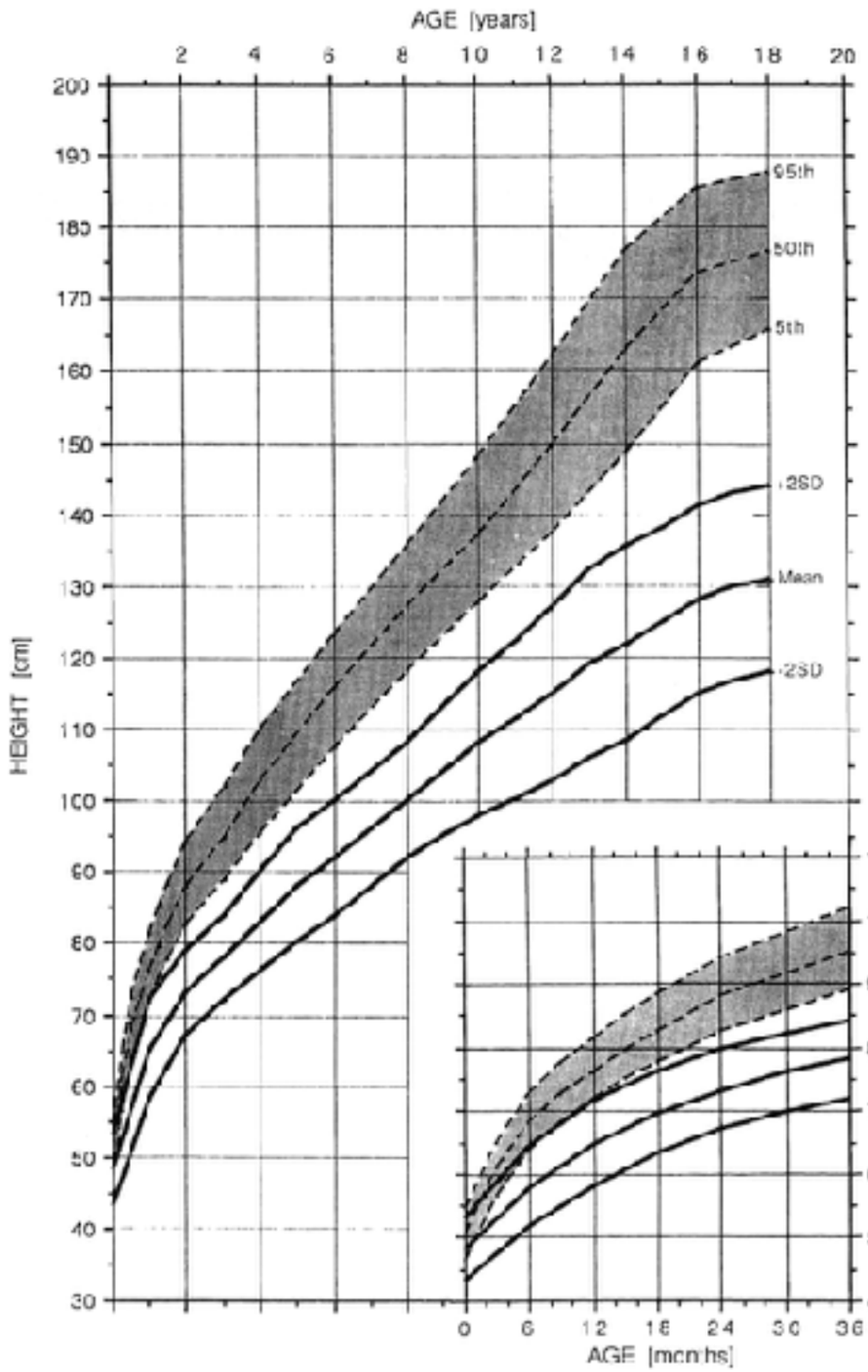
Achondroplasia

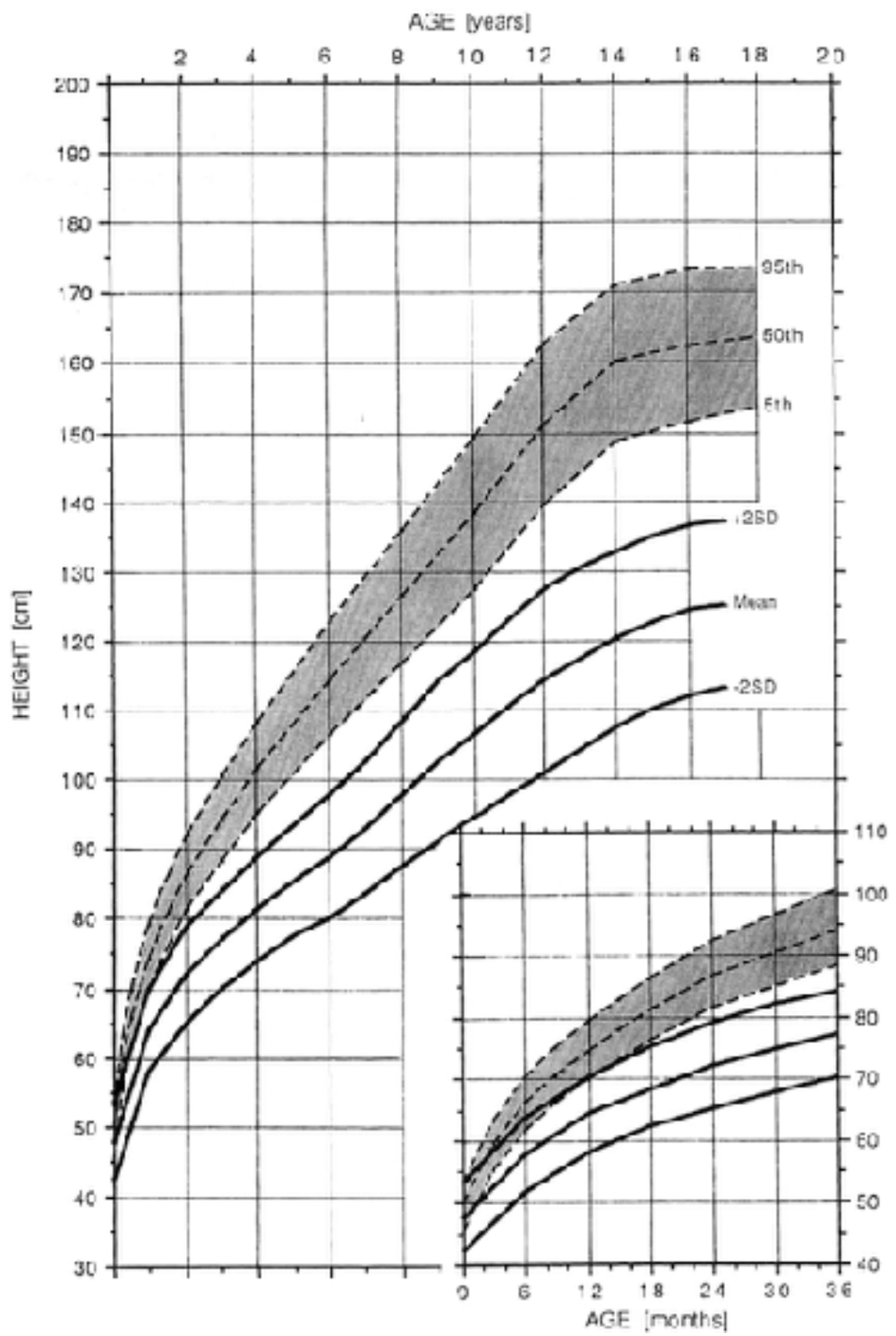


Achondroplasia

- *FGFR3* mutation (75-80% de novo)
- Disproportionate short stature (short limb)
- Rhizomelic shortening
- Trident configuration of hands
- Macrocephaly, prominent forehead
- Small cranial base and foramina
- Midface hypoplasia: obstructive apnea, otitis media
- Normal intelligence

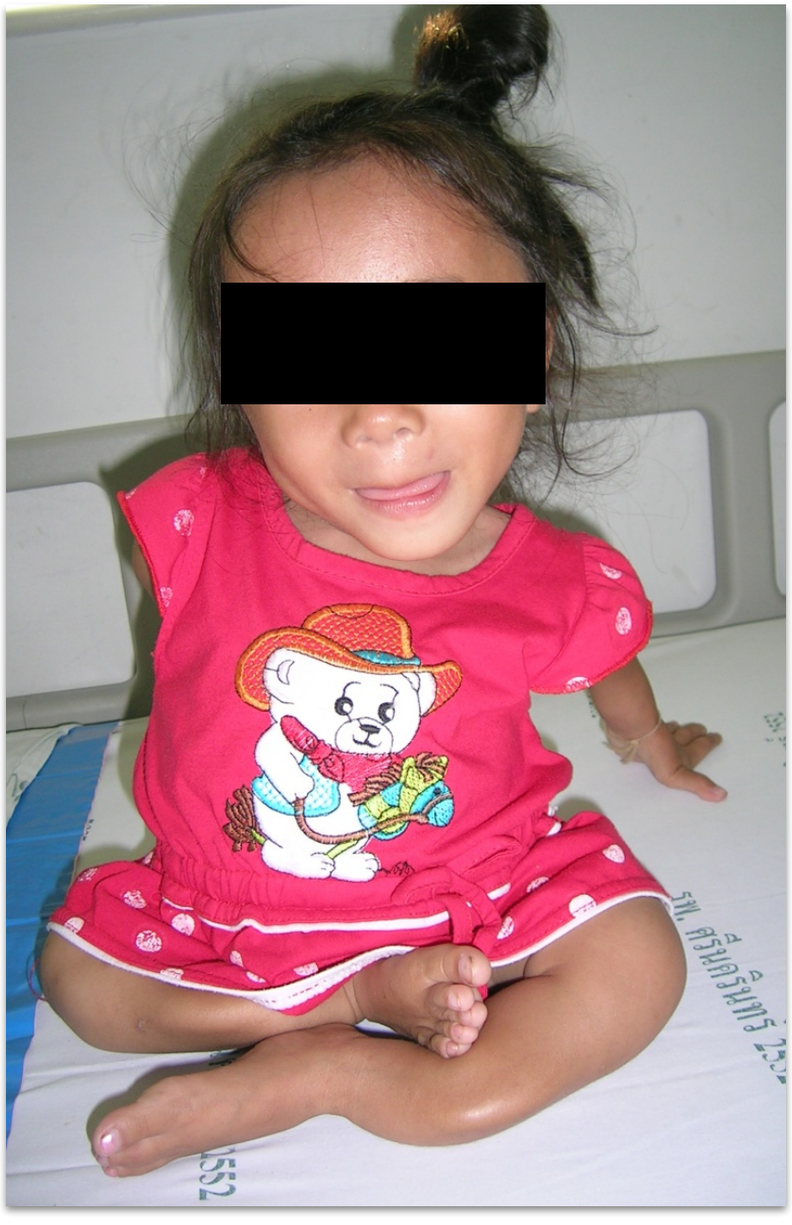
Achondroplasia

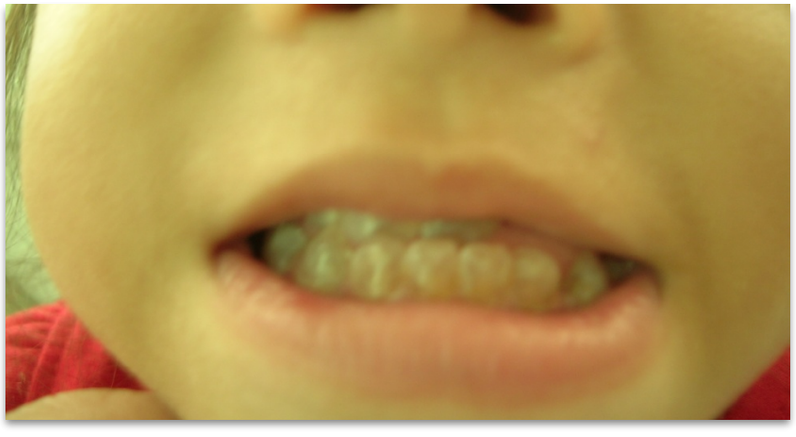




Tracy L. Trotter, Judith G. Hall. Health Supervision for Children With Achondroplasia. Pediatrics Sep 2005, 116 (3) 771-783; DOI: 10.1542/peds.2005-1440

Osteogenesis imperfecta

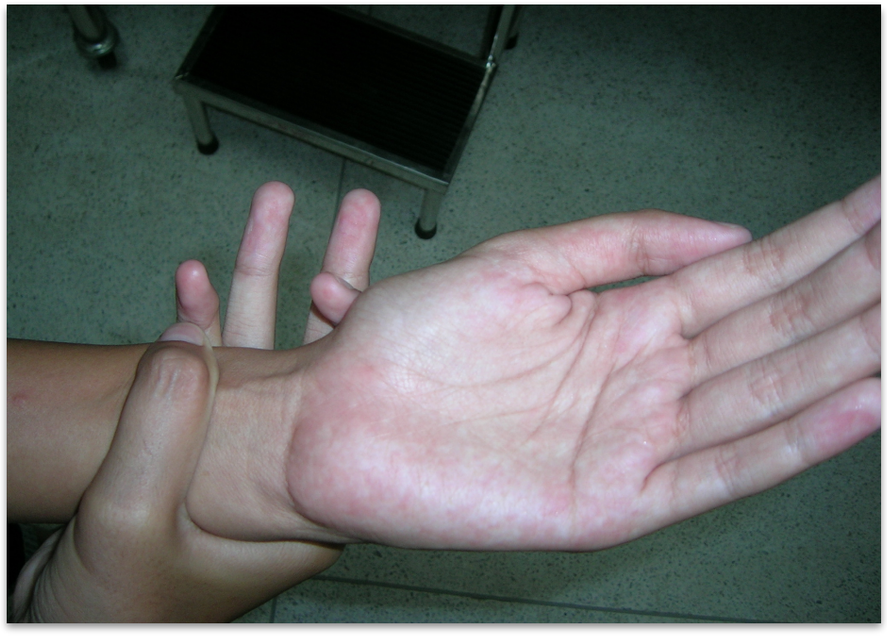




Osteogenesis imperfecta

- *COL1A1* and *COL1A2*
- Fractures with minimal or no trauma
- Short stature, often with bone deformity
- Blue sclerae
- Progressive, post-pubertal hearing loss
- Additional clinical features : ligamentous laxity and other signs of connective tissue abnormality
- Family history of OI,
- Wormian bone
- Osteopenia
- Treatment: bisphosphonate

Marfan syndrome



Marfan syndrome

- *FBN1* mutation
- Three cardinal features
  - Cardiac involvements
  - Skeletal involvements
  - Ocular involvements

Revised Ghent Diagnostic Criteria for Marfan Syndrome

Diagnosis of definitive Marfan syndrome (any of the following)

- **Aortic root ≥2 *z* score and ectopia lentis**
- **Aortic root ≥2 *z* score and *FBN1* mutation**
- **Aortic root ≥2 *z* score and systemic score ≥7**
- **Ectopia lentis and *FBN1* mutation known to be associated with Marfan syndrome**
- **Positive family history of Marfan syndrome and ectopia lentis**
- **Positive family history of Marfan syndrome and systemic score ≥7**
- **Positive family history of Marfan syndrome and aortic root ≥3 *z* score in those <20 y of age *or* ≥2 *z* score in those >20 y of age**

Diagnosis of potential Marfan syndrome

- ***FBN1* mutation with aortic root with a *z* score <3 in those <20 y of age**

Brad T. Tinkle, Howard M. Saal, the COMMITTEE ON GENETICS. Health Supervision for Children With Marfan Syndrome. Pediatrics Oct 2013, 132 (4) e1059-e1072; DOI: 10.1542/peds.2013-2063

Revised Ghent Diagnostic Criteria for Marfan Syndrome

Systemic score

Feature	Value	Feature	Value
Wrist *and* thumb sign	3	Protrusio acetabulae	2
Wrist *or* thumb sign	1	Reduced upper-to-lower segment ratio *and* increased arm-span-to-height ratio	1
Pectus carinatum	2	Scoliosis or thoracolumbar kyphosis	1
Pectus excavatum or chest asymmetry	1	Reduced elbow extension	1
Hindfoot deformity (eg, valgus)	2	Craniofacial features: 3 of the following—dolichocephaly, downward-slanting palpebral fissures, enophthalmos, retrognathia, and malar	1
Pes planus	1	Skin striae	1
Pneumothorax	2	Myopia	1
Dural ectasia	2	Mitral valve prolapse	1

Brad T. Tinkle, Howard M. Saal, the COMMITTEE ON GENETICS. Health Supervision for Children With Marfan Syndrome. Pediatrics Oct 2013, 132 (4) e1059-e1072; DOI: 10.1542/peds.2013-2063

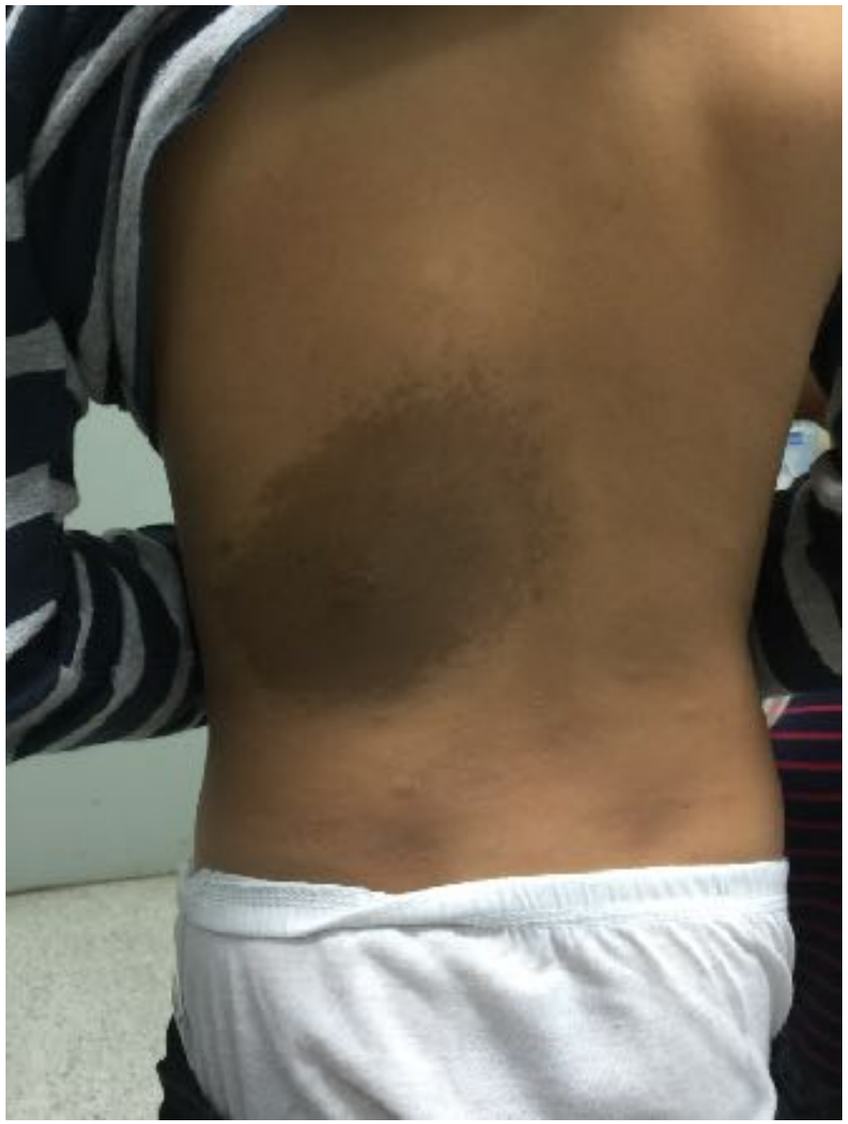
Neurofibromatosis type 1

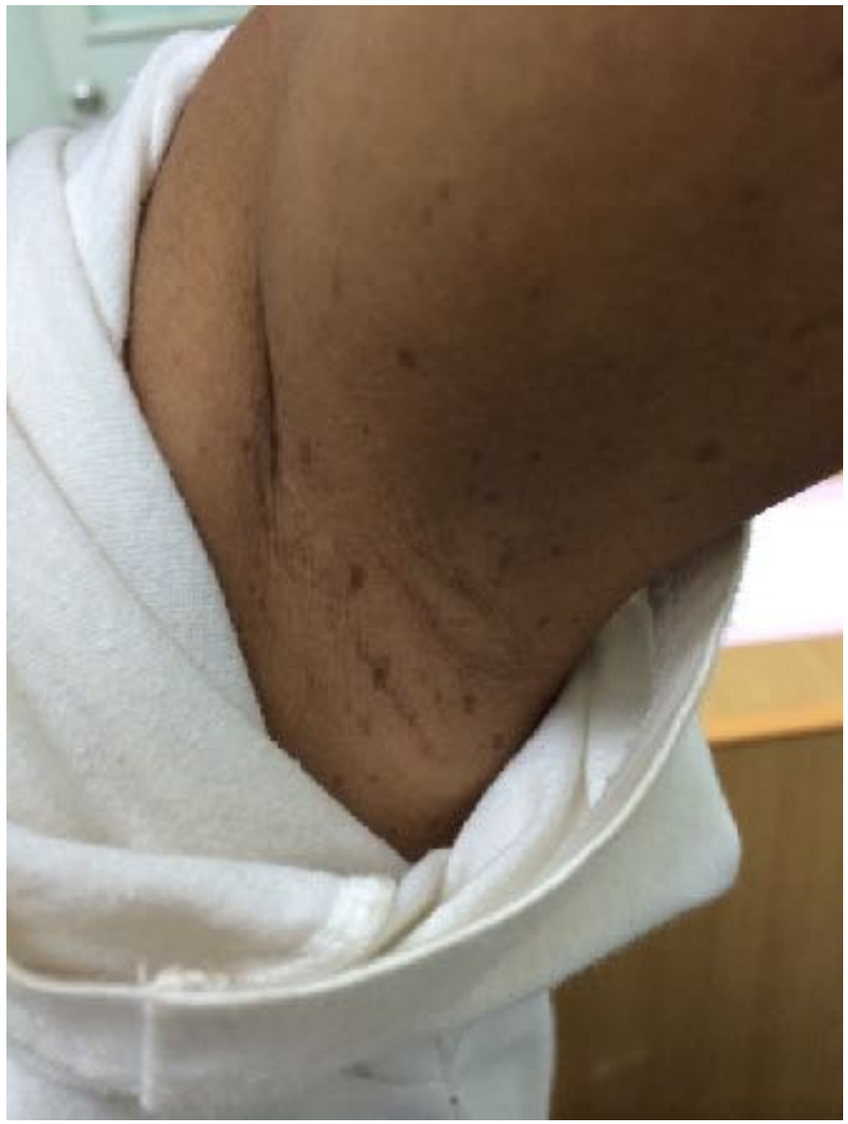
Diagnostic criteria

- **Six or more CALMs equal to or greater than 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients**
- **Two or more neurofibromas of any type or 1 plexiform neurofibroma**
- **Freckling in the axillary or inguinal regions (Crowe sign)**
- **Optic glioma (OPG)**
- **Two or more iris hamartomas (Lisch nodules)**
- **A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis**
- **A first-degree relative (parent, sibling, or child) with NF1 according to the aforementioned criteria**

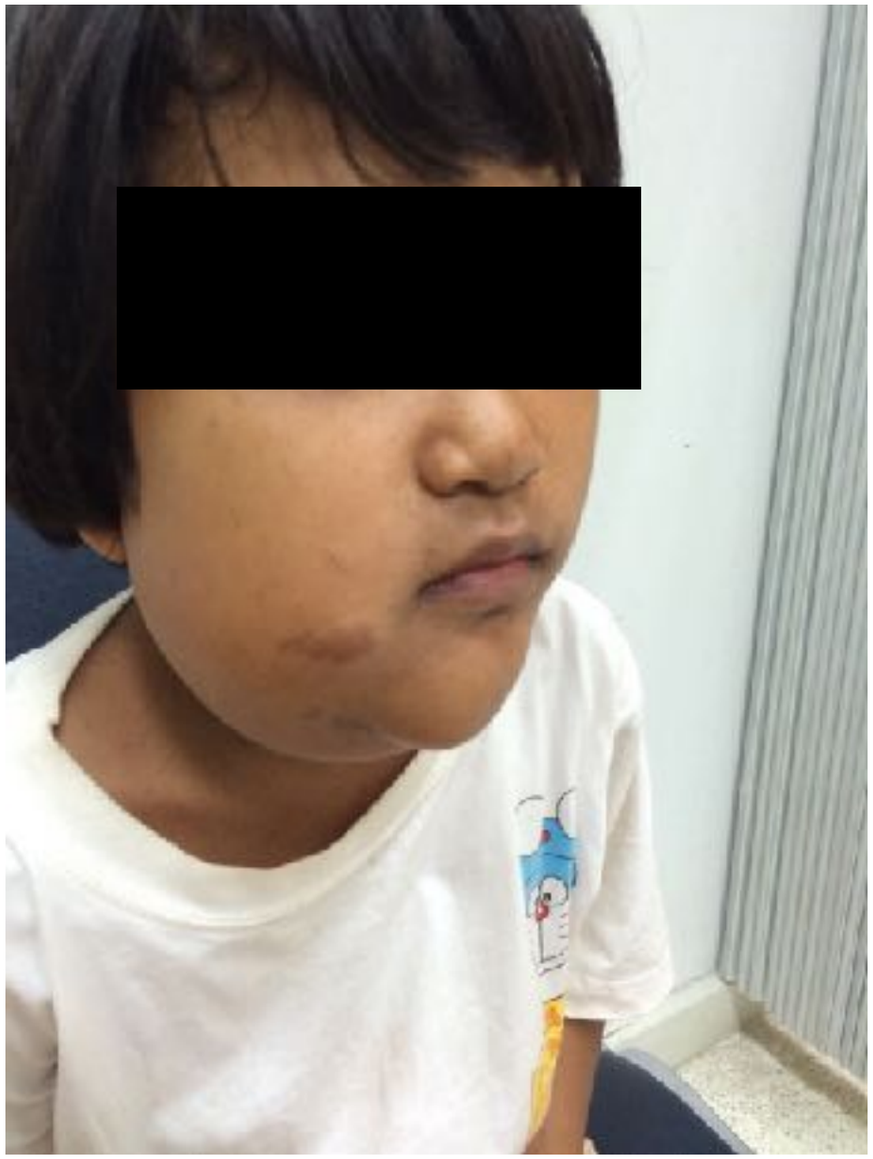
David T. Miller, Debra Freedenberg, Elizabeth Schorry, Nicole J. Ullrich, David Viskochil, Bruce R. Korf, COUNCIL ON GENETICS, AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS. Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics May 2019, 143 (5) e20190660; DOI: 10.1542/peds.2019-0660

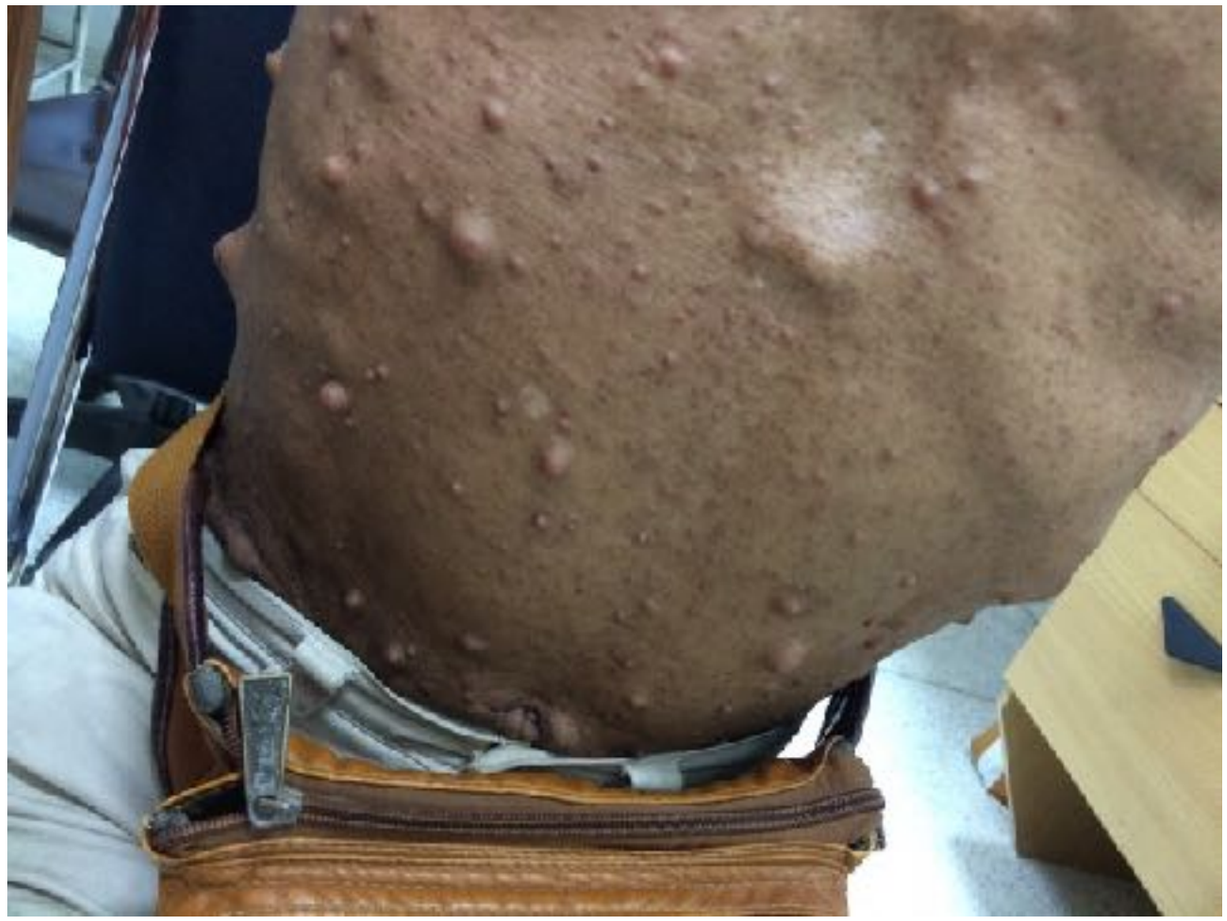
Neurofibromatosis type 1





Neurofibromatosis type 1





Autosomal Recessive

- Males and females are equally likely to be affected
- Parents of an affected child are carriers
- The recurrence risk for each sib of the proband is 1/4
- Consanguinity can be observed but not the most common explanation for an autosomal recessive trait
- Rare recessive disorders in genetic isolates: e.g. Tay-Sachs/ Sandhoff disease
- Chance that gamete from non carrier parent had acquired a mutant allele by spontaneous mutation ~ 1 in 10^5 – 10^6
- Chance that gamete contained the mutant allele from heterozygous carrier parent ~1 in 20 -1000

Autosomal Recessive

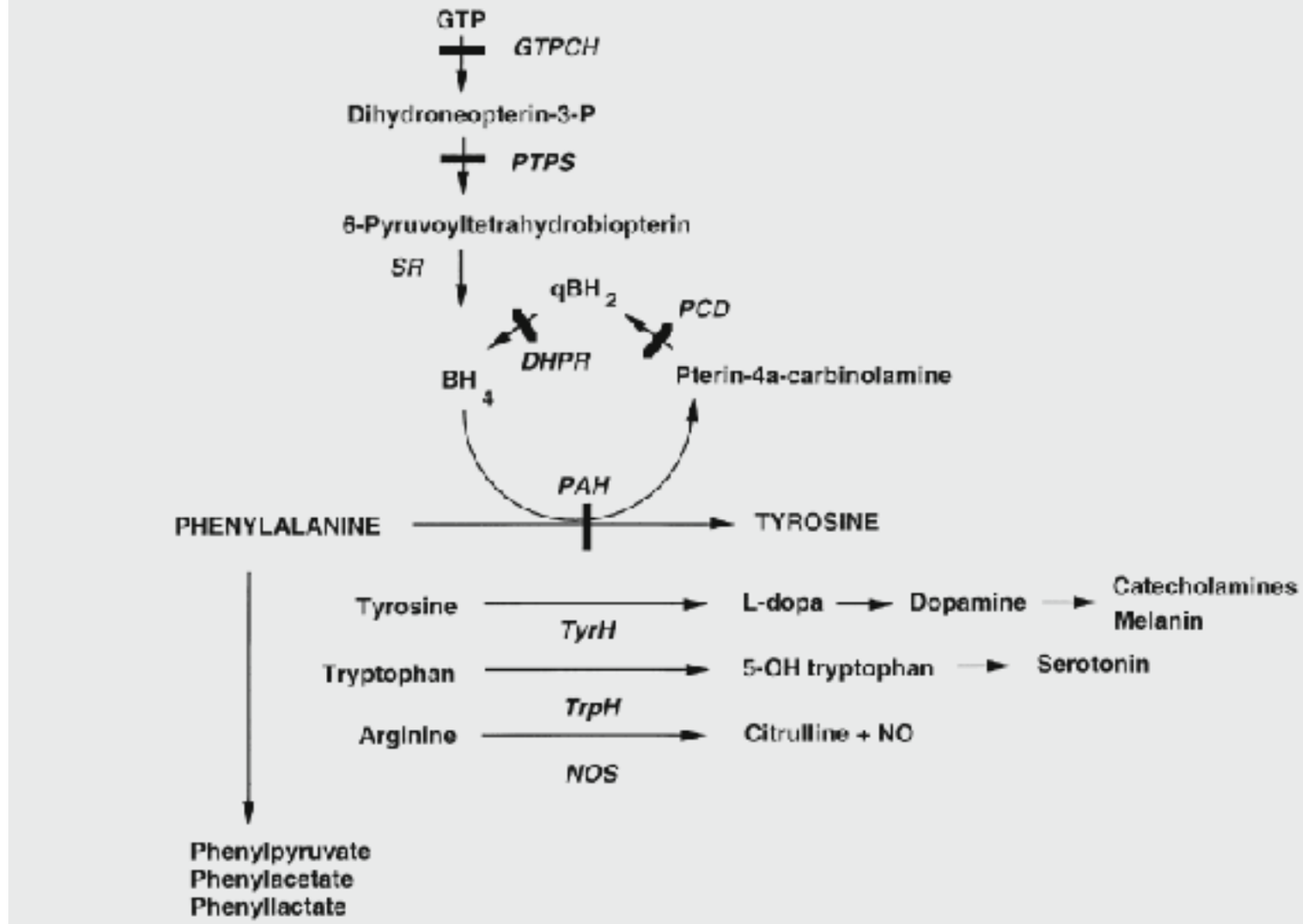
- Most of inborn errors of metabolism
  - Phenylketonuria etc.
- Thalassemia
- SMA
- Etc.

Phenylketonuria

- An inherited disorder that increases the levels of phenylalanine in the blood
- Phenylalanine (Phe) is an essential amino acid
- Phe is found in all proteins and in some artificial sweeteners
- Phenylalanine hydroxylase (PAH) deficiency

- Classification of hypoerphenylalaninemia
  - Classical PKU: Phe > 1200 µmol/l (20 mg/dl) (PAH activity <1%)
  - Hyperphenylalaninemia (HPA): Phe 600 - 1200 µmol/l (10-20 mg/dl) (PAH activity 1-5%)
  - Mild hyperphenylalaninemia: Phe 120 - 600 µmol/l (2-10 mg/dl (PAH activity >5%)

Phenylketonuria



■ **Fig. 17.1.** The phenylalanine hydroxylation system, including the synthesis and regeneration of pterins and other pterin requiring enzymes. *BH2*, dihydrobiopterin (quinone); *BH4*, tetrahydrobiopterin; *DHPR*, dihydropteridine reductase; *GTP*, guanosine triphosphate; *GTPCH*, guanosine triphosphate cyclohydrolase; *NO*, nitric oxide; *NOS*, nitric oxide synthase; *P*, phosphate; *PAH*, PHE hydroxylase; *PCD*, pterin-4a-carbinolamine dehydratase; *PTPS*, pyruvoyl-tetrahydrobiopterin synthase; *SR*, sepiapterin reductase; *TrpH*, tryptophan hydroxylase; *TyrH*, tyrosine hydroxylase. The enzyme defects are depicted by *solid bars* across the *arrows*

John H. Walter, Robin H. Lachmann, Peter Burgard. Hyperphenylalaninaemia. in Jean-Marie Saudubray, Georges van den Berghe, John H. Walter (Editors). Inborn Metabolic Diseases Diagnosis and Treatment. 5th ed. Springer, NY, 2012. p.251-263

Newborn screening

48 hr - 5 days

Congenital hypothyroid & Phenylketonuria

Newborn screening

กิจกรรมตรวจคัดกรองสุขภาพทารกแรกเกิดแห่งชาติ

สรุปผลปฏิบัติการการตรวจคัดกรองฯ ปีงบประมาณ พ.ศ. 2539 - 2562

ปี	จำนวนทารกที่คลอด	จำนวนตัวอย่างส่งตรวจ	% ความครอบคลุม	เรียกตรวจซ้ำ		ซีรั่มส่งตรวจซ้ำ				ผิดปกติ	
				TSH	PKU	TSH	%	PKU	%	TSH	PKU
2555	801,608	786,462	98.11	2,642	33	2,461	93.15	24	72.73	541	6
2556	745,681	760,705	102.01	2,017	26	1,987	98.51	19	69.23	449	5
2557	717,644	721,584	100.55	2,027	28	1,864					
2558	682,392	691,740	101.37	1,818	32	1,184					
2559	675,797	637,226	94.29	1,779	104	1,006					
2560	658,557	643,919	97.76	3,177	165	1,664					
2561	635,836	621,664	97.77	3,080	245	1,385	44.97	127	51.84	313	33
2562	572,937	592,604	103.43	3,890	126	2,749	70.67	71	56.35	587	17
รวม	**18,475,926**	**14,509,728**	**78.53**	**64,400**	**1,915**	**45,548**	**70.73**	**1,134**	**59.22**	**8,051**	**147**

Incidence ~ 1: 74,000 - 125,000

ข้อมูล ณ วันที่ 11 พ.ย. 2562

หมายเหตุ :

1. ผลผิดปกติ หมายถึง ผลที่ได้รับการตรวจยืนยันด้วยซีรั่มและได้รับการรักษาจากสถานบริการเรียบร้อยแล้ว
2. ตั้งแต่ปี 2558 เป็นต้นไป ศูนย์ติดตามการตรวจคัดกรองสุขภาพทารกแรกเกิด สถาบันสุขภาพเด็กแห่งชาติมหาราชินี เป็นผู้ดำเนินการติดตามเด็กที่มีผลเลือดผิดปกติ
3. จำนวนทารกที่คลอด ที่มา: กองยุทธศาสตร์และแผนงาน สำนักงานปลัดกระทรวงสาธารณสุข

* มีตัวอย่างซีรั่มทารกที่ไม่ได้ตรวจคัดกรองครั้งแรกส่งมาเพิ่มเติม

** เริ่มใช้นโยบายสุขภาพถ้วนหน้า ปี พ.ศ. 2548 และปี พ.ศ. 2549 ได้รับบรรจุเข้าเป็นสิทธิประโยชน์แก่เด็กทารกแรกเกิดไทย

ศูนย์ปฏิบัติการตรวจคัดกรองสุขภาพทารกแรกเกิดแห่งชาติ กรมวิทยาศาสตร์การแพทย์

Phenylketonuria

Treatment

- Unrestricted natural foods with very low PHE content
- Restricted natural and manufactured foods with medium PHE content
- Avoid meat, fish, cheese, egg, milk, rice, corn, aspartame
- PHE free amino acid infant formulas
- monitor plasma Phe level (120-360 micromole/l)
- BH4 therapy; Sapropterin (Kuvan®)
- Supplement Large Neutral Amino Acid

X-linked dominant

- Affected males with normal mates have no affected sons and no normal daughters
- Both male and female offspring of female carriers have a 50% risk of inheriting the phenotype
- The pedigree pattern is similar to that seen with autosomal dominant inheritance
- Affected females are about twice as common as affected males
- Affected females typically have milder (although variable) expression of the phenotype
- X-linked dominant disorders with male lethality
  - e.g. Rett syndrome

Fragile X syndrome

- Dynamic mutation of *FMR1*
- Most common inherited mental retardation
- Phenotypic features of males
  - Prepubertal features
    - Infancy and childhood include hypotonia, gastroesophageal reflux, strabismus, seizures, sleep disorders, etc.
    - Normal growth
    - Large HC(>50th percentile) is often seen
    - Delayed attainment of motor milestones and speech
    - Intellectual disability (mean IQ ~40-45)
    - Behavior problems
    - Autism spectrum disorder (ASD) (50%-70%)

Hunter JE, Berry-Kravis E, Hipp H, et al. FMR1 Disorders. 1998 Jun 16 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1384/

Fragile X syndrome

- Prepubertal features
  - Long face,
  - Prominent forehead,
  - Large ears, and
  - Prominent jaw
- Postpubertal features
  - Mitral valve prolapse and aortic root dilatation
  - Anxiety and irritable/aggressive behavior
  - Macroorchidism

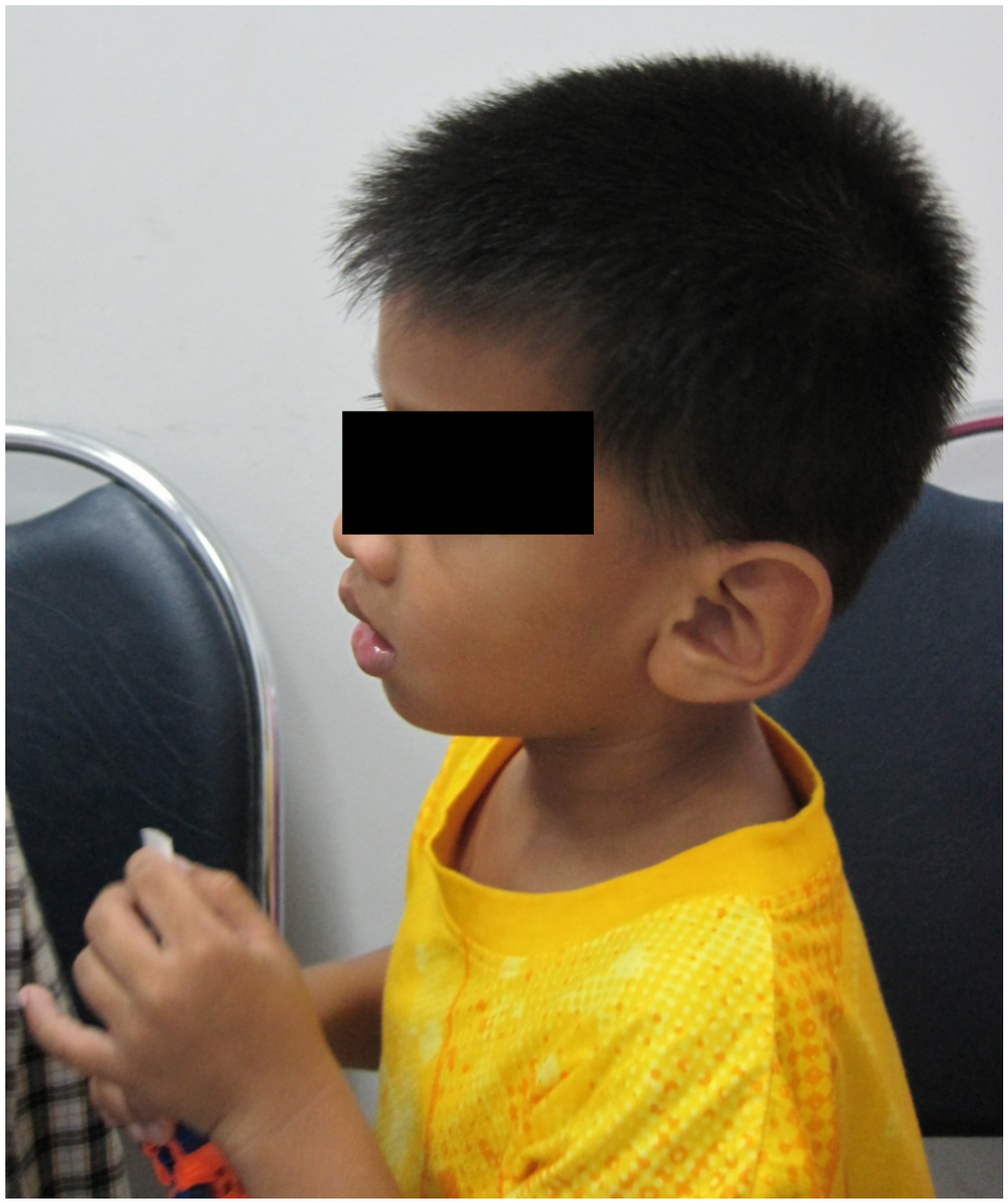
Hunter JE, Berry-Kravis E, Hipp H, et al. FMR1 Disorders. 1998 Jun 16 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1384/

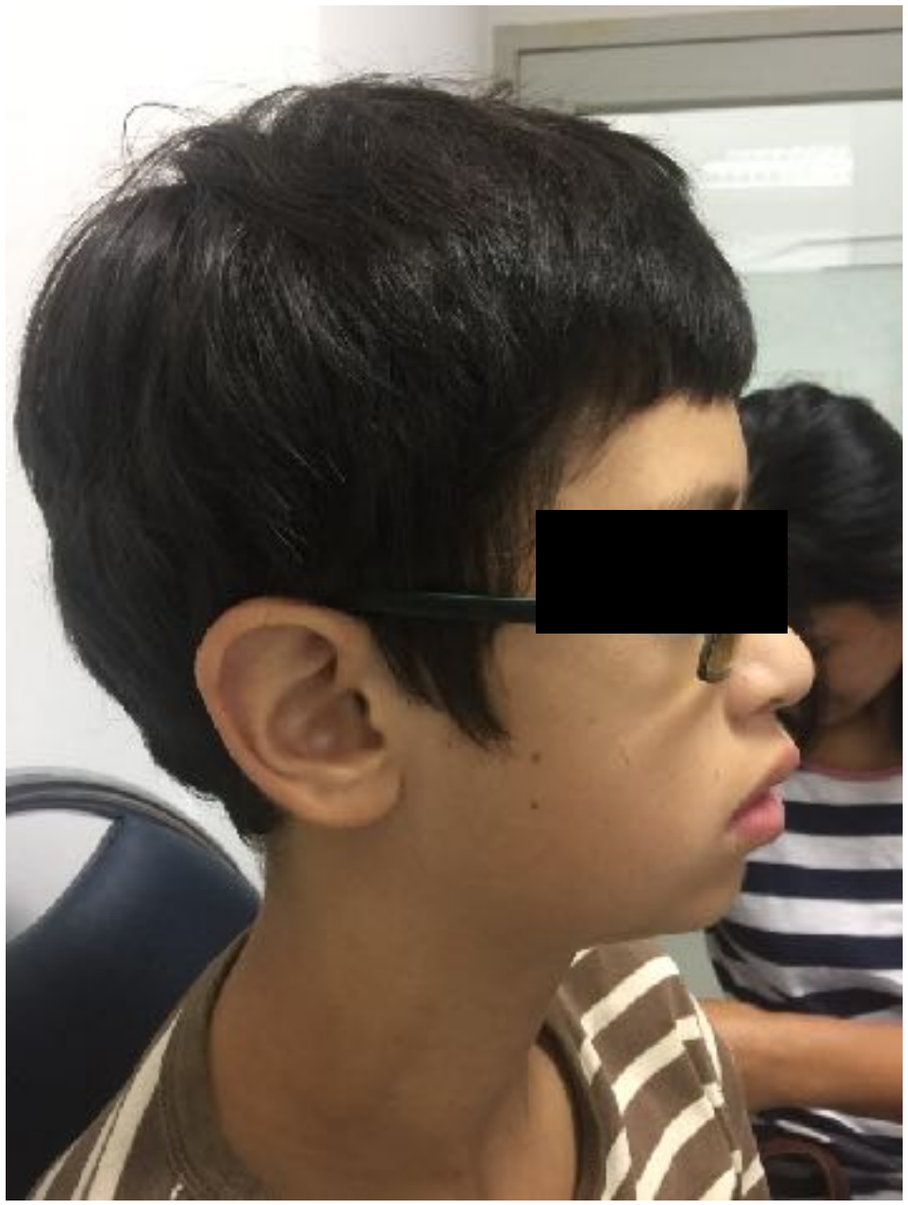
Fragile X syndrome

Variant Type	# of CGG Trinucleotide Repeats	Methylation Status of *FMR1*	Clinical Status	
			Male	Female
Premutation	~55-200	Unmethylated	At risk for FXTAS	At risk for FXPOI & FXTAS
				Potential ↑ risk of other fragile X-assoc disorders
Full mutation	>200	Completely methylated	100% have ID	~50% w/ID, ~50% normal intellect
Repeat size mosaicism	Varies between premutation & full mutation in different cell	Partial: unmethylated in premutation cell line; methylated in full-mutation cell line	Nearly 100% have ID; may be higher functioning 2 than males w/full mutation.	Highly variable: ranges from normal intellect to affected
Methylation mosaicism	>200	Partial: mixture of methylated & unmethylated cell lines		
Unmethylated full mutation	>200	Unmethylated	ID, if present, is typically high functioning.	
			May have anxiety &/ or behavioral issues even w/out ID	

Hunter JE, Berry-Kravis E, Hipp H, et al. FMR1 Disorders. 1998 Jun 16 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1384/

Fragile X syndrome





X-linked recessive

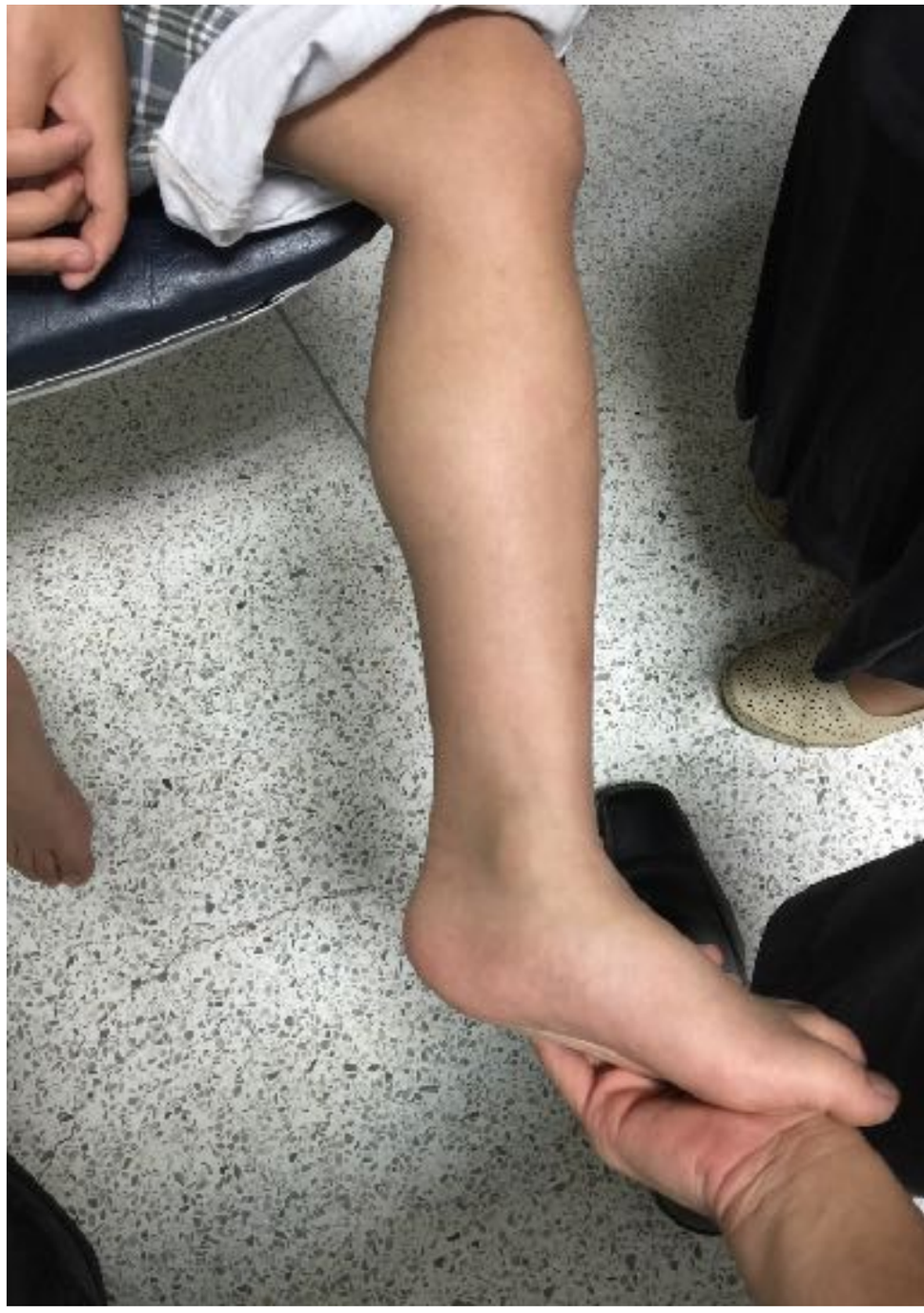
- Heterozygous females are usually unaffected,
  - may express the condition with variable severity by the pattern of X inactivation
- Transmitted mutant allele from an affected man through all his daughters
- No male to male transmission
- A significant proportion of isolated cases are due to new mutation
- Obligate carriers
  - A daughter of an affected male
  - A woman who has one son with the X-linked recessive disease and another close family member with the same X-linked recessive disease
  - A woman who has more than one son with X-linked recessive disease

X-linked recessive

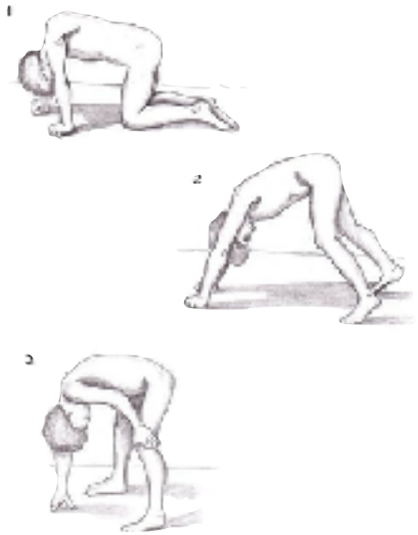
- Hemophilia A
- G6PD deficiency
- Duchenne muscular dystrophy
- etc.

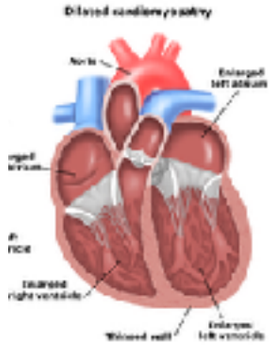
Duchenne muscular dystrophy

- *Dystrophin* gene mutation
- Gower sign positive
- Proximal muscle weakness
- Pseudo calf hypertrophy
- Increase creatine phosphokinase enzyme



Duchenne muscular dystrophy





Proximal muscle weakness

Delayed gross motor

Wheelchair

Cardiomyopathy

Bedridden

cardiopulmonary failure, death

Birth

3-5 years

10 years

20 years

Duchenne muscular dystrophy

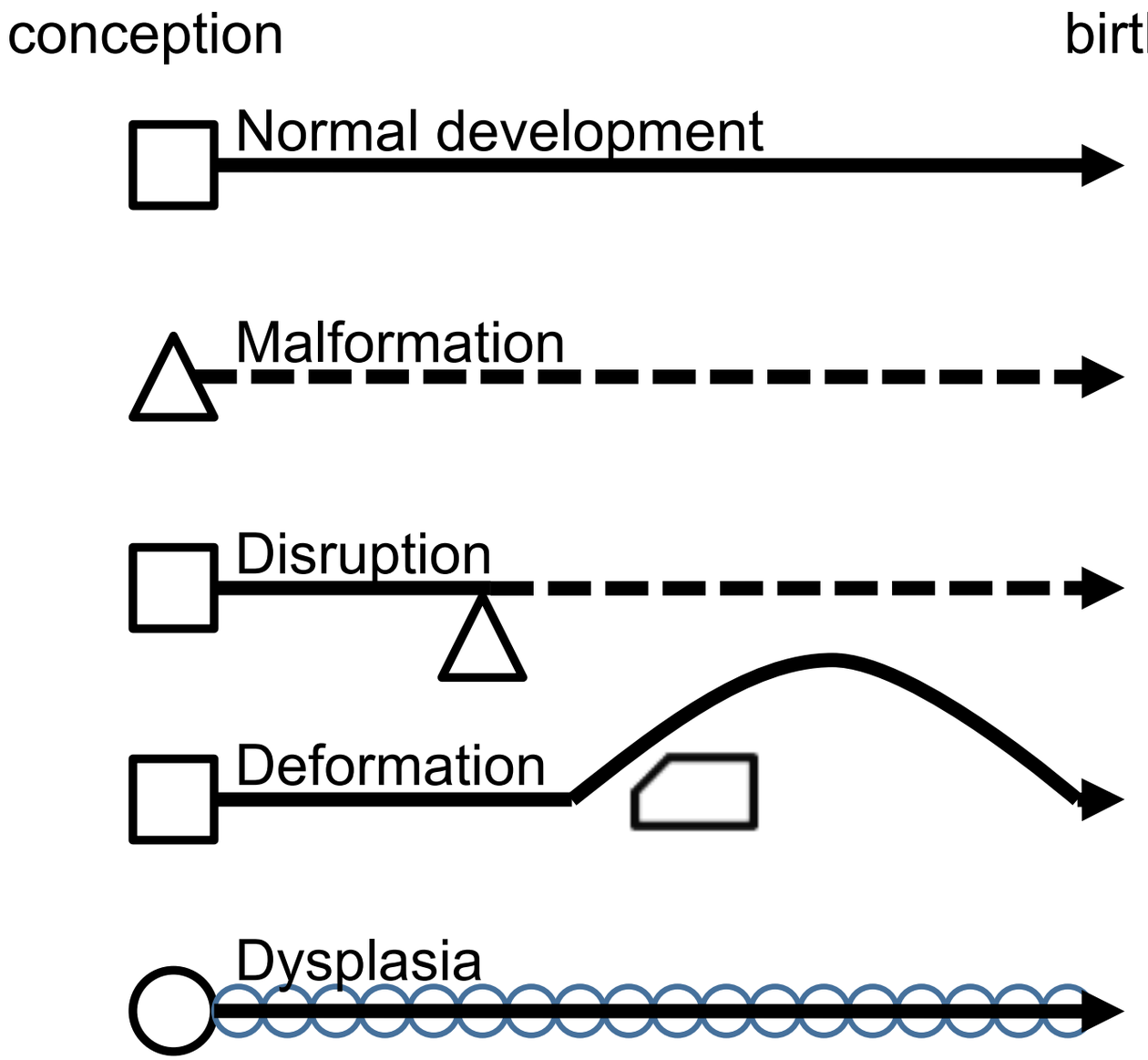
- **Confirm the diagnosis**
  - **Identify causative gene: Dystrophin (*DMD*) gene**
    - **65-80% -> deletion/duplication**
    - **20-35% -> point mutation; (10-15% nonsense mutation)**
  - **Appropriate genetic testing**
    - **Multiplex PCR**
    - **Multiple Ligation-Dependent Probe Amplification (MLPA)**
    - **DNA sequencing**

Duchenne muscular dystrophy

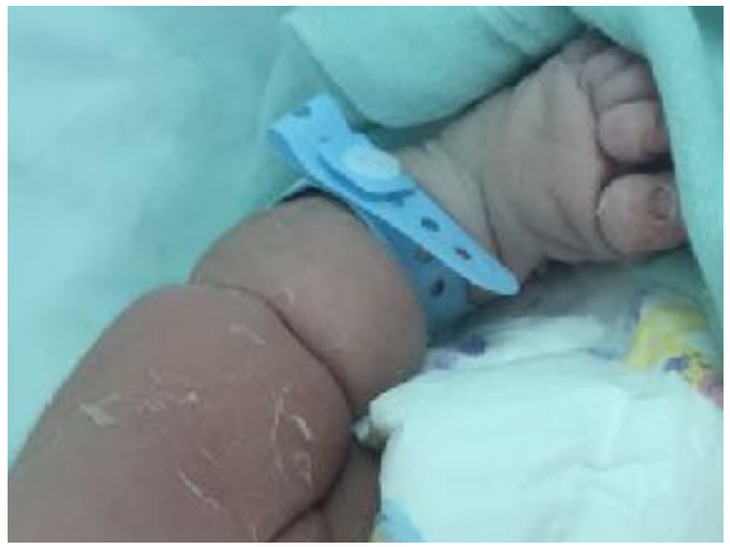
Treatment

- **Prednisolone; 0.75 MKD**
- **Rehabilitation**
- **Deflazacort (Emflaza; PTC Therapeutics)**
- **Eteplirsen (Exondys 51; Sarepta Therapeutics)**
  - **13% of patients with DMD have mutations amenable to skipping exon 51**
- **Ataluren (Translarna; PTC Therapeutics)**

Approach to dysmorphic child



Approach to dysmorphic child



Approach to dysmorphic child

Major anomaly

ความผิดปกติที่มีผลทำให้การทำงานของอวัยวะเสียไป และจำเป็นต้องได้รับการแก้ไข เช่น congenital heart diseases, KUB anomaly, brain anomaly

Minor anomaly

ความผิดปกติที่ไม่มีผลให้การทำงานของอวัยวะนั้นเสียไป พบได้ 2-3% ของประชากรทั่วไป เช่น simian crease, hypertelorism, low set ears

Approach to dysmorphic child

- Major anomaly
    - Anomalies or malformations that create significant medical problems for the patient or that require specific surgical or medical management
    - Major anomalies or malformations generally are not considered a variation of the normal spectrum
        - e.g. congenital heart diseases, KUB anomaly, brain anomaly
- Minor anomaly
    - Features that vary from those that are most commonly seen in the normal population but that, in and of themselves, do not cause increased morbidity.
    - e.g. simian crease, hypertelorism, low set ears

Approach to dysmorphic child

- Syndrome
  - Down syndrome
  - Marfan syndrome
  - etc.
- Association
  - VACTERL
  - etc.
- Sequence
  - Oligohydramnios sequence/ Potter sequence
  - Pierre-Robin sequence
  - Amnion rupture sequence
  - etc.

VACTERL

- Vertebral anomalies
- Anorectal malformation
- Cardiac anomalies
- Tracheoesophageal fistula
- Esophageal atresia
- Renal anomalies
- Limbs anomalies

Potter sequence

Renal hypoplasia

Oligohydramnios

Lungs hypoplasia

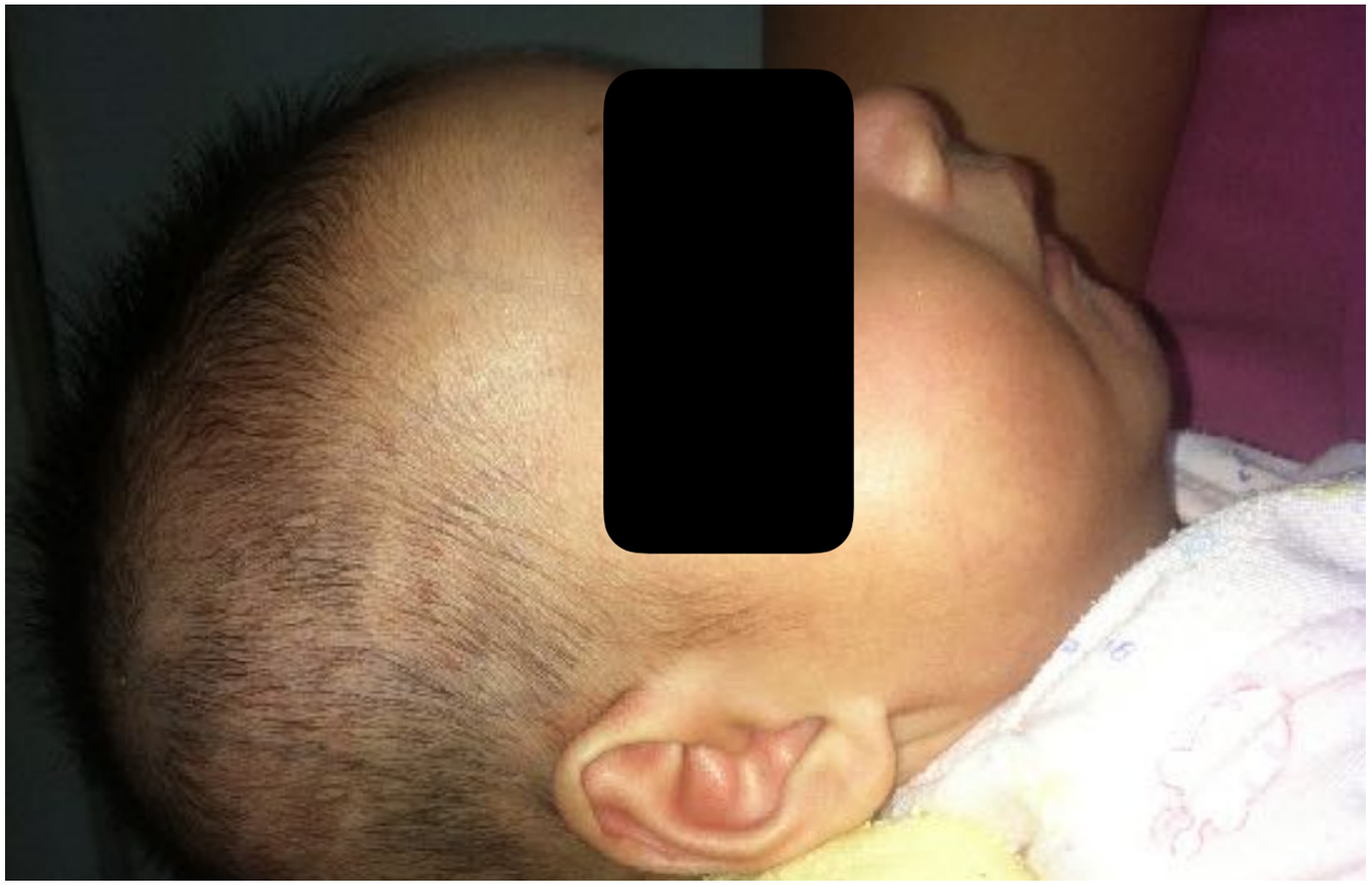
Pierre-Robin sequence

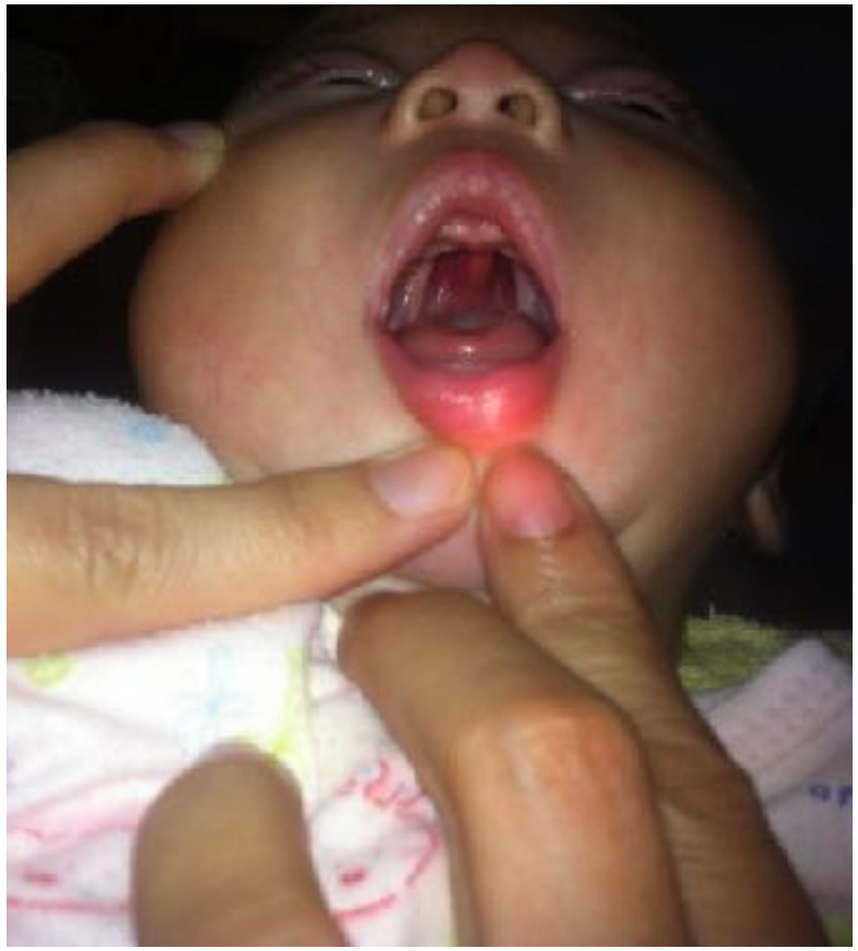
Micrognathia

Glossoptosis

Upper airway obstruction

Pierre-Robin sequence





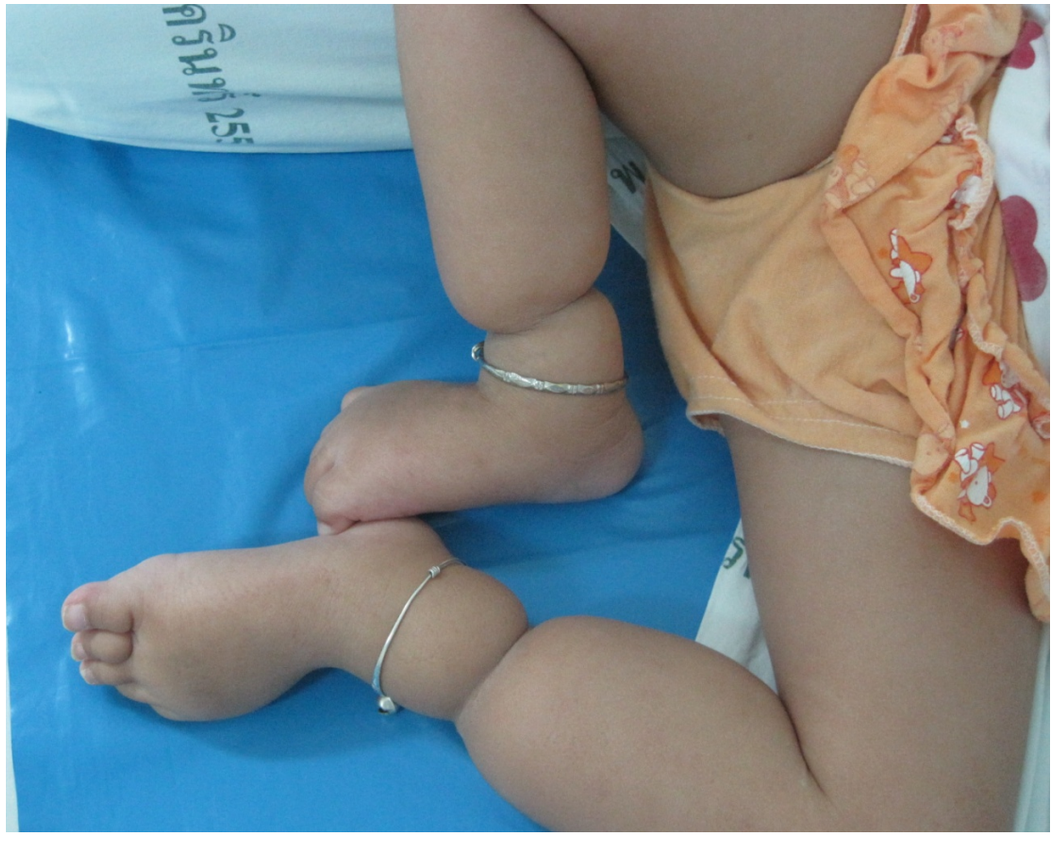
Amnion ruptured sequence

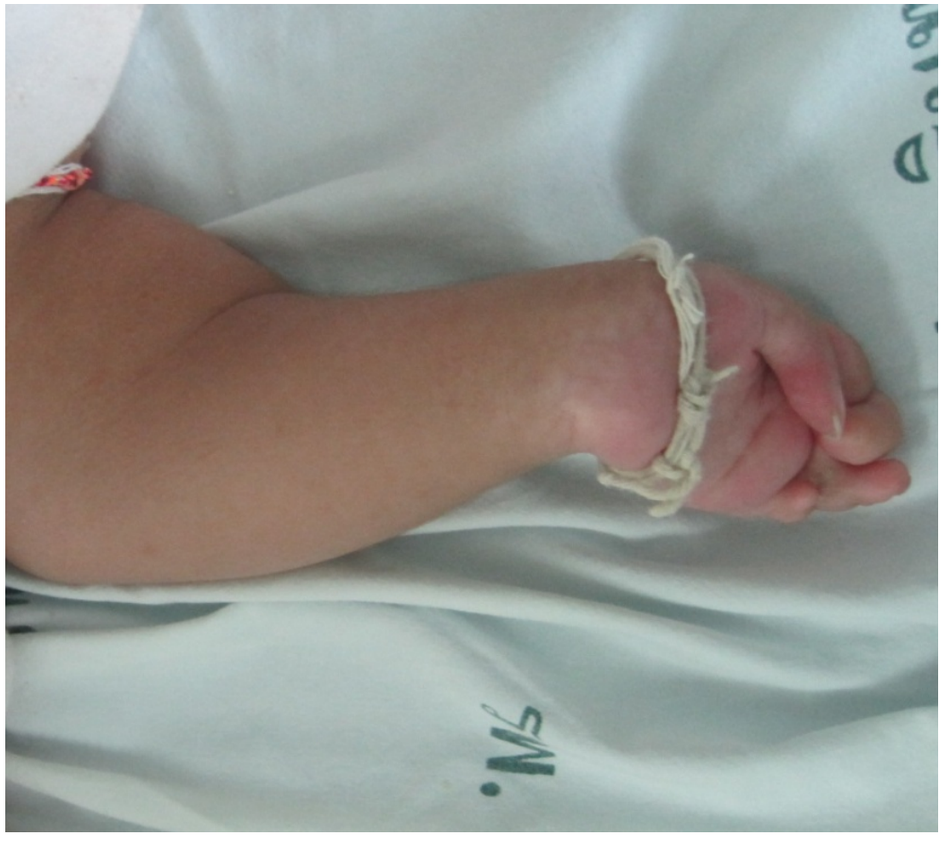
Amnion ruptured

Amniotic band

Limb deficiencies

Amnion ruptured sequence





Question