Single Gene Disorders with non-classic Inheritance

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Group-1, 5th course.

Medical genetics

Single Gene Disorders with non-classic Inheritance

They fall into four categories: Diseases caused by

1. Trinucleotide repeat mutation
2. Mutation in mitochondrial genes
3. Genomic imprinting
4. Gonadal mosaicism

Diseases Caused by Trinucleotide-Repeat Mutations

- Expansion of trineuclotide repeats is an important genetic cause of human disease, particularly neurodegenerative disordersfirst recognised in 1991
- Till now there are 40 diseases under this category

Diseases Caused by Trinucleotide-Repeat Mutations

- Associated with the expansion of trinucleotides in the genome
- These trinucleotides usually share the G and C
- This makes DNA unstable, and may impair gene function
- Expansion depends strongly on the sex of the transmitting parent
  - Fragile X syndrome: Expansions occur during oogenesis
  - Huntington disease: Expansions occur during spermatogenesis

Table 5-8 Examples of Trinucleotide-Repeat Disorders

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Disease	Gene	Locus	Protein	Repeat	No. of Repeats	
					Normal	Disease
Expansions Affecting Noncoding Regions						
Fragile X syndrome	*FMR1 (FRAXA)*	Xq27.3	FMR-1 protein (FMRP)	CGG	6-55	55-200 (pre); >230 (full)
Friedreich ataxia	*FXN*	9q21.1	Frataxin	GAA	7-34	34-80 (pre); >100 (full)
Myotonic dystrophy	*DMPK*	19q13.3	Myotonic dystrophy protein kinase (DMPK)	CTG	5-37	34-80 (pre); >100 (full)
Expansions Affecting Coding Regions						
Spinobulbar muscular atrophy (Kennedy disease)	*AR*	Xq12	Androgen receptor (AR)	CAG	9-36	38-62
Huntington disease	*HTT*	4p16.3	Huntingtin	CAG	6-35	36-121
Dentatorubral-pallidoluysian atrophy (Haw River syndrome)	*ATNL*	12p13.31	Atrophin-1	CAG	6-35	49-88
Spinocerebellar ataxia type 1	*ATXN1*	6p23	Ataxin-1	CAG	6-44	39-82
Spinocerebellar ataxia type 2	*ATXN2*	12q24.1	Ataxin-2	CAG	15-31	36-63
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	*ATXN3*	14q21	Ataxin-3	CAG	12-40	55-84
Spinocerebellar ataxia type 6	*CACNA2A*	19p13.3	α_{1A}-Voltage-dependent calcium channel subunit	CAG	4-18	21-33
Spinocerebellar ataxia type 7	*ATXN7*	3p14.1	Ataxin-7	CAG	4-35	37-306

Diseases Caused by Trinucleotide-Repeat Mutations

There are three mechanisms by which unstable repeats cause diseases:

- Loss of function of the affected gene - the repeats are generally in non-coding part of the gene
- A toxic gain of function by alterations of protein structure – the repeats are in the coding regions of the genes
  - Huntington disease and
  - Spinocerebellar ataxia
- A toxic gain of function mediated by mRNA: noncoding parts of the gene are affected
  - fragile X tremor-ataxia syndrome

Diseases Caused by Trinucleotide-Repeat Mutations

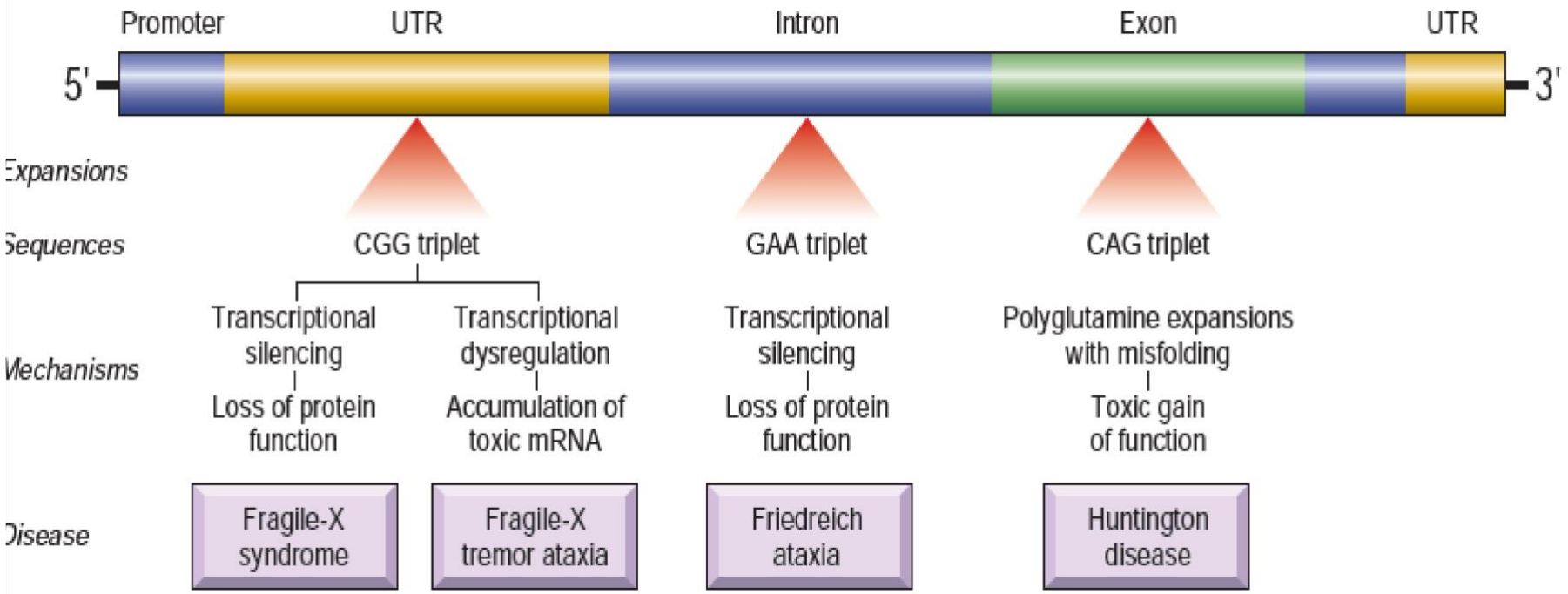

Figure 5-23 Sites of expansion and the affected sequence in selected diseases caused by nucleotide-repeat mutations. UTR, Untranslated region.

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Fragile X Syndrome and Fragile X Tremor/Ataxia

- 1 in 1550 for affected males and
- 1 in 8000 for affected females
- FMR1 gene
- CGG repeats:
- In the normal population ranging from 6 to 55 (average, 29)
- Normal transmitting males and carrier females 55 to 200 repeats – *premutations*
- Affected individuals: 200 to 4000 repeats -*full mutations*

- *Anticipation:* Clinical features of fragile X syndrome worsen with each successive generation - as it is transmitted from a man to his grandsons and great-grandsons

Fragile X Syndrome and Fragile X Tremor/Ataxia

In fragile X syndrome:

Clinical features:

- Males are mentally retarded, IQ 20 to 60
- Long face
- Large mandible
- Large everted ears *and*
- Large testicles (macro-orchidism)
- Hyperextensible joints

- a high arched palate, and
- Mitral valve prolapse

Fragile X Syndrome

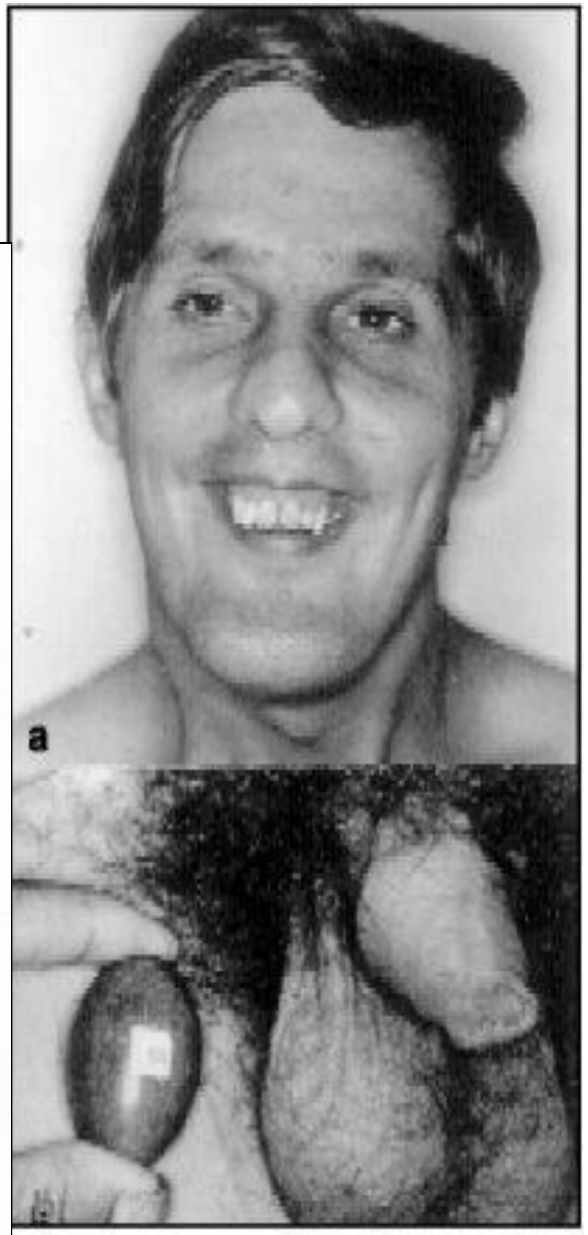
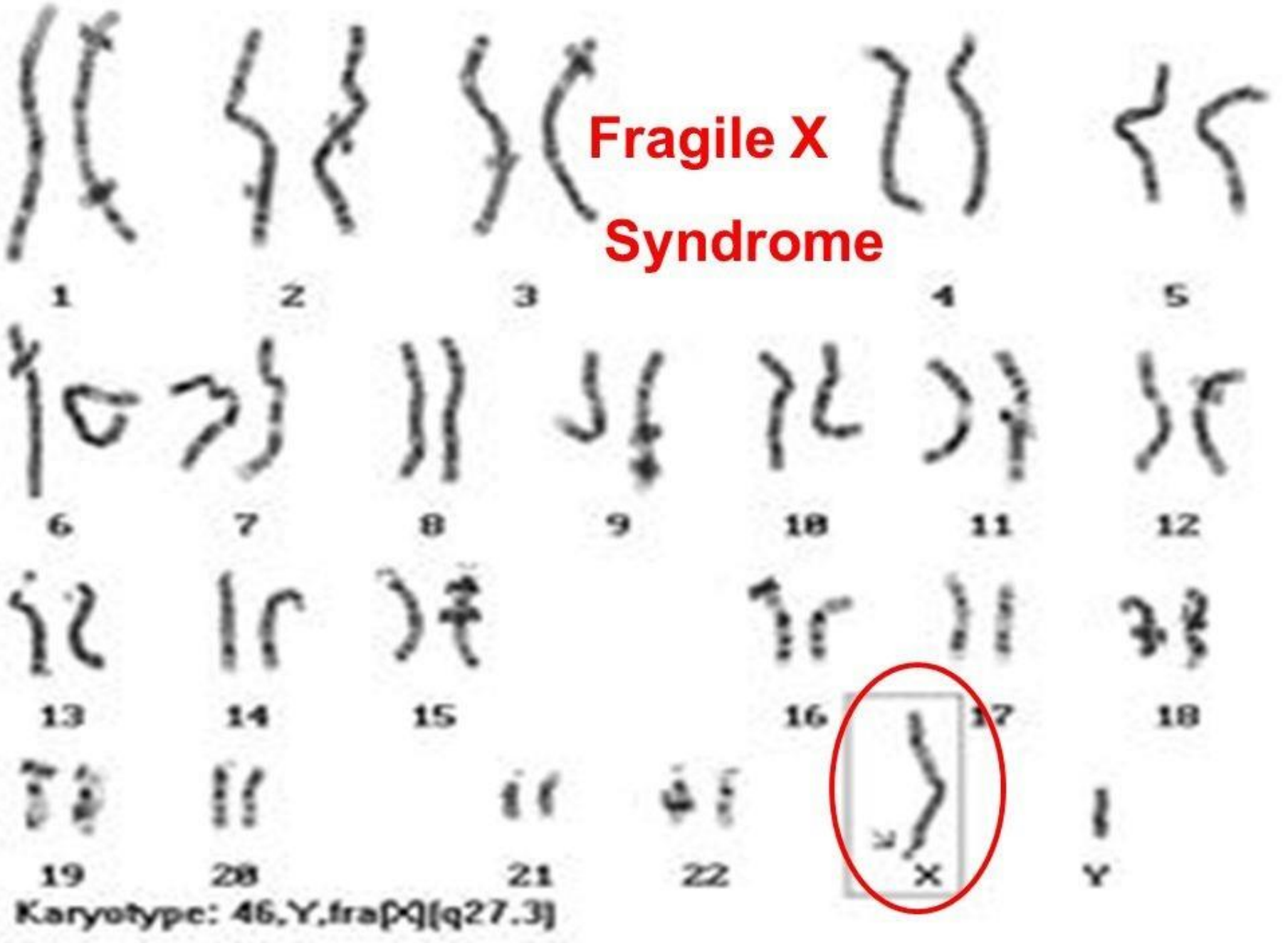


Fig 3. (a) Patient III3 (family 1) with long and narrow face and (b) macro-orchidism (testicular volume= 56 ml).


Fragile X
Syndrome
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y
Karyotype: 46,Y,fra(X)(q27.3)

Fragile X Syndrome

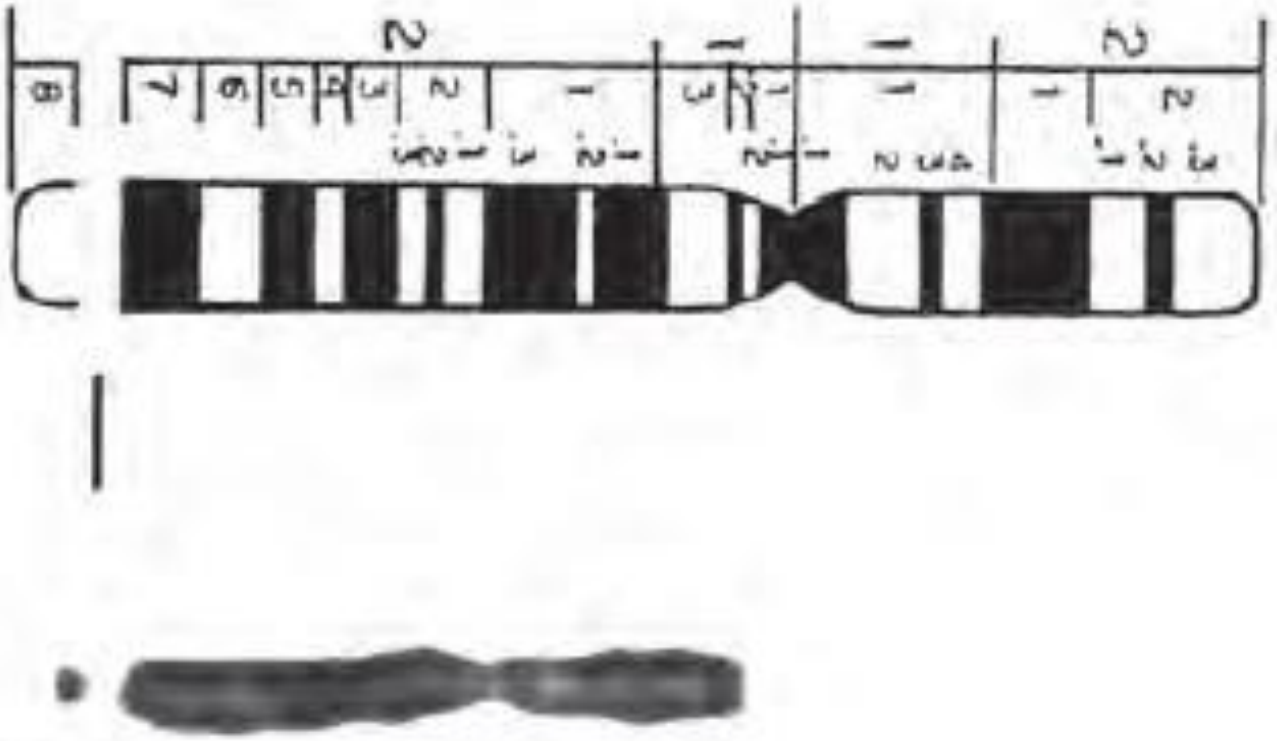
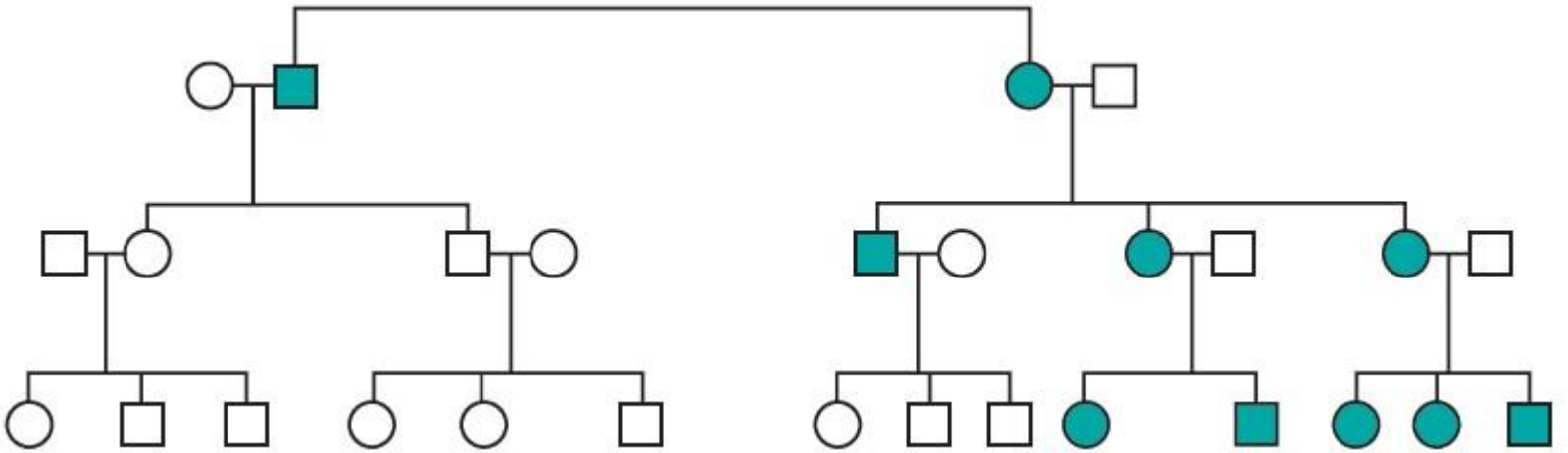


Figure 5-24 Fragile X seen as discontinuity of staining. (Courtesy of Dr. Patricia Howard-Peebles, University of Texas Southwestern Medical Center, Dallas, TX.)

Mutations in Mitochondrial Genes — Leber Hereditary Optic Neuropathy

- *A feature unique to mtDNA is maternal inheritance*
- Human mtDNA contains 37 genes
- 22 for tRNA
- 2 for rRNA
- The remaining 13 genes encode subunits of the respiratory chain enzymes
- Hence, mutations affecting these genes exert their deleterious effects primarily on the organs most dependent on oxidative phosphorylation
  - CNS
  - Skeletal muscle,
  - Cardiac muscle
  - Liver, and
  - Kidneys

Typical Pedigree cahrt in mtDNA associated transmission



Genomic Imprinting

- Imprinting is silencing
- Silencing occurs by methylation of DNA or Histones
- It is an epigenetic phenomenon
- Silencing occurs during gametogenesis

- It is permanent
- Alleles are expressed in a parent-of-origin-specific manner
  - If paternal allele is imprinted (silenced), maternal allele will express and vice versa
- Human diseases involving genomic imprinting include
  - Angelman syndrome and
  - Prader–Willi syndrome

Genomic Imprinting

- Human diseases involving genomic imprinting include
  - Angelman syndrome and
  - Prader–Willi syndrome

- Both are micro deletion syndromes
  - Chr# 15 is involved in deletion
  - del(15)(q11.2q13)

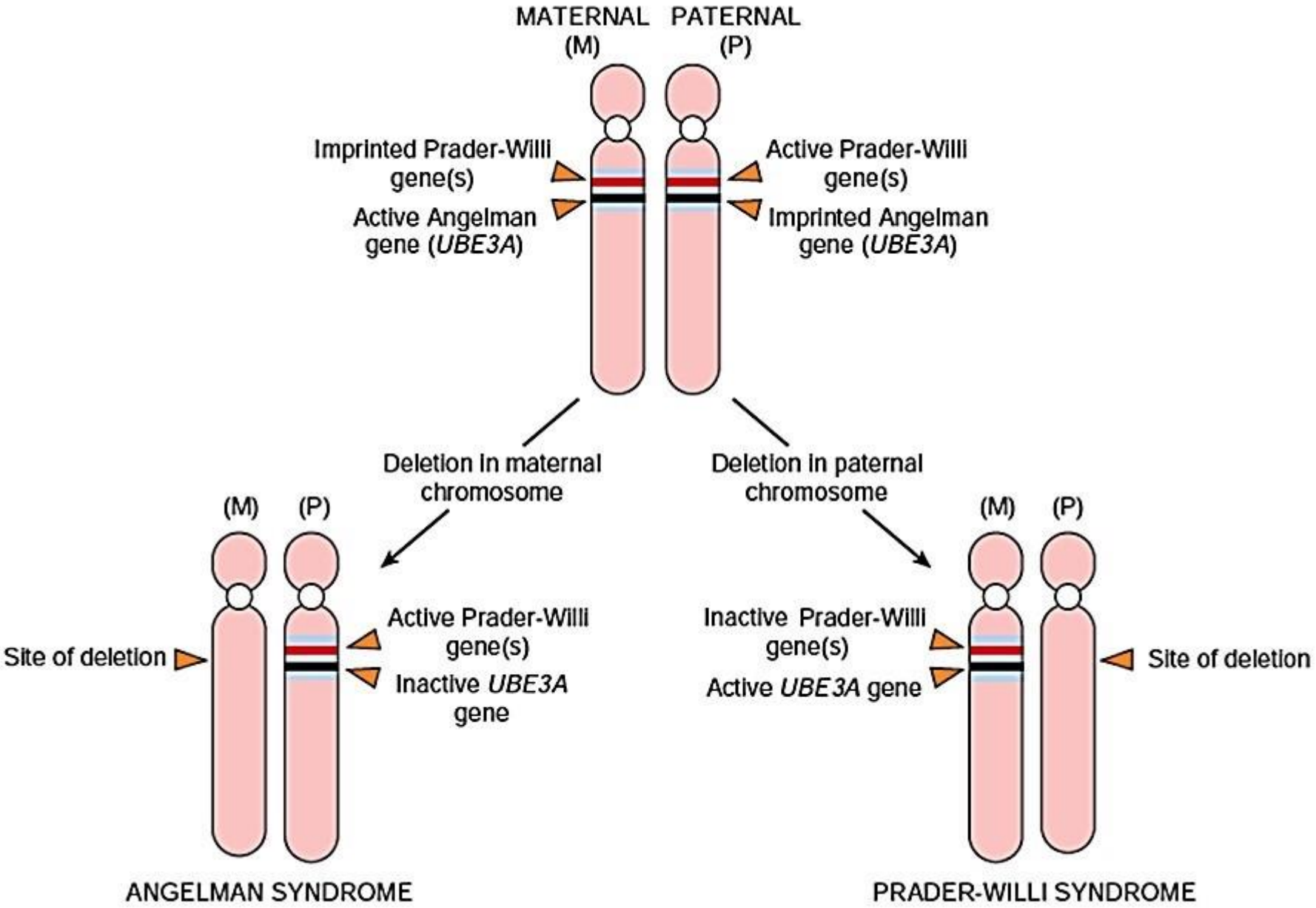


Figure 5-28 Diagrammatic representation of Prader-Willi and Angelman syndromes.

Prader-Willi syndrome

Characterized by

- Mental retardation,
- Short stature
- Hypotonia
- Profound hyperphagia
- Obesity
- Small hands and feet, and
- Hypogonadism

- In 65% to 70% of cases, an interstitial deletion of band q12 in the long arm of chromosome 15, del(15)(q11.2q13), can be detected
  - (causing a 5-Mb deletion) (Micro deletion)
- *It is striking that in all cases the deletion affects the paternally derived chromosome 15.*

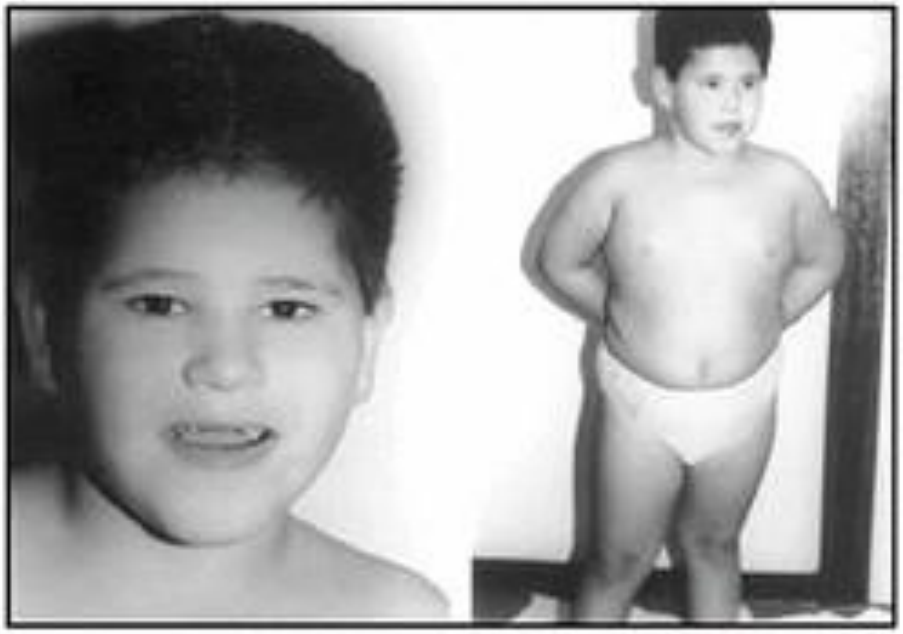
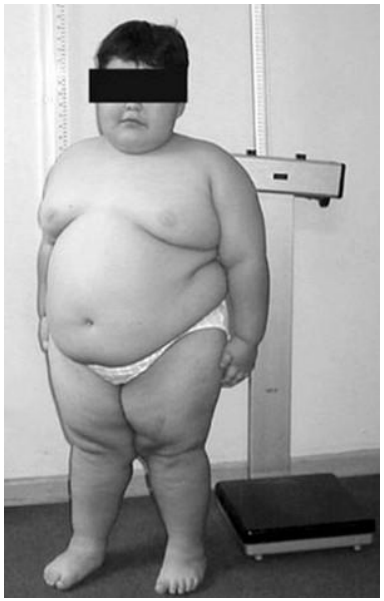
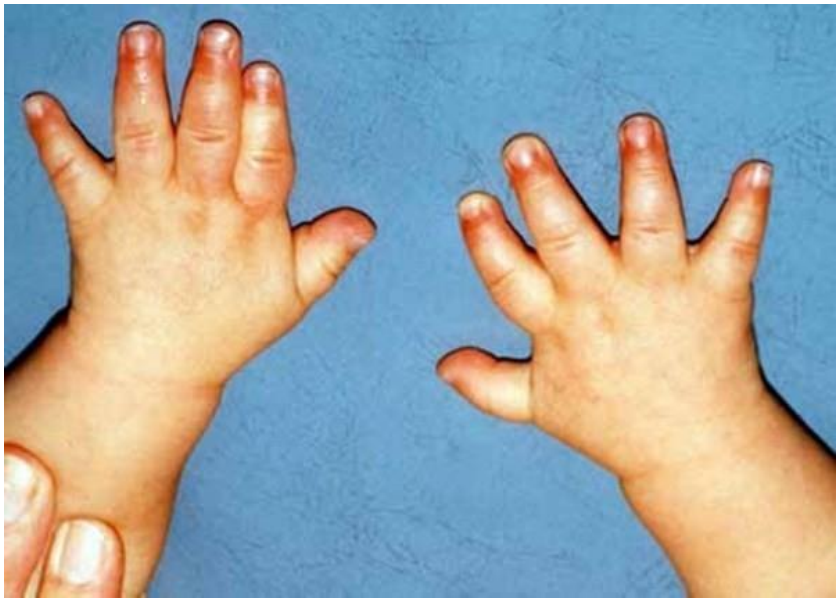


Fig 1. Patient at the age of 6 years and 4 months. (photo published with parents consent).

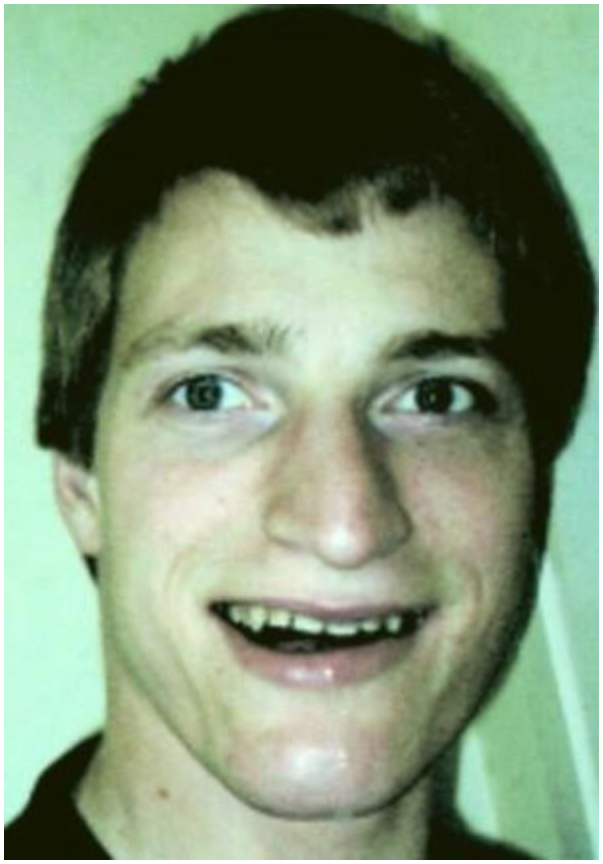


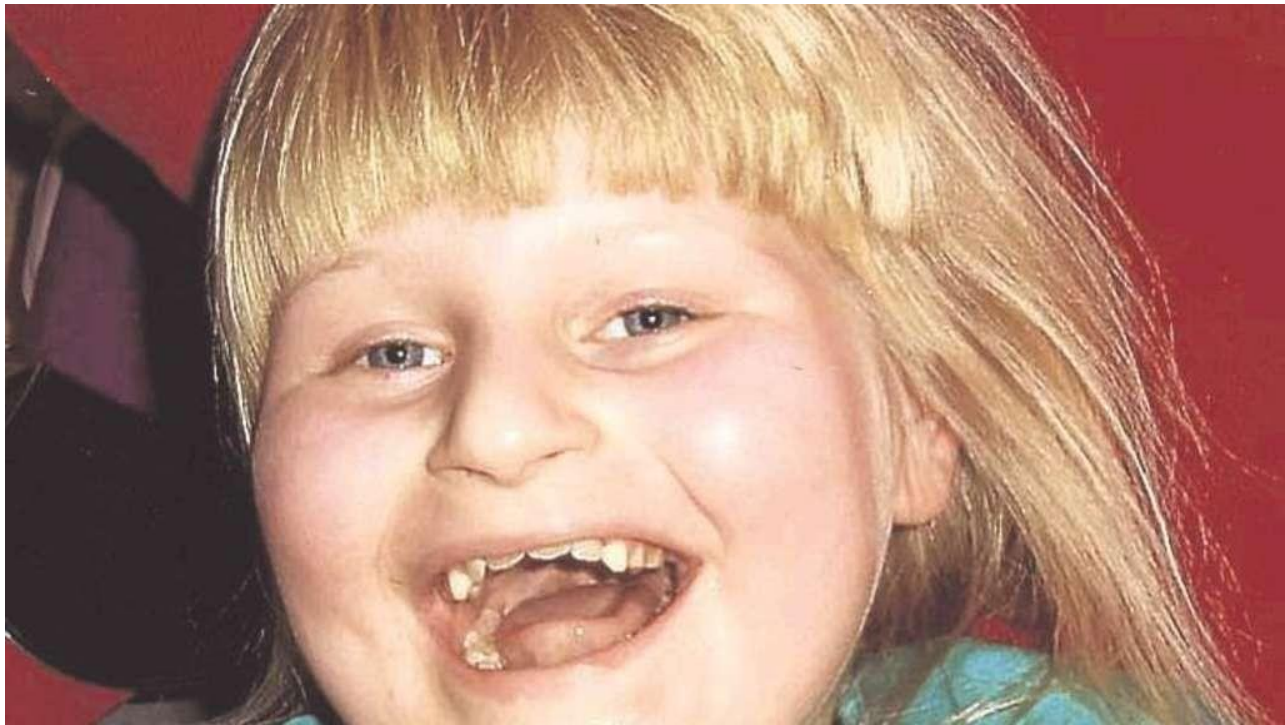


Angelman syndrome

- In contrast patiemts with the phenotypically distinct Angelman syndrome are *born with a deletion of the same chromosomal region derived from their mothers*
- **Patients with Angelman syndrome are:**
  - Mentally retarded
  - In addition they have
- Ataxic gait
- Seizures, and

- Inappropriate laughter
- Because of their laughter and ataxia, they have been referred to as “happy puppets”





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