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# Chromosomal Disorders

**MGL - 5**

**June 29<sup>th</sup> 2014**

# Human chromosome disorders

On rare occasions, a chromosome's structure changes; such changes are usually harmful or lethal, rarely neutral or beneficial

- High frequency in humans
  - most embryos are spontaneously aborted
  - alterations are too disastrous
  - developmental problems result from biochemical imbalance
    - **imbalance in regulatory molecules?**
- Certain conditions are tolerated
  - upset the balance less = survivable
  - characteristic set of symptoms = syndrome

# Important Issues Pertinent To Structural Rearrangements

- **ARE THE INDIVIDUAL'S CHILDREN AT RISK?**
- A balanced rearrangement that does not cause a genetic disorder in the individual can still pose a risk for the individual's offspring
- The chromosomes cannot line up evenly during meiosis
- This may result in the egg or sperm having an unbalanced genetic complement, such as:
  - missing material,
  - extra material,
  - often a combination of both

# Important Issues Pertinent To Structural Rearrangements

## Balanced =

- No DNA was lost when the chromosomes broke
- The individual has all his/her genes
- Rarely causes a genetic disorder
- Will only cause a genetic disorder if one of the breakpoints interrupts a gene - only 2-4% of your DNA is protein-coding sequence

## Unbalanced =

- DNA was lost when the chromosomes broke
- The individual is missing one or more of his/her genes
- Often causes a genetic disorder
- Severity of effect is often proportional to the amount of DNA/genes lost

# Types of chromosome abnormalities

- **Numerical**

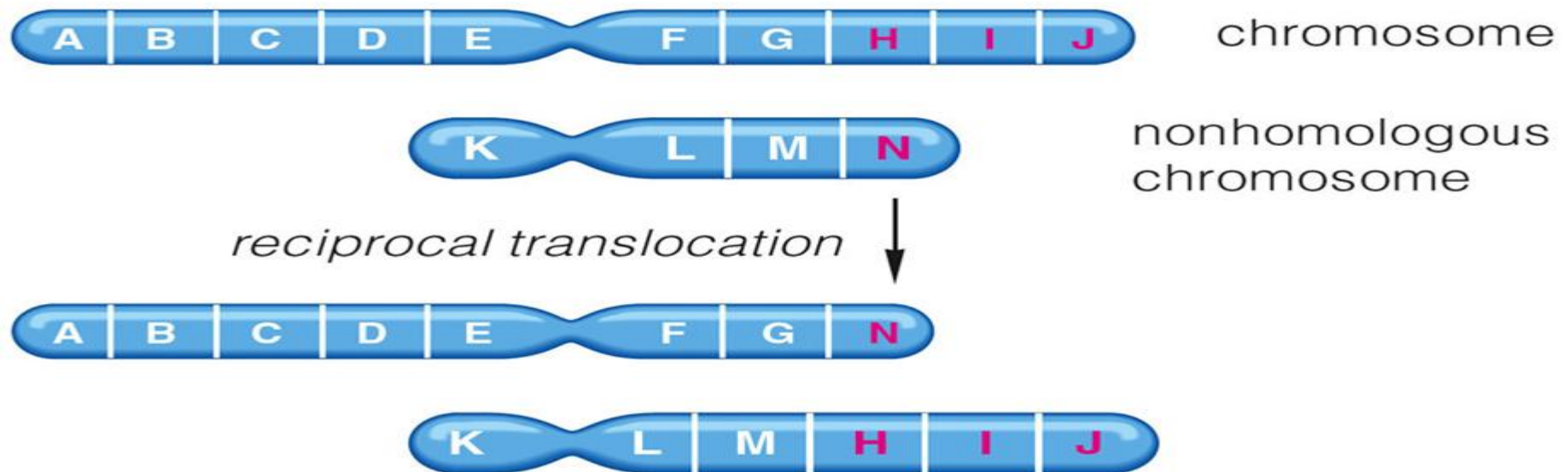
- Aneuploidy (monosomy, trisomy, tetrasomy)
- Polyploidy (triploidy, tetraploidy)

- **Structural**

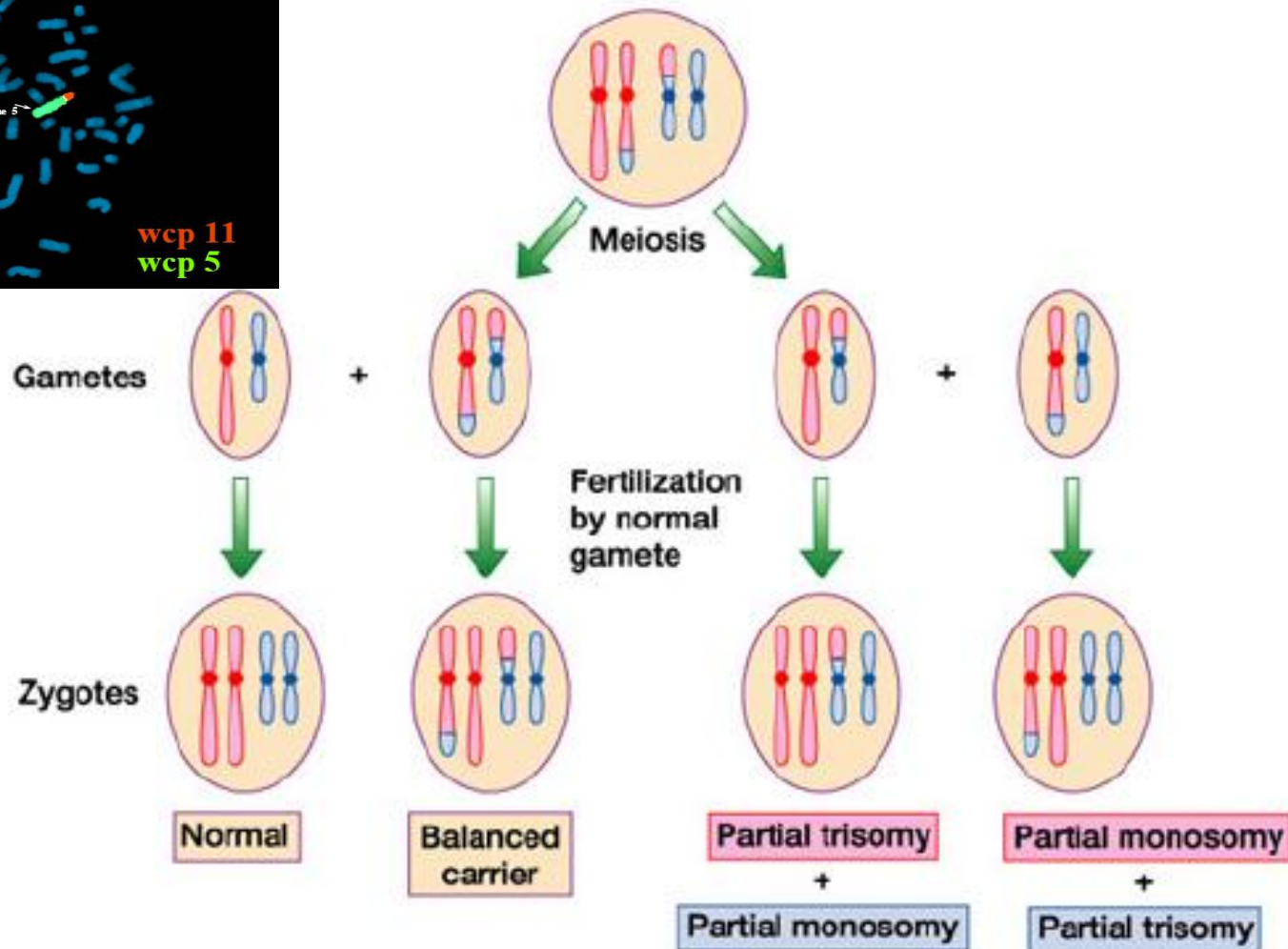
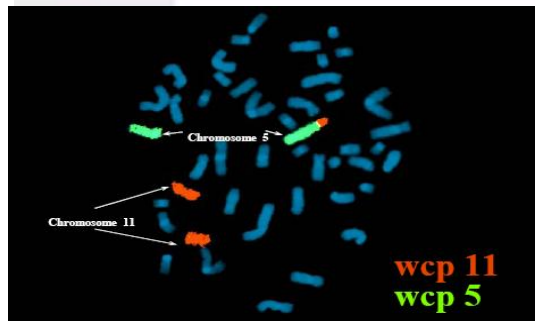
- Translocations
- Inversions
- Insertions
- Deletions
- Rings
- Duplication
- Isochromosomes

# Reciprocal Translocation

- Two nonhomologous chromosomes exchange a portion of their chromosome arms
- Rearrangement of the genetic material results in an individual who carries a translocation but is not missing any genetic material unless a translocation breakpoint interrupts a gene.



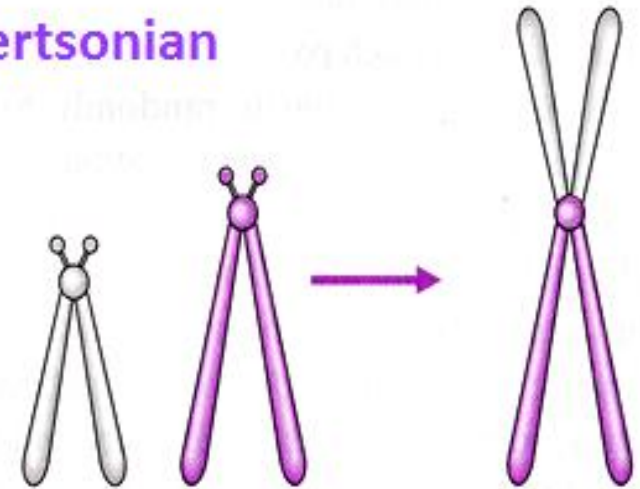
# Consequences of reciprocal translocations



# Robertsonian Translocations

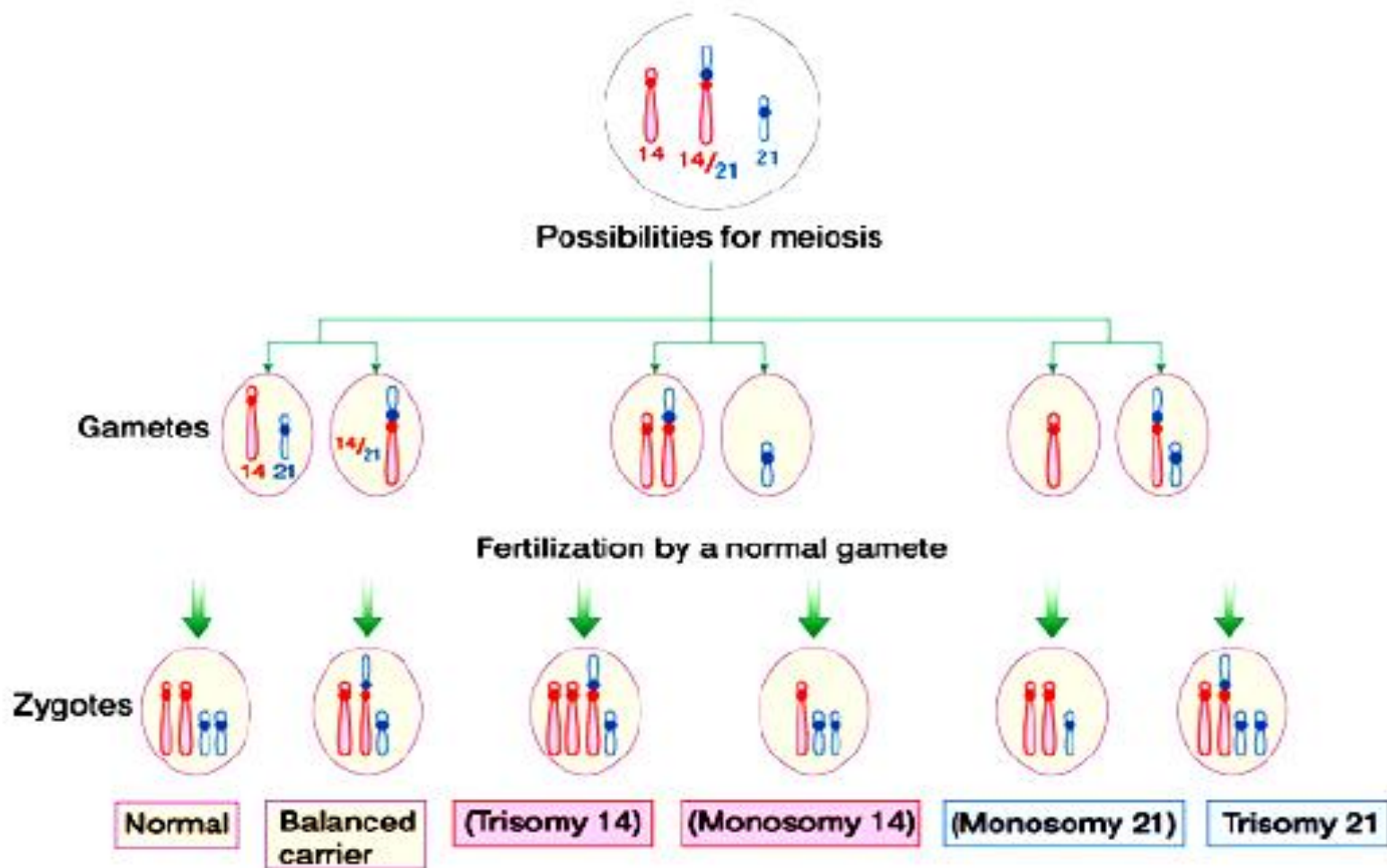
- Involve two acrocentric chromosomes that lose short arm material and often a centromere, fusing to form a single metacentric or submetacentric Chr
- Phenotypically normal – problems at meiosis
- Acrocentric chromosomes
  - D and G groups (13, 14, 15, 21, 22)

Robertsonian



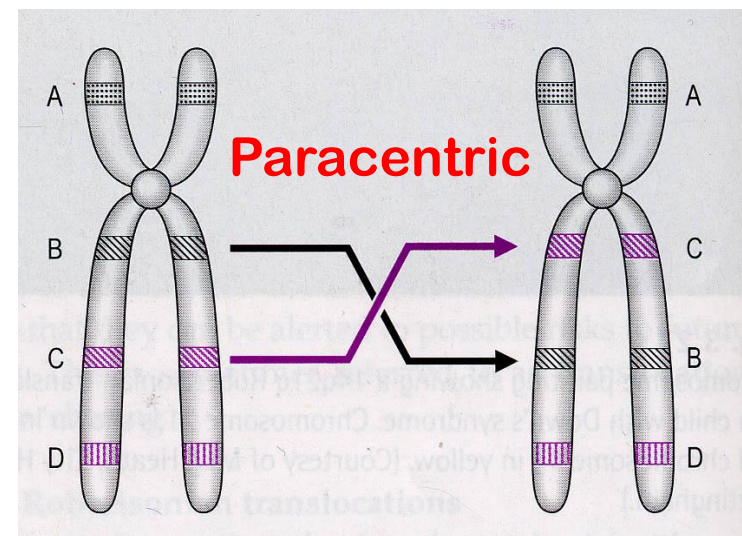
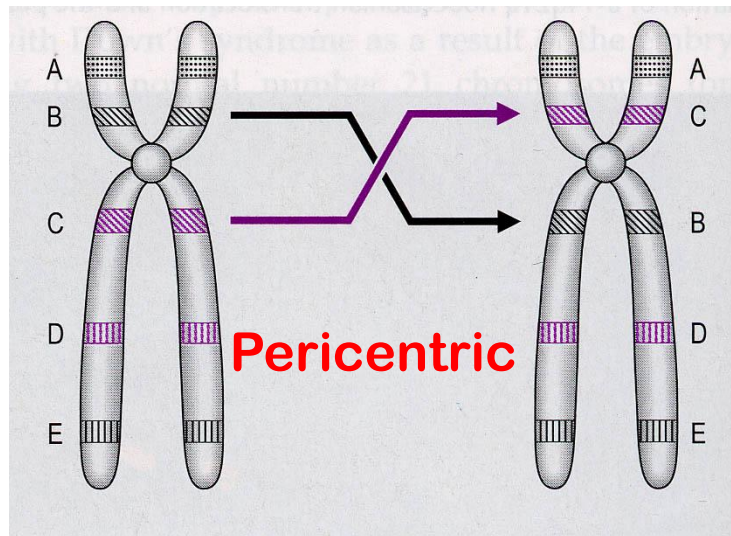


# Consequences of Robertsonian fusions



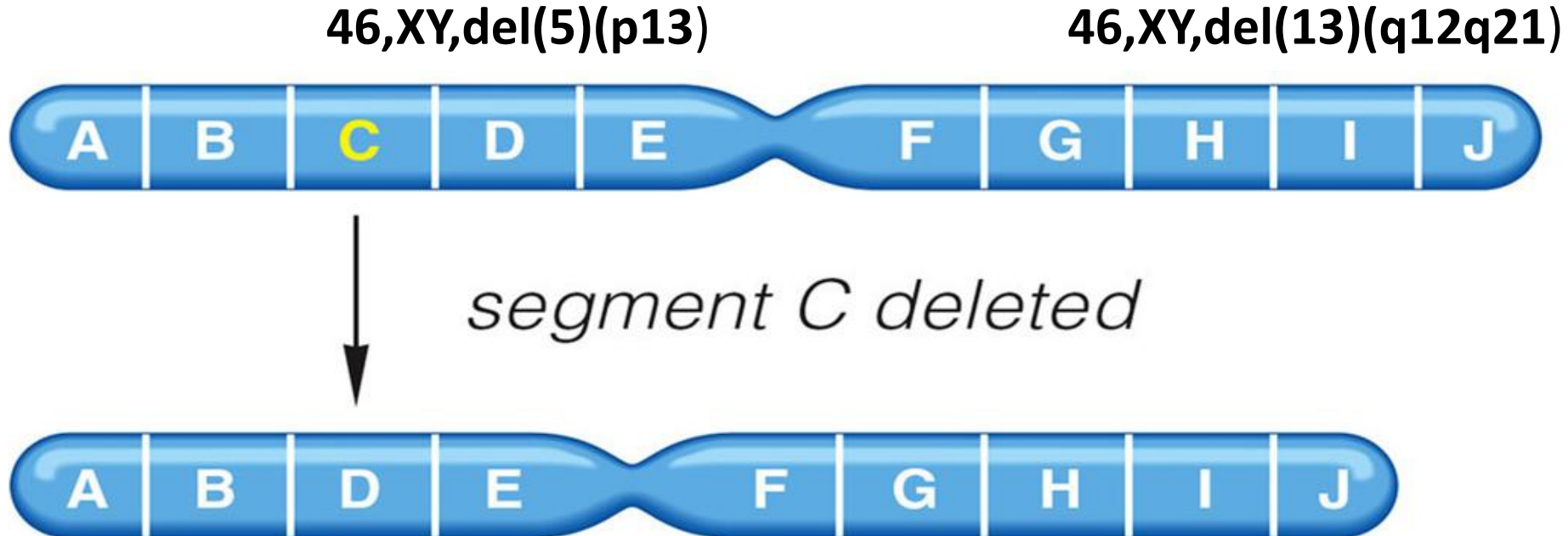
# Structural Chromosome Abnormalities-- Inversions

- An inversion can silence a normally active gene if it moves the gene next to a heterochromatic region of the chromosome (centromere or telomere)
- An inversion can activate a normally inactive gene if it moves the gene away from a heterochromatic region of the chromosome (centromere or telomere)



# Deletions

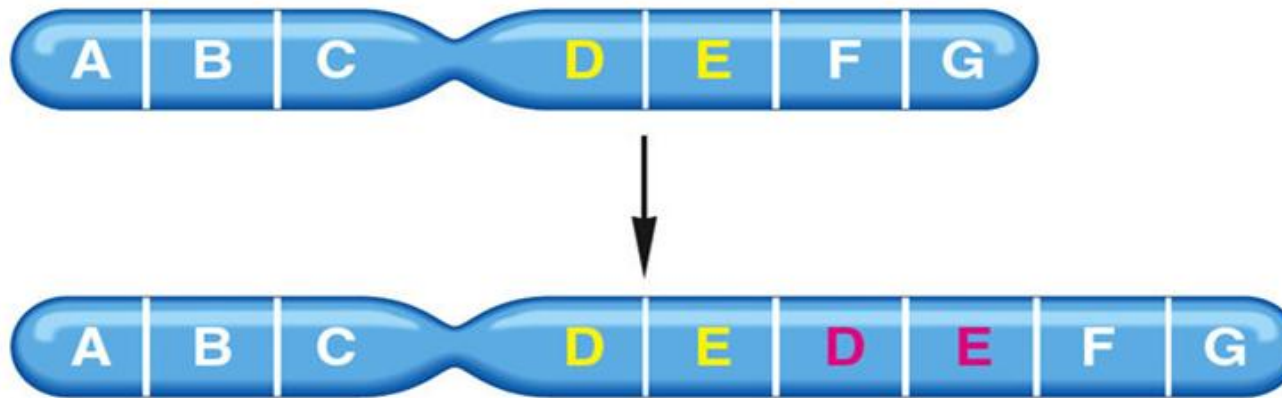
- Usually a *de novo* event that causes a loss of a chromosomal segment (resulting in partial monosomy)
- An interstitial deletion involves two breaks
- A terminal deletion involves one break
- An unbalanced translocation can masquerade as a terminal deletion



# Duplications

- Duplication = doubling of chromosome segments.
- chromosome duplications can be seen in three types; Tandem, reverse tandem, and tandem terminal
- Duplications result in un-paired loops visible cytologically.
- DNA sequences are repeated two or more times; may be caused by unequal crossovers in prophase I

**NORMAL**



**DUBLICATED**

**Normal  
chromosome**



**Duplications**



**Tandem**



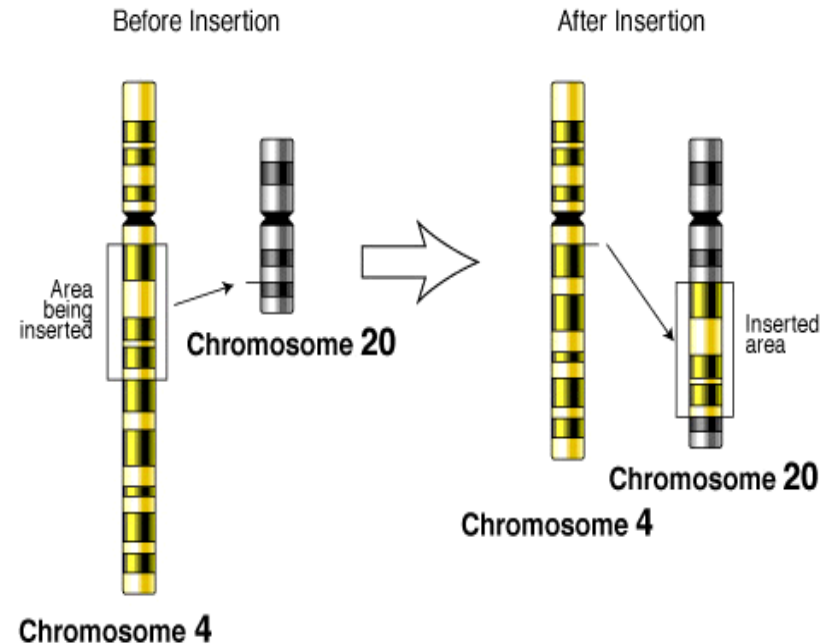
**Reverse  
tandem**



**Terminal  
tandem**

# Insertions

- Segments of chromosome that have been removed and inserted into the same or a different chromosome
- **Direct:** chromosomal segment in the original orientation
- **Inverted:** orientation reversed with reference to the centromere



# Duplications And Deletions Affect The Phenotype

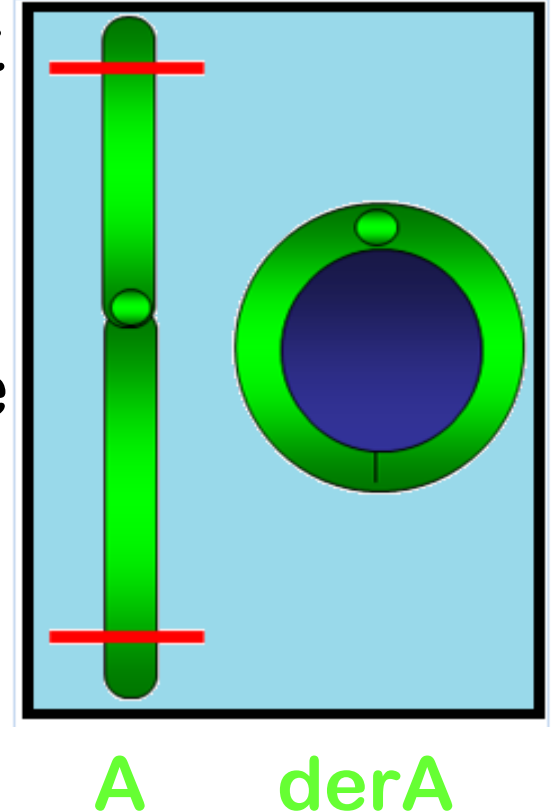
- If a duplication produces one or more extra copies of a gene, the ratio of that gene's protein to the proteins it interacts with is altered
- A deletion can delete the dominant allele of a gene, allowing the remaining recessive allele to control the phenotype - **pseudodominance**
- The phenotypic consequences of a deletion depend on whether the gene(s) in the deletion make their protein(s) in overabundance, or in just enough quantity to fill the body's needs
- If the protein is made in just enough quantity, the deletion will affect the phenotype - **haploinsufficiency**



# Ring Chromosomes

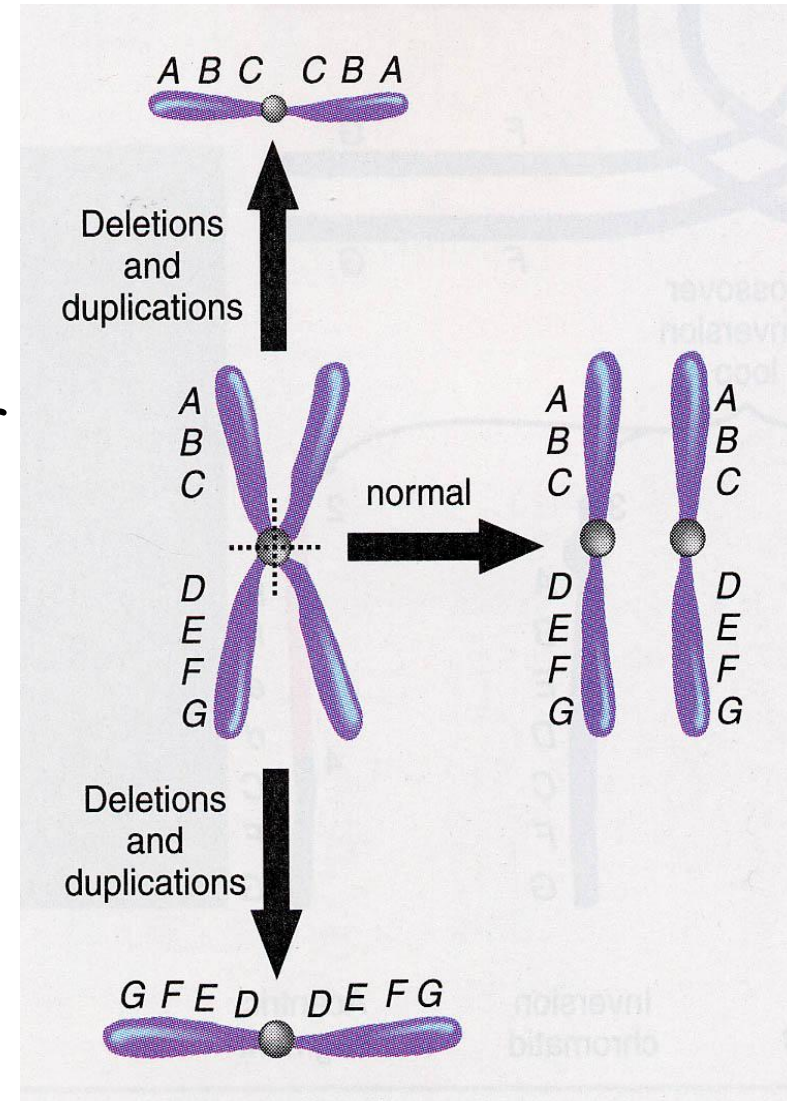
- Two chromosomal breaks, one on each arm, resulting in deletions at both ends
- Usually *de novo*
- Often unstable due to problems in chromatid separation at anaphase
- Results in loss of a ring, double rings, or different sized rings due to breakage

Nomenclature: 46,XY,r(5)(p15q23)



# Isochromosome

- A chromosome that consists of two copies of one chromosome arm with absence of the other arm.
- May result from
  - **Misdivision of the centromere at mitosis or meiosis,**
  - **Through misrepair of chromatid breaks near the centromere, or**
  - **Through crossing over in a small pericentric inversion**
- Could be a translocation between like arms from different chromosomes  
Pallister-Killian 47,XY,+i(12)(p10)





# Causes of chromosomal abnormalities

Polyploidy	Error in cell division in which all chromatids fail to separate at anaphase. Multiple fertilizations.
Aneuploidy	Nondisjunction leading to extra or lost chromosomes
Deletions and duplications	Translocations. Crossover between a pericentric inversion and normal homologue
Translocation	Recombination between nonhomologous chromosomes
Inversion	Breakage and reunion with wrong orientation
Dicentric or acentric fragments	Crossover between paracentric inversion and normal homologue.
Isochromosome	Division of centromeres on wrong plane
Ring chromosome	Loss of telomeres and fusion of ends

# CHROMOSOMAL DELETIONS

Large Deletions

Micro Deletions

# Large Deletions

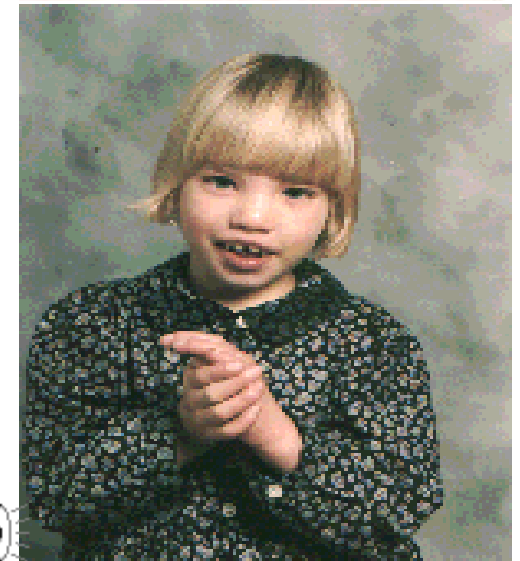
- **Cri du Chat (Cat-cry) Syndrome**
- **Wolf-Hirschhorn Syndrome**
- **DiGeorge Syndrome (DGS)**

# Cri du Chat (Cat-cry) Syndrome

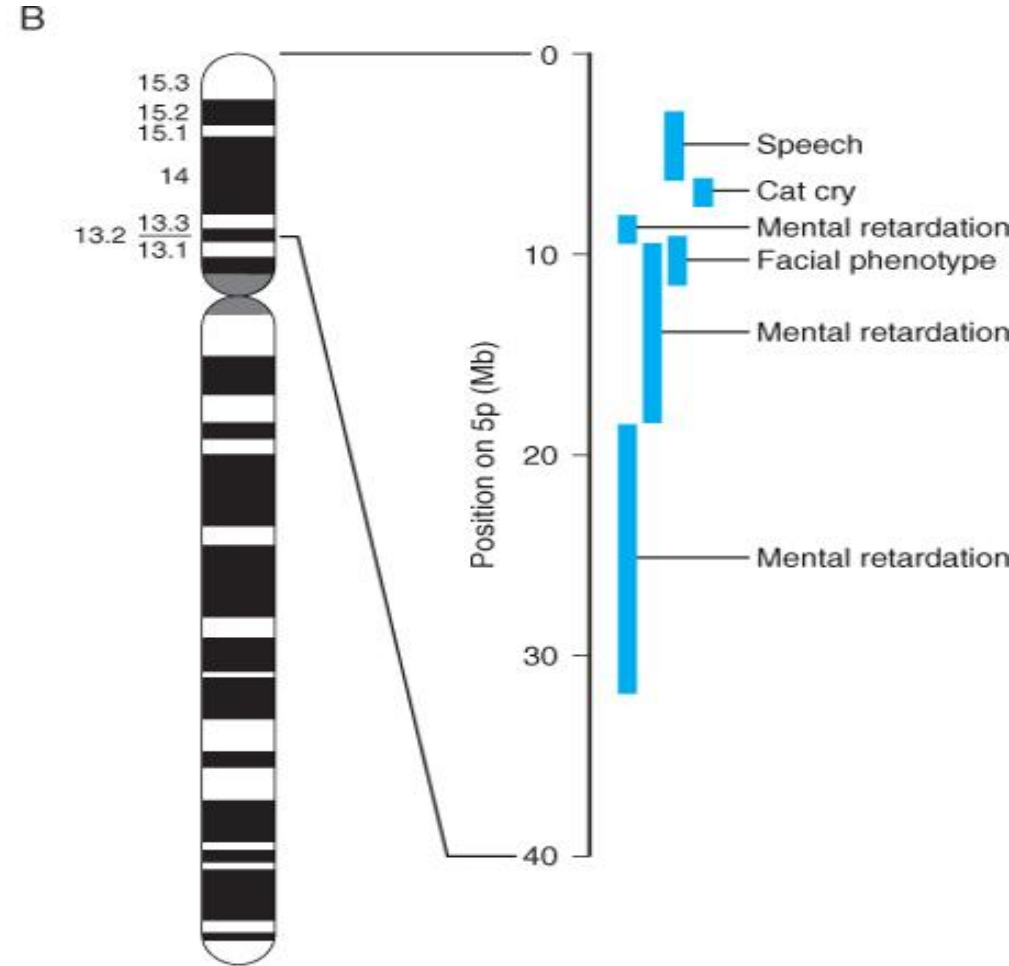
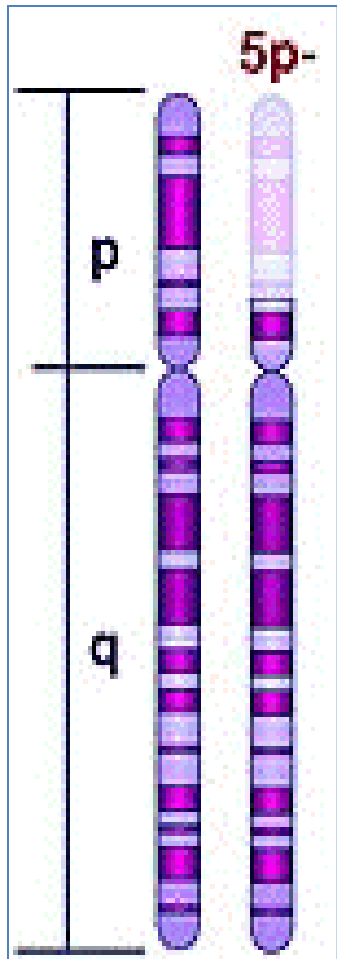
- Karyotype : 46,XX,5p-    46,XY,5p-
- Incidence : 1 in 50,000 births
- Maternal age : Normal

## Clinical features

- Mental retardation
- Microcephaly and round facies
- Mewing cry
- Epicanthic folds
- Hypertelorism,
- Retrognathia



# Cri du Chat (Cat-cry) Syndrome



Phenotype-karyotype map, based on array CGH analysis of del(5p)

# Wolf-Hirschhorn Syndrome (- 4p)

✓ Partial monosomy of the short arm of chromosome 4

✓ *9 putative genes identified in this region*

✓ *Critical region at 4p16.3 – 165 kb segment*

**Incidence: 1/50,000 live births**

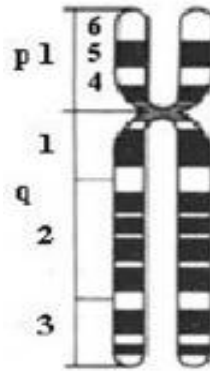
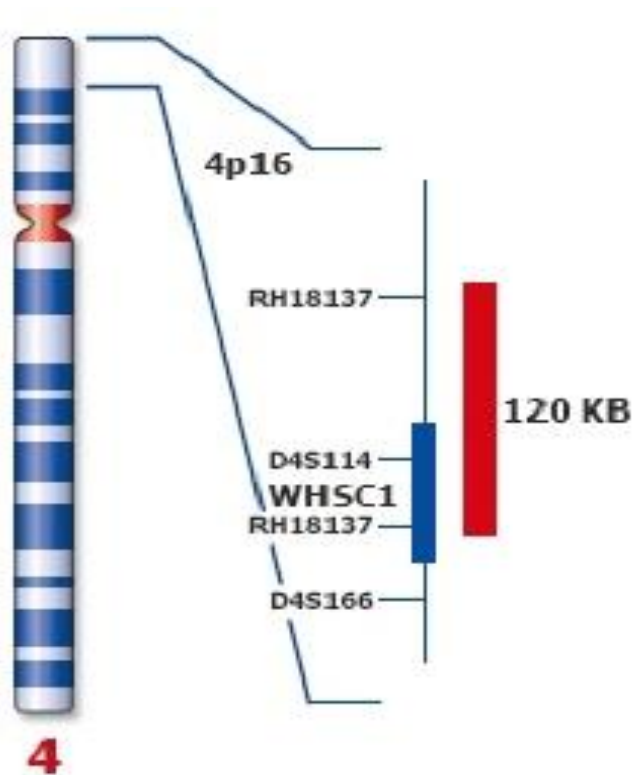
✓ **Clinical features:**

- Distinctive “greek helmet” facies
- Cardiac defects in 50%
- Mental retardation, Microcephaly
- Most are stillborn or die in infancy
- Frequent seizures
- 85-90% de novo deletions
- abnormal facies. Cardiac, renal, and genital abnormalities.



**46,XX,del(4p)**

# Wolf-Hirschhorn Syndrome



*wide-spaced eyes  
and repaired cleft lip*



de novo deletion (*WHSC1*, *WHSC2*) ----- 87%

*WHSC1*=Wolf-Hirschhorn syndrome candidate 1

Translocation of 4p ----- 13%

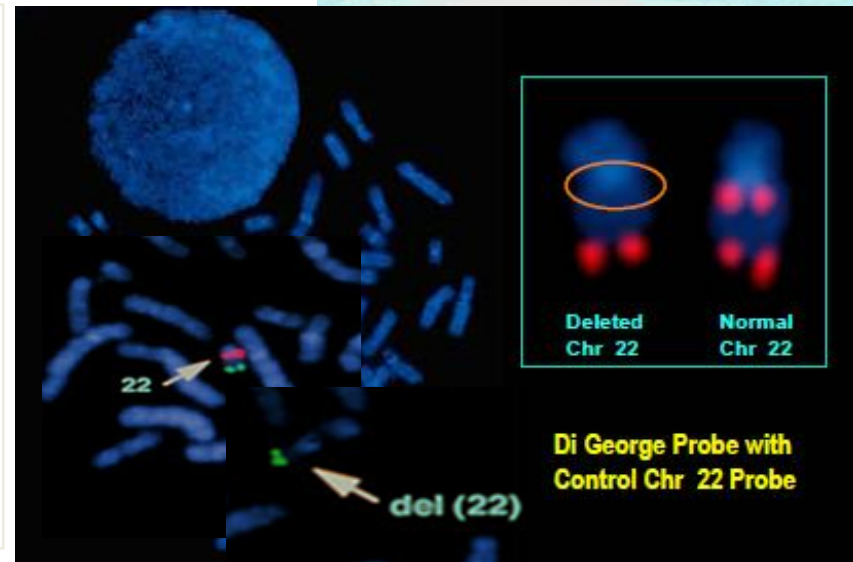
# DiGeorge Syndrome (DGS)

*22q11 Deletion Syndrome*  
*Velocardiofacial Syndrome (VCFS)*

## Disease characteristics:

- Congenital heart disease (74%)
- Palatal abnormalities (69%)
- Characteristic facial features
- Learning difficulties (70 - 90%)

Diagnosis: 22q11 submicroscopic deletion





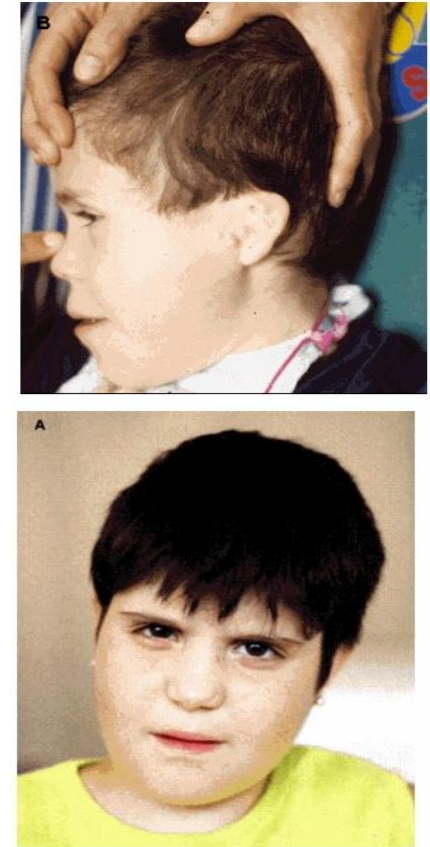
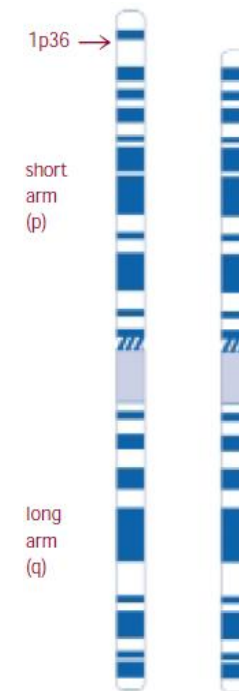
# Microdeletion syndromes

Syndrome	Chromosome
Deletion 1p36	1
Williams	7
Langer-Giedion (Trichorhinophalangeal syndrome type 2)	8
Neurofibromatosis NF-1	17
PWS/AS	15
Rubinstein-Taybi	16
Miller-Dieker	17
Smith-Magenis	17
22q11.2 deletion (DiGeorge/VCFS)	22

# 1p36 deletion syndrome: clinical features

## Characterized by:

- Typical craniofacial features
  - straight eyebrows with deep-set eyes
  - posteriorly rotated, low-set, abnormal ears.
- Developmental delay/mental retardation of variable degree (100%)
- Hypotonia (95%)
- Seizures (44-58%)
- Structural brain abnormalities (88%)
- Congenital heart defects (71%)
- Eye/vision problems (52%)
- Hearing loss (47%)
- Skeletal anomalies (41%)
- Abnormalities of the external genitalia (25%)
- Renal abnormalities (22%)



# Rubinstein-Taybi

## Deletions in band 16p13

### Genetics

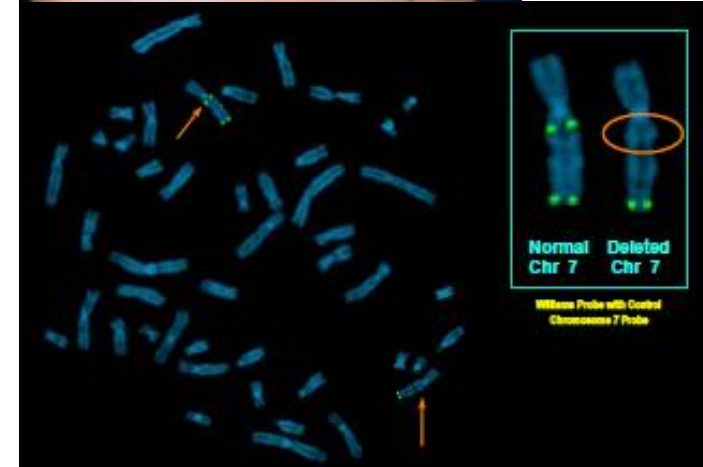
- Association with this disorder mutations in the cyclic adenosine monophosphate (cAMP) response element binding (*CREB*) protein
- Similar transcriptional coactivator located on chromosome 22q13, have also been found in patients with a Rubinstein-Taybi syndrome (RSTS) phenotype.

### Clinical

- • Broad thumbs and/or toes (sometimes angulated)
- • Mental retardation (from mild to severe)
- Beaked nose
- Short stature (delayed bone age)
- Broad nasal bridge
- Malformed ear

# Williams Syndrome

- Supravalvular aortic stenosis (SVAS)
- Mild to moderate MR
- Microdeletion 7q deletion
- of the elastin gene (1-4Mb)
- Hemizygous for 15 genes
- (ELN, Elastin



# Langer-Giedion syndrome

- intellectual deficit
  - redundant skin
  - multiple cartilaginous exostoses - affects mainly the extremities of the long bones
  - characteristic facies
  - cone-shaped phalangeal epiphyses.
  - Growth retardation, microcephaly, hypotonia and hearing problems have also been reported.
  - Prevalence is unknown
- Caused by a microdeletion in chromosome 8q23.3-q24.13 leading to the loss of at least two genes: *TRPS1* and *EXT1*
  - **EXT1**: encodes an endoplasmic reticulum-resident type II transmembrane glycosyltransferase involved in the chain elongation step of heparan sulphate biosynthesis mutations in this gene cause the type I form of multiple exostoses
  - **TRPS1**: transcription factor that represses GATA-regulated genes plays a role in regulating growth of bone and cartilage
  - loss of functional TRPS1 protein contributes to short stature, cone-shaped ends of the long bones (epiphyses), and distinctive facial features in people with Langer-Giedion syndrome

# Miller-Dieker syndrome: clinical features

Autosomal dominant congenital disorder characterised by a developmental defect of the brain, caused by incomplete neuronal migration.

## Clinical features:

- Lissencephaly ('smooth brain')
- Microcephaly (normal at birth)
- Wrinkled skin over the glabella and frontal suture
- Prominent occiput
- Small nose and chin
- Cardiac malformations
- Hypoplastic male external genitalia
- Growth retardation,
- Mental deficiency with seizures and EEG abnormalities
- Life expectancy is grossly reduced, with death most often occurring during early childhood

Caused by a deletion of  
**17p13.3**

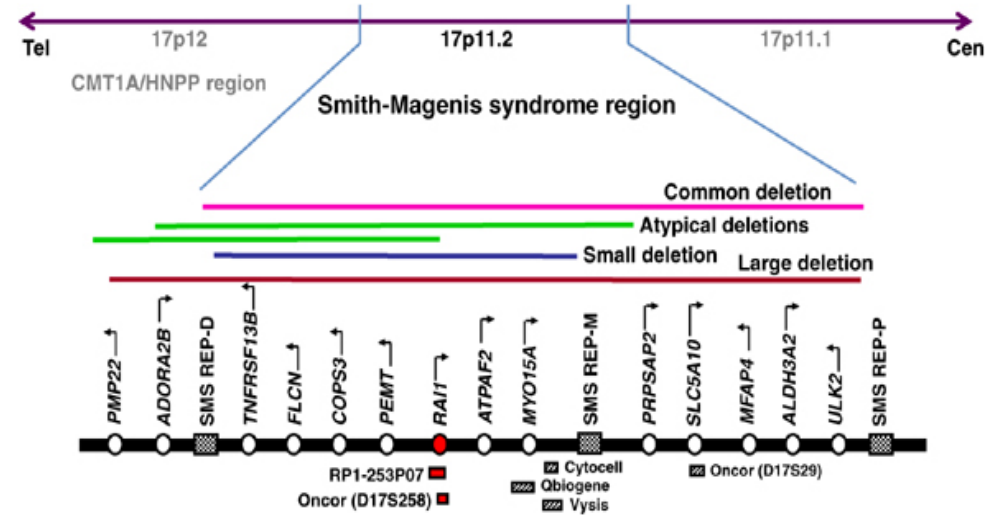


# Smith-Magenis syndrome: clinical features

## Characterized by:

- Distinctive facial features that progress with age
- Developmental delay
- Mental retardation
- Cognitive impairment
- Behavioural abnormalities
- Feeding difficulties
- Failure to thrive
- Hyporeflexia,

Incidence: 1 in 25,000



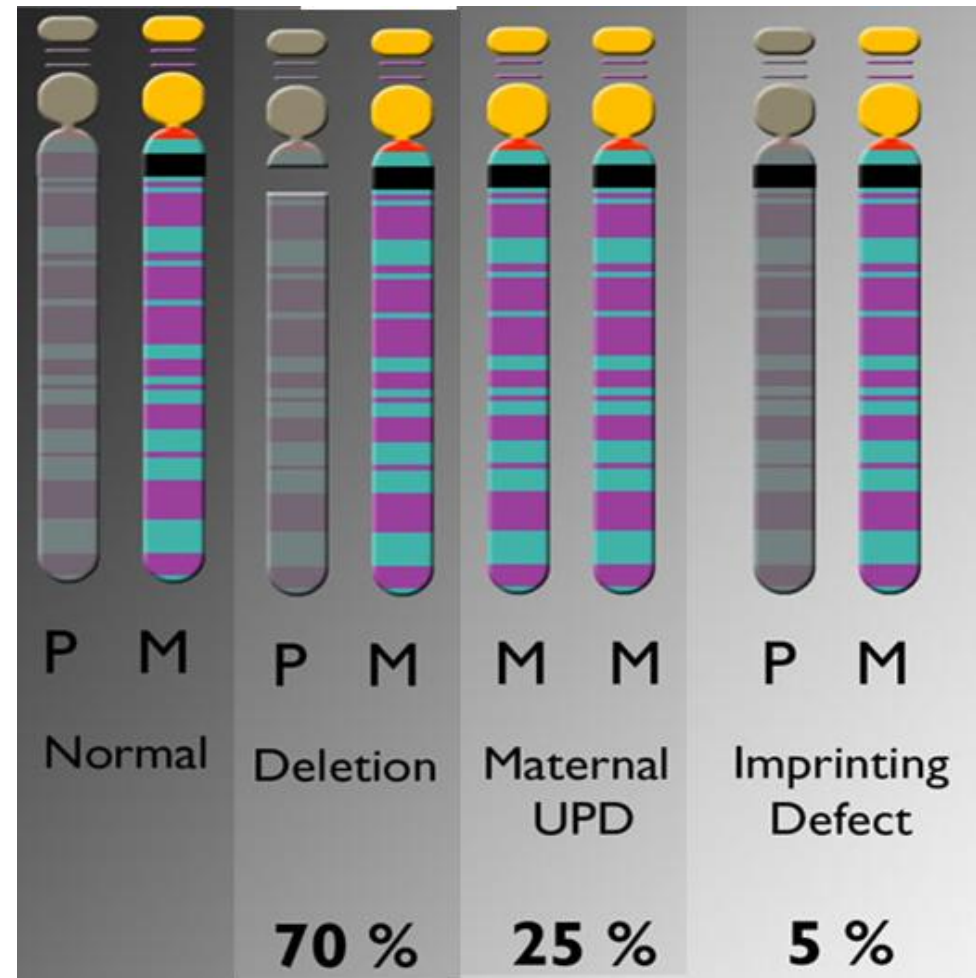
Regulates transcription through chromatin remodelling by interacting with other proteins in chromatin as well as proteins in the basic transcriptional machinery. May be important for embryonic and postnatal development. Possible role in neuronal differentiation



# Prader - Willi Syndrome

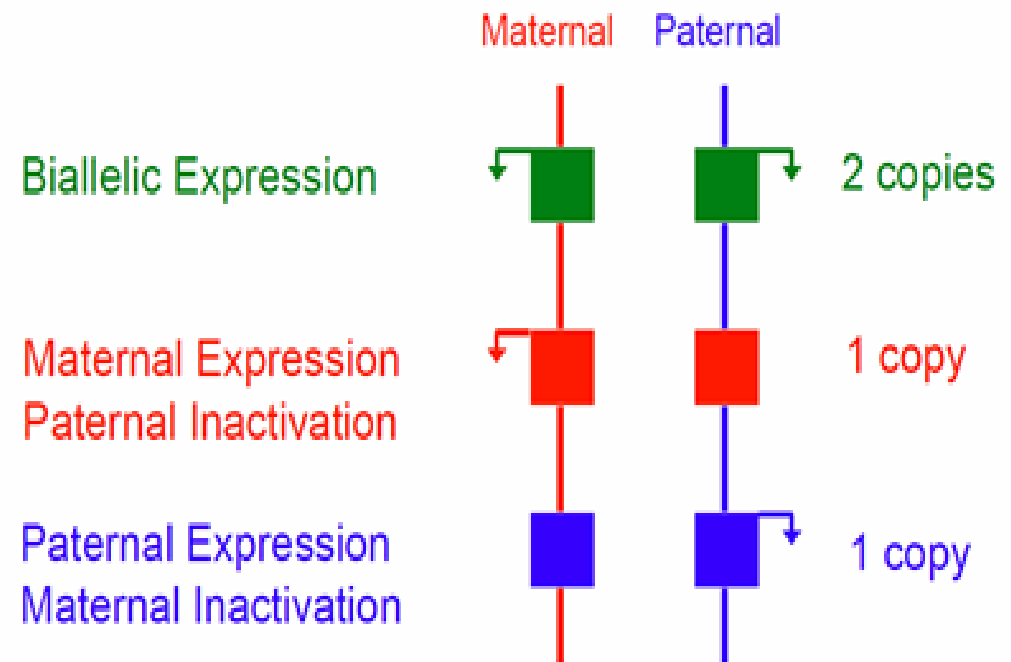
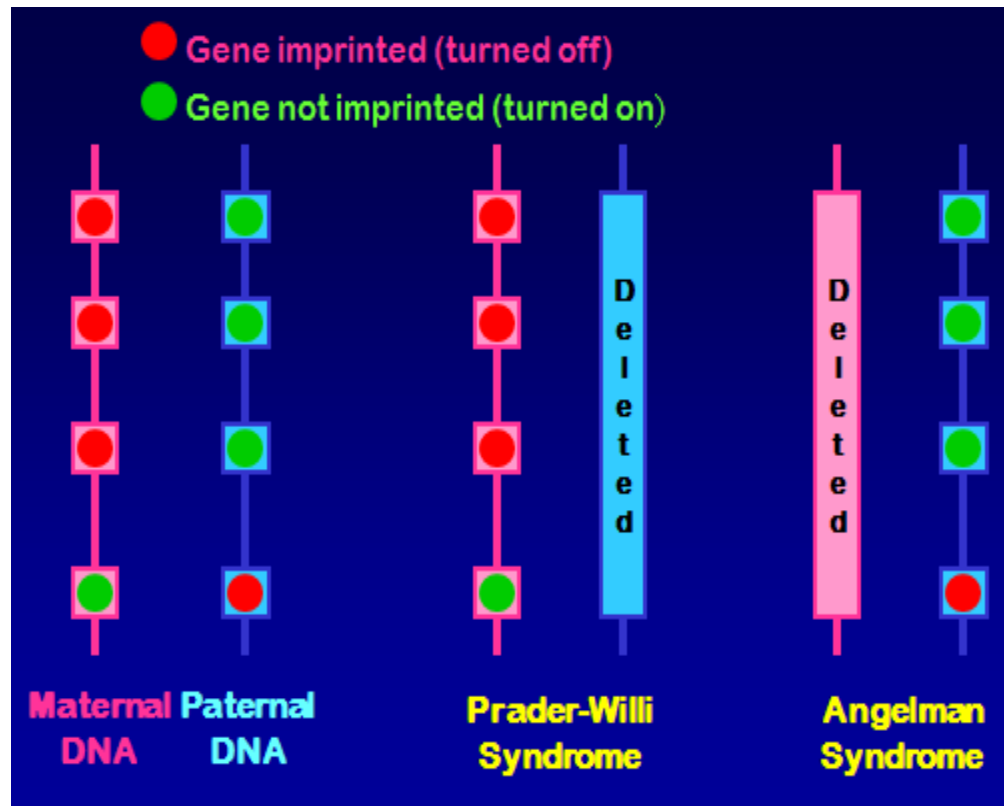
## Phenotype:

- Mild to moderate MR
- Hypotonia, poor feeding in infancy
- Short stature, small hands and feet, small external genitalia
- Hyperphagia (compulsive overeating), obesity
- **Developmental delay, hypogonadism,**
- **Hyperphagia and obesity,**
- **Dysmorphic face,**
- **Hypopigmentation, intellectual disability,**
- **Short status**

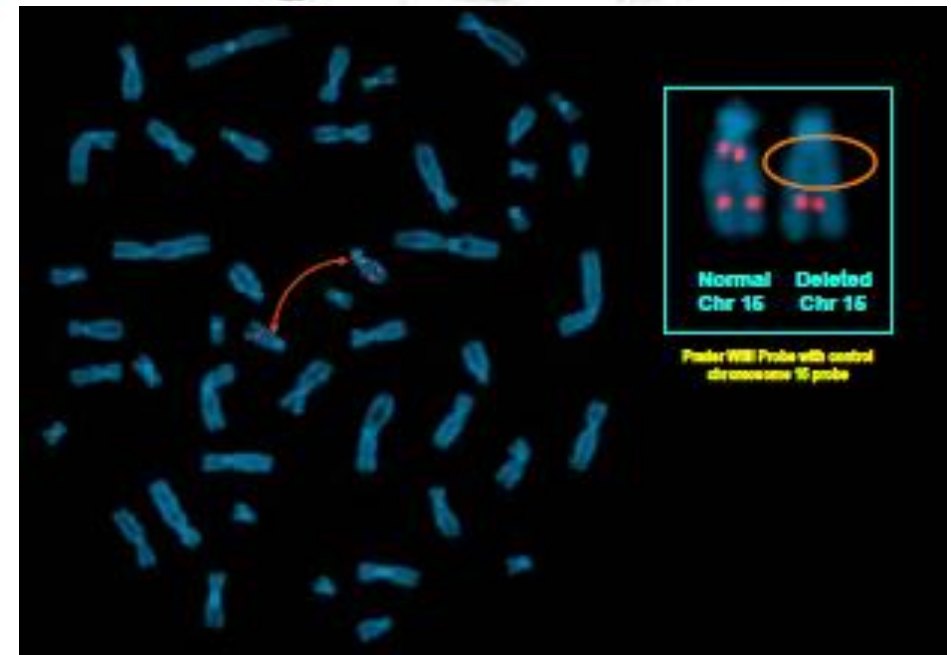
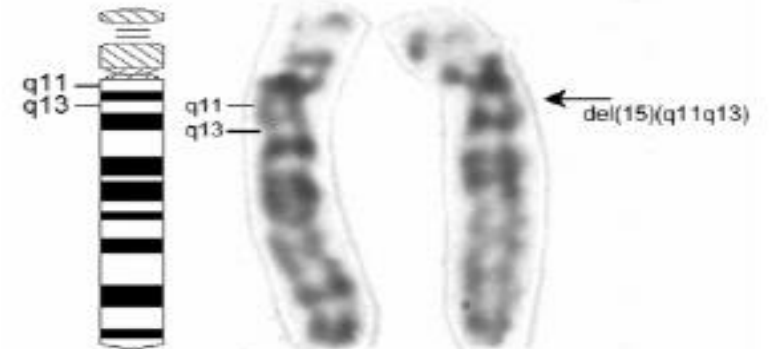
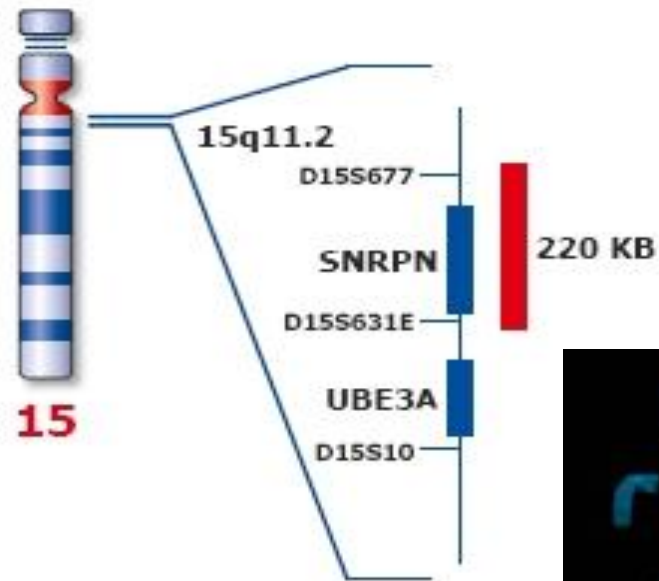




# Prader - Willi Syndrome



# Prader-Willi Syndrome



# Angelman syndrome

15q11-q13 (*SNRPN*, *UBE3A*)

- Severe MR, absence of speech
- Jerky movements
- Inappropriate laughter
- Developmental delay,
- Mental retardation,
- Happy and puppet syndrome,
- Easily provoked laughter
  - 70% have maternally-derived
  - 2% have patUPD15
  - 2-4% E6-AP ubiquitin protein ligase mutation expressed from maternal allele in the CNS
  - 7-9% imprinting center mutation



# NF1 MICRODELETION SYNDROME

- Most common benign tumor of **NF-1**
- It can form at any place along a nerve
- Three subtypes of neurofibroma : cutaneous, subcutaneous, and plexiform
- Neurofibromatosis (about 2/3 have problems limited to skin, AD café-au-lait spots is rare 1/3 have more serious problems)
- Early Onset of Cutaneous
- Facial Dysmorpisms
- Learning Disabilities and speech defects
- Mental Retardation



Café au lait spots

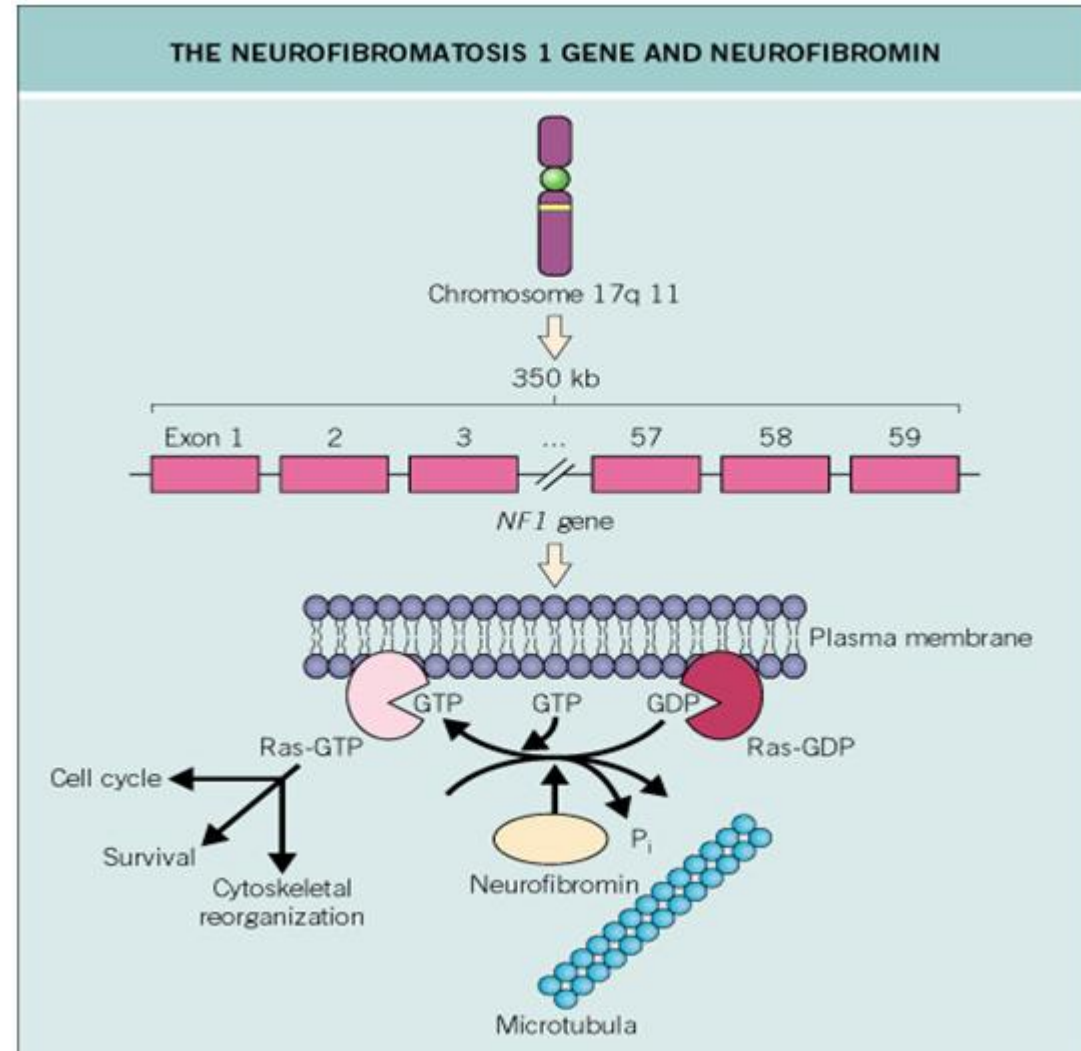


Cutaneous



# ***NF1*: A TUMOUR-SUPPRESSOR GENE**

- ***NF1***: tumor-suppressor gene located on chromosome 17q11.2
- ***NF1***: encodes neurofibromin, a cytoplasmic protein that is expressed in neurons, schwann cells, oligodendrocytes, astrocytes and leukocytes
- Neurofibromin is a negative regulator of the *Ras* oncogene, the inactivation of which leads to cell proliferation and tumor development



# Neurofibromatosis 2

- Autosomal dominant, with 95% penetrance and linkage to **22q11-q13**.
- The gene has been isolated, and encodes a protein named **merlin**

# DUPLICATION SYNDROMES

- Beckwith-Wiedemann
  - Duplication - 11p15 (Paternal)
- Duplication 17p11.2p12
- Cat-Eye Syndrome
  - Duplication of 22q
- Velo-cardio-facial syndrome – features (VCF)  
Duplication – 22q11.21-q11.22
- PWS/AS Duplication – 15q11-q13



# Marker Chromosomes

- Chromosomes of unidentifiable origin (except now chromosomal origin can be identified using SKY, although specific bands cannot yet be identified)
- Occasionally occur as supernumerary chromosomes with or without phenotypic effect
- Parental chromosomes should be analyzed

# OTHER ABNORMALITIES

- **Chromosome breaks**
  - Once chromosome broken by some means
  - Unstable situation as telomeres not at end
  - Usually join up to other piece
- **Dicentric Chromosomes**
  - Chromosomes with two centromeres
- **Double minutes**
  - A minute is an acentric fragment smaller than the width of a chromatid.
  - Double minutes (dmin) are seen in tumor cells as double dots.

# Chromosomal findings in early miscarriages

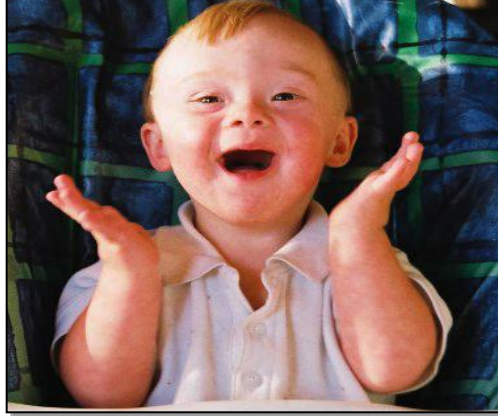
**40% apparently normal**

**60% abnormal:**

- *Trisomy (47 chromosomes – one extra)* **30%**
- *45,X (45 chromosomes – one missing)* **10%**
- *Triploidy (69 chromosomes – three sets)* **10%**
- *Tetraploidy (92 chromosomes – four sets)* **5%**
- *Other chromosome anomalies  
(e.g. structural anomalies)* **5%**

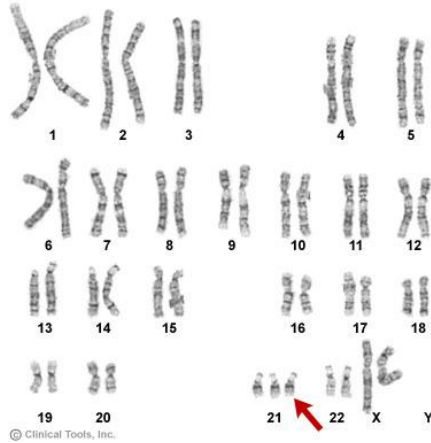
# Indications for postnatal chromosomal analysis

- Suspicion to concrete chromosomal abnormality (concrete syndrome)
- Multiple congenital anomalies or developmental delay
- Mental retardation
- Gonadal dysgenesis
- Infertility
- Miscarriages
- Delivery of dead fetus or death of a newborn child
- Occurrence of certain malignancies



Patient

Karyotype from a female with Down syndrome (47,XX,+21)

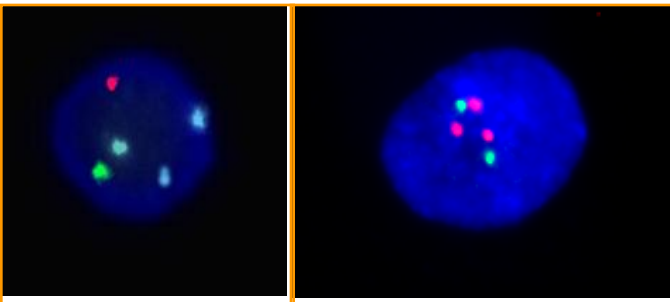
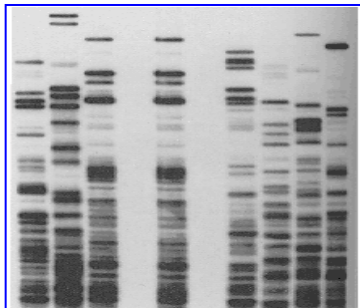


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Basic cytogenetic chromosomal analysis

Molecular cytogenetic analysis (mostly FISH)

Molecular biological analysis



# Methods available for identifying contiguous gene deletions

## **FISH:**

- commercially available probes for most deletion
- may have difficulties detecting small deletions
- may be difficult to characterise the deletion for syndromes associated with variable deletions

## **MLPA:**

- commercially available kits available
- 'microdeletion syndrome' and 'mental retardation' kits available to test for >1 syndrome
- can be confirmed using FISH probes

**CGH:** important in diagnosing cases with unknown genetic aetiology

**qPCR:** Copy number of individual genes

# Diagnostic Potential For Karyotype, FISH, and Chromosomal Micro- array Analysis (CMA) For Selected Disorders

Condition	Locus studied	Karyotype	Disease specific FISH	Telomere FISH	CMA
Aneuploidy	various	~100%	Not detected	Detected by karyotype	~100%
Large deletions, large duplications, translocation of large segments	various	~100%	Not detected	Detected by karyotype	Karyotype better for present
Cryptic Rearrangements of telomeres	various	Not detected	Not detected	~100%	~100% for unbalanced
1p36 deletion	1p36.3	Few	~99%	>95%	~99%
Wolf-Hirschhorn	4p16.3	Most	~99%	>95%	~99%
Cri-du-chat	5p15.2	Most	~99%	>95%	~99%
Williams-Beuren	7q11.2	Almost none	~99%	Not detected	~99%
Prader-Willi	15q11-q13	Unreliable	~70%	Not detected	~70%
Angelman	15q11-q13	Unreliable	~70%	Not detected	~70%
Miller-Dieker lissencephaly	17p13.3	Few	>90%	Some detected	>90%
Smith-Magenis	17p11.2	Some	>95%	Not detected	>95%
Velocardiofacial/DiGeorge 1	22q11.2	Rarely	>95%	Not detected	>95%