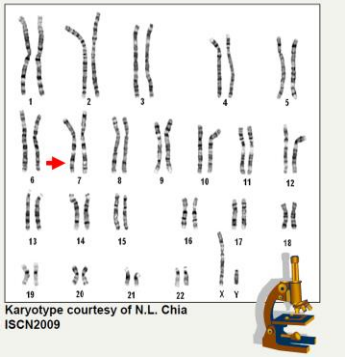


Chromosome Diseases

COL KITTI BURANAWUTI, MD, FACMG

Medical Genomics Division

Phramongkutklao Hospital College of Medicine

DEPARTMENT OF MEDICINE
PHRAMONGKUTKLAO HOSPITAL

EVOLUTION OF G-BANDING TO MICROARRAY

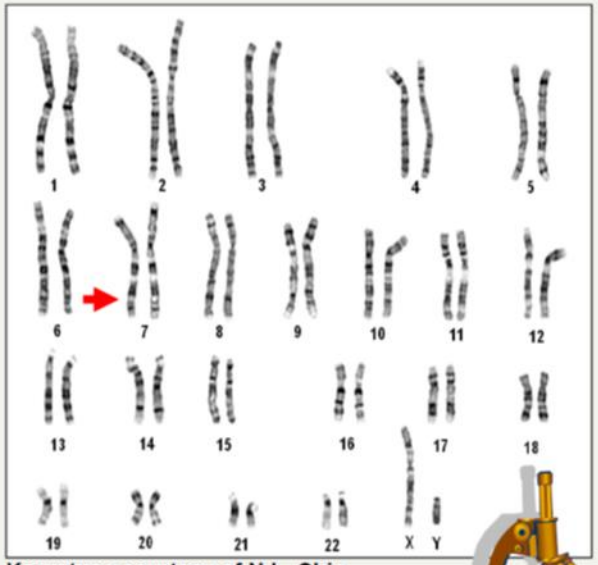
G-band designation (subjective)

7q34 (+/- a band)

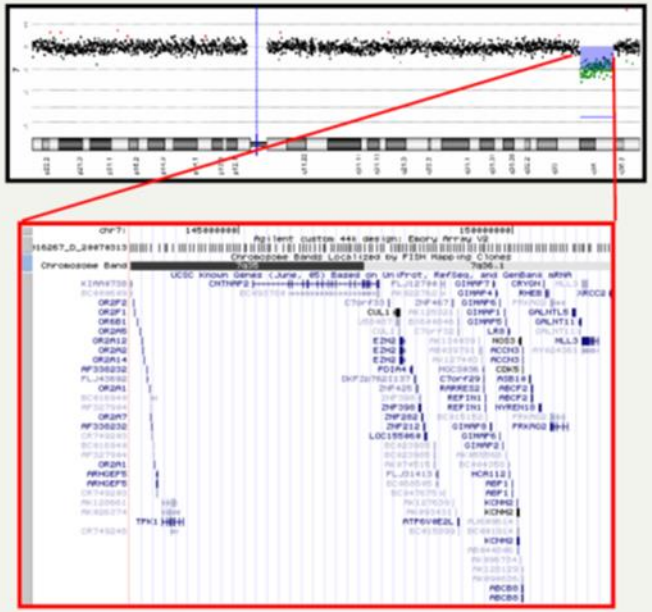
vs.

Array mapping (objective)

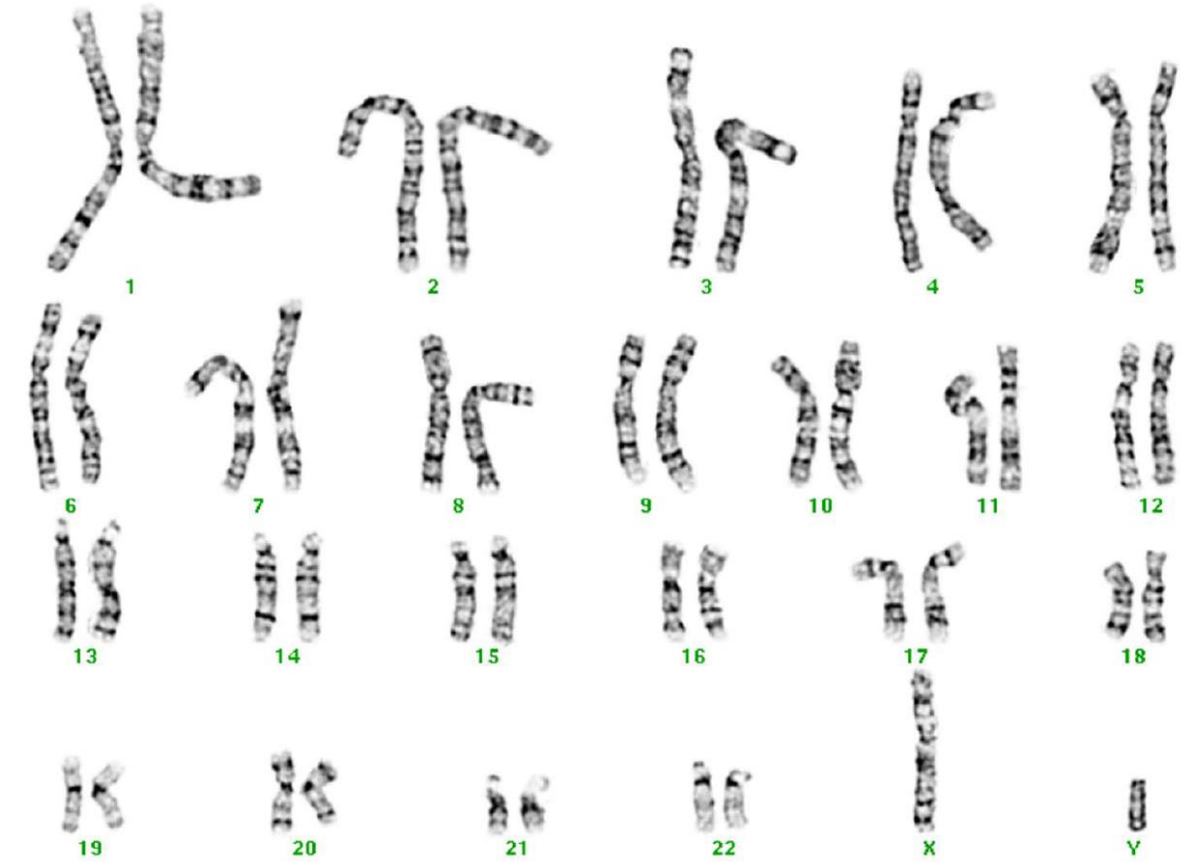
7q35 – q36.1



Karyotype courtesy of N.L. Chia
ISCN2009

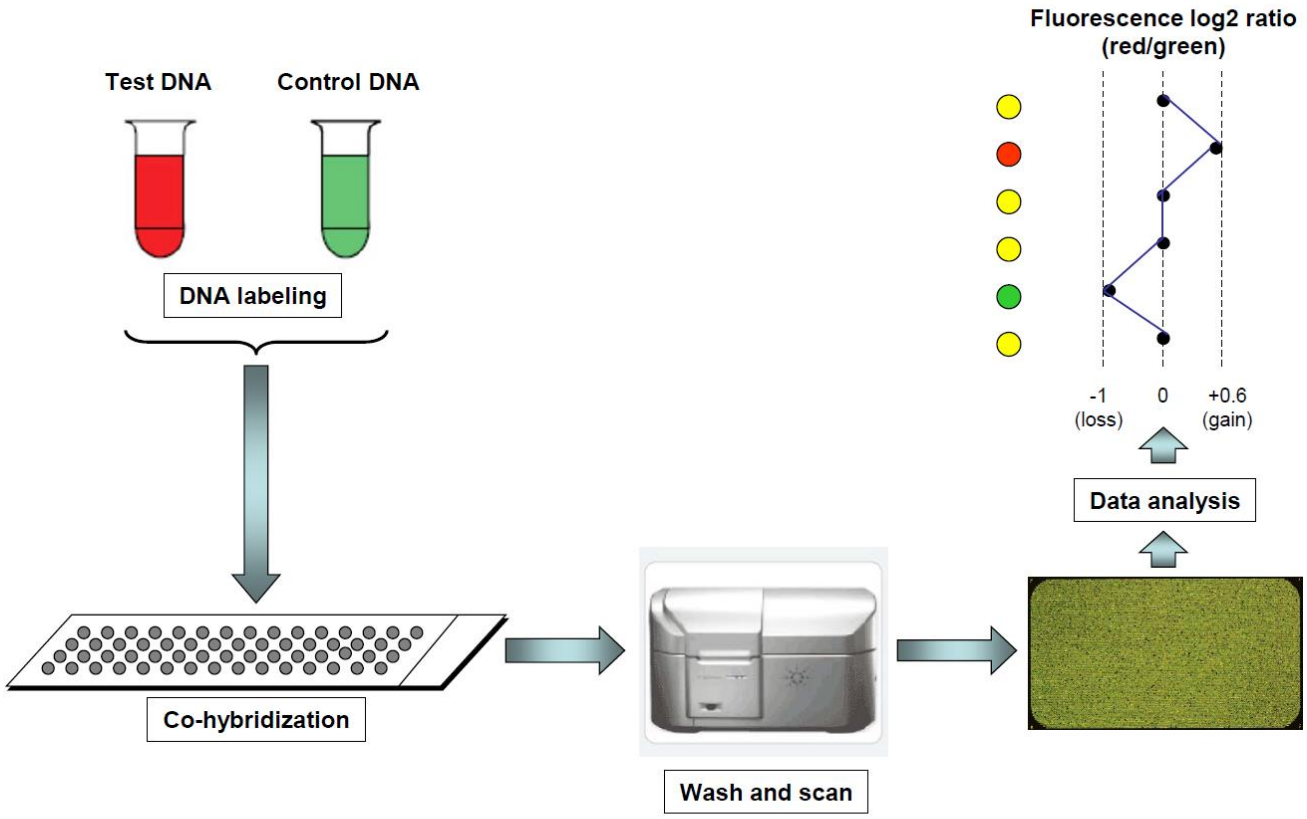


G-BANDED CHROMOSOME ANALYSIS



Normal Male Karyotype 46,XY

ARRAY COMPARATIVE GENOMIC HYBRIDIZATION (ARRAY CGH)



SEX CHROMOSOME ANEUPLOIDY

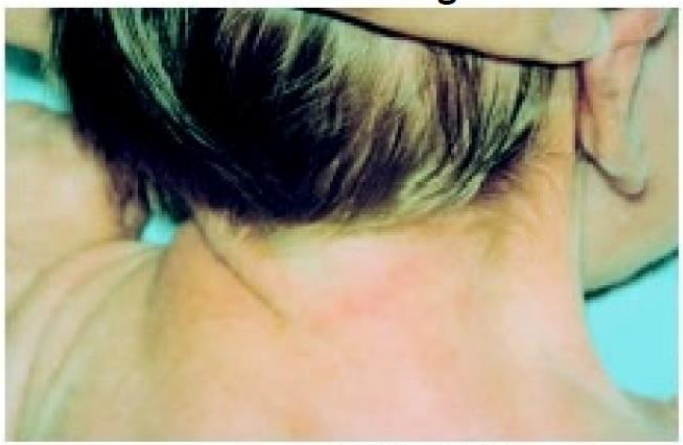
Karyotype	Incidence	Name
45,X	(1/3000)	Turner syndrome
47,XXX	(1/1000)	Trisomy X
47,XXY	(1/1000)	Klinefelter syndrome
47,XYY	(1/1500)	47,XYY syndrome

TURNER SYNDROME (45,X)

Responsible genes: X genes that escape inactivation, *SHOX*
Proteins: *SHOX:* Short stature homeobox protein
Cytogenetic locus: *SHOX:* Xpter-p22.32
Inheritance: sporadic
Clinical Features and Diagnostic Criteria: congenital lymphedema, growth failure, normal intelligence (10% sig delays), coarctation of the aorta, bicuspid aortic valve, HLHS, hyperlipidemia, gonadal dysgenesis (10% 45,X go into puberty), hypothyroidism, diabetes, strabismus, recurrent OM, SNHL, Crohns, renal malformation, osteoporosis.
Clinical Tests: echo, renal US, TFTs, GH testing, FISH SRY
Molecular Tests: Karyotype
Disease Mechanism: *SHOX:* thought to act as a transcription regulator with many down-stream targets that modify growth and stature. SHOX protein has been id'ed in the growth plate from 12 weeks GA to late childhood.
Treatment/Prognosis: GH, HRT, gonadectomy if Y chromosome mosaicism (risk for gonadoblastoma). Need lifelong cardiac follow-up, at risk for aortic dilation and dissection with bicuspid aortic valve.

TURNER SYNDROME (45,X)

Low posterior hairline and neck webbing



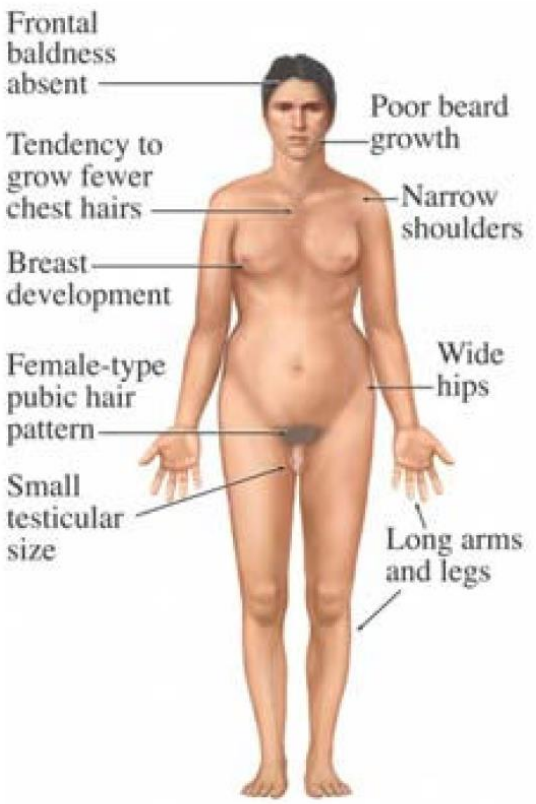
www.healthofchildren.com

Hypertelorism and low set ears

KLINEFELTER SYNDROME (47,XXY)

Clinical Features and Diagnostic Criteria: Tall stature, slightly delayed motor and language skills, inc learning probs, testosterone plateaus age 14, small fibrosed testes, azoospermia and infertility, gynecomastia, inc cholesterol, slightly inc risk of autoimmune disorders and mediastinal germ cell tumors (1% risk). Increased risk of male breast cancer.
Clinical Tests:
Molecular Tests: karyotype, at least one extra chromosome to a 46,XY Karyotype
Disease Mechanism: 1st or 2nd meiotic division nondisjunction of either parent. Maternal>paternal origin. +AMA effect
Treatment/Prognosis: Testosterone in mid-late adolescence for bone density, secondary sex characteristic development, muscle mass, cholestero increase libido, improved energy. Can do testicular biopsy and use any retrieved sperm for ICSI (inc risk sex chrom abnormality so follow with PGD

KLINEFELTER SYNDROME (47,XXY)



health.yahoo.com/media/healthwise/nr551770

TRISOMY X OR TRIPLE X SYNDROME (47,XXX)

- The most common sex chromosome abnormality in females.
- Most individuals are diagnosed incidentally on prenatal genetic screening.
- Do not appear to be at increased risk of having chromosomally abnormal offspring .
- 62 percent (155 pts) were physically normal.
- Most individuals with 47,XXX are never diagnosed.
- Have a tendency to be tall, with many reaching the 80th percentile in height by adolescence, but with an average head circumference between the 25th to 35th percentile.
- Puberty and fertility are generally the normal range, but premature ovarian failure can occur.
- Prospective study shows that their verbal and performance IQ scores were 15 to 20 points lower than those of their siblings. Thus, monitoring for developmental delays and psychologic problems is recommended.

DOUBLE Y SYNDROME (47,XYY)

- Have tall stature and may have mild delay in motor and language development.
- A significant proportion of XYY males require special educational intervention but are generally educated in mainstream school settings.
- Normal pubertal development, and most are fertile. Due to the subtlety of the phenotype and lack of associated health problems, many individuals with 47,XYY remain undiagnosed throughout their lifespan.
- Increased rate of antisocial behavior in XYY males was related to a lack of judgment and lower socioeconomic status due to a lower mean intelligence quotient (IQ) score (by 10 points), which led them into difficulties with the law and involvement in minor crimes.
- Higher rates of attention deficit hyperactivity disorder and autism spectrum disorders are reported in 47,XYY. A neurodevelopmental evaluation is recommended in patients diagnosed with 47,XYY, given the high prevalence of learning disabilities and behavioral problems.

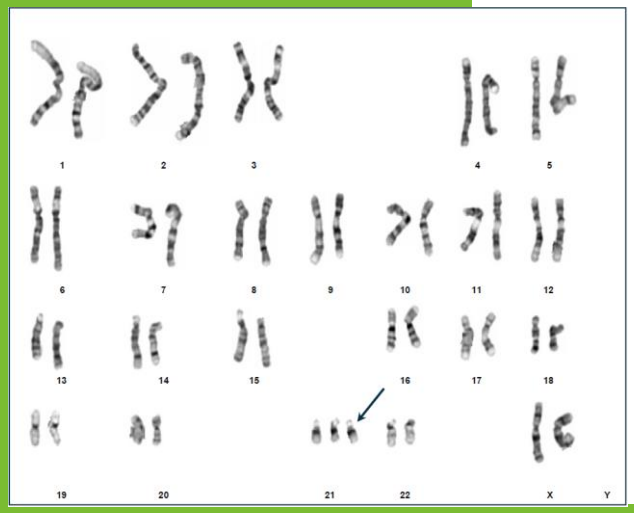
COMMON CHROMOSOME ABNORMALITIES

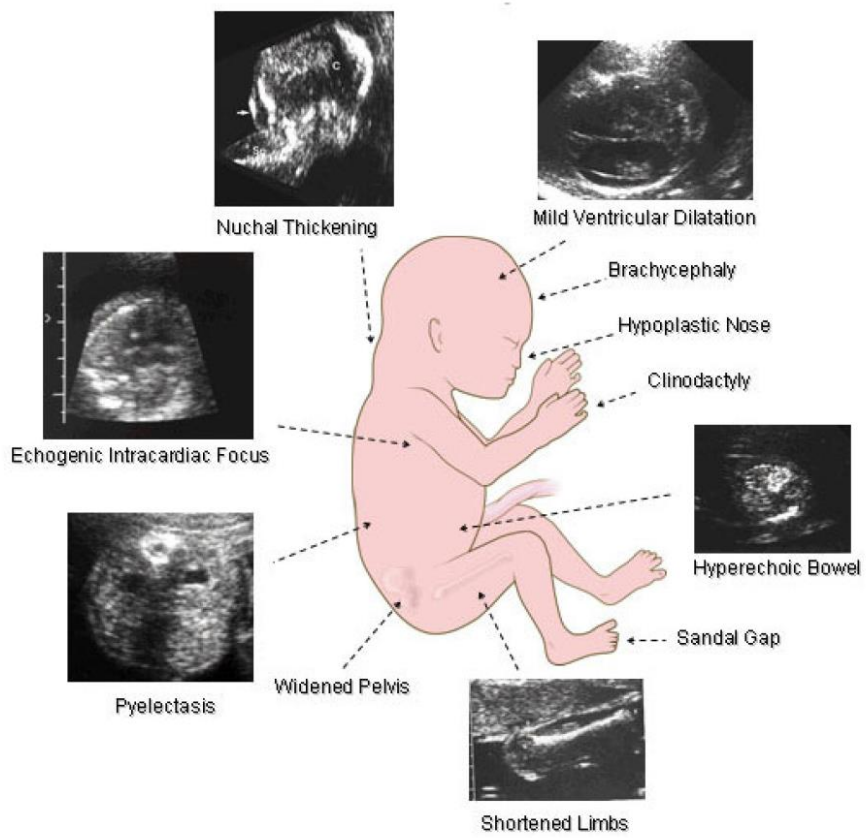
Abnormality	Birth Frequency
Trisomy 21	1 in 800
Trisomy 18	1 in 6000
Trisomy 13	1 in 10000
47,XXY (Klinefelter synd.)	1 in 1000 males
47,XYY	1 in 1000 males
47,XXX	1 in 1000 females
45,X (Turner synd.)	1 in 5000 females

TRISOMY 21 (DOWN SYNDROME)

Cytogenetic locus (loci): (21.22.1-22.2 has been called the DS critical region though there have been cases of duplication outside of this region who manifest DS
Inheritance: 95% de novo, 5% due to Robertsonian translocation or isochromosome 21
Clinical Features and Diagnostic Criteria: mild-mod ID, hypotonia, growth delay, strabismus, adult cataracts, myopia, conductive HL, macroglossia, hypodontia, joint hyperflexibility, hypogenitalism, congenital heart defect, duodenal atresia, hirschprung, thyroid disease, early onset Alzheimers, transient myeloproliferation, ALL
Clinical Tests: prenatal US abnormalities detected in 50%, maternal serum screen: high free beta HCG, low PAPP-A,
Molecular Tests: maternal fetal free DNA testing, karyotype is diagnostic
Disease Mechanism: 90% due to maternal meiosis nondisjunction (¾ MI error, ¼ MII error)
Treatment/Prognosis: Supportive care, overall life expectancy is reduced

TRISOMY 21 (DOWN SYNDROME)

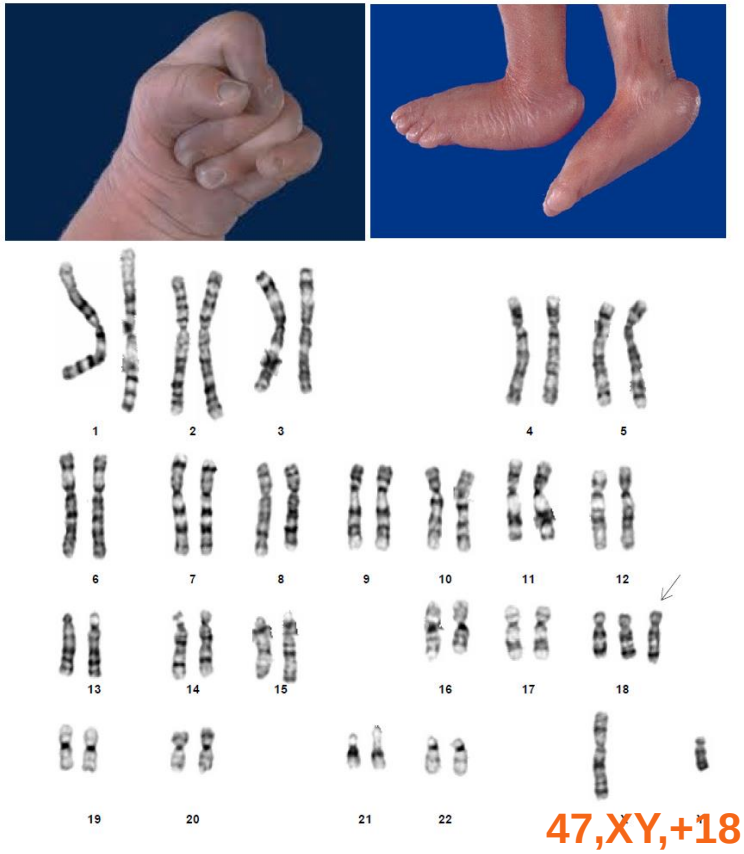




47,XX,+21

www.fetalcenter.com/images/Trisomy_21

TRISOMY 18 (EDWARDS SYNDROME)



Common Features

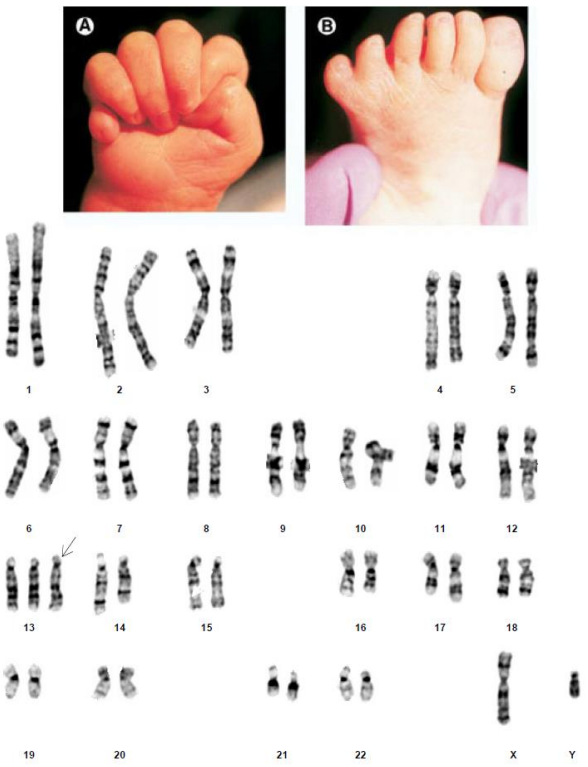
- Severe ID
- IUGR, microcephaly
- Weak, feeble activity and cry (hypoplastic muscles)
- Clenched hand position w/ 2 & 5 over 3 & 4
- Clubfoot or rocker-bottom feet
- Small, low set ears
- Omphalocele
- Early lethality
  - most die in first month;
    5-10 % survive > 1 yr

Images from:
http://library.med.utah.edu/WebPath/jpeg3/PERI228.jpg
medgen.genetics.utah.edu

TRISOMY 18 (EDWARD SYNDROME)

Inheritance: Less than 1% due to a translocation
Clinical Features and Diagnostic Criteria: clenched hand, fingers 2/5 overlap 3/4, IUGR, rocker bottom feet, micrognathia, prominent occiput, microphthalmia, VSD, ASD, PDA, generalized muscle spasm, renal anomalies, ID. Mosaic Tri 18 has variable but usually somewhat milder expression.
Clinical Tests: Echo, abdominal US. Maternal serum screen: low AFP, hCG, and UE3.
Molecular Tests: karytype is diagnostic
Disease Mechanism: Maternal nondysjunction (90%), mosaicism (10%)
Treatment/Prognosis: 50% die in first week, 90% die by one year

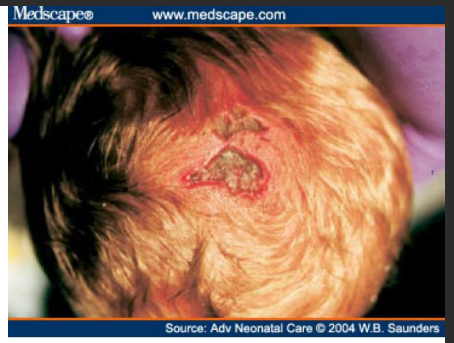
TRISOMY 13 (PATAU SYNDROME)



47,XY,+13

Common Features

- Severe ID
- IUGR, microcephaly,
- Midline anomalies
  - cleft lip/palate, holoprosencephaly, scalp defect, CHD, omphalocele
- Polydactyly, postaxial
- Early lethality
  - most die in first month; 5% survive > 6 months



Cutis Aplasia

www.prenatalpartnersforlife.org

Image from: Medscaape.com

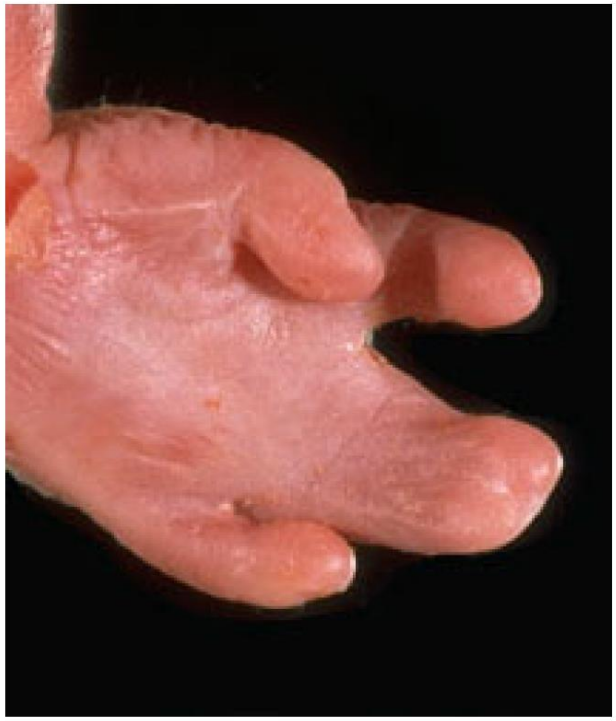
TRISOMY 13 (PATAU SYNDROME)

Inheritance: 20% due to a translocation
Clinical Features and Diagnostic Criteria: The least common of the live born trisomy disorders. Holoprosencephaly, polydactyly, seizures, HL, microcephaly, midline CL/P, omphalocele, cardiac and renal anomalies, ID. Mosaic Tri 13: very broad phenotype from typical features of full trisomy to more mild ID and physical features and longer survival.
Clinical Tests: Brain MRI, EEG, audiogram, echo, renal US
Molecular Tests: Karyotype is diagnostic
Disease Mechanism: 75% are due to maternal nondysjunction, 20% to a translocation, and 5% to mosaicism. Defect in fusion of the midline prechordial mesoderm in the first three weeks of gestation cause the major midline dysmorphic features.
Treatment/Prognosis: 44% die in the first month, >70% die within one year. Severe ID exists in all survivors.

TRIPLOIDY

Cytogenetic abnormality: 69,XXY>69,XXX (69,XYY very rare)
Inheritance: Sporadic without inc risk of recurrence
Clinical Features and Diagnostic Criteria: >99% lost in first trimester, accounts for 6-10% of all SAb's and 16-20% of all chromosomally abnormal SAb's. Dysplastic calvaria with large posterior fontanelle, ¾ finger syndactyly, ASD, VSD, hydrocephalus, holoprosencephaly. Parent of origin effect: If Maternal: small placenta, severe asymmetric IUGR with a large head If Paternal: hydropic large placenta, well grown to mod symmetric IUGR, nl or microcephalic head
Clinical Tests: Prenatal US, maternal serum hCG low
Molecular Tests: Karyotype
Disease Mechanism: Gynogenic triploidy (digyny): NDJ producing diploid oocyte, fertilization of ovulated primary oocyte, or polar body retention. Androgenic triploidy (Diandry) NDJ producing a diplod sperm or dispermy (most common)
Treatment/Prognosis: Very poor prognosis, may be better if triploid mosaic

TRIPLOIDY



library.med.utah.edu

Classic 3/4 finger syndactyly of triploidy

MECHANISM OF TRIPLOIDY

Dispermy (66%) - most common cause

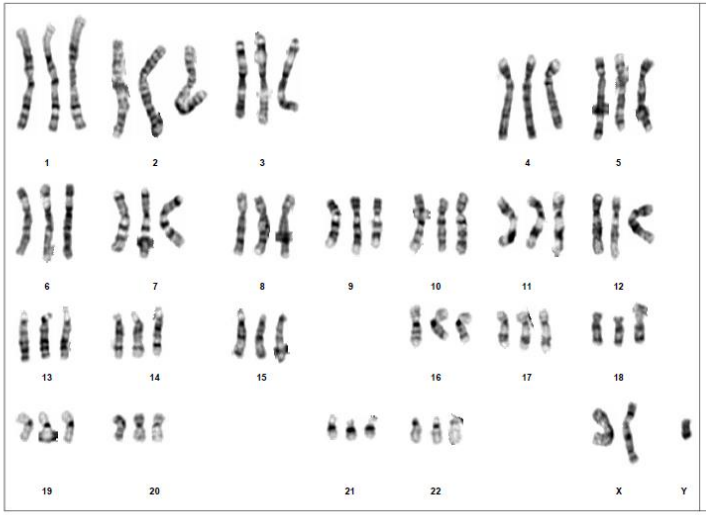
Meiotic failure (34%)

- in spermatogenesis (24%)
- in oogenesis (10%)

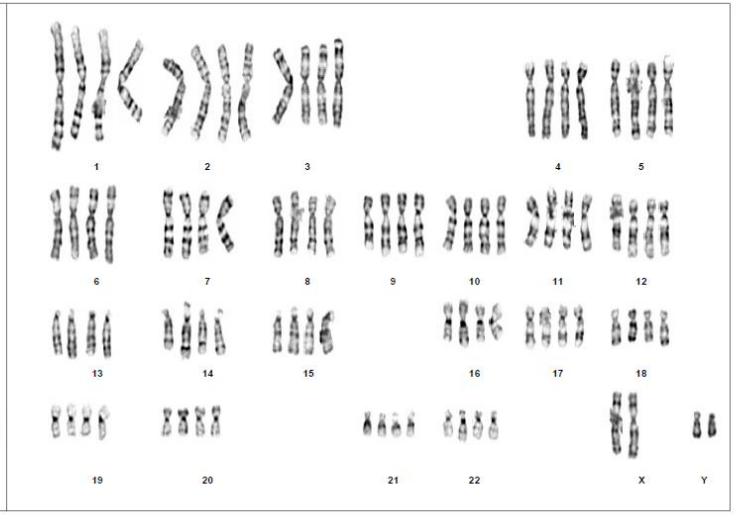
Paternal	Maternal
large placenta	small placenta
small fetus	large fetus
partial hydatidiform mole	early loss
IUGR	
oligohydramnios	
congenital heart defect	
syndactyly	

RISK OF RECURRENT OF TRIPLOIDY

Triploid Karyotype
69,XXY



Tetraploid Karyotype
92,XXYY



No increased risk for recurrence

MICRODELETION / MICRODUPLICATION SYNDROME

- Complex phenotypes due to dosage imbalance of multiple, unrelated genes which happen to be contiguous on chromosome. In some cases, clinical syndrome defined before genetic basis known.

- AKA
  - Contiguous gene syndromes
  - Segmental aneusomy syndromes
  - Genomic Disorders (subset mediated by segmental duplications – seg dup)

- Mechanisms include deletion, duplication, and

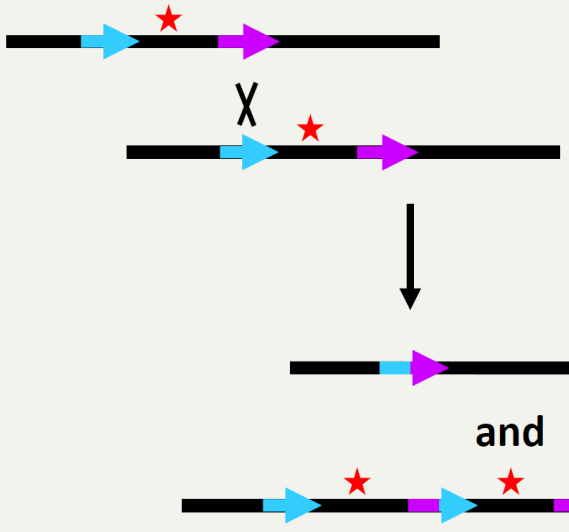
  UPD = any deviation from normal, biparental inheritance.

MICRODELETION/MICRODUPLICATION SYNDROME

		Mechanism
Wolf-Hirschhorn	4p16.3	non-rec
Cri-du-Chat	5p15	non-rec
Williams	7q11.23	seg dup
Langer-Giedion	8q24	non-rec
Wilms tumor-aniridia (WAGR)	11p13	non-rec
Beckwith-Wiedemann	11p15	non-rec
Prader-Willi/Angelman	15q11-13	seg dup
Smith-Magenis	17p11.2	seg dup
Miller-Dieker	17p13.3	non-rec
DiGeorge/VCFS	22q11.2	seg dup

MECHANISMS OF STRUCTURAL REARRANGEMENTS

Segmental duplications (Low Copy Repeats; Direct Repeats)
100-400 kb, >99% sequence identity



Unequal Recombination
(non-allelic homologous
recombination or NAHR)

Deletion

and

Duplication

Primary mechanism for common, recurring microdeletion/
microduplication syndromes in humans (Genomic Disorders)

GENOMIC DISORDERS IN HUMANS

Disorder	*Location*	*Type*	*Size*	*Duplicon*
Williams; autism	7q11.2	del/dup	2 Mb	100 kb
PWS/AS; aut mat	15q11-q13	del/dup	4 Mb	450 kb
CMT; HNPP	17p12	del/dup	1.5 Mb	24 kb
SMS; PLS	17p11	del/dup	5 Mb	200 kb
NF 1	17q11.2	del	1.5 Mb	100 kb
DGS/VCF	22q11.2	del/dup	3 Mb	200 kb
Male infertility	Yq	del	3.5 Mb	200 kb
Sotos	5q35	del	2.2 Mb	140 kb

see review by Mefford and Eichler (2009) Curr Opin Genet Dev

DIGEORGE SYNDROME OR VCFS

- ~1/4,000 – most common mdel syndrome
- Thymus hypo/aplasia

  → cellular immunodeficiency
- Parathyroid hypo/aplasia → hypocalcemia
- DD, ID
- Cardiovascular:
  - Conotruncal heart defects, aortic arch defects
- Dysmorphic features:
  - Micrognathia, ear anomalies, cleft palate, short palpebral fissures, short upper lip

DIGEORGE SYNDROME OR VCFS

del(22)(q11.2)

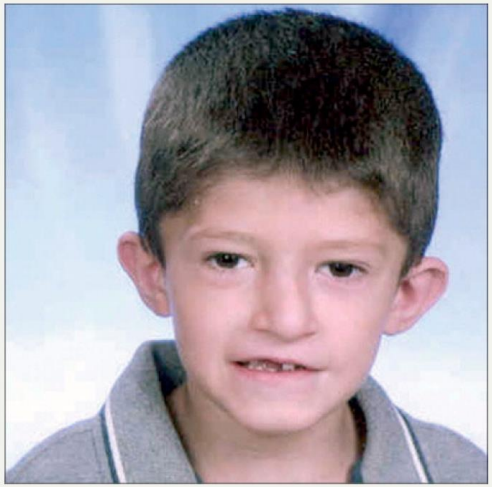


Image from www.thelancet.com

Image from www.pediastaff.com

22q Foundation - www.22q.org

MILLER-DIEKER SYNDROME (MDS)

- Lissencephaly, type I - complete agyria (absent gyri) or w/ limited pachygyria (broad gyri)
  - severe ID, spasticity, seizures
- Microcephaly, bitemporal narrowing, vertical furrows on forehead
- prominent forehead, short nose, upturned nares, protuberant upper lip, thin vermillion border, small jaw
- Isolated lissencephaly sequence (ILS) - same or milder brain malformation with normal or subtle facial features

MILLER-DIEKER SYNDROME (MDS)

17p13.3: Normal vs. Lissencephalic Brain

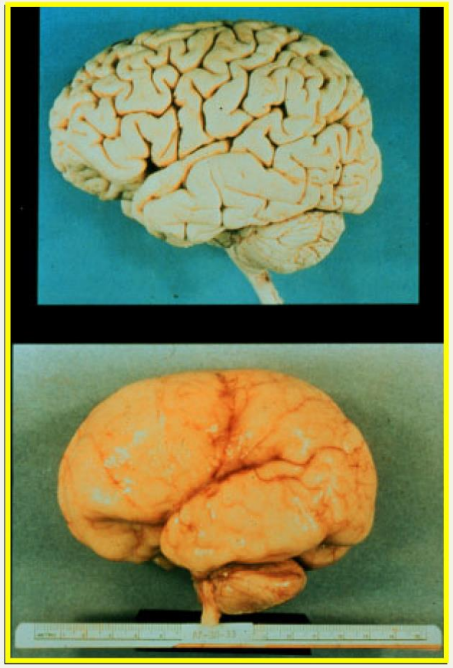
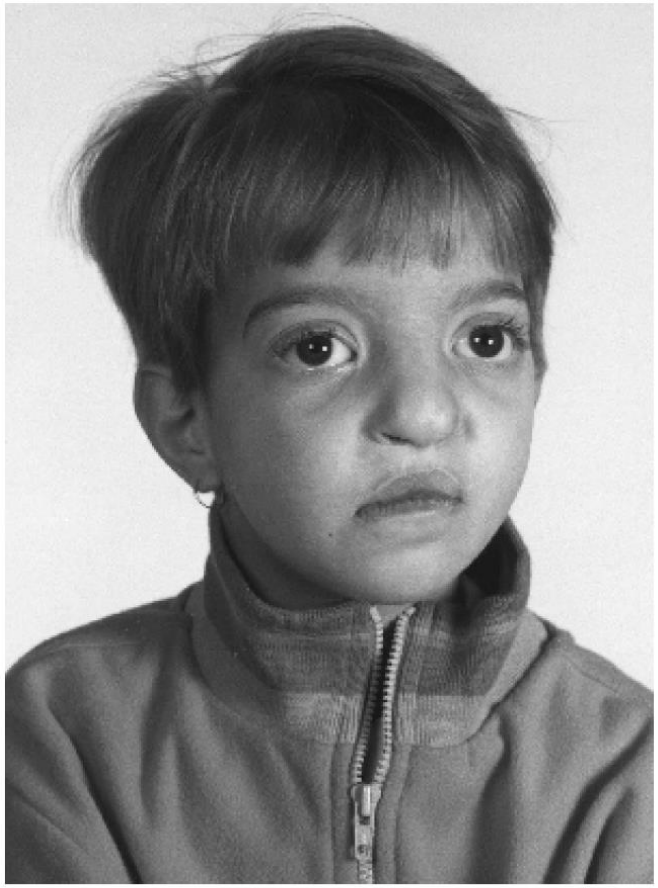


Image from Bill Dobyns

WOLF-HIRSCHORN SYNDROME (4P DELETION SYNDROME)

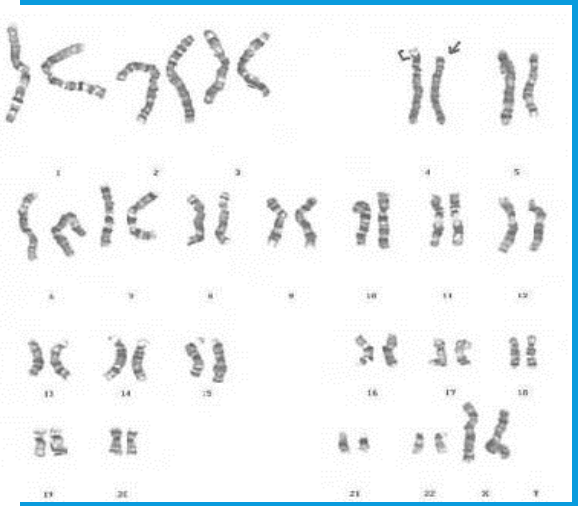
Responsible genes: 4p deletion, critical region includes two genes, *WHSC1* and *WHSC2* of unknown significance
Protein: unknown
Cytogenetic locus: 4p; critical region: 165-kb region between markers D4S166 and D4S3327
Inheritance: 87% de novo, 13% due to unbalanced translocation from a balanced parent
Clinical Features and Diagnostic Criteria: "greek warrior helmet appearance", microcephaly, pre and postnatal growth deficiency, ID of variable degree, seizures, facial asymmetry, ptosis, IgA deficiency, structural brain anomalies, CL/P, CHD (ASD>PVS>VSD>PDA>AI>TOF), renal US
Clinical Tests: Distinctive EEG, Brain MRI, echo, plasma IgA level
Molecular Tests: HR karyotype for 4p16.3 deletion (60-70%), FISH/array CGH for critical region deletion (>95%)
Disease Mechanism: The function of *WHSC1, WHSC2,* and *LETM1* in normal development and in WHS patients is not known
Treatment/Prognosis: 2/3 develop valproate responsive atypical absence seizures, standard treatment of other medical problems

WOLF-HIRSCHORN SYNDROME



medgen.genetics.utah.edu

Facial Features:
'Greek warrior helmet appearance' of the nose (the broad bridge of the nose continuing to the forehead)
Microcephaly
High forehead with prominent glabella
Ocular hypertelorism
Epicanthus
Highly arched eyebrows
Short philtrum
Downturned mouth
Micrognathia
Poorly formed ears with pits/tags



CRI-DU-CHAT (5P DELETION SYNDROME)

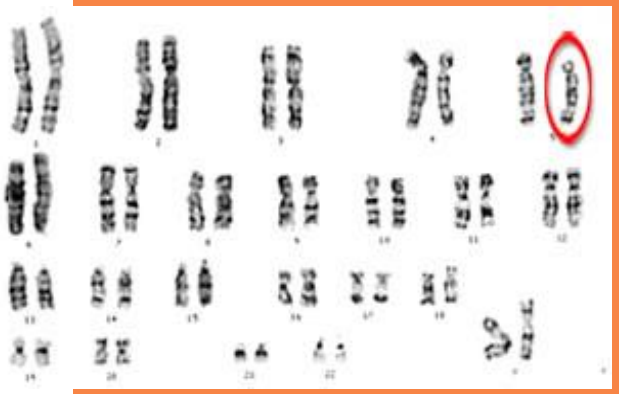
Responsible gene(s): RPS14?, microRNA 145 and 146a?
Protein(s):
Cytogenetic locus: 5p15.2
Inheritance: 12% due to unequal segregation of a translocation or recombination involving a pericentric inversion in one of the parents, 85% sporadic de novo deletions (80% are on the paternal chromosome)
Clinical Features and Diagnostic Criteria: Cat-like cry (abnormal laryngeal development), slow growth, microcephaly, ID, hypotonia, strabismus, characteristic facial features. Cat-like cry only when deletion limited to band 5p15.32
Molecular Tests: Most are visible, a few are submicroscopic and diagnosed by FISH for the critical region.
Disease Mechanism: A study of 50 patients with deletions ranging from 5p15.2 to 5p13 and found no correlation with size of deletion and degree of mental impairment
Treatment/Prognosis: Supportive care

CRI-DU-CHAT (5P DELETION SYNDROME)

Facial Features

Microcephaly
Round face
Hypertelorism
Micrognathia
Epicanthal folds
Low-set ears

www.specialchild.com/archives/poster-child023



THE END
THANK YOU!

CHROMOSOME DISEASES