

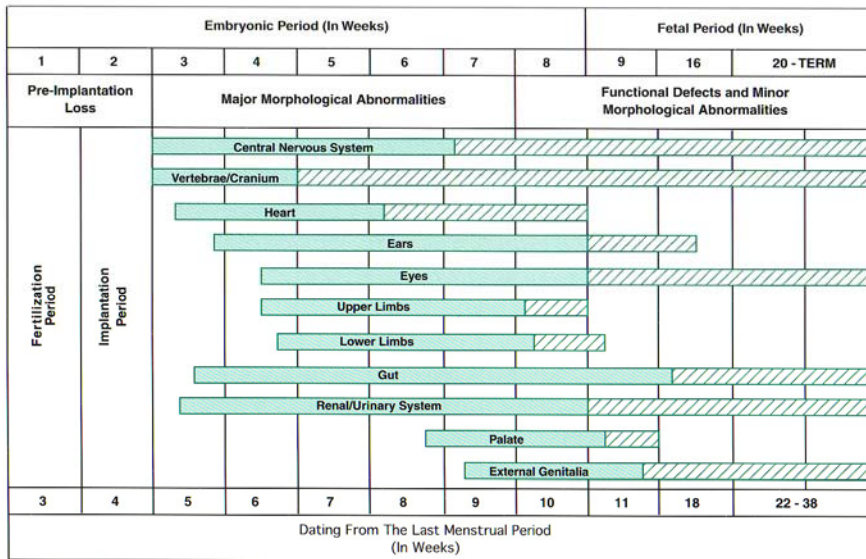
Dysmorphology

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Dysmorphism

- Morphologic developmental abnormalities. This may be seen in many syndromes of genetic or environmental origin.

CRITICAL PERIODS FOR BIRTH DEFECTS IN HUMAN DEVELOPMENT



Denotes highly sensitive stages in development for that particular system
 Less sensitive stages for teratogens

Adapted from Sadler, T.W. Langmans Medical Embryology 1990

Malformation

- A recognized dysmorphic feature. A structure not formed correctly. This can either be the cause of genetic factors or environment.

Deformation

- An external force resulting in the inability of a structure to form correctly.
- Example: club feet in a woman with oligohydramnios, fibroid tumors or multiple gestation.

Disruption

- Birth defect resulting from the destruction of a normally forming structure. This can be caused by vascular occlusion, teratogen, or rupture of amniotic sac (amniotic band syndrome).

Common Dysmorphic features

- Wide spacing between eyes, ***hypertelorism***
- Narrow spacing between eyes, ***hypotelorism***
- Palpebral fissure length
- Epicanthal folds



Common Dysmorphic Features

- Philtrum length
- Upper lip
- Shape of nose

Syndrome

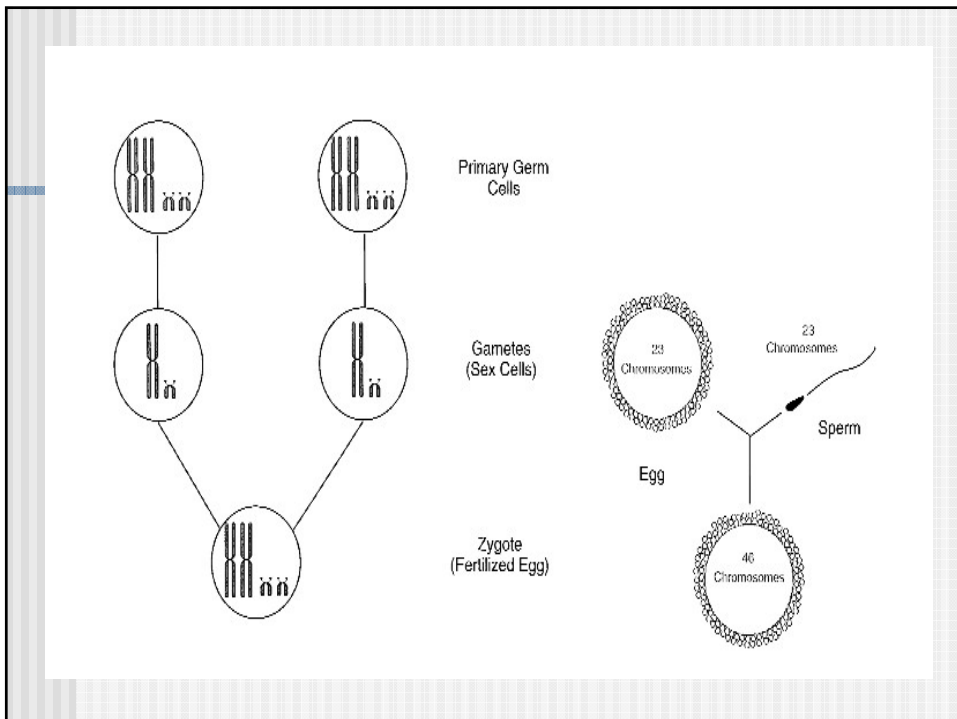
- A number of malformations seen together

Cause of Syndromes

- Chromosomal aneuploidy
- Single Gene abnormalities
- Teratogen exposure
- Environmental

Chromosomal Aneuploidy

- **Nondisjunction** resulting in the addition or loss of an entire chromosome
- **Deletion** of a part of a chromosome
- **Microdeletion syndromes** (small piece missing which is usually only detected using special techniques)



Common Chromosomal Syndromes caused by Nondisjunction

- Down syndrome (trisomy 21)
- Patau syndrome (trisomy 13)
- Edwards syndrome (trisomy 18)
- Turner syndrome (monosomy X)
- Klinefelter syndrome (47,XXY)

Clinical Features at birth of Down syndrome

- Low set small ears
- Hypotonia
- Simian crease
- Wide space between first and second toe
- Flat face

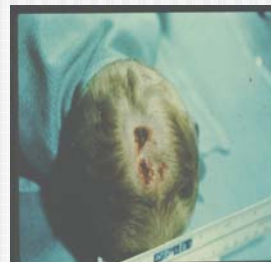


Clinical Features of Down Syndrome

- Small stature
- Congenital heart defects (50-70%)
- Acquired and congenital hearing impairment.
- Duodenal atresia
- Hirshsprungs disease

Trisomy 13

- Occurs in 1/5000 live births.
- Clinical features include holoprosencephaly, cutis aplasia, microcephaly, microphthalmia, cleft lip +/- palate, polydactyly, congenital heart defects.



Trisomy 18

- Occurs in .3/1000 newborns
- Clinical features include weak cry, polyhydramnios, growth deficiency, low-set malformed auricles, clenched hand with overlapping fingers, rocker bottom feet, congenital heart defects.



Trisomy 18

- 30% of babies with trisomy 18 die in the first month of life.
- Only 10% of these children survive their first year of life.



Turner Syndrome

- Occurs in 1/2500 life born females.
- Approximately 99% of all 45,X conceptions are miscarried.



Turner Syndrome

- At birth some patients have puffy hands and feet.
- This is believed to be related to abnormal lymphatic drainage.
- A webbed neck, shield chest are also early signs.

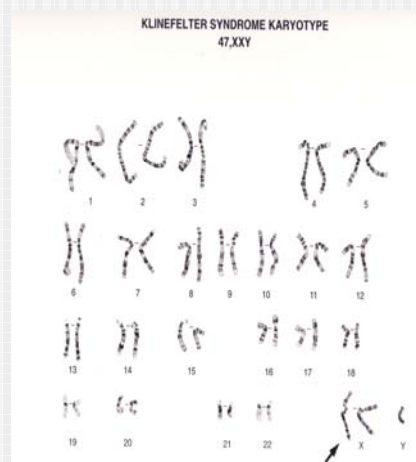
Turner Syndrome

- Often patients are not diagnosed until 5-6.
- Short stature
- Broad chest
- Low hairline
- Webbed neck
- Cubitus valgus
- Renal anomalies and cardiac defects including bicuspid aortic valve and coarctation of the aorta are more common.



Klinefelter Syndrome

- Occurs in 1/5000 live born males
- IQ 10-15 points below siblings.
- Often not diagnosed in the newborn period.
- Clinical features include tall stature, behavioral problems, **post pubertal** small testes.



Small visible chromosome deletions

- Wolf-Hirshorn (4p-)
- Cri du Chat (5p-)

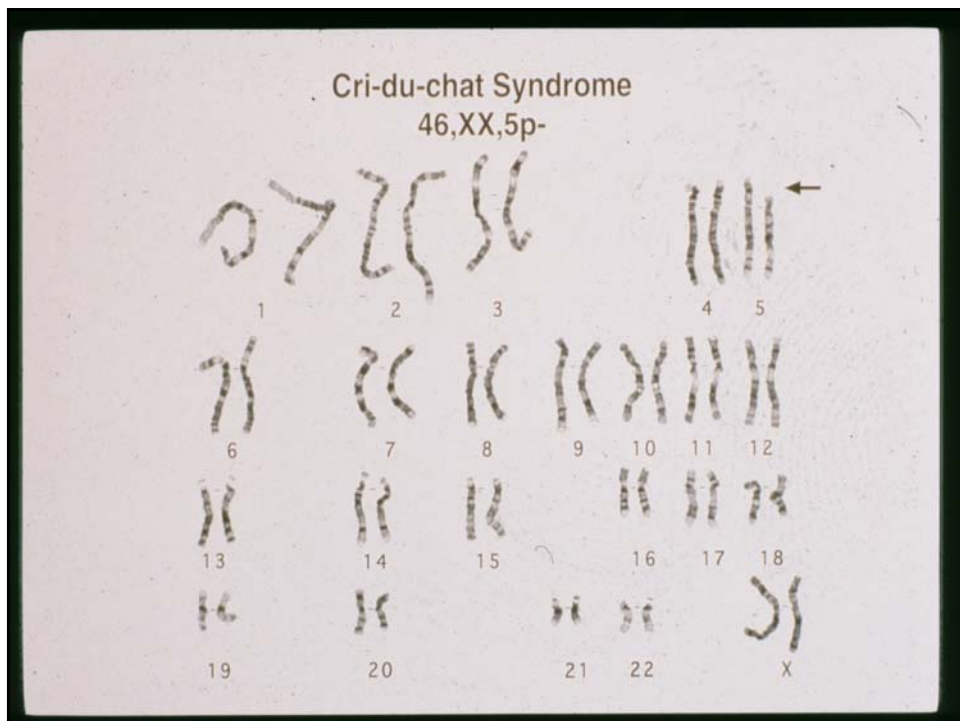
Wolf Hirshorn

- Results from a terminal deletion of the short arm of 4.
- Features includes hypertelorism, broad nasal bridge, cleft lip +/- palate, down turned mouth.
- Severe mental retardation.



Cri du Chat

- Partial deletion of the short arm of chromosome 5.
- Features include microcephaly, growth deficiency, high pitched cat-cry, congenital heart disease, hypotonia.



Features of Contiguous Gene Syndromes

- Syndromes described before chromosomal etiology was known.
- Cytogenetic abnormalities are frequently detectable only by high resolution chromosomal analysis.
- Not all patients with the syndrome have a detectable cytogenetic abnormality.

Contiguous Deletion syndromes

- Angelman syndrome
- Prader-Willi syndrome
- Velocardial Facial
- Williams syndrome
- Smith-Magenis syndrome

Prader-Willi Syndrome

- Obesity
- Hypotonia
- Small hands and feet
- Up slanting palpebral fissures
- IQ 60-70
- Small penis and cryptorchidism in males.

Prader-Willi during infancy

- Severe hypotonia
- Failure to thrive



Prader-Willi Syndrome

- Approximately 60% of cases are caused by a **paternal** deletion of chromosome 15q11.2.
- 40% are a result of uniparental disomy.



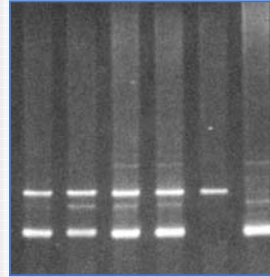
Angelman Syndrome

- Approximately 70% result from a **maternal** deletion of 15q11
- Severe postnatal growth deficiency
- Mental retardation
- "puppet-like gait"
- Paroxysms of inappropriate laughter.
- Absent or limited speech.
- Seizures



Prader-Willi vs Angelman Syndrome

- Difficult to differentiate during infancy.
- FISH analysis with a deletion is seen in both.
- **Only methylation studies can differentiate.**



Lanes 1 - 4 = normal individuals
Lane 5 = Prader-Willi syndrome
Lane 6 = Angelman syndrome

22q11 Deletion syndrome

- Includes DiGeorge, Velocardial-facial syndrome and Sprintzen syndrome
- Occurs in 1/5000
- Caused by an interstitial deletion of chromosome 22q11 in over 80% of cases.

Features of 22q11

- There are over 180 features seen in 22q11 deletions.
- None are pathanamonic
- Micrognathia
- Low-set ears
- Short palpebral fissures
- Blunted nose – older patients have bulbous nose
- High arched palate
- Cleft palate and or Bifid uvula.

Single Gene Abnormalities

- Mutation in the single gene resulting in a dysmorphic phenotype

Autosomal Dominant Syndromes

- One abnormal gene results in an identifiable phenotype.

Common Autosomal Dominant Disorders

- Neurofibromatosis
- Marfan Syndrome
- **Most** Skeletal dysplasia's including Achondroplasia

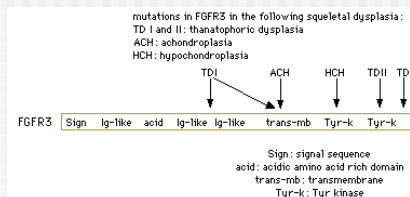
Achondroplasia

- Inherited in an autosomal dominant fashion
- Rhizomelic shortening of limbs
- Short fingers held in a "trident" configuration
- Enlarged head with depressed nasal bridge



Achondroplasia

- Approximately 98% result from a new or inherited mutation of the FGFR3 locus.



Neurofibromatosis

- Occurs in 1/3000 individuals
- Features includes >6 café au lait spots, 2 or more neurofibromas, Lisch nodules, optic gliomas, angiofibromas axillary or inguinal freckling.



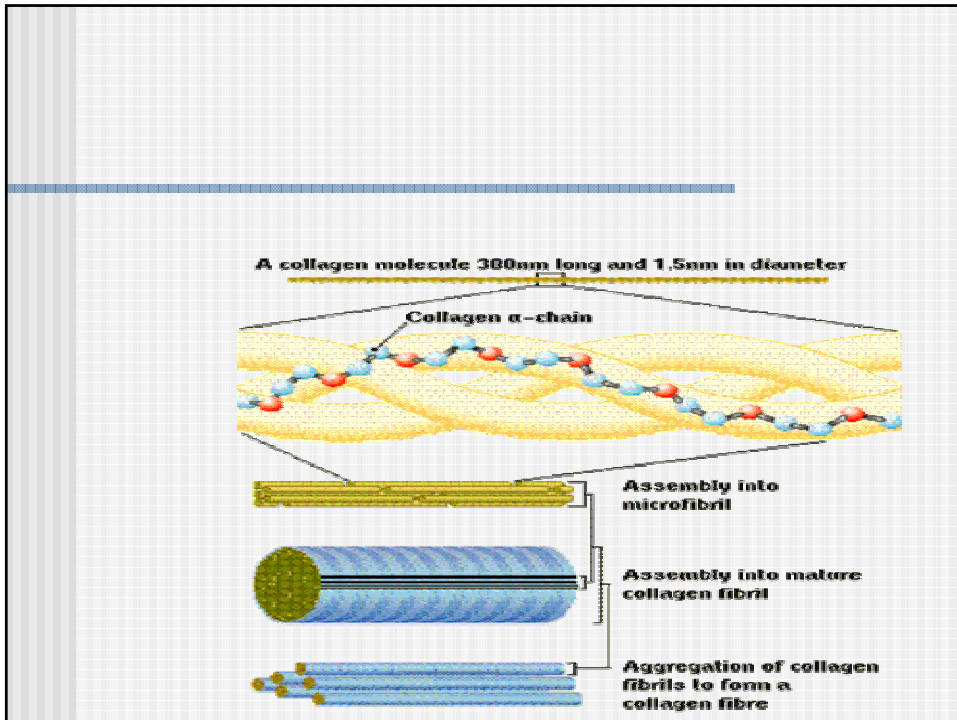
Ophthalmologic Features

- Optic Glioma
- Lisch Nodules (Iris Hamatoma)



Osteogenesis Imperfecta

- Type I: Mildest, blue sclera, multiple fractures during childhood
- Type II: lethal, prenatal fractures
- Type III: progressive deforming some prenatal fractures.
- Type IV: major dental anomalies and skeletal finding.



Osteogenesis imperfecta Type I

- Fractures
- Osteopenia
- Blue sclera
- Hearing loss
- Short stature



Osteogenesis Imperfecta vs Child Abuse

- Children with multiple bone fractures with an inconsistent story are often thought to be the victims of child abuse.
- This is probably TRUE in most cases
- Signs of OI include poor mineralization of the bones, hyperflexibility and blue sclera and hearing impairment.
- Skin biopsy for collagen will detect abnormalities in over 80% of patients with OI.
- DNA analysis of the Col2A1 gene is 95% sensitive.
- If there are other signs of trauma such as retinal hemorrhages, bruises, and signs of sexual abuse a skin biopsy is not warranted.

Autosomal Recessive Syndromes

- The majority of disorders are inherited in this fashion.
- We all carry approximately 6-8 lethal genes.
- If we have a child with someone who carries the same "bad gene" there is a 25% chance of having an affected child.

Common Autosomal Recessive Disorders

- Cystic Fibrosis
- Sickle cell anemia
- Tay Sachs Disease

Cystic Fibrosis

- 1/20 Caucasians is a carrier of 1 abnormal gene
- Clinical Features include respiratory difficulty, pancreatic insufficiency.
- The earlier the diagnosis the better the prognosis
- GI symptoms are often the first sign of CT
- There are over 800 known CF mutations.
- $\Delta F508$ is the most common.

Cystic Fibrosis Newborn Screening

- Currently being offered in 13 states
- Illinois planning to begin in July 2006
- The trypsinogen level is measured (IRT)
- If elevated, DNA mutation for the most common 50 mutations will then be studied.

Advantages of Prenatal Screening for CF

- Diagnosis the disorder prior of lung disease.
- Begin enzyme treatment before significant malabsorption leading to failure to thrive.
- Failure to thrive can result in microcephaly and low IQ scores.

Tay Sacs Disease

- 1/27 Ashkenazi Jewish individuals are carriers.
- Features include cherry red spot in retina and loss of developmental milestones.
- Neurodegenerative leukodystrophy



Teratogens and Dysmorphology

- Medications or drugs the developing fetus is exposed to can result in a number of birth defects.
- The timing of exposure and dose are important in determining the extent of the damage caused by a particular teratogen.

Drugs resulting from Teratogen exposure

- Fetal Alcohol Syndrome

Heat Exposure

- When a woman is exposure to high temperatures around 6 weeks gestation there appears to be an increased risk of spina bifida.

Diabetic Embryopathy

- High levels of glucose at critical points of development are **teratogenic**.
- Defects include congenital heart defects, caudal regression, limb defects and ear anomalies.

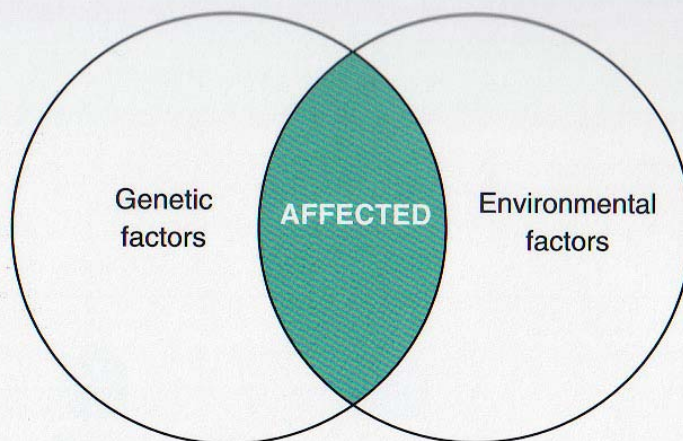
Syndromes with Multifactorial inheritance patterns

- The majority of human disorders are inherited in a **multifactorial fashion**.
- Multifactorial inheritance is defined as involving both genetic and environmental factors.

Common Human Disease with Multifactorial inheritance

- Retinitis Pigmentosa
- Hirschsprung Disease
- Diabetes Mellitus type 1
- Neural tube defects
- Cleft lip +/- palate
- Congenital heart disease

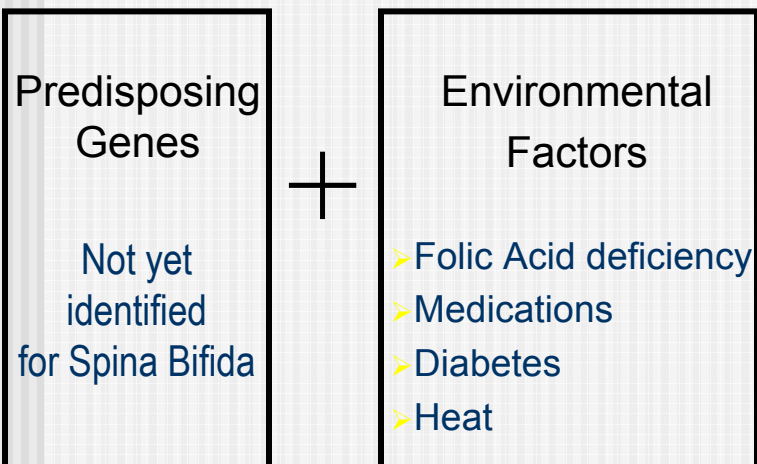
Multifactorial Disorder



Multifactorial Disorder Example: Spina Bifida

- Defect of development of the neural tube.
- Occurs within 28 days of conception.
- Involves paralysis – wide range of severity, impaired bowel and bladder function, can cause hydrocephalus, usually normal intelligence.

Multifactorial Disorder Example: Spina Bifida



Folic Acid Supplementation

- 400 μ g per day PRECONCEPTIONALLY can prevent up to 75% of occurrences (Prescription Prenatal Vitamins contain 1 mg).
- When there is a previous affected child, an increased dose of 4mg per day PRECONCEPTIONALLY can prevent up to 85% of recurrences.

Institute of Medicine 1998

Conclusion

- There are many factors which are involved in the formation of structures .
- They interaction between genetics and environment is essential especially during early developmental stages.