# Dysmorphology

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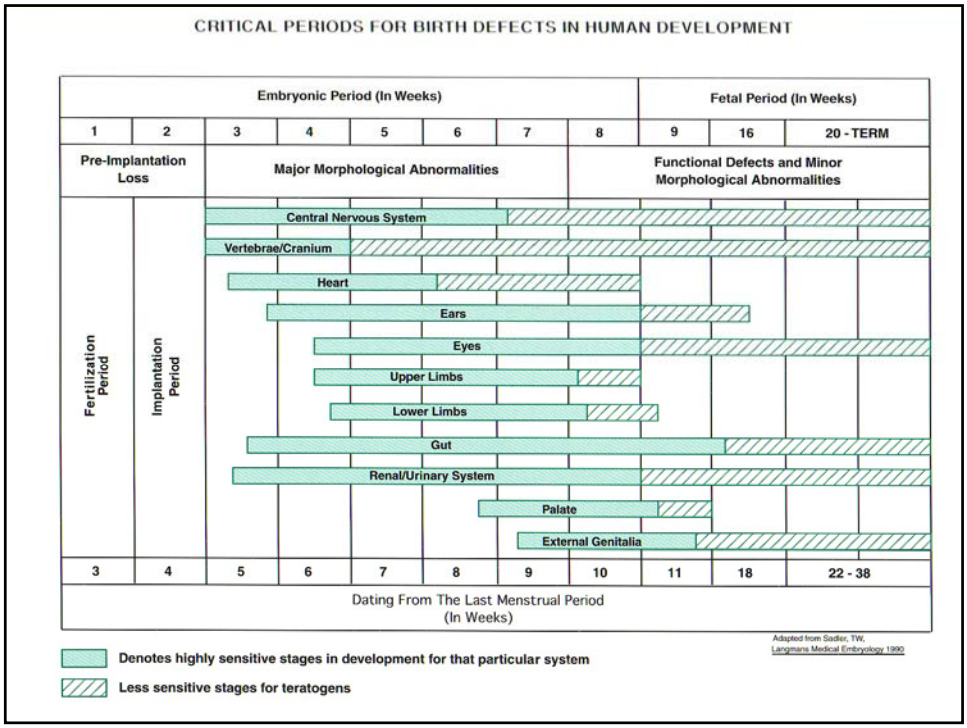
## Dysmorphism

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




# 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

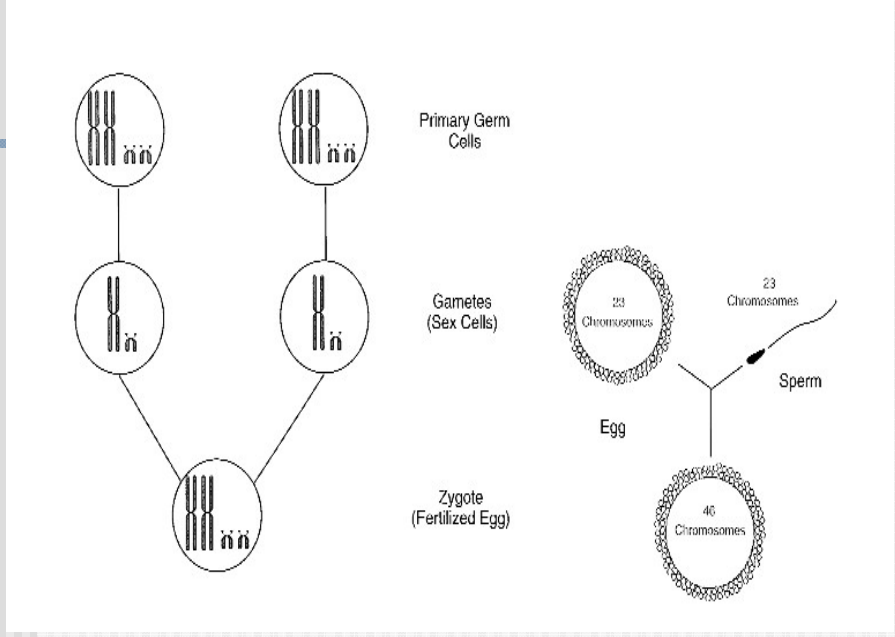
- A number of malformations seen together

## Cause of Syndromes

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

# Chromosomal Aneuploidy

- **Nondisjuction** 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)

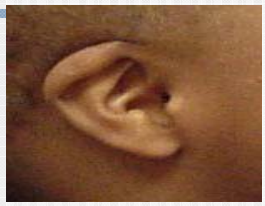


## Common Chromosomal Syndromes caused by Nondisjuction

- 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

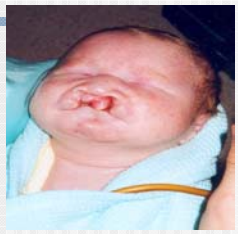


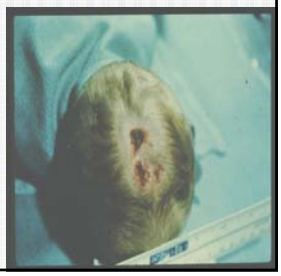
# Clinical Features of Down Syndrome

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

# Trisomy 13

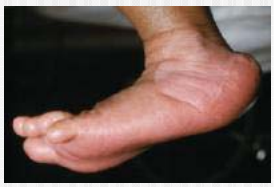
- Occurs in 1/5000 live births.
- Clinical features include holoprosencephaly, cutis aplasia,microcephaly, microapthalmia, cleft lip +/- palate, polydactyly, congenital heart defects.





# 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

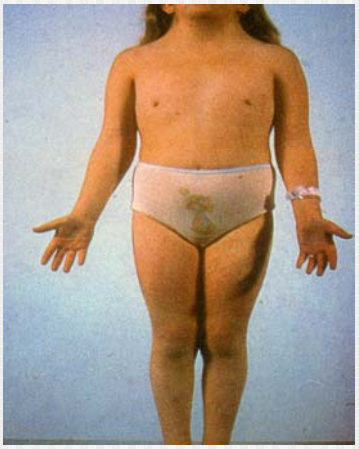
- Occurs in 1/2500 life born females.
- Approximately 99% of all 45,X conceptions are miscarried.

# Turner Syndrome

- At birth some patients have puffy hands and feet.
- This is believe 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

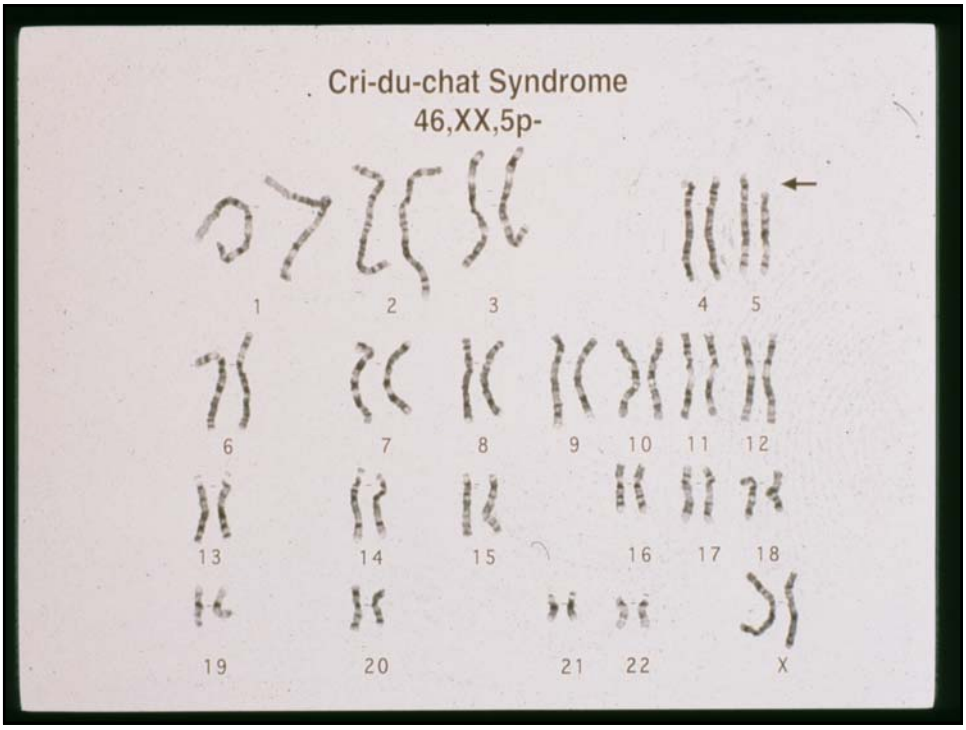
- Wolf-Hirshorn (4p-)
- Cri du Chat (5p-)

# 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

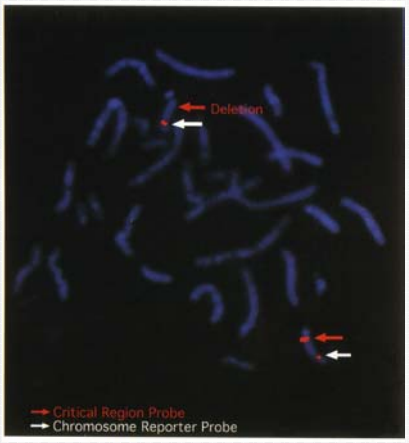
- Obesity
- Hypotonia
- Small hands and feet
- Up slanting palpebral fissures
- IQ 60-70
- Small penis and cryptorchidism in males.

# 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.

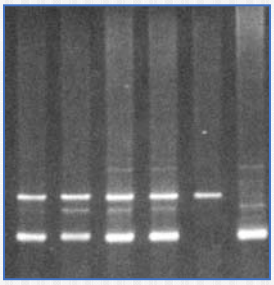



# Angelman Syndrome

- Approximately 70% result from a **maternal** deletion of 15q11
- Severe postnatal growth deficiency
- Mental retardation
- "puppet-like gait"
- Parozysms 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 methlyation 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

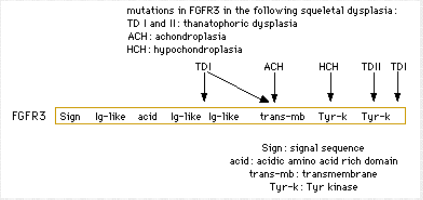
- Neurofibromatosis
- Marfan Syndrome
- ***Most*** Skeletal dysplasia's including Achondroplasia

# Achondroplasia

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

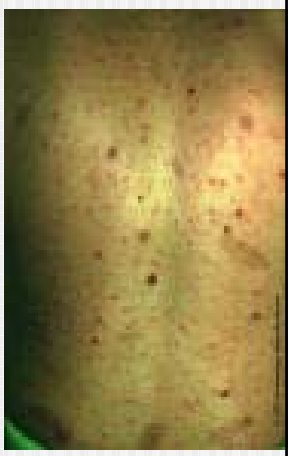
# Achondroplasia

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



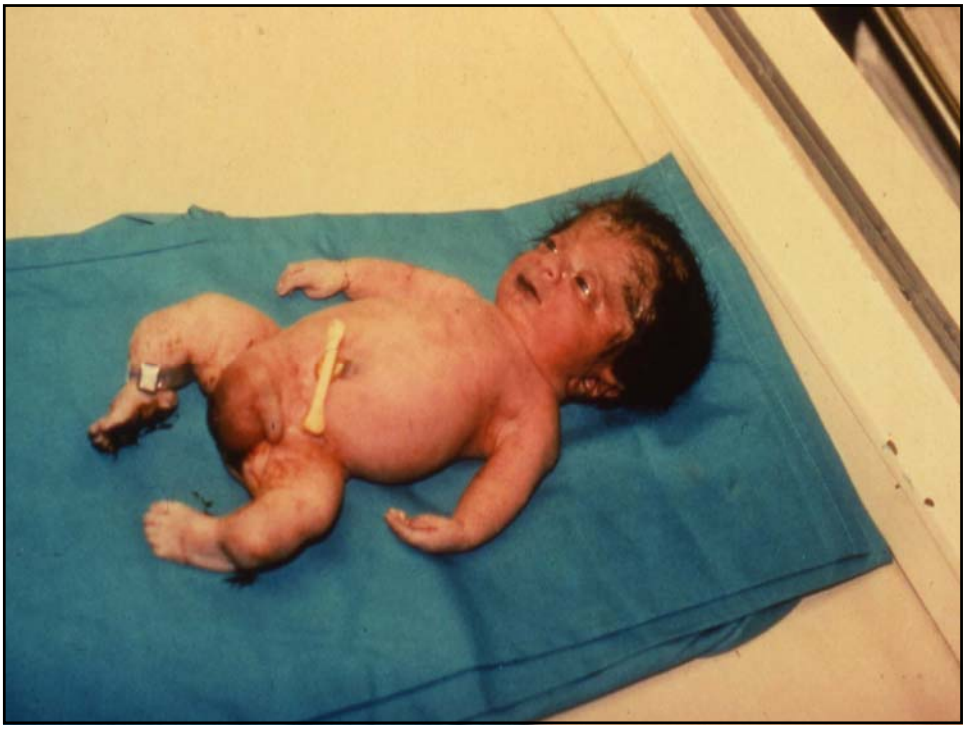
# Neurofibromatosis

- 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.



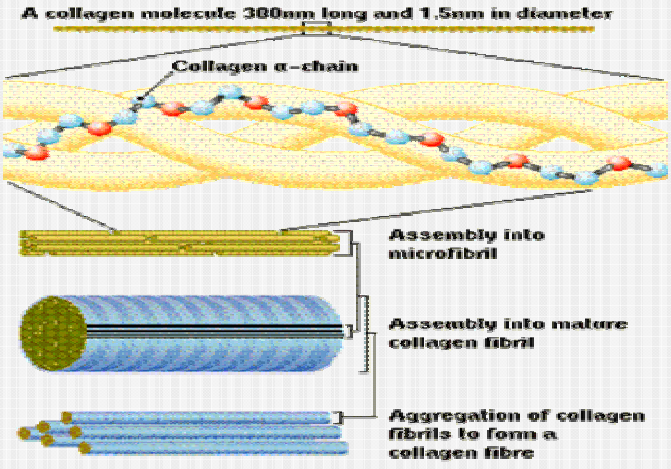
# Ophthalmologic Features

- Optic Glioma
- Lisch Nodules (Iris Harmatoma)



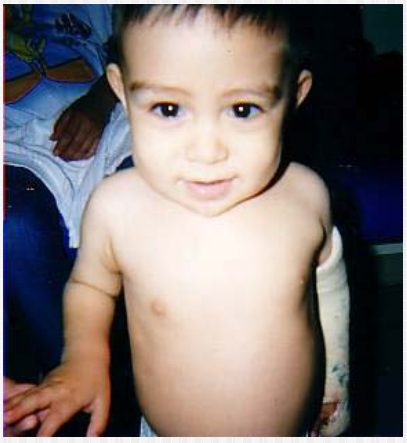
## Osteogenesis Imperfecta

- 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 brakes 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.
- ΔF508 is the most common.

## Cystic Fibrosis Newborn Screening

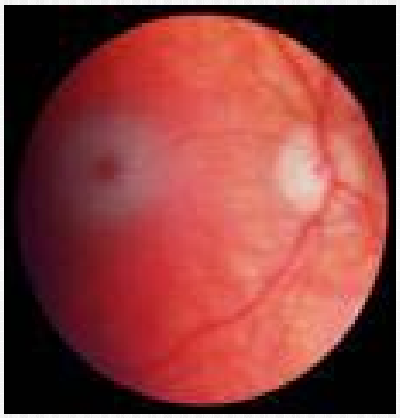
- Currently being offered in 13 states
- Illinois planning to begin in July 2006
- The trysinogen level is measured(IRT)
- If elevated, DNA mutation for the most common 50 mutations will then be studied.

## 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.

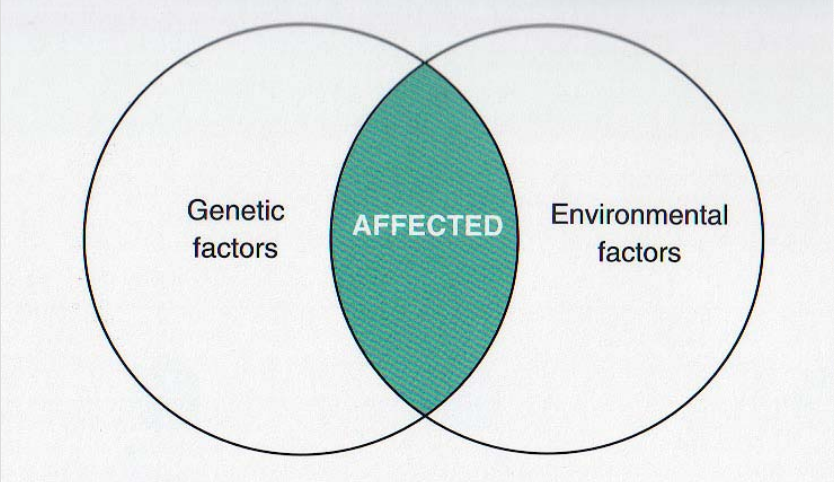
## Syndromes with Multifactorial inheritance patterns

- 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

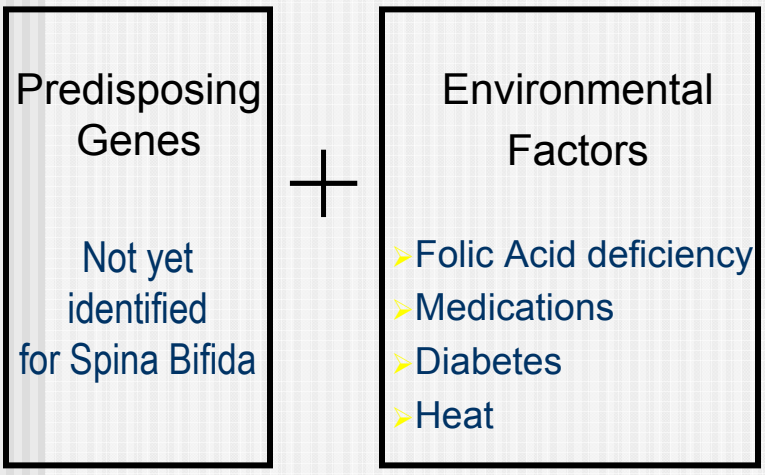



Counseling Aids for Geneticists, 1995

## 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

- 400μg 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.