



Congenital disorders



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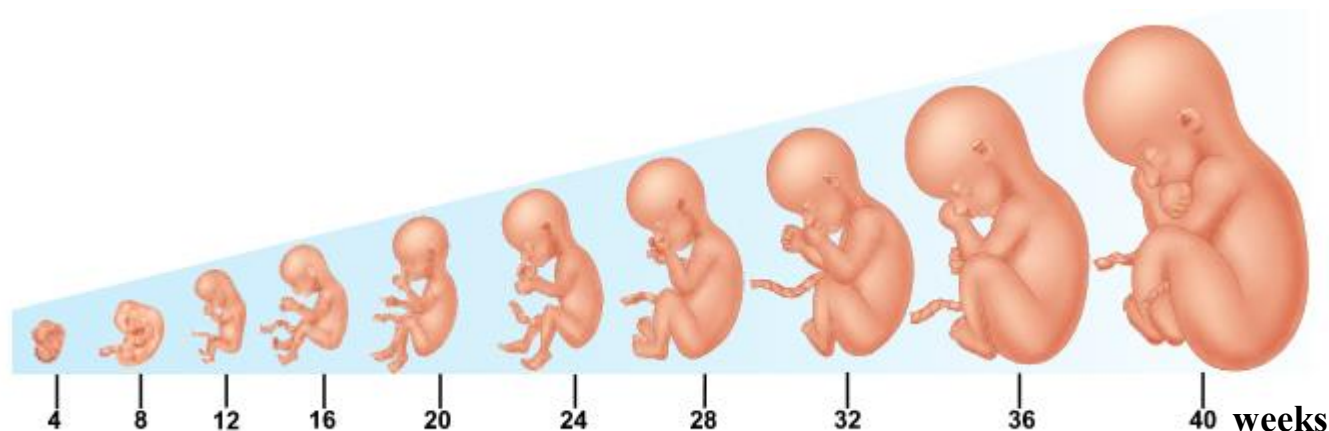
Congenital disorders can be defined as **structural** or **functional** anomalies that occur **during intrauterine life**.

Also called **birth defects**, **congenital anomalies** or **congenital malformations**, these **conditions develop prenatally** and may be identified before or at birth, or later in life.



Fetal development

- Fetal development is an **orderly** and **intricate** process.
- It begins before you even know you're pregnant and ends with the birth of your baby.
- Between **conception** and **delivery**, there are **many detailed steps** that have to occur.
- There are **three stages** of fetal development:
 - Germinal
 - Embryonic
 - Fetal



جدول ۱-۶ رخدادهای عمده در نمو و تکوین یک نوزاد انسانی		
مرحله	زمان بارداری پس از	دولتی/جنینی
پیش رویانی (۳ هفته اول)		
First cell division	30 hours	40-50 cm
Zygote reaches uterine cavity	4 days	
Implantation	5-6 days	
Formation of bilaminar disc	12 days	0.2 mm
Lionization in female	16 days	
Formation of trilaminar disc and primitive streak	19 days	1 mm

1

رویانی Organogenesis 4-8 ماه دوم		
Brain and spinal cord are forming	4 weeks	4 mm
First signs of heart and limb buds		
Brain, eyes, heart and limbs developing rapidly	6 weeks	17 mm
Bowel and lungs beginning to develop	ماه دوم	
Digits have appeared. Ears, kidneys, liver and muscle are developing	8 weeks	4 cm
Palate closes and joints form	10 weeks	6 cm
Sexual differentiation almost complete	12 weeks	9 cm

2

Fetal development:

1. Pre-embryonic
2. Embryonic
3. Fetal

جنینی (زهرسانی)		
Fetal movement felt	16-18 weeks	20 cm
Eyelids open. Fetus is now viable with specialized care	24-26 weeks	35 cm
Rapid weight gain due to growth and accumulation of fat as lungs mature	28-38 weeks	40-50 cm

3

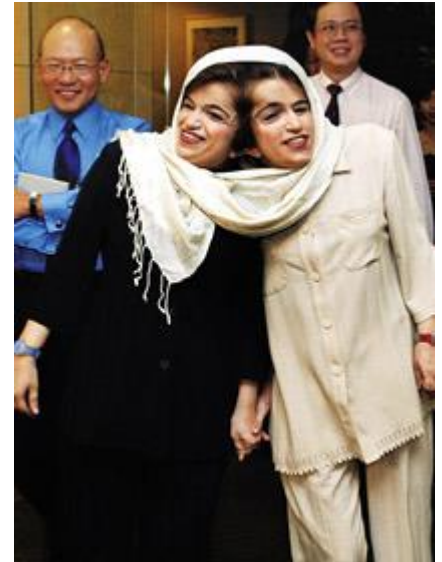
CONGENITAL ANOMALIES

* as **BABY DEVELOPS IN UTERO**

↳ **IMPACT HEALTH, DEVELOPMENT, SURVIVAL**



- * CLEFT LIP
- * ESOPHAGEAL ATRESIA
- * CONGENITAL DIAPHRAGMATIC HERNIA
- * GASTROSCHISIS
- * OMPHALOCELE
- * BILIARY ATRESIA
- * BLADDER EXSTROPHY
- * OPEN NEURAL TUBE DEFECTS



Omphalocele: Failure of the intestines to return into the



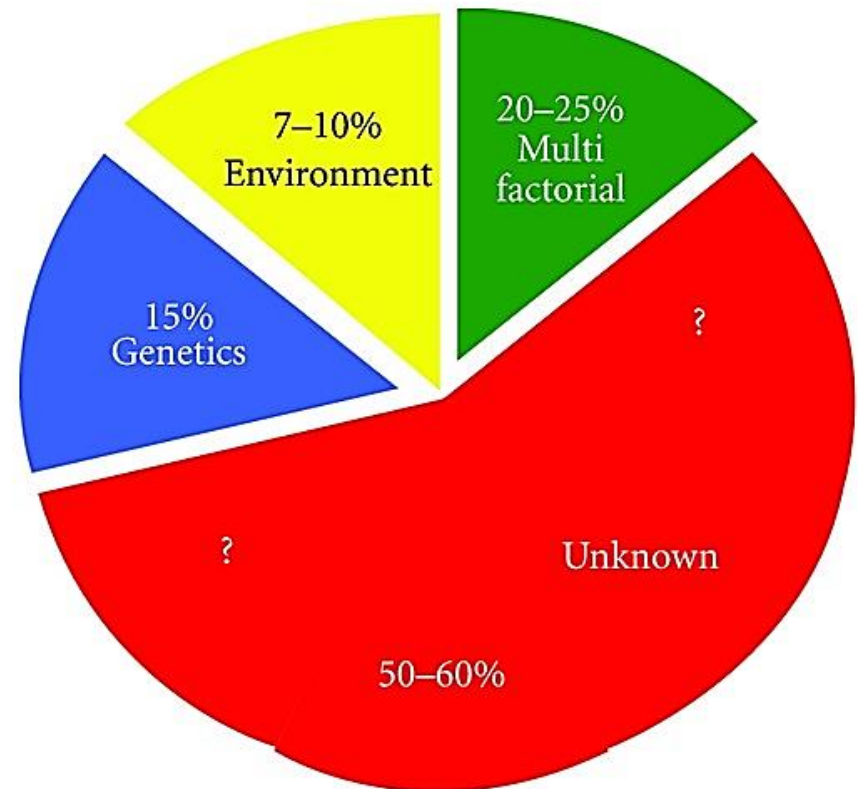
Omphalocele: Failure of the intestines to return into the abdomen

Gastroschisis: It is a birth defect in which the intestine protrudes through a hole in the abdominal wall, next to the navel.



What causes birth anomalies?

- Smoking, drinking alcohol, or taking certain drugs during pregnancy.
- Having certain medical conditions, such as being obese or having uncontrolled diabetes before and during pregnancy.
- Taking certain medications
- Infections
- Chromosomal problems
- Genetic problems
- Having someone in your family with a birth defect.



چارچوب ۶-۱ خاستگاه‌های اندام و بافت

اکتودرمی

Central nervous system

CNS

Peripheral nervous system

PNS

Epidermis, including hair and nails

صورتاقت

Subcutaneous glands

Dental enamel

سنگ دندان

غدد زیر پوستی

مزودرمی

Connective tissue

کلیه

بافت پیوندی

Cartilage and bone

عقربند استخوان

Smooth and striated muscle

عضله صاف و محفظه

Cardiovascular system

Urogenital system

سیستم قلبی عروقی / ادراری تناسلی

اندودرمی

Thymus and thyroid

تیوس و تیروئید

Gastrointestinal system

Liver and pancreas

سیستم هضم و دفع (احشاء)

کبد و پانکراس

تجمع بافت

صورتاقت

الیه

خون و لیمف

عضله و استخوان

بافت پیوندی

عضله

غده و احشاء

BACKGROUND

* INFECTION of DEVELOPING FETUS or NEWBORN that CAN OCCUR in UTERO, DURING DELIVERY, or AFTER BIRTH

* **COMPLICATIONS INCLUDE:** PRETERM BIRTH, DELAYED DEVELOPMENT of FETUS, PHYSICAL MALFORMATIONS, & LOSS of PREGNANCY

SYMPTOMS

* VARY DEPENDING on SPECIFIC UNDERLYING INFECTION but SHARE NON-SPECIFIC SIGNS & SYMPTOMS:

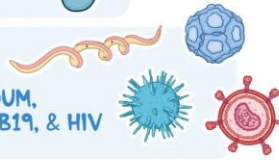
- ~ FEVER
- ~ MICROCEPHALY
- ~ LETHARGY
- ~ ↓ BIRTH WEIGHT
- ~ CATARACTS
- ~ HEARING LOSS
- ~ JAUNDICE
- ~ "BLUEBERRY MUFFIN" RASH
- ~ REDDISH-BROWN SPOTS on SKIN
- ~ HEPATOSPLENOMEGALY
- ~ CONGENITAL HEART DISEASE

TOXOPLASMA GONDII



OTHER AGENTS:

~ TREPONEMA PALLIDUM, VZV, PARVOVIRUS B19, & HIV



RUBELLA



CYTOMEGALOVIRUS (CMV)



HERPES SIMPLEX VIRUS (HSV)



TRANSMISSION

* TRANSMITTED to FETUS THROUGH PLACENTA

* INFANT MAY CATCH INFECTION WHILE PASSING THROUGH BIRTH CANAL

* MOTHER can PASS INFECTION to INFANT THROUGH BREAST MILK



جدول ۱۶-۷ عناصر تراوژنیک (ناهنجاری زای) عفونی

عقونت	آثار
ویروس‌ها	Chororeinitis, deafness, microcephaly
Cytomegalovirus	Microcephaly, microphthalmia
Herpes simplex	Microcephaly, cataracts, retinitis, cardiac defects
Rubella	Microcephaly, chorioretinitis, skin defects
Varicella zoster	Microcephaly, chorioretinitis, skin defects
باکتری‌ها	Hydrocephalus, osteitis, rhinitis
Syphilis	Hydrocephalus, microcephaly, cataracts, chorioretinitis, deafness
انگل‌ها	Hydrocephalus, microcephaly, cataracts, chorioretinitis, deafness

1. Emelia: فقدان مادرزادی یکی از اندام‌ها یا همه آن‌ها، م
2. Measles, Mumps, Rubella

Be careful in taking drugs during pregnancy

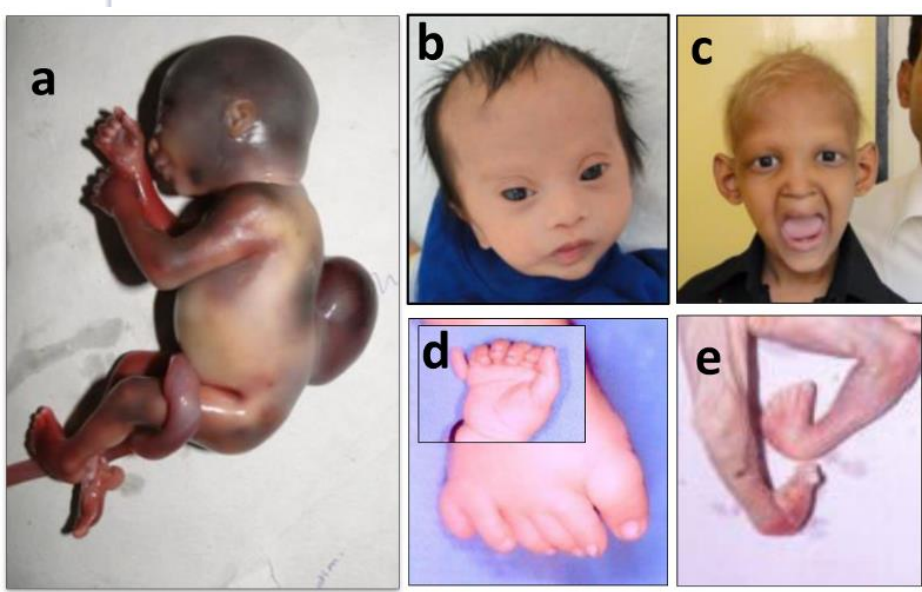
جدول ۱۶-۶ دواهایی با تأثیر تأیید شده ناهنجاری‌ها در انسان	
دارو	آثار
ACE inhibitors	Renal dysplasia
Alcohol	Cardiac defects, microcephaly, characteristic facies
Chloroquine	Chorioretinitis, deafness
Diethylstilbestrol	Uterine malformations, vaginal adenocarcinoma
Lithium	Cardiac defects (Ebstein's anomaly)
Phenytoin	Cardiac defects, cleft palate, (digital) hypoplasia
Retinoids	Ear and eye defects, hydrocephalus
Streptomycin	Deafness
Tetracycline	Dental enamel hypoplasia
Thalidomide	Phocomelia, cardiac and ear abnormalities
Valproic acid	Neural tube defects, characteristic facies
Warfarin	Nasal hypoplasia, stippled epiphyses
ACE. angiotension-converting enzyme.	

TERATOGENIC DRUGS

IN FIRST TRIMESTER OF PREGNANCY

- Analgesic
- Antidepressant
- Metal toxic
- Anticonvulsant
- Antithyroid
- Sedative/ hypnotics
- Anticoagulant
- Vitamin A
- Aminoglycosides





[a] **Meningo-myelocele** – a **major** malformation [b] **Hypertelorism and upslant of eyes** in a child with characteristic facial phenotype of a child with **Down syndrome** due to trisomy 21 [c] **Ectodermal dysplasia** showing absence of teeth and sparse, light coloured hair [d] **Polydactyly** – a **minor** malformation [e] **Talipoequinovarus** – an example of deformation.

Primary (genetic)

Chromosomal abnormalities

- Numeric
 - polyploidy
 - polysomy
 - monosomy
- Structural
 - deletions
 - duplications
 - insertions
 - translocations

Monogenic

- Point mutations
 - nonsense
 - mis-sense
 - frameshift
- Dynamic mutations
 - triplet amplification
- Epigenetic regulation
 - imprinting defects
 - uniparental disomy

Polygenic

- oligohydramnios
- uterine malformations

Secondary (environmental)

Biologic agents

- Viruses
 - cytomegalovirus
 - rubella
 - herpes viruses
- Bacteria
 - *Treponema pallidum*
- Parasites
 - *Toxoplasma gondii*

Chemical agents

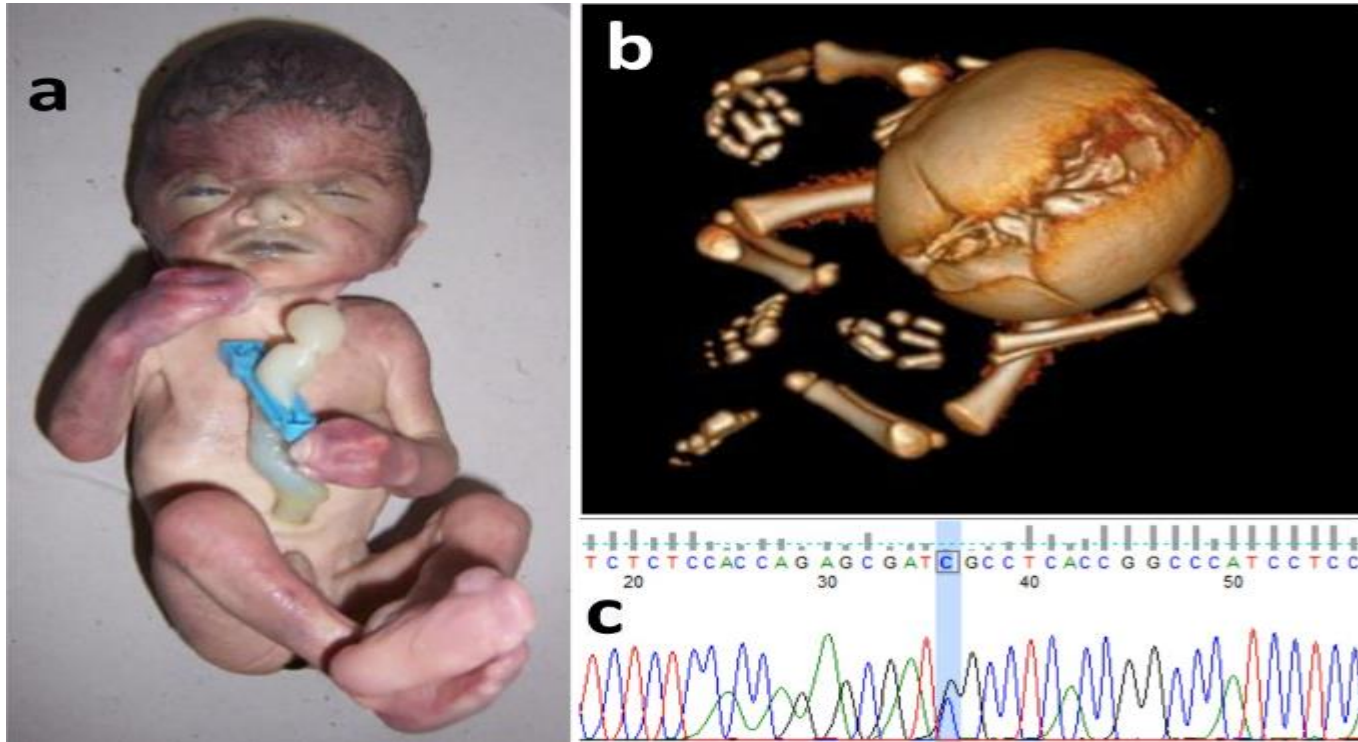
- Drugs
 - antineoplastics
 - anticonvulsants
 - antibiotics
- Abuse substances
 - alcohol
 - smoke
 - cocaine
 - opiates
- Metabolic conditions
 - hyperglycemia, hyperinsulinemia
 - hyperphenylalaninemia
 - hyperandrogenism
- Physical agents
 - ionizing radiation
 - electromagnetic radiation
- Vascular disruptions
 - subclavian artery vascular disruption
 - twin-twin disruption sequence
- Mechanical causes (deformations)
 - amniotic bands
 - twinning
 - uterine tumors

Single gene congenital disorders

ناهنجاری ها	وراثت	
جدامانده سیستم اعصاب مرکزی hydrocephalus megalocephaly Microcephaly	XR AD AD/AR	نوعی سندرم Noonan خلع ریه میکرو سفال مگالوسفال
چشمی Aniridia Cataracts Microphthalmia	AD AD/AR AD/AR	اندریا کاتاراکت میکروفthalmia AP: AR: XR
اندام حرکتی Brachydactyly Ectrodactyly Polydactyly	AD AD/AR/XR AD	براکتیداکتیلی اکترو داکتیلی پلی داکتیلی برانی درکتی
سایر Infantile polycystic	AR Kidneys	نیو کیستیک ریدز AD, AR → بالغ
نشانه ها Apert EEC Meckel Roberts Van der Woude	AD AD AR AR AD	Craniosynostosis, syndactyly Ectodermal dysplasia, ectodactyly, cleft lip / palate Encephalocele, polydactyly, polycystic kidneys Cleft lip/palate, phocomelia Cleft lip/palate, lip pits

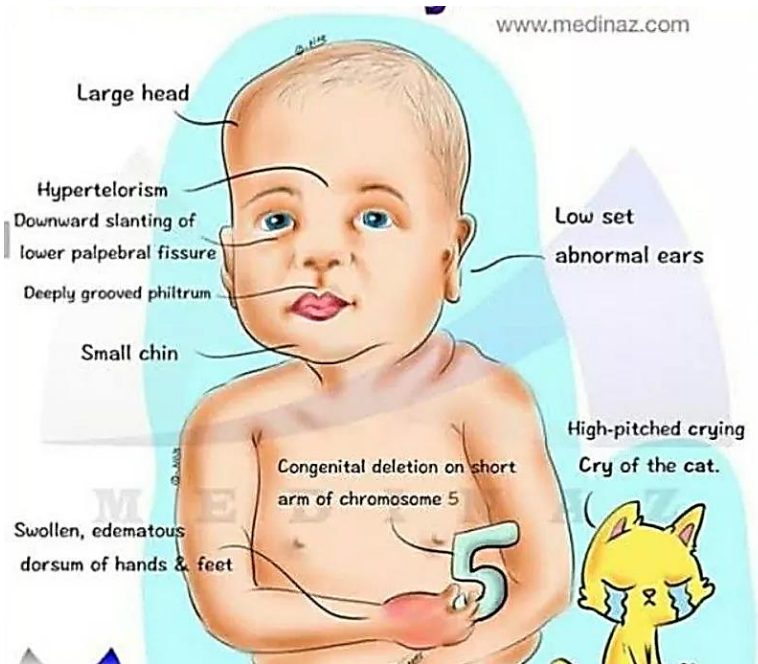
AD: autosomal dominant; AR: autosomal recessive; XR: sex-linked recessive

Single gene birth anomalies



[a] A fetus with **Apert syndrome** showing tower skull and syndactyly [b] CT scan of the head showing closed coronal sutures and wide open sagittal suture [c] Sequencing results of a part of **FGFR2** gene showing the **p.Ser252Trp** mutation.

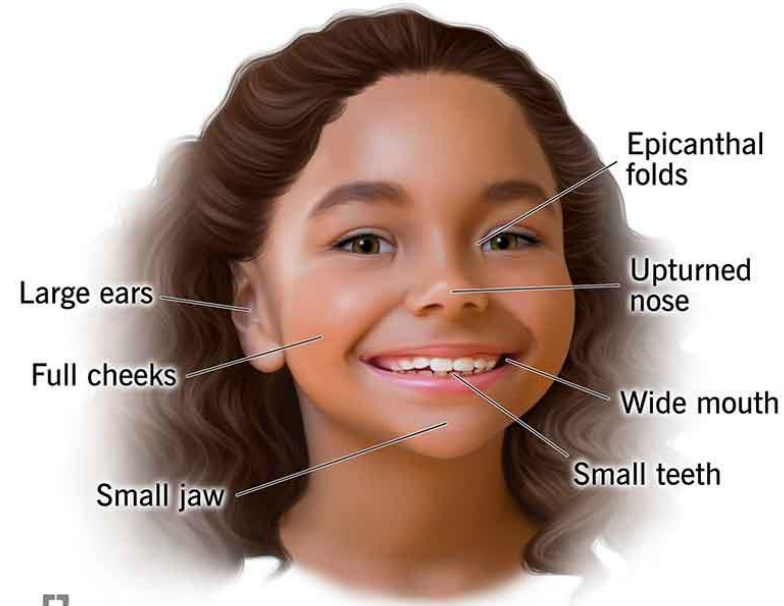
Chromosomal microdeletions in birth anomalies



Chromosome 5p microdeletion syndrome –also known as **Cri-du-chat syndrome**

Williams syndrome showing mild to moderate intellectual disability with characteristic face, missing a small piece of **chromosome 7q11**

Williams syndrome



Type of birth defect	Description	Examples	Comment
Major malformation (single major anomaly in 3% of births, multiple malformations in 0.7% neonates)	Morphological defects that occur due to errors in the normal development and differentiation of an embryo	Meningocele, posterior urethral valve, ventricular septal defect, cleft lip	If untreated, will lead to significant impairment of the function of the organ leading to mortality or morbidity
Minor malformation (14% and 3% of neonates have a single and multiple minor malformations respectively)		Polydactyly, ear tag, Single palmar crease	Only of cosmetic importance, but of use in diagnosis of etiology
Normal variants	Clinical features which are at the far end of normal distribution	Low set ears, hypertelorism	May be present in normal individuals but in association with other birth defects can be of help in the diagnosis of a syndrome

Type of birth defect	Description	Examples	Comment
Deformation	Abnormal shape of a normally formed structure due to distortion caused by mechanical forces	Talipes equinovarus in a child with amyoplasia or congenital myopathy due to oligohydramnios or intrauterine crowding	May have good prognosis with postnatal intervention. Risk of recurrence in the family is usually not increased if the causative factor does not recur
Disruption	Damage or dissolution of a part following normal development	Amputation of digits due to damage by constricting amniotic band or phenomenon	Usually do not recur in the family
Dysplasia	Morphological defects caused by abnormal maturation and organization of cells into tissue	Achondroplasia (involvement of bones), Ectodermal dysplasia (hair, teeth, sweat glands and nails are involved)	Involvement of multiple organs in the body where the particular tissue is present. Mostly are single gene disorders .



Disorders that Show Multifactorial Inheritance

Congenital Malformations

- ▶ Cleft lip/palate
- ▶ Congenital dislocation of the hip
- ▶ Congenital heart defects
- ▶ Neural tube defects
- ▶ Pyloric stenosis
- ▶ Talipes

Acquired Diseases of Childhood and Adult Life

- ▶ Asthma
- ▶ Autism
- ▶ Diabetes mellitus
- ▶ Epilepsy
- ▶ Glaucoma
- ▶ Hypertension
- ▶ Ischemic heart disease
- ▶ Manic depression
- ▶ Multiple sclerosis
- ▶ Parkinson disease
- ▶ Psoriasis
- ▶ Rheumatoid arthritis
- ▶ Schizophrenia

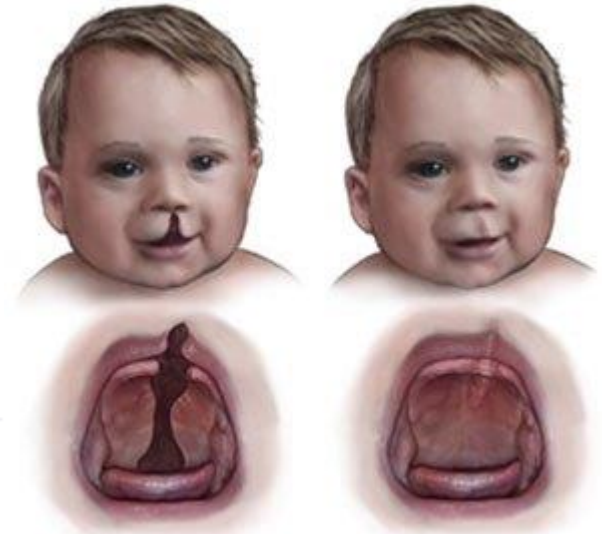
What is a multifactorial birth defect?

Multifactorial birth defects are caused by a combination of **genes** and **environmental** exposures.

In other words, a person can **inherit a gene** that **increases sensitivity** to an **environmental** trigger.

Examples include:

- **Cleft Lip or Palate**
- Certain **Heart** Defects
- **Neural Tube** Defects

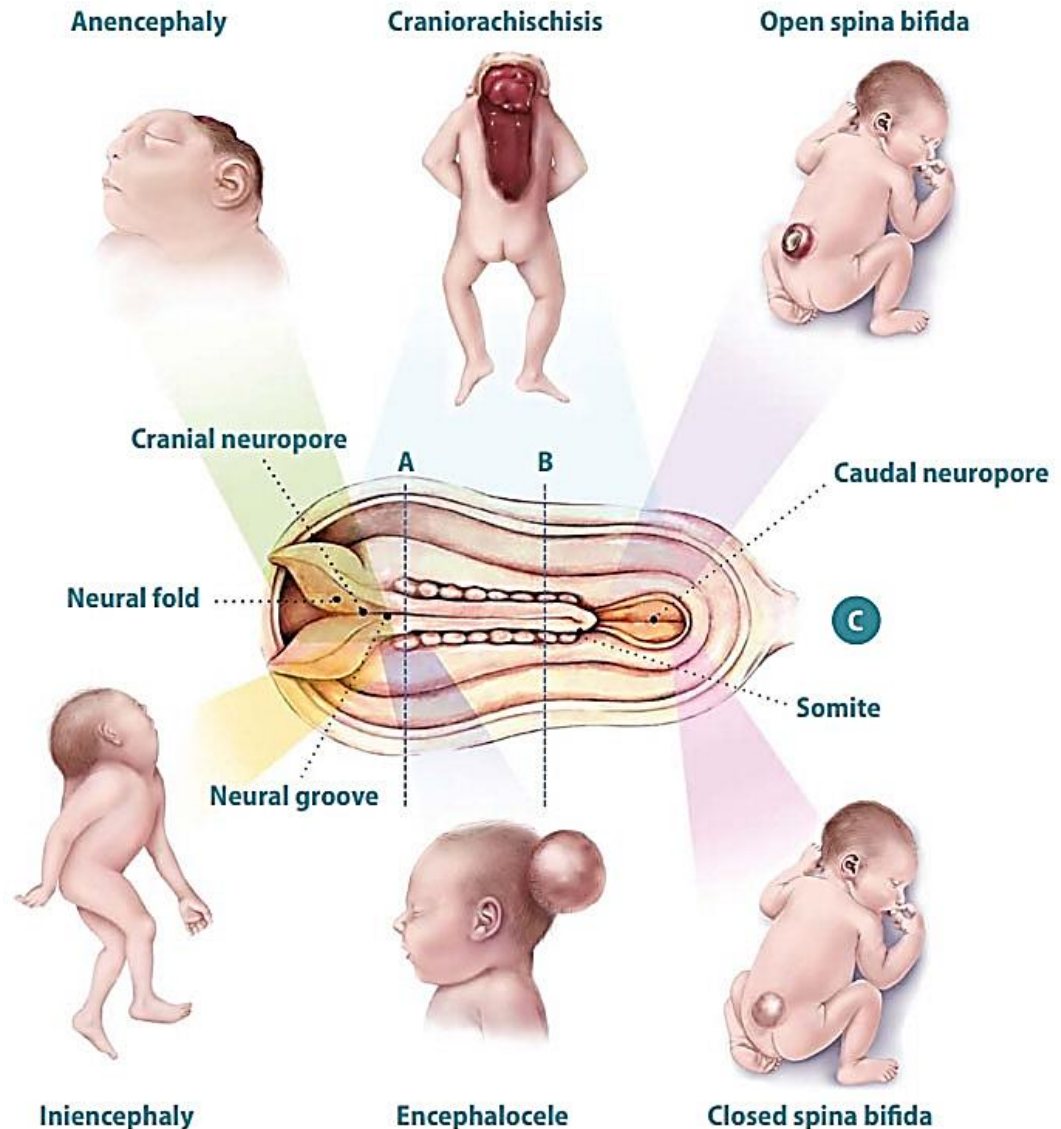


Cleft Lip and Palate

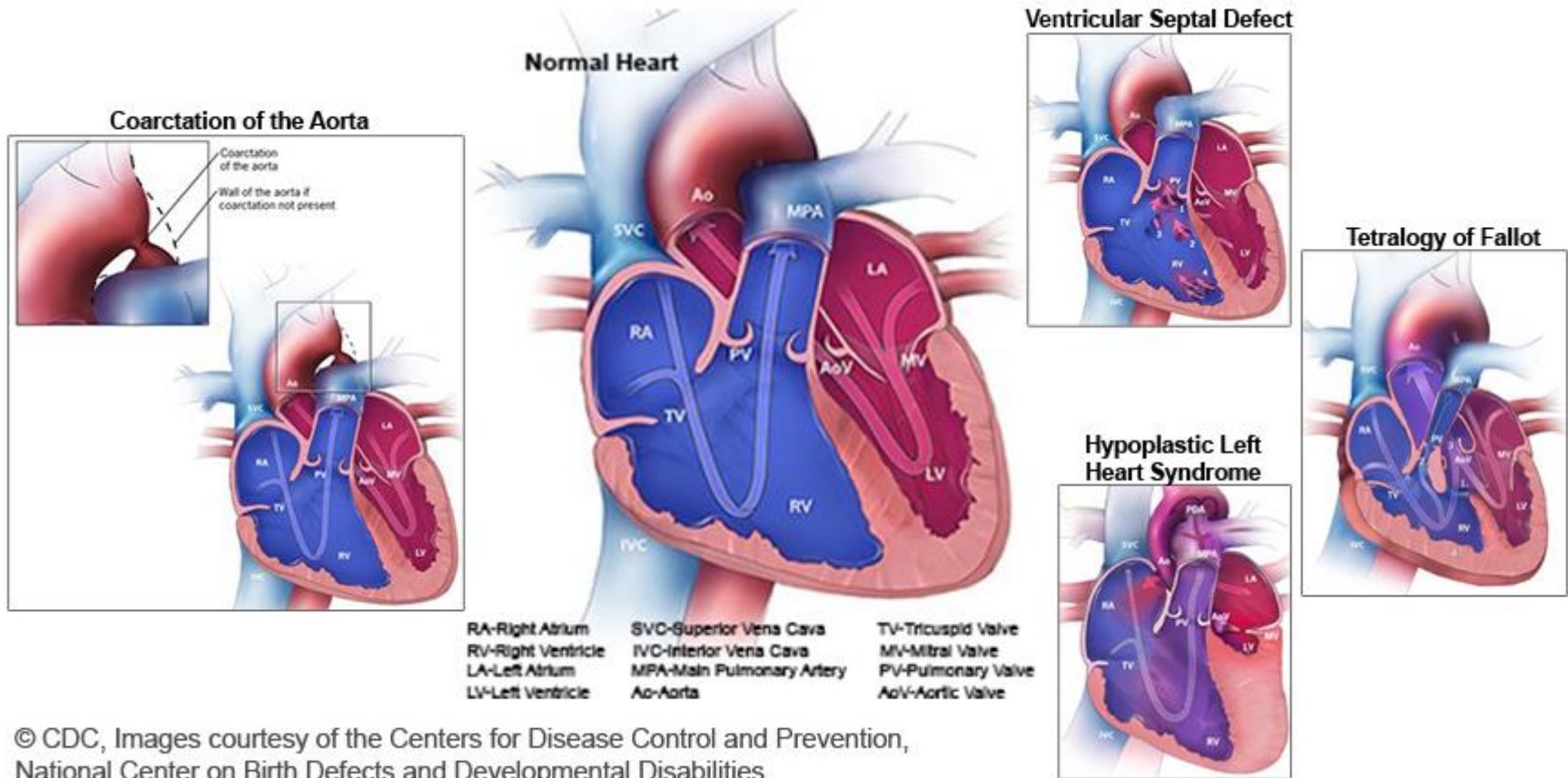
NTDs

NTDs occur when the neural tube **does not close properly**. The neural tube forms **the early brain and spine**. These types of birth defects develop **very early during pregnancy**, often before a woman knows she is pregnant.

The two most common NTDs: **spina bifida** (a spinal cord defect) and **anencephaly** (a brain defect).

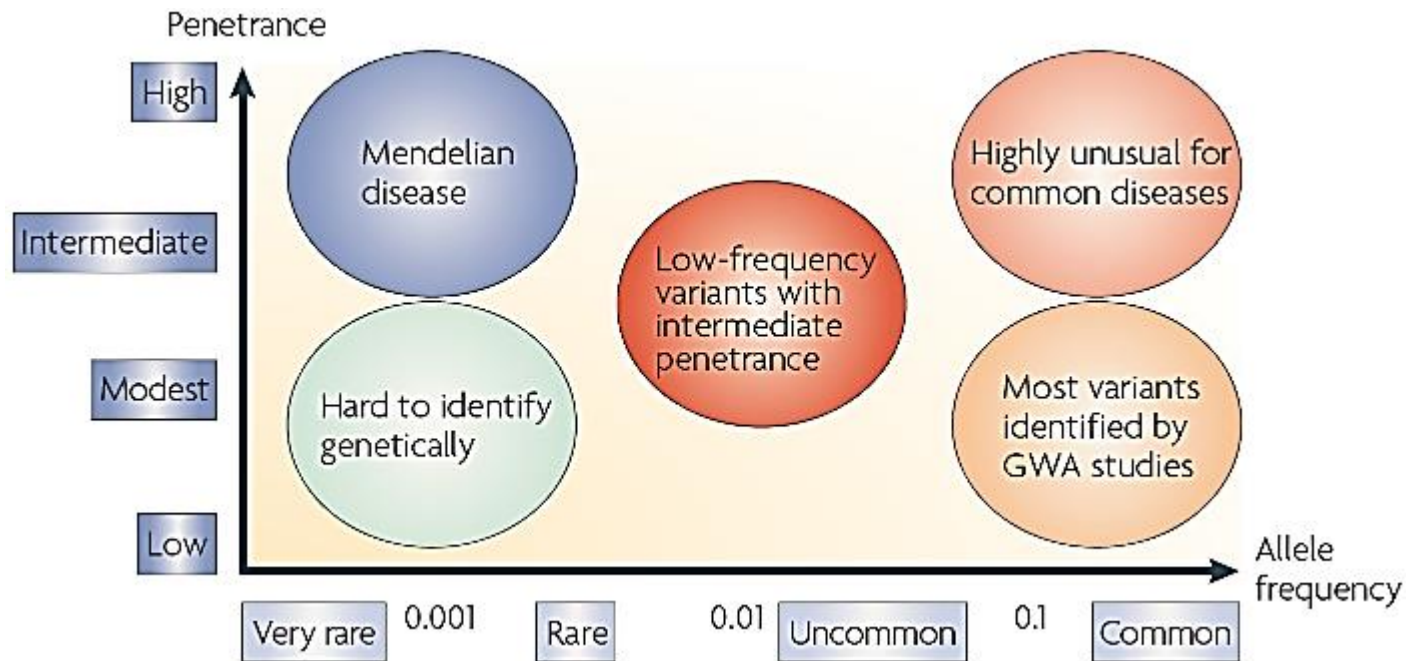


Congenital heart defects (**CHDs**) are the most common type of birth defect.



© CDC, Images courtesy of the Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities

What factors cause multifactorial inherited diseases?

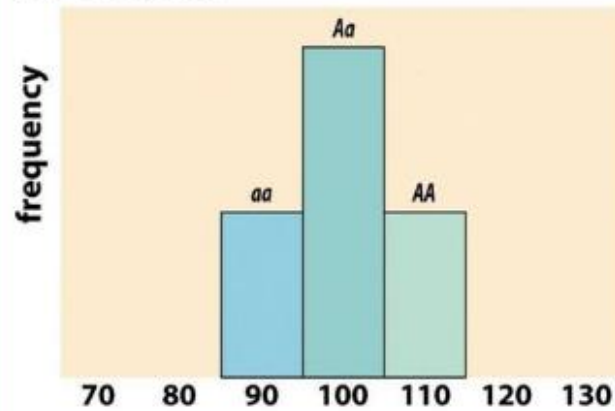


Genome-wide association studies (**GWAS**) are effective in detecting common alleles that contribute to the inherited component of **common multifactorial diseases**. Typically, the alleles identified by this approach have modest effect sizes that cannot **fully account for disease susceptibility**. This discrepancy may exist because it is hard to identify rare alleles with a low to modest penetrance using GWAS. Penetrance is a measure of the proportion of individuals in a population carrying a particular allele that expresses the related phenotype. In contrast to multifactorial diseases, Mendelian diseases have a high penetrance and very rare allele frequency.

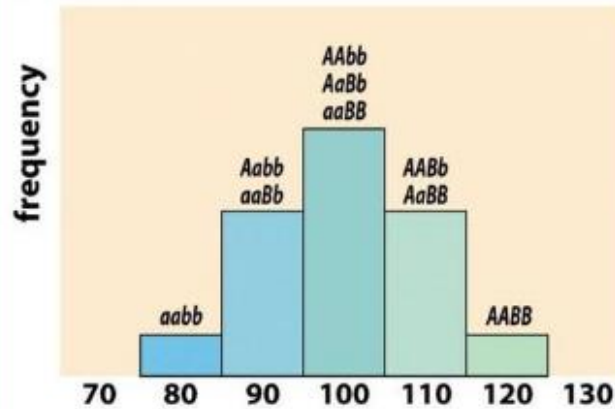
Polygenic Inheritance and the Normal Distribution

- À Inheritance and expression of a phenotype being determined by many genes at different loci, with each gene exerting a small additive effect.
- À Show a continuous distribution in the general population, which closely resembles a normal distribution.
- À It can be seen that as the number of loci increases, the distribution increasingly comes to resemble a normal curve,

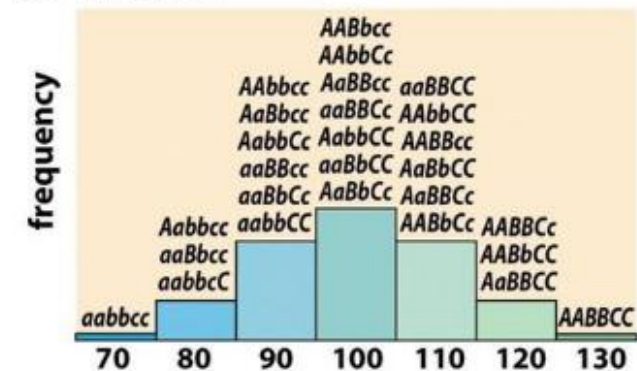
(A) one locus



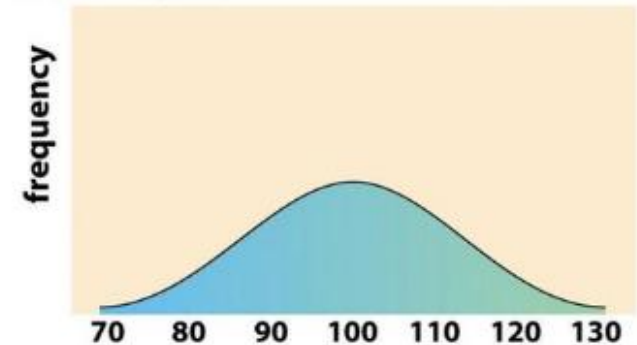
(B) two loci



(C) three loci

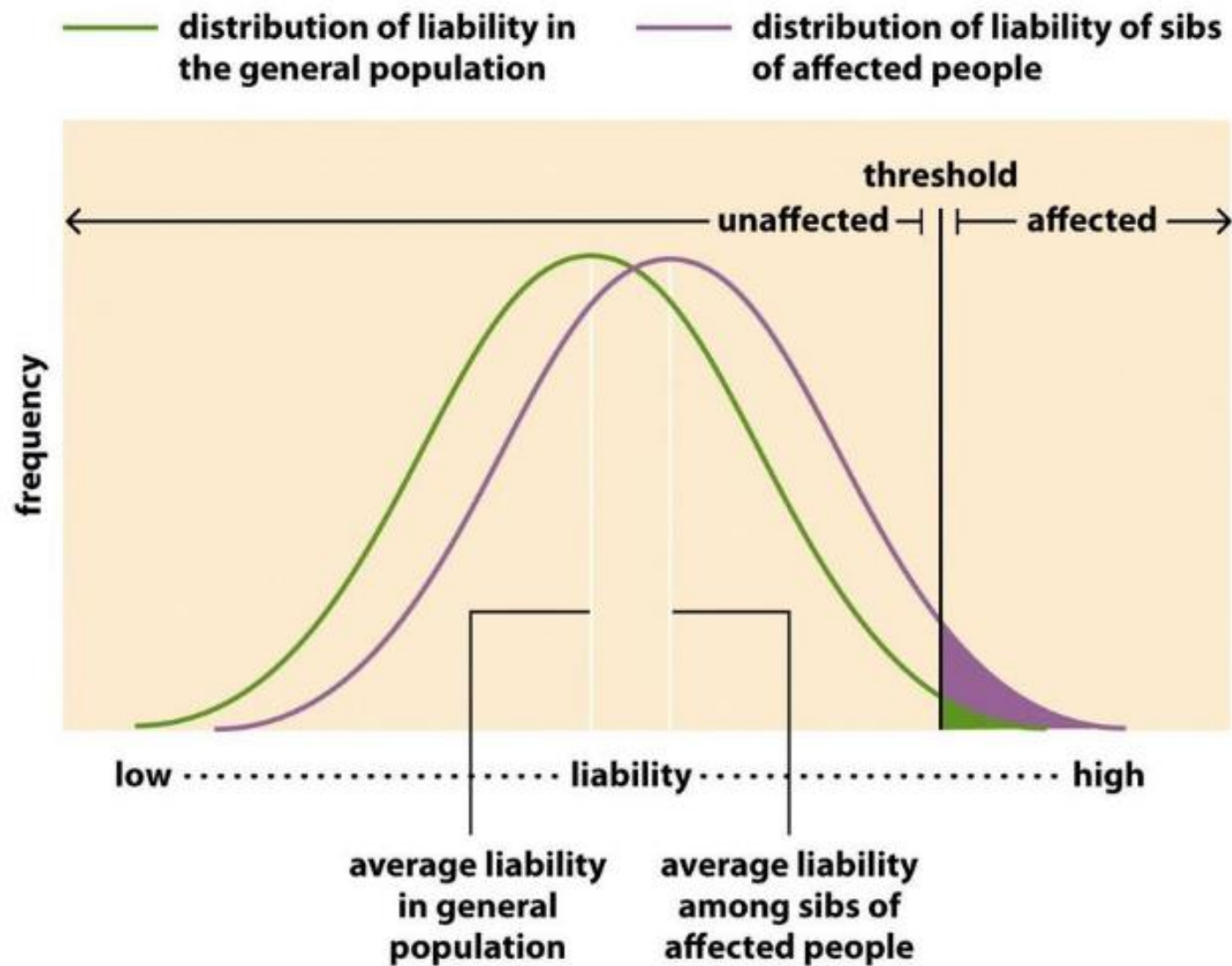


(D) many loci



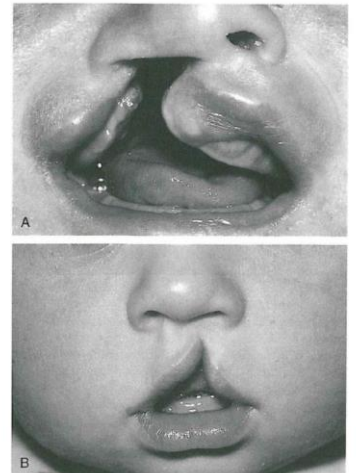
The Liability/Threshold Model

- À Extend the polygenic theory for the inheritance of **discontinuous** multifactorial disorders.
- À All of the factors which influence the development of a multifactorial disorder-genetic or environmental-can be considered as a single entity known as **liability**
- À To account for a discontinuous phenotype with a continuous distribution, a threshold exists above which the abnormal phenotype is expressed



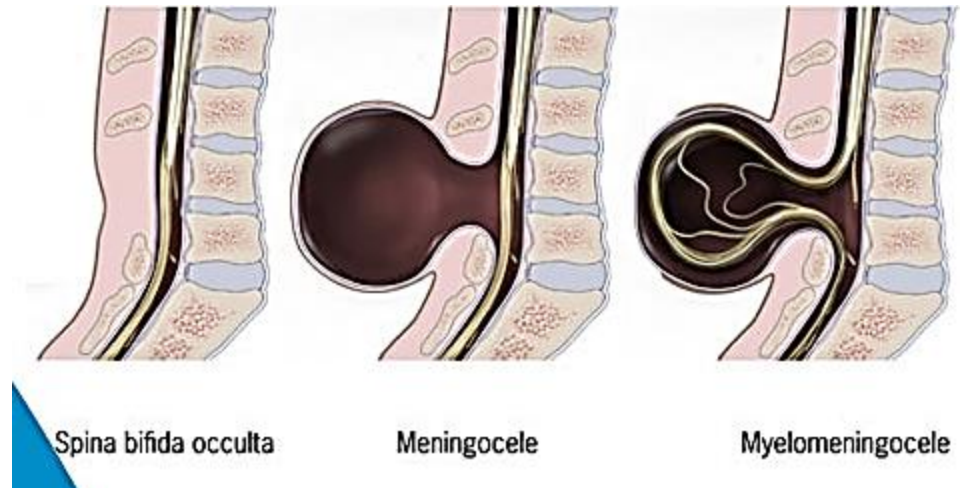
Consequences of the Liability /Threshold Model

- ∧ Provides a simple explanation for the observed patterns of familial risks in conditions
- ∧ The incidence of the condition is greatest among relatives of the most **severely** affected patients, presumably because they are the most extreme deviants along the liability curve
- ∧ For example, in cleft lip/palate the proportion of affected first-degree relatives is
 - ∧ 6% if the index patient has bilateral cleft lip and palate,
 - ∧ 2% if the index patient has a unilateral cleft lip



*What is **the most common** fetal anomaly?*

- Heart defects
- Cleft lip/palate
- Down syndrome
- NTDs: Spina bifida
- Clubfoot
- Hypospadias



Rare birth defects

Phocomelia syndrome is a **rare** birth defect characterized, in most instances, by **severe malformation of the extremities**. Infants born with this condition will have **arms** and/or **legs** that are severely shortened or sometimes **completely** absent.





فوکوملیا: ناهنجاری بدو تولد با علل مختلف محیطی و ژنتیکی

۱. عوارض استفاده از داروی **تالیدومید در زمان بارداری** منجر به نقایص **بدو تولد بیش از ۱۰ هزار نوزاد** در سراسر جهان شد، یکی از دلایل عمده **فوکوملیا** مصرف این دارو توسط مادران در دوران بارداری است.

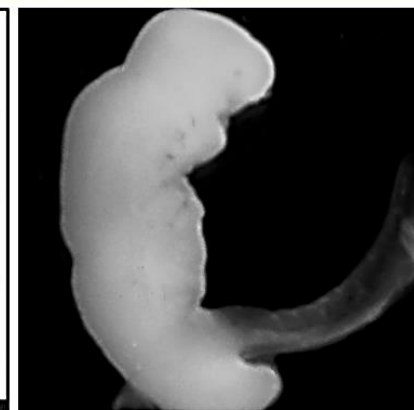
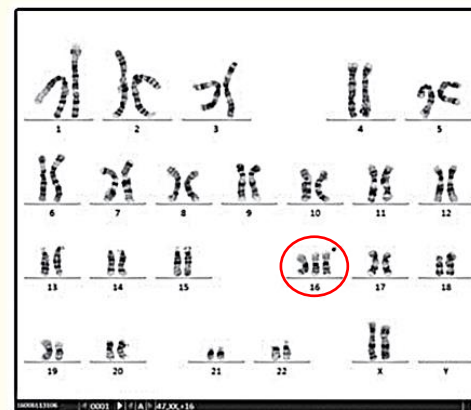
۲. سندرم **Roberts** یا **تالیدومید کاذب**، ناهنجاری بدو تولد نادری است که با مالفورماسیون های متعدد به صورت **عدم تشکیل استخوان های بلند اندام ها (فوکوملیا)**، ناهنجاری های جمجمه و صورت مانند **شکاف کام و لب شکری** مشخص می شود و دارای **منشا ژنتیکی** می باشد.

Roberts syndrome is caused by mutations in the establishment of the cohesion 1 homologue 2 (ESCO2) gene located on chromosome 8.



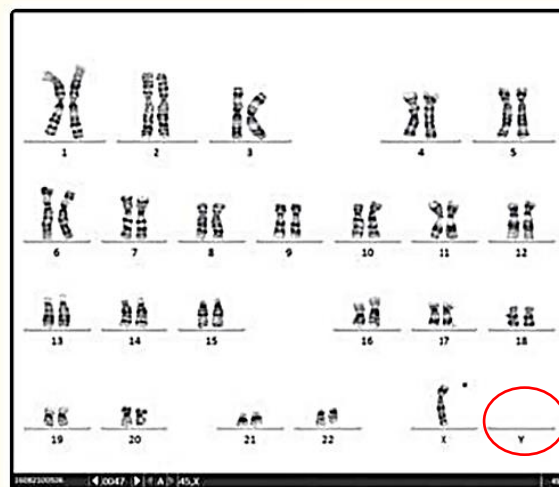
Genetic Abnormalities in the Conceptus: *Aneuploidy* and *Copy Number Changes*

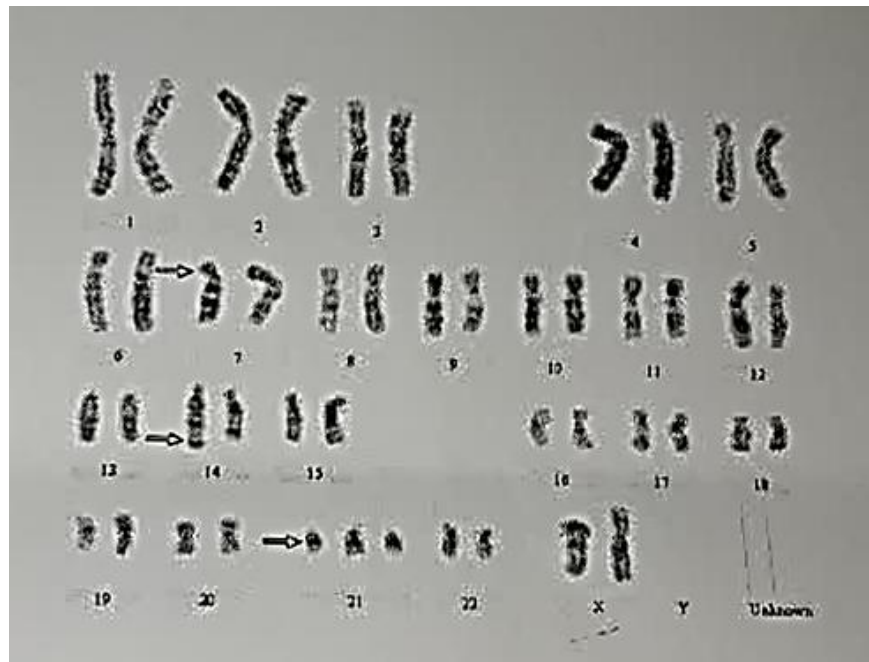
- Aneuploidy is a common finding in both **sporadic** and **recurrent losses**.
- The overall incidence of **cytogenetic abnormalities** is somewhat lower in recurrent than in sporadic losses (30–50% vs 70%, respectively).
- This is because **recurrent pregnancy loss (RPL)** is often attributable to a **non-genetic cause**.
- Although chromosomal abnormalities are generally similar in recurrent and sporadic losses, **trisomies** are less common in RPL.



*Genetic Abnormalities in the Conceptus: **Aneuploidy***

- Nonetheless, aneuploidy accounts for a meaningful proportion of recurrent losses.
- Among those with RPL and prior chromosomally **normal** losses, subsequent losses are also **likely** to be chromosomally normal.
- When prior losses are attributable to **aneuploidy**, subsequent losses are also likely to be aneuploid.
- Cases of **chromosomally abnormal RPL** may be related to a yet undiscovered meiotic regulation defect.
- While **therapeutic** options are **limited**, in vitro fertilization (IVF) with preimplantation genetic testing may be useful in cases of recurrent aneuploidy loss.



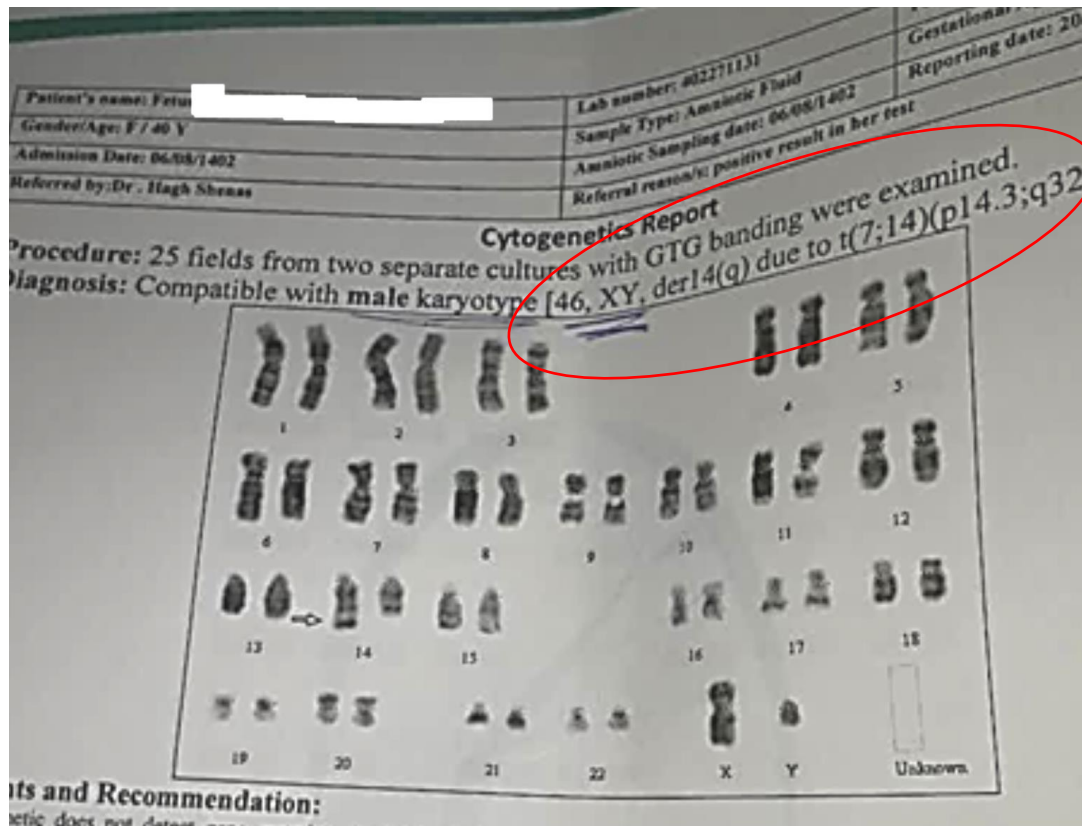


فرزند اول

Procedure: 20 fields from two separate cultures with GTG banding were examined.

Diagnosis: The karyotype is indicative of apparently a female Down syndrome with chromosomal constitution of $47XX, 21+, t(7;14)(p14;q32.3)$.

Conclusion: Due to the possible recurrence of the genetic condition, prenatal diagnosis for parent at 10-12 weeks of gestation is recommended in the future pregnancies.



جنین دوم

رای قاضی ویژه کمیسیون

درخصوص درخواست مورخ ۱۴۰۲/۰۸/۲۵ خانم [نام] فرزند [نام] باکدملی [نام] مبنی بر سقط جنین، با توجه به محتویات پرونده و به طور مشخص مستندات و مدارک پزشکی ارائه شده و تحصیلی، معاینات انجام شده، نظریه متخصصان مربوطه به شرح منعکس در صورتجلسه کمیسیون و اینکه حسب سونوگرافی صورت پذیرفته، نامبرده در حال حاضر دارای **حاملگی ۱۸ هفته و ۴ روز** از زمان شروع آخرین قاعدگی می باشد. و همچنین اینکه طبق آزمایشات فنی معموله جنین وی دچار بارشیل تریزومی کروموزوم ۷ و آرنزی کوریوس کالوزوم می باشد و سایر امارات و قرائن مندرج در پرونده، شرایط مقرر در بند ج ماده ۵۶ قانون حمایت از خانواده و جوانی جمعیت احراز می گردد. از این رو با لحاظ اظهارات و اعلام رضایت ولی/زوج، جنین/زوجه مزبور، رای بر جواز اسقاط جنین ناهنجار موصوف با اعتبار حداکثر تا پایان روز ۱۴۰۲/۰۸/۲۵ صادر می شود. رای صادره ظرف مدت یک هفته از تاریخ ابلاغ قابل اعتراض در شعبه اختصاصی دادگاه تجدیدنظر استان اصفهان می باشد.

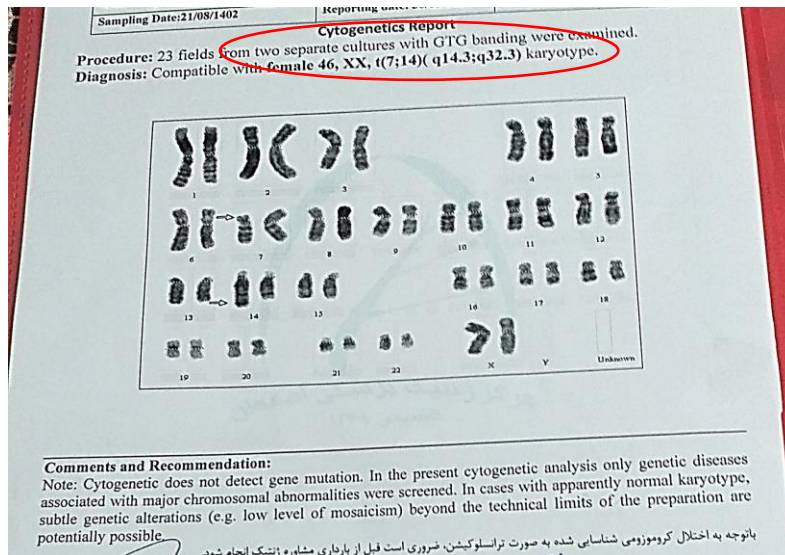
نوروزی

قاضی ویژه کمیسیون ماده ۵۶ قانون حمایت از خانواده

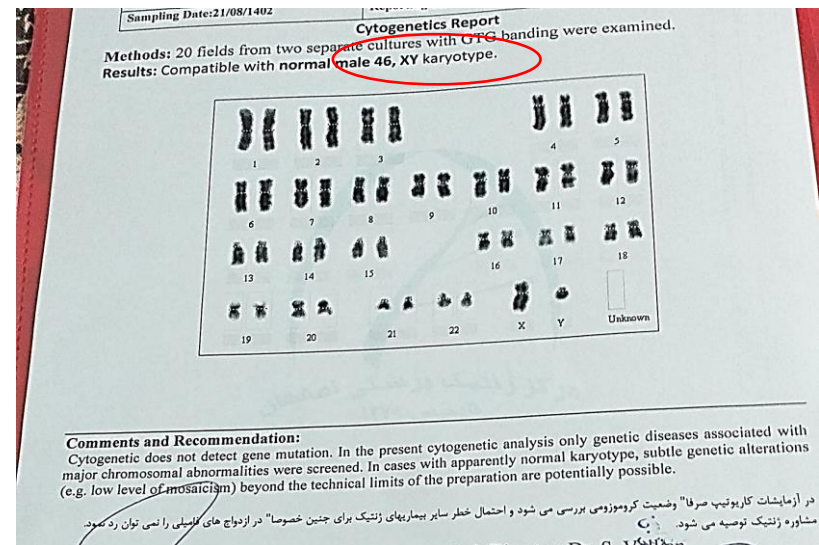
و جوانی جمعیت در استان اصفهان

کاریوتایپ مادر و پدر

مادر



پدر



نمونه ی توالی یابی والدین جهت پیشگیری از تولد نوزاد ناهنجار

Gene	Variant coordinates	Chromosomal location	Associated disease	Phenotype MIM number	Zygosity ^c	ACMG Classification ^d	Inheritance ^e
CFTR NM_000492	Exon27 c.42761>C p.S1426P	chr7- 117306995 T>C	Cystic fibrosis	219700	Het	Likely Pathogen	AR
IFNAR2 NM_000874	Exon6 c.498_499insTC p.V169Sfs*18	chr21- 34621116 T>TTC	Immunodeficiency 45	616669	Het	Likely Pathogen	AR

مادر

Gene	Variant coordinates	Chromosomal location	Associated disease	Phenotype MIM number	Zygosity ^c	ACMG Classification ^d	Inheritance ^e
DNM2 NM_001005360	Exon2 c.214C>T p.Q72X	chr19- 10870466 C>T	Lethal congenital contracture syndrome 5	615368	Het	Likely Pathogen	AR
TNFRSF13B NM_012452	Exon3 c.204dupA p.L69Tfs*12	chr17- 16852291 A>AT	Immunodeficiency, common variable, 2	240500	Het	Likely Pathogen	AR

پدر

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