

An Approach to Birth Defects:
Perspectives in
Dysmorphology



Adam and Eve
Romulus Vuia (1922)



Cassatt children, Mary Cassatt

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Objectives



See course web page for full objectives

Read : 280-284, 289-290 (not Bayes theorem section)

- Understand that birth defects are common and have a major impact on health
- Recognize normal variants, major anomalies, and minor anomalies, and know they may serve as clues to diagnoses
- Know that four basic different kinds of errors of morphogenesis can occur. Understand what they are and how they might arise.
- Know what is meant by syndrome, field defect or sequence, and association
- Be familiar with how to sensitively and comprehensively approach birth defects in patients

In the United States...

- Every 8 seconds a baby is born; 10,799 babies are born daily
- Every 3 minutes a baby is born with a birth defect
- 17 babies die due to a birth defect each day
- More than 1 in 5 infant deaths are due to birth defects

**Birth defects are the leading cause of infant mortality with
20 - 25% of perinatal deaths due to lethal birth defects** ✦

10% of deaths in infants weighing 500 - 1500 gm
50% of deaths in infants > 1500 gm

•* CDC annual estimate of 150,000 babies born with birth defects
•Source: National Center for Health Statistics, 1998 final natality and 1998 period linked birth/infant death data.
Prepared by March of Dimes Perinatal Data Center, July 2000



✦

Incidence of
Major Birth Defects in Infants

3%



Causes of Birth Defects

- Multifactorial: 20-30%
- Single gene disorders: 10-20%
- Chromosomal: 15%
- Infection: 2.5%
- Maternal diabetes: 1.5%
- Maternal medications: 1-2%
- Rest unknown

Empiric Recurrence Risks (%) for Selected Birth Defects

Condition	Affected Relatives(s)		
	<u>None</u>	<u>1 sib/parent</u>	<u>2 sibs / sib & parent</u>
Cleft lip/palate	0.1	4	10-11
Neural Tube Defect	0.1	3	8
Heart Defect	0.3	4-5	10-11

The risk of having any one major birth defect is less than 1% but this risk increases significantly if other relatives have same birth defect



Dysmorphology: study of abnormal forms

Dysmorphic: abnormal appearing

A dysmorphologist helps assess the extent, etiology, recurrence risk and management options of congenital anomalies.

Congenital: at birth, eg. born with

Anomaly: abnormality

*Just because it's congenital
it doesn't mean it's genetic.*

What are the problems?

When did they happen?

How did they arise?

Why did they occur?

What is the diagnosis?

Who else is at risk?

Where can the patient/family get help?



Dysmorphology exam helpful when there is:

- Abnormal growth and/or proportions
- Abnormal or unusual features and birth defects
- Abnormal genitalia and/or puberty
- Psychomotor delays, speech delays, or mental retardation
- Abnormal neuromuscular function
- Bleeding tendencies
- Blindness or deafness
- Metabolic problems (eg. regression in abilities and/or behavior, unusual body odors, excessive unexplained illness)



**Purposes of a
Clinical Genetics Evaluations**

- Recognize medical problems
- Make accurate diagnosis
- Provide prognosis and natural history information
- Discuss management
- Deliver appropriate medical care
- Minimize related complications
- Optimize quality of life
- Determine and provide recurrence risks
- Offer genetic and psychosocial counseling
- Provide anticipatory guidance and education

Classification of Observable Differences



- Major anomalies
- Minor anomalies
- Normal variations

Why? Because anomalies and variants can serve as indicators of altered morphogenesis and clues to patterns of malformation

PHYSICAL EXAM

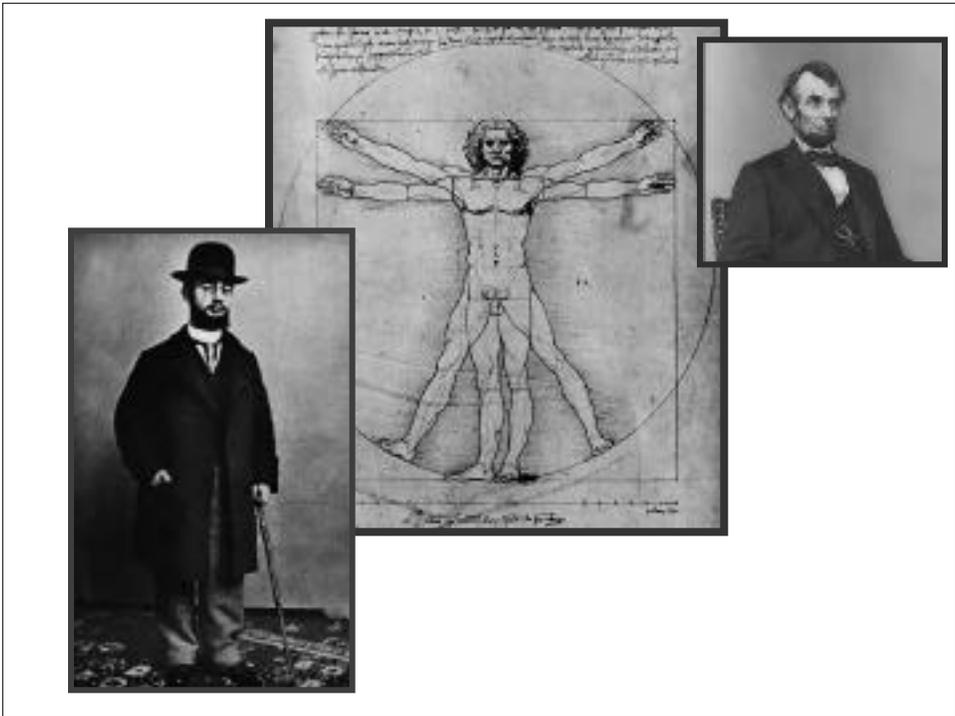
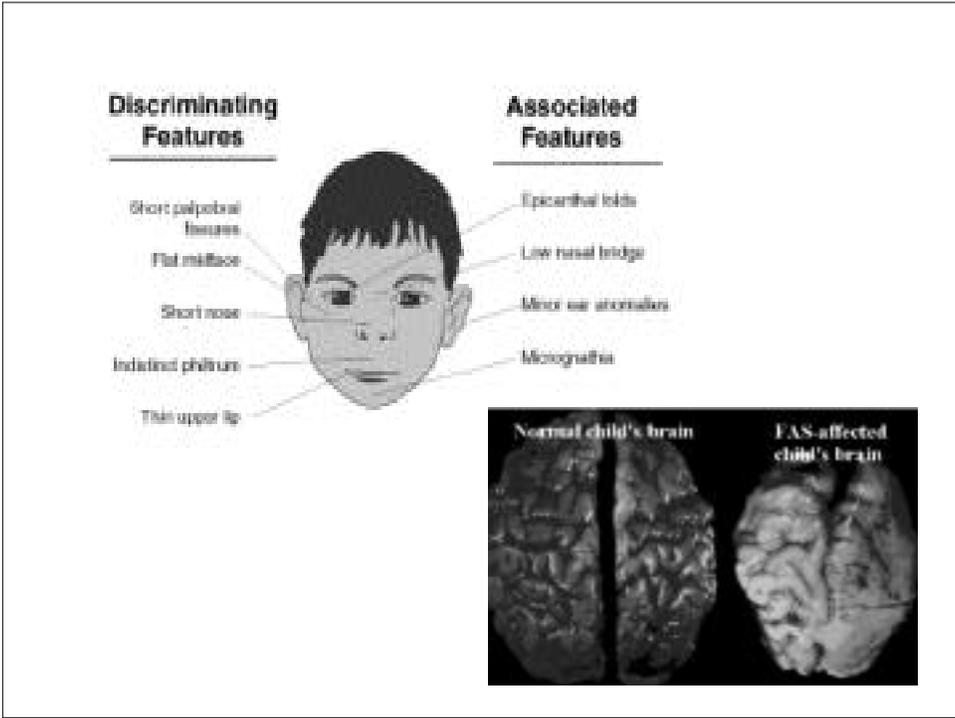
NAME: _____	DATE: _____	EXTREMITIES - PROPORTIONS
BGG #: _____	AGE: _____	General description:
DOB: _____		laxity:
		contratures:
		digital abnormalities:
VITAL SIGNS		LOWER segment: _____ cm
BP: RA _____	LA _____	UPPER segment: _____ cm (HT-LS)
RL _____	LL _____	US/LS ratio: _____ = _____ % (SD)
HR: RR _____	LR _____	ARM SPAN: _____ cm
RDP _____	LDP _____	WRIST SIGN: _____
HEIGHT: _____ in _____ cm (%)		THUMB SIGN: _____
WEIGHT: _____ lbs _____ kg (%)		HAND: R _____ cm (%)
		L _____ cm (%)
HEAD - NECK		MIDDLE FINGER: R _____ cm (%)
General description:		L _____ cm (%)
HEAD CIRCUM.: _____ cm (%)		PALM: R _____ cm (%)
Cranium/Sutures:		L _____ cm (%)
Hair distribution:		FOOT: R _____ cm (%)
Eyes: IC: _____ cm (%)		L _____ cm (%)
OC: _____ cm (%)		Finger to Hand: _____ cm (%)
IP: _____ cm (%)		Hand to Height _____ cm (%)
RPE: _____ cm (%)		Foot to Height _____ cm (%)
LPE: _____ cm (%)		
Ears: shape:		NERVOUS SYSTEM
placement:		Mental status:
R _____ cm (%)		Cranial nerves:
L _____ cm (%)		Muscle bulk and tone:
Philtrum: _____ cm (%)		Sensation:
Lips:		Motor strength: _____
Palate and mouth:		Deep tendon reflexes:
Teeth:		
Chin:		
Neck:		
TRUNK - ABDOMEN		DIAGRAM TO DOCUMENT FINDINGS
General description:		R FRONT L R BACK L
sternum:		
Breast: spine: Tanner Stage: _____		
Heart:		
Lungs: Chest circumference: _____ cm		
Inter nipple distance: _____ cm		
IND / CC = _____ (%)		
Abdomen:		
Umbilicus:		
Genitalia:		
penile length: _____ cm (%)		
testicular vol.: _____ cm (%)		
Tanner Stage:		
SKIN		RIGHT HAND
General description:		LEFT HAND
Freckles - Iris: _____ Axillary: _____ Inguinal: _____		
# CAL spots: _____ Size range: _____ cm		
# Neurofibromas: _____ Size range: _____ cm		
Hypopigmented lesions:		
Other lesions:		

A Range of Phenotypic Variation is Normal



- “Normal” spectrum of human variation of morphological features with absolutely no medical significance (eg. Epicanthal folds, ‘attached’ vs. ‘unattached ear lobes’,
- Observed in $> 4\%$ of the population



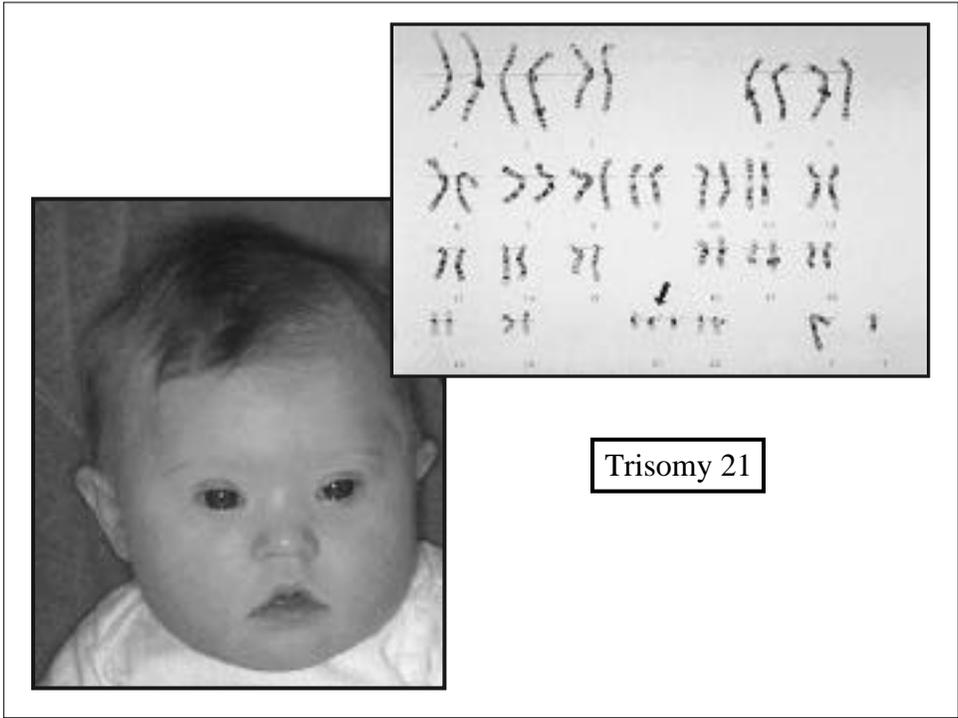


Minor Anomaly



- Minor variations of normal morphological features of little or no known medical, surgical, or cosmetic significance
- Observed in < 4% of the population



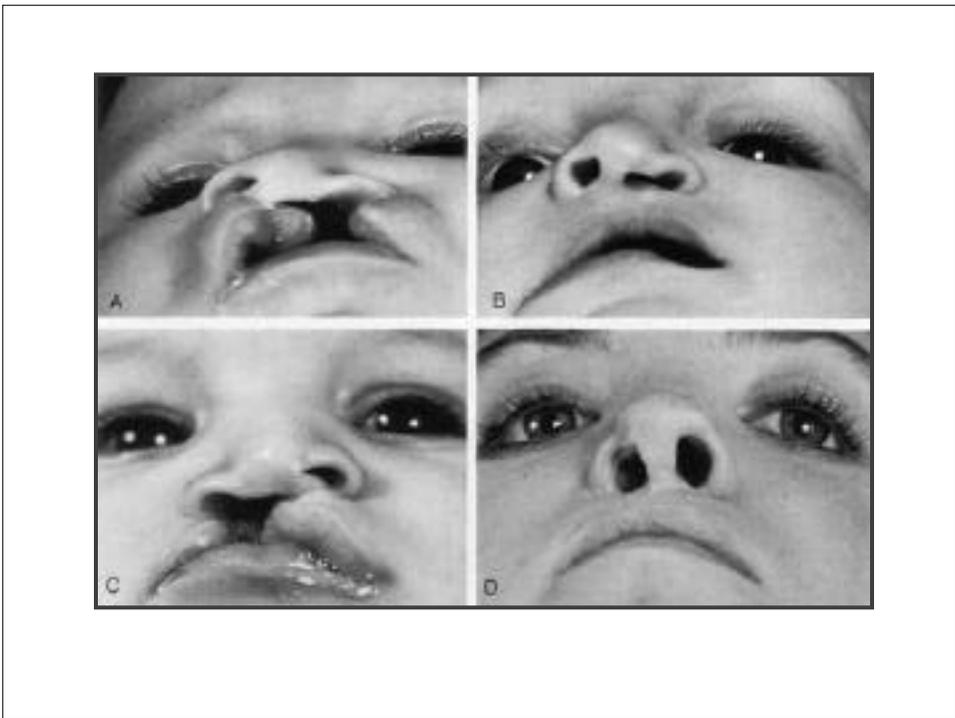


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Major Anomaly

- Abnormality that has medical, surgical, or cosmetic significance



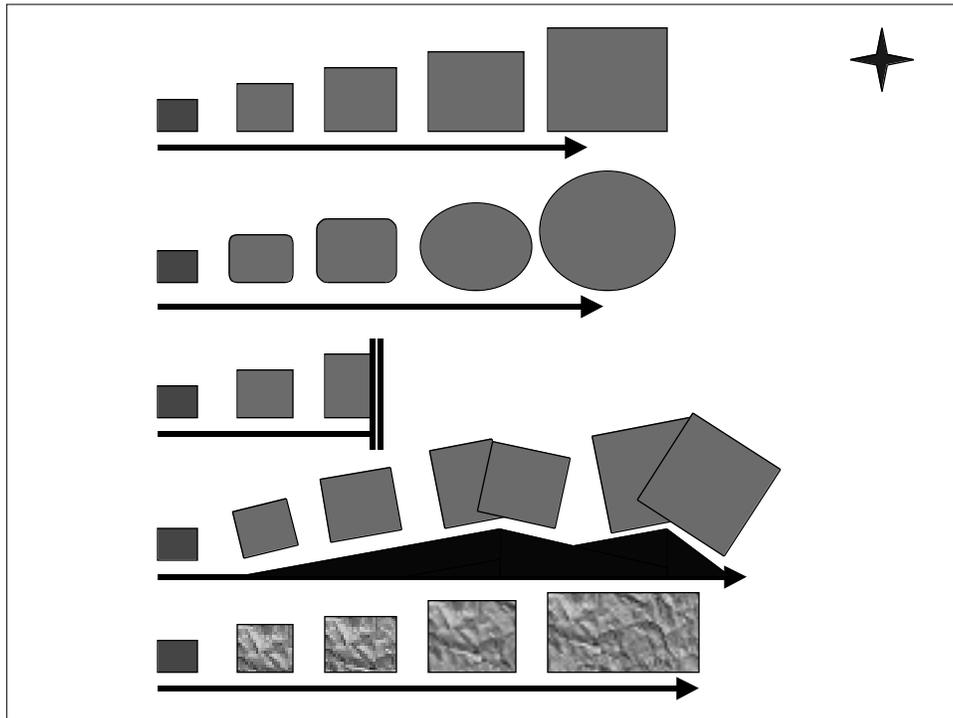




Types of Morphologic Abnormalities



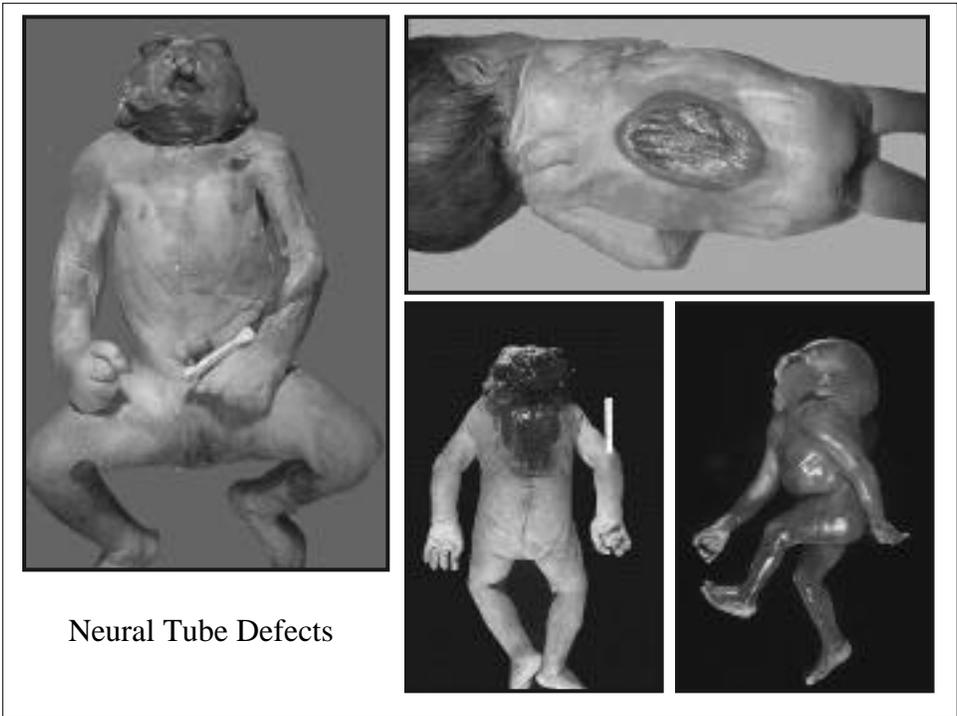
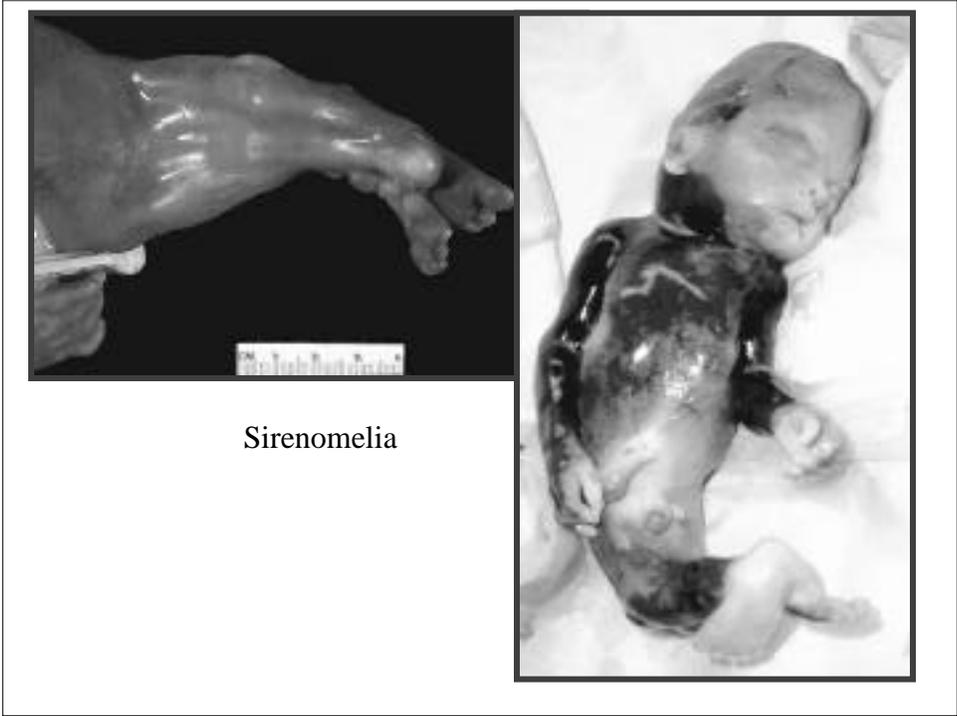
- Malformation
- Deformation
- Disruption
- Dysplasia



Malformation

- Defect of morphogenesis in an organ or structure due to an intrinsically abnormal problem with formation, growth, or differentiation of an organ or structure
 - hypoplasia of an organ or structure (microtia), incomplete closure (NTDs, cleft palate), incomplete separation (syndactaly)







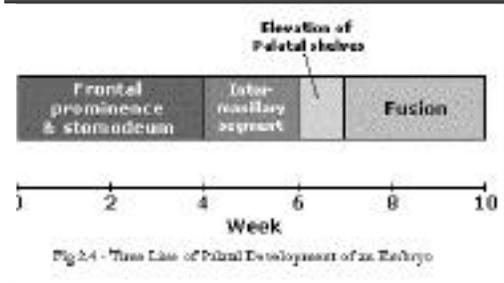
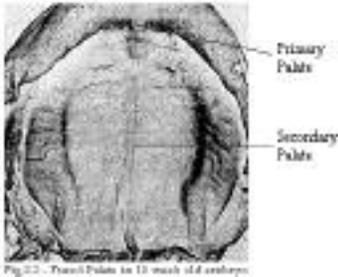
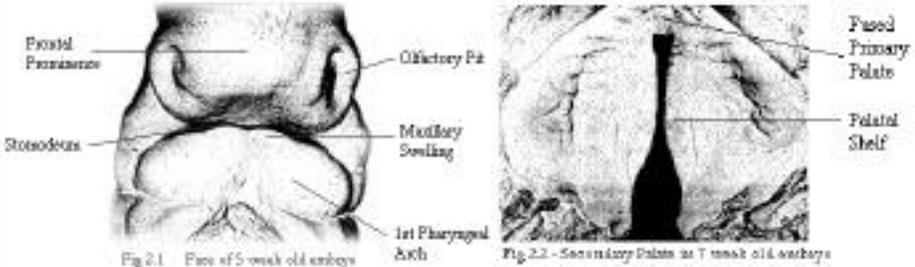
Omphalacele

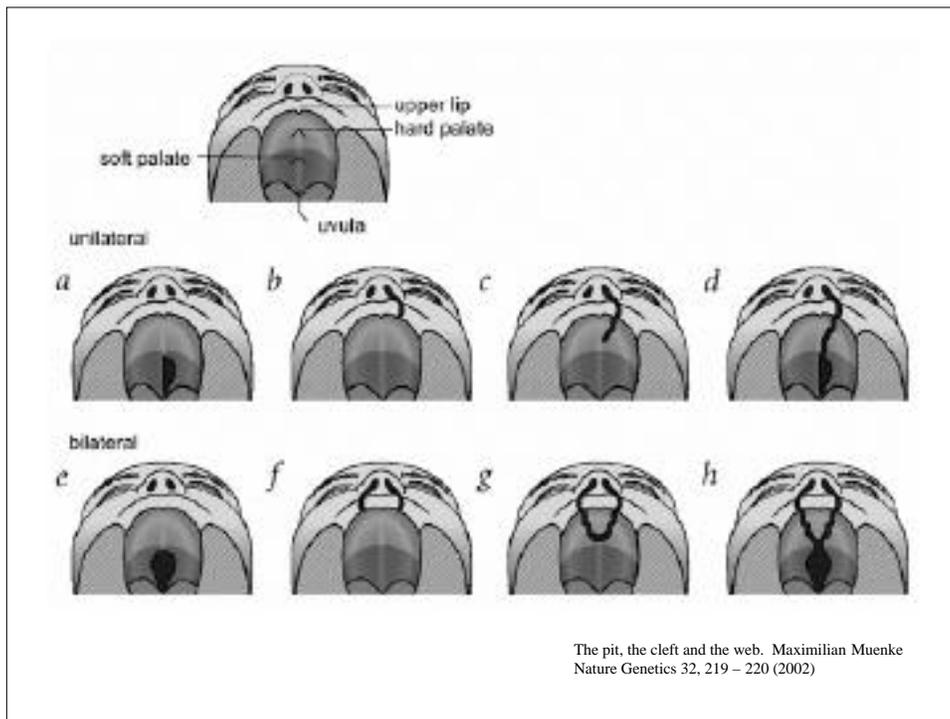
Gastroschisis





Timing is everything!





Malformations are Not Specific

- The same morphological defect, or even a similar pattern of abnormalities, may occur as:
 - An isolated anomaly in an otherwise normal individual
 - A feature in a syndrome, sequence, or association
 - A feature of a chromosome disorder, a single gene defect, multifactorial disorder, or secondary to a teratogenic effect

Autosomal
dominant
Van de Woude
syndrome



Muenke
Nature Genetics 32,
219 – 220 (2002)

Etiologic Heterogeneity

- Grossly similar phenotypic abnormalities and underlying defects of morphogenesis may have very different etiologies.
 - Consider cleft lip and/or palate, most are sporadic, but can be due to:
 - Intrauterine teratogen exposure
 - 22q deletion
 - Primary mandibular hypoplasia
 - Trisomy 13
 - Amniotic Bands
 - Focal dermal hypoplasia
 - Non-syndromic failure of palate closure
 - Kinest dysplasia
 - Gorlin syndrome
 - Autosomal dominant Van de Woude syndrome

Deformation



- Abnormal form or position of a body or region of the body caused by extrinsic non-disruptive mechanical forces on a normally developing structure (fetal constraint)
 - clubfoot, congenital hip dislocation, craniofacial asymmetry, over folded ear.....



Deformity of ear helix due to uterine compression



Deformations due to oligohydramnios

Disruption



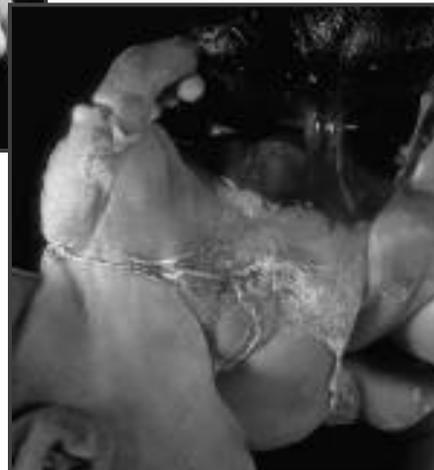
- Defect resulting from a destructive breakdown of, or interference with, a normally developing structure resulting in death of cells or tissue destruction.
- May be secondary to mechanical forces, infections, or even vascular events.
 - Loss of digit due to amniotic band constriction, lack of normal limb development due to intrauterine vascular accident



Disruption of lip formation due to amniotic bands



Amniotic Bands causing multiple disruptions



Dysplasia



- Error of morphogenesis due to the abnormal cellular organization of function in a specific type of tissue most often due to single gene defects
 - Achondroplasia, ectodermal dysplasia, osteogenesis imperfecta,



Ectodermal dysplasia

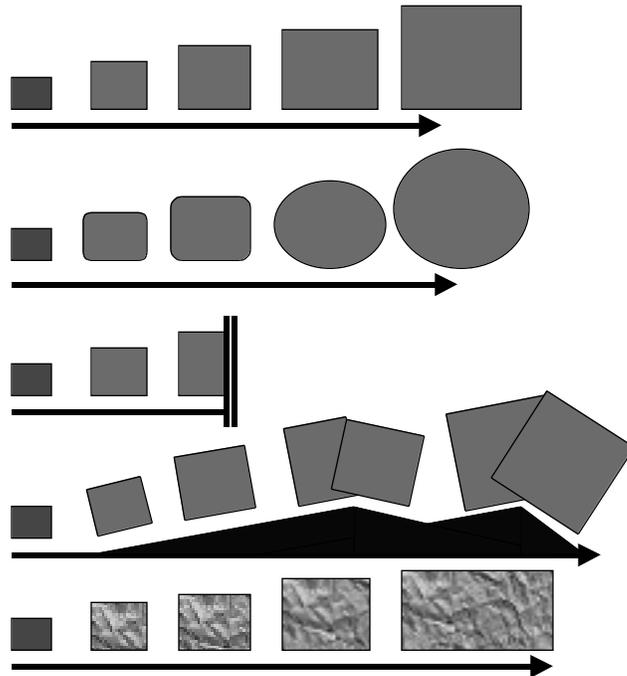


Achondropalsia
Autosomal Dominant



Diastrophic Dysplasia

Autosomal Recessive



Recognizable Patterns of Anomalies

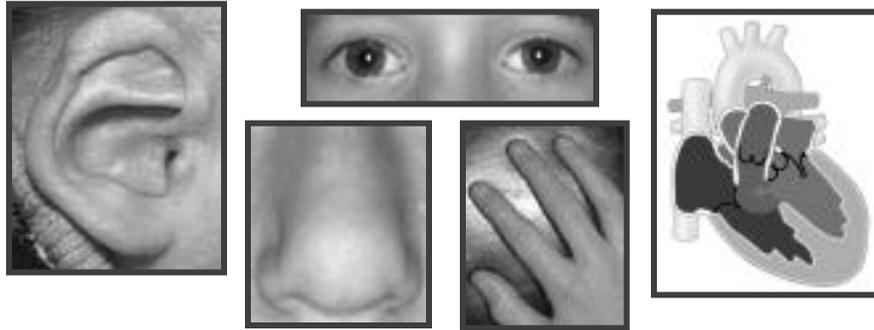


- Syndromes
- Associations
- Sequences or field defects

Consider a genetic condition or syndrome when...



- Multiple anomalies
- More than 3 minor anomalies
- More than one major anomaly
- One major anomaly and a few minor anomalies



Velocardiofacial Syndrome (22q11 deletion)

'Long' face with characteristic facial features:

eyes: Narrow palpebral fissures, puffy lids

ears: over-folded helix and attached lobule;

nose: pear-shaped; square nasal bridge

Hands with tapered fingers and short nail base

Short stature

Developmental delays

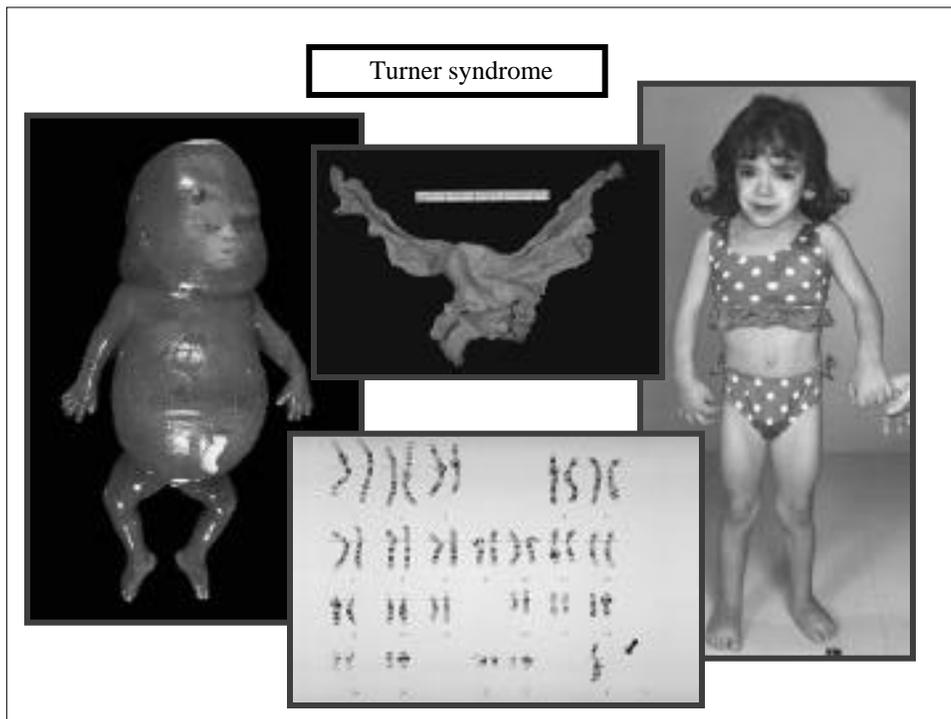
Cardiac anomalies

Palatal defects

Syndrome



- Multiple anomalies in one or more tissues or structures thought to be pathologically related due to a specific etiologic mechanism (chromosome disorder, single gene defect, environmental agent, or unknown factor), not due to a related sequence of defects or field defect.
 - Down syndrome, Williams syndrome, FAS, Turner syndrome, Gorlin syndrome....
- From Greek meaning “running together”



Sequence/Field Defect ★

- Constellation of defects derived from a cascade of effects related to a single known, or presumed, localized abnormality (malformation, deformation, disruption)
 - Potter sequence
 - Renal dysplasia, pulmonary hypoplasia, facial dysmorphism
 - Mandibular hypoplasia (Robin sequence)
 - Cleft palate
 - Meningomyelocele
 - Club foot, hip dislocation, hydrocephalus



Association

- Non-random occurrence of a combination of several anomalies not yet identified as a specific sequence or syndrome that occur more often together than by chance alone.
 - VATER and CHARGE associations

Reasons Why Difficulty in Diagnosing Syndromes may be Encountered

- Some are very rare disorders - not well described
- Problems with lumping and splitting
- Variable expression
- Incomplete penetrance
- Sex influenced or limited expression
- Pleiotropy
- Etiologic heterogeneity

Genetic heterogeneity

- Even when phenotypically similar disorders have clear genetic etiologies, locus heterogeneity, and sometimes even allelic heterogeneity, may complicate laboratory testing and influence diagnosis, counseling, management, and prognosis
 - Locus heterogeneity: Tuberous Sclerosis, PKD
 - Allelic heterogeneity: Craniosynostosis, CF



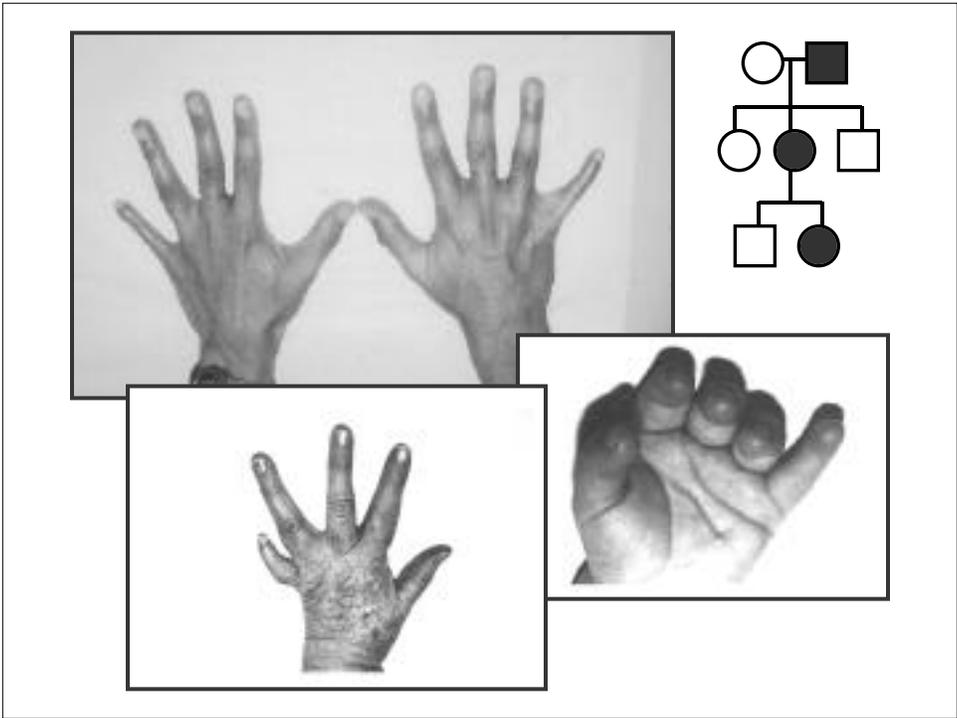
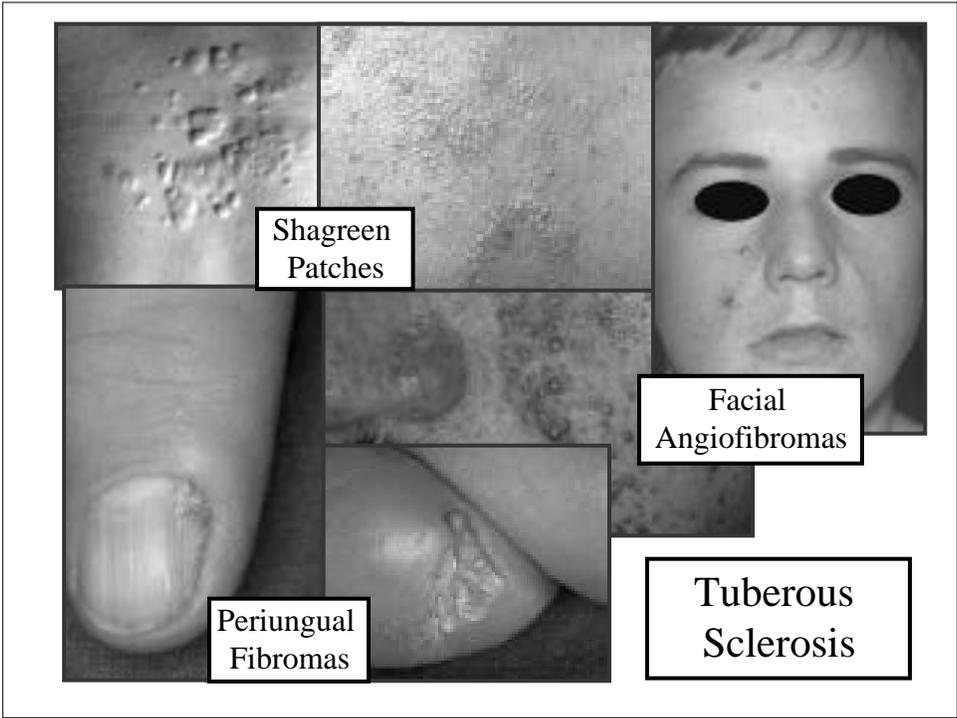
Variable Expression

- Morphological features may be expressed at different degrees of severity in individuals resulting in different levels of dysfunction and problems for individuals having the “same” abnormality, even when due to the same etiology
- Each individual with a particular syndrome, sequence, or association will not have every known feature of that disorder, or all the same features as one another, even if in the same family
- The degree of variable expression may correlate with the degree of pleiotropy in single gene disorders



Incomplete Penetrance

- An “all or none” phenomena referring to the presence or absence of observable phenotypic expression of features of a dominant disease in an individual known to have a mutant allele
- Some individuals with Tuberous Sclerosis appear to have incomplete penetrance



Sex-Influenced or Limited Expression



- Some congenital anomalies and/or genetic syndromes due to autosomal defects are more easily recognized, or only recognized, in individuals of a particular gender
 - Sex influenced: Genital hypoplasia, hypospadias, virilization with hypertrophy of the clitoris
 - Sex limited: Hereditary prostate cancer

Making a diagnosis, even if it's a bad diagnosis, is more useful for patients and their families than having no diagnosis, but a wrong diagnosis is worse than no diagnosis.

Management of Congenital Anomalies

- Conduct careful clinical evaluation
- Review family, prenatal history, and perinatal history
- Obtain diagnostic studies
 - Imaging studies: Photographs, X-rays
 - Laboratory studies: Chromosome, DNA, biochemical assays
- Provide medical management and genetic counseling
- If deceased, request autopsy and specific pathological analyses
- If fetal death or still born, provide parents an opportunity to see and hold baby
 - Name, photograph, obtain hair, memorialize, bury...
- Provide referrals to social work/psychological services and support groups as appropriate

Talking about Birth Defects



- Explain medical concerns openly and honestly
- Humanize abnormal findings and note normal findings
- Use diagnostic/medical terms as appropriate
- Avoid extensive differential diagnoses
- Be careful about premature prognostication
- Check facial expressions and body language
- Listen to family concerns and adhere to their agendas when possible
- Be supportive but not unrealistic or enmeshed
- Provide frequent, honest updates of accurate information
- Provide psychosocial support services