26th Annual General Pediatric Review & Self-Assessment

Nicklaus Children's Hospital

Genetics

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Nicklaus Children's Hospital

Miami, FL

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Disclosure of Relevant Relationship

Dr. Bauer has not had (in the past 24 months) any relevant conflicts of interest or relevant financial relationship with the manufacturers of products or services that will be discussed in this CME activity or in his presentation.

Dr. Bauer will support this presentation and clinical recommendations with the "best available evidence" from medical literature.

Dr. Bauer does not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.

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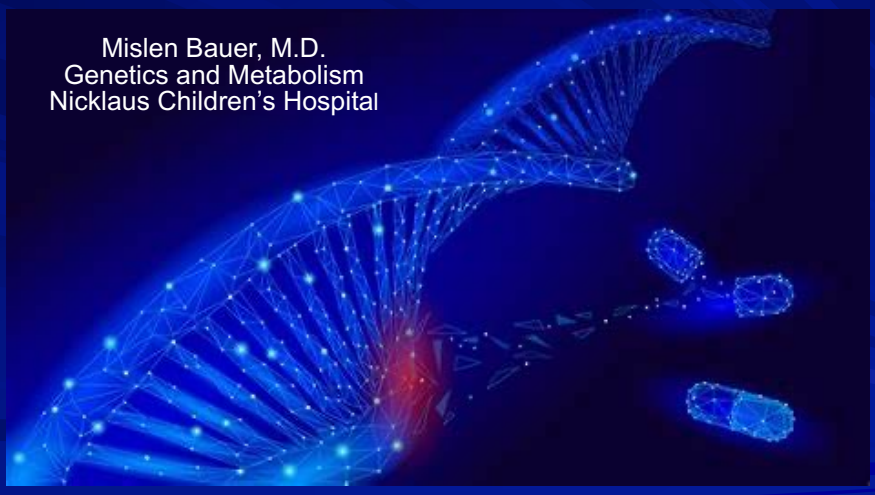
Pediatric Board Review 2023

Mislen Bauer, M.D.
Genetics and Metabolism
Nicklaus Children's Hospital



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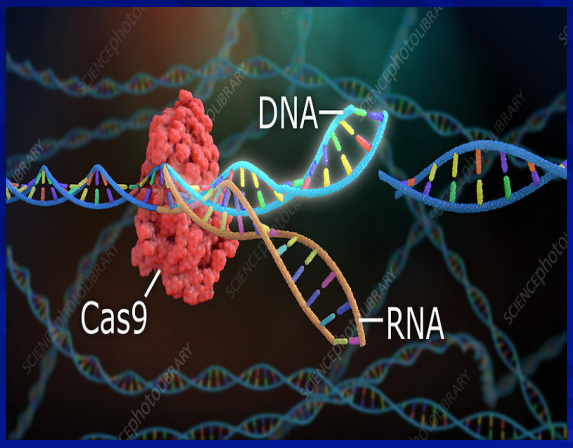
GENETICS

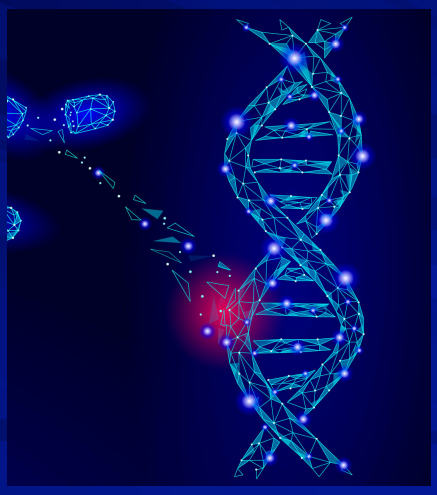
THE FUTURE IS NOW



New breakthroughs can cure diseases and save lives,
but how much should nature be engineered?

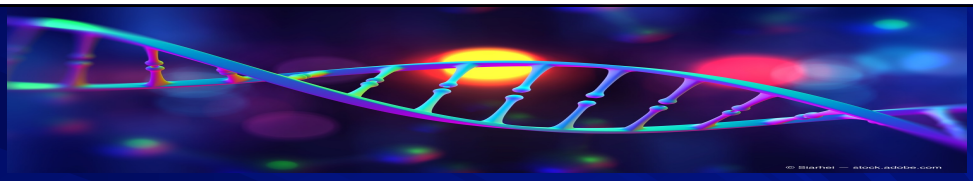
4

Genetic Etiologies



- Chromosome Abnormality
- Single Gene Disorder
- Multifactorial Disorder

5



Genetic Disorders

Chromosome Abnormalities

6

Question #1

- A 1 day old infant in the newborn nursery is found to have a harsh holosystolic murmur on physical examination. The neonate was born at 39 weeks gestation to a 36 years old woman who opted to defer prenatal screening. Review of medical records shows no family history of genetic or chromosomal disorder. The infants`s vital signs are appropriate for his age. The rest of the PE shows a flat facial profile, protruding tongue, and small ears. Which of the following likely occurred prior to conception?

7

A. Chromosomal deletion

B. Chromosomal translocation

C. Gene inactivation

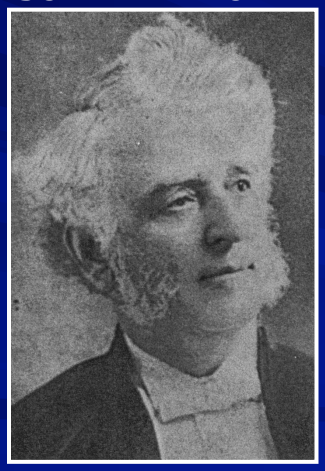
D. Meiotic nondisjunction

E. Trinucleotide repeat expansion

8

Down Syndrome

John L.H. Down



1828-1896

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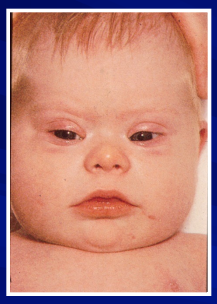
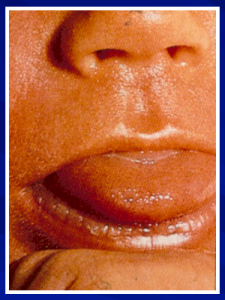
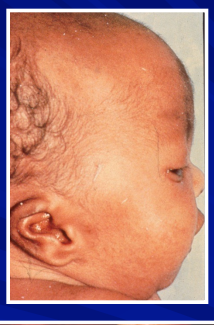
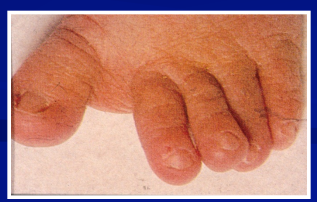
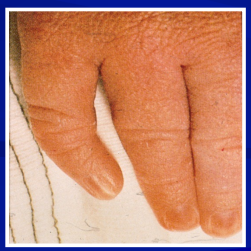
Down Syndrome











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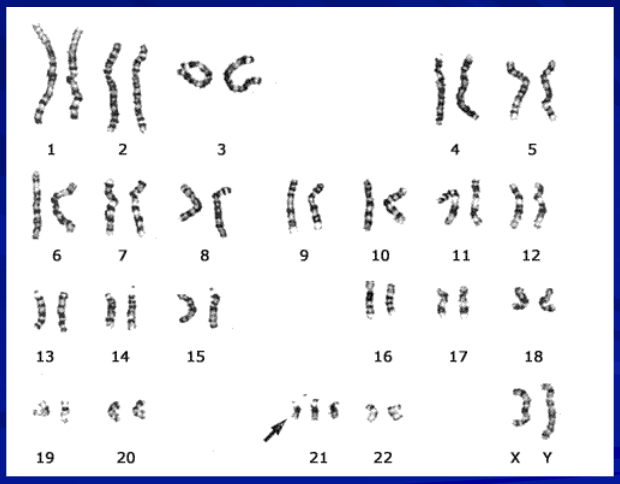
Trisomy 21
Down Syndrome



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Trisomy 21 (Down Syndrome)

- **Clinical Features**
  - Upslanting palpebral fissures, epicanthal folds
  - Depressed nasal bridge
  - Flat Occiput
  - Single transverse crease, fifth finger clinodactyly, sandal gap
  - Hypotonia
  - Developmental delay
- **Etiology**
  - 95% sporadic non-disjunction
  - 4% translocation
  - 1% mosaic

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Question #2

- A newborn is examined after an induced vaginal delivery for fetal growth retardation. On visual inspection the infant has low set ears, a small mandible, and a prominent occiput. The neonate has a weak cry and an increased tone of the extremities, including clenched hands with second and fifth digits on top of the third and fourth digits. Cardiac auscultation reveals a harsh, IV/VI holosystolic murmur heard best at the left sternal border. The infant is transferred to the neonate intensive care unit for further workup and management, which of the following is the most likely chromosomal abnormality in this infant?

13

A. 5p deletion

B. 22q11 deletion

C. 47,XX,+13

D. 47,XX+18

E. 47,XX+21

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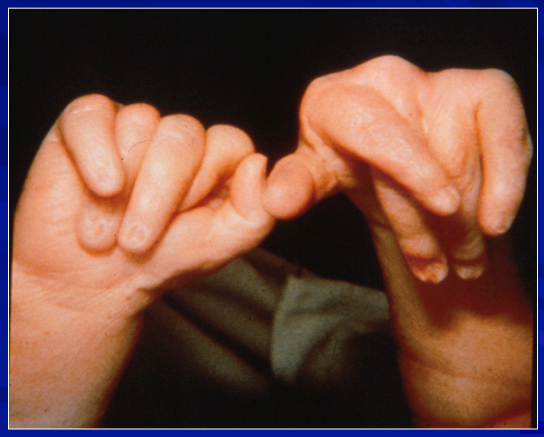
Trisomy 18 (Edwards Syndrome)



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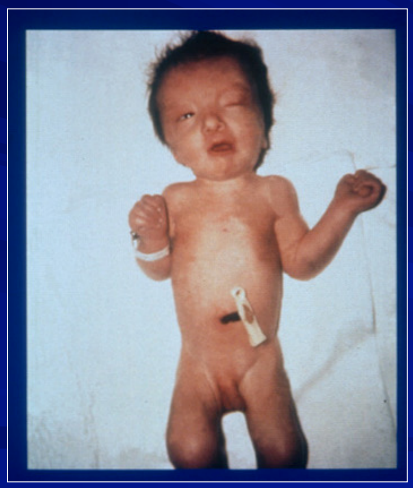
Trisomy 18 (Edward Syndrome)



- Microcephaly
- Developmental delay
- Heart defects
- Clenched hands with overlapping fingers
- Micrognathia
- Rocker-bottom feet

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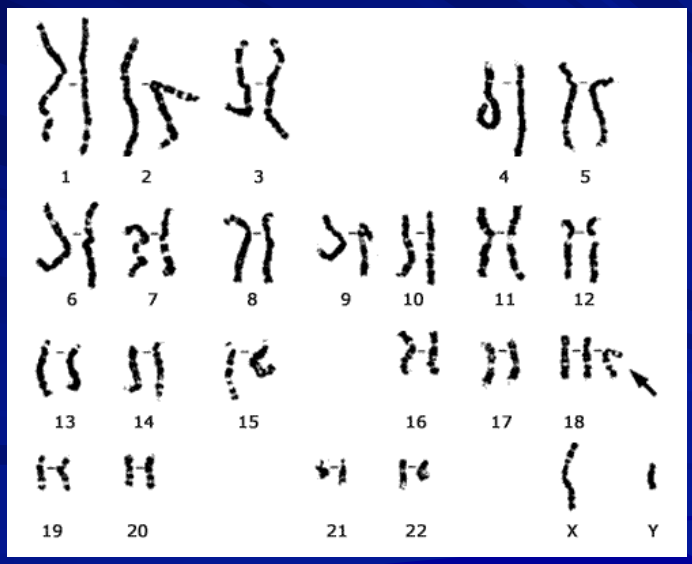
Trisomy 18



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Question # 3

A small for gestational age infant is born prematurely to a 38 year old woman who had inconsistent prenatal care. Physical examination shows a small head and eyes as well as cleft lip and palate. There is a small, round punched out lesion with an overlapping thin membrane on the patient`s scalp. A small, membranous sac with a loop bowel protrudes from the patient`s abdominal midline. The infant is transferred to the neonate intensive care unit for further workup and management.

18

Which of the following is most likely responsible for this patient condition?

A. Down Syndrome
B. Edwards Syndrome
C. Maternal nicotine use
D. Maternal phenytoin ingestion
E. Maternal rubella infection
F. Patau Syndrome
G. Williams Syndrome

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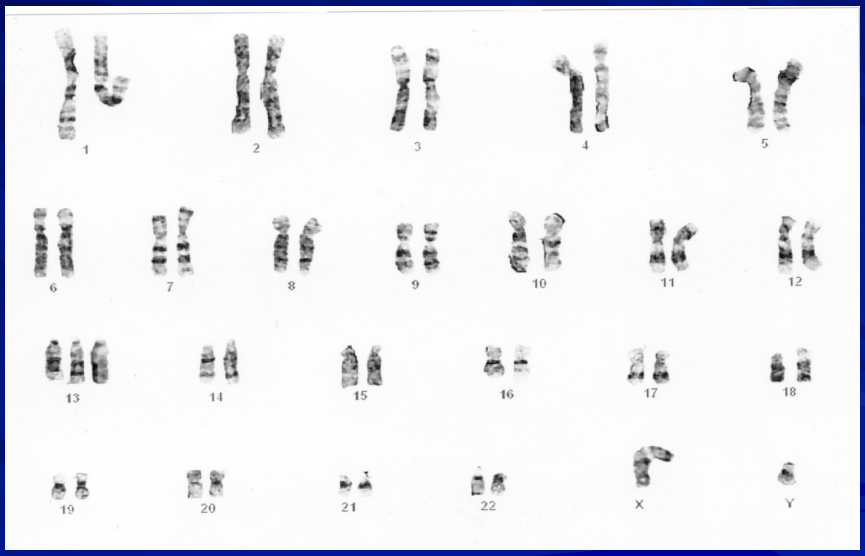
Trisomy 13 (Patau Syndrome)

- Oral facial clefts
- Low set ears
- Polydactyly
- Brain abnormalities (i.e. holoprosencephaly)

- Heart defects
- Developmental delay
- Microcephaly

20

Trisomy 13



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Question # 4

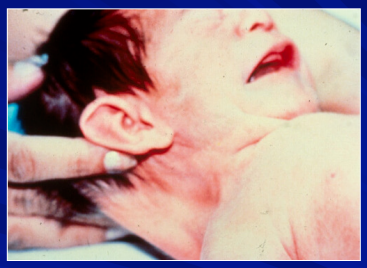
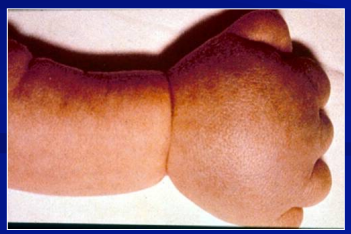
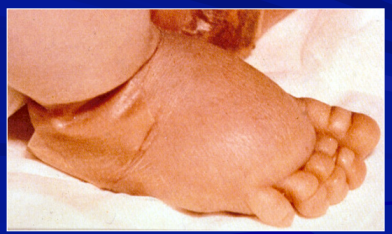
A 12 years old girl is brought to the pediatrician by her parents, who are concerned about her loss of interest in playing sports at school. During recent competition, she walked off the field in the middle of the game, complaining about the pain in her legs. The patient has no other medical conditions and takes no medications. Her vaccination schedule is up to date. PE shows pulsatile vessels within intercostal spaces and diminished femoral pulses relative to brachial pulses. The patient`s symptoms are most likely associated with which of the following conditions?

22

A. DiGeorge syndrome
B. Down syndrome
C. Friedreich ataxia
D. Kartagener syndrome
E. Marfan syndrome
F. Tuberous sclerosis
G. Turner syndrome

23

45,X (Turner Syndrome)

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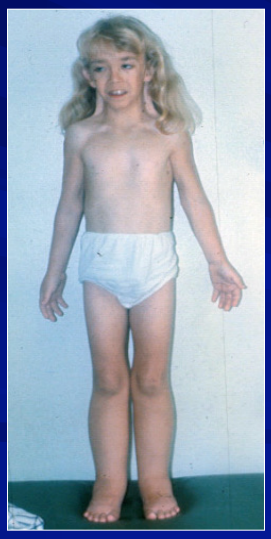
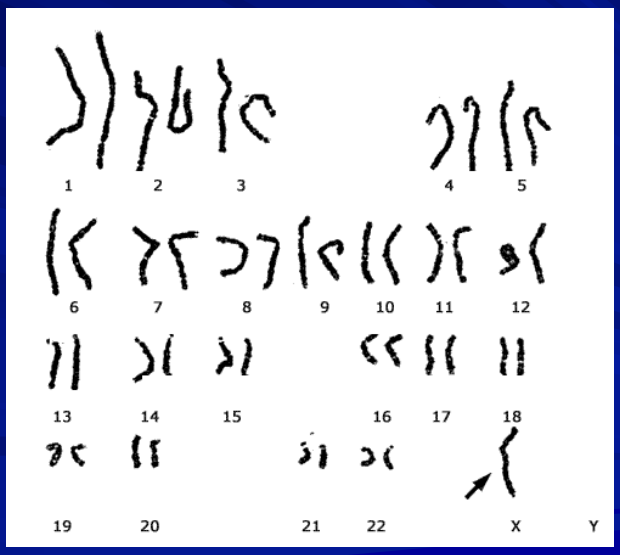
45,X (Turner Syndrome)



- Congenital heart defects (Aortic coartation)
- Renal anomalies
- Infertility/Abnormal pubertal development
- Short stature
  - Growth hormone treatment
- Usually normal intelligence

25

45,X



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Question # 5

A 15 year old patient is referred to the pediatrician by the teacher who is concern with the patient learning abilities and behavior. Patient`s reading and writing skills are significantly impaired compared with other classmates, and the patient often misbehaves in class despite receiving numerous detentions. Neuropsychological assessment shows mild intellectual disability. Cytogenetic studies show a karyotype containing 47 chromosomes.

28

Which of the following findings are most likely to be present on further evaluation?

A. Arachnodactyly, scoliosis, aortic root dilatation.

B. Macroorchidism, large jaw and ears.

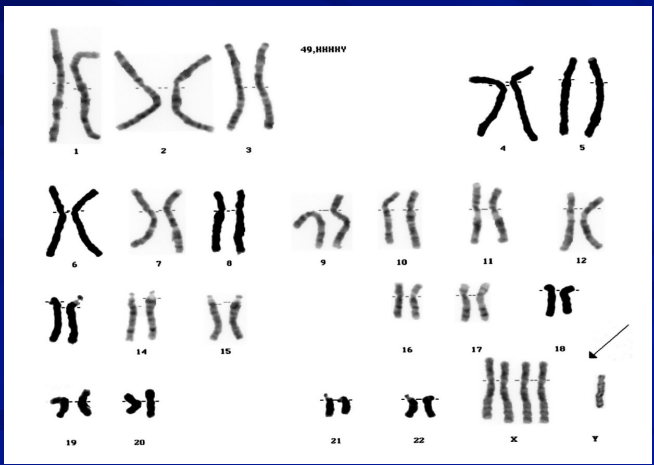
C. Short stature, broad chest, amenorrhea.

D. Short stature, hypotonia, obesity.

E. Tall stature, gynecomastia, azoospermia.

29

47,XXY; 48, XXXY



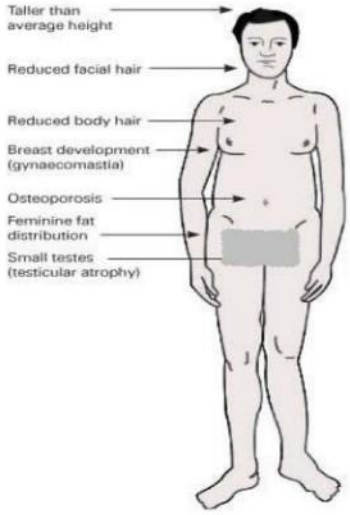
30

KLINEFELTER'S SYNDROME

- Have 47 chromosomes (XXY) & a sex chromatin Barr body or 48(XXXY); more the number of X more the chances of mental impairment
- Cause:
  - **Nondisjunction of XX homologue**
- Found only in males, detected at puberty
- Incidence ---1 in 500 males

S/S

Sterility, testicular atrophy, hyalinization of seminiferous tubules, gynecomastia.



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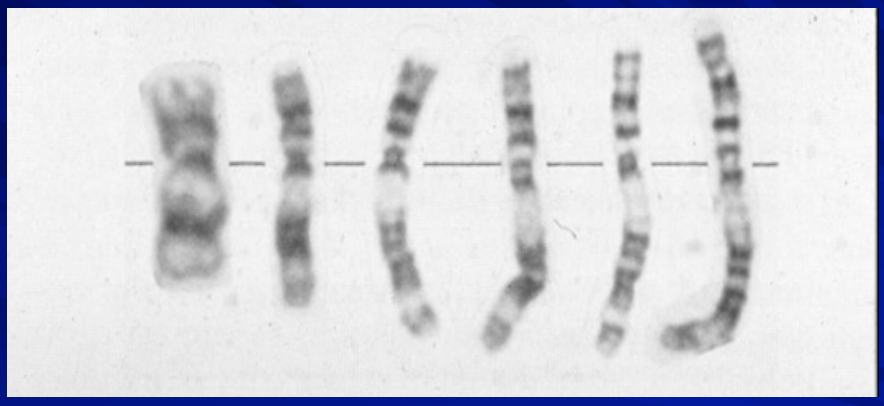
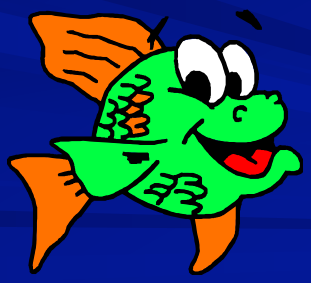


G-banded chromosomes at various band levels

32

FISH

Fluorescent In situ Hybridizationn



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Question # 6

A boy is admitted to the neonatal intensive care unit shortly after being born to a 28 yo woman who has poor prenatal care. His temp is 99F, BP is 70/30 mmHg, pulse is 128/min, and respirations are 40/min. Pulse oximetry shows 85% on room air. PE is significant for orbital hypertelorism, a submucous cleft palate, and bifid uvula. An echocardiogram reveals right ventricular hypertrophy, pulmonary stenosis with ventricular septal defect, and overriding aorta. The patient`s diagnosis is eventually confirmed by fluorescence in situ hybridization.

34

These findings are most consistent with which of the following mechanisms?

A. Abnormal ciliary motility

B. Chromosome microdeletion

C. Defect in fibrillin synthesis

D. Genomic imprinting

E. Nucleotide repeat expansion

35

Deletion 22q11

(DiGeorge Syndrome/
Velocardiofacial Syndrome,
Shprintzen Syndrome)

- Congenital heart disease
- Cleft palate
- Velopharyngeal insufficiency
- Immunodeficiency
- Hypocalcemia
- Learning disabilities

36

Deletion 22q11 (DiGeorge Syndrome)

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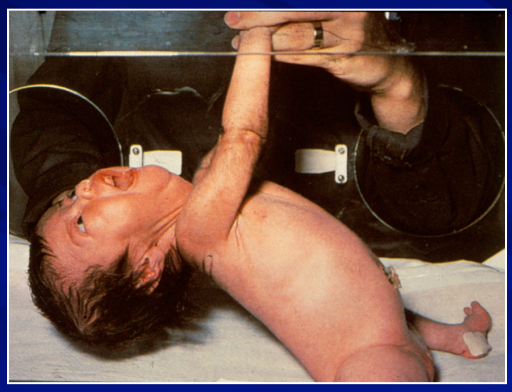
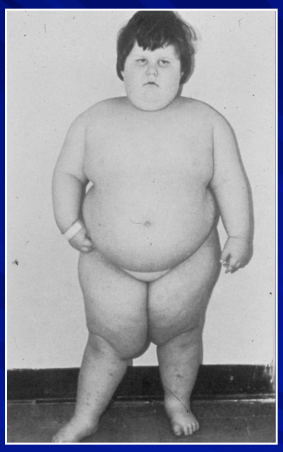
Question #7

A 3 yo boy is referred to you because of obesity, he is in the 97 percentile for weight and 10 percentile for height. Developmental landmarks were all delay. He has a history of hypotonicity, and he is still receiving PT. The hands and feet are small. There is not family history of obesity. Which of the following is the most likely diagnosis on this patient?

A. Prader-Willi Syndrome.
B. Laurence- Moon- Biedl Syndrome.
C. Lesch- Nyhan Syndrome.
D. Hurler syndrome.
E. Williams syndrome.

38





Age: 4 ½ years

Prader-Willi Syndrome

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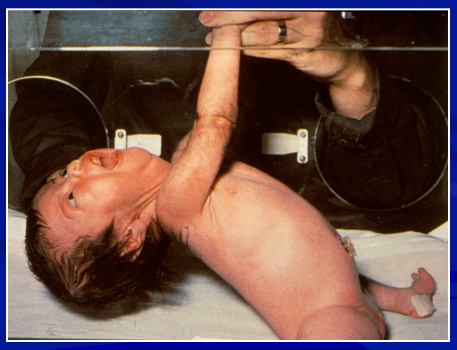
Prader-Willi Syndrome

- Hypotonia
- Neonatal feeding difficulties
- Hypogonadism
- Developmental delay
- Short stature
- Small hands/feet
- Hyperphagia (with age)
- Obesity



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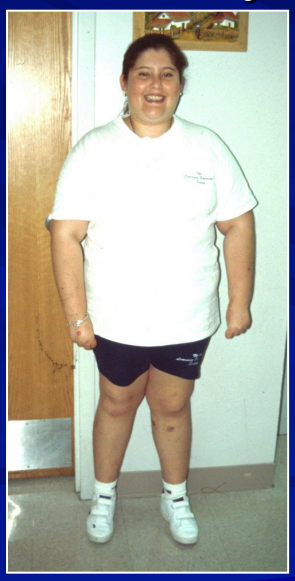
Prader-Willi Syndrome



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Angelman Syndrome

- Hypotonia
- Seizures
- Hand flapping
- Spontaneous laughter
- Lack of speech
- Developmental delay

42

Chromosome 15

- Prader-Willi Syndrome
  - Paternal chromosome 15 deletion
  - Maternal Uniparental Disomy
    - Child inherits both copies of chromosome 15 from the mother
- Angelman Syndrome
  - Maternal chromosome 15 deletion
  - Paternal Uniparental Disomy
    - Child inherits both copies of chromosome 15 from the father

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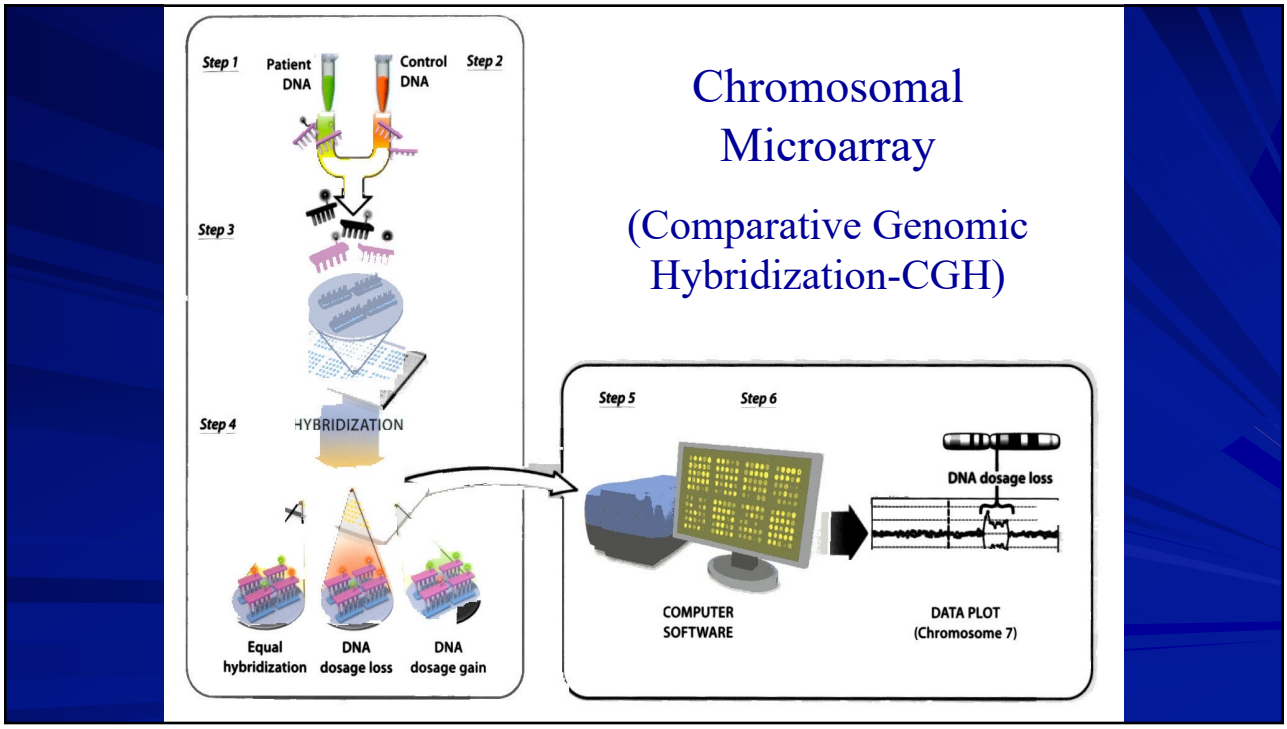

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Autistic Spectrum Disorder

- Chromosomal microarray has identified many regions of the genome association with autistic spectrum disorder
  - 1q21.1, 2p16.3,2q24.2, 4q32-qter, 6p21.32, 15q11.2 ….

45

Question # 8

A 16 year old boy with mild intellectual disability is brought to the office to be evaluated for ADHD. The parents state that he has always been impulsive and inattentive and that teachers are concerned about his inattentiveness and poor grades. Review of medical records shows a history of gross motor and speech delay for which he received PT and ST during childhood. On PE the boy has a long narrow face, a prominent mandible, and large testes. There is hyperlaxity of his fingers and thumb joints. Which of the following is the most likely diagnosis in this patient?

46

A. Down syndrome mosaicism
B. Ehlers-Danlos syndrome
C. Fragile X syndrome
D. Klinefelter syndrome
E. Marfan syndrome
F. Prader-Willi syndrome

47

Fragile X Syndrome

48

Fragile X Syndrome

- Clinical Features
  - Developmental delay (especially with regard to speech)
  - Autistic like behaviors
  - Long face, prominent ears
  - Macroorchidism (in adolescence)
- Genetics
  - Caused by expansion of a trinucleotide repeat, CGG, on the X chromosome (Xq27.3)
    - Normal repeat size: 5-44 (“gray zone” – 45-58)
    - Pre-mutation repeat size: 59-200
    - Full mutation repeat size: >200
  - Males with full mutation always affected
  - Females with full mutation – 50% show some clinical signs
  - Prenatal testing available

49

Single Gene Disorders

- Autosomal Dominant
- Autosomal Recessive
- X-Linked
  - Recessive
  - Dominant

50

Autosomal Dominant

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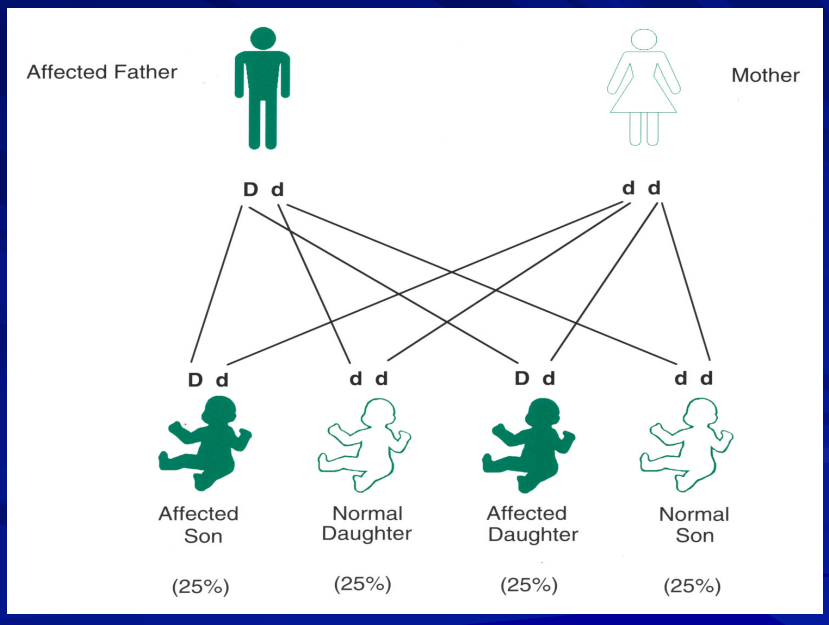
Autosomal Dominant Inheritance



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Question # 9

A married couple comes to the physician for routine prenatal counseling. The husband is 120 cm (3ft 11 in) tall with disproportionally short upper and lower extremities, a large head, and a prominent forehead. He is unable to provide a biological family history as he was adopted. His spouse is of average height with normal constitutional features and her family history is nonsignificant. They are concerned about their unborn child`s height. Which of the following is the best response to their concerns?

53

A. The condition is not inheritable
B. The risk depends on the child`s biological sex.
C. The risk depends on the mother`s carrier status.
D. The risk for the child to be short is about 25%.
E. The risk for the child to be short is about 50%.

54

Achondroplasia

55

Achondroplasia

- Features
  - Short limb dwarfism
  - Frontal bossing
  - Megalocephaly
  - Foramen magnum stenosis
  - Midface hypoplasia
  - Trident hand
- Autosomal Dominant Inheritance
  - Complete Penetrance
  - 80% due to new mutations
- Etiology
  - Caused by variants in the FGFR3 gene
  - Detection rate by DNA testing - >99%
- Prenatal diagnosis available for at risk families

56

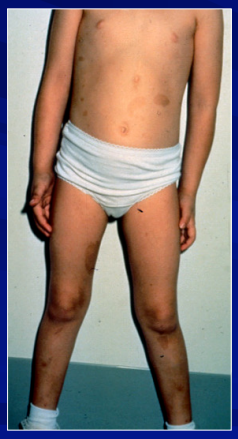
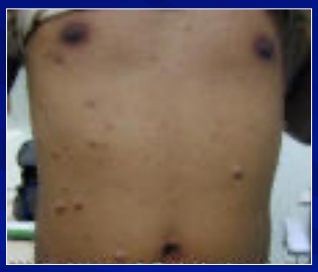
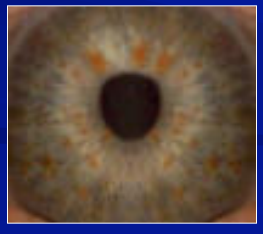
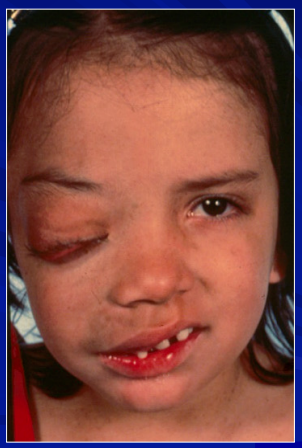
Question # 10

A one-year-old boy comes to the emergency room due to right tibial fracture. Upon physical exam you noticed multiple brown spots and swelling of the right upper eyelid. Mother referred that she also has similar brown spots. What will be the risk of this mother of have another baby with the same genetic disorder?

A. 0 % risk
B. 25% risk
C. 50% risk
D. 75% risk
E. 100% risk

57

Neurofibromatosis Type 1

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Neurofibromatosis Type 1

- Features
  - Café-au-lait spots (need >6)
  - Axillary and inguinal freckling
  - Neurofibromas (2 or more) or one plexiform neurofibroma
  - Lisch nodules
  - Optic Glioma
  - Typical skeletal anomalies
  - Learning disabilities
  - Increased risk for malignancy

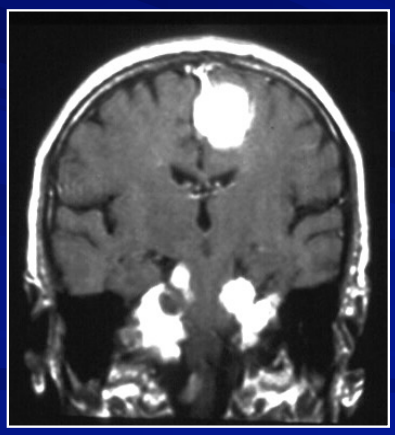
59

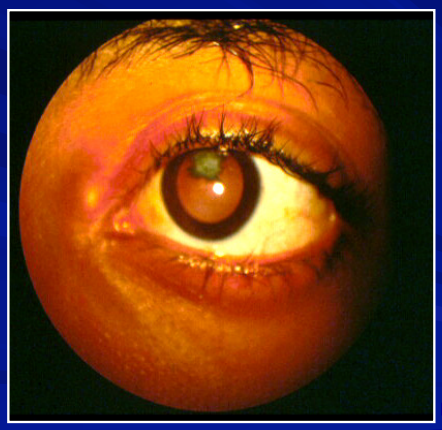
Neurofibromatosis Type 1

- Autosomal Dominant Inheritance
  - Complete penetrance, variable expression
  - 50% of cases are due to a new variant
- Etiology
  - Caused by variants in the NF-1 gene
  - Gene locus - 17q11
  - Protein - neurofibromin, 50-60% of affected individuals have variants that result in a truncated protein
  - Genetic testing is available

60

Neurofibromatosis Type 2





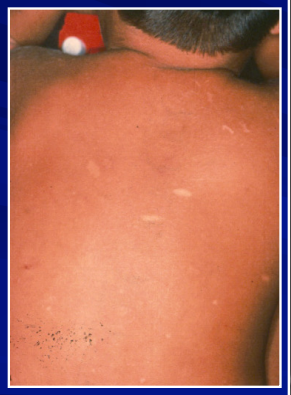
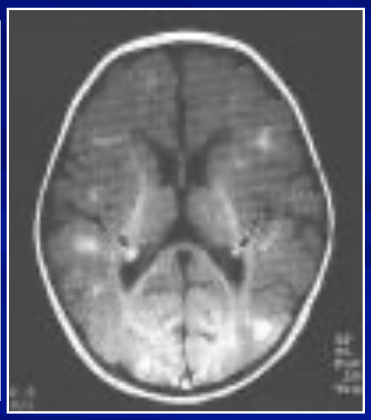
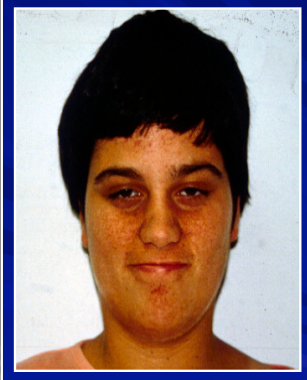
61

Neurofibromatosis Type 2

- Features
  - Bilateral vestibular schwannomas
  - Cortical cataract
  - Schwannomas of the cranial nerves, spinal nerves, and peripheral nerves
  - Gliomas
  - Ependyomas
  - Meningiomas
- Autosomal Dominant Inheritance
  - Complete penetrance, variable expression
  - High rate of new variant
- Etiology
  - Caused by variant in NF-2 gene
  - Gene locus - 22q12.2
  - Protein - “merlin” or “schwannonmin”
  - Genetic testing available

62

Tuberous Sclerosis

63

Tuberous Sclerosis

- Clinical Features
  - Cortical tubers
  - Seizures; developmental delay
  - Facial angiofibroma
  - Subependymal nodule/giant cell astrocytoma
  - Cardiac rhabdomyoma
  - Hypomelanotic macules (ash leaf spots)
  - Shagreen patch
  - Retinal hamartoma
  - Renal cysts

64

Tuberous Sclerosis

- Caused by variants in at least 2 genes
  - TSC1 – 9q84
  - TSC2 – 16p13.3
- 2/3 of cases are new variants
  - Most caused by variants in TSC2
- 1/3 of cases are familial
  - Half are caused by variants in TSC1 and half in TSC2
- Recurrence risk: 50%

65

Question # 11

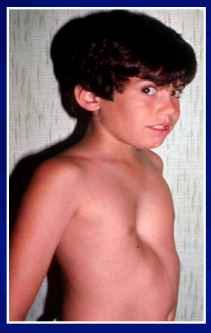
A 17 yo male, competitive distance runner comes to you for a physical examination, prior to participating in athletic event. He is tall and pubertal development is normal for age. He has hypermobility of joints, high arched palate, and an upper arm span exceeding his height. Which of the following studies should be part of his participation clearance examination?

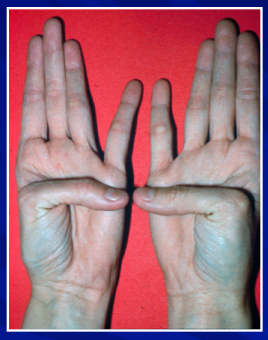
66

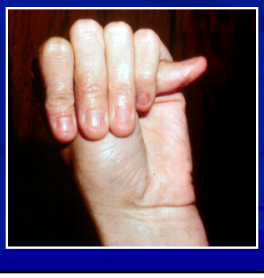
A. Ultrasonography of the kidneys
B. Echocardiography
C. Computer tomography (CT scan) of the head
D. Liver- spleen scan
E. X rays studies of the long bones

67

Marfan Syndrome






Nasal lens subluxation in Marfan's patient


68

Marfan Syndrome

- Features
  - Dislocated lens (usually upward)
  - Dilated aortic root
  - Pectus excavatum or carinatum, decreased upper/lower segment ratio, arm span > height, flat feet, scoliosis
  - Long, thin fingers
  - Joint laxity
- Etiology
  - Caused by variants in the fibrillin gene
    - FBN1 (15q21.1)
    - Fibrillin is usually a component of extracellular microfibrils that are distributed in the body's connective tissues
- Genetic testing by DNA analysis available

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Question # 12.

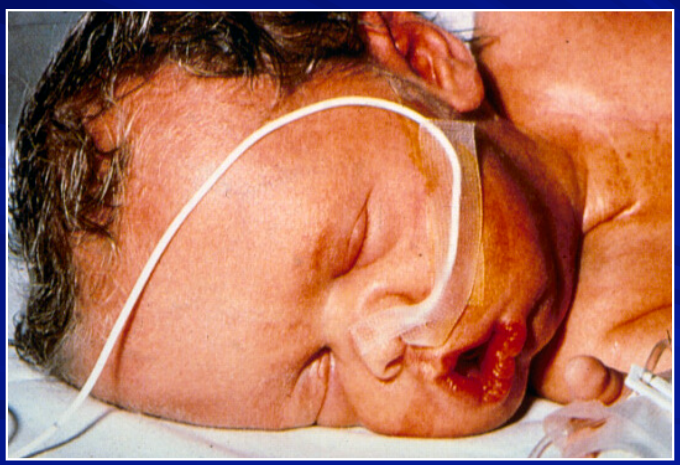
An 8 year old boy is brought to the clinic due to behavioral problems. The patient has a history of intellectual disability and is in special education classes. For the last few months, his teachers have reported that he has had increasing difficulty following directions and maintaining his attention. The parents have recently noticed that the child seems to have muscle weakness in his hands. The patient`s mother developed similar weakness several years ago. Vital signs are normal. Eye examination shows bilateral lenticular opacities. Firm percussion over the thenar eminence results in prolonged thumb abduction with slow muscle relaxation. Further work up most likely reveal which of the following?

70

A. Expanded trinucleotide repeats
B. Mitochondrial DNA variants
C. Partial chromosome deletion
D. Uniparental disomy
E. X-linked frameshift variant

71

Myotonic Dystrophy



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Myotonic Dystrophy

- Features
  - Myotonia, muscle weakness
  - Cataract
  - Frontal balding
  - Cardiac conduction defects
  - Intestinal pseudo-obstruction
- Autosomal Dominant Inheritance
  - Variable expression
  - Anticipation
- Etiology
  - Caused by expansion of a CTG repeat in the DM protein kinase gene
  - Gene locus - 19q13.2-13.3
  - 5-37 repeats - Normal
  - 38-49 repeats - Premutation
  - >50 repeats - Clinically Affected

73

Question # 13.

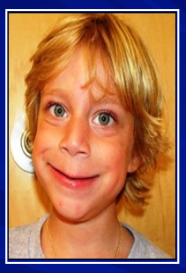
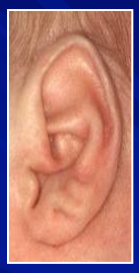
Routine physical examination of a 2 years old boy reveals enlargement of the upper and lower left limbs. History of large umbilical hernia, macroglossia and hypoglycemia. Which of the following conditions is associated with these physical findings?

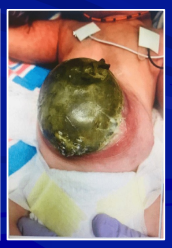
A. Lymphoma
B. Acute lymphocytic leukemia
C. Rhabdomyosarcoma
D. Neuroblastoma
E. Wilms Tumor

74

Beckwith Wiedemann Syndrome

- Clinical Features
  - Macroglossia
  - Macrosomia and/or Hemihypertrophy
  - Neonatal hypoglycemia
  - Increased risk for certain types of tumors such as Wilms tumor and hepatoblastoma
  - Omphalocele or umbilical hernia
  - Crease or pits on the ears
  - Normal Intelligence



75

Beckwith Wiedemann Syndrome

- Caused by abnormal gene expression on chromosome 11.
  - 50% due to loss of methylation on maternally inherited imprinting center 2 (KvDMR)
  - 5% due to gain of methylation in maternally inherited imprinting center 1 (H19 DMR).
  - 20% due to paternal uniparental disomy
  - 10% due to maternal CDKN1C variants
  - 1% due to chromosomal translocations/inversions

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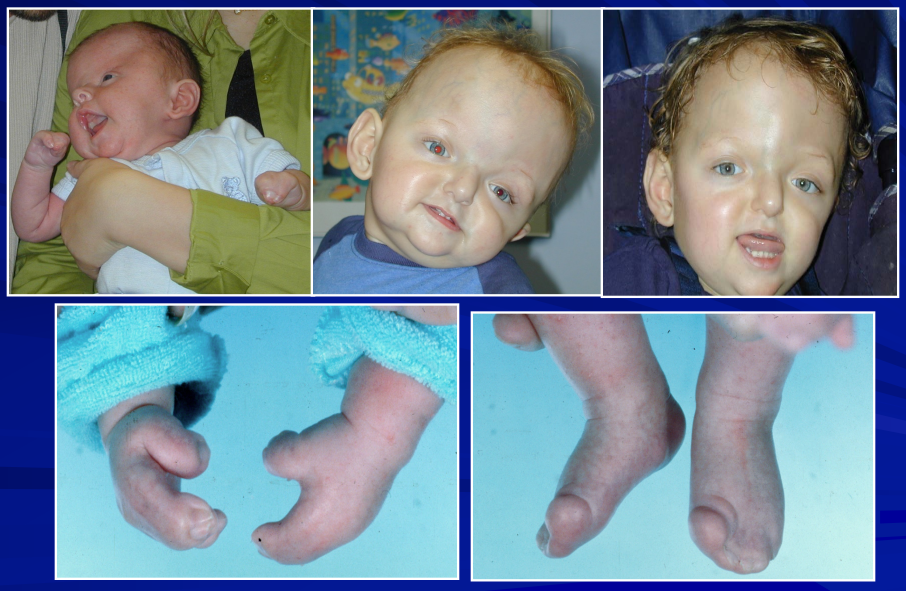
Apert Syndrome



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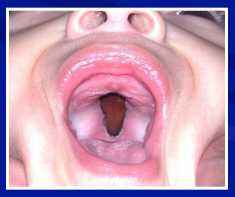
Apert Syndrome

- **Clinical Features**
  - Midface hypoplasia, mandibular prognathism
  - Shallow orbits, hypertelorism
  - Acrobrachycephaly
  - Choanal stenosis/atresia
  - Narrow/cleft palate
  - Craniosynostosis (usually coronal)
  - Osseous and/or cutaneous syndactyly
  - Moderate to severe acne

78

Pierre Robin Sequence

- Pierre Robin Sequence
  - Cleft palate, micrognathia, and glossoptosis
  - Consider Sticker Syndrome
    - 20% of children with PRS will have Stickler Syndrome
- Stickler Syndrome
  - Clinical Features
    - Cleft palate/Pierre Robin Sequence
    - Hearing loss
    - Flat face/depressed nasal bridge
    - Myopia, retinal detachment
    - Hyperextensible joints
  - Genetics
    - Autosomal dominant and autosomal recessive forms
    - Caused by variants in multiple genes in type 2 or 11 collagen
    - Variants in Type 2 or 11 collagen



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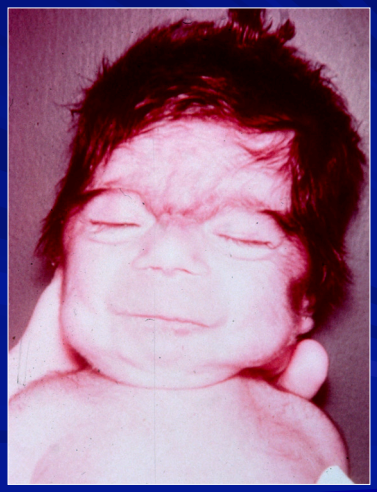
Cornelia de Lange

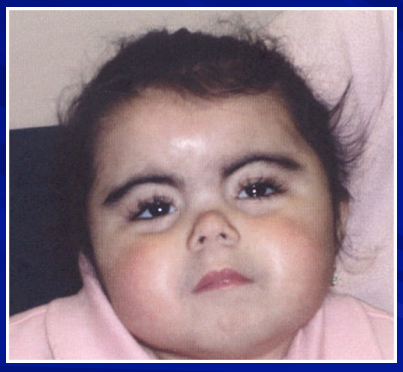
- Clinical Features
  - Synophrys, arched eyebrows, long eyelashes, small upturned nose, small, widely spaced teeth, microcephaly
  - Growth retardation
  - Hirsutism
  - Upper limb reduction defects
  - IQ: 30-102
  - Cardiac defects, myopia, hearing loss, genital anomalies



80

Cornelia de Lange

- Genetics
  - Autosomal Dominant
    - Variants in NIPBL (60%) and SMC3 (1%) genes
    - <1% have an affected parent
  - X-linked (5%)
    - Variants in SMC1A gene
    - SMC1A is not inactivated during X inactivation therefore carrier mothers may show some clinical features.



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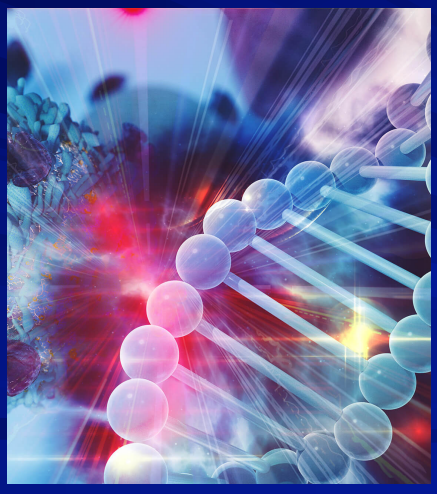
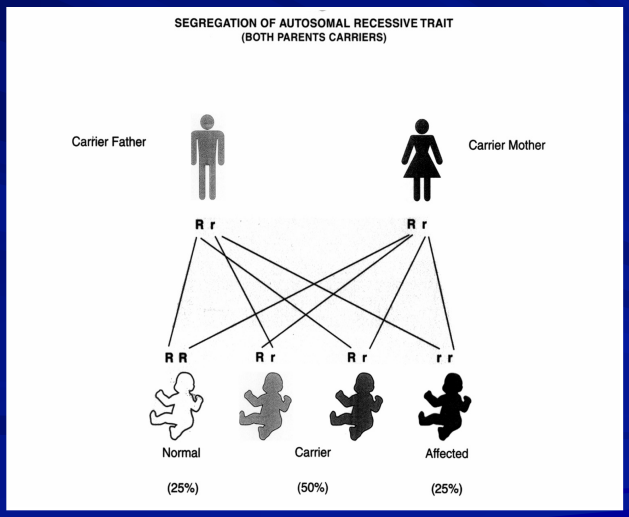
Single Gene Disorders



- Autosomal Recessive conditions

82

Autosomal Recessive



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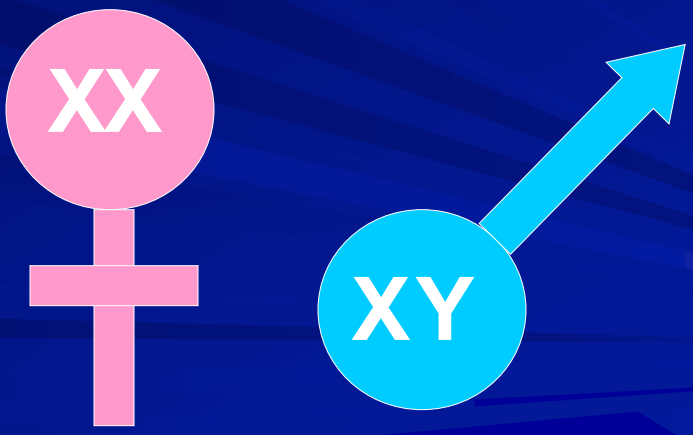
Metabolic Disorders

- Many metabolic disorders are inherited in an autosomal recessive pattern:
  - Phenylketonuria
  - Galactosemia
  - Congenital Adrenal Hyperplasia
  - Glycogen Storage Disease
  - Fatty Acid Oxidation Disorders
  - Mucopolysaccaridoses
- Newborn Screening

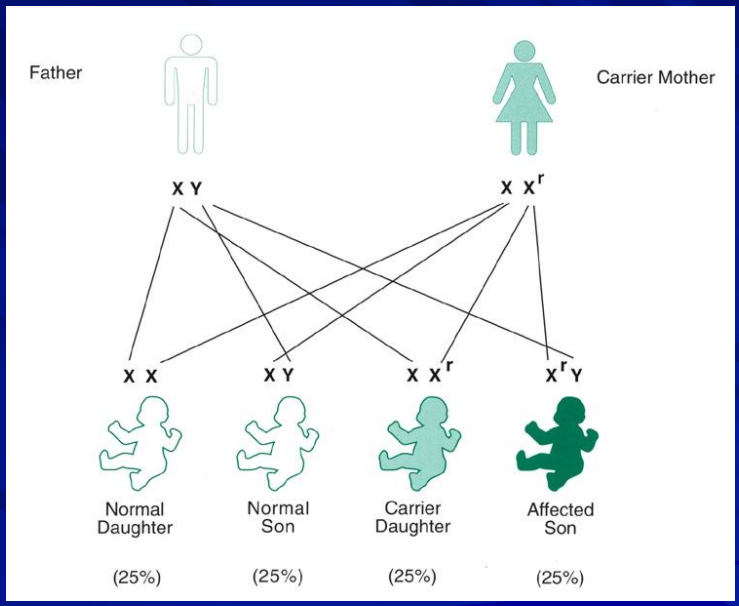
84

X-Linked Inheritance



85

X-Linked Recessive



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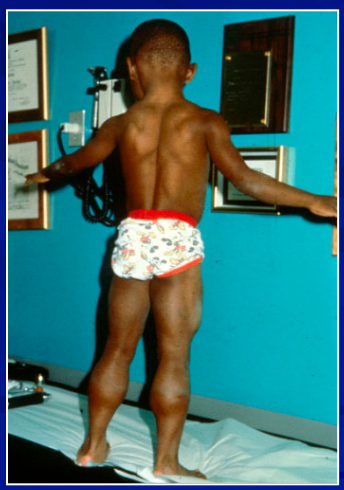
Question # 14

A mother comes to you because she is worried that her 5 years old son is having difficulties climbing the stairs. Of significance mother has an uncle that passed away during the teenage years due to pneumonia. Upon physical examination you noticed hypertrophy of his calves. Which would be the mode of inheritance in this case?

A. Autosomal dominant
B. Autosomal recessive
C. Mitochondrial
D. X-linked recessive
E. X-linked dominant

87

Duchenne Muscular Dystrophy (DMD)



88

DMD

- Clinical Features
  - Presents in early childhood with delayed milestones (especially sitting and standing)
  - Proximal weakness, waddling gait, and difficulty climbing
  - Cardiomyopathy
  - Death typically in the second to third decade

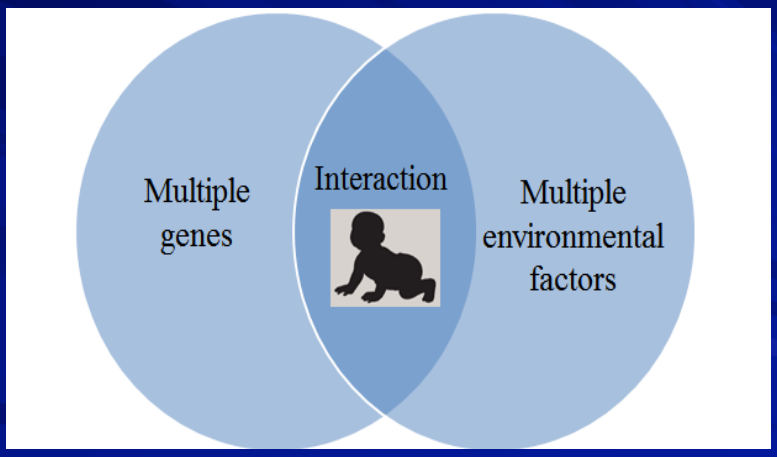
89

DMD

- Genetics
  - Caused by variants/deletions in the Dystrophin (DMD) gene on the X chromosome (Xp21.3-p21.2)
  - Approximately 2/3 of mothers are carriers (in sporadic cases)
  - Recurrence risk for affected male: 25%
  - Recurrence risk for carrier female: 25%
  - Probability of normal child (male or female): 50%

90

Multifactorial Disorders



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Multifactorial Inheritance

- Combination of genes and environment
- Empiric Risks
- Threshold Effect

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Question #15

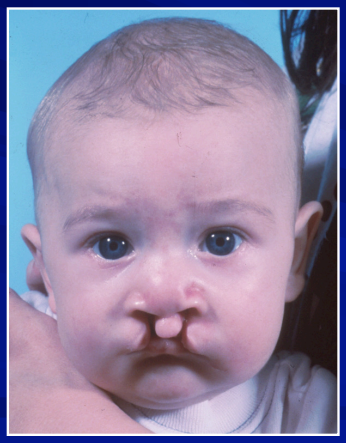
A primigravid woman at 22 week gestation comes to the office with her partner to discuss a cleft lip and palate identified on prenatal ultrasound. The father requests a paternity test of the fetus because no one of his side of the family has ever had a cleft lip or palate. During your discussion with the family you explain to them that children with cleft lip and palate often have no history of the condition because it is most commonly due to which of the following?

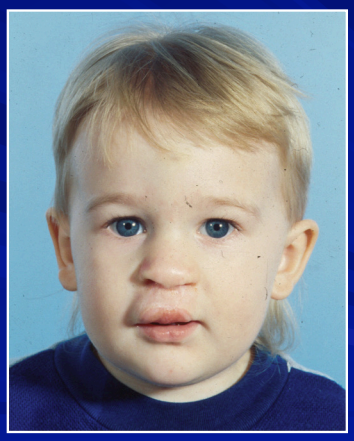
93

A. Autosomal recessive inheritance
B. Embryologic disruption
C. Mitochondrial variants
D. Polygenetic and environmental interactions
E. Skewed- X inactivation

94

Oral Clefts





95

Oral Clefts

- Incidence: 1/700 livebirths
- Isolated finding in 90%
- May be associated with genetic syndrome, disruption (amniotic band), or teratogenic exposure
- Recurrence risk when isolated: 3-5%
- Risk increases with positive family history

96

Neural Tube Defects

- Associated with chromosome abnormalities and many genetic syndromes
- Isolated
  - Recurrence risk: 3-5%
- Prevention
  - Consumption of folic acid
    - .4mg for low risk population
    - 4mg for a high risk population (previously affected)

97

Question # 16

A 2 months old boy is brought to the emergency department due to progressively worsening "floppiness" and poor feeding. The infant was born in Eastern Europe via an uncomplicated vaginal delivery to a 38 years old woman and then immigrated to the United States with his family. The parents describe the infant as a "good baby" who rarely cries and sleeps through the night but has lately been difficult to rouse for breastfeeding. Stools have also decreased to every other day and are small and pellet-like. PE shows a hypotonic infant with a large anterior fontanelle, large tongue, and a reducible umbilical hernia. He has a low tone and is unable to hold his head erect on his own. No other abnormalities are seen. Which of the following is the most likely cause of this patient`s condition?

98

A. Botulism

B. Down Syndrome

C. Galactosemia

D. Hirschsprung disease

E. Hypothyroidism

F. Phenylketonuria

99

100

101