Dysmorphic Syndromes

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Objectives of Lecture
• describe the frequency of birth defects
• recognize the genetic contribution to birth defects
• distinguish normal variation from dysmorphic features
• develop an approach for syndrome recognition

Scope of Medical Genetics
• clinical genetics & dysmorphology
• cytogenetics
• biochemical genetics
• molecular genetics
• genetic counseling

When to Consider a Dysmorphic Syndrome
• presence of ≥1 anomalies
• phenotypic variation from parents or sibs
• abnormal growth (pre- +/- postnatal; delay or overgrowth)
• bilaterality of abnormal features
• neurologic symptoms: developmental delay, seizures, sensory deficits, etc.
Integrated Approach to Congenital Anomalies

- Simultaneously gather data: consider therapies
- History: deal with urgent problems; meet family
- Physical exam: define long-term problems; discuss therapies
- Lab studies: formulate overall plan
- Construct overall plan: review status periodically

Achondroplasia

- Incidence: 1/25,000
- Inheritance: autosomal dominant
- Features: short-limbed dwarfism; macrocephaly with frontal bossing; gibbus→lordosis; tibial bowing
- Compl's: hypotonia, apnea, cord compression
- 1° defect: FGFR3 (fibroblast growth factor receptor 3)

Thanatophoric Dysplasia

- Incidence: 1/50,000
- Inheritance: sporadic
- Features: short-limbed dwarfism; curved long bones, narrow thorax, flattened vertebrae; death 2° pulmonary hypoplasia
- 1° defect: FGFR3 (fibroblast growth factor receptor 3), same as achondroplasia
**Marfan Syndrome**

- **incidence:** 1/12,000
- **inheritance:** autosomal dominant
- **features:** tall, thin habitus; ectopia lentis; scoliosis, pectus deformity, striae, arachnodactyly, joint laxity; MVP, aortic root dilatation
- **Rx:** atenolol; losartan (TGFβ antagonist)
- **1° defect:** fibrillin

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**Osteogenesis Imperfecta**

- **incidence:** 1/15,000
- **inheritance:** autosomal dominant
- **features:** osteopenia; bone fragility; blue sclerae; dentinogenesis imperfecta; hearing loss; scoliosis; Wormian bones
- **primary defect:** type I collagen (COL1A1 or COL1A2 gene)
- **Rx:** bisphosphonates; GH supplementation is experimental

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**Russell-Silver Syndrome**

- **incidence:** uncommon
- **inheritance:** sporadic; 10% have uniparental disomy for chromosome 7; 35% have imprinting defect (or matUPD) at 11p15
- **features:** growth retardation, macrocephaly, blue sclerae, triangular face, limb asymmetry
Holt-Oram Syndrome
• incidence: 1/100,000
• inheritance: autosomal dominant
• features: congenital heart disease (ASD>>VSD); thumb defects (triphalangeal, hypoplastic, absent); radial defects
• 1º defect: TBX5, a transcription factor gene

Noonan Syndrome
• incidence: 1/1000 - 1/2,500
• inheritance: autosomal dominant
• features: characteristic facial features, webbed neck, pectus deformity, congenital heart disease, short stature (postnatal)
• 1º defect: PTPN11 gene (50%); SOS1>RAF1>KRAS>others (genetically heterogeneous)

Treacher-Collins Syndrome
• incidence: 1/10,000
• inheritance: autosomal dominant
• features: short, downslanting palpebral fissures; lid colobomas; hypertelorism, hypoplastic ears, atretic ear canals, micrognathia, cleft palate
• 1º defect: TCOF (“Treacle”), a nucleolar protein
Goldenhar Syndrome
(facio-auriculo-vertebral spectrum)

- incidence: 1/10,000
- inheritance: sporadic
- features: hemifacial microsomia, ext/middle ear anomalies, macrostomia, micrognathia, epibulbar dermoids, colobomas, C-spine anomalies, hearing loss
- 1° defect: disruption of stapedial artery
- 1st & 2nd branchial arch defects

Cornelia deLange Syndrome

- frequency: 1 in 25,000
- inheritance: sporadic; autosomal dominant-acting mutations
- features: pre- and postnatal growth retardation, characteristic facies (synophrys, low anterior hairline, anteverted nares, long philtrum, 'carp' mouth); MR, cardiac defects, upper limb anomalies
- 1° defect: "Nipped-B-like" gene, also called "delangin"

Rett Syndrome

- frequency: 1 in 15,000
- inheritance: X-linked dominant
- features: developmental arrest at 6-12 months, acquired microcephaly, epilepsy, loss of purposeful hand movements, autism, growth failure
- 1° defect: MECP2 gene (methyl-CpG-binding protein)
- differential diagnosis: Angelman sx
### Fetal Alcohol Syndrome

- **incidence**: 1/1,000? (1/3 all infants born to chronic alcoholic mothers)
- **features**: pre/postnatal growth deficiency; microcephaly, short palpebral fissures, thin upper lip, smooth philtrum, small distal phalanges and nails; developmental delay, behavioral problems, moderate MR

### 10 Most Common Findings in Fetal Alcohol Syndrome

- microcephaly
- eye anomalies
- smooth philtrum
- thin upper lip
- small jaw
- hypertonia
- finger anomalies
- hyperactivity
- growth deficiency
- diminished IQ

### Fetal Dilantin Syndrome

- **incidence**: 10% exposed fetuses
- **features**: pre/postnatal growth deficiency; hypertelorism, epicanthal folds, thin upper lip, smooth philtrum, small distal phalanges and nails; developmental delay, moderate MR
Multifactorial Disorders
• occur from genetic/environmental interaction
• Mendelian inheritance not exhibited
• examples: cleft lip +/- palate
  club foot
  neural tube defects
  diabetes mellitus

Neural Tube Defects
• incidence: 1/1,000 births
• inheritance: usually sporadic; may be part of syndrome or chromosomal anomaly
• spectrum: mild (spina bifida occulta) to severe (anencephaly)
• recurrence: 3-5% if isolated
• prevention: 400ug folic acid daily

Approach to Syndrome Recognition
• obtain careful histories
• obtain thorough physical exam
• include anthropometric measurements when indicated
• direct search based on most unusual features
• consider confirmatory lab tests if available
References

• Committee on Genetics: Health supervision for children with achondroplasia. Pediatrics 116:771, 2005
• Committee on Substance Abuse and Committee on Children with Disabilities: Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. Pediatrics 106(2):358, 2000 (all can be found online at http://aappolicy.aappublications.org)
• monographs on several single gene disorders can also be found online at http://www.genetests.org (click on GeneReviews tab)