EPIDEMIOLOGY (CAUSES) OF BIRTH DEFECTS

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* No disclosures
WHAT IS A BIRTH DEFECT?

• Every structural defect is an inborn error of morphogenesis

  • How is morphogenesis controlled? Gene Regulation? Epigenetic? Stochastic?

• How does one define a structural birth defect?

  • Is autism a structural birth defect? Adult onset disease? Infection?
INCIDENCE OF BIRTH DEFECTS

• 3% of all pregnancies is associated with a congenital birth defect

• By kindergarten, almost 5% of children have a disorders considered to be congenital (genetic or heritable)

• .7% infants are delivered with multiple congenital anomalies
GENETICS OVER A LIFETIME

Fetal  Newborn  Childhood  Adolescence  Adulthood
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Fetal  Newborn  Childhood  Adolescence  Adulthood

Down syndrome
GENETICS OVER A LIFETIME

Fetal    Newborn    Childhood    Adolescence    Adulthood

Down syndrome
Neural tube defects
GENETICS OVER A LIFETIME

Fetal   Newborn   Childhood   Adolescence   Adulthood

↓

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Down syndrome
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Metabolic disorders
GENETICS OVER A LIFETIME

Fetal  Newborn  Childhood  Adolescence  Adulthood

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- Neural tube defects
- Metabolic disorders
- Mitochondrial disorders
- Autism

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GENETICS OVER A LIFETIME

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GENETICS OVER A LIFETIME

Fetal
- Down syndrome
- Neural tube defects

Newborn
- Metabolic disorders

Childhood
- Mitochondrial disorders
- Autism

Adolescence

Adulthood
- Diabetes
- Schizophrenia
GENETICS OVER A LIFETIME

Fetal

Newborn

Childhood

Adolescence

Adulthood

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Neural tube defects

Metabolic disorders

Mitochondrial disorders

Autism

Diabetes

Schizophrenia

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- Metabolic disorders
- Mitochondrial disorders
- Autism
- Diabetes
- Schizophrenia
- Neurogenic disorders
- Cancer

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Newborn
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- Autism

Childhood
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Adulthood
ETIOLOGIES OF CONGENITAL ANOMALIES

- Chromosomal: 10%
- Multifactorial: 25%
- Mendelian disorders: 8%
- Environmental: 7%
- Unknown: 50%
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- microRNAs
• Account for about 50% of fetus/neonates with multiple congenital anomalies
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CHROMOSOMAL ABNORMALITIES AND KARYOTYPE

Ideogram
CHROMOSOMAL ABNORMALITIES AND KARYOTYPE

Ideogram

single nucleotide polymorphism microarray

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CHROMOSOMAL ABNORMALITIES

- Down syndrome - 94% of cases are full trisomy, 2.4% are 21 trisomy/mosaicism, 3.3% translocations

- Trisomy 18 - 5 to 10% survive at least the first year of life. Second most common multiple malformation syndrome, about 0.3% per 100 newborns. More than 130 abnormalities have been noted in patients with the 18 trisomy syndrome.

- Trisomy 13 - 1/5000. Median survival is 2.5 days. 5% survive 6 months.

- Trisomy 8 - majority of patients are mosaic, growth variable from small to tall, dysmorphic, micrognathia, camptodactyly, increased risk for cancers, very rare cardiac defects

- Trisomy 9 - variable levels of mosaicism, congenital heart defects in 2/3 of cases, high incidence of intracranial defects including NTDs and subarachnoid cysts.

- Triploidy - while frequently found at conception (2%), most are lost. ASYMMETRIC IUGR, syndactyly of the 3rd and 4th fingers. extra set of chromosomes are frequently paternal.

- Deletion 3p syndrome - microcephaly, polydactyly

- Duplication 3q - abnormal head shape, hypertrichosis, long philtrum

- Deletion 4p - microcephaly with broad and beaked nose (clefts)

- Deletion 5q - Cri du Chat, microcephaly

- Deletion 9p - craniosynostosis, hypoplastic suprorbital ridges
DOWN SYNDROME

Hypotonia
Hyperextensibility
Short stature
Brachycephaly
Mild microcephaly
Thin calvarium
Small nose with low nasal bridge
Small ears
Relatively brachdactyly
Fifth finger clinodactyly
40% cardiac anomaly
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Seizures
Cataracts
TE fistula
Duodenal atresia
Omphalocele
Pyloric stenosis
Hirschsprung disease
Imperforate anus
Leukemia 1%
Thyroid disease
Fatal perinatal liver disease
• Deletions/duplications of DNA segments of

• Account for about 5-17% of individuals with multiple congenital anomalies with previous normal karyotypic analysis

• Recently shown to be responsible for about 14% of children with intellectual disability and congenital anomalies

• More frequent in intellectual disability and craniofacial/cardiovascular defects < less common in autism/epilepsy alone
TERATOGENS

Epilepsy is the most common neurologic disorder seen in pregnancy

Fetuses exposed to anticonvulsants have a 2 to 7 times greater risk of malformations than the general population

Fetal malformations have been described due to exposure to dilantin, valproate and carbamazepine

Anomalies include dysmorphic facies, NTDs, genital, skeletal and cardiac malformations

Cardiac anomalies include VSD, ASD, pulmonary stenosis and aortic stenosis

Antidepressants (serotonin uptake inhibitors) - ???
MULTIFACTORIAL

- What does this really mean?
- Recurrence risk is higher than the general population but does not follow a known pattern of inheritance
- Usually quoted to be 5-10% based on a first degree relative
  - Neural tube defects, congenital heart defects, cleft lip and palate and club feet
MULTIFACTORIAL INHERITANCE

- Probable reflects some heritability but is a historical mix of varying modes of inheritance and oligogenic inheritance

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<th>CCVM</th>
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<td>AD</td>
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<tr>
<td>NOTCH1</td>
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<td>BAV, calcification</td>
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ENVIRONMENTAL

• Diabetes
• Maternal Obesity
• IVF
METHYLATION (SILENCING)

• Genes are silenced by methylation (CH3)
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PRENATAL DISORDERS OF METHYLATION

• Beckwith Wiedemann
• Prader-Willi
• Angelmann syndrome
• ? antiepileptics
• ? fetal alcohol syndrome
MICRORNAS

• Short pieces of non
MITOCHONDRIAL
MENDELIAN DISORDERS

- Autosomal dominant
- Autosomal recessive
- X-linked recessive
- X-linked dominant
- Y-linked