BASELINE GENETIC RISK

- 3-5% of live births will have a major congenital abnormality
- 10% to 15% of live births will have a minor congenital abnormality
- Down Syndrome (Trisomy 21)
  - Most common trisomy of live births
    - 1,800 live births
4  DEFINITIONS

- **Aneuploidy**
  - A haploid gamete or diploid cell lacks expected number of chromosomes - n or 2n
  - **Trisomy**
    - An additional chromosome is present
    - Meiotic non-disjunction in Meiosis I
  - **Polysomy**
    - Additional chromosome is a sex chromosome

- **Monosomy**
  - 2n - 1

- **Polyploidy**
  - 3N = 69
  - Usually caused by dispermy

- **Mosaicism**
  - 1 individual has 2 or more genotypes from the same zygote
  - Different cells have a different chromosomal makeup
  - True effect depends not only on how many cells affected but which cells are affected

- **Chimerism**
  - 1 individual has 2 or more genotypes from different zygotes
  - Two non-identical twin embryos merge together
  - May have patches of non-matching DNA

- **Deletions**
  - Chromosome breaks and a piece is lost
  - Involves loss of genetic information
  - Can be considered a "partial monosomy"

- **Inversions**
  - Two breaks in one chromosome - fragment inverted and rejoined within the chromosome
  - Rearrangements usually do not involve loss of genetic material
  - Individuals usually have a normal phenotype
  - **Centric -** Inverted area includes centromere
  - **Paracentric -** Inverted area does not include centromere
EXAMPLES

- Deletion
  - 46,XX,del(1)(q24q31)
  - Female with a deletion of chromosome 1 on the long arm (q) between bands q24 to q31

INVERSIONS

- 46,XY,inv(3)(p23q27)
- 46,XY,inv(1)(p12p31)

TRANSLOCATIONS

- Robertsonian translocations
  - Exchange of short arms of the acrocentric chromosomes
  - 13, 14, 15, 21, and 22
  - Considered balanced
- Reciprocal translocations
  - Two non-homologous chromosomes break and exchange fragments
MEIOSIS FACTS

- Difference in meiosis I is the most unique
- Difference in female and male gamete formation
  - Female meiosis I arrested in Prophase I (dictyotene) in oocyte development at 5 months embryonic age
  - Meiosis I completed at ovulation
  - Meiosis II completed at fertilization

MEIOSIS FACTS

- Meiosis I
  - Pairing and crossing over of two chromatids of homologous chromosomes
  - Crossing over necessary for subsequent separation of homologues
  - Nondisjunction
  - Decreased numbers of crossovers
  - Aging affects function of the spindle apparatus of the oocyte
MULTIFACTORIAL DISORDERS

FACTS
- 1/1000 risk
- 2-3% recurrence if one affected sibling
- 4-6% recurrence if 2 affected sibs
- Traits/disorders affected by genetic/environmental factors
- Risk falls with degree of relationship
- If two sexes have different probability of being affected, least likely sex—if affected—more likely sex to produce an affected offspring

EXAMPLES
- NTDs
- Hydrocephaly
- Cleft lip
- Cardiac Disorders
- Diaphragmatic hernia
- Posterior urethral valves
- Renal agenesis
- Pyloric stenosis
- Omphalocele

PREGNANCY LOSS

First Trimester
- Aneuploidy - 40-60%
  - Trisomy - 50%
  - 16 most common
  - 45, X - 25%
  - Triploid - 20%
  - Unbalanced translocation (5%)

Second Trimester
- 10-30% aneuploid
  - Trisomy 13
  - Trisomy 18
  - Trisomy 21
  - 45,X

Stillbirth
- Trisomy 18 (10%)

MODES OF INHERITANCE
17 AUTOSOMAL DOMINANT INHERITANCE

- Manifests in the heterozygote
- Equal in males and females
- Vertical inheritance through generations
- Affected parents have 50% risk offspring affected
- Penetrance
  - Some individuals carrying the gene do not develop the disease
- All-or-none phenomenon
- Variable expression
  - Variable severity of a genetic trait
  - Different individuals show different degrees of disorder
  - All develop the disease in some manner but to varying degrees

18 AUTOSOMAL DOMINANT DISORDERS

- Achondroplasia
- Huntington Chorea
- Neurofibromatosis
- Marfans
- Familial Polyposis
  - Normal Parents
  - New mutation
  - Form Fruste - subclinical in parent
EXAMPLES

AUTOSOMAL RECESSIVE INHERITANCE

- Manifests only in homozygotes
- Parents of affected individual both heterozygous (carriers) are phenotypically normal
- Offspring of heterozygous parents
  - 1 in 4 chance of being affected
  - Ratio of affected to normal offspring is 1:3
  - "Horizontal" inheritance

EXAMPLES
X–LINKED DOMINANT INHERITANCE

- Trait never passed from father to son
- All daughters of affected male and normal female - affected
- All sons of affected male and normal female - normal

- Vitamin D-resistant rickets

X–LINKED RECESSIVE INHERITANCE

- Occurs only in males (with few exceptions)
  - Transmitted from carrier females to affected males
  - Daughter of affected male and carrier female can be affected

- Affected males related through their mothers
- Criss-cross pattern of inheritance
- Appears to 'skip a generation'

Hemophilia
- Inability to form blood clots due to deficiency of factor VIII
- About 1 in 10,000 males
- Christmas disease
- Due to deficiency of factor IX
- X-linked but at a different locus from that of factor VIII

Duchenne muscular dystrophy
- Affects males
  - Muscular degeneration; weakness begins age of 3 to 5 years, wheelchair bound by ten years, and can die in early 20's from respiratory failure
  - Deficiency of the protein dystrophin in skeletal muscle, caused by a mutation of the dystrophin gene

Becker muscular dystrophy
- Affects males
- Weakness begins in adolescence, progresses slowly and is not lethal
X-LINKED RECESSIVE INHERITANCE

- Red-green color blindness
  - Inability to distinguish red from green
- Glucose-6-phosphate dehydrogenase (G-6PD) deficiency
  - African, Asian, Middle Eastern and Mediterranean decent
  - Enzyme helps to produce glutathione
    - Protect cells from oxidative stress
  - RBC's exposed to oxidative stress hemolyze due to lack of glutathione
- Oxidative stressors
  - Foods
  - Infections
  - Drugs

MITOCHONDRIAL INHERITANCE

- Mitochondrial DNA contains ~ ten genes involved in oxidative phosphorylation
  - Capable of mutation
  - Leber optic atrophy - classic example
  - Essentially all mitochondria from mother
    - Ovum has ~ 100,000 copies
    - Sperm has fewer than 100 copies
  - Affected fathers produce no affected offspring
  - Offspring of affected mothers all affected

- Leber's hereditary optic neuropathy
- Mitochondrial encephalomyopathy
- Myoclonic epilepsy and ragged-red fibers (MERRF)
- Leigh syndrome, subacute sclerosing encephalopathy
- Kearns-Sayre syndrome (KSS)
- Myoneurogenic gastrointestinal encephalopathy (MNGIE)

Affected males do not transmit the trait to any of their children
Affected females transmit the trait to all of their children
IMPRINTING

- For some genes, the origin of the gene is important
  - Gene inherited from father acts differently from that inherited from mother
  - Uniparental Disomy
    - Both chromosomes come from a single parent
  - Example
    - Small deletion of long arm of chromosome 15 while the homologous chromosome remains intact (15q11-13)
    - Deletion of paternal origin results in Prader-Willi Syndrome
    - Deletion of maternal origin results in Angelman Syndrome
  - Two genetic syndromes have very different clinical findings

IMPRINTING - EXAMPLES

**PRADER-WILLI**
- Neonatal hypotonia
- Developmental deficiency
- Severe obesity
- Short stature
- Hypogonadism
- Mild to moderate mental retardation
- Small hands and feet

**ANGELMAN**
- Ataxia, seizures
- Hyperactivity
- Severe mental retardation
- Absence of speech
- Inappropriate laughter
- ‘Happy puppet’ syndrome

TRANSLOCATIONS

- Robertsonian translocations
  - Exchange of short arms of acrocentric chromosomes
    - 13, 14, 15, 21, and 22
  - Considered balanced
- Reciprocal translocations
  - Two non-homologous chromosomes break and exchange fragments

Risk of unbalanced translocation:
- 2 to 8 percent if an affected child already born
- 0-3 percent if identified for other reasons (infertility evaluation)
Aneuploidies and Syndromes

A Review

### Down Syndrome
- Developmental delay
- Nuchal skin fold thickening
- Cardiac defects – Atrioventricular septal defect
- Hypotonia
- Flat facies
- Slanted palpebral fissures
- Small ears
- Hypoplasia of midphalanx of fifth finger
- Wide iliac wings

### Trisomy 18 (Edward’s Syndrome)
- 1/8000 live births
- Clenched fists
- Rocker bottom feet
- Micrognathia
- Cardiac abnormalities
- Short sternum
- Severe developmental delay
- Single umbilical artery
- 30% die 1st month
- 50% die 2nd month
- < 10% survive 1 yr
- Female 3:1
- Recurrence < 1%
- Primary nondisjunction (47, XY +18)
- 30% die 1st month
- 50% die 2nd month
- < 10% survive 1 yr
- Female 3:1
- Recurrence < 1%
- Primary nondisjunction (47, XY +18)
Trisomy 13 (Patau’s Syndrome)

- 1/20,000 live births
- Cleft lip and/or palate
- Omphalocele
- IUGR
- Holoprosencephaly
- Single umbilical artery
- Primary nondisjunction
- 50% die 1st month
- < 3% live to age 1

Cri du chat (5p-)

- Deletion in short arm chromosome 5
- 1/20,000 live births
- High pitched monotonous cry
- Round face
- Marked epicanthal folds
- Mental retardation

Turner’s Syndrome (45, X)

- 1/2500 live births
- Sporadic
- Most frequent chromosomal abnormality
- 7% of spontaneous abortions
- Cystic hygromas
- Anasarca
- Renal anomalies
- Coarctation of aorta
- Primary amenorrhea
- Short stature
- Webbed neck
- No hair, breasts
- Gonadal dysgenesis
- E2 & Test Low
- FSH, LH high
Turner Syndrome

- 2% of recognized 45,X embryos survive to term
- 98% are lost
- Result of non-disjunction
- Can occur at either meiotic division in either spermatogenesis or oogenesis
- 80% result of paternal nondisjunction
- Can also result from early mitotic nondisjunction
  - Mosaic 46,XX/45,X

Klinefelter’s Syndrome (47,XXY)

- 1 in 850 to 1 in 500 live births
- Pubic and axillary hair
- Scant facial hair
- Tall body habitus
- Female fat distribution
- 20 fold increase in risk of breast cancer

Klinefelter’s Syndrome

- Child must get the Y chromosome from his father
- Nondisjunction in either meiotic division in mother
- Only occurs in first meiotic division in father
- If nondisjunction occurred in father, zygote would have to get both X and Y chromosome in same sperm
  - In spermatogenesis this could only result from a mistake in first division
  - Second meiotic division of spermatogenesis separates either the two X or two Y chromatids into different gametes
Gender Chromosome Abnormalities

- XYY syndrome
  - 1/1000 male births
  - Nondisjunction in second meiotic division of spermatogenesis
  - Found in almost 1/50 males in prison populations
  - Aggressive behavior and less intelligence than siblings
- XXX syndrome (47,XXX)
  - Very normal phenotype
  - As number of X chromosomes increases mental deficiencies increase

Cystic Fibrosis

- 1/2500 live births
- Carrier 1 in 22 to 1 in 30 Caucasians
- Autosomal recessive
- Delta F 508 on Chromosome 7 most common mutation
- Many other mutations
- Not all mutations identified
- Non-affected sibling of patient with CF has a 2/3 chance of being a carrier
- ACOG recommends offering screening to everyone – not just Caucasian individuals

McCune Albright Syndrome

- Polyostotic Fibrous Dysplasia
- Cafe au le spots
- Autonomous endocrine hyperfunction
  - Precocious puberty
  - Gonadotropin independent
- Skeletal dysplasia
  - Fibrous dysplasia
  - Hypophosphatemia
Neural Tube Defects

- Polygenic Inheritance
- 1 in 2000 risk
  - Decreased from 1 to 2 per 1000 following the supplementation of foods with folic acid
- Recurrence 2-3%
- Multifactorial

Sickle Cell Disease

- Autosomal Recessive
- 8 percent (1 in 12) of African Americans are carriers
- 0.15% of African Americans have SS
- 2 parents with trait
  - 25% risk of an affected child
  - Risk of SS for African American
    - $\frac{1}{12} \times \frac{1}{12} \times \frac{1}{4} = \frac{1}{576}$

Rokitansky-Kuster-Hauser

- Mullerian Agenesis
- 1/4000 births
- 46, XX
- Vaginal agenesis
- Normal ovarian function
- Normal growth & development
- 1/3 have urinary tract abnormalities
- Need karyotype
  - Distinguish between testicular feminization
  - Primary amenorrhea
Testicular Feminization (Androgen Insensitivity)

- Male pseudohermaphrodite
- 46XY
- X-linked recessive
- 25% risk of affected child
- 25% risk of carrier
- End-organ insensitivity to androgens
- Blind vagina - no uterus
- Absent to sparse hair

- Body responds normally to antimullerian hormone
- Testosterone & LH increased
- 5% risk of malignant tumors
- Remove gonads after puberty

Kallman Syndrome

- Gonadotropin Deficiency
- Hypogonadotropic hypogonadism
- Anosmia
- Color blindness
- Cleft lip & palate

Omphalocele

- 1/5800 live births
- Associated with trisomy 13 and trisomy 18
  - 35-58%
- 30% association with other fetal anomalies
- Umbilical cord inserts into center of sac
- 30-40% mortality
- Recurrence
  - Less than 1%
Gastroschisis

- 1/10,000 live births
- Vascular compromise umbilical vein, omphalomesenteric artery
- No significant increase in other fetal anomalies
  - 10 percent
  - Cord is connected to abdominal wall

Ethnic Genetic Disorders

- **Fragile X**
  - Fragile X mental retardation 1 (FMR1) gene - X chromosome
  - Increase CCG trinucleotide repeats
    - Unaffected
      - 5–44 repeats
    - Grey Zone
      - 45 to 54 repeats
    - Prenatalization
      - 55 and 200 repeats
    - Affected
      - Greater than 200 repeats
    - Displays genetic anticipation
    - Neither dominant or recessive
  - Intellectual disability and cognitive impairment
    - Long and narrow face
    - Prominent forehead
    - Large ears
    - Decreased muscle tone

- Disease Specific Genetic Screening
  - | Test | Carrier Frequency | Role group |
  - | | | |
  - | | | |
  - | | | |
  - | | | |

- Molecular diagnosis includes: expanded CCG repeat in intron 1 of FMR1 gene
- Genetic counseling should be offered in cases
- Newborn screening for Fragile X chromosomal disease
- Molecular diagnosis testing available in some centers

- **Unaffected**
  - 5–44 repeats
  - Grey Zone
  - 45 to 54 repeats

- **Prenatalization**
  - 55 and 200 repeats

- **Affected**
  - Greater than 200 repeats

- **Fragile X mental retardation 1 (FMR1) gene - X chromosome**

- **Intelectual disability and cognitive impairment**

- **Long and narrow face**

- **Prominent forehead**

- **Large ears**

- **Decreased muscle tone**
Spinal Muscular Atrophy

- Defect in SMN1 gene
- Encodes SMN protein necessary for motor neuron survival
- Autosomal recessive
- Gene frequency: 1 in 100
- Carrier testing available
- ACOG recommended screen
- PIGD available

- Neuromuscular disorder
- Affects motor neurons in spinal cord causing progressive muscle degeneration and weakness

Screening Test
- Offered to a large, low-risk group
- Identifies smaller group who may benefit from further testing
- Inexpensive
- Low risk to patient
- Easy

Diagnostic Test
- Offered to high-risk group
- Provides a definitive result
- Expensive
- Higher risk to the patient
- More difficult to perform
Prenatal genetic screening

- Assessment of risk of patient having a fetus affected by a genetic disorder

Prenatal genetic diagnostic testing

- Determines with as much certainty as possible whether a specific genetic disorder or condition is present in the fetus

- Fetal chromosomes evaluated for presence/absence of abnormalities in chromosome number, deletions, and duplications, or fetal DNA evaluated for specific genetic disorders

- No one screening test is superior to another in all test characteristics

- Screening should be an informed patient choice that fits the clinical circumstances, values, interests, and goals

GENERAL INTRODUCTION

- Importance of prenatal genetic screening

  - Reassurance
    - Majority of patients undergo screening or diagnostic testing for this reason
  
  - Prepare for a child with special needs
  
  - Therapeutic alteration of outcome (rare)
  
  - Terminate pregnancy

Counseling

- Patient should be counseled regarding the adjusted likelihood of carrying a fetus with the evaluated aneuploidies

- Potential for fetus to be affected by genetic disorders not evaluated by screening or diagnostic testing

- Prenatal diagnosis of fetal aneuploidy

  - Expectant management
  
  - Education for preparedness and expectations
  
  - Delivery at a tertiary care center
  
  - Potential need for hospice
  
  - Terminations of pregnancy

  - Expectant management with special needs adoption
GROUPS WITH INCREASED GENETIC RISK

- Pregnant women
- Advanced maternal age
- Certain ethnic groups
  - Ashkenazi Jews
  - French Canadians
  - Cajun
- Previous affected fetus
- Fetus with major anomaly
- Men/women carrying chromosomal abnormalities
  - Translocation
  - Inversion
  - Aneuploidy

FACTORS AFFECTING GENETIC RISK

- Environment
- Genetics
- Socioeconomic status
- Maternal diabetes
- Maternal weight
- Maternal alcohol use
- Family History of NTD
- Medication exposures

PRENATAL ANEUPLOIDIES

- Other
- Sex Chromosome
- Trisomy 13
- Trisomy 18
- Trisomy 21

COMMON CYTOGENETIC ABNORMALITIES

- Trisomy 21
  - 1 in 800 live births
- Trisomy 18
  - 1 in 8000 live births
- Trisomy 13
  - 1 in 20,000 live births
- 45,X
  - 1 in 10,000 live births
- 47,XXX; 47,XXY; 47,XYY
  - 1 in 900 live births
- De(5p)
  - 1 in 20,000 live births

METHODS OF GENETIC SCREENING

- Maternal serum screening
- Ultrasound
- Combinations of the above
- Circulating Cell Free DNA analysis
- Microarray
- Preimplantation genetics