SEX

• “Despite the fact that women are significantly different from men, there is considerable reproductive evidence that they belong to the same species”
  » British Medical Journal

SEX

• What are the questions ?
• Why sex ?
  – Virtually all metazoans have it
  – But why two ?
• How is it determined ?
  – Humans are different from alligators and fruit flies
X and Y chromosomes

- The X is BIG (5-6% of genome) with lots of genes (mostly encoding somatic function) markers, and disease-associated mutations.
- The Y is small (though variable in length)...but it does have some genes
Y-chromosome genes

Sex Determination
Sex Determination

- Humans are different from alligators and fruit flies
- Klinefelter syndrome individuals (47,XXY) have male phenotype
- Study rare exceptions to the rule (Sex Reversal:
  - XX males, XY females)
- Hypothesis: Y chromosome material translocated to X in XX males

X and Y chromosomes at meiosis
Sex-determining region Y

-85% of XX-males have Y-derived sequences
-Single gene, SRY, with conserved HMG DNA-binding domain
-Sry confers male development in transgenic mice
-20% of XY-females have deletions or point mutations in SRY (HMG domain)
-SRY NECESSARY BUT NOT SUFFICIENT FOR SEX DETERMINATION
Dosage compensation

X-inactivation—the Lyon Hypothesis—in Somatic Cells

- Early
- Random…usually
- Complete…mostly
- Permanent and clonally propagated
  - Female is MOSAIC of cells, each cell is functionally HEMIZYGOUS
X-inactivation
Evidence for X-inactivation

- Genetic
- Cytologic
- Biochemical

Barr Body

Number of sex chromatin (Barr bodies) bodies is equal to Xn-1
G6PD

Ornithine Transcarbamylase
Implications of Lyonization

- Greater variability of clinical manifestations in heterozygous females than in hemizygous males
- Skewed X-inactivation
X-inactivation

- **X-Inactivation Center (XIC)**
- **XIST X_Inactive-Specific Transcript**
  - Female-specific expression in karyotypically normal individuals
  - Amount of XIST transcript is proportional to number of X chromosomes minus one
  - Association with Barr body
- Inactivation of *Xist* prevents inactivation
- Counting, Establishment, Maintainance
Klinefelter Syndrome

- 1/1000 males
- Post-pubertal testicular failure
  - Small testes, hyalinized tubules, azospermia
  - Infertility, variable hypogonadism
  - Social pathology
- At least 2 X’s and one Y in at least some cells (usually 47,XXY)
- Nondisjunction in PI or MI
- Multiple X’s---MR
Turner syndrome

- 1/5,000 females
- Gonadal dysgenesis, disappearance of eggs
- Sexual immaturity
  - Amenorrhea
  - Infertility
- Short stature
- Somatic abnormalities
- Something wrong with the second X in some cells
Turner syndrome
Why Turner Syndrome?

- Males don’t have Turner syndrome
- Hypothesis: X-linked genes that
  - 1. escape inactivation
  - 2. have Y-chromosome homologs
Fragile X Syndrome

- Frequency: ~1/3500 males, ~1/6000 females
- Phenotype
  - Facial abnormalities
  - Macroorchidism
  - Connective tissue abnormalities
  - Moderate mental retardation (mild in females)
    - (ADDH, autism)
- Fragile site (FRAXA) at Xq27.3
Inheritance of Fragile X Syndrome

X-linked….but…

• 20% of obligate carrier males are phenotypically and karyotypically normal—Normal Transmitting Males (NTM)
• MR in females ONLY if mutation inherited from mother
• Penetrance (MR) is a function of position in the pedigree and increases in successive generations—Sherman Paradox
**FMR1** Gene

- 38 kb gene at Xq27.3
- Encodes a 614-AA RNA-binding protein (FMRP)
- 5’-UTR contains a polymorphic CGG triplet repeat
- Normal 6 to 52 repeats (mode 30)
- Affected 100s to 1000s of repeats (>230)
- Mitotically unstable
**Premutation**

- 60 -- 200 CGG repeats
  - Normal Transmitting Males
  - Most carrier females
- Unmethylated and transcribed
- Unstable. Expands in female meiosis
- Risk of expansion depends on repeat length
  - $\leq 20\%$ for $n<70$ \hspace{1cm} $>99\%$ for $n>90$
- No full mutation from normal repeat
Sherman Paradox

Molecular Diagnosis of FRAX
Size of premutation alleles

Triplet Repeat Diseases
And FISH!

**Table 8.5. Indications for Karyotype**

<table>
<thead>
<tr>
<th>Known or suspected chromosome abnormality</th>
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<tbody>
<tr>
<td>Multiple congenital anomalies and/or growth and mental retardation</td>
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<tr>
<td>Disorder of sexual differentiation</td>
</tr>
<tr>
<td>Undiagnosed mental retardation</td>
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<tr>
<td>Selected hematologic malignancies</td>
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<tr>
<td>Multiple miscarriages</td>
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</tbody>
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**Down Syndrome**

- Growth retardation
- Mental retardation—variable
- Somatic abnormalities
  - Abnormal facies (flattened face and occiput, large tongue, small ears, epicanthal folds)
  - Congenital heart disease (40%)—AV canal
  - GI abnormalities (5%)—duodenal stenosis
  - Leukemia (10 to 20 x increased risk)
  - Ear infections
  - Thyroid problems
  - Premature aging (cataracts, Alzheimer Disease)
- Pathogenesis: overexpression of genes on 21q
Down syndrome

### Down syndrome--Cytogenetics

- **Trisomy 21** 95%
  - Maternal nondisjunction in 95%
  - 80% of these are MI (maternal age effect)
- **Unbalanced translocation** 4%
  - (9% <30 yo mothers; <2% >35 yo
  - 60% are 14q21q
    - 50% of these are de novo—**50% are inherited!**
  - <40% are 21q isochromosome—nearly all de novo
- **Mosaicism** (milder phenotype) <3%
- **Cytogenetic analysis is essential!**
Down syndrome—maternal age effect

Down syndrome—recurrence risks

- ~1% for Trisomy 21
- ~10 to 15% for unbalanced translocation if mom is carrier; <5% if dad is carrier
- **Note:** each first degree relative of a balanced translocation carrier has a 50% chance of being a balanced translocation carrier.
Screening for Down syndrome risk

- Maternal age
- Second trimester screening
  - Low alpha-fetoprotein (AFP)
  - Low unconjugated estriol
  - High chorionic gonadotrophin (hCG)
- First trimester screening
  - Nuchal translucency
  - High free beta-subunit of hCG
  - Low pregnancy-associated plasma protein A

Prenatal diagnosis of Down syndrome

- Amniocentesis
- Chorionic villus sampling (CVS)

- Standard cytogenetic analysis
- FISH