Basic Genetic Principles for the Non-Geneticist

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Disclosures

- Consultant - Teva Pharmaceuticals
- Clinical Expert Panel Member, Illumina Inc.
Human Genome - Encyclopedia
23 Chromosome Pairs
Chromosome = Volume
Gene = Chapter, recipe
(~20,000)

OATMEAL MUFFINS

1 cup quick-cooking rolled oats
1 cup milk
1 cup sifted all-purpose flour
½ cup sugar
3 teaspoons baking powder
½ teaspoon salt
1 well-beaten egg
¼ cup salad oil or melted shortening

OVEN 425°

Combine rolled oats and milk; let stand 15 minutes. Sift flour, sugar, baking powder, and salt into bowl. Combine egg, oil, and oatmeal mixture. Add all at once to sifted dry ingredients, stirring just to moisten. Fill greased muffin pans 3/4 full. Bake at 400° for 20 to 25 minutes.
Nucleotide base pairs = Letter
Genome = 3,000,000,000 bp
The Exome
1-2% of the genome ~50,000,000 bp

DNA → Gene → Protein
From Gene to Protein
Proteins
Cellular Building Blocks

- Structural proteins
- Hormones
- Enzymes
- Receptors
- Etc…
Genetic Aberrations

- Chromosomal
  - Numeric
  - Structural
- Submicroscopic
  - Deletions/Duplications
- Sequence Variants
Genetic Aberrations

● Chromosomal
  ▪ Numeric
  ▪ Structural

● Submicroscopic
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Genetic Aberrations

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Aneuploidy

Trisomies:
- Down syndrome   trisomy 21
- Edwards syndrome trisomy 18
- Patau syndrome  trisomy 13
- Sex Chromosome Anomalies:
  - Klinefelter syndrome 47,XXY
  - Jacobs Syndrome 47,XYY
  - Trisomy X 47,XXX

Monosomy
- Turner syndrome monosomy X (45,X)
Mosaic Aneuploidy

- **Definition:** Presence of ≥2 different cell lines with different chromosomal constitution
Mitotic/Post-zygotic Nondisjunction

Gamete → Normal

Zygote → Normal

Zygote → Trisomic

Nulisomy

nondisjunction
Meiotic Nondisjunction & Trisomic Rescue

- Primordial Germ Cell
- Gamete
- Zygote
- Embryo

Meiosis
- Fertilization
- Partial Trisomic Rescue
Mosaicism Continuum
From Cleavage-Stage to Blastocyst
Mosaicism Continuum
From Blastocyst to Feto-Placental Unit

Consequence of Mosaicism

We all have some degree of mosaicism, so the clinical relevance depends on:

- Chromosome involved (some more harmful than others)
- % abnormal cells
- The tissue distribution (placental, fetal)
- Other ramifications (UPD)

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Balanced Translocation
Unbalanced Translocation
Genetic Aberrations

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Microdeletion Syndromes

DiGeorge / VCF
3.5 Mb del 22q11

Williams-Beuren
1.5 Mb del 7q11.23

Prader Willi
4 Mb del 15q11-13
## Microdeletion Syndromes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OMIM#</th>
<th>Gene(s)/Locus</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>1p36 Microdeletion</td>
<td>607872</td>
<td>Multiple</td>
<td>ip36</td>
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<tr>
<td>1q21.1.1 Distal microdeletion</td>
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<td>1q22.1 Microdeletion with suspected thrombocytopenia/absent radius (TA)</td>
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<td>1q41-42 Microdeletion/ Dysmorphism</td>
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<td>2p15-16.1 Microdeletion</td>
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<td>17p13.1 Microdeletion</td>
<td>613776</td>
<td>TPS3</td>
<td>TPH1</td>
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### Disorder Details

- **Ojeda–neurofibromatosis, X-linked**: OMIM #175700
- **GL3**: Location 17q11.1
- **Multiple TP53**
- **Craniofacial dysostosis, X-linked**: OMIM #613776
- **TP53**
- **SYAMA**: Location 11q23.1

### Additional Resources

- **CoGEN**: A database for genetic information and resources.
Pathogenic CNVs
22q11 deletion DiGeorge/VCF
Variant of Uncertain Significance (VUS)

CHRNA7 duplication
Genetic Aberrations

- Chromosomal
  - Numeric
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- Sequence Variants
Sequence Variants

1. Pathogenic variant (mutation)
2. Likely pathogenic variant
3. Variant of unclear significance (VUS)
4. Likely benign variant
5. Benign variant

ACMG Standards and guidelines for the interpretation of sequence variants 2015
Likely Benign Variant

aag ttg \textcolor{red}{aag} cac

50 shades of Gray

aag ttg \textcolor{red}{tgg} cac

50 shades of Grey
Likely Pathogenic Variant

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<table>
<thead>
<tr>
<th>aag ttg</th>
<th>agg cac</th>
<th>1 big egg</th>
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<tbody>
<tr>
<td>aag ttg</td>
<td>tgg cac</td>
<td>1 bug egg</td>
</tr>
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</table>
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Implication of a Pathogenic Variant

Normal CFTR Channel moves chloride ions to the outside of the cell.

Mutant CFTR Channel does not move chloride ions, causing sticky mucus to build up on the outside of the cell.
## Prenatal Diagnosis of Anomalies

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Method</th>
<th>Detection</th>
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<tbody>
<tr>
<td>Trisomy</td>
<td>qfPCR, FISH</td>
<td>30%</td>
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<tr>
<td>Unbalanced abnormalities</td>
<td>Karyotype</td>
<td>5%</td>
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<tr>
<td>Pathogenic Copy Number Variants (CNVs)</td>
<td>CMA</td>
<td>3%-6.5%</td>
</tr>
<tr>
<td>Point mutations / small indels</td>
<td>WES/WGS</td>
<td>6%-80%</td>
</tr>
</tbody>
</table>

Modes of Inheritance

- Grandfather
- Grandmother
  - Father
  - Mother
    - Sister
    - Me
    - Brother
  - Uncle
    - Cousin
  - Aunt
    - Cousin
Autosomal Dominant

[Genetic chart showing autosomal dominant inheritance pattern with affected and unaffected individuals and family tree representation.]

U.S. National Library of Medicine
Autosomal Dominant

Examples

- Neurofibromatosis (NF)
- Tuberous sclerosis complex (TSC)
- Achondroplasia
- Marfan syndrome
- Familial adenomatous polyposis (FAP)
Autosomal Recessive
Autosomal Recessive

Examples

- Cystic fibrosis (CF)
- Spinal muscular atrophy (SMA)
- Tay Sachs disease
- Thalassemias
- Sickle cell anemia
- Congenital adrenal hyperplasia (CAH)
X-Linked Recessive

[Diagram showing genetic inheritance patterns for X-linked recessive traits, with labels for unaffected father, carrier mother, unaffected son, unaffected daughter, carrier daughter, affected son, and a genetic chart illustrating the inheritance pattern.]
X-linked Recessive

Examples

- Duchenne & Becker muscular dystrophy
- Hemophilia A/B
- Color blindness
- G6PD deficiency
X-Linked Dominant Affected Mother

U.S. National Library of Medicine
X-linked Dominant

Examples

- X-linked Hypophosphatemic Rickets
- Alport
- Aicardi (male lethal)
- Rett (male lethal)
Non-Mendelian Inheritance

- Multifactorial Inheritance
- Triplet repeat expansion disorders
- Genomic imprinting
- Uniparental disomy (UPD)
- Mitochondrial DNA mutations
Multifactorial Inheritance

- Conditions affected by multiple genes & Environment
- Examples:
  - Pyloric Stenosis
  - Neural tube defects (NTDs)
  - Cleft lip/palate
- Threshold Phenomenon
Triplet Repeat Expansion Disorders

- Healthy individuals have variable No. of repeats
- Repeat size > threshold = disease

Examples:
- Myotonic Dystrophy (CTG)
- Huntington disease (CAG)
- Fragile X (CGG)

>200 Full mutation
55-200 Premutation
5 - 55 Normal

38 kb
Genomic Imprinting

An epigenetic phenomenon where certain genes are expressed from only one of the two alleles, in a parent-of-origin-specific manner

● Imprinting = Inactivation by methylation
● Imprinted alleles are silenced without altering the DNA
Imprinting During Development

- Imprinting is erased and re-established in the germline
- Maintained during mitotic divisions
Uniparental Disomy (UPD)

Both chromosome copies inherited from one parent
- Clinically significant if involves imprinted genes
- Increases risk of autosomal recessive disorders

- **Isodisomy:**
  2 copies of the homolog are inherited from one parent

- **Heterodisomy**
  2 different homologs are inherited from one parent
UPD Caused by Trisomy Rescue

Disomic 15 oocyte

Haploid sperm

Trisomy 15 conceptus

In 2/3 cases Normal

Prader-Willi Syndrome

In 1/3 cases heterodisomic UPD15mat
UPD Caused by Monosomy Rescue

Nulisomy 15 oocyte → Duplication → Nulisomy 15 conceptus

Haploid sperm

isodisomic UPD15pat

Angelman Syndrome
Mitochondrial Inheritance

- Cellular source of energy
- Contains circular DNA molecules 16,569 bp long
- Encodes 13 polypeptides of oxidative-phosphorylation
- Inherited exclusively from the mother through the oocyte which contains ~ $10^5$ mtDNA molecules
- Mutations usually affect muscle and nerve
Mitochondrial Inheritance

Examples:

- Mitochondrial myopathy
- Diabetes mellitus and deafness (DAD)
- Leber's hereditary optic neuropathy (LHON)
- Leigh syndrome
- Myoclonic Epilepsy with Ragged Red Fibers (MERRF)
Genetics 101