Medical Genetics: Case #4

4 year old boy who is behind in his developmental milestones, has a long face, large mandible, large everted ears. Similar findings in his older brother. His older sisters are apparently normal.

1. Probable Diagnosis?

answer on next slide
TRUE / FALSE?

1. This child probably has an X-linked mental retardation syndrome.  
   - True

2. The disease is caused by an expansion of triplet repeats in the 5’ - UTR of the FMR-1 gene.  
   - True

3. This is the SECOND most common genetic cause of mental retardation. (Trisomy 21, Down syndrome)  
   - True

4. The frequency in the male population is approximately 1:2000 - 4000.  
   - True

5. Carrier females rarely show symptoms of mental retardation.  
   - True

6. Children of this patient’s sister (if she is a carrier) are likely to show a more SEVERE form of the disease.  
   - True

Triplet repeat instability happens preferentially in women - if the FMR-1 gene is passed from a woman to her child, it has a chance of enlarging. Phenomenon of genetic anticipation (occurs in carrier females): severity increases through successive generations. But remember that since it is X-linked, those who will be most affected and will suffer from mental retardation are the sons of the women with greatly expanded triplet repeats.  
   - All true.
TRUE / FALSE?

1. This child probably has an X-linked mental retardation syndrome.
2. The disease is caused by an expansion of triplet repeats in the 5’ - UTR of the FMR-1 gene.
3. This is the SECOND most common genetic cause of mental retardation. (Trisomy 21, Down syndrome)
4. The frequency in the male population is approximately 1:2000 - 4000.
5. Carrier females rarely show symptoms of mental retardation.
6. Children of this patient’s sister (if she is a carrier) are likely to show a more SEVERE form of the disease.
Medical Genetics: Fragile X Syndrome

American College of Medical Genetics guidelines:

Testing any person with unexplained mental retardation, developmental delay, or autism, especially if physical or behavioral characteristics commonly associated with the fragile X syndrome are evident.

Test for Fragile X in people with unexplained MR, because Fragile X is so common. There is no cure, but it is still useful for parents to know why their child suffers from mental retardation and probably also in deciding whether to have more children.
Medical Genetics: Fragile X Syndrome

- Results from decreased expression of the fragile X mental retardation protein (FMR1) on the X chromosome.
- Usually caused by expansion of a microsatellite triplet repeat (CGG) in the 5' UTR of the FMR1 gene
  - Triplet repeat expansion leads to DNA hypermethylation and decreased transcription.
  - Maternal effect
  - Hypermethylation of new expansions only occurs when the X chromosome comes from the mother

**KEY CONCEPT:**

**Triplet Repeat Disease**

**Fragile X Syndrome:**
- expansion of triplet repeat (CGG) in 5' untranslated region of the FMR1 gene
- this expansion causes DNA hypermethylation of the translated part of the FMR1 gene - get decreased expression of the FMR1 protein
- lack of FMR1 protein causes mental retardation - MR only in males, because females have expression of FMR1 protein from their other (normal) X chromosome.

--------------

Triple Repeat Diseases (in general):
- (background info:) most short repeats are stable - use them for forensics testing, identity testing etc.
- a subset of repeats are unstable (can grow or shrink) - get disease if it's in a critical region of genome
Medical Genetics: Fragile X Syndrome

• The Severity of the disease is determined by the number of triplet repeats.
  – Normal: 5-45
  – Gray-zone: 46-60
  – Pre-mutation: 61-199
  – Full mutation: >200

• Two methods of testing
  – PCR – conceptually simple
  – Southern Blot – conceptually difficult

Question: how many repeats are typically added each generation. It seems that as you add more repeats, you get more instability, and start adding more and more each generation. It’s a slippery slope, I guess. There are probability charts, so if a woman with 65 repeats (for example) asks you whether she will have an affected child, you can tell her the probability that she will have a child with 200+ repeats.
Medical Genetics: Fragile X Syndrome

• Pre-mutation Phenotypes
  – Fragile X-associated **tremor/ataxia syndrome**
    • Late onset progressive cerebellar ataxia and intention tremor in males who have a premutation.
      – Age related penetrance (17% by 50-59 years, 38% by 60-69 years, 47% by 70-79 years and 75% by 80 years)
      – Can be seen in female carriers (ataxia and tremor)
  – **FMR1-related premature ovarian failure**
    • Cessation of menses before the age of 40 in female carriers
      – 21% (15-27%) prevalence amongst women who have pre-mutations (61-199 repeats)

(61-199 triplet repeats) - obviously phenotype less severe than full-blown mutations (200+ repeats)
but more common in men

test women who are having trouble getting pregnant for Fragile X
Medical Genetics: Fragile X Syndrome

"I don't have time to talk about these but you might want to read a little bit about these - especially Myotonic Dystrophy and Huntington Disease.... Do you guys every watch that show House? You know, with the woman with the... Huntington's?... It's just personal between me...anyway, it's a good episode."

Myotonic Dystrophy and Huntington Disease discussed in CNS block after Spring Break.

- **Myotonic Dystrophy**
  - CTG 3’ UTR Myotonin-protein kinase (DMPK), AD, 1:20,000 (ish)
- **Huntington Disease**
  - CAG (polyglutamine) HD gene, AD 1:20,000 (ish)
- **Kennedy's Disease**
- **Spinocerebellar Ataxia-I**
- **Machado-Joseph Disease**
Medical Genetics: Case #5

- 20 year old man with fragile, bruisable skin that heals with 'cigarette-paper' scars and joint hypermobility.
Medical Genetics: Case #5

TRUE / FALSE?

1. This is **NOT** Marfans syndrome:
   1. an autosomal dominant disease that results from fibrillin mutations
   2. with a population frequency of about 1:10,000.

2. This is most likely **Ehlers-Danlos syndrome (Type I)**
   1. an autosomal dominant disease that results from mutations in the collagen alpha-1(V) gene (COL5A1), the collagen alpha-2(V) (COL5A2)
   2. With a population frequency of about 1:10,000.

3. Other complications of this disease include; rupture of large vessels, spontaneous rupture of the bowel, and diverticula of the bowel.

All true.
TRUE / FALSE?

1. This is NOT Marfans syndrome:
   1. an autosomal dominant disease that results from fibrillin mutations
   2. with a population frequency of about 1:10,000.

Symptoms of Marfans syndrome include:
   Increased height
   disproportionately long limbs and digits *spider digits*
   **mild** joint laxity *(Ehlers Danlos has severe joint laxity)*
   vertebral column deformity
   a narrow, highly arched palate with crowding of the teeth, subluxation of the lens
Symptoms of Marfans syndrome include:

Mitral valve prolapse, mitral regurgitation, dilatation of the aortic root, and aortic regurgitation.

The major life-threatening cardiovascular complications of Marfan’s syndrome is aneurysm of the aorta and aortic dissection.
Medical Genetics: Case #5

Marfan’s Syndrome:

- Long digits
- High Arched Palate
Medical Genetics: Ehlers Danlos Syndrome

TRUE / FALSE?

1. This is **NOT** most likely Marfans syndrome:
   1. an autosomal dominant disease that results from fibrillin mutations
   2. with a population frequency of about 1:10,000.

2. This is most likely Ehlers-Danlos syndrome (Type I)
   1. an autosomal dominant disease that results from mutations in the collagen alpha-1(V) gene (COL5A1), the collagen alpha-2(V) (COL5A2)
   2. With a population frequency of about **1:10,000**.

3. Other complications of this disease include; rupture of large vessels, spontaneous rupture of the bowel, and diverticula of the bowel.
Many ‘types’ of EDS with a variety of clinical symptoms with a broad range of severity.

- COL5A1, COL5A2 – Autosomal Dominant (classic)
- COL3A1 – Autosomal Dominant (Vascular)
- COL1A1 – Autosomal Dominant
- Lysyl-hydroxylase – Autosomal RECESSIVE (kyphoscoliosis)
- Procollagen N-peptidase – Autosomal RECESSIVE

**KEY CONCEPT:**
Dominant Mutation vs. Loss of Function

There are many type of Ehlers Danlos Syndrome (EDS), that range in severity and have varying clinical symptoms.
- Autosomal dominant forms caused by mutations in collagen. Get “Dominant negative effect” - the one bad copy interferes with functioning of the good copy.
- Autosomal recessive forms caused by mutations in genes that code for proteins that metabolize collagen to its final form (more rare). This is a loss of function mutation. If you had one good copy, you would be fine.
Medical Genetics: Case #6

45 year old male with persistent crushing substernal chest pain. ER evaluation shows EKG changes consistent with an acute MI, and elevated troponin-T and CK-MB. Lipid panel reveals a cholesterol of 450 most of which is LDL.

Most Probable Diagnosis?
TRUE / FALSE?

1. This patient may have an autosomal dominant mutation which affects cholesterol metabolism.

2. This patient may have a mutation in the receptor for LDL.

3. The frequency of LDL receptor mutations is approximately 1:500, making familial hypercholesterolemia one of the most common inherited autosomal dominant diseases.

4. Having two copies of mutant LDL receptors is compatible with life. (cholesterol = 5-6 x normal)

5. Many different mutation in the LDL receptor account for familial hypercholesterolemia including large and small deletions, point mutations affecting LDL binding, internalization, trafficking, etc.
Medical Genetics: Familial Hypercholesterolemia

TRUE / FALSE?

1. This patient may have an autosomal dominant mutation which affects cholesterol metabolism.
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5. Many different mutation in the LDL receptor account for familial hypercholesterolemia including large and small deletions, point mutations affecting LDL binding, internalization, trafficking, etc.
Medical Genetics: Familial Hypercholesterolemia

Heterozygotes have serum cholesterol levels ~2x normal.

KEY CONCEPT: Gene Dosage Effects

Homozygotes have very high (~5-6x normal) serum cholesterol.

Early and severe coronary artery disease.

Myocardial infarction before age 30 if untreated.
Medical Genetics: Familial Hypercholesterolemia

Bonus Question: What is this?

xanthelasma
QUESTIONS?

There was one question; I added it to slide 6 because that’s what it was about.
Dr. Datto "You are not responsible for this for the exam, but for life, you are." Student has marked these diseases as "not testable"
Still true. Dr. H
Medical Genetics: Case #7

6 month old boy who is behind in his developmental milestones, the patient has a mousy odor (phenylacetic acid), eczema and fair colored skin and hair. Recent onset of seizures.

Most Probable Diagnosis?
Medical Genetics: Case #7

TRUE / FALSE?

1. This child likely has phenoketouria (PKU) an autosomal recessive inborn error of metabolism.
2. PKU is a disease caused by a mutation in phenylalanine hydroxylase (PAH).
3. The disease frequency is 1:10,000 – 1:15,000.
4. >100 mutations in PAH accounts for 98-99% of PKU (15 or so common mutations), the remaining 1-2% is due to mutations in other genes.
5. Newborn screening through a blood test for amino acid levels is the standard of care.
6. Early treatment (before 30 days) prevents retardation (Usually)
7. Treatment can be discontinued as an adult, sort of.
8. Pregnant women with a history of PKU should not drink diet soft drinks.
Medical Genetics: Phenoketouria (PKU)

TRUE / FALSE?

1. This child likely has phenoketouria (PKU) an autosomal recessive inborn error of metabolism.
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7. Treatment can be discontinued as an adult, sort of.
8. Pregnant women with a history of PKU should not drink diet soft drinks.
KEY CONCEPT:
Different deficiencies in a metabolic pathway can lead to a single disease phenotype.
Medical Genetics: Phenoketouria (PKU)

1. In addition to testing for PKU, neonates are usually tested for the following genetic disease.

Newborn Screening Panel: Core Panel (Department of Health and Human Services recommendations: http://mchb.hrsa.gov/screening/summary.htm)

<table>
<thead>
<tr>
<th>9 OA</th>
<th>5 FAO</th>
<th>6 AA</th>
<th>3 Hb Pathies</th>
<th>6 Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA</td>
<td>MCAD</td>
<td>PKU</td>
<td>Hb SS*</td>
<td>CH</td>
</tr>
<tr>
<td>GA I</td>
<td>VLCAD</td>
<td>MSUD</td>
<td>Hb S/βTh*</td>
<td>BIOT</td>
</tr>
<tr>
<td>HMG</td>
<td>LCHAD</td>
<td>HCY*</td>
<td>Hb S/C*</td>
<td>CAH*</td>
</tr>
<tr>
<td>MCD</td>
<td>TFP</td>
<td>CIT</td>
<td></td>
<td>GALT</td>
</tr>
<tr>
<td>MUT*</td>
<td>CUD</td>
<td>ASA</td>
<td></td>
<td>HEAR</td>
</tr>
<tr>
<td>3MCC*</td>
<td></td>
<td>TYR I*</td>
<td></td>
<td>CF</td>
</tr>
<tr>
<td>Cbl A,B*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROP</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BKT</td>
<td></td>
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</tr>
</tbody>
</table>
Case Study #8

• 45 year old female with right sided colon mass. Resection showed a poorly differentiated colon cancer with mucinous histology and infiltrative signet ring cells. This patient has no family history of colon cancer.
Case Study #8

• True/False

• Given the mucinous histology of this patients colon cancer, its right sided location and her age, this patient is at increased risk for having HNPCC.

• Given the mucinous histology of this patients colon cancer, its right sided location and her age, this patient’s tumor likely has ‘microsatellite instability’.

• Germline mutations in two genes involved in DNA mismatch repair (MLH1, MSH2) account for 90% of HNPCC.

• The mutations in these genes are loss of function mutations (eg. Inactivating mutations of tumor supressor genes)?

• Inheritance of only one mutant copy of MLH1 or MSH2 is sufficient to cause colon cancer? (autosomal dominant)
Case Study #8

- Given the mucinous histology of this patient's colon cancer, its right-sided location, and her age, this patient is at increased risk for having HNPCC (Hereditary nonpolyposis colon cancer).

- Given the mucinous histology of this patient's colon cancer, its right-sided location, and her age, this patient's tumor likely has microsatellite instability.

- Germline mutations in two genes involved in DNA mismatch repair (MLH1, MSH2) account for 90% of HNPCC.

- The mutations in these genes are loss of function mutations (eg. Inactivating mutations of tumor suppressor genes)?

- Inheritance of only one mutant copy of MLH1 or MSH2 is sufficient to cause colon cancer? (autosomal dominant)

**KEY CONCEPT:**

Oncogenes vs. Tumor Suppressor Genes
Case Study HNPCC

- HNPCC is diagnosed by (True False):
- Clinical History?
  - Loss of MLH1, MSH2, MSH6 or PMS2 IHC staining in tumor tissue?
- Functional studies of microsatellite instability?
- Mutation analysis of MLH1, MSH2, MSH6 or PMS2 in peripheral blood?

All true.
Case Study HNPCC

- HNPCC is diagnosed by (True False):
- Clinical History?
- Loss of MLH1, MSH2, MSH6 or PMS2 IHC staining in tumor tissue?
- Functional studies of microsatellite instability?
- Mutation analysis of MLH1, MSH2, MSH6 or PMS2 in peripheral blood?
Case Study HNPCC

Clinical History.

- **Amsterdam II Criteria (61% Sensitive 67% Specific for MSI)**
  - Three or more family members, one of whom is a first-degree relative of the other two, with HNPCC-related cancers
  - Two successive affected generations
  - One or more of the HNPCC-related cancers diagnosed before age 50 years
  - Exclusion of familial adenomatous polyposis (FAP)

- **Bethesda Criteria (94% Sensitive, 25% Specific for MSI)**
  - Colorectal cancer diagnosed in an individual younger than than age 50 years
  - Presence of synchronous or metachronous colorectal, or other HNPCC-associated tumors
  - Regardless of age Colorectal cancer with the MSI-H histology diagnosed in an individual younger than age 60 years
  - Colorectal cancer diagnosed in one or more first degree relatives with an HNPCC-related tumor, with one cancer diagnosed before age 50 years
  - Colorectal cancer diagnosed in two or more first- or second-degree relatives of any age
Case Study HNPCC

- MSI by PCR
  - BAT25, BAT26, D2S123, D5S346, and D18S69 or D17S250
  - MSI-High = 2 or more markers with novel bands
  - MSI-Low = 1 marker with novel bands
  - If lane 1 is normal and lane 2 is tumor then?
  - Have we diagnosed HNPCC?

Not yet, bc in addition to inherited MSI/HNPCC, it could also be spontaneous loss of this pathway - loss of both copies by somatic mutation.
Case Study HNPCC

- MSI by IHC
  - MLH1
  - MSH2
  - MSH6
  - PMS2

- Have we diagnosed HNPCC?

No, because it still could just be a somatic loss.
Germline mutations in two genes involved in DNA mismatch repair (MLH1, MSH2) account for 90% of HNPCC.

- Mutations that cause Lynch Syndrome
  - MLH1 and MSH2 account for approximately 90% of families with HNPCC
  - MSH6 account for approximately 7%-10% of families with HNPCC
  - PMS2 account for fewer than 5% of families with HNPCC.
- At least 20% of mutations in MSH2 and 5% of mutations in MLH1 are large deletions or genetic rearrangements – Rest are point mutations

Since HNPCC can be caused by deletions or mutations, if you do an assay that detects mutations and don't find any, that does not rule out HNPCC, bc it would not have detected deletions. In other words, there is residual risk with such an assay. If you do find a mutation, you have finally diagnosed HNPCC!
Case Study HNPCC

- Patients with HNPCC (Lynch Syndrome) are at increased risk of developing (True/False):
  - Colon Cancer – 80%, median age 44 years?
  - Endometrial Cancer – 20-60%, median age 46?
  - Stomach Cancer – 11-19%, median age 56 years?
  - Ovarian Cancer – 9-12%, median age 42.5 years?

Percentages represent risk of developing cancers among patients with HNPCC.
**Case Study HNPCC**

- **Cancer Risks in Individuals with HNPCC up to Age 70 Years Compared to the General Population**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>HNPCC Risk</th>
<th>HNPCC Mean Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
<td>44 years</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
<td>46 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11%-19%</td>
<td>56 years</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9%-12%</td>
<td>42.5 years</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>2%-7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4%-5%</td>
<td>~55 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>49 years</td>
</tr>
</tbody>
</table>

Of people who get colon cancer, 3% have HNPCC. Impt to keep this in mind, bc if you have HNPCC, it increases risk of developing other cancers -- pts may need more vigilant screening.
Hampel et al, (2005) Screening for the Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) NEJM
Case Study HNPCC

• Things to think about:
  – Is MSI a symptom or cause?
  – For patients without mutations why is the expression of MSH2 or MLH1 lost?
    • Promoter methylation – how?
    • Regulation of protein stability, translation or gene expression – how?
  – What will you do in your practice?

in terms of screening etc. - not one right answer
Cytogenetic Disorders: Case Studies

Michael Datto MD PhD
Duke University Medical Center
Visualizing the Human Genome (Literally)

- **G-banding**
  - Standard for diagnostic testing in the U.S.
  - Banding pattern is obtained using protease pretreatment of the metaphase chromosomes followed by staining with Giemsa
  - Dark bands are AT-rich, associated with heterochromatin
  - **Light bands are CG-rich, associated with euchromatin (gene rich)**
  - Resolution typically limited to 3-10 Mb
Chromosome Nomenclature

- Long arm = q
- Short arm = p
- Bands
- Regions

22q11.2

just an example of what a region would be named

"petite"
When do I need to order a Karyotype?

- Preimplantation genetic diagnosis (rare)
- Prenatal diagnosis for Down Syndrome, for example - especially for advanced maternal age
- Products of conception if woman has had multiple miscarriages - look for explanation in genome
- Infertility or multiple miscarriages parent can carry balanced chromosomal balanced translocation that is lethal to offspring
- Determination of carrier status for an individual having a family history of a chromosome abnormality
- Assessment of individuals with congenital malformations and/or unexplained developmental delay
- Evaluation of adolescents with delayed growth and/or sexual development
- Evaluation of neoplastic specimens chromosomal abnormalities in tumors can help with diagnosis and prognosis
Medical Genetics: Case #1

New born male with a large atrial septal defect. The pregnancy was uncomplicated with the exception of advance maternal age of 46. The only other physical finding is a flat facial profile. Siblings are not affected and there is no history of spontaneous abortions in the mother.

Suspected diagnosis?
Medical Genetics: Case #1

Characteristic Physical Findings

Down Syndrome - flat face, atrial septic, and AMA gave it away

flat face, low ears - typical of Down Syndrome
KEY CONCEPT:
Disease Syndromes Associated with abnormal chromosome number (aneuploidy): +21, +13 (1:23,000), +18 (1:7,500)

Diagnosis?
Medical Genetics: Down Syndrome

TRUE / FALSE?

1. The incidence of trisomy 21 in children born to women over 45 is 4% (1 in 25)
2. The incidence of trisomy 21 in children born to women under 20 is 0.075% (1 in 1300)
3. 1 in 700 babies born in the US have Down Syndrome
4. Most trisomy 21 conceptions die in utero.
5. A diagnosis of trisomy 21 can be performed using chorionic villi sampling as early as 10-12 weeks gestation
6. A diagnosis of trisomy 21 can be performed using amniotic fluid as early as 16 weeks gestation

very small risk of loss of pregnancy
Medical Genetics: Down Syndrome

TRUE / FALSE?

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TRUE / FALSE?

1. Aproximately 40% of Down Syndrome patients have congenital heart disease (Endocardial Cushion Defects – ASDs, VSDs, valve malformations)

2. Down Syndrome patients have 10-20x increased risk of developing either acute lymphoblastic leukemia, or acute megakaryoblastic leukemia.

3. Virtually all Down Syndrome patients over 40 have neuropathologic changes characteristic of Alzheimer disease.
   
   This may be because amyloid precursor protein is on chromosome 21.

4. Although 80% of Down Syndrome patients have an IQ between 25 and 50, some have normal or near normal intelligence.

Phenotype of Down Syndrome has a lot of variability - a lot of this is because some Down Syndrom patients are chimeric - have two different cell types: normal and trisomy 21 cells. Chimeric individuals (also known as mosaicism) often have normal or near normal intelligence.

All true.
TRUE / FALSE?

1. Approximately 40% of Down Syndrome patients have congenital heart disease (Endocardial Cushion Defects – ASDs, VSDs, valve malformations)

2. Down Syndrome patients have 10-20x increased risk of developing either acute lymphoblastic leukemia, or acute megakaryoblastic leukemias.

3. Virtually all Down Syndrome patients over 40 have neuropathologic changes characteristic of Alzheimer disease

4. Although 80% of Down Syndrome patients have an IQ between 25 and 50, some have normal or near normal intelligence.
Medical Genetics: Down Syndrome

- Instead of 47,XY,+21, you receive a diagnosis from the cytogenetics laboratory of 46,XY,der(14;21)(q10;q10).
- What the heck does that mean?

**KEY CONCEPT:** Robertsonian translocation (unbalanced translocations)

Translocation between chr 14 and 21. Entire long arm of 21 stuck on to long arm of 14. (business end of both stuck on to each other). Called a Robertsonian translocation.
During segregation, a few things can happen during meiosis:
- germ cell gets a 14 and 21 - normal baby!
- germ cell can get the translocation and a normal 21 - end up with Down Syndrome (trisomy 21)
- germ cell can get the translocation and a normal 14 - not viable (remember, only trisomies 13, 18, and 21 are viable)
This is why it is important to get genetic testing, especially if you have one child with Down Syndrome - if you have a Robertsonian translocation then it is an inherited form of Down Syndrome, and you run a risk of having another Down Syndrome child.
Medical Genetics: Down Syndrome

TRUE / FALSE?

1. This described karyotype has 3 copies of the genetic information contained on chromosome 21.

2. Cytogenetic analysis should be performed on both the mother and father. Yes, the translocation could be inherited from either parent.

3. This is somewhat common (3-4% of Down Syndrome)

4. The parents should be counseled that they have a very high likelihood of having another Down Syndrome child in subsequent pregnancies (in theory about 1 in 3)

All true.
TRUE / FALSE ?

1. This described karyotype has **3 copies** of the genetic information contained on chromosome 21.
2. Cytogenetic analysis should be performed on both the mother and father.
3. This is somewhat common (**3-4% of Down Syndrome**)
4. The parents should be counseled that they have a very high likelihood of having another Down Syndrome child in subsequent pregnancies (in theory **about 1 in 3**
Medical Genetics: Case #2

25 year old male who comes to the clinic due to infertility. He is tall (ish) with long legs, has little body hair and has small (ish) atrophic testes. Mild gynecomastia is also present. The patient has a normal IQ, and is without any other medical history or complaints.
Medical Genetics: Case #2

KEY CONCEPT:
Disease Syndromes Associated with abnormal sex chromosome number: XXY, XYY (0.1%), XXX (0.1%), X0 (1:2,500)

Karyotype performed on peripheral blood mononuclear cells

Dx: Klinefelter

Klinefelter Syndrome XXY - often undetected until later in life, like when they try (unsuccessfully) to have babies.
Medical Genetics: **Klinefelter Syndrome**

**TRUE / FALSE ?**

1. Klinefelter Syndrome is a very common cause of hypogonadism in the male: **1 in 500 live births.**
2. Klinefelter Syndrome patients are **20x** more likely to get breast cancer than normal males.
3. Klinefelter Syndrome is **not usually diagnosed before puberty** and the presentation describe in this vignette is common.
4. Even with two or three additional X chromosomes, a single Y chromosome is sufficient to determine the male sex.

**All true.**
Medical Genetics: Klinefelter Syndrome

TRUE / FALSE?

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3. Klinefelter Syndrome is not usually diagnosed before puberty and the presentation described in this vignette is common.
4. Even with two or three additional X chromosomes, a single Y chromosome is sufficient to determine the male sex.
16 year old girl presents with amenorrhea and a failure to develop secondary sex characteristics. Also noteworthy is the patient’s short stature, webbed neck and symptoms suggestive of hypothyroidism.

A routine karyotype on peripheral blood mononuclear cells reveals two cell populations 46,XX and 45,X.
Dx: Turner Syndrome. Lack of secondary sex characteristics, webbed neck, short trunk.
TRUE / FALSE?

1. This patient has Turner Syndrome – characterized primarily by hypogonadism in phenotypic females
2. Turner Syndrome is very common (1:2000 live births)
3. Turner Syndrome is a frequent cause of primary amenorrhea (1/3 of all cases)
4. The mosaic karyotype is NOT an artifact

30% of Turner Syndrome patients are mosaic. Most Turner Syndrome conceptions die in utero. Severity is dictated by degree of mosaicism. More mosaic --> less severe phenotype.

All true.
TRUE / FALSE?

1. This patient has Turner Syndrome – characterized primarily by hypogonadism in phenotypic females
2. Turner Syndrome is very common (1:2000 live births)
3. Turner Syndrome is a frequent cause of primary amenorrhea (1/3 of all cases)
4. The mosaic karyotype is NOT an artifact. 30% of Turner Syndrome patients are mosaic (more mosaic = less severe phenotype)
TRUE / FALSE?

1. Coarctation of the aorta and bicuspid aortic valve are common congenital heart defects in Turner Syndrome patients.

2. Lymphedema in TS patients can cause swelling of the hands and feet and the characteristic ‘webbed neck’ appearance.

3. In normal females one X chromosome is NOT entirely inactivated.

There are in fact regions on chromosomes that are expressed from both X chromosomes (or one copy on X and one on Y in the case of a male) - these are called pseudoautosomal regions. This explains why Turner's causes problems and the characteristic phenotype.
TRUE / FALSE?

1. **Coarctation** of the aorta and **bicuspid aortic valve** are common congenital heart defects in Turner Syndrome patients.

2. **Lymphedema** in TS patients can cause swelling of the hands and feet and the characteristic ‘webbed neck’ appearance.

3. In normal females one X chromosome is **NOT** entirely inactivated.
Medical Genetics: Case #4

Newborn child presents with an atrial septal defect, cleft lip and palate, and developmental delay.

This child goes on to develop a T-cell immunodeficiency and hypocalcemia.

Suspected diagnosis?
TRUE / FALSE?

1. This patient likely has a deletion in 22q11.2, causing DiGeorge syndrome / velocardiofacial syndrome.
2. T-cell immunodeficiency in this syndrome is caused by thymic hypoplasia.
3. Hypocalcemia in this syndrome is caused by parathyroid hypoplasia.
4. Fluorescence in situ Hybridization is the diagnostic modality of choice in these cases.

All true.
TRUE / FALSE?

1. This patient likely has a deletion in 22q11.2, causing DiGeorge syndrome / velocardiofacial syndrome.

2. T-cell immunodeficiency in this syndrome is caused by thymic hypoplasia.

3. Hypocalcemia in this syndrome is caused by parathyroid hypoplasia.

4. Fluorescence in situ Hybridization is the diagnostic modality of choice in these cases.

KEY CONCEPT: Diseases caused by chromosomal deletions

DiGeorge is just one of many diseases caused by chromosomal deletions. There are regions in the chromosome that are flanked by repeat sequences that are susceptible to deletions or duplications. 21q11.2 has such a region - and deletion of this causes DiGeorge. Duplication of this locus causes a disease similar to DiGeorge.
Medical Genetics: 22q11.2

Review of FISH: Fluorescently labeled DNA that is complementary to a specific region of interest in a chromosome.
The probe in this particular case is a dual-color mixture of two separate probes for chromosome 22. The green signal is an internal control and is located at 22q13. It allows for quick identification of both #22 chromosomes. The red signal is located at the DiGeorge region at 22q11.2.

Deletion? No because we have two chromosome 22s, both with a red and green region. If there were a deletion, one chromosome would have the red missing.

http://www.dynagene.com
Medical Genetics: 22q11.2

TRUE / FALSE?
1. Deletions in 22q11.2 are common (1: 4,000)
2. Congenital heart defects are common in 22q11.2 deletion syndromes
3. Thymic hypoplasia is common in 22q11.2 deletion syndromes
4. The manifestation of disease symptoms is highly varied among patients, and diagnosis is typically made using clinical presentation and cytogenetic findings

All true.
TRUE / FALSE?

1. Deletions in 22q11.2 are common (1: 4,000)
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4. The manifestation of disease symptoms is highly varied among patients, and diagnosis is typically made using clinical presentation and cytogenetic findings.
This background is an array looking for SNPs (single nucleotide polymorphisms). Each dot represents a different probe, and its intensity tells you whether that SNP is present or absent. We look for copy number abnormalities, deletions, duplication. We can use these arrays for all sorts of things we used to use FISH for.

QUESTIONS?