Non-Traditional Types of Gene Disorders (NTGD)

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GL- 8
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Classification of genetic disorders

- Chromosomal
- Single gene
  - Autosomal recessive
  - Autosomal dominant
  - X-linked recessive
  - X-linked dominant
- Nontraditional GD
- Multifactorial
- Somatic mutations (cancer)
Non-Traditional Types of Gene Disorders (NTGD)

- Mosaciasm
- Uniparental Disomy
- Imprinting
- Trinucleotide expansion
- Mitochondrial
- Fragile X Syndrome
Mosaicism

Gonadal Mosaicism:
- The presence of a mutation in all or part of the germ line but not in the rest of the body.
- This implies that a mutation occurred in a precursor sperm or egg cell.
- Gonadal mosaicism has been observed in humans:
  - Osteogenesis imperfecta,
  - Duchenne muscular dystrophy,
  - Achondroplasia,
  - Hemophilia A.

Germ line Mosaicism (rather than a new mutation)
- When an individual presents with an autosomal dominant disorder for the first time in a family.
Mosaicism

A mutation occurring during cell proliferation, in either somatic or during gametogenesis, leads to a proportion of cells carrying the mutation.
Germline Mosaicism

No previous family history of this disorder

All or part of a parent’s germ line is affected by a disease mutation, but the somatic cells are not
Mosaicism

- **Mosaicism** is the presence of one or more genetically distinct cell lines within an individual.
- **Somatic mosaicism** usually indicates the presence of a post-zygotic mutation, which can affect a certain percentage of the cells in one or more tissues/organs.
- **Examples:**
  - Down Syndrome
  - Alternatively, somatic mosaicism can be restricted to a certain part of the body, such as Segmental Neurofibromatosis.
  - Certain diseases are only seen in a mosaic state (i.e. McCune-Albright Syndrome which causes premature puberty, café-au-lait spots and bone disease). This is probably because they are lethal in the non-mosaic state.
  - Hepatic urea cycle due to deficiency of ornithine transcarbamylase (X-linked)
Uniparental Disomy

- **Uniparental disomy** (UPD) is defined as the presence of two homologous chromosomes inherited in part or in total from only one parent.
- This means that one parent has contributed two copies of a chromosome and the other parent has contributed no copies.
- The incidence of UPD is estimated to be as high as 2.8 to 16.5 per 10,000 conceptions.

- **Isodisomy**: If the parent passed on two copies of the same chromosome (as results from non-disjunction in meiosis II).

- **Heterodisomy**: If the parent provides one copy of each homolog (as results from non-disjunction in meiosis I),
Examples

• **Cases of PWS & AS**
  Two CF patients with short stature, inherited two identical copies of most or all of their maternal chr. 7. In both cases, the mother happened to be a carrier for CF

• Father-to-son transmission of hemophilia, affected boy inherited both X & Y from father

• Expression of X-linked in homozygous form in a female offspring of a carrier mother and a normal father
### Recessive Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>UDP type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pycnodysostosis</td>
<td>1 pat</td>
</tr>
<tr>
<td>Junctional epidermolysis bullosa, Herlitz type</td>
<td>1 mat</td>
</tr>
<tr>
<td>Spinal muscular atrophy III (juvenile type)</td>
<td>5 pat</td>
</tr>
<tr>
<td>Complement deficiency of C4A+C4B</td>
<td>6 pat</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>6 pat</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>7 mat</td>
</tr>
<tr>
<td>Osteogenesis imperfecta (COL1A2 mutation)</td>
<td>7 mat</td>
</tr>
<tr>
<td>Cystic fibrosis and Kartagener syndrome</td>
<td>7 pat</td>
</tr>
<tr>
<td>Congenital chloride diarrhea</td>
<td>7 pat</td>
</tr>
<tr>
<td>Chylomicronemia, familial</td>
<td>8 pat</td>
</tr>
<tr>
<td>Cartilage / hair hypoplasia</td>
<td>9 mat</td>
</tr>
<tr>
<td>Beta-thalassemia major</td>
<td>11 pat</td>
</tr>
<tr>
<td>Complete congenital achromatopsia (rod monochr.)</td>
<td>14 mat</td>
</tr>
<tr>
<td>Bloom syndrome (with Prader-Willi syndrome)</td>
<td>15 mat</td>
</tr>
<tr>
<td>Hydrops fetalis alpha-thalassemia</td>
<td>16 pat</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>X mat</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>XY</td>
</tr>
</tbody>
</table>
Genomic Imprinting

Mechanism of Imprinting

• Must occur before fertilization
• Must be able to confer transcriptional silencing
• Must be stably transmitted through mitosis in somatic cells
• Must be reversible on passage through the opposite parental germline (i.e., if an allele is maternally imprinted, this must be removed in the gametes of a male offspring
• Methylation
Genomic Imprinting

1. Transient Neonatal Diabetes
   Uniparental Disomy Chro. 6
   * Insulin Absent in Newborn
   * Spontaneous correction at Age 3

1. Insulin - Chromosome 11p
   * Biparental Expression
   * Uniparental Expression at Yolk Sac
Triplet Repeat Disorders

• The biologic basis of this phenomenon is now known to be due to specific areas of instability in the human genome.
• In normal individuals, the triplet repeat sequences are stable during meiosis and mitosis and the sequence copy number is transmitted as a polymorphism from parent to child.
• In families affected by these disorders, the area is unstable, leading to progressive amplification of the gene sequence with each succeeding generation.
• This molecular finding has two important clinical correlations:
  1. A direct relationship between the severity of the phenotype and repeat copy number,
  2. Identification of the "premutation" in a clinically asymptomatic individual
In certain inherited disorders symptoms become more severe in each successive generation.
## Triplet Repeat Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Repeat</th>
<th>Normal # of copies</th>
<th>Disease # of copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X syndrome</td>
<td>CGG or</td>
<td>6-50</td>
<td>200-2000</td>
</tr>
<tr>
<td></td>
<td>CCG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freidreich ataxia</td>
<td>GAA</td>
<td>6-29</td>
<td>200-900</td>
</tr>
<tr>
<td>Haw River syndrome</td>
<td>CAG</td>
<td>7-25</td>
<td>49-75</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>CAG</td>
<td>10-34</td>
<td>40-121</td>
</tr>
<tr>
<td>Jacobsen syndrome</td>
<td>CGG</td>
<td>11</td>
<td>100-1000</td>
</tr>
<tr>
<td>Myotonic dystrophy type 1</td>
<td>CTG</td>
<td>5-37</td>
<td>50-1000</td>
</tr>
<tr>
<td>Myotonic dystrophy type 2</td>
<td>CCTG</td>
<td>&lt; 10</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Spinal and bulbar muscular atrophy</td>
<td>CAG</td>
<td>14-32</td>
<td>40-55</td>
</tr>
<tr>
<td>Spinocerebellar ataxia</td>
<td>CAG</td>
<td>4-44</td>
<td>40-130</td>
</tr>
</tbody>
</table>
MITOCHONDRIAL GENETICS
Mitochondrion

- A cellular organelle probably of endosymbiotic origin that resides in the cytosol of most nucleated (eukaryotic) cells.
- This organelle produces energy by oxidising organic acids and fats with oxygen by the process of **oxidative phosphorylation** and generates oxygen radicals (reactive oxygen species ROS) as a toxic by-product.
- Contains small circular DNA.
- No crossing over or DNA repair.
- Many copies of the mitochondrial genome per cell.
- 37 genes, no histones, no introns.
- Maternal inheritance
Mitochondrial Inheritance

- Each cell contains hundreds of mitochondria, each of which contains multiple copies of a 16.5 Kb circular DNA molecule.
- The entire human mitochondrial chromosome has been cloned and sequenced.
- Oxidative Phosphorolation to produce ATP
- Although most proteins functioning in the mitochondria are encoded by nuclear genes, some are encoded by mitochondrial genes, and mutations can lead to energy failure.
Mitochondrial Inheritance

- Each cell contains hundreds of mitochondria, each of which contains multiple copies of a 16.5 Kb circular DNA molecule.
- The entire human mitochondrial chromosome has been cloned and sequenced.
- It consists of 16,569 base pairs of DNA, 37 genes, and encodes
  - 2 ribosomal RNA
  - 22 Transfer RNA
  - 13 polypeptide coding for OP
  - 90 nuclear genes coding peptide transported to mt to participate in OP
  - No intrones, some nucleotide participates in more than one gene
- Although most proteins functioning in the mitochondria are encoded by nuclear genes, some are encoded by mitochondrial genes, and mutations can lead to energy failure.
Model for mitochondrial DNA replication that involves the formation of a D loop structure

1. Supercoiled circular mtDNA (approximately 100 coils) uncoils
2. New heavy strand starts to form in displacement loop
3. Loop expands
4. Loop expands; new light strand starts. Replication structure resembles a letter D
5. Replication complete; two circular mtDNAs supercoil
Figure 9-2 Human Molecular Genetics, 3/e. (© Garland Science 2004)
Mt Enzymes

- Mitochondria perform cellular respiration after the cytosolic glycolysis step.
- The enzymes needed, include:
  a. Pyruvate dehydrogenase.
  b. Electron transport and OP enzymes.
  c. Citric acid cycle enzymes.
  d. Fatty acid oxidation enzymes
Mitochondrial Function
Nuclear genome
(24 linear double-stranded DNA molecules – 3200 Mb; ~30,000 genes)

Mitochondrial genome
(1 circular double-stranded DNA 16.6 kb; 37 genes)

- Highly conserved (coding)
- Highly conserved (other)
- Transposon-based repeats
- Heterochromatin
- Other non-conserved
Mitochondrial Inheritance

• In humans, at fertilization, the ovum contributes significantly more cytoplasm to the zygote than does the sperm.
• The sperm mitochondria degenerate upon penetration of the ovum.
• Mitochondria in offspring are exclusively maternal in origin.
• Phenotype results from maternal transmission
Mitochondrial Inheritance

- Mutations in mitochondrial genes are also the cause of several single gene disorders.

- Mutation rate in mt is 10 times more than in nuclear DNA due to the lack of DNA repair mechanism and free oxygen radicals?
Mitochondrial Inheritance

• **Heteroplasmcy:**
  Variable expression of mt diseases

• **Replicative Segregation:**
  ▪ Chance variation like Genetic drift ,
  ▪ Selective advantage, deletion cause shorter DNA and faster replication

• **Tissue requirement:**
  CNS needs 20% of the total body requirement of ATP,
Normal mitochondria

Dysfunctional or mutant mitochondria

Progenitor cell showing heteroplasmcy of mitochondria

At cell division, mitochondria are distributed unequally and do not necessarily reflect the ratio found in the progenitor cell.

Threshold 70% mutant

80% mutant
DISEASE

60% mutant
NORMAL

40% mutant
NORMAL

100%
NORMAL

When the level of mutant mitochondria exceeds a certain threshold, the cell expresses dysfunction.

http://bmj-sti.highwire.org/content/77/3/158.full
Mitochondrial inheritance

Complications

- Incomplete penetrance
- Variable expression
## The human nuclear and mitochondrial genomes

<table>
<thead>
<tr>
<th></th>
<th>Nuclear Genome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>3200 Mb</td>
</tr>
<tr>
<td><strong>No. of different DNA molecules</strong></td>
<td>23 (in XX cells) or 24 (in XY cells); all linear</td>
</tr>
<tr>
<td><strong>Total no. of DNA molecules per cell</strong></td>
<td>46 in diploid cells, but varies according to ploidy</td>
</tr>
<tr>
<td><strong>Associated protein</strong></td>
<td>Several classes of histone &amp; nonhistone protein</td>
</tr>
<tr>
<td><strong>No. of genes</strong></td>
<td>~ 30 000 ~35-000</td>
</tr>
<tr>
<td><strong>Gene density</strong></td>
<td>~ 1/100 kb</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mitochondrial Genome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>16.6 kb</td>
</tr>
<tr>
<td><strong>No. of different DNA molecules</strong></td>
<td>One circular DNA molecule</td>
</tr>
<tr>
<td><strong>Total no. of DNA molecules per cell</strong></td>
<td>Often several thousands (but variable)</td>
</tr>
<tr>
<td><strong>Associated protein</strong></td>
<td>Largely free of protein</td>
</tr>
<tr>
<td><strong>No. of genes</strong></td>
<td>37</td>
</tr>
<tr>
<td><strong>Gene density</strong></td>
<td>1/0.45 kb</td>
</tr>
<tr>
<td>Repetitive DNA</td>
<td>Over 50% of genome</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Transcription</td>
<td>The great bulk of genes are transcribed individually</td>
</tr>
<tr>
<td>Introns</td>
<td>Found in most genes</td>
</tr>
<tr>
<td>% of coding DNA</td>
<td>~ 1.5%</td>
</tr>
<tr>
<td>Codon usage</td>
<td>Slightly different see slide</td>
</tr>
<tr>
<td>Recombination</td>
<td>At least once for each pair of homologs at meiosis</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Mendelian for sequence on X and autosomes; paternal for sequence on Y</td>
</tr>
</tbody>
</table>
# Examples of Diseases Due to Mutations and Deletions in Mitochondrial DNA

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>MIM No.</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHON</td>
<td>535000</td>
<td>Leber's hereditary optical neuropathy (Missence M)</td>
</tr>
<tr>
<td>MELAS</td>
<td>540000</td>
<td>Mitochondrial encephalomyopathy</td>
</tr>
<tr>
<td></td>
<td>540050</td>
<td>Lactic acidosis with stroke-like signs (Single base M)</td>
</tr>
<tr>
<td>MERRF</td>
<td>545030</td>
<td>Myoclonic epilepsy and ragged red fibers (Single base M)</td>
</tr>
<tr>
<td>MMC*</td>
<td>590050</td>
<td>Maternally inherited myopathy and cardiomyopathy</td>
</tr>
<tr>
<td>NARP*</td>
<td>551500</td>
<td>Neurogenic muscular weakness with ataxia and retinitis pigmentosa</td>
</tr>
<tr>
<td>CEOP*</td>
<td>258470</td>
<td>Progressive external ophthalmoplegia</td>
</tr>
<tr>
<td>KSS*</td>
<td>530000</td>
<td>Kearns-Sayre syndrome (ophthalmoplegia, pigmental degeneration of the retina, and cardiomyopathy)</td>
</tr>
<tr>
<td>PEAR*</td>
<td>557000</td>
<td>Pearson syndrome (bone marrow and pancreatic failure)</td>
</tr>
<tr>
<td>ADMIMY*</td>
<td>157640</td>
<td>Autosomal dominant inherited mitochondrial myopathy with mitochondrial deletion in the D loop (type Zeviani)</td>
</tr>
</tbody>
</table>
TRINULEOTIDID EXPANSION
Repeat location

Coding disorders

Diseases with a CAG expansion within the coding region, produces an enlarged polyglutamine tract Huntignton, Spinocerebellar ataxia type 1...)

Non coding disorders

1. Untranslated 5’ (Fragile X, syndrome, Spinocerebellar Ataxia type 2..)
2. Untranslated 3’ (myotonic dystrophy)
3. Intron (Friedreich ataxia, )
TRINUCLEOTID EXPANSION

Fragile X Syndrome
Friedreich Ataxia
Spinal and Bulbar Muscular Atrophy
Myotonic Dystrophy
Myotonic Dystrophy
Spinocerebellar Ataxia Type I
Huntington Disease
Dentatorubral-Pallidolysian Atrophy (Haw River Syndrome)
Machado-Joseph Disease
### Examples of disorders caused by STR expansions

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Unit</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington disease</td>
<td>HD</td>
<td>CAG</td>
<td>Coding sequence</td>
</tr>
<tr>
<td>Spinobulbar atrophy</td>
<td>AR</td>
<td>CAG</td>
<td>Coding sequence</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 1</td>
<td>SCA1</td>
<td>CAG</td>
<td>Coding sequence</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 2</td>
<td>SCA2</td>
<td>CAG</td>
<td>Coding sequence</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 7</td>
<td>SCA7</td>
<td>CAG</td>
<td>Coding sequence</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>ZFN9</td>
<td>CCTG</td>
<td>Intron</td>
</tr>
<tr>
<td>Fredreich ataxia</td>
<td>X25</td>
<td>AAG</td>
<td>Intron</td>
</tr>
<tr>
<td>DMI-associated cataract</td>
<td>SIX5</td>
<td>CTG</td>
<td>Promoter</td>
</tr>
<tr>
<td>Progressive myoclonus epilepsy</td>
<td>Cys b</td>
<td>12 bp</td>
<td>Promoter</td>
</tr>
<tr>
<td>Fragile X</td>
<td>FRAXA</td>
<td>CTG</td>
<td>5’ UTR</td>
</tr>
<tr>
<td>Fragile XE</td>
<td>FRAXE</td>
<td>CCG</td>
<td>5’ UTR</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 12</td>
<td>SCA12</td>
<td>CAG</td>
<td>5’ UTR</td>
</tr>
</tbody>
</table>
FRAGILE S SYNDROME
Fragile X Syndrome

- The most common cause of inherited mental retardation (MR).
- Second only to Down syndrome as an etiology for MR.
- Incidence of approximately 1 in 4000 males and 1 in 8000 females.
- Found among all ethnic groups and occurs in families with no history of mental retardation.
- 1 in 259 women are carriers of the fragile X premutation.
  - Only the mother has to be a carrier for the fetus to be at risk for fragile X syndrome.
Background

• X-linked disease
• Mutation is located at Xq27.3
• Fragile Mental Retardation 1 (FMR1) Gene
• Polymorphic \((CCG)_n\) repeat in the 5’ untranslated region of exon 1
  ➢ Hypermethylation of a CpG island upstream of the mutation
**Fragile X Syndrome:** in males and females with full mutation (200-2,000 repeats) or mosaicism (full mutation+premutation). Life-long disorder.

**Fragile X tremor ataxia syndrome (FXTAS):** predominantly older (>50 years) males with premutation (61-199 repeats). Manifestations: gait ataxia, intention tremor, cognitive impairment (frontal lobe dementia).

**Premutation-related disorders:** POI, females with emotional problems and perseverative thinking, children (mainly boys) with ADHD, intellectual disability and/or autism.
Fragile X Syndrome

- Males:
  - Moderate to severe mental retardation, learning disabilities
  - Long face, prominent ears, macro-orchidism
  - Physical phenotype can be subtle, especially in young boys
  - Hyperactivity, autism (approx. 1/3), hand flapping, hand biting, disordered speech and language
  - Males are generally unable to live independently
Characteristics in Males

- Macroorchidism (enlarged testicles)
- Cognitive difficulties
- Attention and behavioral problems
- Connective tissue abnormalities
- Anticipation
Fragile X Syndrome

- Females:
  - Less frequent and less severe in females
  - Mild to moderate mental retardation, learning disabilities
    - About 1/3 of females have significant intellectual disability.
  - Long face, prominent ears (more subtle in females than in males)
  - Poor eye contact, attention problems, shyness and social anxiety
FMR-1 gene: a triplet repeat disease

- Stable allele
- Unstable allele
- Premutation
- Expansion to full mutation
- Abnormal methylation of FMR-1 gene
- Absence of FMR-1 protein

\[(CGG)_n\]

- \(n < 45\)
- \(55 \geq n \leq 200\)
- \(n \geq 200\)
## Risk of Premutation Expansion: size of repeat and gender

<table>
<thead>
<tr>
<th>Maternal Repeat Size</th>
<th>% Of Offspring With a Full Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59</td>
<td>3.7%</td>
</tr>
<tr>
<td>60-69</td>
<td>5.3%</td>
</tr>
<tr>
<td>70-79</td>
<td>31.1%</td>
</tr>
<tr>
<td>80-89</td>
<td>57.8%</td>
</tr>
<tr>
<td>90-99</td>
<td>80.1%</td>
</tr>
<tr>
<td>&gt;100</td>
<td>94-100%</td>
</tr>
</tbody>
</table>

Source: Nolin et al., 2003
Fragile X syndrome - consequences of expansion

- Methylation of the C (CGG) - due to mispaired Cs in secondary structures, are templates for methylation.

- Methylation of the promoter is accompanied (reason unknown), leading to lack of transcription initiation.

Disease mechanism - protein loss of function
One Gene (FMR1): Three (or More) Disorders

Gene

mRNA

FMRP

Clinical

Typical (CGG) < 45

Premutation (CGG) 55-200

Full mutation (CGG) > 200

Premutation: M: 1:800, F: 1:250

Full Mutation: M: 1:4000, F: 1:6000

Normal

Primary ovarian insufficiency (POI), fragile X-associated tremor ataxia syndrome (FXTAS) due to excess mRNA

Fragile X syndrome due to lack of FMRP
FRAXA- rare folate-sensitive fragile sites: mutation stages

- At the loci of fragile sites there are naturally occurring polymorphisms of the number of copies of tandem repeats of the trinucleotide repeat CGG.
- The fragile site is seen cytogenetically.
- The gene associated with the repeat is apparently normally expressed.
- Beyond the premutation is the full mutation where the fragile site is seen and the relevant gene is transcriptionally silenced.
Genetic Anticipation Explained

A Fragile X family

- Progressive increase in size of CGG repeat
- Requires a female transmission to go to full mutation
Fragile X syndrome has a complicated inheritance.
46, Y, fra(X)(q27.3)
FRAGILE X SYNDROME

Fragile Site
Fragile X seen in:

- 16-50% prevalence of Autism/ASD in Fragile X Syndrome
- ~15% of women with *FMR1* premutation
- 0.8-7.5% *FMR1* premutation in sporadic POI
- 13% *FMR1* premutation in familial POI
A Spectrum of Clinical Involvement

Fragile X Associated Conditions Among Carriers:

- Premature ovarian failure (POF)
  - 20% of premutation carriers have POF vs 1% in general population
  - Premutation alleles were found in 14% of women with a family history of POF and no known history of fragile X syndrome

- Fragile X Associated Tremor and Ataxia (FXTAS)
  - Neurological condition in some male adult carriers of the FMR1 premutation.
    - First described by Hagerman et al in 2001.
  - 30-40% of men 50+ years old with a premutation have FXTAS
    - Estimated 13-fold increased risk of these symptoms compared with non-carriers
  - Has been reported in female premutation carriers (also >50 y.o.), though symptoms milder.
Summary

- FXS: Fragile X Syndrome
  - Associated with 200+ repetitions of CGG on the FMR1 gene
- FXTAS: Fragile X associated Tremor and Ataxia Syndrome
  - Neurodegenerative disease associated with 55-200 repetitions of CGG on the FMR1 gene (premutation)
- Major symptoms include gait ataxia and progressive intention tremor
- Pathogenic affect thought to be caused by intranuclear inclusions (protein aggregations) in the brain.
- It is believed that the repetitions of CGG causes over expression of FMR1 mRNA which has a negative affect on the cell.

http://wizard1.ucdavis.edu
Rules of Inheritance

**Autosomal Recessive**
- Appears in both sexes with equal frequency
- Trait tend to skip generations
- Affected offspring are usually born to unaffected parents
- When both parents are hetzyg, ~1/4 of the progeny will be affected
- Appears more frequently among the children of consanguine marriages

**Autosomal Dominant**
- Appears in both sexes with equal frequency
- Both sexes transmit the trait to their offspring
- Does not skip generations
- Affected offspring must have an affected parent unless they possess a new mutation
- When one parent is affected (het.) and the other parent is unaffected, ~ 1/2 of the offspring will be affected
- Unaffected parents do not transmit the trait

**X-Linked Dominant**
- Both males and females are affected; often more females than males are affected
- Does not skip generations. Affected sons must have an affected mother; affected daughters must have either an affected mother or an affected father
- Affected fathers will pass the trait on to all their daughters
- Affected mothers if heterozygous will pass the trait on to 1/2 of their sons and 1/2 of their daughters

**X-Linked Recessive**
- More males than females are affected
- Affected sons are usually born to unaffected mothers, thus the trait skips generations
- Approximately 1/2 of carrier mothers’ sons are affected
- It is never passed from father to son
- All daughters of affected fathers are carriers

**Mitochondrial**
- Trait is inherited from mother only
- All children of a mother are at risk to be affected or carriers
- An individual will be affected with a mitochondrial disorder if the percentage of mitochondria possessing mutated mtDNA reaches a threshold value beyond which the normal mtDNA does not compensate for the mutated mtDNA.

**Y-Linked Dominant**
- Only males are affected
- It is passed from father to all sons
- It does not skip generations