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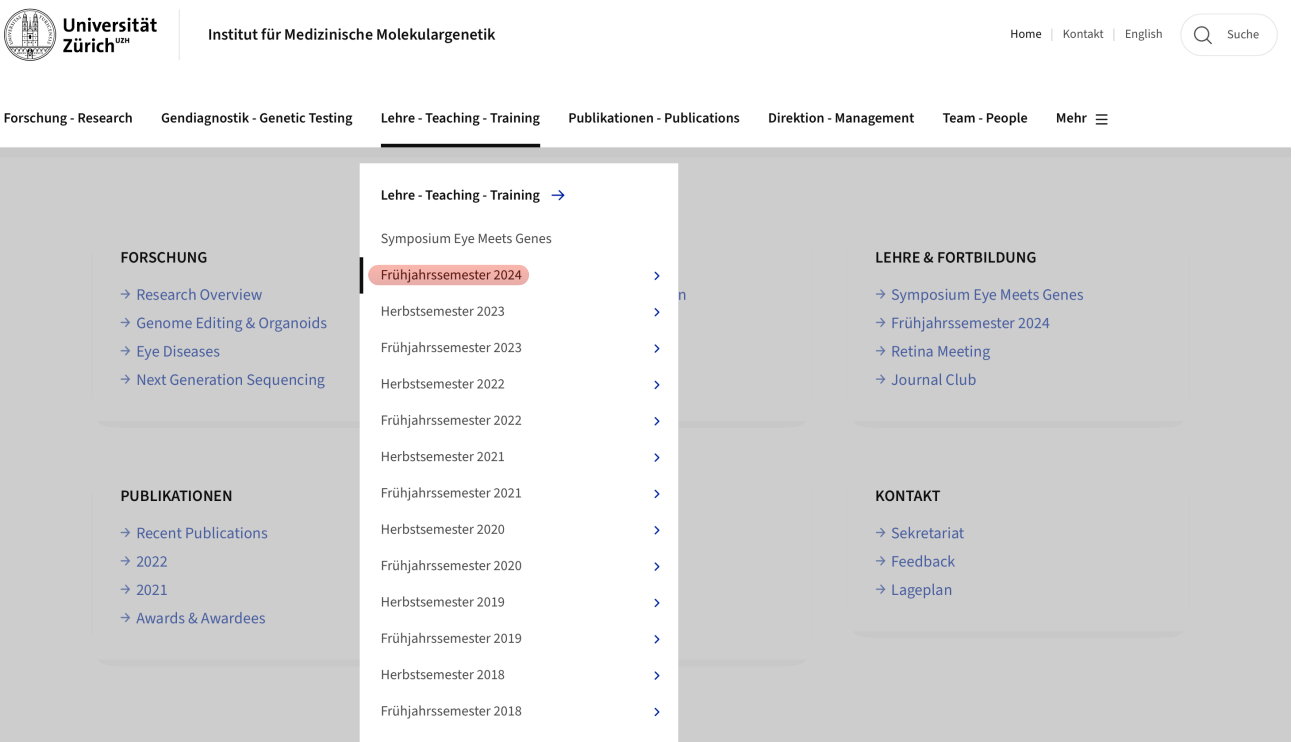
Institute of Medical Molecular Genetics

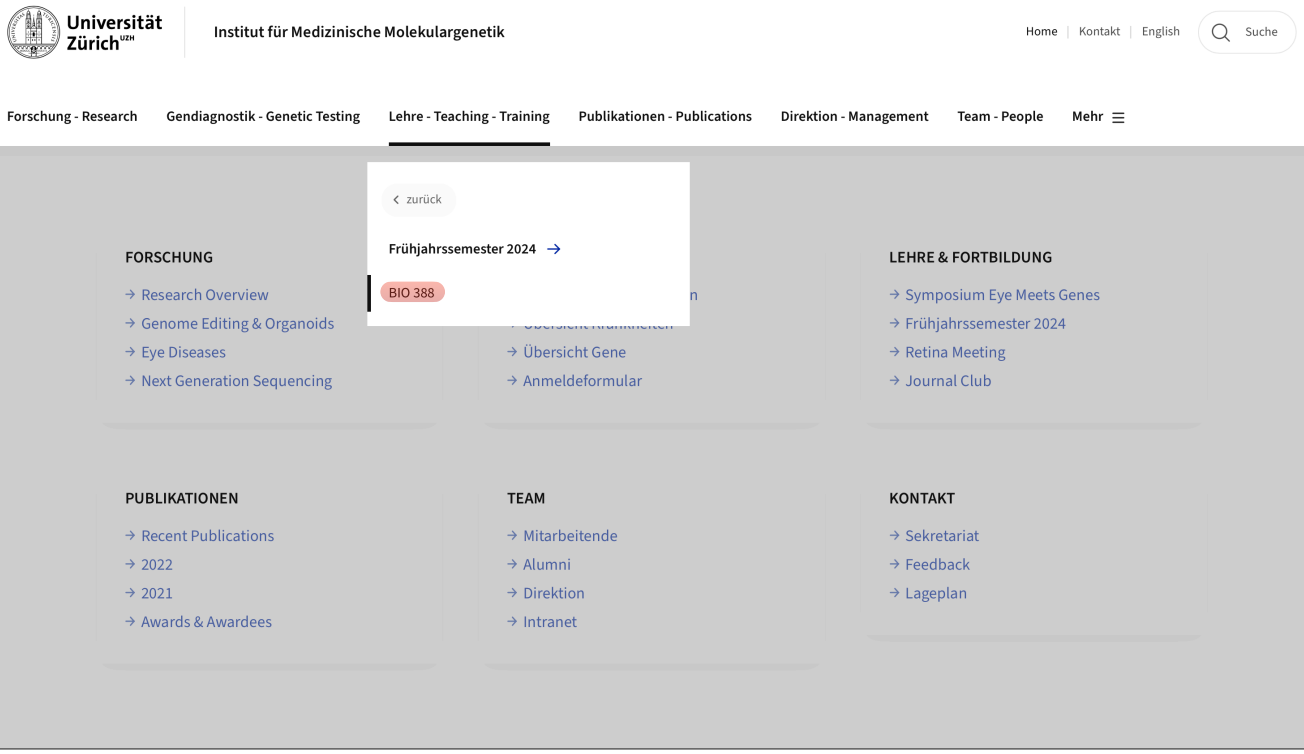
▸ Dynamic mutations & anticipation

▸ Imprinting mutations & diseases

Prof. Dr. Wolfgang Berger

April 29th 2024





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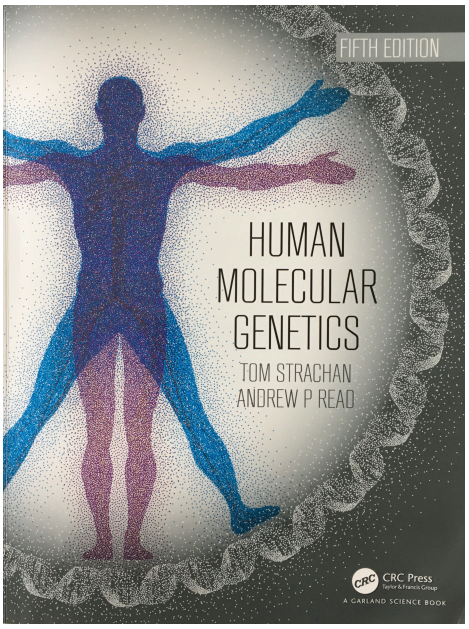
BIO 388 | Human Genetics

We present and discuss a selection of issues relevant for understanding the concepts of modern medical genetics. A broad spectrum of topics will be covered ranging from the use of genetics in forensics to clinical studies of hereditary disorders. A key objective of this course is to elucidate the role of interactions between genes and environment in health and disease.

Handouts 29.04.2024
Handouts 06.05.2024

Literature & resources



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Seattle (WA): University of Washington, Seattle; 1993-2024.
ISSN: 2372-0697

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GeneReviews, an international point-of-care resource for busy clinicians, provides clinically relevant and medically actionable information for inherited conditions in a standardized journal-style format, covering diagnosis, management, and genetic counseling for patients and their families. Each chapter in *GeneReviews* is written by one or more experts on the specific condition or disease and goes through a rigorous editing and peer review process before being published online.

GeneReviews currently comprises 893 chapters and has over seven million users annually.

The two general formats for *GeneReviews* are: chapters focused on a single gene or phenotype (~95%) and overviews summarizing causes of common genetic conditions (e.g., genetic hearing loss, Alzheimer disease) (~5%).

To ensure continuing relevant and medically actionable content, each *GeneReviews* chapter is updated every four to five years (or as needed) by the author(s) in a formal and comprehensive process curated by the *GeneReviews* editors. Additional revisions may occur more frequently as needed to reflect significant changes in clinically relevant information.

Genetic counseling and testing terms used in *GeneReviews* are hyperlinked to definitions in the *GeneReviews* Glossary. Resource Materials include additional information on key genetics concepts used in *GeneReviews*.

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OMIM® – Online Mendelian Inheritance in Man®

Welcome to OMIM®, Online Mendelian Inheritance in Man®. OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 15,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 by a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.

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Online Mendelian Inheritance in Man (OMIM®)

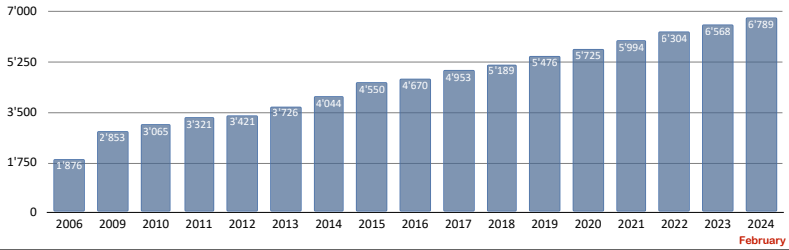
Number of Entries in OMIM (Updated February 6th, 2024) :

Source: http://omim.org/statistics/entry

MIM Number Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Gene description *	16,350	769	51	37	17,207
Gene and phenotype, combined +	21	0	0	0	21
Phenotype description, molecular basis known #	6,364	386	5	34	6,789
Phenotype description or locus, molecular basis unknown %	1,390	110	4	0	1,504
Other, mainly phenotypes with suspected mendelian basis	1,639	100	3	0	1,742
Totals	25,764	1,365	63	71	27,263

> 10,000

Mendelian disorders: identification of genes



Human monogenic (Mendelian) disorders with a known molecular genetic cause:

1982: 5
1990: 150
2024: > 6´700

Repeat expansion diseases

Disease	Mode of inheritance	Gene	Location of repeat	Repeat sequence	Unaffected	Intermediate or grey zone	Affected
Very large expansions outside coding sequences						*mutable normal reduced penetr.*	
Fragile X	XL	*FMR1*	5' UTR	CGG	5-44	45-54 55-200	>200
Friedreich ataxia	AR	*FXN*	intron 1	GAA	5-33	34-65	66 or more than 1500
Myotonic dystrophy	AD	*DMPK*	3' UTR	CTG	5-34	35-49	>49
Spinocerebellar ataxia 8 (SCA8)	AD	*ATXN8OS, ATXN8*	3' UTR,	CTG, CAG	15-50	50-70?	>70
Moderate expansions within coding sequences							
Huntington disease	AD	*HTT*	exon 1	CAG	<26	27-35 36-39	>39
Kennedy disease (SBMA)	XR	*AR*	exon 1	CAG	<35	36-37	>37
SCA1	AD	*ATXN1*	exon 8	CAG	6-44	36-38 39-44	>39
SCA2	AD	*ATXN2*	exon 1	CAG	<32		>31
SCA6	AD	*CACNA1A*	exon 47	CAG	<19	19	20-33
SCA7	AD	*ATXN7*	exon 3	CAG	<20	28-33 34-36	>36 (up to 460)
Machado-Joseph disease	AD	*ATXN3*	exon 10	CAG	<44	45-51	52-86
DRPLA	AD	*ATN1*	exon 5	CAG	6-35	20-35	>47

W. Berger, March 2012 (source: Gene Reviews @ NCBI)

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Fragile X Syndrome

Frequency:

1 : 4000 (males) – 1 : 6000 (females)

Clinic:

- developmental delays (learning difficulties up to severe intellectual disability)
- seizures in about 25% of affected patients
- macroorchidism, characteristic / striking face appearance (large and prominent ears) -> craniofacial features
- behavioral abnormalities (autistic behavior, ADHS: attention deficit/hyperactivity syndrome)

Fragile X Syndrome

Genetics:

- X-linked, FMR1 gene in Xq28
- triplett expansion in first exon of FMR1
- point mutations are extremely rare

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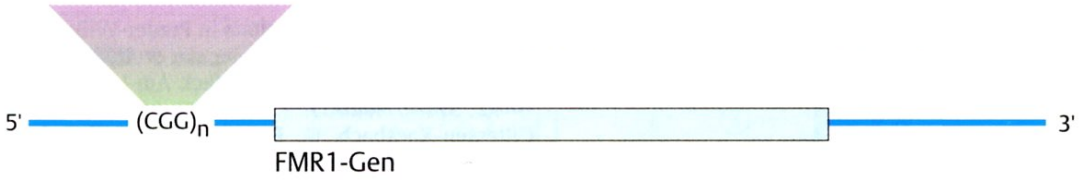
Fragile X Syndrome

CGG expansion in FMR1



normal allele:	n = 5 - 44
intermediate allele:	n = 45 - 54
premutation:	n = 55 - 200
full mutation:	n = >200 bis >1000

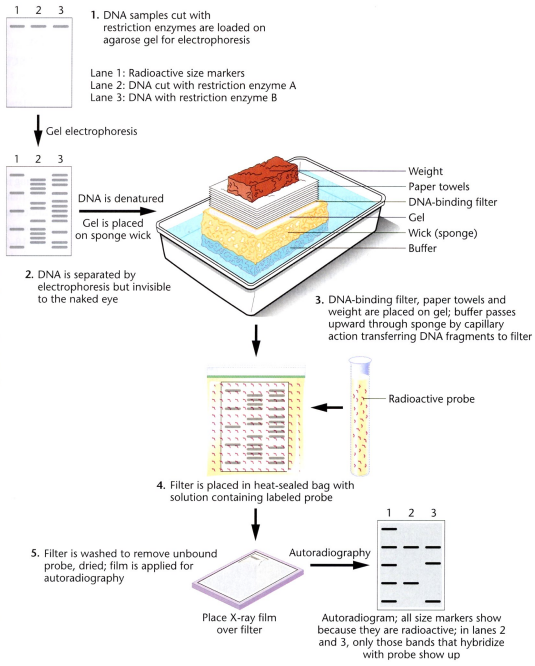
genetic testing: PCR, Southern-Blot

Fragile X Syndrome

CGG expansion in FMR1

Variant Type	# of CGG Trinucleotide Repeats	Methylation Status of *FMR1*	Clinical Status	
			Male	Female
Premutation	~55-200	Unmethylated	At risk for FXTAS [1]	• At risk for FXPOI & FXTAS • Potential ↑ risk of other fragile X-assoc disorders [1]
Full mutation	>200	Completely methylated	100% have ID.	~50% w/ID, ~50% normal intellect
Repeat size mosaicism	Varies between premutation & full mutation in different cell lines	Partial: unmethylated in premutation cell line; methylated in full-mutation cell line	Nearly 100% have ID; may be higher functioning [2] than males w/full mutation.	Highly variable: ranges from normal intellect to affected
Methylation mosaicism	>200	Partial: mixture of methylated & unmethylated cell lines		
Unmethylated full mutation	>200	Unmethylated	• ID, if present, is typically high functioning. • May have anxiety &/or behavioral issues even w/out ID	

Southern Blot Analyse:



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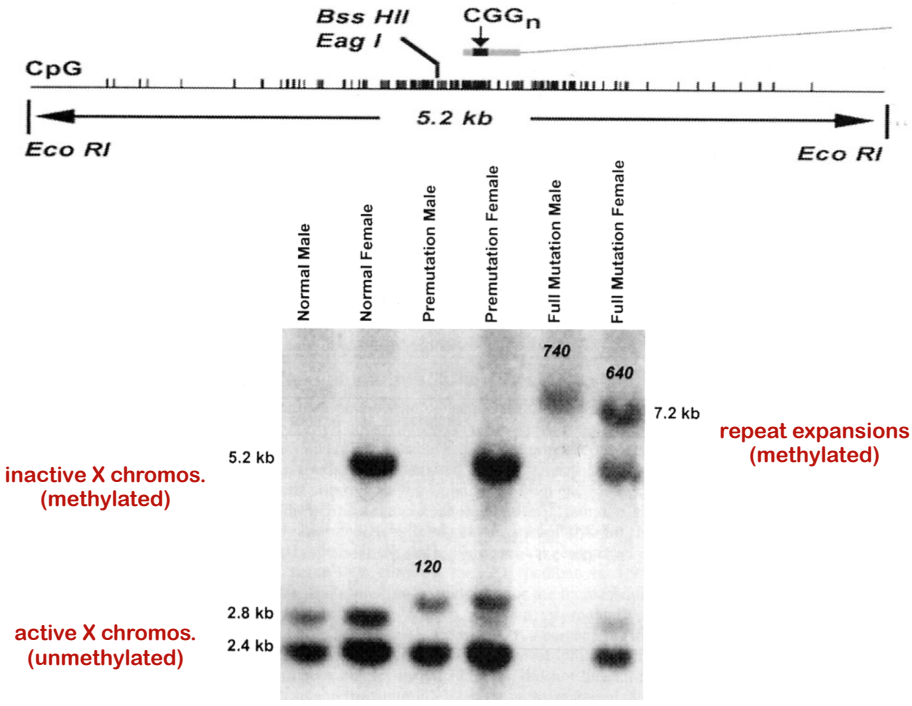

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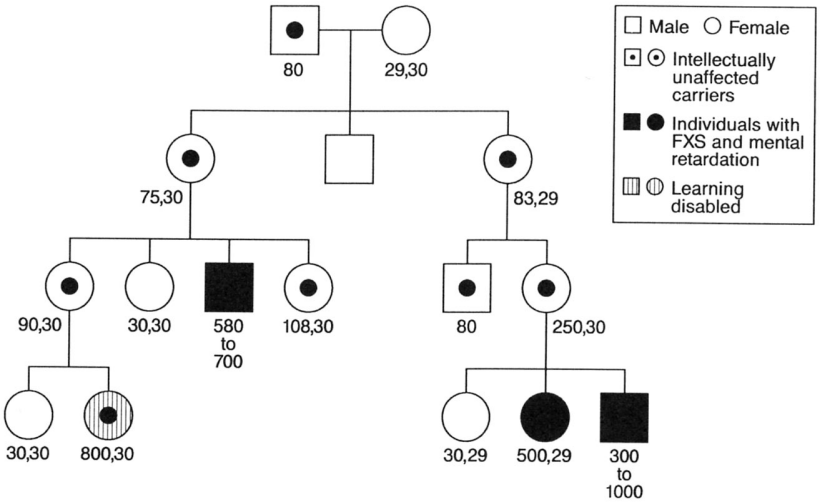


Figure 7.1 A family with FXS: the numbers represent repeats at FMR1 in each X chromosome.

Risk of expansion in maternal transmission

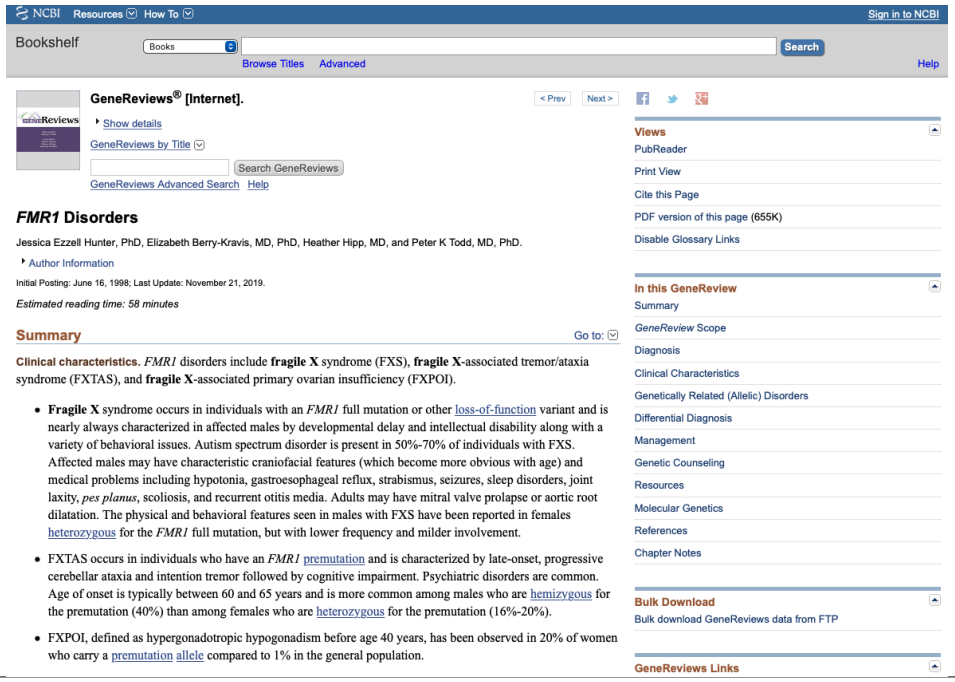
Table 5. Risks for Expansion from a Maternal Premutation to a Full Mutation When Transmitted to Offspring

Number of Maternal Premutation CGG Repeats	Total Maternal Transmissions	Expansions to Full Mutations (%) [1]
55-59	27	1 (3.7%)
60-69	113	6 (5.3%)
70-79	90	28 (31.1%)
80-89	140	81 (57.8%)
90-99	111	89 (80.1%)
100-109	70	70 (100%)
110-119	54	53 (98.1%)
120-129	36	35 (97.2%)
130-139	18	17 (94.4%)
140-200	19	19 (100%)

Adapted from Nolin et al (2003)

Source: Gene Clinics @ NCBI

Gene Clinics / Gene Reviews



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FMR1 Disorders

Jessica Ezzell Hunter, PhD, Elizabeth Berry-Kravis, MD, PhD, Heather Hipp, MD, and Peter K Todd, MD, PhD.

Author Information

Initial Posting: June 16, 1998; Last Update: November 21, 2019.

Estimated reading time: 58 minutes

Summary Go to:

Clinical characteristics. *FMR1* disorders include **fragile X** syndrome (FXS), **fragile X**-associated tremor/ataxia syndrome (FXTAS), and **fragile X**-associated primary ovarian insufficiency (FXPOI).

- **Fragile X** syndrome occurs in individuals with an *FMR1* full mutation or other loss-of-function variant and is nearly always characterized in affected males by developmental delay and intellectual disability along with a variety of behavioral issues. Autism spectrum disorder is present in 50%-70% of individuals with FXS. Affected males may have characteristic craniofacial features (which become more obvious with age) and medical problems including hypotonia, gastroesophageal reflux, strabismus, seizures, sleep disorders, joint laxity, *pes planus*, scoliosis, and recurrent otitis media. Adults may have mitral valve prolapse or aortic root dilatation. The physical and behavioral features seen in males with FXS have been reported in females heterozygous for the *FMR1* full mutation, but with lower frequency and milder involvement.
- FXTAS occurs in individuals who have an *FMR1* premutation and is characterized by late-onset, progressive cerebellar ataxia and intention tremor followed by cognitive impairment. Psychiatric disorders are common. Age of onset is typically between 60 and 65 years and is more common among males who are hemizygous for the premutation (40%) than among females who are heterozygous for the premutation (16%-20%).
- FXPOI, defined as hypergonadotropic hypogonadism before age 40 years, has been observed in 20% of women who carry a premutation allele compared to 1% in the general population.

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Other *FMR1*-related diseases

Fragile X-associated tremor/ataxia syndrome (FXTAS)

- presence of a premutation in *FMR1*
- white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem (the major neuroradiologic sign) with either intention tremor or gait ataxia (the two major clinical signs)
- other minor clinical criteria include parkinsonism, moderate to severe working memory deficits, or executive cognitive function deficits

***FMR1*-related premature ovarian failure (POF / POI)**

- cessation of menses before age 40 years in a woman with an *FMR1* premutation

Other *FMR1*-related diseases

Table 2. Risk of FXTAS by Age in Males with an *FMR1* Premutation

Age in Years	Risk
50-59	17%
60-69	38%
70-79	47%
≥80	75%

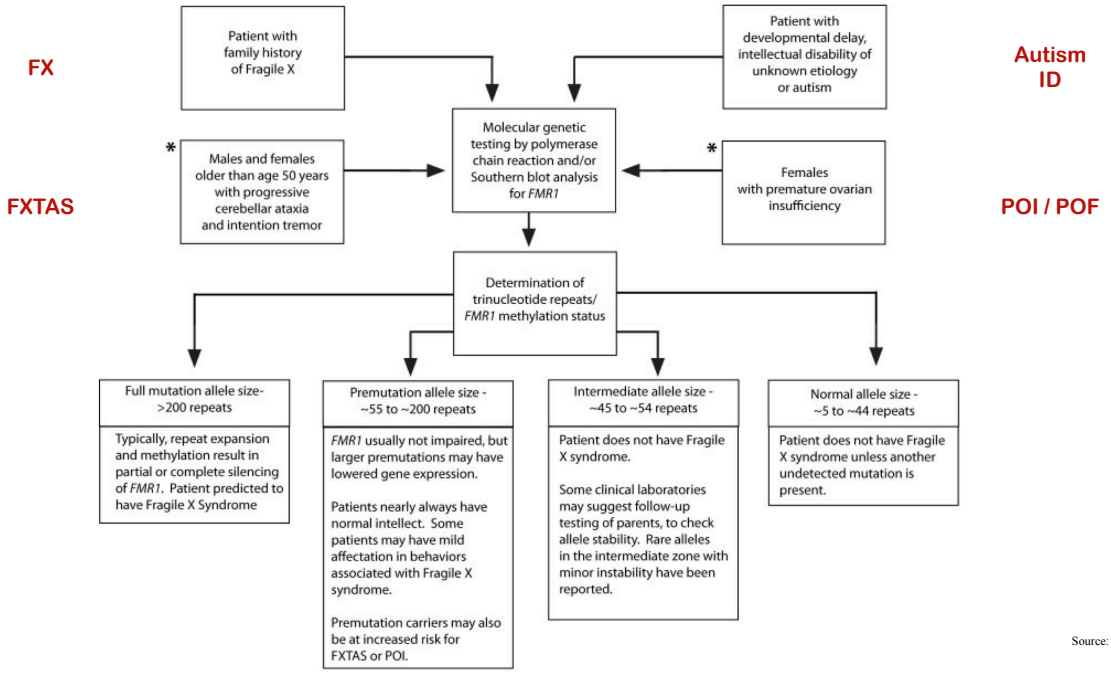
Table 4. Odds Ratios for POF by Premutation Size

Premutation Size in CGG Repeats	Odds Ratio for POF
59-79	6.9
80-99	25.1
>100	16.4

Sherman 2005

Source: Gene Reviews at NCBI

Clinical testing for FMR1 expansion



Source: Gene Clinics @ NCBI

Myotonic Dystrophy (Curschmann-Steinert)

Frequency:

1 in 10´000

Clinical characteristics:

- most frequent neuromuscular disease
- first symptoms in adolescence or adulthood but also congenital forms
- progressive disease course
- accompanying symptoms: cataract, intellectual disability

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Myotonic Dystrophy (Curschmann-Steinert)

Genetics:

- autosomal dominant inheritance
- *DMPK gene*, chromosome 19q13.3
- triplet expansion in 3´-UTR of *DMPK*

Disease	Mode of Inheritance	Gene	Location of repeat	Repeat sequence	Unaffected	Intermediate or grey zone	Affected
Very large expansions outside coding sequences						mutable normal reduced penetr.	
Fragile X	XL	*FMR1*	5' UTR	CGG	5-44	45-54 55-200	>200
Friedreich ataxia	AR	*FXN*	intron 1	GAA	5-33	34-65	66 or more than 1500
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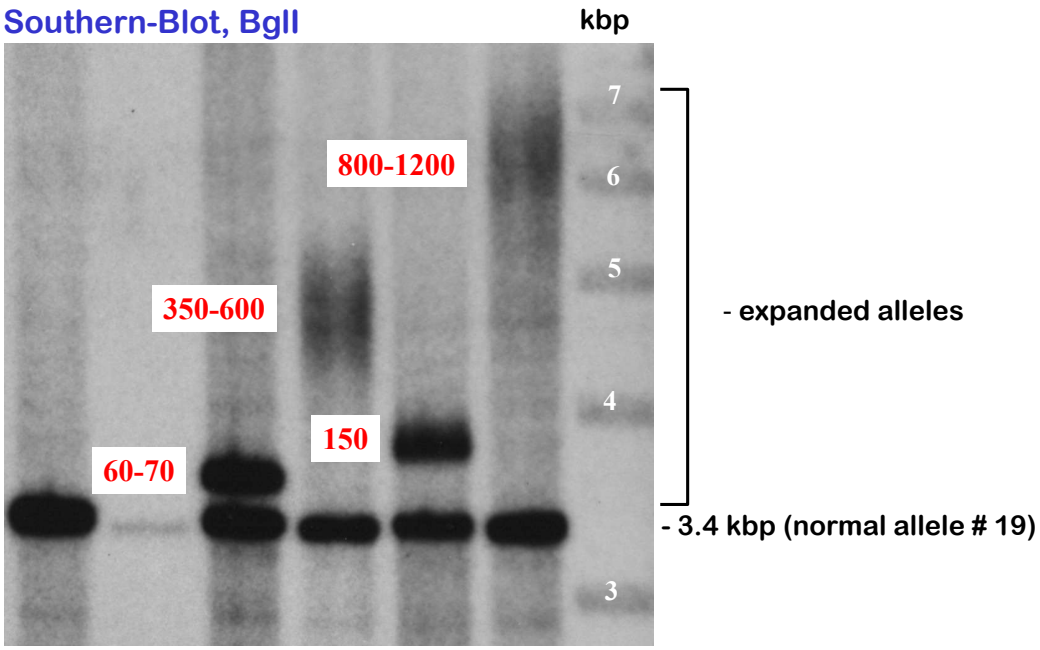
W. Berger, March 2012 (source: Gene Reviews @ NCBI)

Myotonic Dystrophy (Curschmann-Steinert)



Correlation between repeat number and symptoms

Table 2. Correlation of Phenotype and CTG Repeat Length in Myotonic Dystrophy Type 1

Phenotype	Clinical Signs	CTG Repeat Size [1, 2]	Age of Onset	Average Age of Death
Mutable normal (premutation)	None	35 to 49	NA [3]	NA [3]
Mild	Cataracts Mild myotonia	50 to ~150	20 to 70 yrs	60 yrs to normal life span
Classic	Weakness Myotonia Cataracts Balding Cardiac arrhythmia Others	~100 to ~1000	10 to 30 yrs	48 to 55 yrs
Congenital	Infantile hypotonia Respiratory deficits Intellectual disability Classic signs present in adults	>2000 [4]	Birth to 10 yrs	45 yrs [5]

From de Die-Smulders et al [1998], Mathieu et al [1999], International Myotonic Dystrophy Consortium [2000]

Source: Gene Clinics @ NCBI

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Myotonic Dystrophy Type 2

Proximal Myotonic Myopathy (PROMM)

Frequency:

1 : 8,000 (type 1 and 2)

Symptoms:

- myotonia (90% of affected individuals) and muscle dysfunction (weakness, pain, and stiffness) in >80%
- less common: cardiac conduction defects
- posterior subcapsular cataracts
- insulin insensitive type 2 diabetes mellitus
- testicular failure

Myotonic Dystrophy Type 2

Proximal Myotonic Myopathy (PROMM)

Repeat expansion:

- *CNBP (zinc finger protein 9, ZNF9*) is the only gene known to be associated with myotonic dystrophy type 2
- *CNBP* intron 1 contains a complex repeat motif: (TG)n(TCTG)n(CCTG)n
- expansion of the CCTG repeat causes DM2
- the number of CCTG repeats in expanded alleles ranges from approximately 75 to more than 11,000 with a mean of approximately 5000 repeats
- the detection rate of a *CNBP* CCTG expansion is more than 99% with the combination of routine PCR and Southern blot analysis

Chorea Huntington (Veitstanz)

Frequency:

~ 1 : 30'000

Clinic:

- **disease manifestation in the 35th - 45th year of life**
- **movement disorders**
- **change in behaviour and personality (psychiatric abnormalities)**
- **cognitive impairment**
- **reduced life span**
  (40% of all choreatics die in the first 10 years of illness, a further 30% after a maximum of 15 years of illness)

Chorea Huntington (Veitstanz)

Genetics:

- autosomal dominant mode of inheritance
- IT15 gene (huntingtin), chromosome 4p16.3
- triplet expansion (CAG) in the translated region

-> polyglutamine disease

Anticipation:

Earlier age of onset and increase in severity in subsequent generations

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Chorea Huntington (Veitstanz)

Genetic testing:

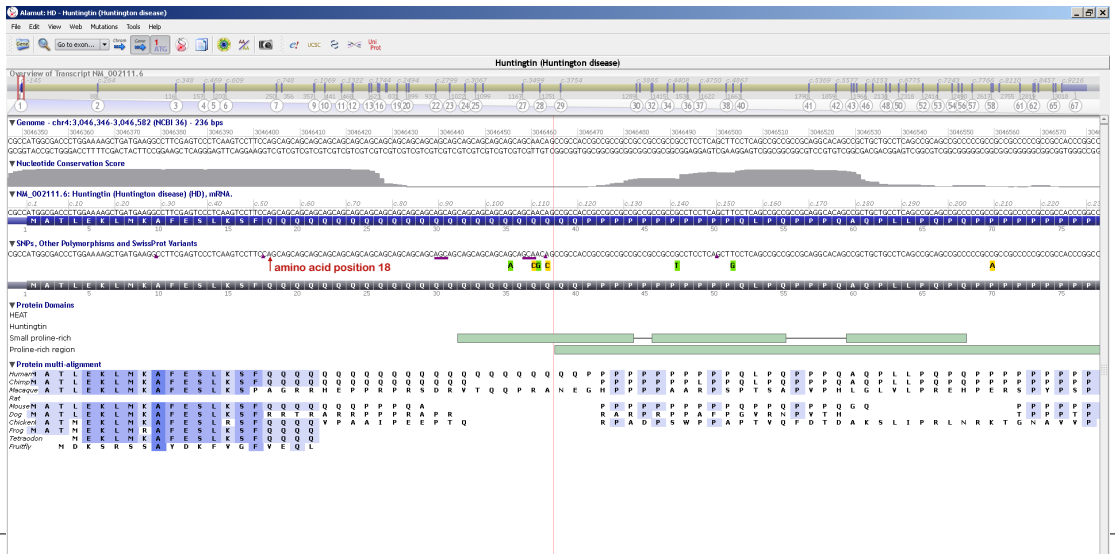
- always as integrated part of a genetic counselling session
- issue of pre-symptomatic/prenatal molecular genetic testing
- guidelines for carrying out molecular genetic diagnostics must be followed

Gene Clinics @ NCBI:

normal:	up to 26 CAGs
intermediate:	27-35 CAGs (risk for children)
disease causing:	36 or more CAGs
	36-39 CAGs: reduced penetrance
	40 or more CAGs: full penetrance

Chorea Huntington (Veitstanz)

Exons: 67; **Transcript length:** 13,475 bps; **Translation length:** 3,142 residues
Genomic size: 170 kbp



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Chorea Huntington (Veitstanz)

Table 2. Selected *HTT* Allelic Variants

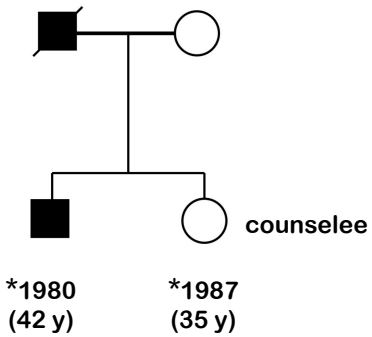
Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequences
Normal	c.52CAG(<26) (<26 CAG repeats)	p.Gln18(<26)	NM_002111.6 NP_002102.4
Intermediate	c.52CAG(27_35) [2] (27 to 35 CAG repeats)	p.Gln18(27_35)	
Pathologic	c.52CAG(36_39) [3] (36 to 39 CAG repeats)	p.Gln18(36_39)	
	c.52CAG(>40) [4] (>40 CAG repeats)	p.Gln18(>40)	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions
2. Intermediate *HTT* alleles
3. Reduced-penetrance HD-causing *HTT* alleles
4. Full-penetrance HD-causing *HTT* alleles

Source: Gene Reviews at NCBI

Chorea Huntington (Veitstanz)



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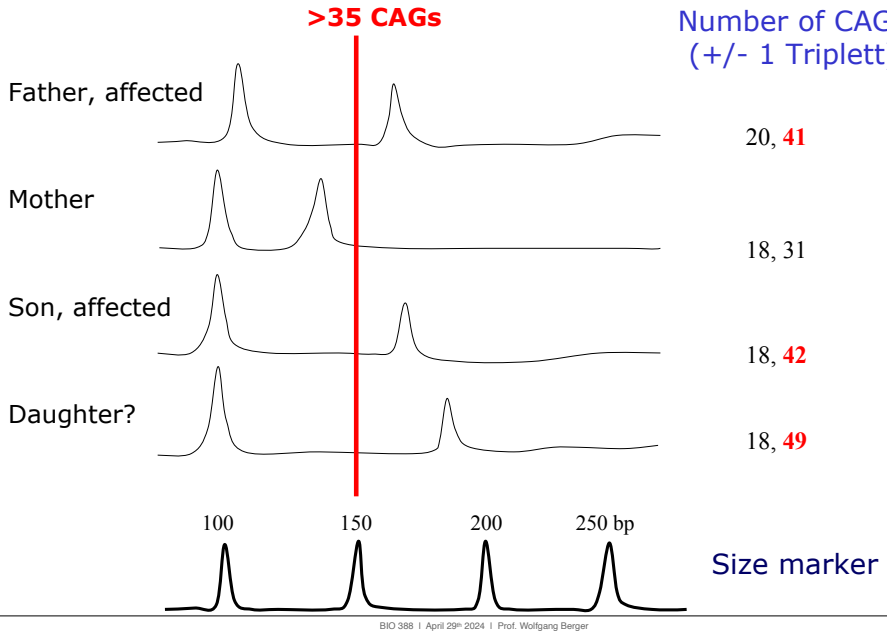
PCR fragment analysis:



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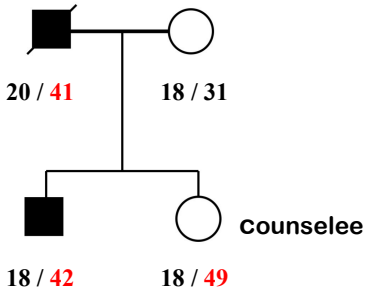
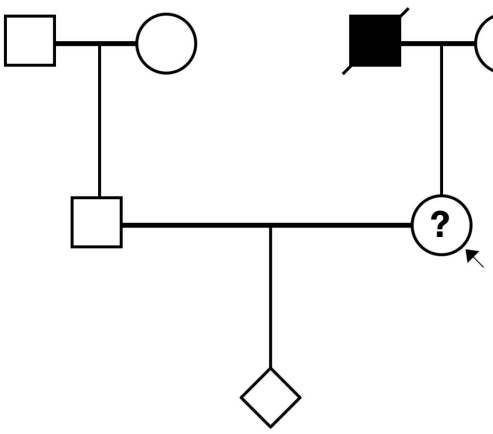


Chorea Huntington (Veitstanz)

prenatal testing and the right not to know

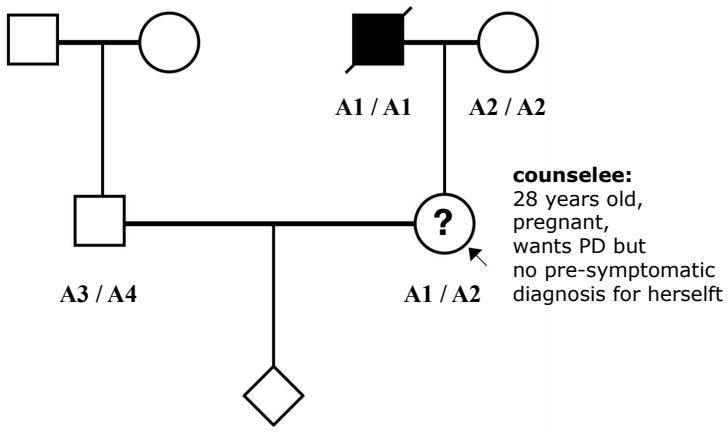


counselee:
28 years old,
pregnant,
wants PD but
no pre-symptomatic
diagnosis for herselft

embryo
(12th week of gestation)

Chorea Huntington (Veitstanz)

prenatal testing
non-disclosure PD / PID



Anticipation

Definition:

Earlier age of onset of the disease, more severe symptoms and disease progression in successive generations.

CH/HD: Inverse correlation of repeat length and age of onset!
(The longer the expansion, the earlier the disease onset.)

Friedreich Ataxia (FRDA)

Frequency: ~ 1 : 25´000 - 50´000

Clinical manifestations and symptoms:

- slowly progressive ataxia with onset usually before age 25 years (mean age at onset: 10-15 yrs)
- typically associated with dysarthria, muscle weakness, spasticity (particularly in the lower limbs), scoliosis, bladder dysfunction, absent lower-limb reflexes, loss of position and vibration sense
- approximately two thirds of individuals with FRDA have cardiomyopathy
- up to 30% have diabetes mellitus
- change in behaviour, dementia

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Friedreich Ataxia (FRDA)

Genetics:

- autosomal recessive mode of inheritance
- FRDA gene (frataxin, FXN), chromosome 9q13
- triplet expansion (GAA) in the first intron of the FRDA gene
  - normal range: 5-33 GAAs
  - premutation: 34-65
  - pathological: from 66 to >1700 GAAs
- expansion in both alleles in more than 95% of patients, in 4% only in one allele, point mutations rare

Repeat expansion diseases

Disease	Mode of inheritance	Gene	Location of repeat	Repeat sequence	Unaffected	Intermediate or grey zone	Affected
Very large expansions outside coding sequences						*mutable normal reduced penetr.*	
Fragile X	XL	*FMR1*	5' UTR	CGG	5-44	45-54 55-200	>200
Friedreich ataxia	AR	*FXN*	intron 1	GAA	5-33	34-65	66 or more than 1500
Myotonic dystrophy	AD	*DMPK*	3' UTR	CTG	5-34	35-49	>49
Spinocerebellar ataxia 8 (SCA8)	AD	*ATXN8OS, ATXN8*	3' UTR,	CTG, CAG	15-50	50-70?	>70
Moderate expansions within coding sequences							
Huntington disease	AD	*HTT*	exon 1	CAG	<26	27-35 36-39	>39
Kennedy disease (SBMA)	XR	*AR*	exon 1	CAG	<35	36-37	>37
SCA1	AD	*ATXN1*	exon 8	CAG	6-44	36-38 39-44	>39
SCA2	AD	*ATXN2*	exon 1	CAG	<32		>31
SCA6	AD	*CACNA1A*	exon 47	CAG	<19	19	20-33
SCA7	AD	*ATXN7*	exon 3	CAG	<20	28-33 34-36	>36 (up to 460)
Machado-Joseph disease	AD	*ATXN3*	exon 10	CAG	<44	45-51	52-86
DRPLA	AD	*ATN1*	exon 5	CAG	6-35	20-35	>47

W. Berger, March 2012 (source: Gene Reviews @ NCBI)

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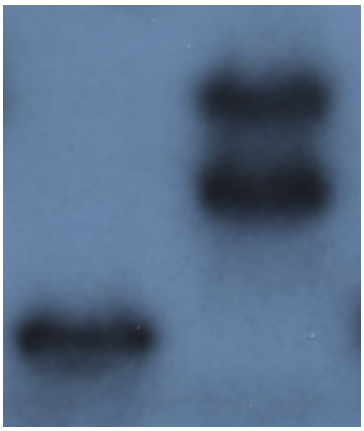
Friedreich Ataxie (FRDA)

Detection of repeat expansions upon Southern blot analysis

N **P**



8.2 kbp (~ 800 – 900 GAAs)

6.8 kbp (~ 400 GAAs)

5.6 kbp

Triplet Expansions

- triplets: CGG, CTG, CAG, GAA
- in coding region of genes (Huntingtin) as well as in 5´ or 3´-untranslated regions (*FMR1, DMPK*) but also in introns (*FXN*)
- large expansions (> 200 – 1000 triplets)
- moderate expansions (< 100 triplets)
- testing approaches: Southern-blot and/or PCR
- reliable size estimationof large expansions requires Southern-blot analysis

Genomic Imprinting

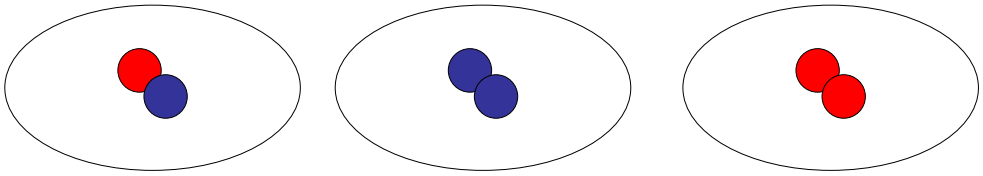
Definition: parent-of-origin-specific gene expression
(either maternal **or** paternal gene
is expressed)

first observation of imprinting effects in 1984 (Solter/Surani):

pronucleus transplantation experiments
in mouse

2 paternal genomes or 2 maternal genomes

Pronucleus Injection Experiments



fertilized oocyte	2 paternal genomes	2 maternal genomes
↓	↓	↓
normal embryonic development	no embryo normal development of extra-embryonic tissues	no extra-embryonic tissues beginning embryonic development

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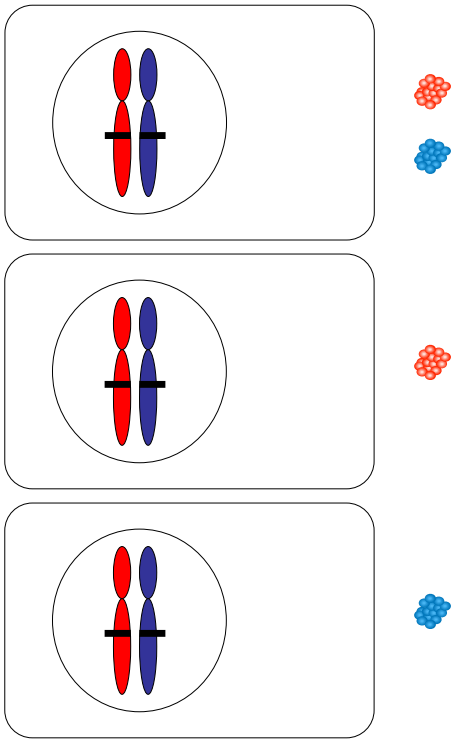

biallelic gene expression
(maternal and paternal allele)

maternal gene expression
(paternal allele inactive / silenced)

paternal gene expression
(maternal allele inactive / silenced)

Genomic Imprinting

> 250 human genes are imprinted

1991: discovery of the first imprinted gene in mice (*IGF2R*, insulin-like growth factor receptor)

maternally expressed, maternal deletion of chromosome 13 is lethal

imprinted regions in the human genome:

7q32
11p15.5
15q11-q13

mechanisms: methylation, antisense RNA, ???

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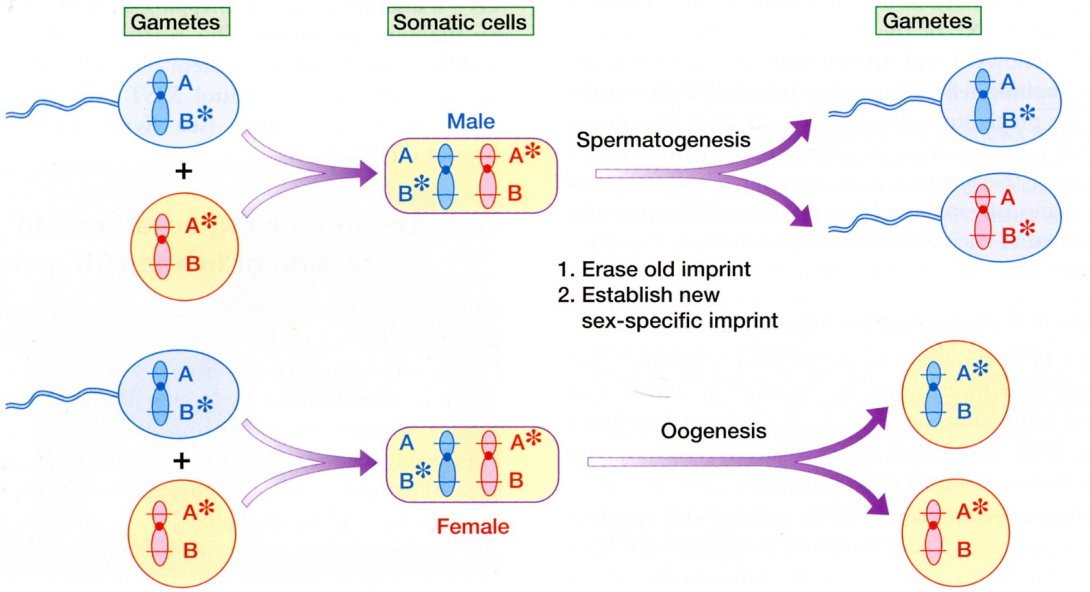
Genomic Imprinting

IMPRINT is erased in the germ line and re-established in a parent-of-origin-specific manner!

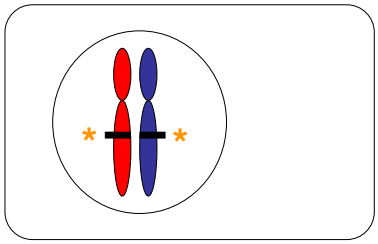
Genomic Imprinting



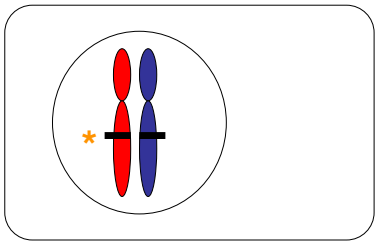
Human Imprinting Diseases

Reasons:

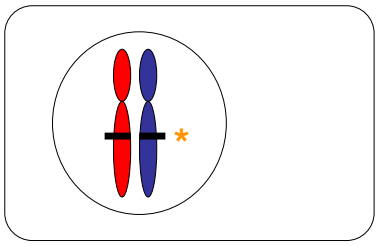
1. maternal or paternal deletions
2. maternal or paternal uniparental disomies
3. imprinting defects
4. others (?)



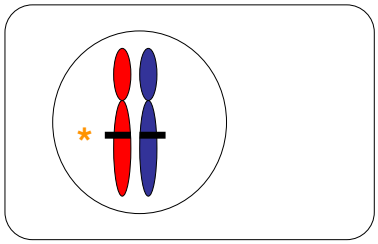
biallelic expression



maternal expression

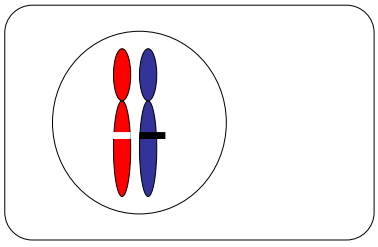


paternal expression



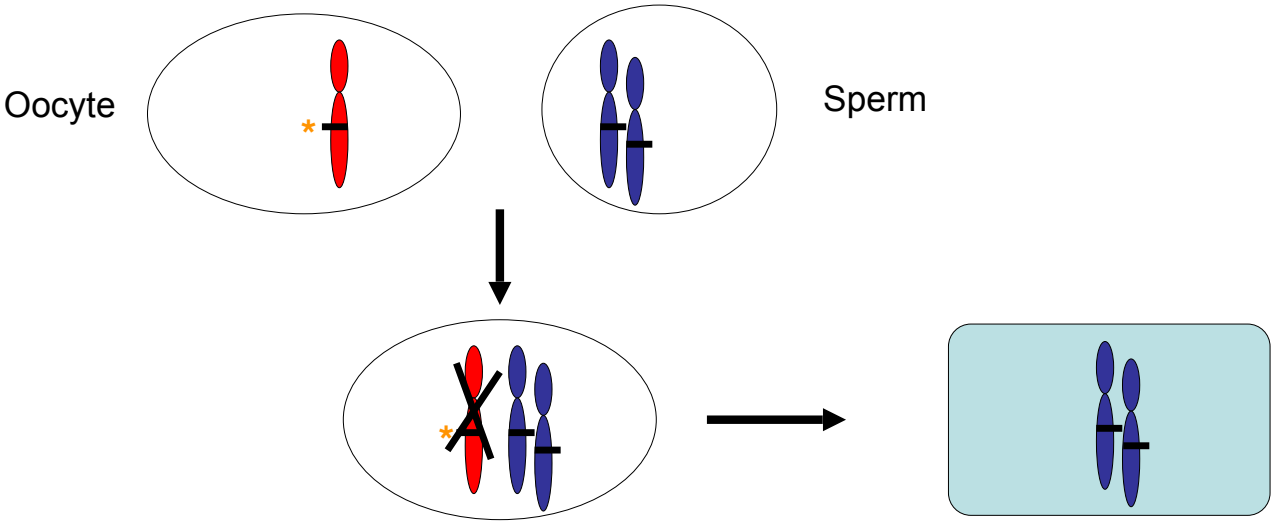
maternal expression

maternal deletion



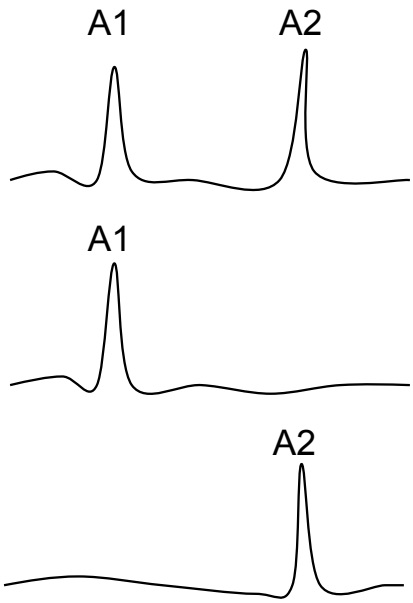
gene product missing, because inactivity on the paternal allele

Uniparental Disomy (UPD)

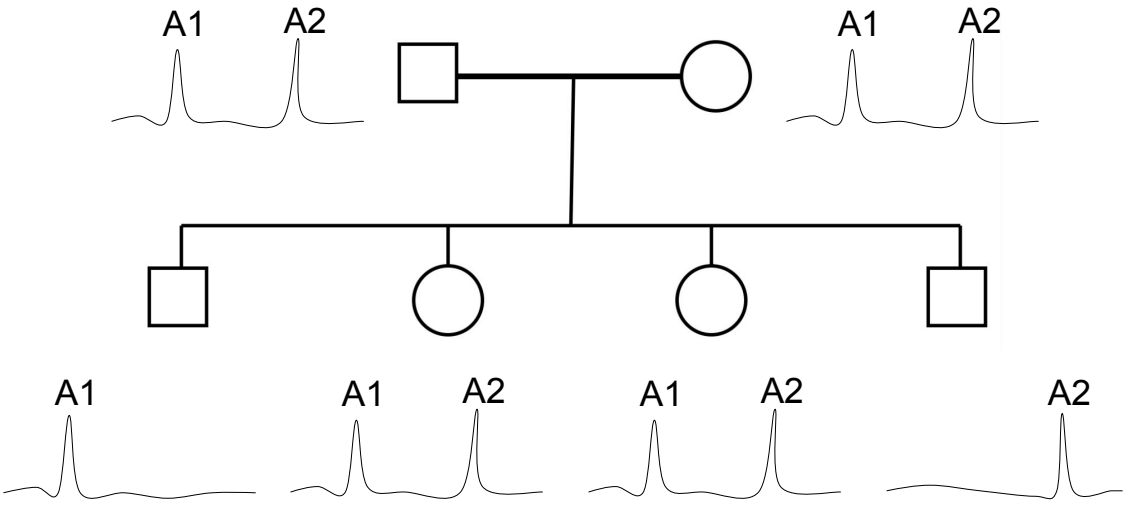


paternal uniparental disomy (pUPD)

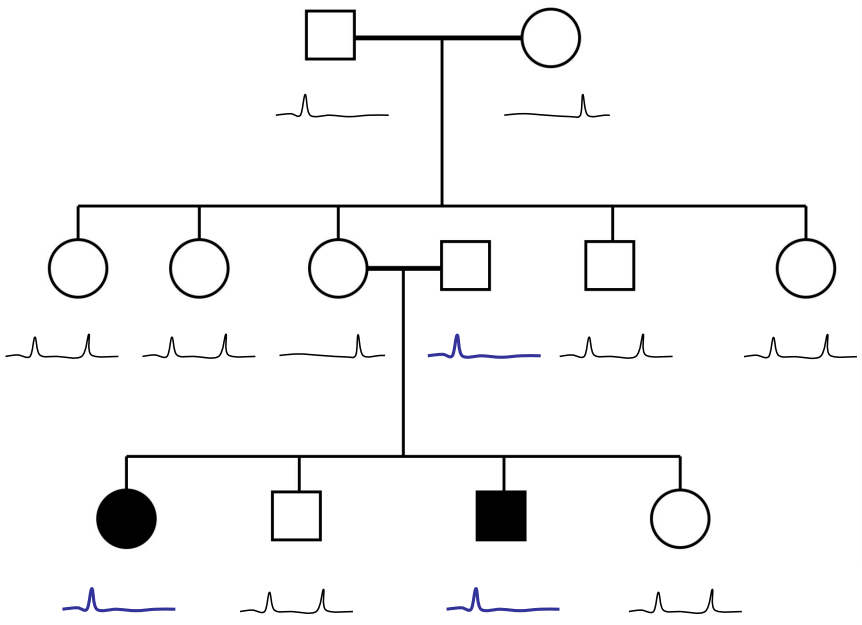
Genotyping (allele discrimination of a DNA marker)
Fragment analysis (capillary electrophoresis)



Segregation analysis of genetic markers (alleles)



Segregation analysis of genetic markers



Human Imprinting Diseases:
Prader Willi Syndrome (PWS)

Prevalence: 1:10,000-22,000

Symptoms: muscle hypotonia, feeding difficulties
morbid obesisty
short stature
intellectual disability
genital hypoplasia (hypogonadism)
incomplete pubertal development
infertility (in most patients)

Chromosome: 15q11.2-13.3

70% of individuals with PWS have a paternal deletion on chromosome 15 involving bands 15q11-q13

> 99% of individuals with PWS have a diagnostic abnormality in the parent-specific methylation imprint

Genetic testing in PWS

Table 1. Testing Used in Prader-Willi Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Methylation analysis	Methylation abnormality	99%	
FISH/Quantitative PCR	Deletion of PWCR [1]	70%-75%	
Uniparental disomy (UPD) studies	UPD of PWCR	25%-29%	
Sequence analysis [2]	Imprinting center defect	<1%	

PWCR=Prader-Willi critical region
1. Deletion varies in size, but always includes the PWCR.
2. Sequence analysis detects small deletions that account for approximately 15% of imprinting center mutations [Buiting et al 2003]. Most imprinting defects are epimutations (i.e., alterations in the imprint, not the DNA).

Source: Gene Reviews @ NCBI

Recurrence Risk in PWS (Counselling)

Genetic Mechanism	Risk to Sibs of a Proband with PWS
Deletion PWS/AS region	<1% [1]
Uniparental disomy (UPD)	<1% [2]
Imprinting defect with mutation	≤50% [3]
Imprint defect without mutation	<1% [3]
Apparently *de novo* balanced chromosome translocation breaking within the PWS/AS critical region [4, 5]	<1% [5]

Source: Gene Reviews @ NCBI

Human Imprinting Diseases:
Angelman Syndrome

Prevalence: 1:12,000-20,000, ´Happy Puppet Syndrome´

Symptoms: atactic movements
severe speech impairment
severe developmental delay or
intellectual disability
frequent laughing, smiling, and excitability

Chromosome: 15q11-q13.3

parent-specific DNA methylation imprints in the 15q11.2-q13 chromosome region detects approximately 78% of individuals with AS (maternal deletions, paternal UPD, imprinting defect)

UBE3A mutations in an additional approximately 11% of individuals, 1% have chromosome rearrangements, the remaining are unexplained

Recurrence Risk in AS (Counselling)

Molecular Class [1]	Families	Genetic Mechanism	Risk to Sibs
Ia	65%-75%	5-7 Mb deletion	<1%
Ib	<1%	Unbalanced chromosome translocation or inherited small interstitial deletion	Possibly as high as 50%
IIa	3%-7%	Paternal UPD	<1%
IIb	<1%	Paternal UPD with predisposing parental translocation	Approaching 100% if father has a 15;15 Robertsonian translocation
IIIa	0.5%	ID with deletion in the IC	As high as 50% if mother also has IC deletion
IIIb	2.5%	ID without deletion in the IC	<1%
IV	11%	*UBE3A* mutation	As high as 50% if mother also has a mutation
V	10%-15%	"Other" - no identifiable molecular abnormality	Undetermined risk

1. Based on terminology by Jiang et al [1999]

Source: Gene Reviews @ NCBI

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Pedigree with Imprinting Defect