Update on the Genetics of Ataxia

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Outline

- Definitions
- Review of genetics
- Autosomal Dominant cerebellar ataxias
- Autosomal Recessive cerebellar ataxias
- FXTAS and others

Definition

- Ataxia: from Greek root “ a taxis”; “without order, or incoordination”
- Neurological definition: Uncoordinated or inaccurate movement not due to weakness, too little or too much muscle tone, loss of sensation, or the disturbance caused by involuntary movements

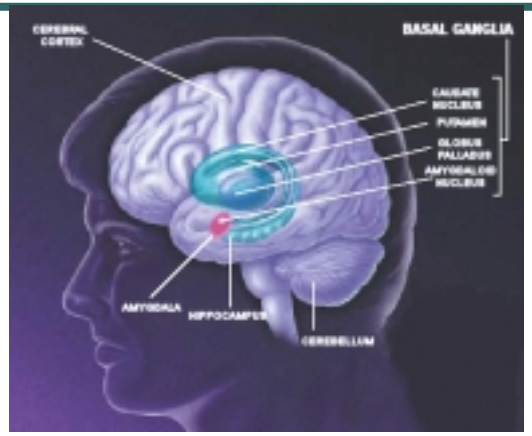
What causes ataxia?

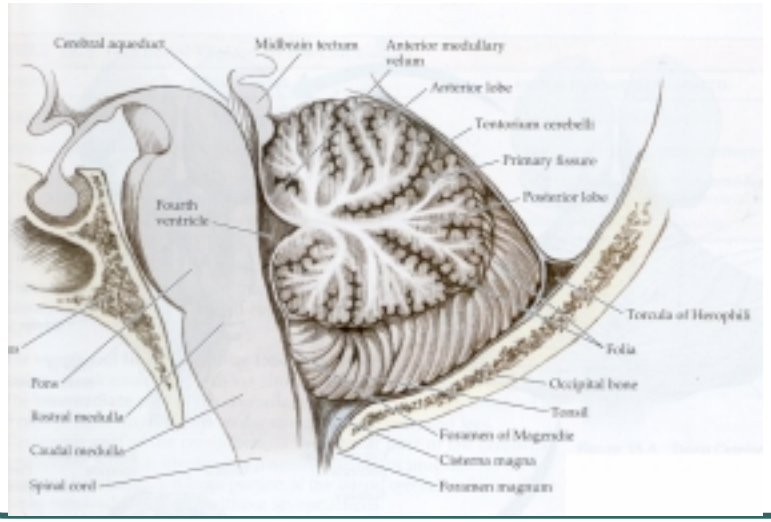
- ***Inherited ataxias***
- Non-genetic neurodegenerative
- Multiple sclerosis
- Tumors
- Strokes
- Infections and immune problems
- Alcohol or medications
- Vitamin deficiencies

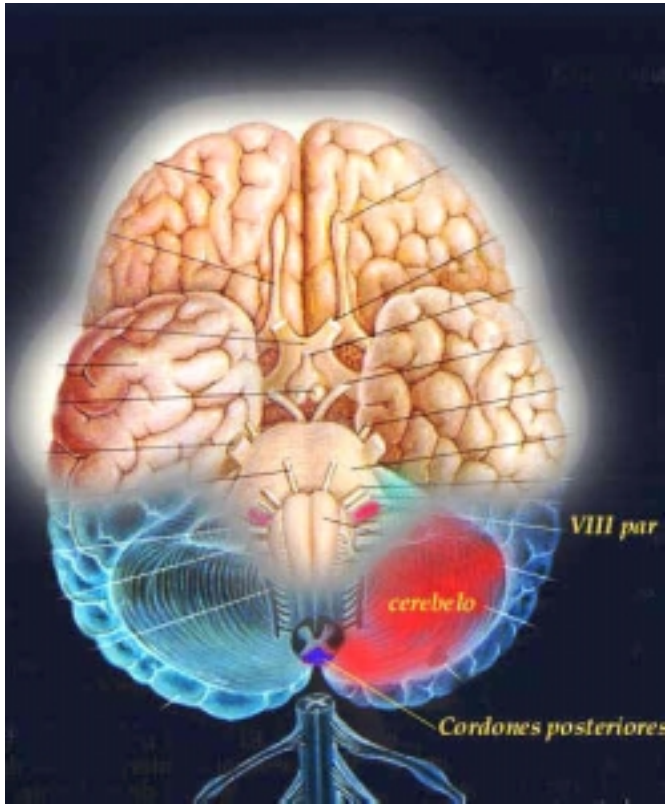
How is hereditary ataxia diagnosed?

- Symptoms of poor coordination, unsteady gait, slurred speech
- Abnormal signs on the neurological examination
- Complete family history is taken
- Tests to rule out other causes of ataxia
  - MRI brain scan
  - Blood tests

What part of the brain is affected in ataxia?







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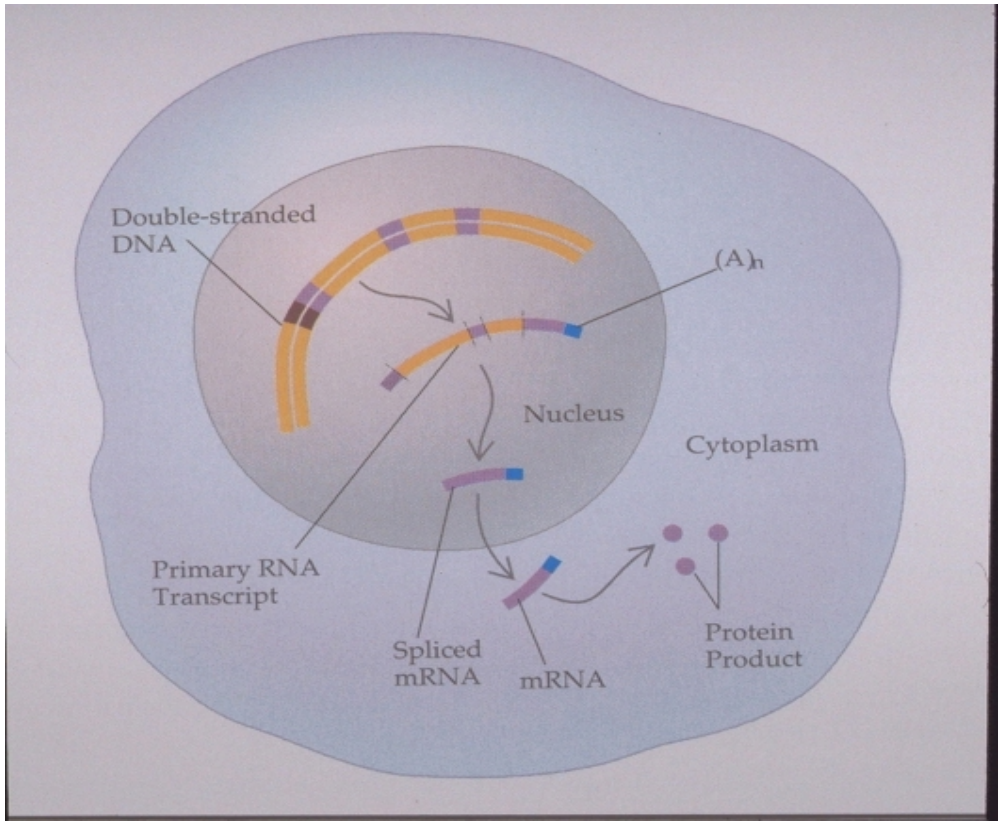
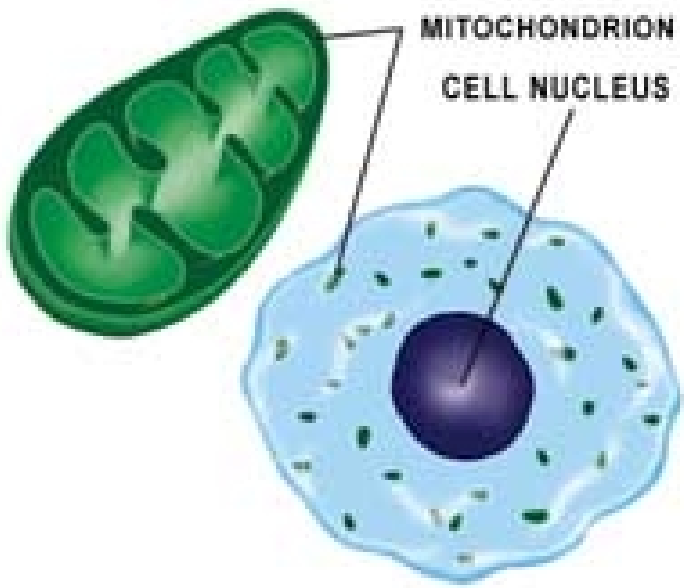
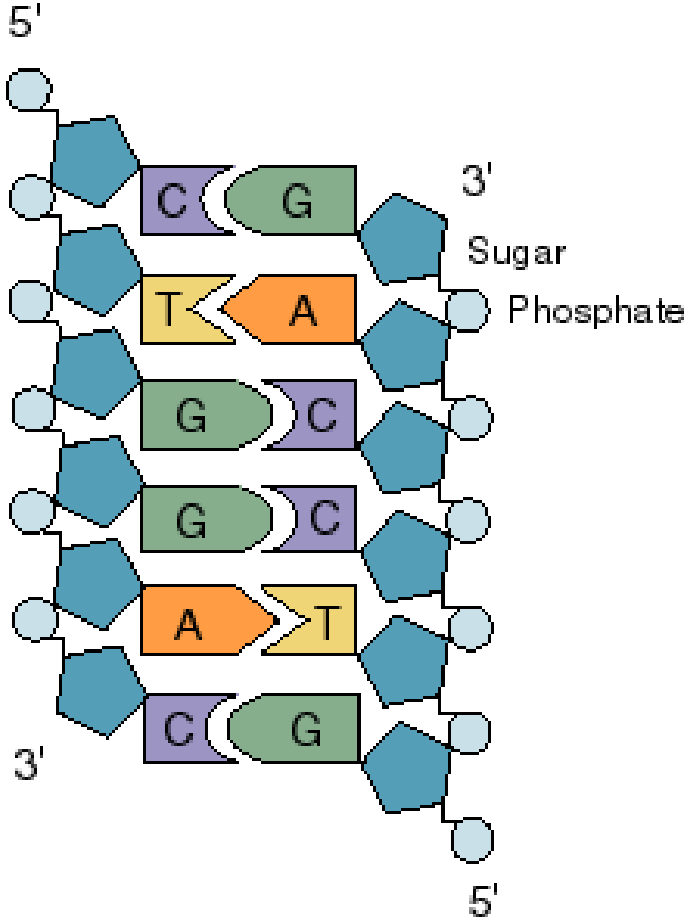




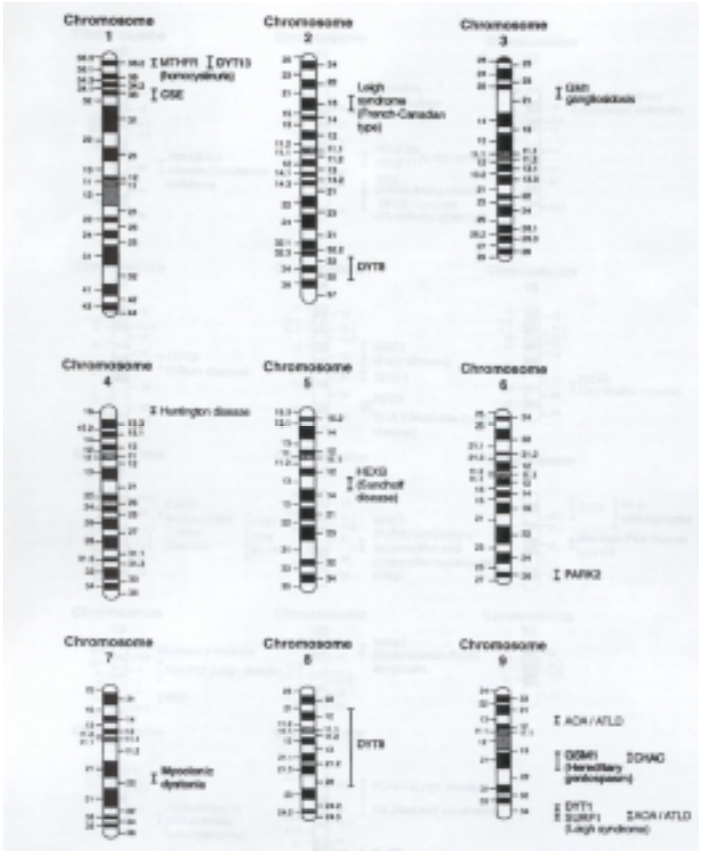
Review of genetics

- Chromosomes are in the nucleus, half inherited from mother and half from father
- Mitochondrial DNA is inherited from mother
- Chromosomes are made of DNA, which itself is composed of building blocks called **C T A G**



Types of mutations

- Deletion of DNA
- Expansion of DNA
- Point mutation
- Translocation

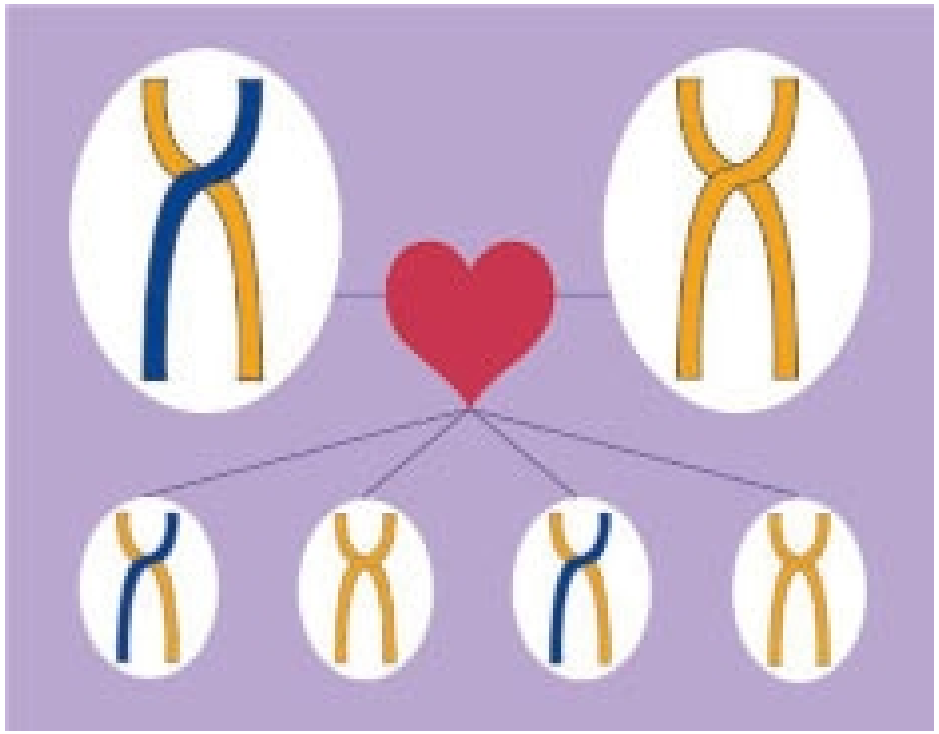


Patterns of inheritance

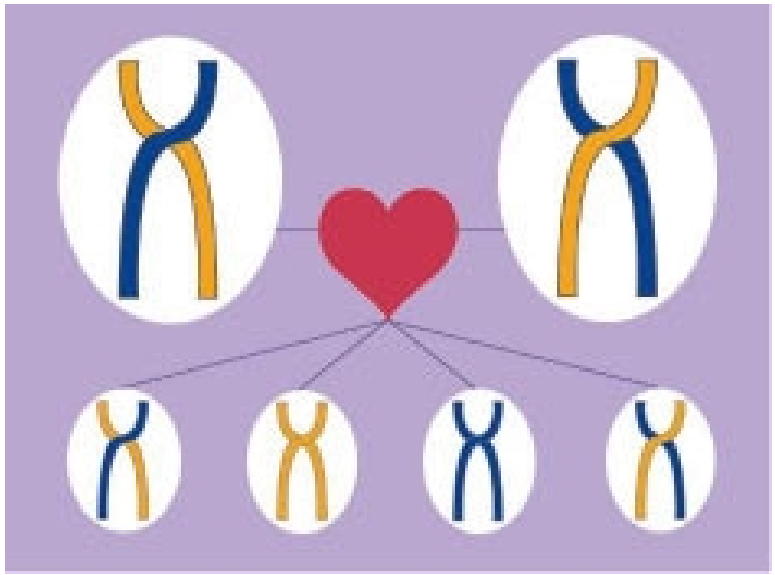
- Autosomal dominant
- Autosomal recessive
- X-linked recessive
- Mitochondrial

Patterns of inheritance: autosomal DOMINANT

- Affects males and females equally
- Either parent must carry the gene, and are likely to be affected themselves
- Each child of an affected parent has a 50% chance of inheriting the disorder



Patterns of inheritance: autosomal recessive



- Affects males and females equally
- Each parent must carry the gene for the disorder; parents usually NOT affected
- Each child has a 25% chance of inheriting the disorder

Ataxia genes

- First gene discovered in 1993 (Spinocerebellar ataxia 1)
- Each additional gene that is discovered is given the next number in order
- These abnormal genes direct the production of abnormal proteins which cause the nerve cells to malfunction

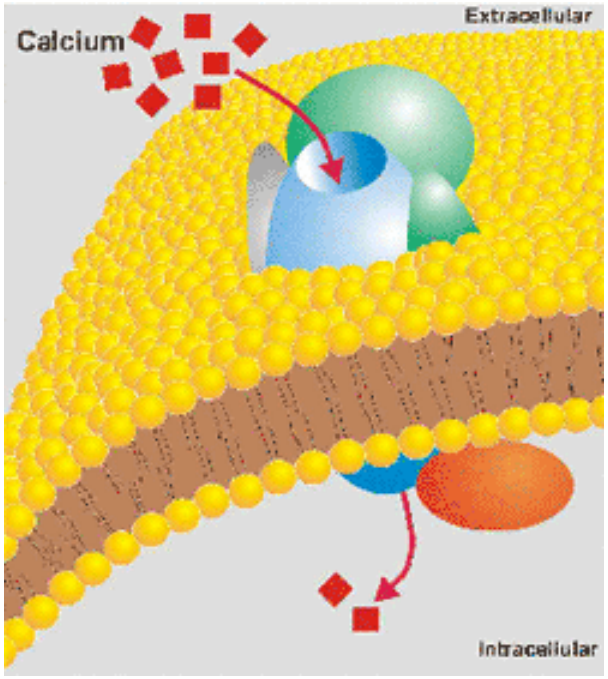
Autosomal dominant cerebellar ataxias

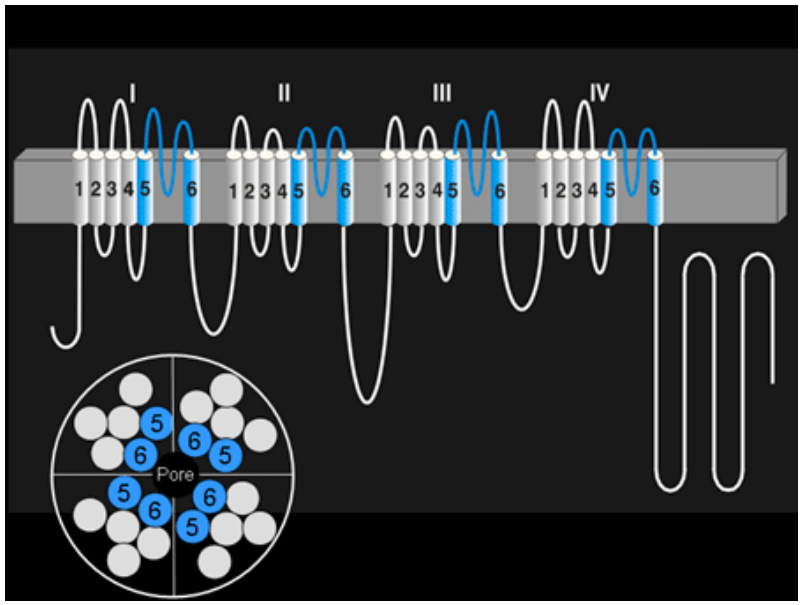
- Spastic ataxia
- Spinocerebellar ataxias
  - 17 with genes identified
- Episodic ataxias
  - 2 with genes identified

Episodic ataxias

- Each are the result of ion channel mutations
- EA1: potassium channel
  - Attacks start in childhood, then go away
  - Attacks last seconds-minutes.
- EA2: calcium channel
  - SCA6 and a form of severe migraine headache are also caused by mutations of the same gene.
  - Attacks last minutes- hours; develops into permanent ataxia

Calcium channels

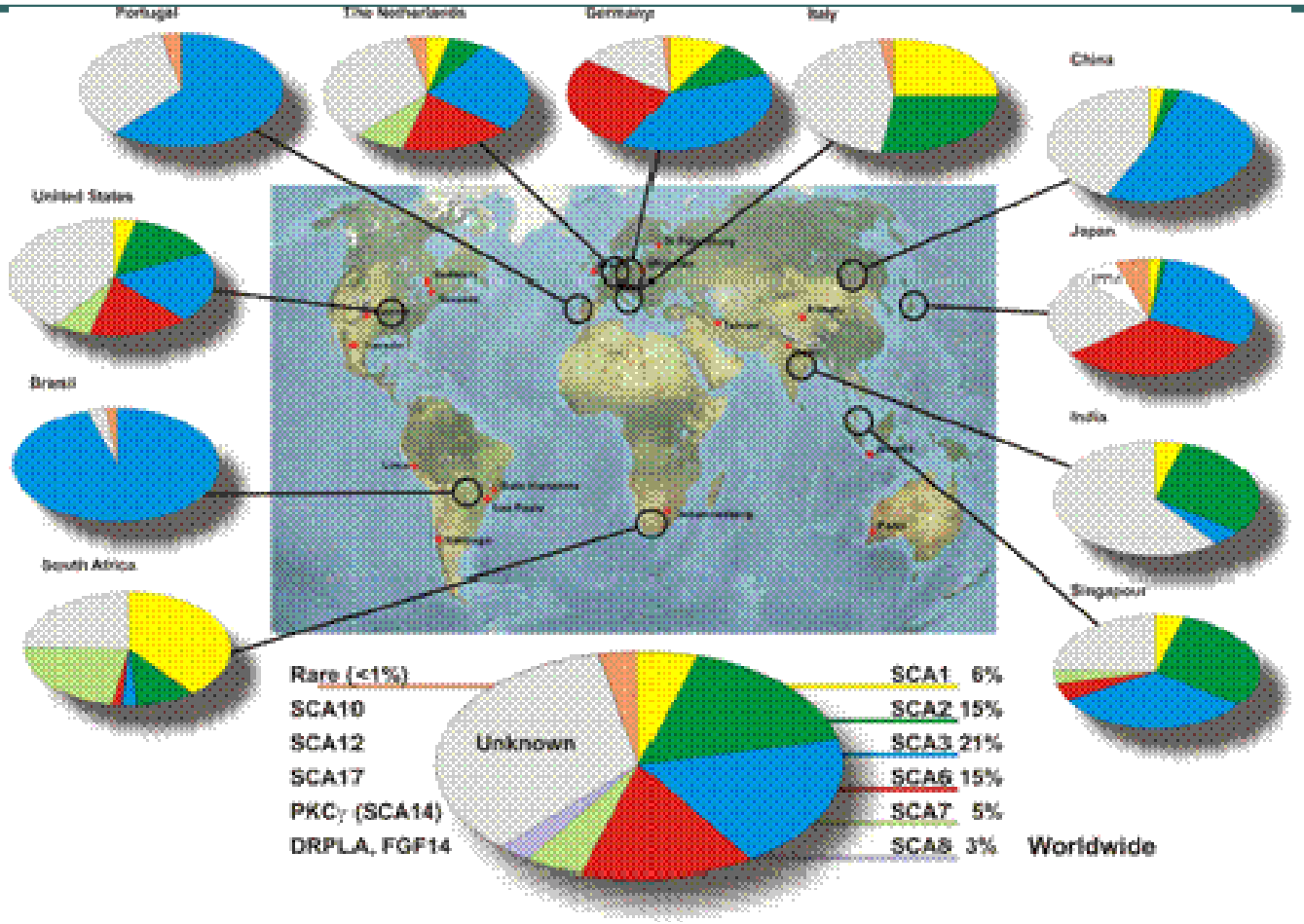




DISEASE	GENE	REPEAT TYPE	PROTEIN
SCA1	*SCA1*	CAG<36	Ataxin-1
SCA2	*SCA2*	CAG<31	Ataxin-2
SCA3	*MJD*	CAG<47	MJD protein-1
SCA6	*CACNA1A*	CAG<18	Ca.channel α-1A
SCA7	*SCA7*	CAG<35	Ataxin-7
SCA8	*SCA8*	CTG<50	
SCA10	*SCA10*	ATTCT	Ataxin-10
SCA12	*PPP2R2B*	CAG<45	Protein phosphatase
SCA14	*PRKCG*		PK C y
SCA17	*TBP*	CAG<44	TATA B.P.
DRPLA	*DRPLA*	CAG<35	Atrophin-1

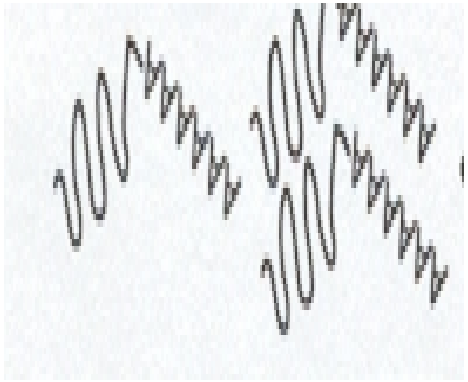
Distribution of SCAs

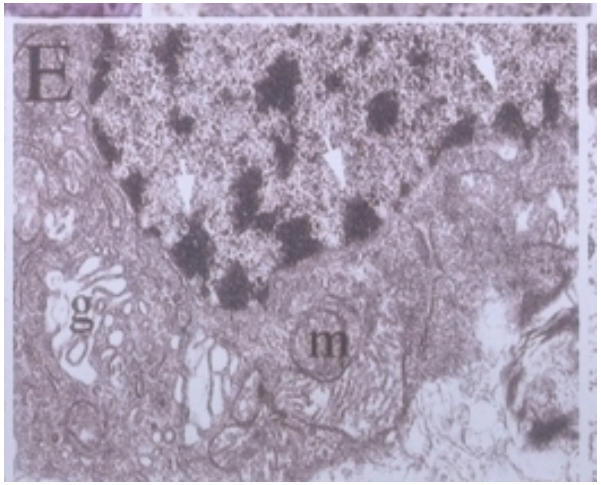
from T. Bird, www.geneclinics.org



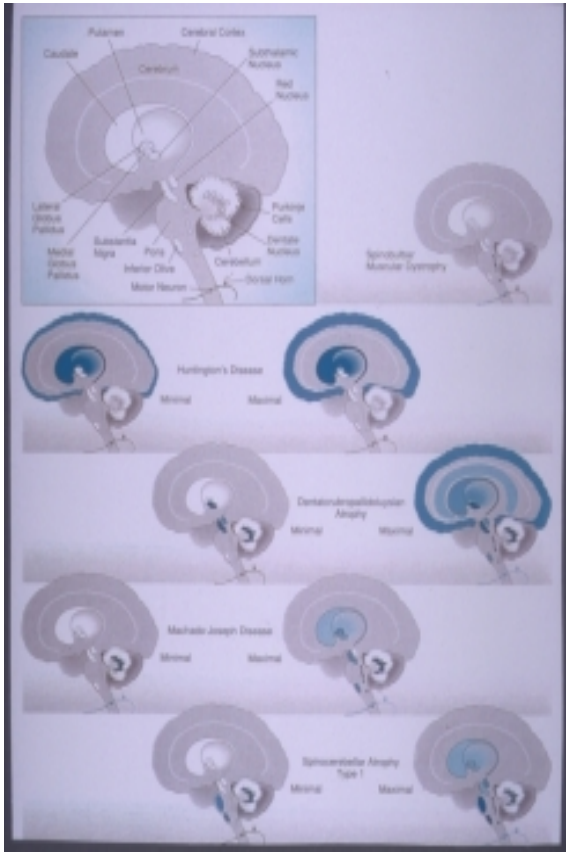
Trinucleotide repeat diseases

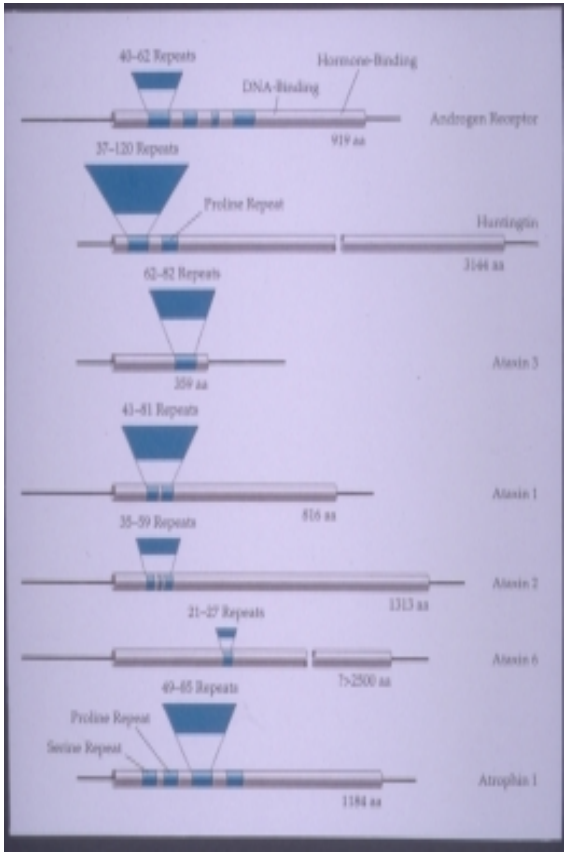
- SCA 1-3, 6-7, 12 and 17 and DRPLA
- CAG codes for the amino acid building block glutamine
- These proteins have a polyglutamine expansion
- Nerve cells have build-up of protein
- All have anticipation: earlier onset and increasing severity of disease in subsequent generations





CAG repeat diseases





Diagrams: Young A," HD and other trinucleotide Repeat Disorders" in Molecular Neurology, Martin, ed. Scientific American, 1998

Other features which may be seen in SCA

- Neuropathy: loss of sensation for vibration, position, temperature; on exam reflexes are reduced or absent
- Over-active reflexes
- Slow or incomplete eye movements
- Parkinson's signs: rigidity, tremor, slowness
- Loss of memory

DISEASE	*% OF SCA*	*AGE OF ONSET*	*OTHER FEATURES*
SCA1	**6 (5-27)**	**30's**	Neuropathy, brisk reflexes
SCA2	**15 (13-24)**	**20s-30s**	Slow eye movements, neuropathy, memory loss
SCA3	**21 (11-36)**	**30s**	Parkinsonism, reduced eye movements, sensory loss, muscle twitches
SCA6	**15**	**40s-50s**	Sometimes episodic
SCA7	**5**	**20s-30s**	Visual loss

DISEASE	*% SCA*	*AGE OF ONSET*	*OTHER FEATURES*
SCA8	**2-5**	**39y**	Brisk reflexes, loss vibratory sense
SCA10	**Rare**	**36y**	Occ. seizures
SCA12	**Rare**	**33y**	Early tremor, late memory loss
SCA14	**Rare**	**28y**	Myoclonus
SCA17	**Rare**	**6-34y**	Memory loss, parkinsonism

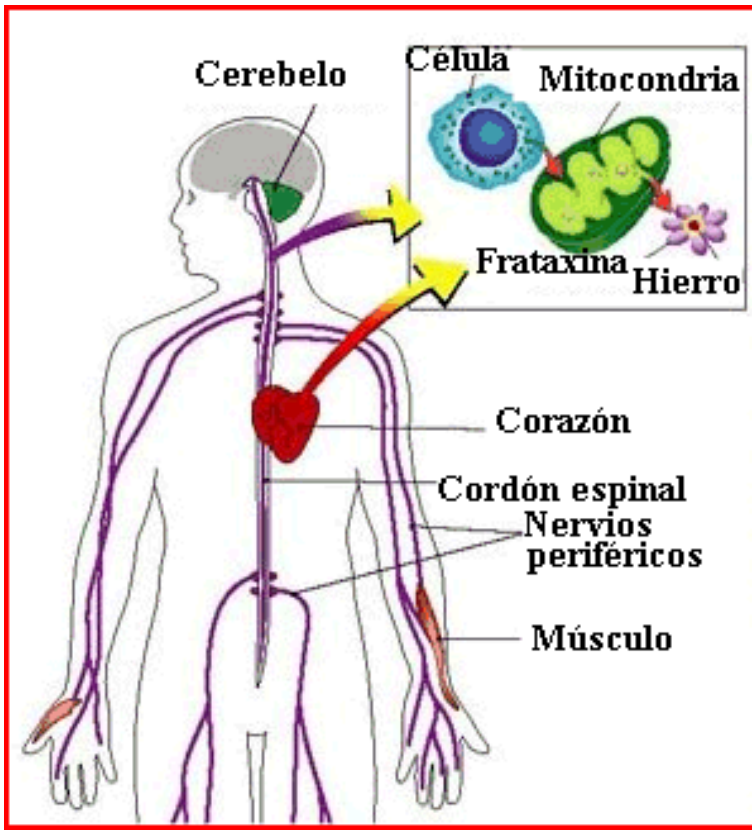
Autosomal recessive ataxias

- Parents not affected
- Friedreich's ataxia – most common

DISEASE	*GENE*	*MUTATION*	*PROTEIN*
FRIEDREICH'S ATAXIA	FRDA	GAA expansion	FRATAXIN
ATAXIA-TELANGECTASIA	ATM	Multiple	SERINE-PROTEIN KINASE ATM
ATAXIA WITH VITAMIN E DEFICIENCY	TTPA		VIT. E TRANSFER PROTEIN
ATAXIA WITH OCULOMOTOR APRAXIA	APTX		Aprataxin
AUTOSOMAL RECESSIVE SPASTIC ATAXIA OF CHARLEVOIX-SAGUENAY	SACS		Sacsin

DISEASE	*FREQ.*	*ONSET*	*FEATURES*
FRIEDREICH'S ATAXIA (FRDA)	**1-2/50,000**	USUALLY 4-25Y	LOSS OF REFLEXES, SENSORY LOSS, HEART AFFECTED
ATAXIA-TELANGECTASIA	**1/40-100,000**	1-10Y	TELANGECTASIA, IMMUNE DEF., CANCERS
ATAXIA WITH VIT E. DEFICIENCY	**RARE**	USUALLY. <20Y	SIMILAR TO FRDA; HEART NOT AFFECTED
ATAXIA WITH OCULOMOTOR APRAXIA	**UNKNOWN**	CHILDHOOD	INABILITY TO MOVE EYES, SEVERE NEUROPATHY

FRDA is a multisystem disorder



X-linked ataxias

- Extremely rare, affect single families
- Affect boys (XY), not girls (XX)
- Sometimes associated with spasticity (rigidity), mental retardation, deafness, anemia.

FXTAS

- Fragile X Tremor Ataxia Syndrome
- Progressive tremor, ataxia and cognitive decline
- Found in grandfathers and female carriers of boys with Fragile X syndrome (mental retardation)
- Recent report from Belgium of 122 males over 50 yr., with “SCA” without known mutation; 5 had FMR1 premutation

Ataxia with mitochondrial disorders

- Also very rare
- Associated with other neurological symptoms: seizures, neuropathy, deafness, heart problems, vision loss

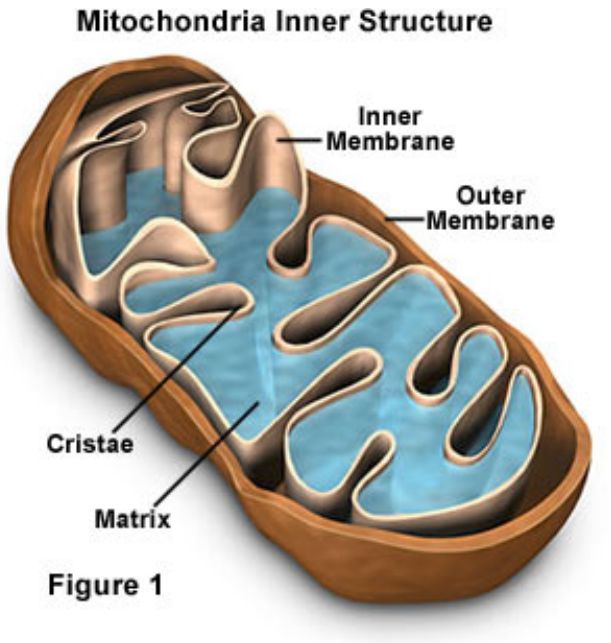
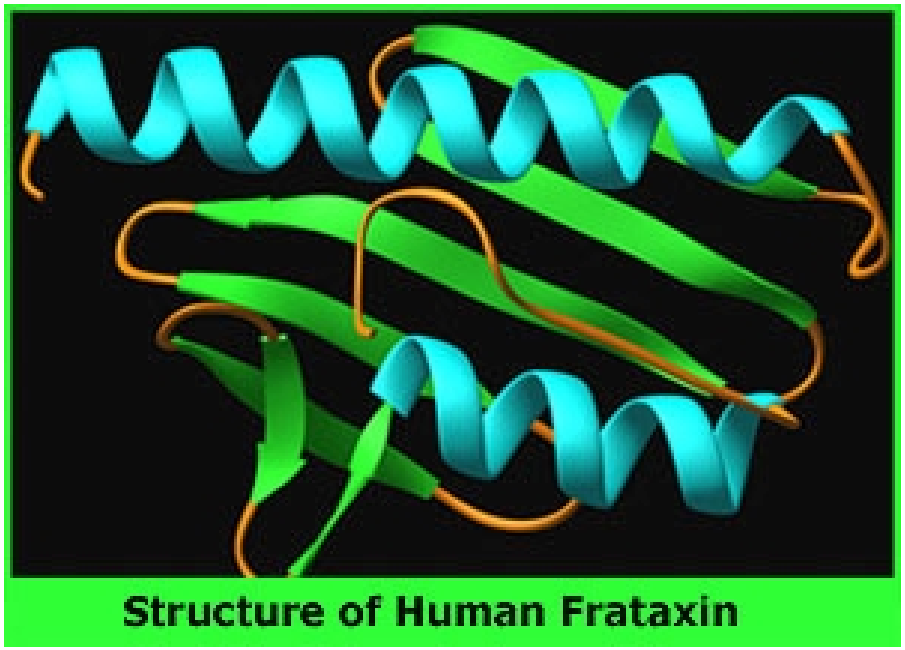


Figure 1

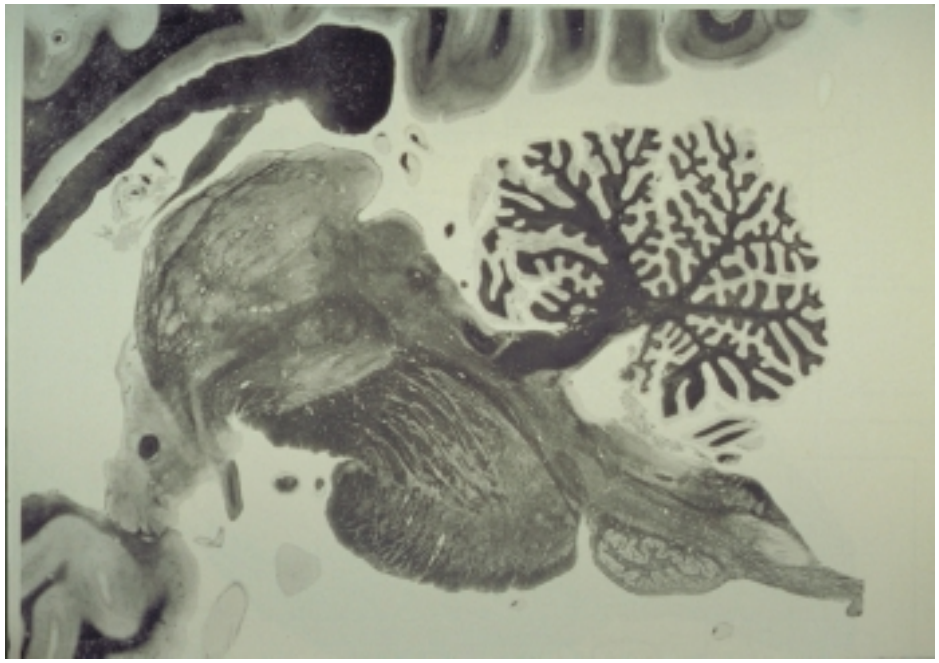
How genetic studies help

- Correct diagnosis
- Understanding mechanism of cell and organ damage
- Will lead to new and more effective treatments



Structure of Human Frataxin

Resources



- www.ataxia.org
- www.geneclinics.org

Thank you!

- Mike Fernandes
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  - Terry Tempkin, nurse practioner
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