Fragile X Tremor Ataxia Syndrome (FXTAS)

Le point de vue du neurologue

- Gaëtan Garraux
- CHU de Liège
- www.movere.org

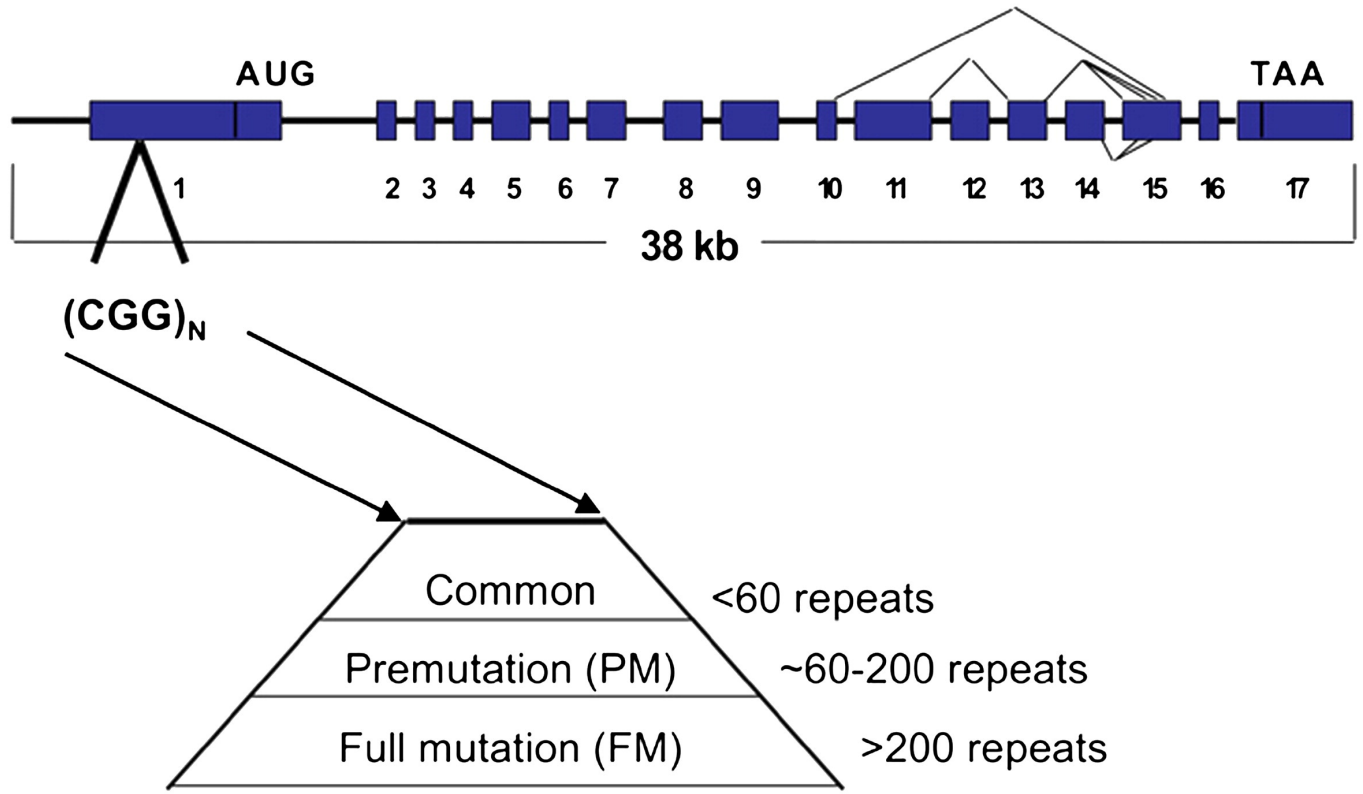
Background

FXTAS was first described by Hagerman and coll. (2001) as they collected family history from mothers of children with fragile X syndrome, a trinucleotide repeat expansion disorder (>200 CGG repeats) in a non-coding segment of the *FMR1* gene on chromosme X

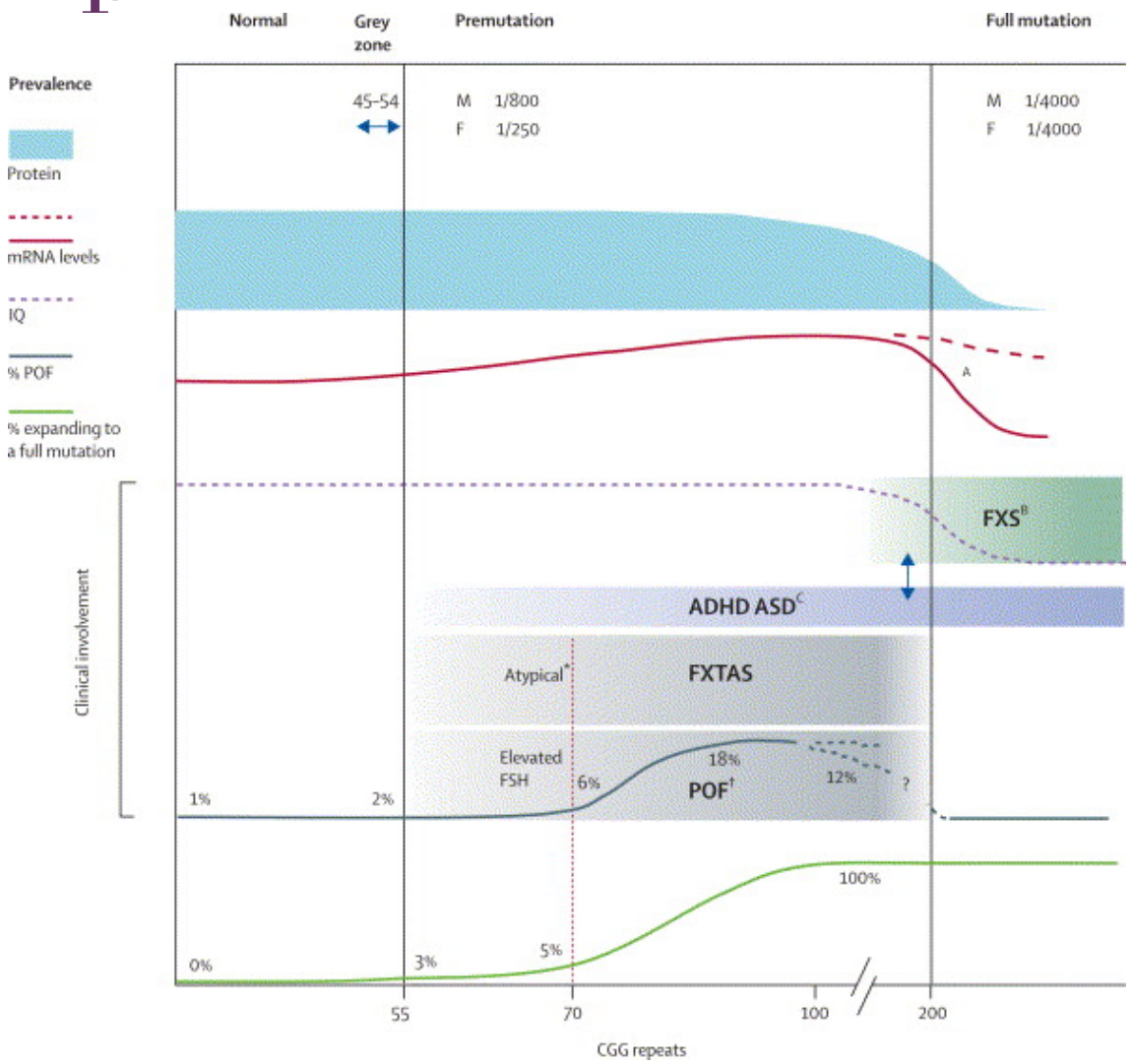
These mothers who are themselves carriers of premutations forms of the repeat expansion (55-200 CGG repeats) often stated that one of their parents – also a premutation carrier – had limb tremor and/or a balance disorder

Examination of these grandparents (often males) revealed a common clinical presentation chielfy characterized by intention tremor and cerebellar ataxia

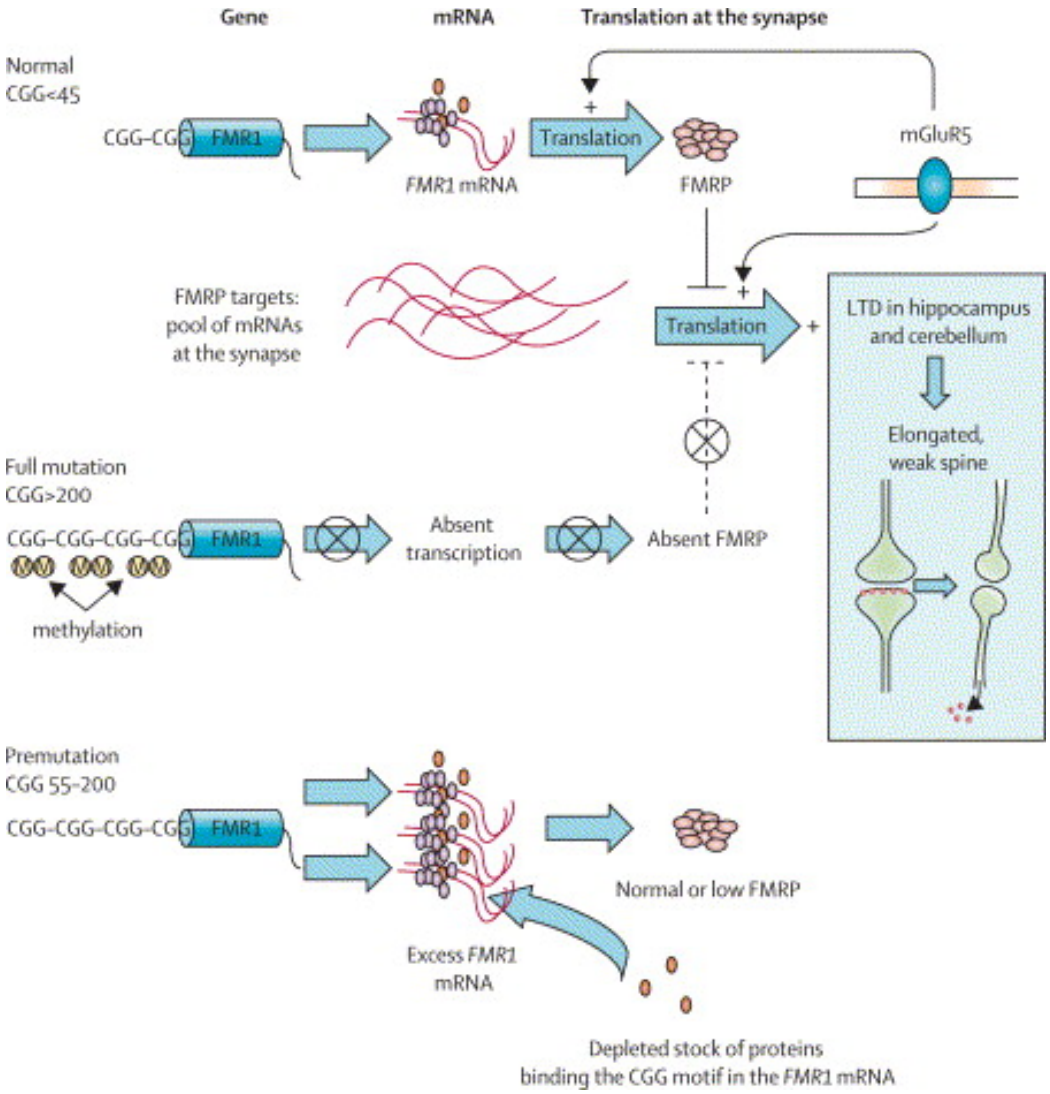
Genotype


AUG
TAA
1
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
38 kb
(CGG)N
Common
<60 repeats
Premutation (PM)
~60-200 repeats
Full mutation (FM)
>200 repeats

Overall genotype-phenotype relationship



Molecular biology



Genotype-phenotype relationship

Premutation carriers (55-200 repeats)

Normal intelligence

Primary ovarian failure

20% of females

(never seen in female with the full mutation)

FXTAS

40% of males carriers over age 50

(nerver seen in males with the full mutation)

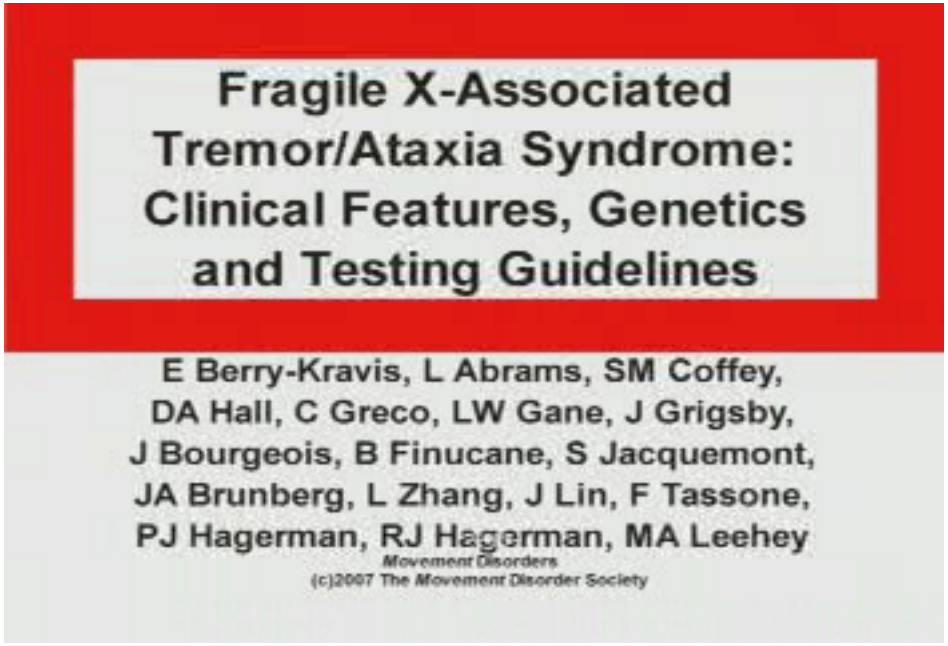
8% of females over age 40

Clinical phenotype of premutation carriers (55-200 repeats)

Premutation				
Female reproductive symptoms		POF (<40 years) Early menopause (<45 years)	Adulthood	F 20 %† F 30 %†
FXTAS	Cognitive decline, dementia, apathy, dysinhibition, irritability, depression	Gait ataxia, intention tremor, parkinsonism, neuropathy, autonomic dysfunction,	>50 years	M 33 %‡ F unknown
Neurodevelopmental disorder	ADHD, autism, or developmental delay	Mild features of FXS	Childhood	8 % (1/13)[88]

FXS=fragile-X syndrome. M=male. F=female. POF=premature ovarian failure. ADHD=attention deficit hyperactivity disorder. *Frequency of those signs in prepubertal boys;[11] a third of boys with FXS are without classic facial features.[14] Macro-orchidism is present in 90% of adult males. †Maximum penetrance reported for allele size approximately 80 to 90 CGG repeats.[4] ‡Penetrance is correlated with age[12] and repeat size.[13]

Clinical presentation of FXTAS



Clinical presentation of FXTAS

- Ataxic gait in 50% of male carriers over age 50
(> 3 mis-steps in tandem walking)

- Mild and moderate intention tremor in 50% and 17% of male carriers, respectively

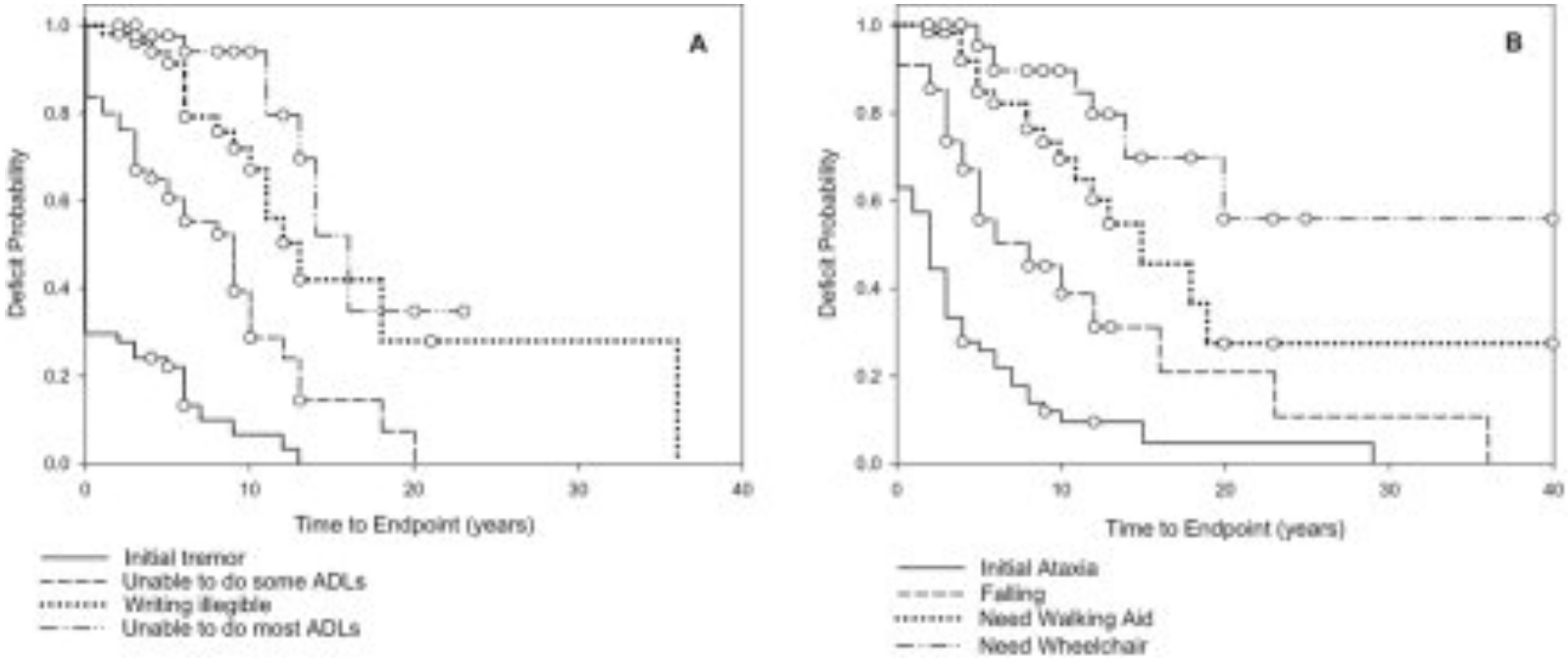
- Parkinsonism; rest tremor is uncommon

- Cognitive disturbances: memory & executive deficits; Langage is preserved; dementia in 40% of males (cortical-subcortical pattern)

- Neuropsychiatric features: anxiety, irritability, agitation, hostility, obsessive-compulsiveness, apathy, depression, obsessive thinking

- Axonal sensory>motor neuropathy

Clinical progression of tremor and ataxia



Movement Disorders
Volume 22, Issue 2, pages 203-206, 28 NOV 2006 DOI: 10.1002/mds.21252
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FXTAS: non-motor symptomps

Table 2 Prevalence of non-motor symptoms in subjects compared to age-adjusted estimates

Symptom	Subjects (N=50; %)	Men>60 years (%)	Chi-square test/p value
Sleep disorders			
Symptoms suggestive of rapid eye movement behavioral disorder (REM-BD)	10	2	16.3/<0.0001
Heavy snoring (possible sleep apnea)	24	25	0.03/0.87
Restless leg syndrome (RLS)	16	10	2.00/0.16
Autonomic dysfunction			
Erectile dysfunction (ED)	56	34	10.8/0.001
Orthostatic intolerance	16	16	0.0/1.00
Bladder dysfunction	24	30	0.86/0.35
Sensory disturbances			
Hearing loss	50	30	9.52/0.002
Peripheral neuropathy	20	26	0.94/0.33

Clinical features in daughters of men with FXTAS

Table 1. Prevalence of neurological symptoms, medical problems, ovarian and menstrual dysfunction, and psychiatric and behavioral symptoms in daughters of men with FXTAS compared to non-carrier female controls

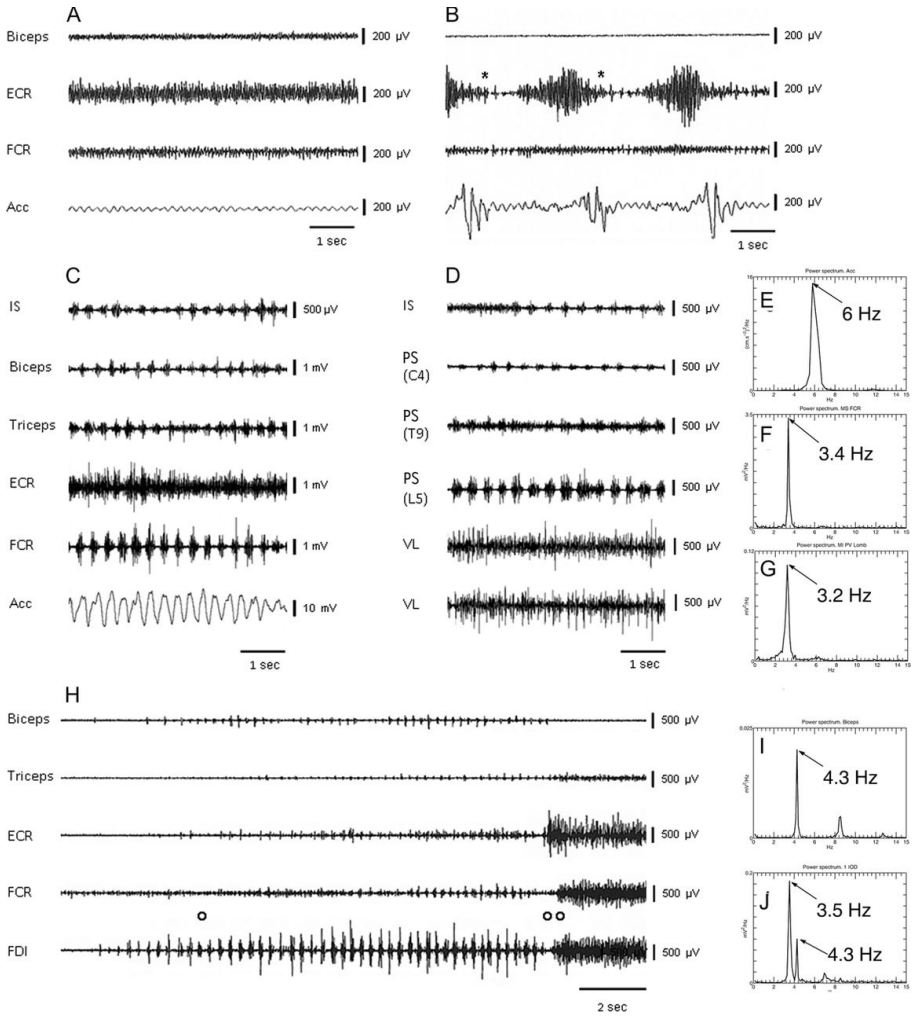
	Daughters of men with FXTAS ($n = 110$)		Controls ($n = 43$)		
Variables	*n*	Percentage	*n*	Percentage	p-Value
Neurological symptoms					
Tremor	15	13.64	0	0.00	0.00653*
Balance problems	30	27.27	0	0.00	0.00002*
Memory problems	42	38.89	3	6.98	0.00006*
Dizziness	29	28.43	2	5.13	0.00257*
Burning or pain in the leg	19	17.43	4	10.26	0.43972
Weakness of the leg	9	8.26	0	0.00	0.06277
Problems in orgasm	13	12.87	0	0.00	0.01995*
Medical problems					
Diabetes	4	3.64	0	0.00	0.57717
Thyroid problems	22	20.18	4	9.30	0.15112
Hypertension	20	18.18	3	6.98	0.12879
Migraine headache	38	35.19	10	26.32	0.42228
Ovarian and menstrual dysfunction					
Menopausal symptoms	60	74.07	15	38.46	0.00025*
POI	10	14.08	0	0.00	0.05888
Infertility	20	26.67	4	14.29	0.29420
Psychiatric and behavioral symptoms					
Sleep problems	69	62.73	14	32.56	0.00106*
Anxiety	71	65.14	15	34.88	0.00099*
Depression	58	53.21	20	46.51	0.47667
Psychiatric medications and/or counseling	67	63.21	25	58.14	0.58139

FXTAS, fragile X-associated tremor/ataxia syndrome; POI, primary ovarian insufficiency.
*Significant after p-value adjustment.

Distinctive clinical features between male and female premutations carriers

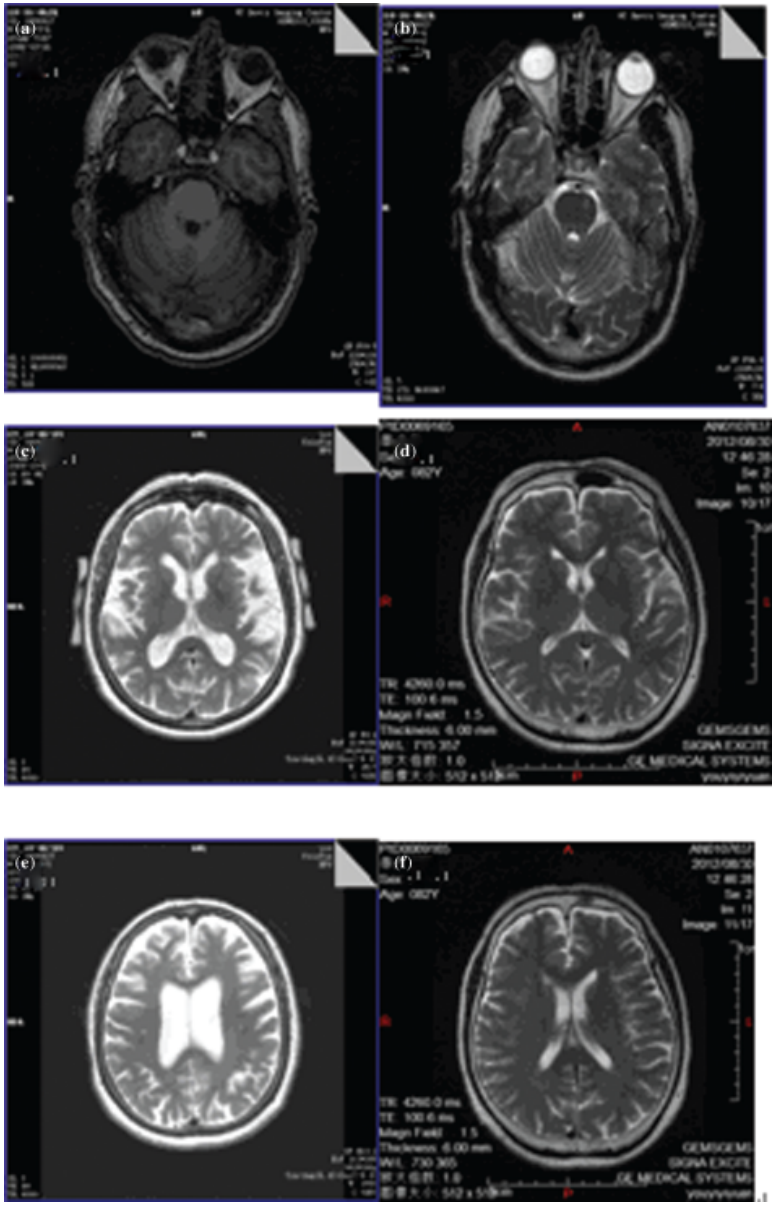
Premutation FraX males	Premutation FraX females
Subtle facial features (broad forehead, large ears)	Usually not evident or very subtle facial features
Normal intelligence	Normal intelligence
Executive function deficits	Subtle executive function deficits
Short-term memory deficits	
Obsessionality	Increased emotionality
Cognitive decline	Anxiety
Mood disorders (principally depression)	Depression
ASD	
ADHD	
Alcohol and substance misuse	Alcohol misuse
FXTAS	FXTAS
	POI
	Thyroid disorders
	Chronic muscle pain
	Hypertension
	Fibromyalgia
	Muscle pain

Polymyographic recordings of tremors



Apartis E et al. Neurology 2012;79:1898-1907

Brain MRI



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Volume 22, Issue 14, pages 2018-2030, 6 JUL 2007 DOI: 10.1002/mds.21493
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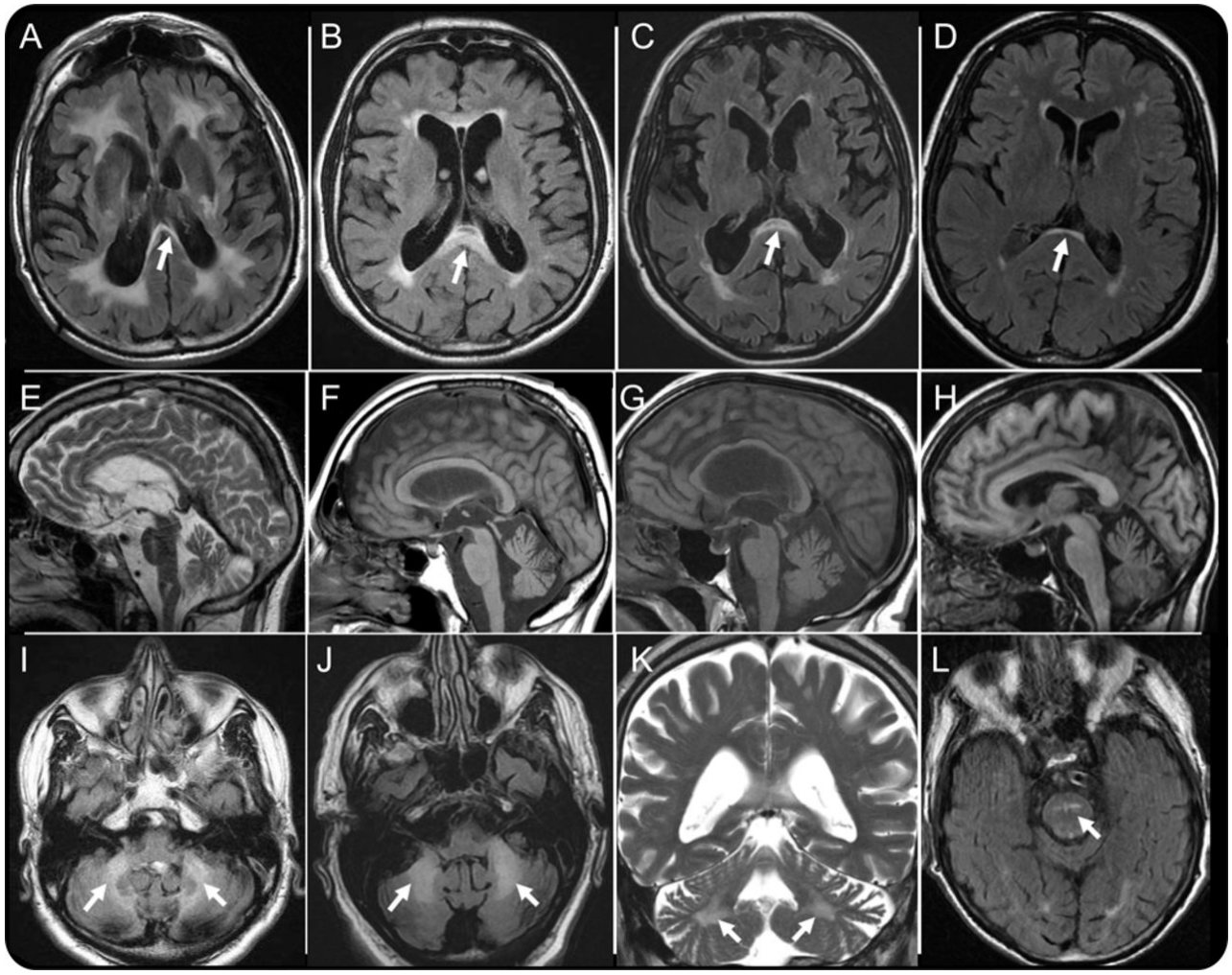
Brain MRI



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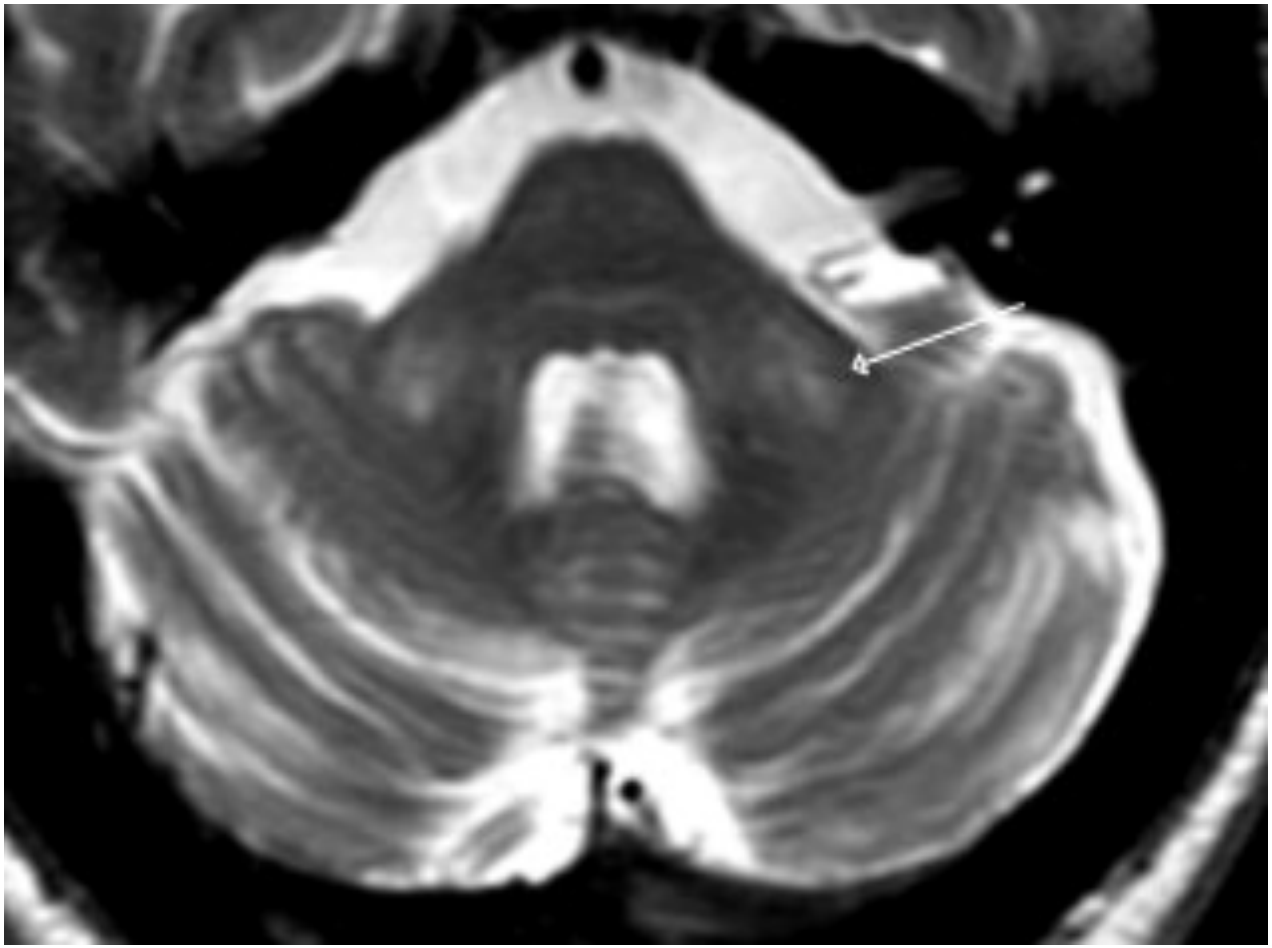
Middle cerebellar peduncles sign



Movement Disorders
Volume 22, Issue 14, pages 2018-2030, 6 JUL 2007 DOI: 10.1002/mds.21493
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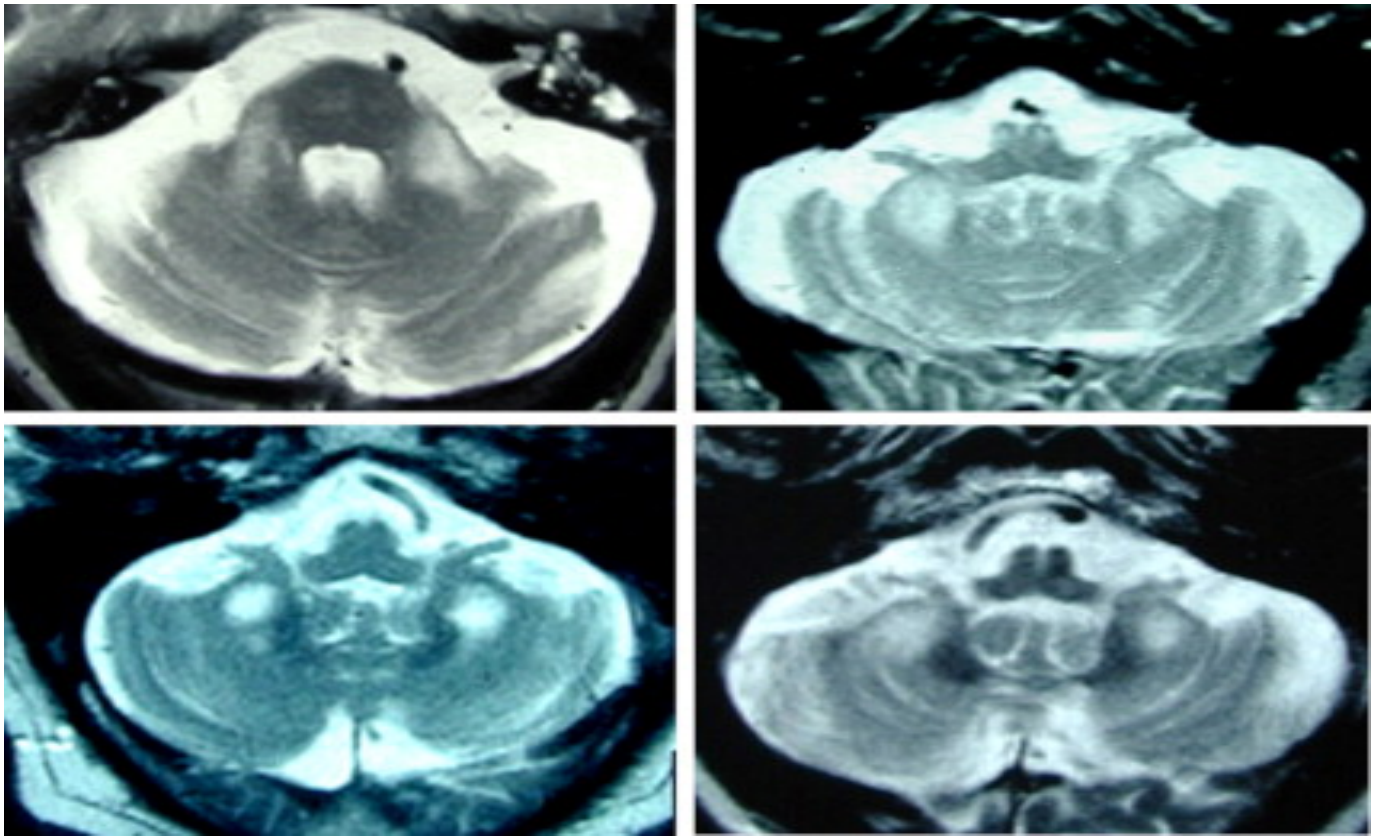
Middle cerebellar peduncles sign



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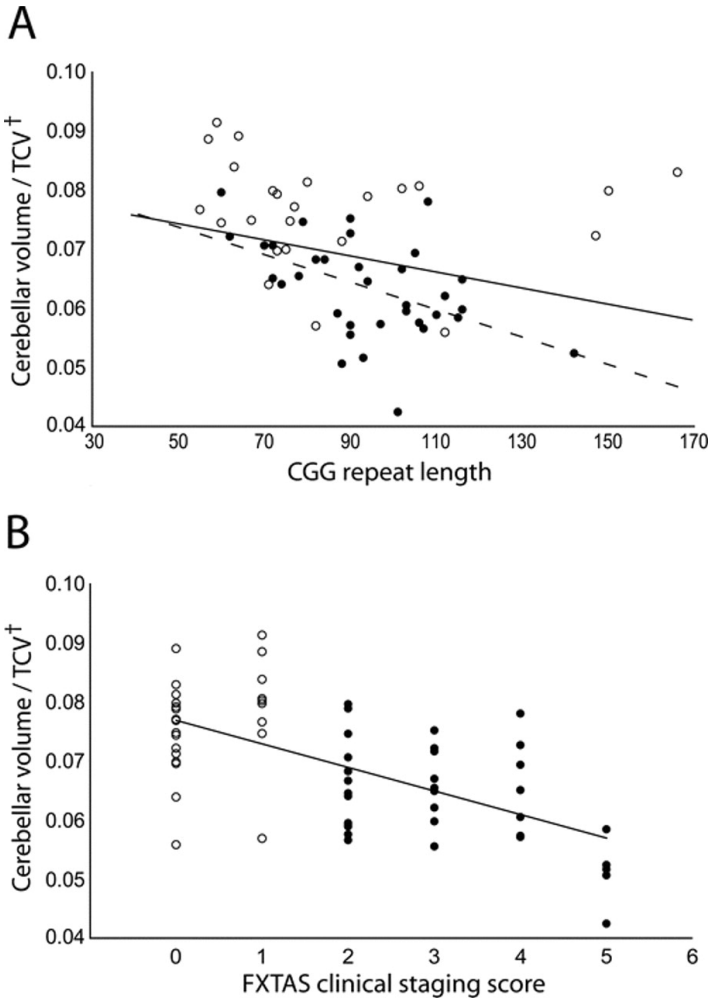
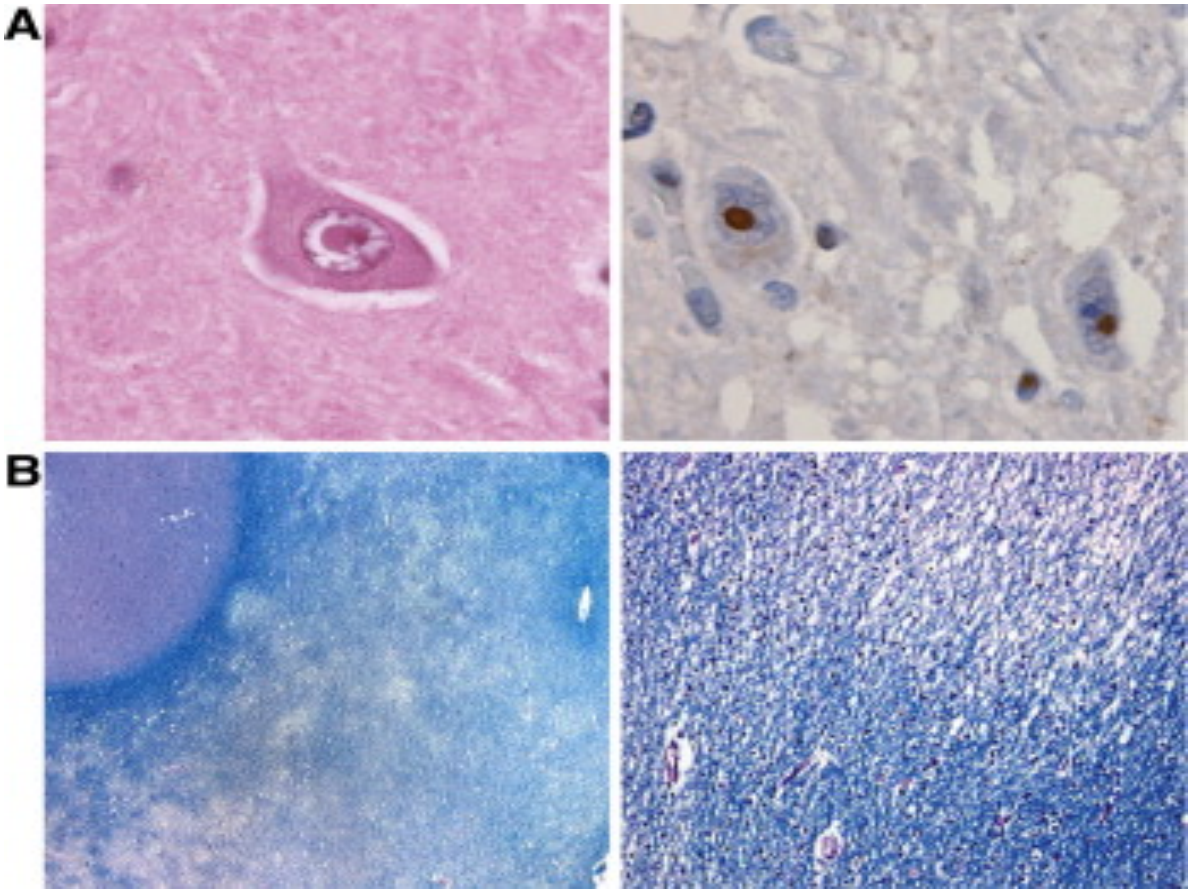
Relationship between cerebellar atrophy and genotype/phenotype



Neuropathology of FXTAS



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Epidemiology and clinical significance of FXTAS

Prevalence estimates for FXTAS and several other neurodegenerative disorders per 100 000 population

Disorder	Prevalence*	Study	OMIM†
FXTAS‡	2–6 $(10–30)_{60}$	Jacquemont et al., 2004a, current work	#300623
Essential tremor	400–4000 $(1300–5000)_{60}$	Louis et al., 1998	#190300
Inherited ataxias§	5–20	Sridharan et al., 1985; Polo et al., 1991; van de Warrenburg et al.. 2002	Multiple (e.g., #164400, #183090, #109150)
Parkinson disease	13 $(>1000)_{55}$	de Rijk et al., 1997; Van Den Eeden et al., 2003	#168600
Progressive supranuclear palsy	6 $(14)_{55}$	de Rijk et al., 1995; Schrag et al., 1999	#601104
Multiple system atrophy	2–5 $(17–29)_{55}$	de Rijk et al.,1995; Schrag et al., 1998, 1999; Vanacore, 2005	
Corticobasal degeneration	5–7	Togasaki and Tanner, 2000	#600274
Amyotrophic lateral sclerosis	4–8	Annegers et al., 1991; Chancellor and Warlow, 1992; Nelson, 1996; Traynor et al., 1999	#105400

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Epidemiology and clinical significance of FXTAS

TABLE 2. *Frequency of* FMR1 *premutation alleles in populations with movement disorders*[a]

	Premutation allele/sample size	
Clinical diagnosis	Men	Women
PD[b]	1/903	1/225
Atypical PD	0/40	0/11
Essential tremor	0/270	0/78
MSA[c]	2/366	3/297
MSA-P[d]	1/341	
MSA-C[d]	4/280 (4/167)[e]	
Cerebellar ataxia	16/1049[f]	1/549
Total	18/2628	5/1160

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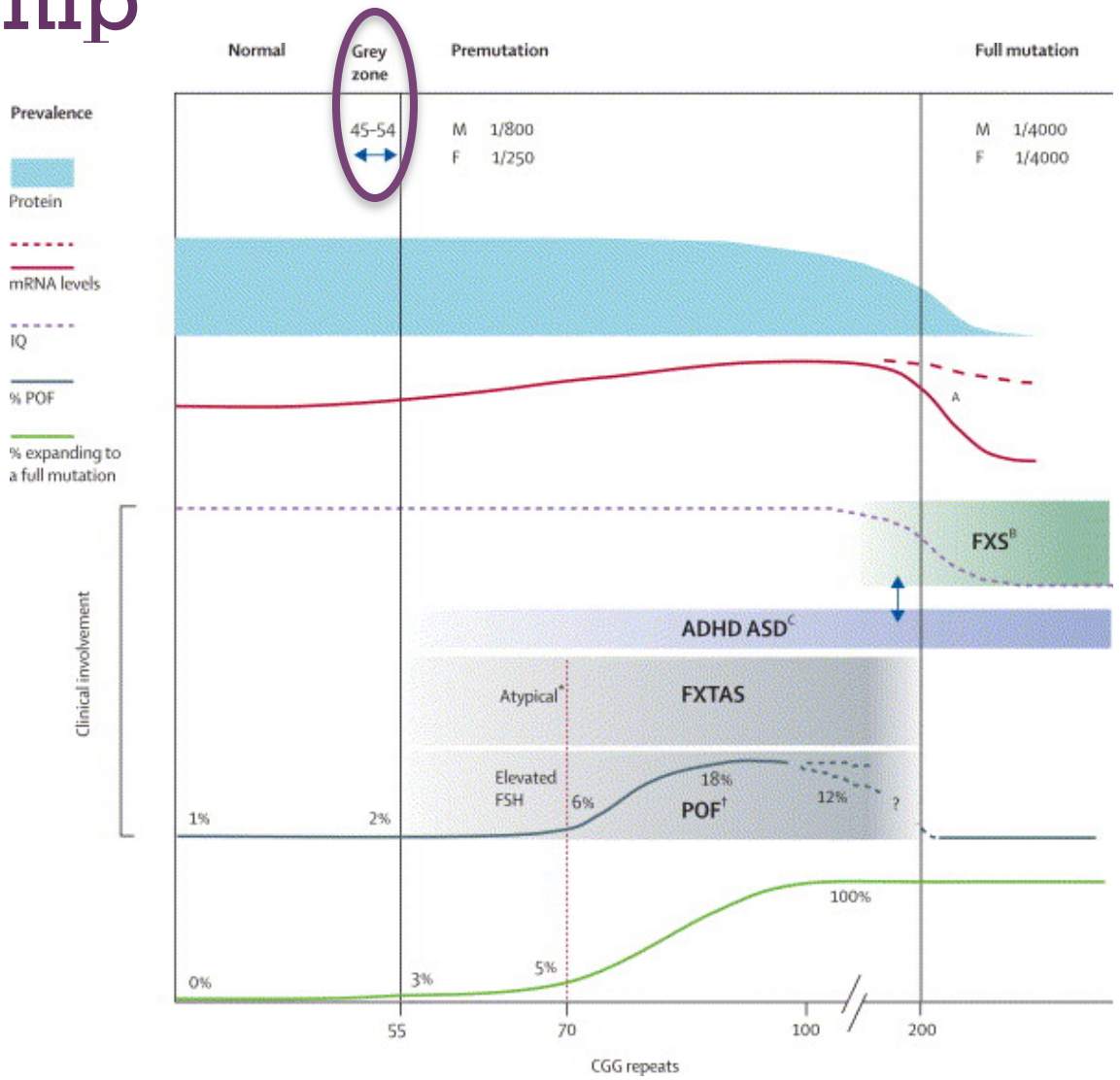
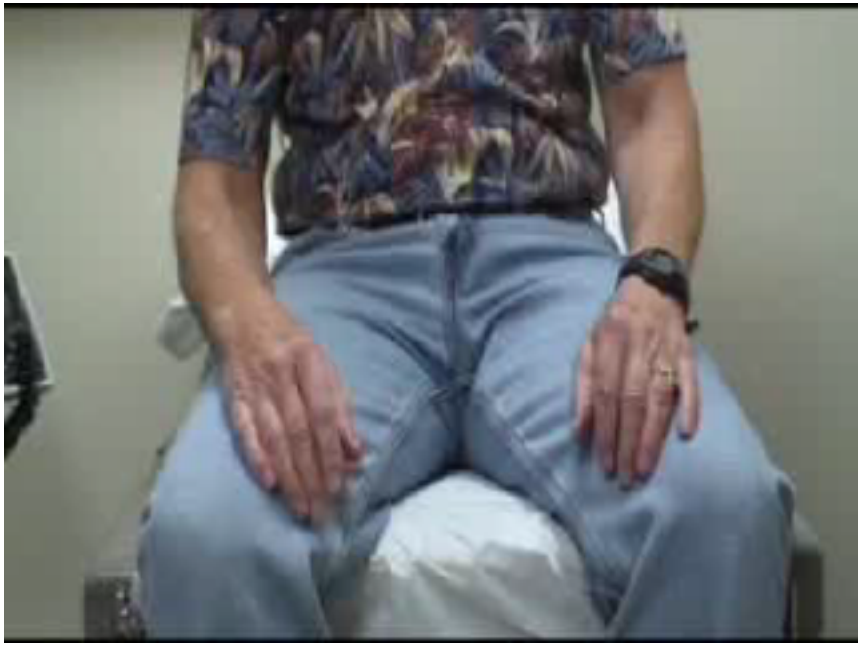
Overall genotype-phenotype relationship

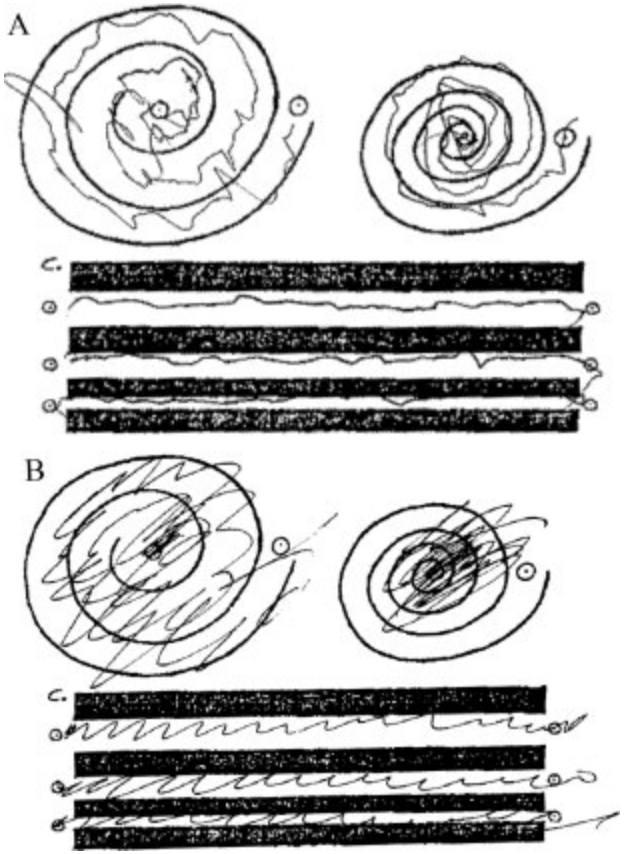


Gray zone carriers (45-54 repeats)



Gray zone carriers (45-54 repeats)

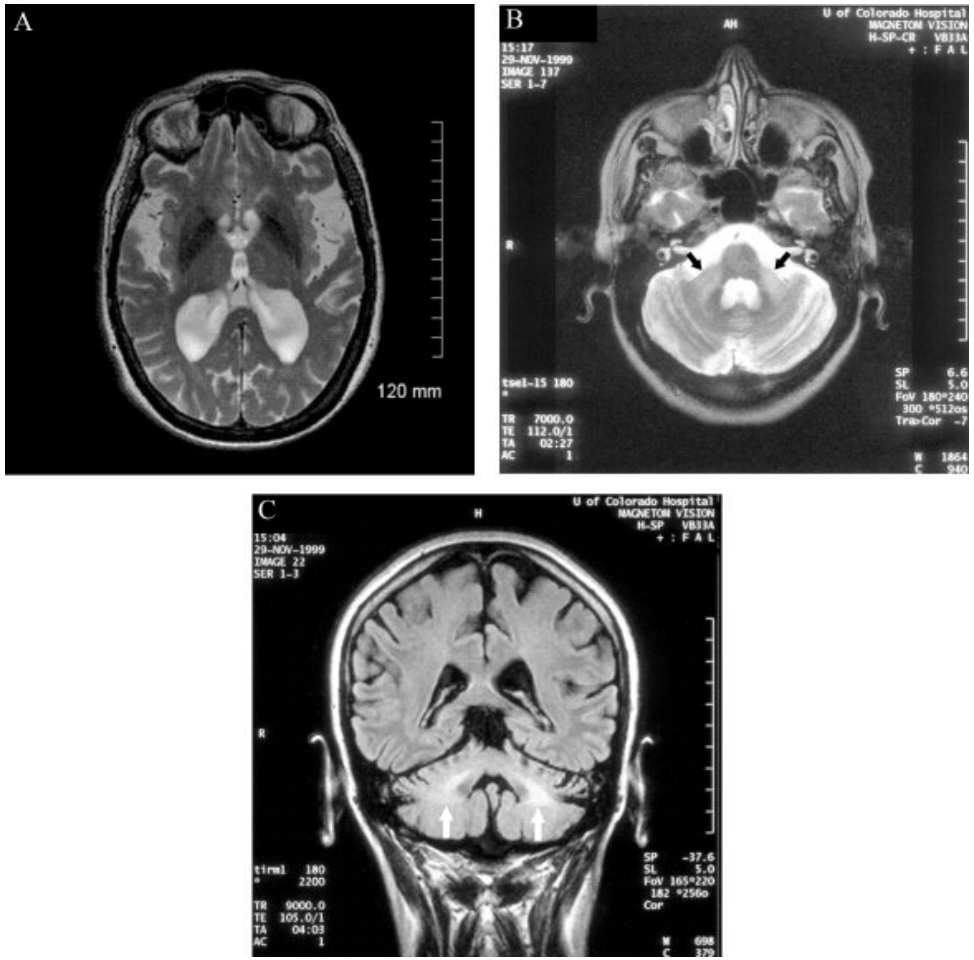
Case # 1



Movement Disorders
Volume 27, Issue 2, pages 297-301, 11 DEC 2011 DOI: 10.1002/mds.24021
http://onlinelibrary.wiley.com/doi/10.1002/mds.24021/full#fig2

Gray zone carriers (45-54 repeats)

Case # 2



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FXTAS diagnostic criteria

Current FXTAS diagnostic categories*

Definite FXTAS
Intention tremor *or* gait ataxia
and either
MCP sign†
or
Intranuclear inclusions on postmortem examination

Probable FXTAS
Intention tremor *and* gait ataxia
or
MCP sign† and a minor clinical symptom: parkinsonism, executive function deficits, or moderate short-term memory deficiency

Possible FXTAS
Intention tremor *or* gait ataxia
and
White matter lesions in the cerebrum or moderate generalized brain atrophy

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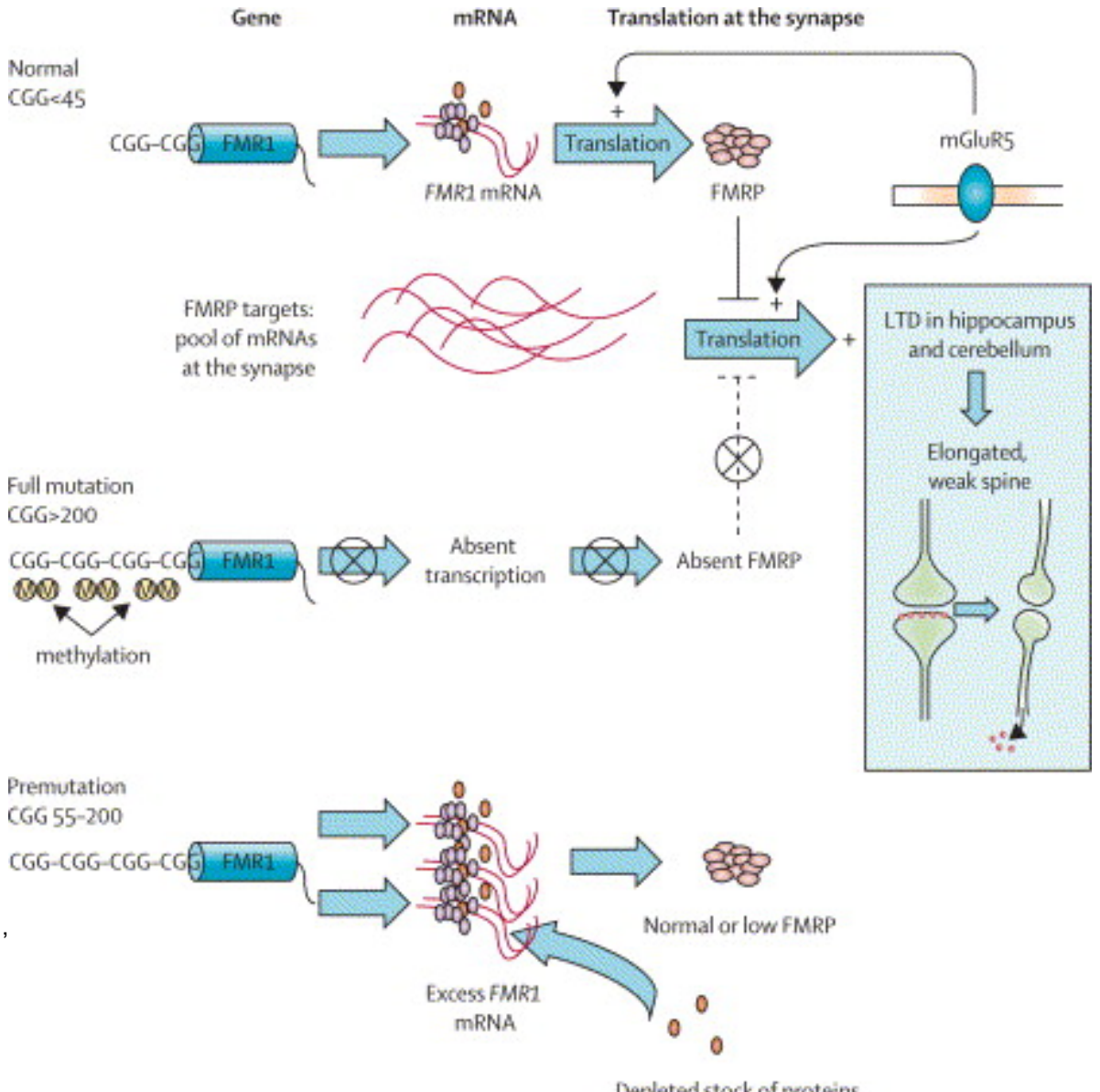
Revised FXTAS diagnostic criteria

(Apartis et al. 2012)

Genetic	500 to 200 CGG repeats in the *FMR1* gene
Major clinical	Intention tremor
	Cerebellar gait ataxia
Minor clinical	Parkinsonism
	Modereate to severe working memory
	Executive function deficits
	Peripheral neuropathy
Major radiologiqcal	MRI WM lesions involving middle cerebellar peduncles
	MRI corpus callosum splenium hypoerintensities
Minor radiological	MRI lesion involving cerebral white matter.
	Moderate to severe brain atrophy
Definite	One major clinical and one major radiologique or presence FXTAS incusions
Probable	Two major clinical or one minor clinical & one major radiological
Possible	One major clinical & one minor radiological,

DNA testing: for whom ?



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DNA testing: for whom ?

TABLE 4. *Testing guidelines for fragile X-associated tremor/ataxia syndrome*[a]

Clinician should test for *FMR1* mutation if the patient has any of the following:
Onset of cerebellar ataxia of unknown cause in an individual over 50 yr
Onset of action tremor of unknown cause in individual over 50 yr with parkinsonism or cognitive decline
Prior diagnosis of multiple system atrophy, cerebellar subtype
MCP sign on T2/FLAIR images of MRI in a patient with signs consistent with FXTAS[b]
Positive family history of *FMR1* mutation in an individual who could be a carrier based on position in pedigree if signs consistent with FXTAS are present[b]
Family or patient history of infertility/premature menopause in a patient with signs consistent with FXTAS[b]

Treatment options

	Symptom	Therapy, interventions	Future potential therapy
Full mutation			
FXS*	ADHD	Stimulants	mGluR5 antagonists
	Anxiety , hyperarousal, aggressive outbursts	SSRIs, atypical antipsychotics, occupational therapy, behavioural therapy, counselling	mGluR5 antagonists
	Seizures	Carbamazepine, valproic acid	mGluR5 antagonists
	Cognitive deficit	Occupational therapy, speech therapy, special education support	mGluR5 antagonists
Premutation			
POF	Premature ovarian failure	Reproductive counselling, egg donation Hormone replacement therapy	Cryopreservation of ovarian tissue
FXTAS†	Intention tremor	Beta-blockers	
	Parkinsonism	Carbidopa/levodopa	
	Cognitive decline, dementia, Anxiety, apathy, dysinhibition, irritability, depression	Acetylcholinesterase inhibitors, Venlafaxine, SSRIs	
	Neuropathic pain	Gabapentin	

FXS=fragile-X syndrome. ADHD=attention-deficit hyperactivity disorder. POF=premature ovarian failure. SSRIs=selective serotonin reuptake inhibitors. *These data are based on a survey in two large referral centres.[43] †There have been no controlled studies to assess drugs for FXTAS. These data were collected through a questionnaire study (n=56).[44] Drugs for anxiety were more frequently prescribed than those for neurological signs.

***Table 2:* Therapy for *FMR1* related disorders**