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# Overview of Premutation Disorders

Fragile X Association of Germany 10-1-16

Randi Hagerman MD

Distinguished Professor of Pediatrics

Endowed Chair in Fragile X Research

University of California at Davis Medical Center

MIND Institute

Funding from NICHD HD 036071

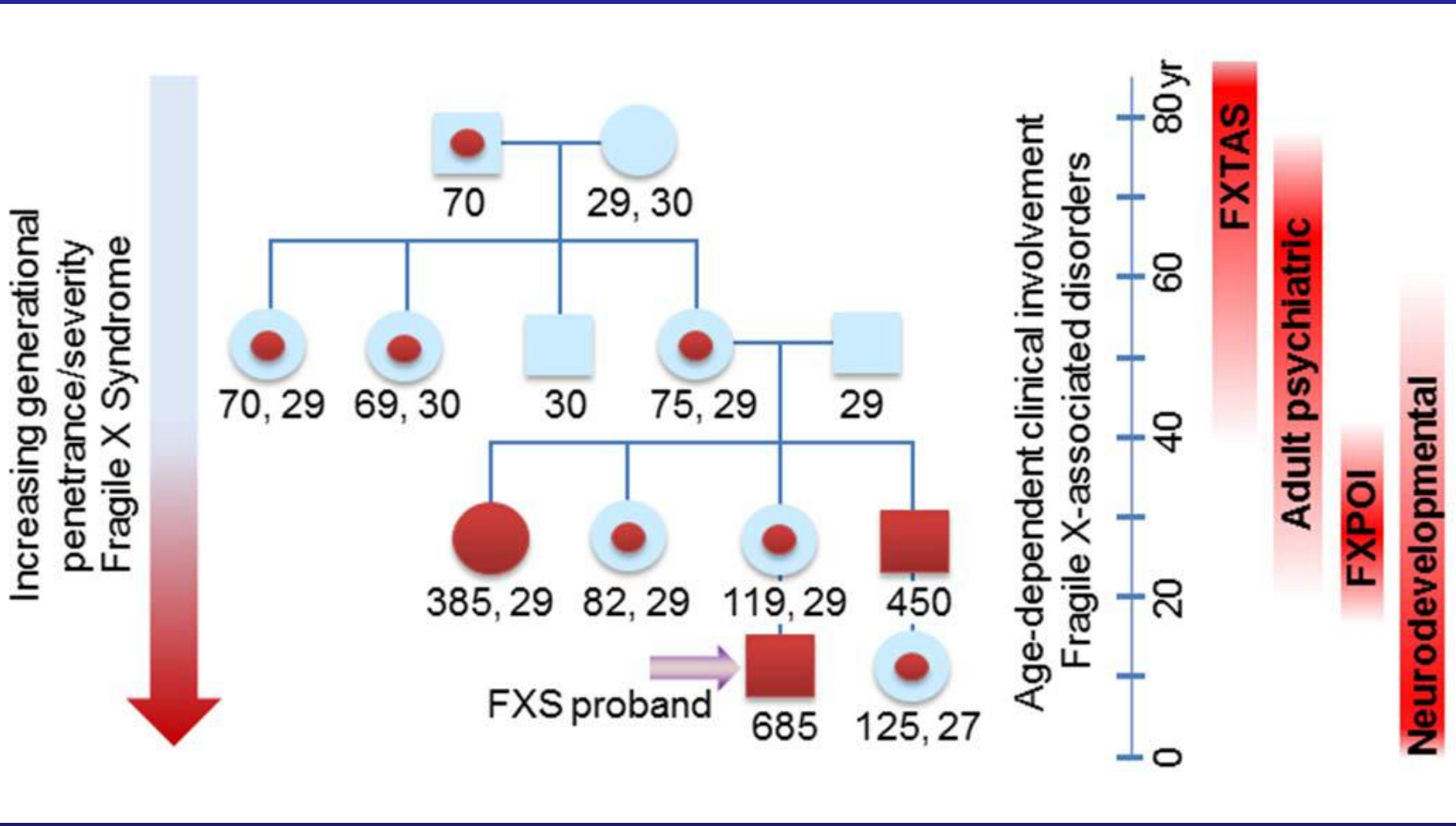
Conflicts: Ovid, Zynerba

# Two different mutations in the same *FMR1* gene

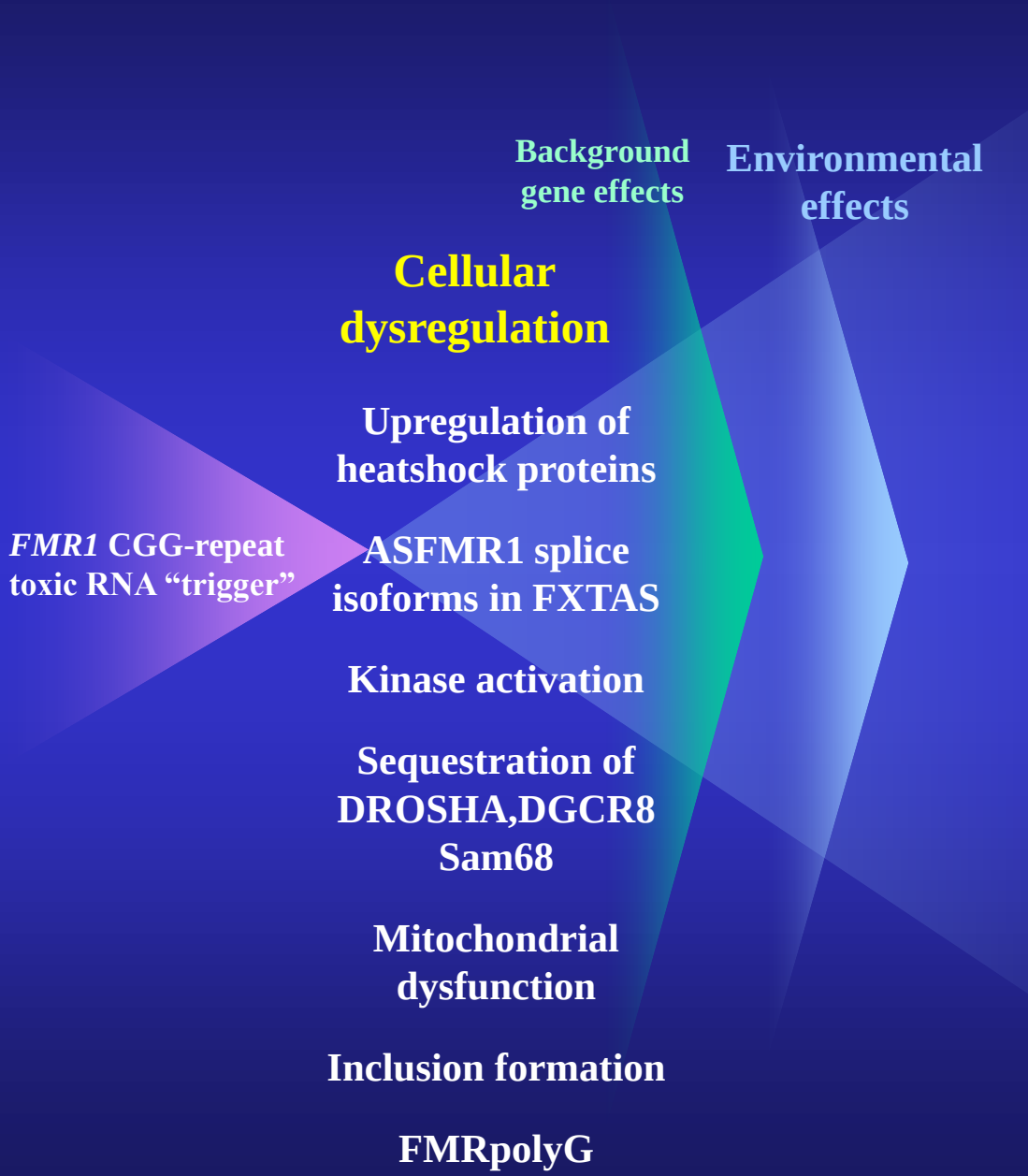
**1/130-250 females**
**1/250-810 males** **1/3600-5000**

| | Typical | Premutation | Full mutation |
|---|---|---|---|
| | $(CGG)_{< 45}$ | $(CGG)_{55 - 200}$ | $(CGG)_{> 200}$ |
| mRNA | | | |
| FMRP | | | |
| Clinical | **normal** | Primary Ovarian Insufficiency (FXPOI)<br>Fragile X-associated Tremor Ataxia Syndrome (FXTAS)<br>Depression and anxiety<br>ADHD, OCD, seizures and ASD | Fragile X syndrome (FXS) |

# Age- and generational involvement in fragile X-associated disorders



# Spectrum of Premutation Involvement




**Neurodevelopmental problems**
- Social anxiety → ASD
- ADHD
- Cognitive deficits

**Psychiatric involvement**
- Anxiety
- Stress
- Depression

**Endocrine dysfunction**
- FXPOI

**Immune dysregulation**
- Hypothyroidism
- Fibromyalgia
- Lupus- MS features

**Neurological problems**
- Neuropathy-chronic pain
- Migraine, sleep apnea, RLS
- Memory problems, foggy thinking
- Hypertension , erectile dysfunction

**FXTAS**

tremor, ataxia, Parkinsonism
autonomic dysfunction, EF deficits, memory and cognitive decline

# Features of Premutation Involvement

| | |
|---|---|
| **Autonomic problems** | |
| Constipation/irritable bowel syndrome | Hagerman et al (2008);[58] Hunsaker et al (2011)[59] |
| Erectile dysfunction | Greco et al (2007)[60] |
| Problems swallowing | Leehey et al (2007)[45] |
| Gastrointestinal reflux | Leehey et al (2007)[45] |
| Orthostatic hypotension | Leehey et al (2007)[45] |
| Hypertension* | Coffey et al (2008);[45] Hamlin et al (2012)[61] |
| Urinary urgency & incontinence | Leehey et al (2007);[45] Leehey et al (2011)[62] |
| Cardiac arrhythmia | Leehey et al (2011)[62] |
| Dizzy spells or vertigo | Leehey et al (2011)[62] |
| **Sensory** | |
| Olfactory dysfunction* | Juncos et al (2012)[v] |
| Hearing loss* | Juncos et al (2011)[v] |
| Neuropathy* | Berry-Kravis et al (2007);[10] Jacquemont et al (2003);[4] Hagerman et al (2007);[46] Soontarapornchai et al (2008);[63] Juncos et al (2011)[v] |
| **Sleep problems** | |
| Insomnia* | Chonchaiya et al (2010)[64] |
| Sleep apnea* | Hamlin et al (2011)[65] |
| Daytime sleeping | Hamlin et al (2011)[65] |
| **Motor symptoms** | |
| Tremor†,*; ataxia†,* | Hagerman et al (2001);[3] Jacquemont et al (2003);[4] Juncos et al (2011);[5] Apartis et el (2012)[7] |
| Muscle weakness | Leehey et al (2007)[45] |
| Parkinsonism†,* | Jacquemont et al (2003);[4] Healey et al (2009);[12] Hall et al (2010);[11] Madeo et al (2012)[14] |
| **Psychiatric** | |
| Depression*; anxiety* | Bourgeois et al. (2011);[13] Seritan et al. (2013)[66] |
| Irritability | Bacalman et al. (2006)[67] |
| **Chronic pain** | |
| Fibromyalgia*<br>Neuropathic pain* | Winarni et al. (2012);[68] Rodriguez-Revenga et al. (2009);[69] Coffey et al. (2008);[45] Leehey et al. (2011);[70] Apartis et al. (2012)[7] |
| **Immune-mediated disorder** | |
| Hypothyroidism*<br>Fibromyalgia* | Winarni et al. (2012);[68] Rodriguez-Revenga et al. (2009);[69] Coffey et al. (2008);[45] Leehey et al. (2011);[70] Behrn et al.[71] |

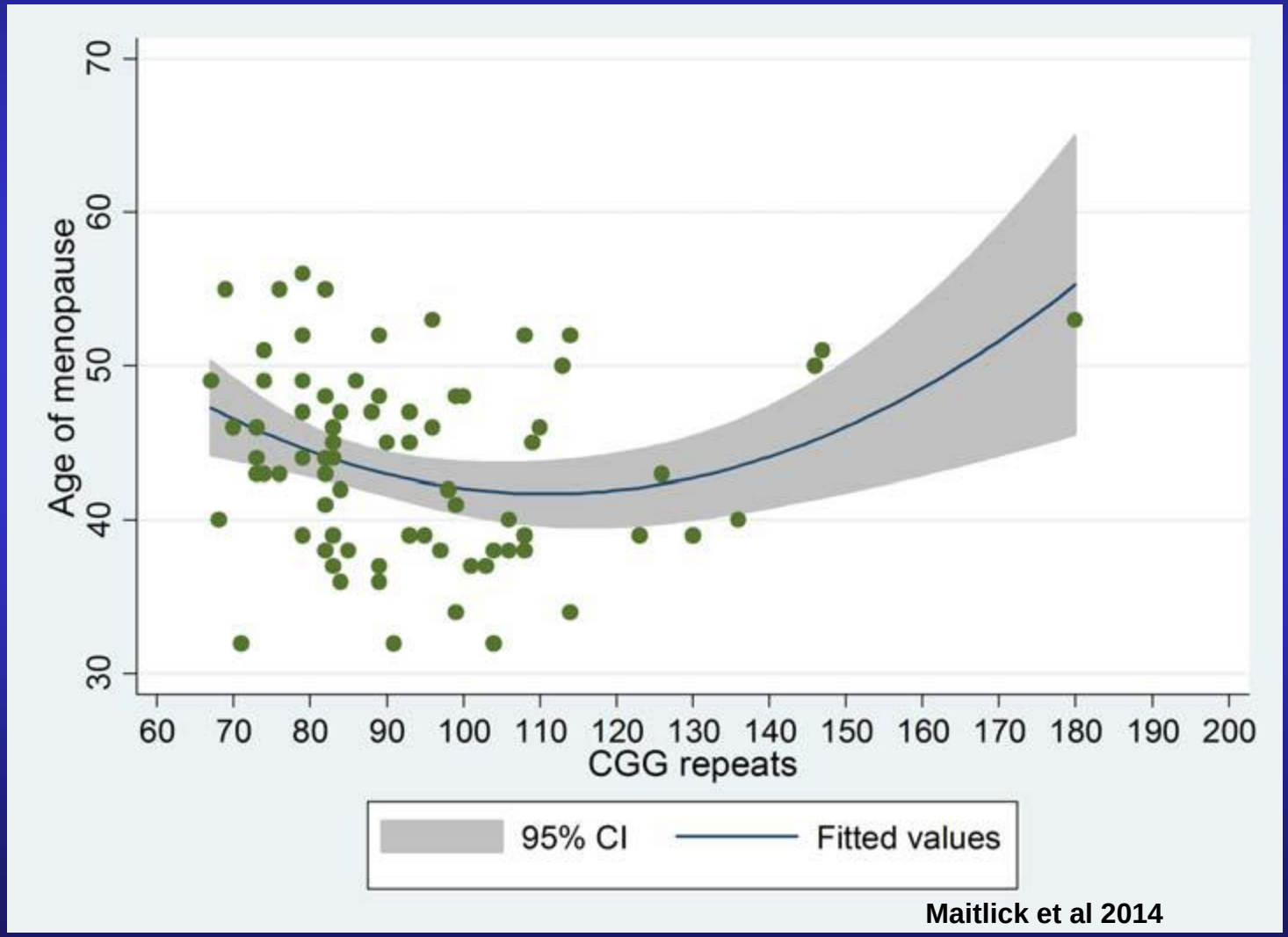
*Features that occur in a greater number of those with FXTAS compared to age-matched controls. †Established features.

*Table 2:* Established and expanded features of FXTAS

***Means significantly higher in FXTAS vs controls**
**Many problems start far earlier such as hypertension, anxiety, depression, fibromyalgia, hypothyroidism, hearing loss, vertigo tinnitus, insomnia**

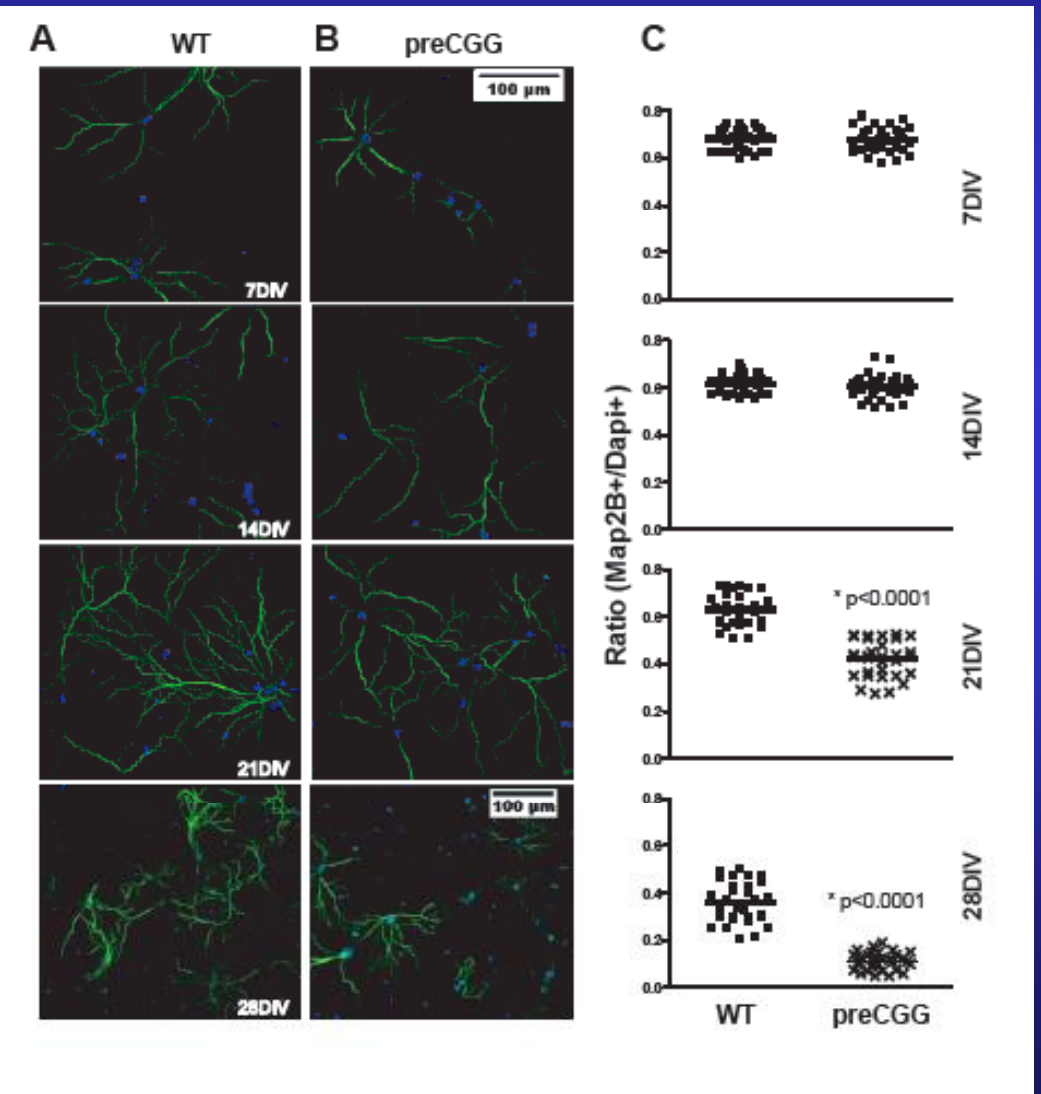
**Hagerman and Hagerman 2013 Lancet Neurology; Wheeler et al 2014 JND**

# Fragile X-associated Primary Ovarian Insufficiency (FXPOI) in 16-20%




Maitlick et al 2014

# Enhanced cell death in premutation neurons

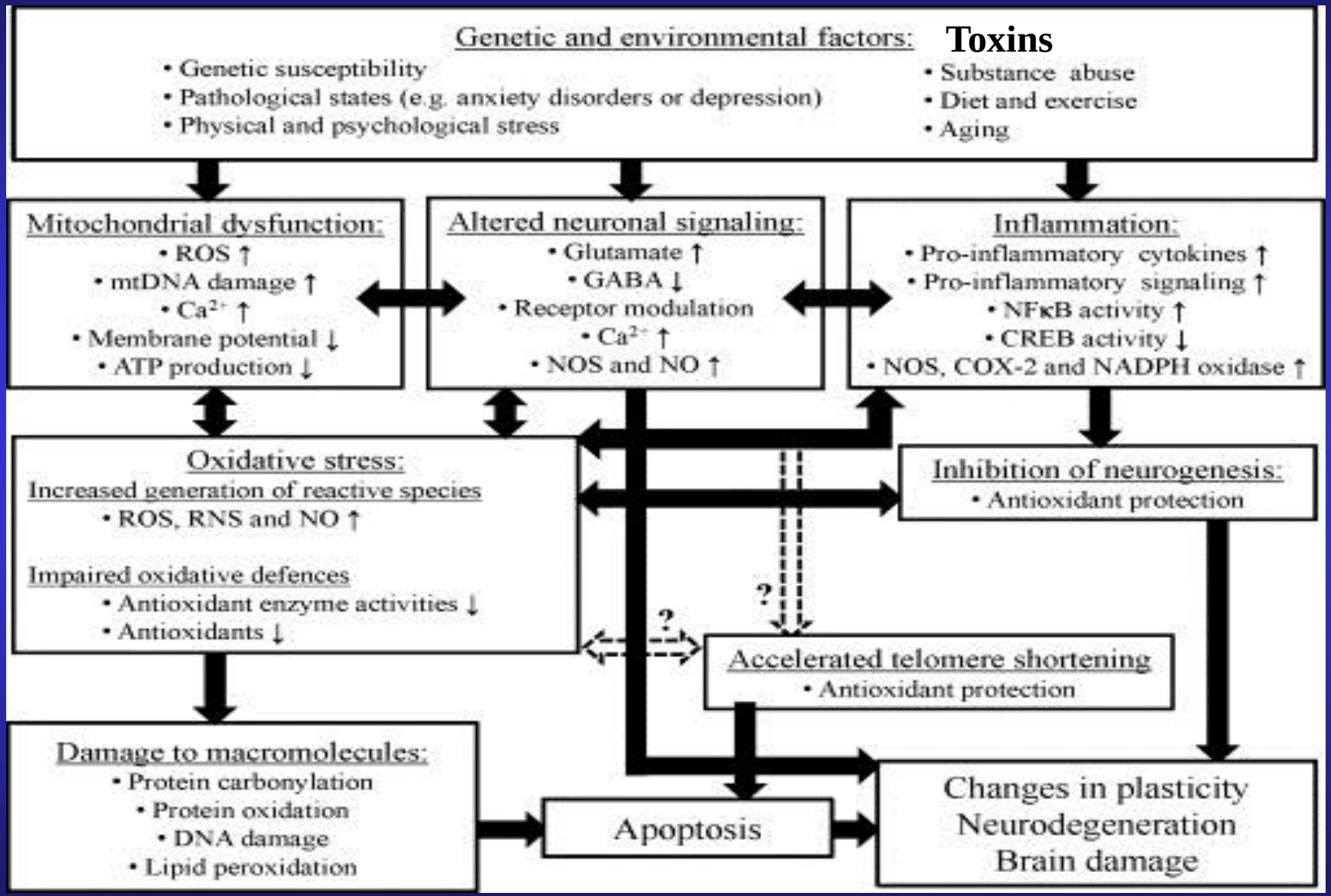



Oxidative stress
Mitochondrial dysfunction
Kaplan et al 2012

**Decreased cell survival by 21 days**

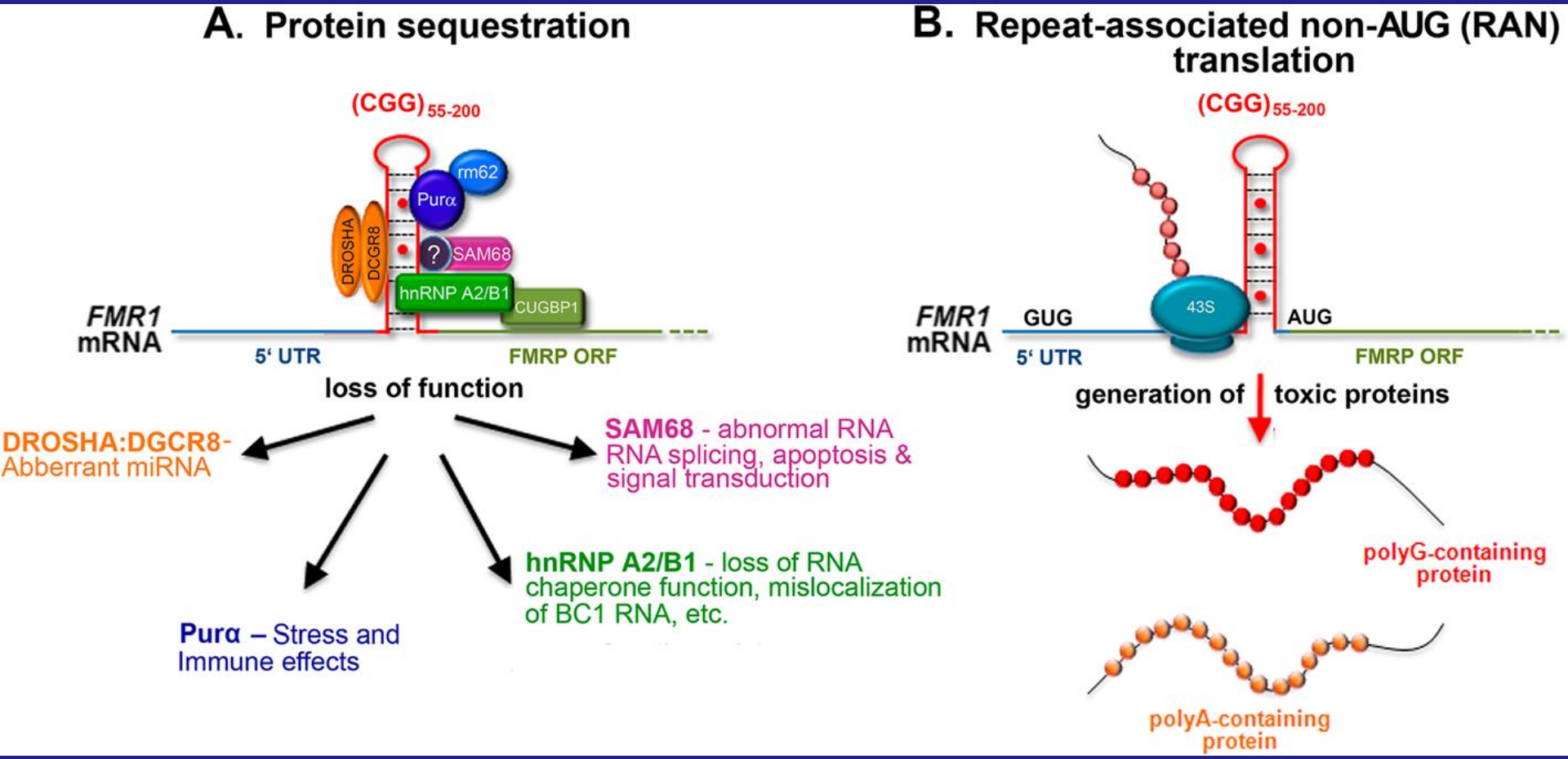
Chen et al 2009 HMG

# Genetic and Environmental Interactions



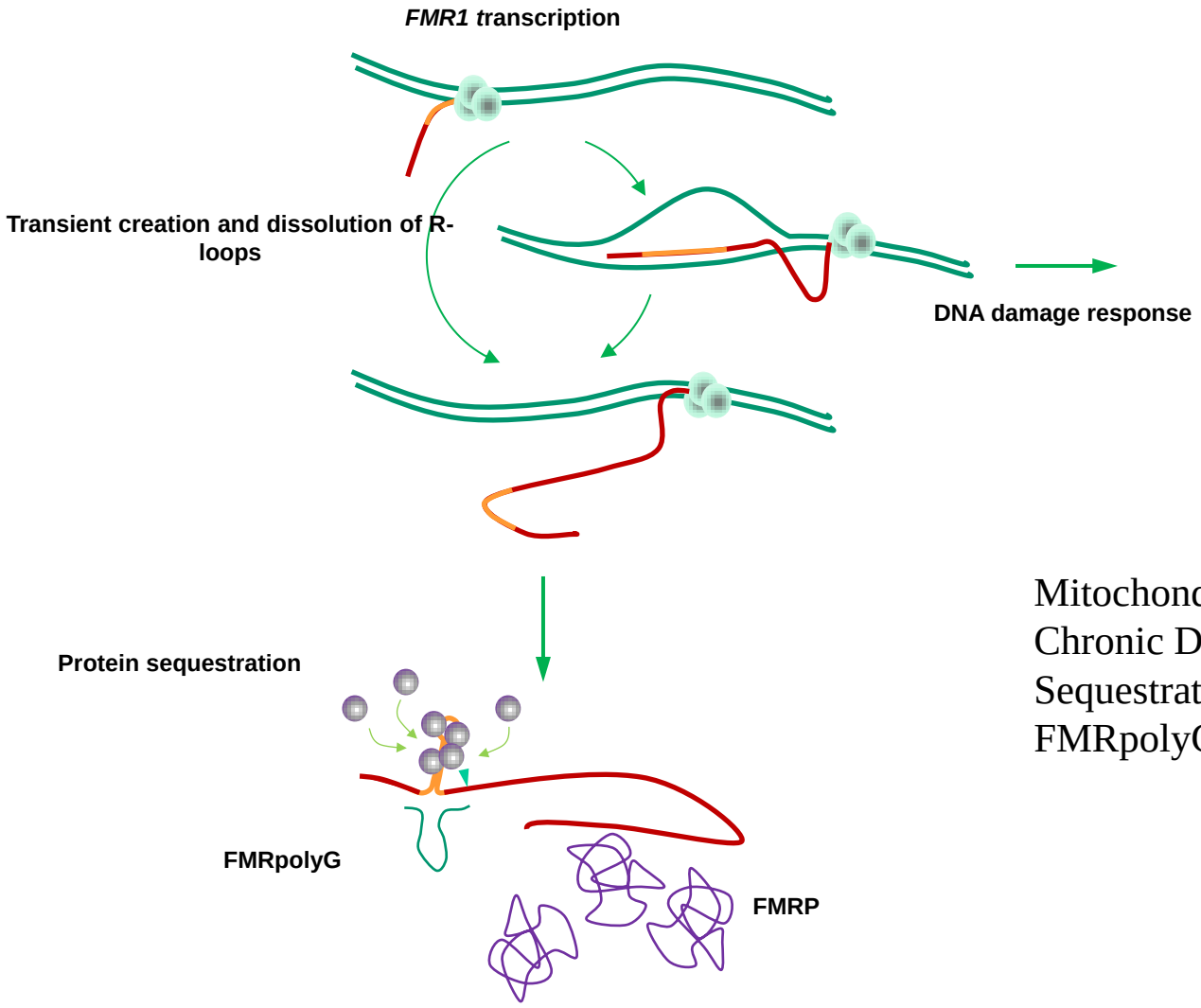

**Iiris et al 2010 Neurosciences Research 2010**

# Molecular Mechanisms of Toxicity in Premutation Carriers



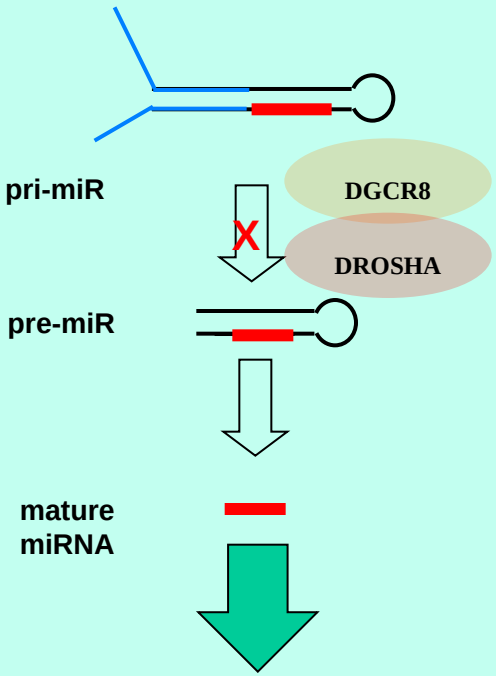

Berman et al 2014 JND

# Mechanisms of premutation involvement



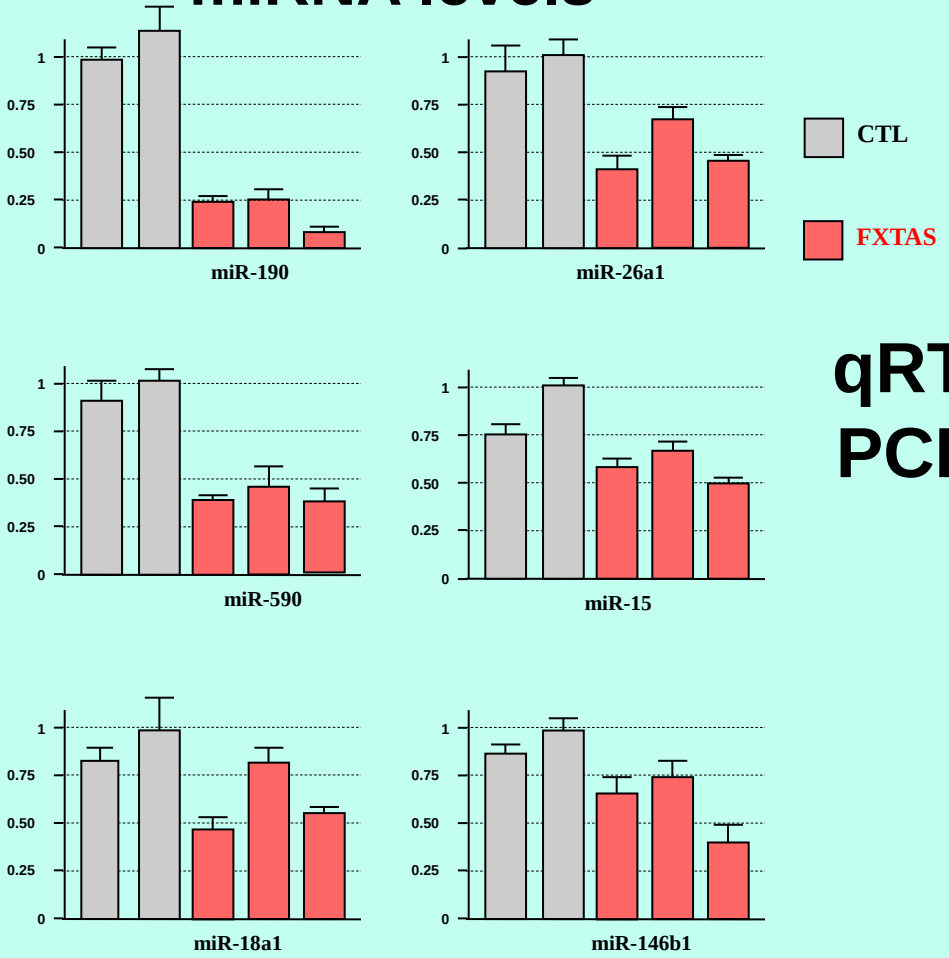

Mitochondrial dysfunction
Chronic DNA damage repair
Sequestration
FMRpolyG

# Expanded CGG repeat inhibits DGCR8/DROSHA activity




**Predicted decrease in miRNA levels**

## Observed decreases in miRNA levels



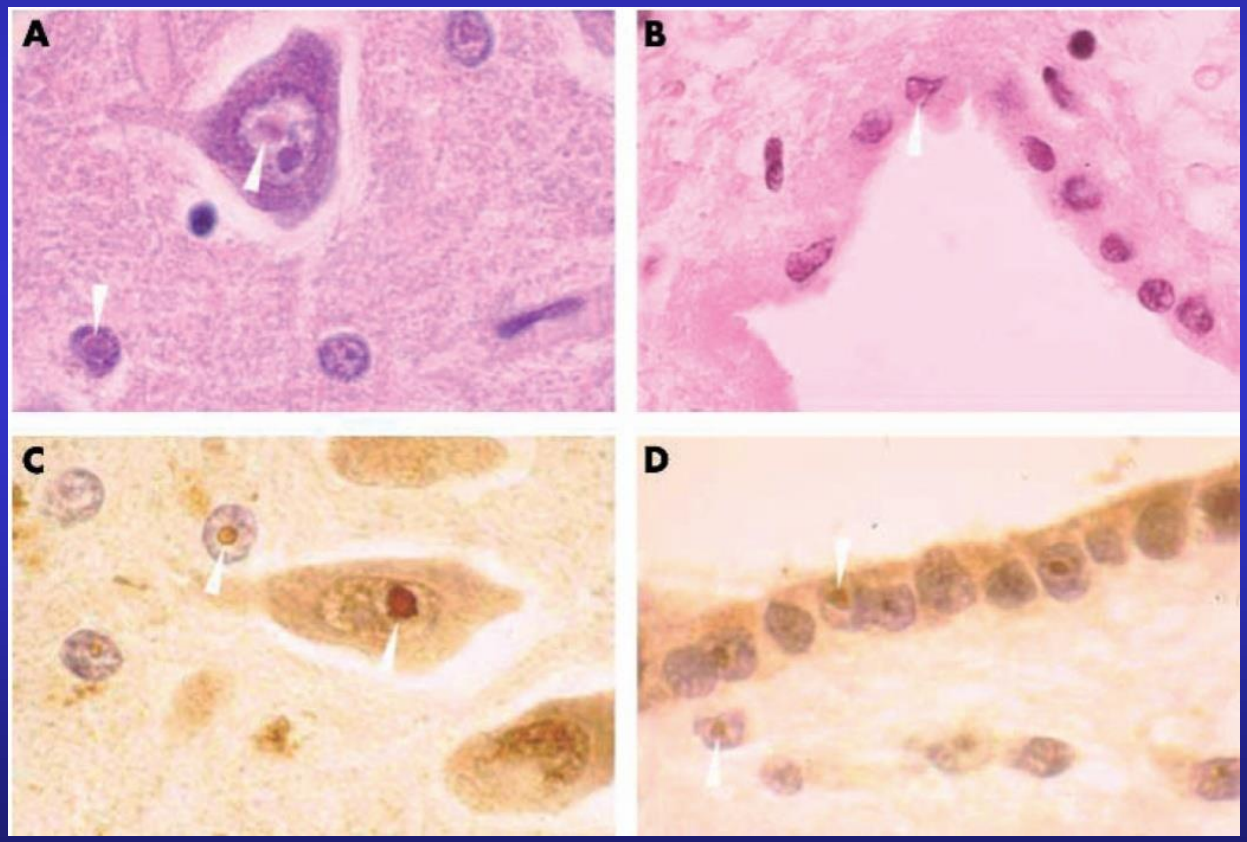

**qRT-PCR**

Sellier C … Charlet et al 2013

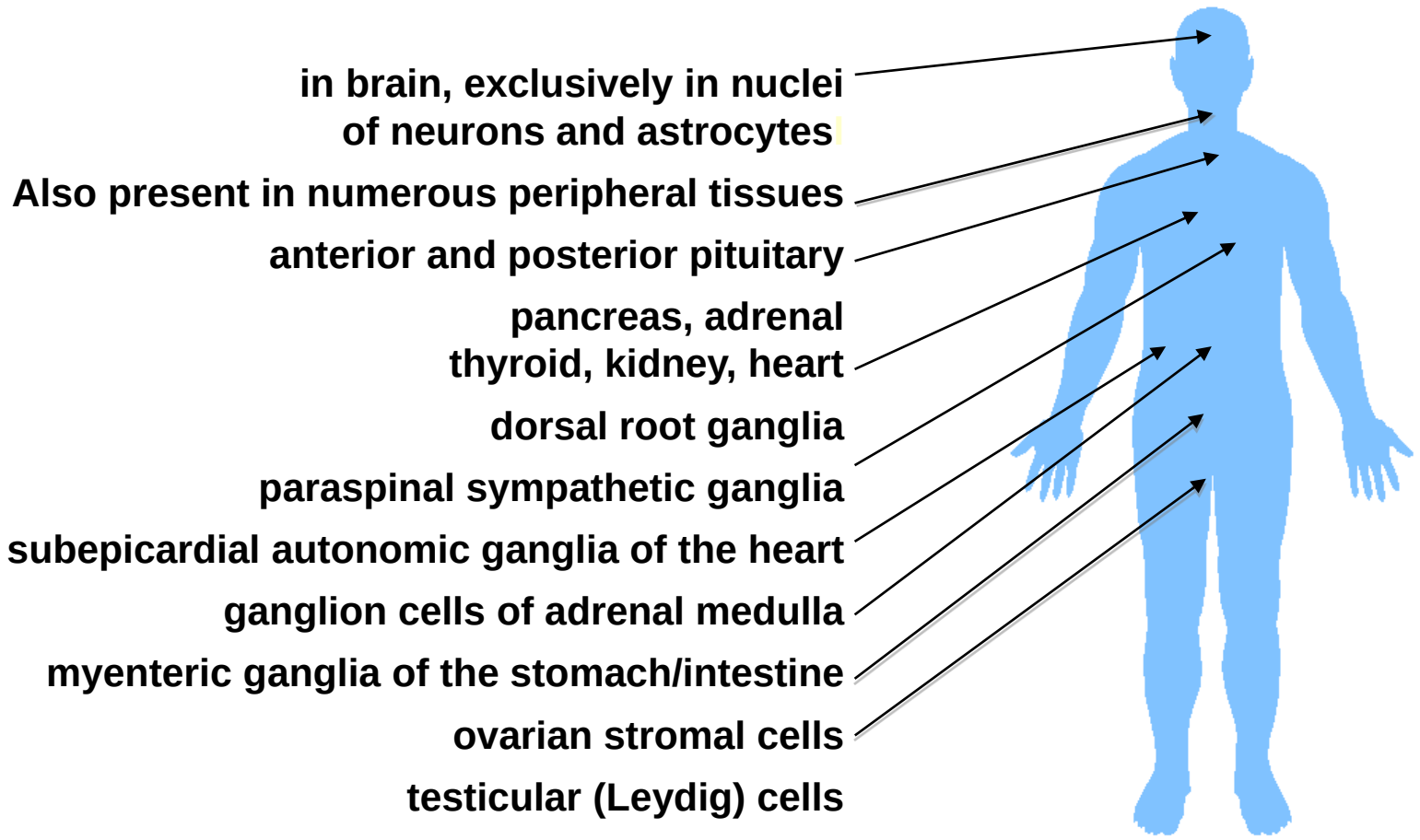
# Other symptoms

- Cardiac arrhythmia; bradycardia, pacemaker
- Back pain and disc problems: perhaps connective tissue changes may relate
- Foggy thinking memory problems
- Workup for Lupus ANA+ comes and goes
- Internal tremor
- Non-epileptic seizures
- Pulmonary fibrosis
- Myelodysplasia
- CHF and Kidney failure may be late changes

Inclusions first reported by Greco et al 2002, 2006 in neurons and astrocytes and in other tissues (Hunsaker et al 2011) and in Purkinje cells (Ariza et al 2016)

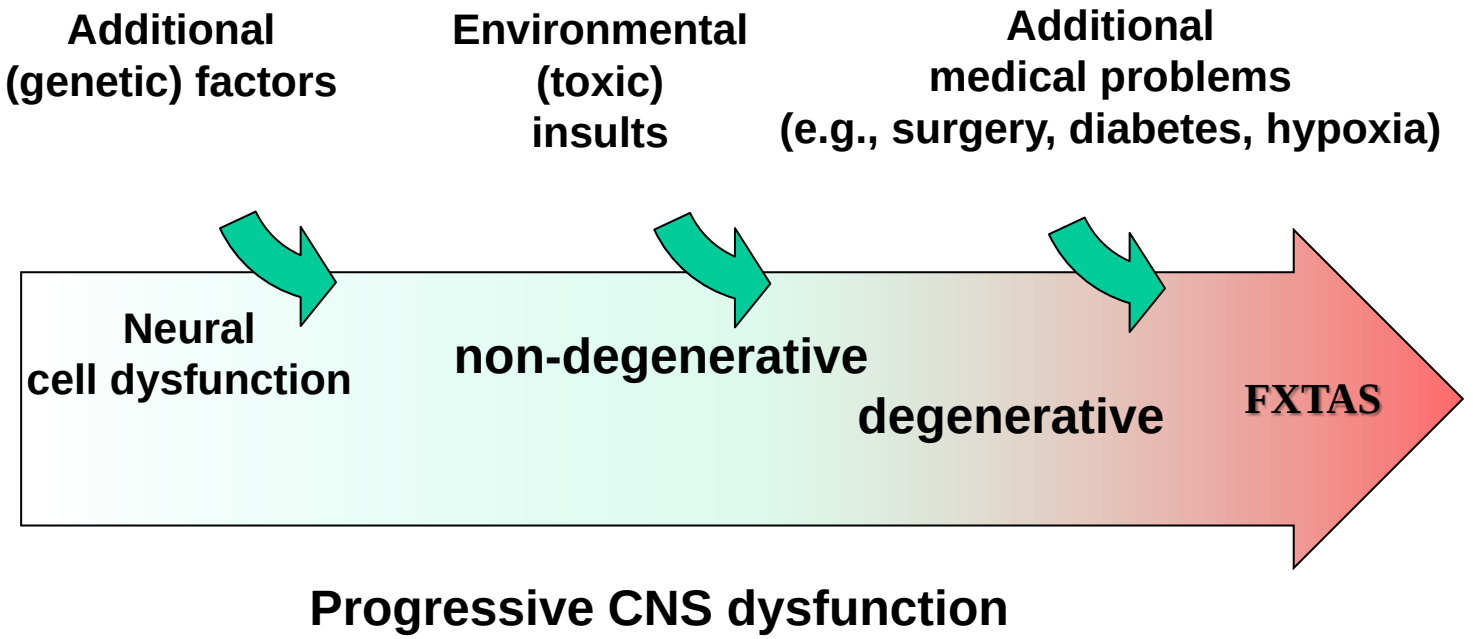


# Broad distribution of intranuclear inclusions in FXTAS




Greco et al., 2002 Brain; Willemsen et al., 2003 Hum Mol Genet; Greco et al., 2006 Brain
Greco et al., 2007 J Urology; Brouwer et al., 2008 Psychoneuroendocrinology
Godken et al., 2009 Neuropathology; Hunsaker et ak 2011 Acta Pathologica

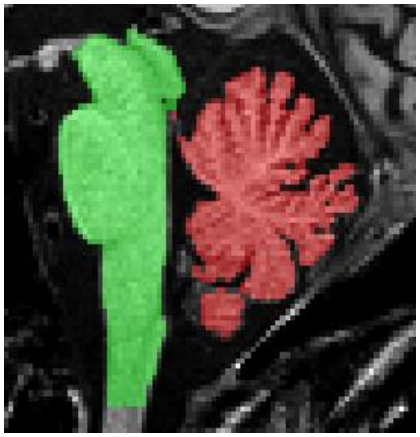
# Model for progression of dysfunction in premutation disorders



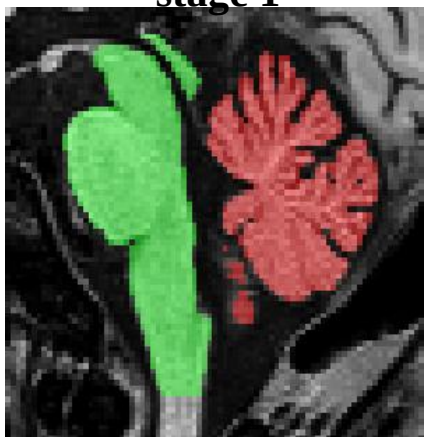

Also highlights possible approaches for intervention

# Changes in cerebellum and brain stem in controls and carriers

**A A 68-year-old control**



**B A 69-year-old at stage 1**

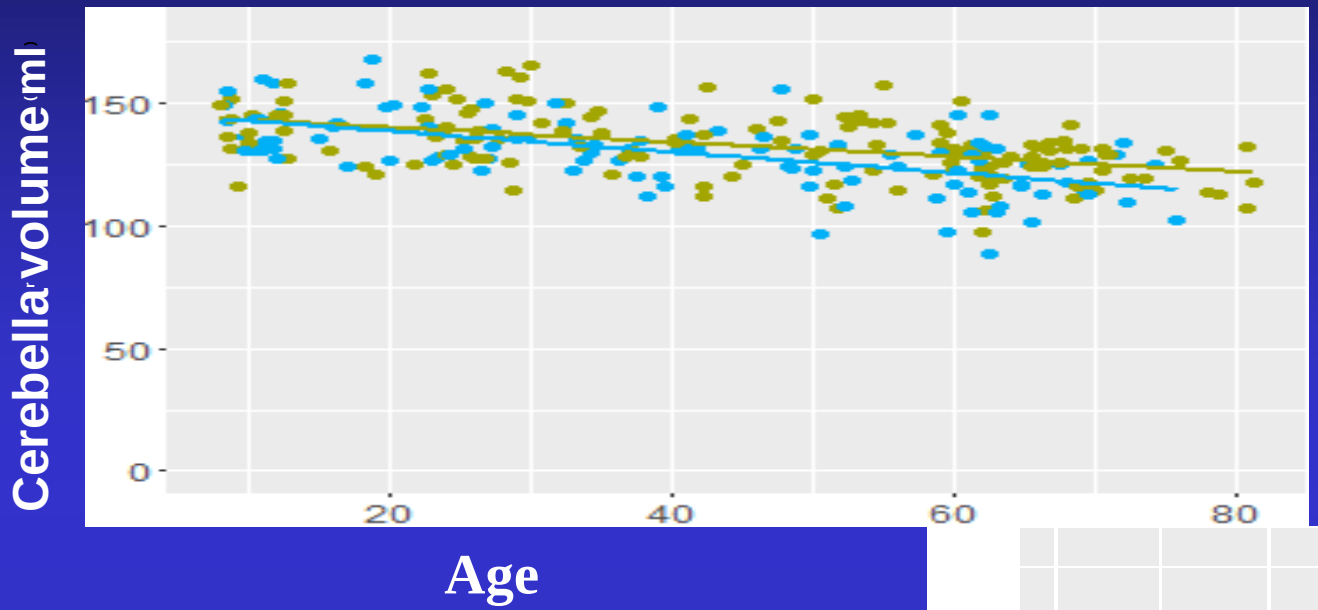


**C A 68-year-old at Stage 4**

**322 males (age 8-81 years), 142 controls,**
**109 asymptomatic carriers, 72 FXTAS+ carriers**

**Jun Yi Wang et al 2016 in review**

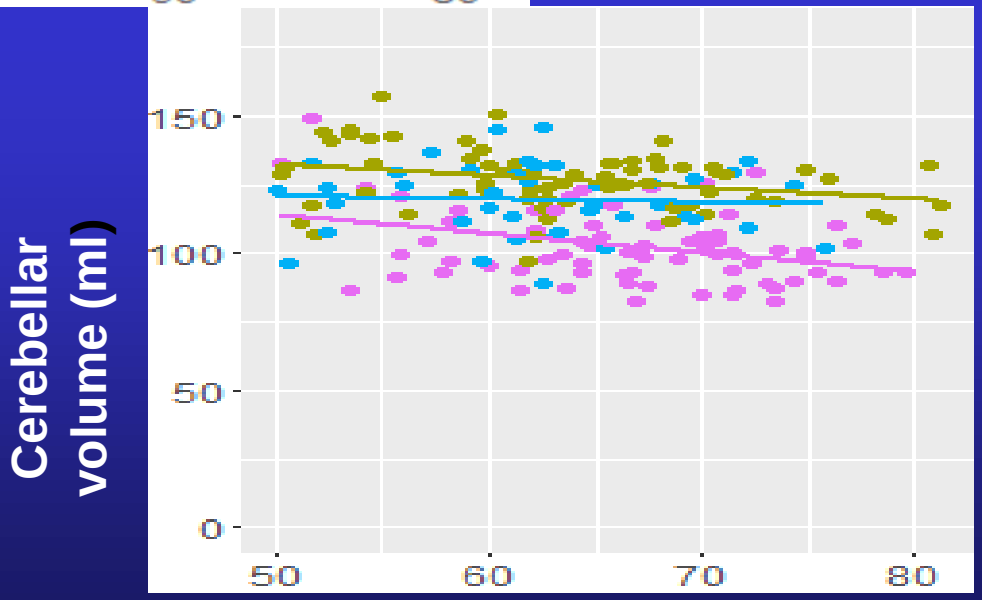
# Cerebellar Volume




Green=controls

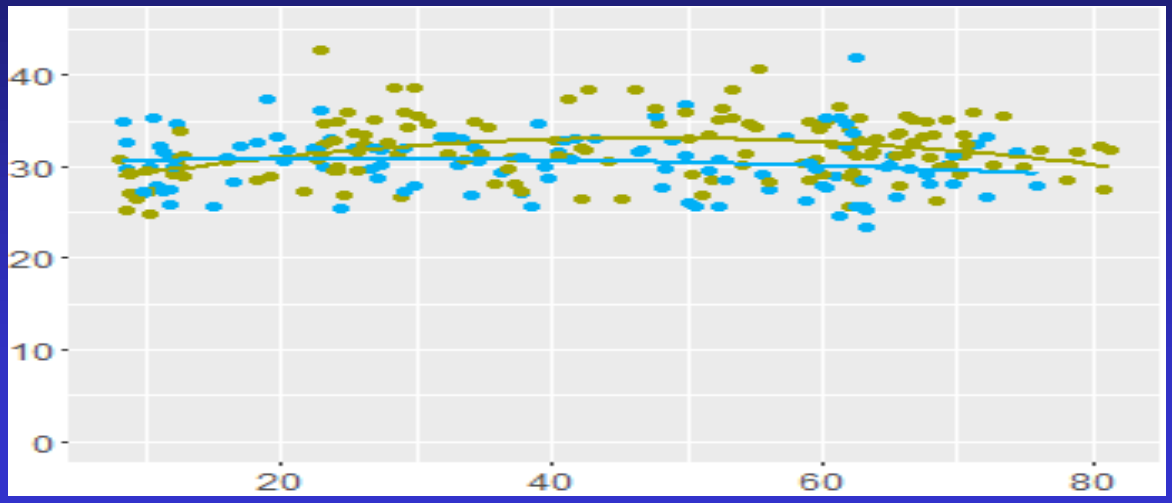
Blue= carriers

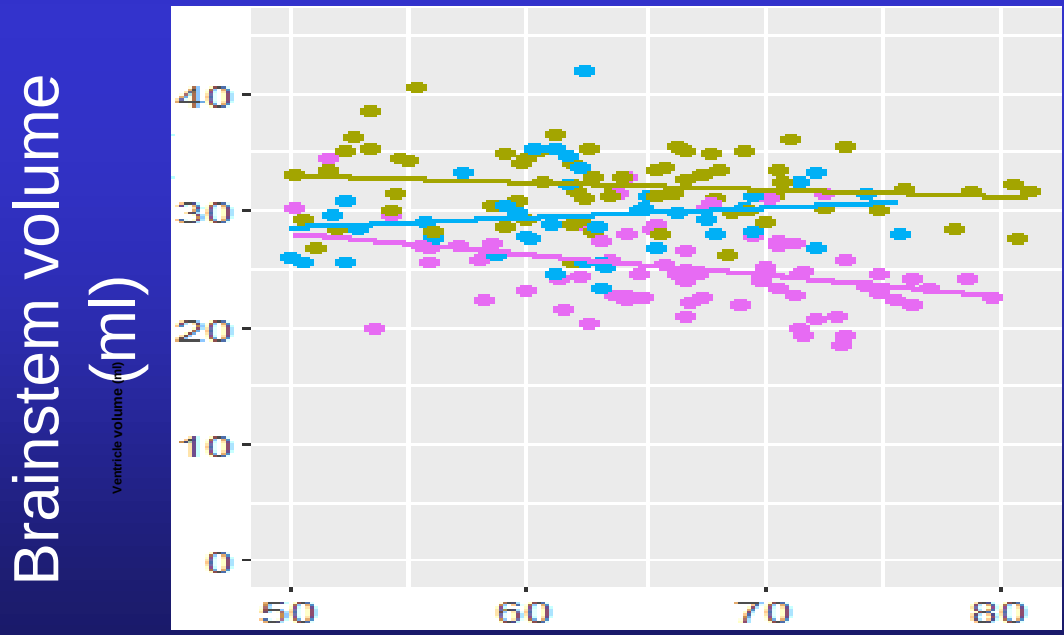
Purple=FXTAS




Jun Yi Wang et al 2016

# Brainstem Volume



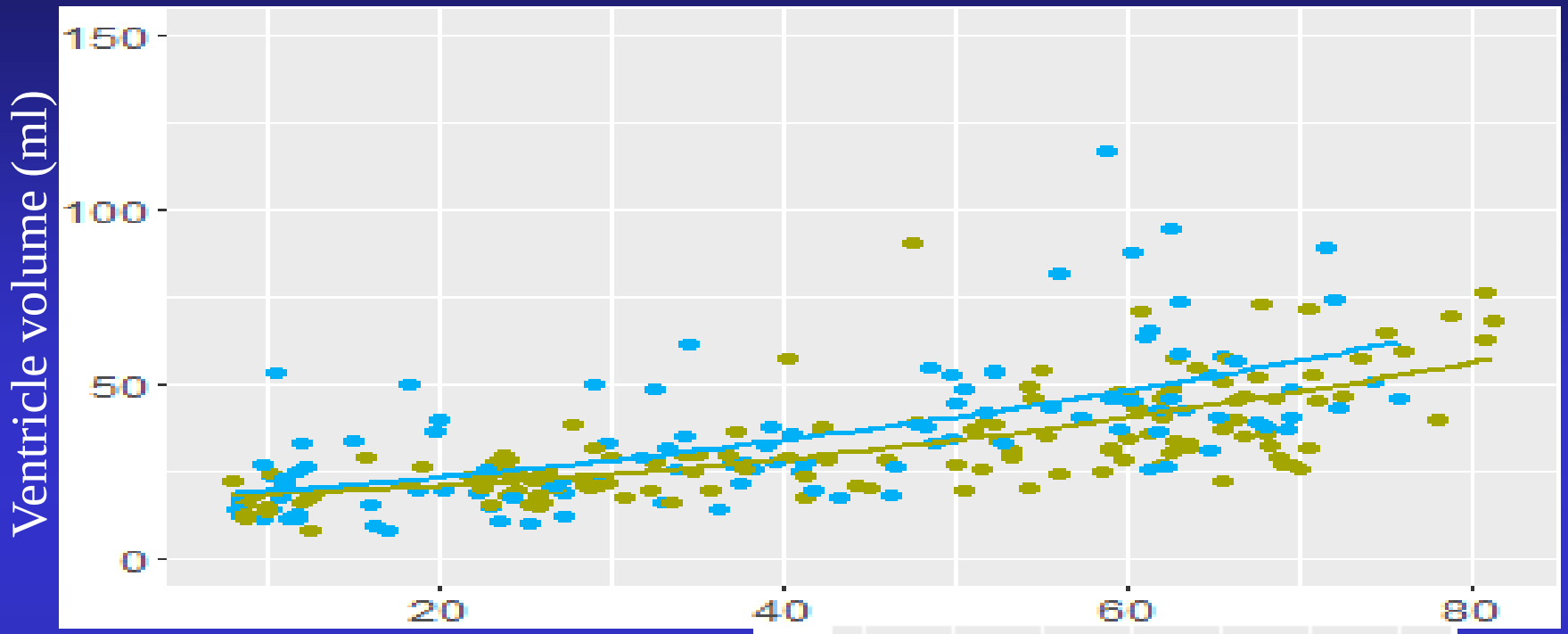

**Green=controls**

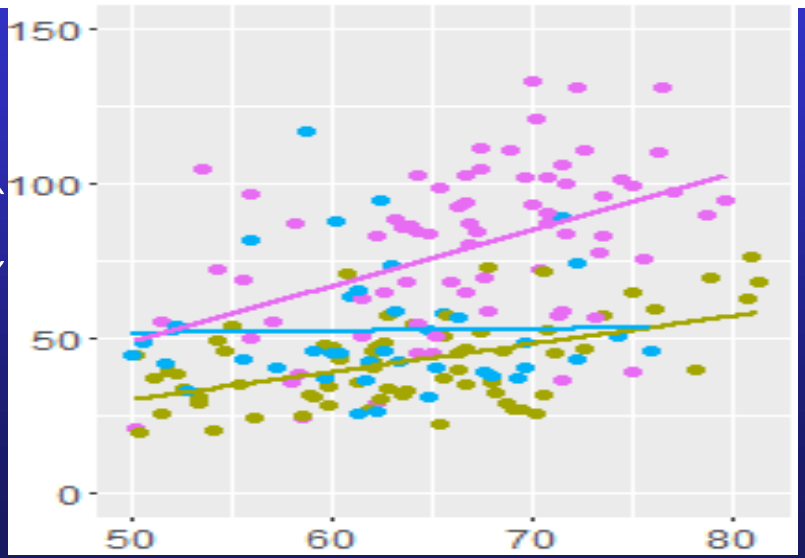
**Blue= carriers**

**Purple=FXTAS**

**Jun Yi Wang et al 2016**

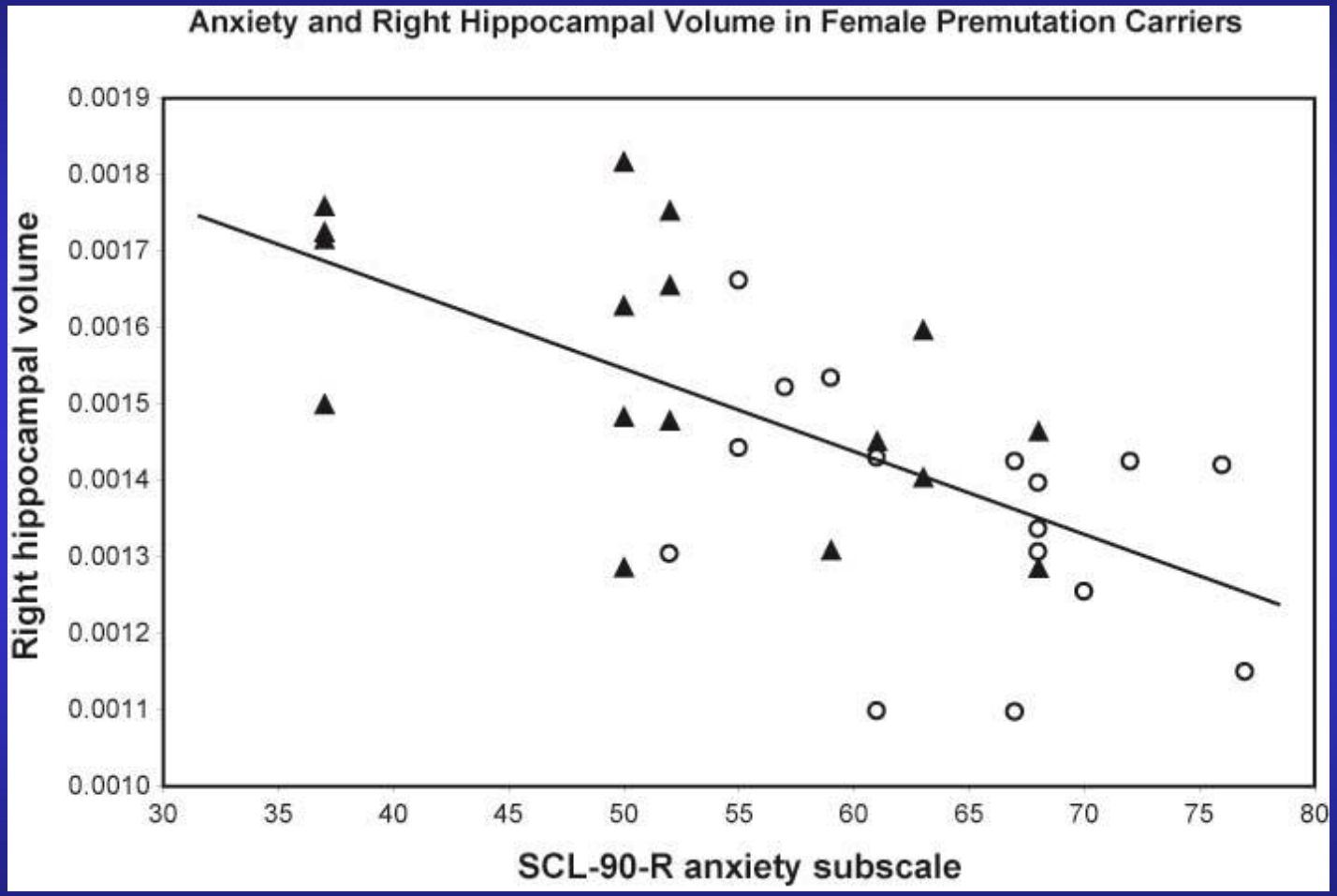
# Ventricular Volume




Age

# Anxiety and Hippocampal Volumes in Females with the Premutation



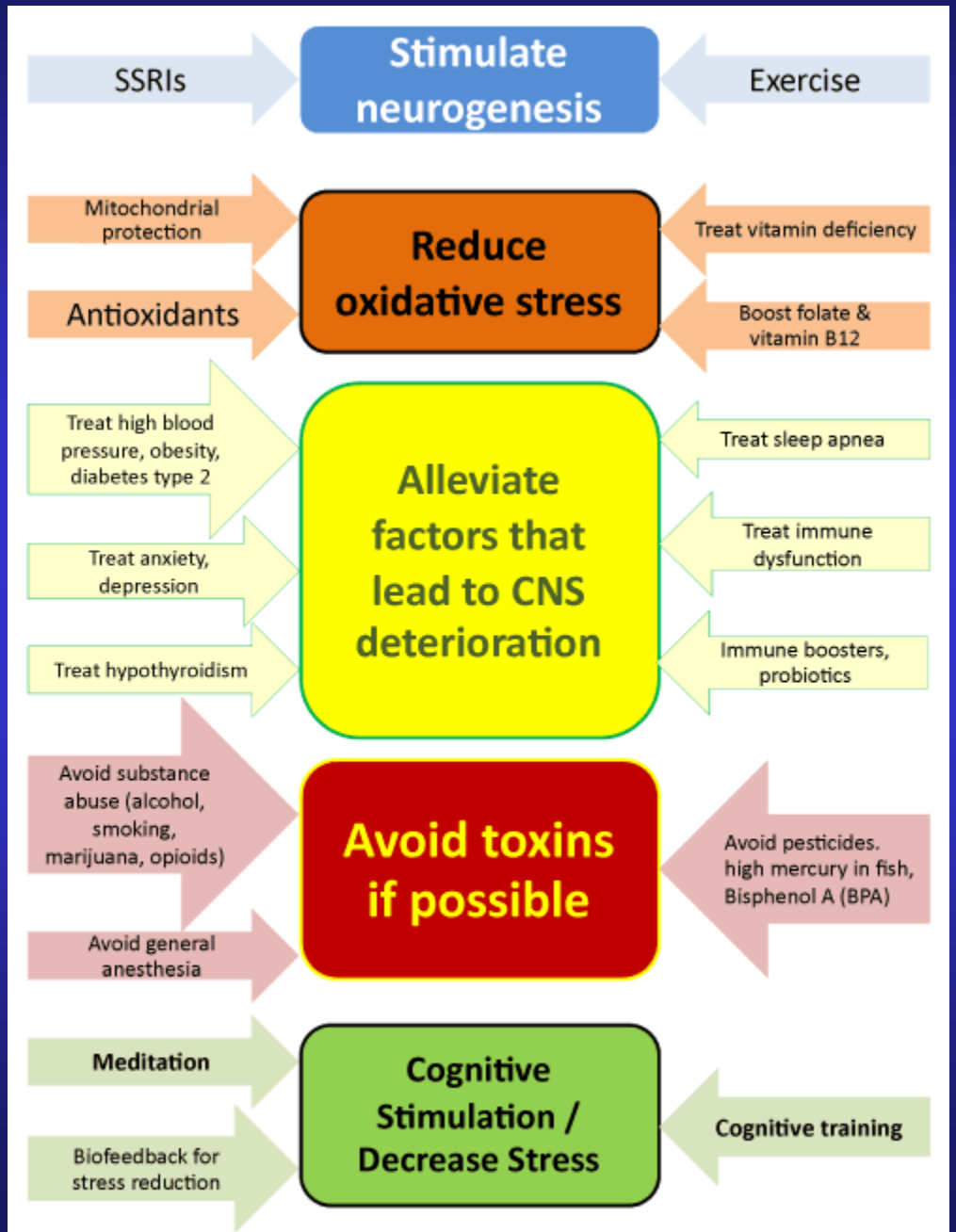

**Circles with FXTAS, triangles without (r=-0.634; p<0.001)**

**Adams et al 2009**

# Health Maintenance

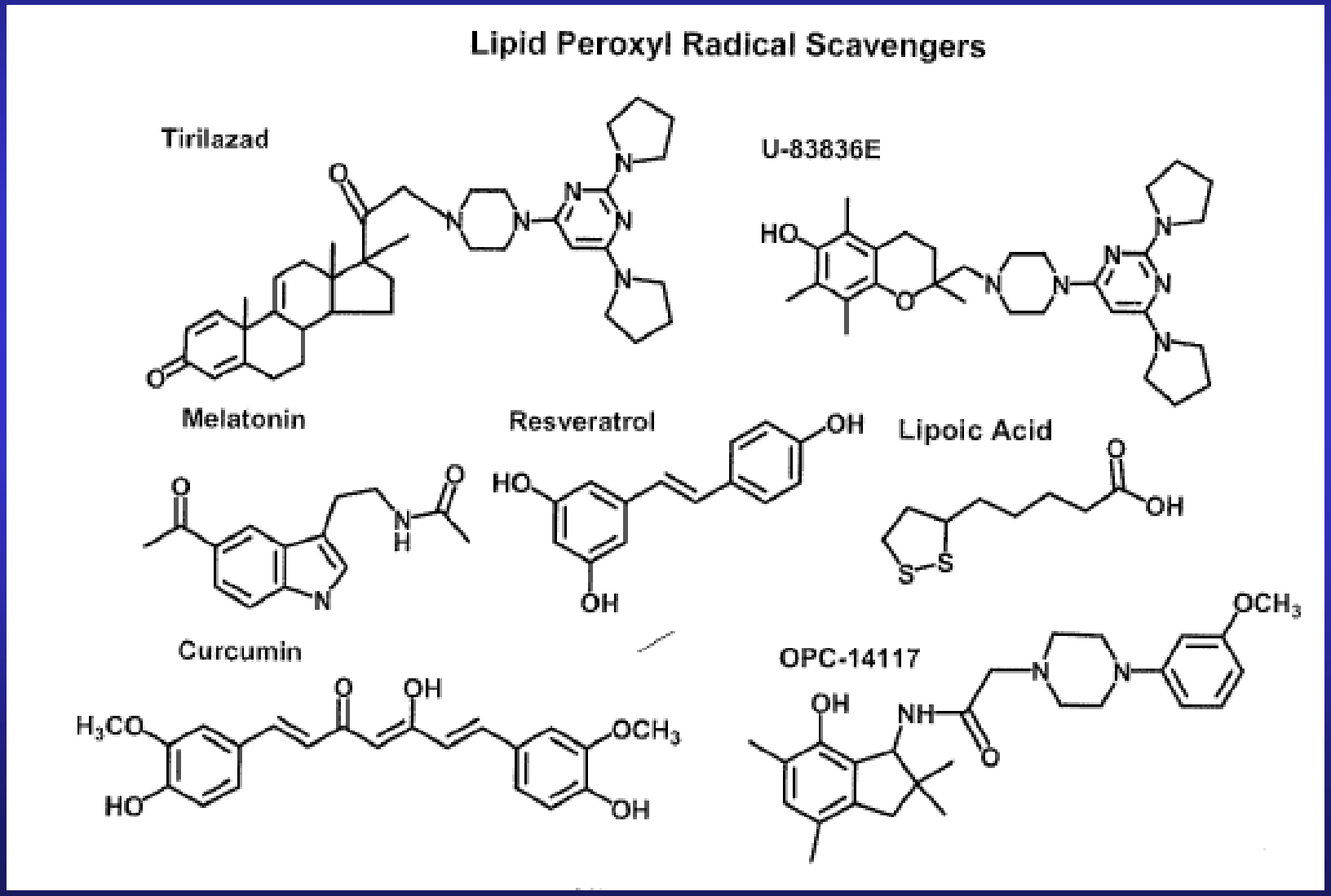
- Check your blood pressure regularly, CBC and thyroid function yearly; treat hypertension; treat thyroid disease, anemia or hypoxia w/sleep apnea
- Treat migraines, avoid toxins in environment
- Treat depression, anxiety with SSRIs &/or counseling and exercise daily
- Take a multiple vitamin and get vit D, folate and B12 levels checked. Deficiency is common
- Take antioxidants: Vit C,D,E, NAC, omega 3s berries,green tea etc. Folate and B12 supplementation slows brain atrophy with age, lowers homocysteine
- Avoid weight gain, metabolic syndrome and type 2 diabetes.

# Treatments for premutation carriers




**Polussa et al 2014 Brain Disorders and Therapy**

# Antioxidants



# Where is the delineation between FXTAS and other premutation problems?

- The fragile X-associated tremor ataxia syndrome (FXTAS) was defined in 2003 before we knew about many other problems
- It has a phenotype well entrenched with minor changes to definition such as adding neuropathy and  wmd in splenium of the corpus callosum
- However, there are life long changes to the CNS that start in early adulthood.

# Diagnostic Criteria for FXTAS put together with what we knew in 2003

***Inclusion criterion*: 55 – 200 CGG repeats**

| | | |
|---|---|---|
| MRI | *major* | *Middle cerebellar peduncle (MCP) lesions* |
| | minor | Cerebral white matter hyperintensity |
| | minor | Moderate to severe generalized atrophy |
| Clinical exam | *major* | *Intention tremor* |
| | *major* | *Gait ataxia* |
| | minor | Parkinsonism |
| | minor | Short term memory deficits |
| | minor | Executive function deficits |

***Diagnostic categories***

| Definite | Probable | Possible |
|---|---|---|
| 1 clinical *major*<br>AND<br>1 MRI *major*<br><br>Inclusions (*post mortem*) | 2 clinical *major*<br>OR<br>1 MRI *major* AND<br>1 clinical minor | 1 clinical *major*<br>AND<br>1 MRI minor |

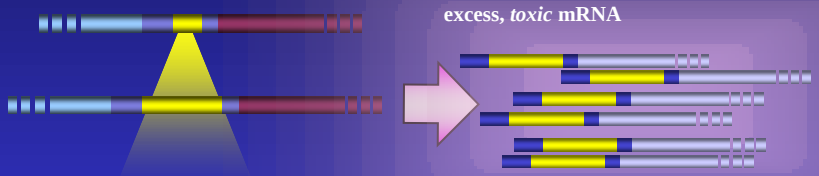
Jacquemont et al 2003 AJHG

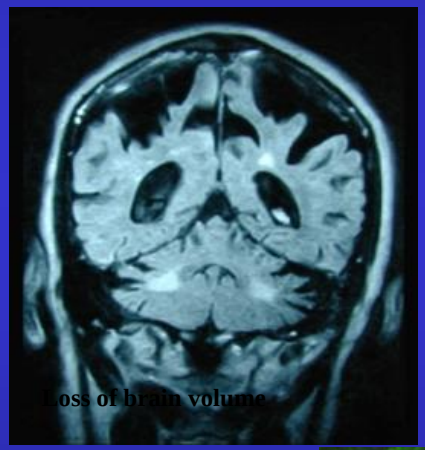
# A different course in women with FXTAS

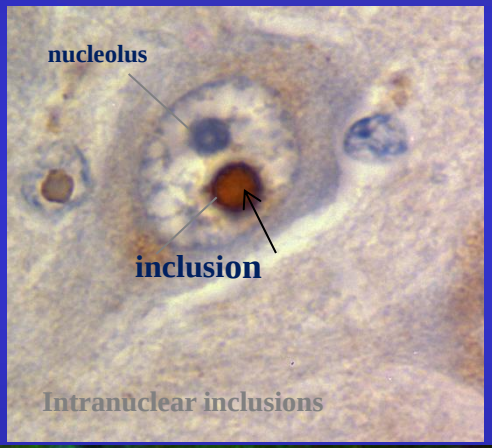
CGG repeats

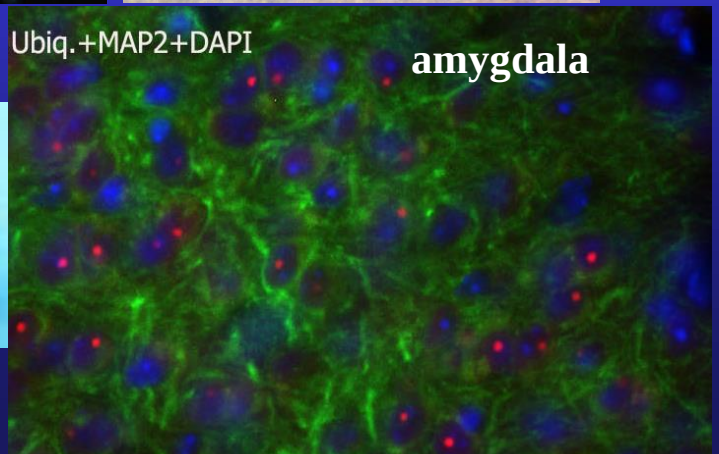
< 45 (normal)

55-200

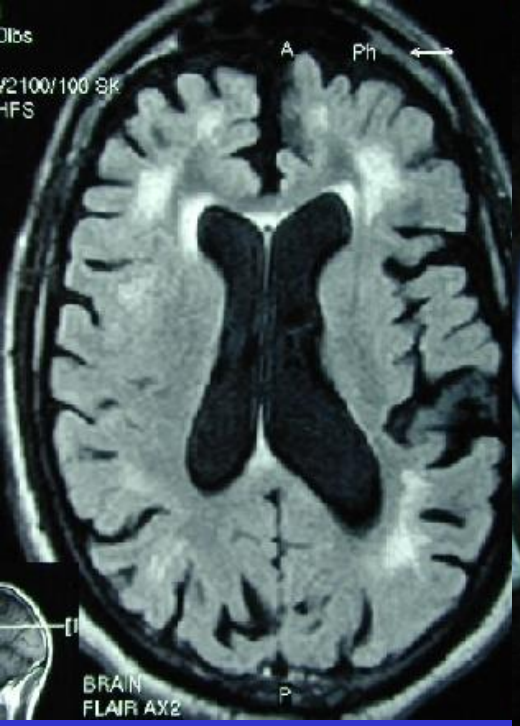


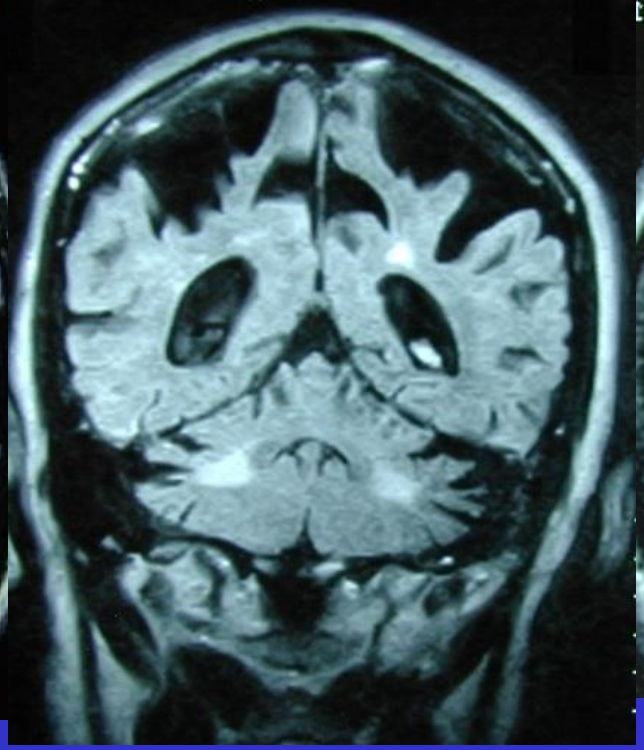



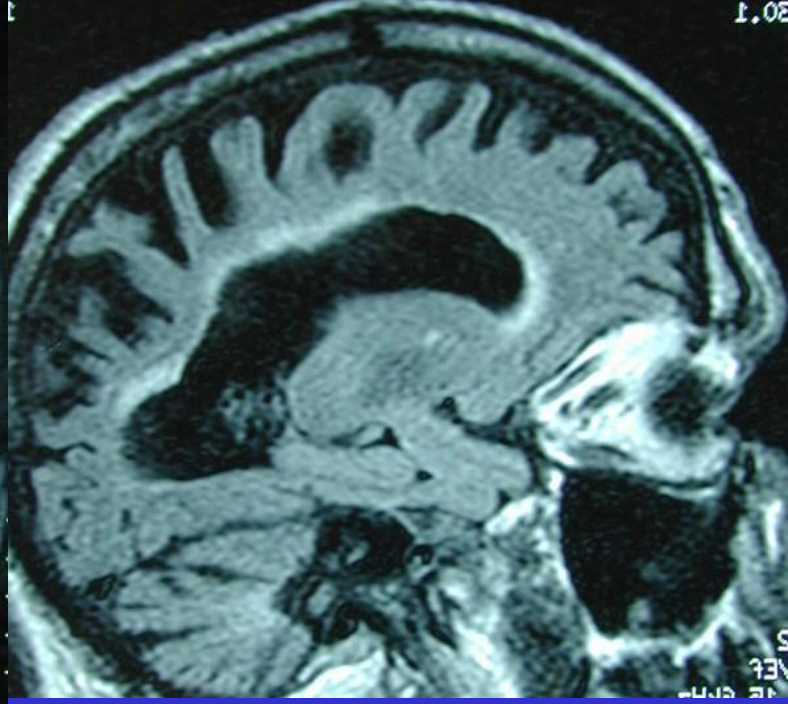



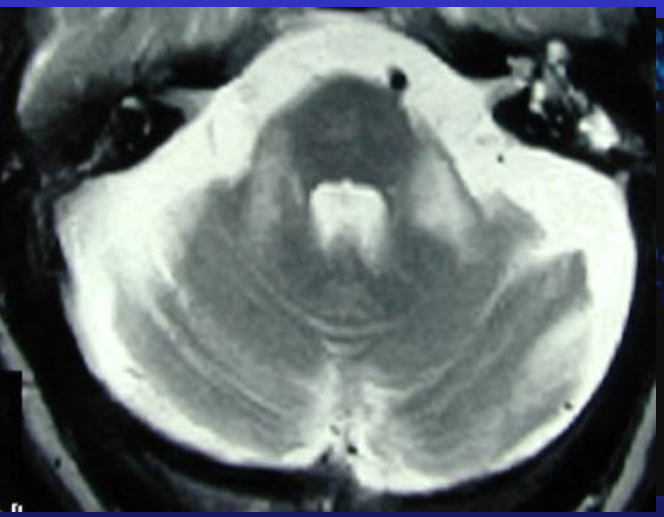



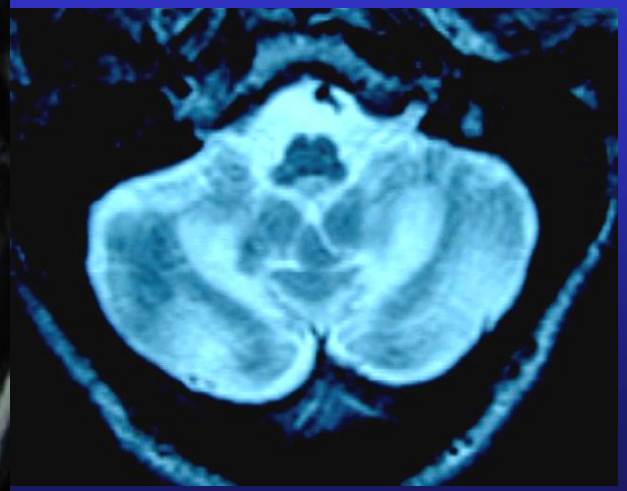

**Women with FXTAS were not described until 2004 (Hagerman et al 2004 AJHG) and only 13% have the MCP Findings on MRI studies (Adams et al 2007), less dementia (Seritan et al 2008, 2016) Inclusions reported in 2002 (Greco et al 2002, 2006)**

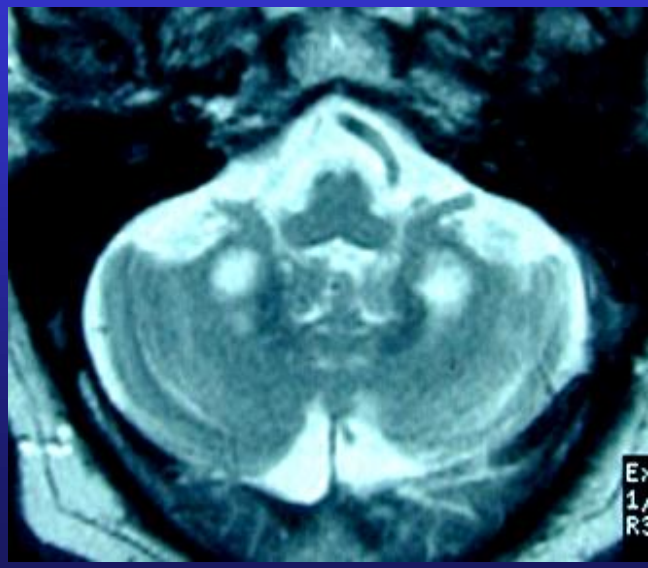

A
Ph
BRAIN
FLAIR AX2
P





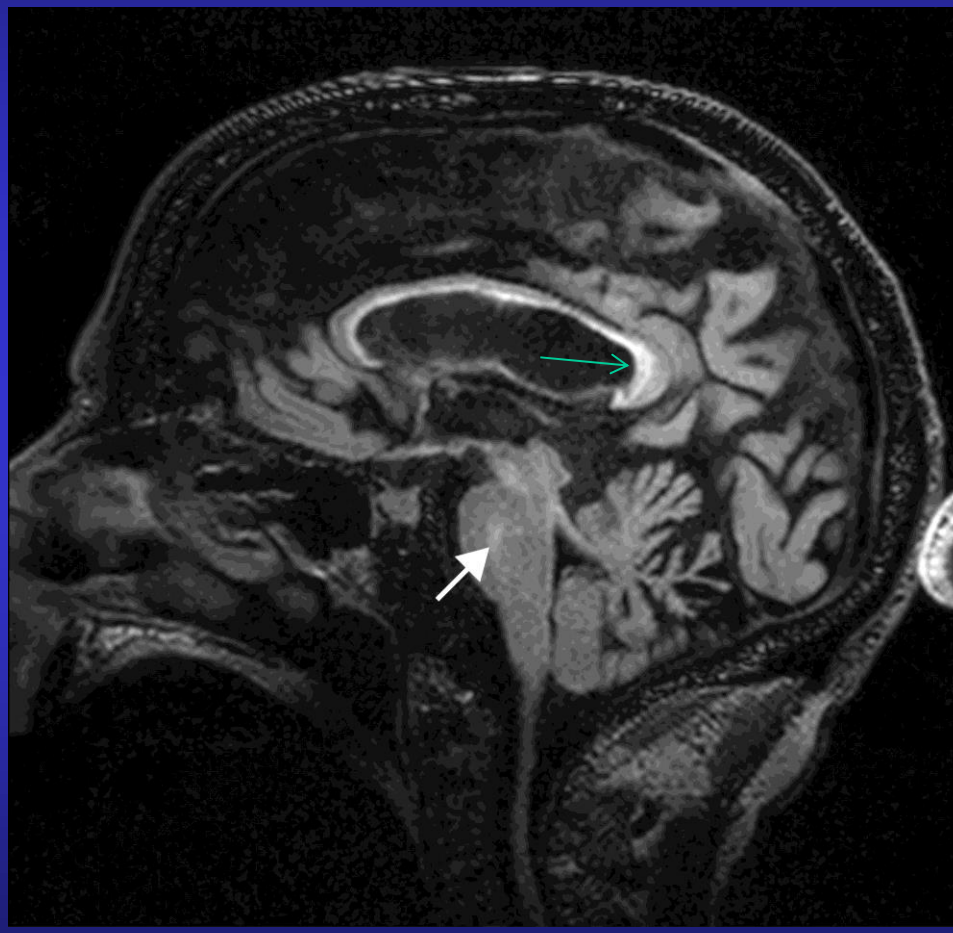






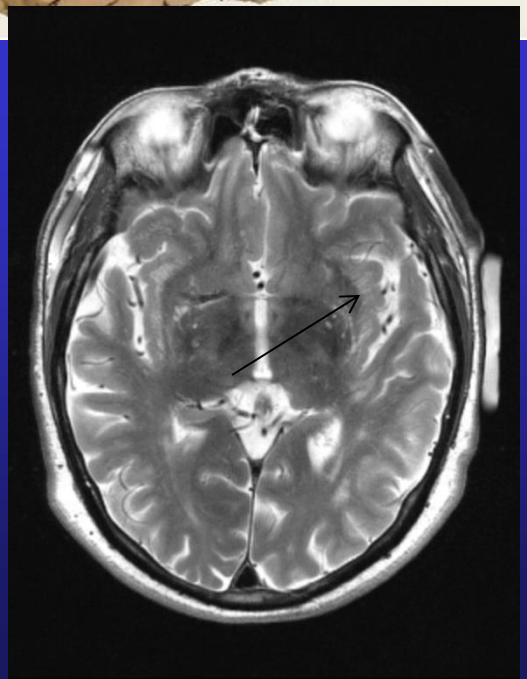
# Other MRI Findings in FXTAS

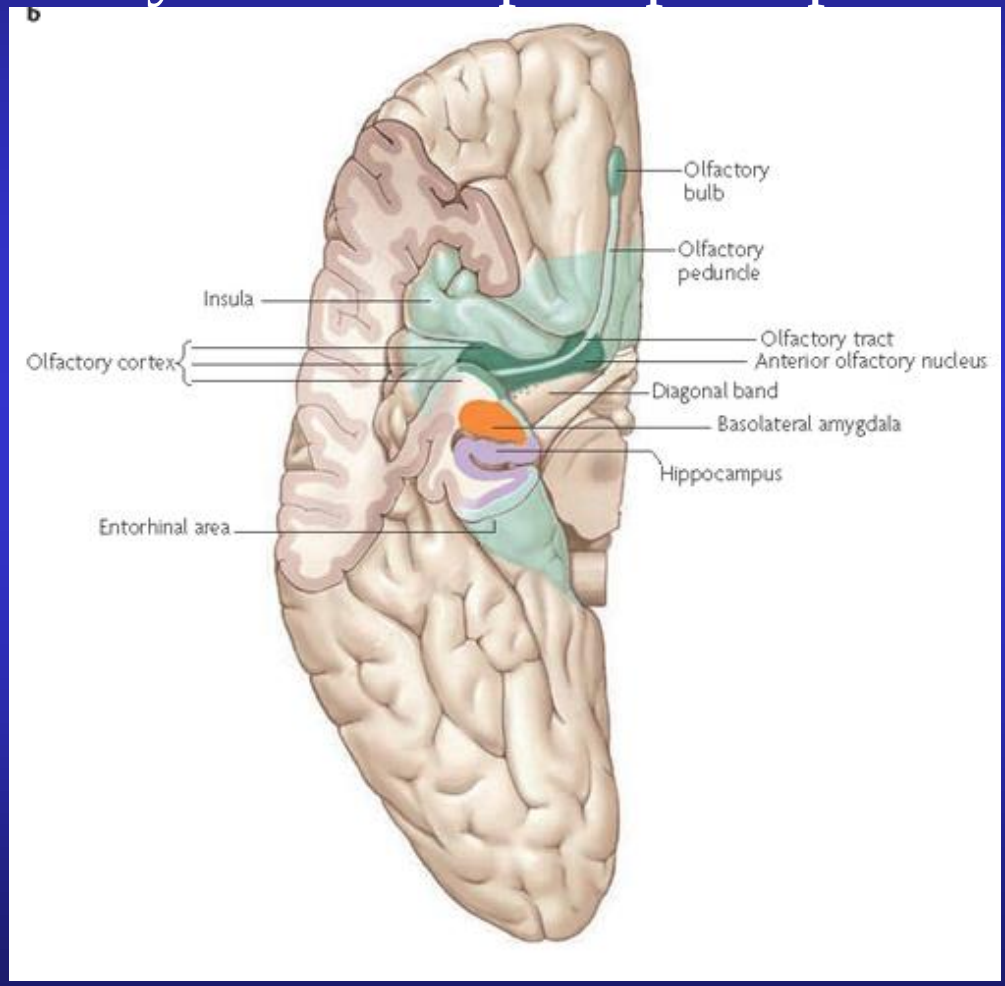
- White matter disease in the pons
- Thinning of the corpus callosum and wmd in splenium
- Involvement of the insula



# Insula Sign in some premutation carriers with FXTAS

early involvement of insula may influence pain perception



# FXTAS in unmethylated full mutation carrier

- Loesch et al 2011 Clin Genet: 65yo truck driver (240-480 repeats) with history of alcoholism and smoker 30 yrs; age 54 heavy daily ETOH and disorientation episodes; 58y cholestectomy and subsequent tremor and ataxia; aggression; hallucinations; urinary incontinence

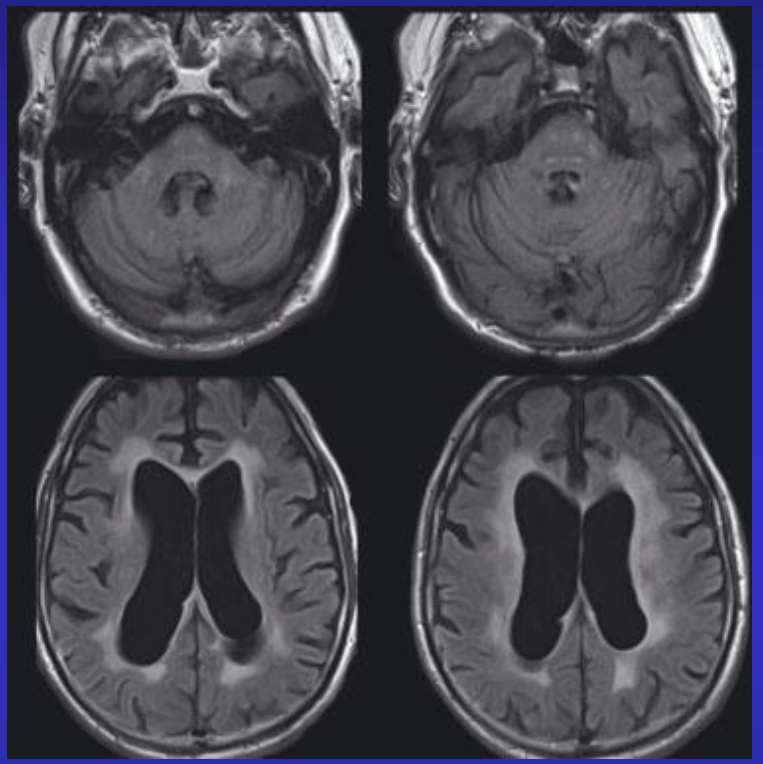


Table 1. Standard cognitive test data

| Test | Scores from 1998 | Scores from 2010 |
|---|---|---|
| WAIS-III[a] | | |
| FSIQ | 71 | 52 |
| VIQ | 69 | 61 |
| PIQ | 78 | 51 |
| DS | 8 forwards 3 backwards | 4 forwards 2 backwards |
| MMSE[b] | | 9/30 |
| CPST[c] | | Inability to shift set |

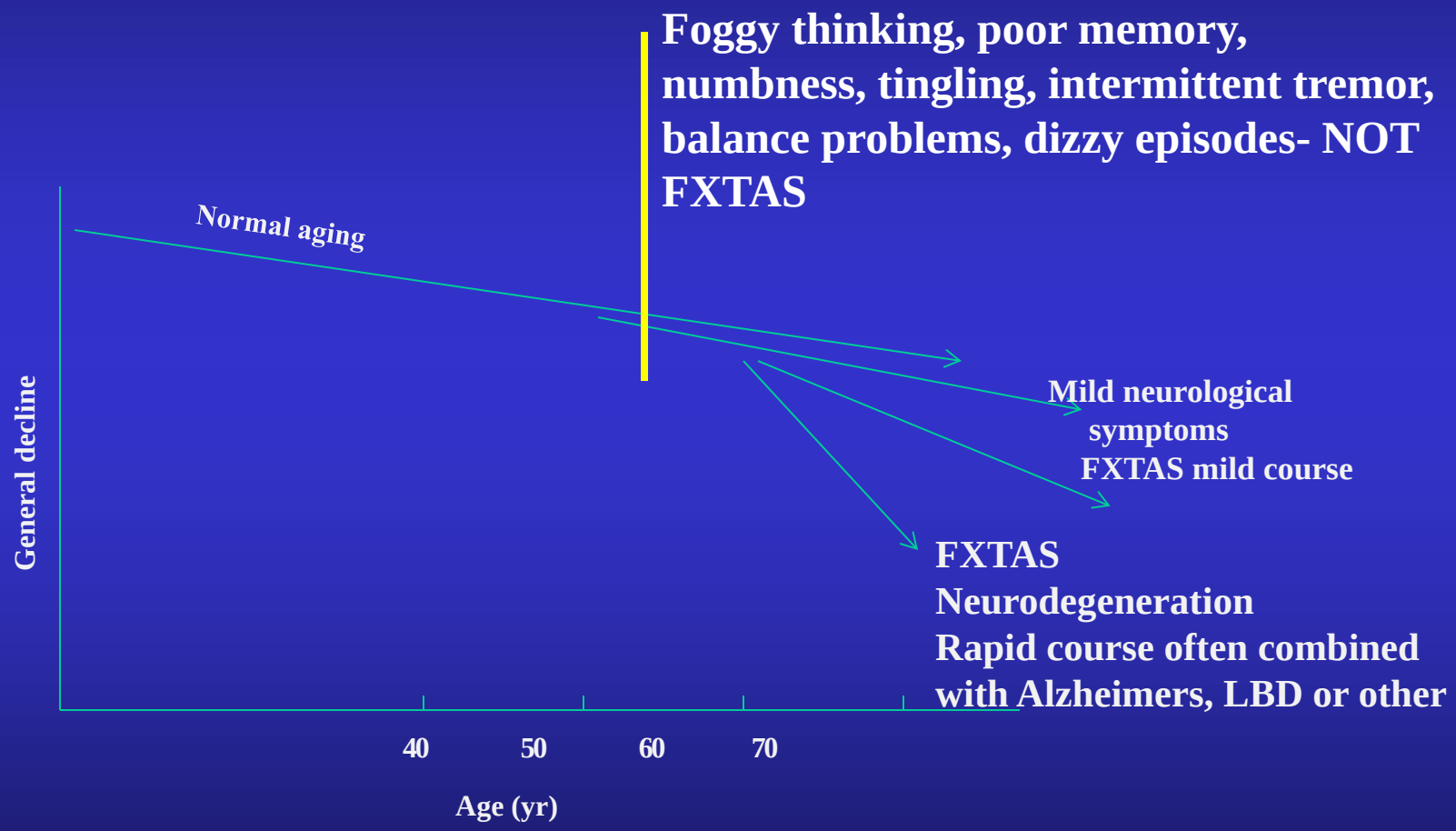
- Additional cases now reported Pretto et al 2013, Santa Maria et al 2014.

# Mild symptoms should be differentiated from FXTAS

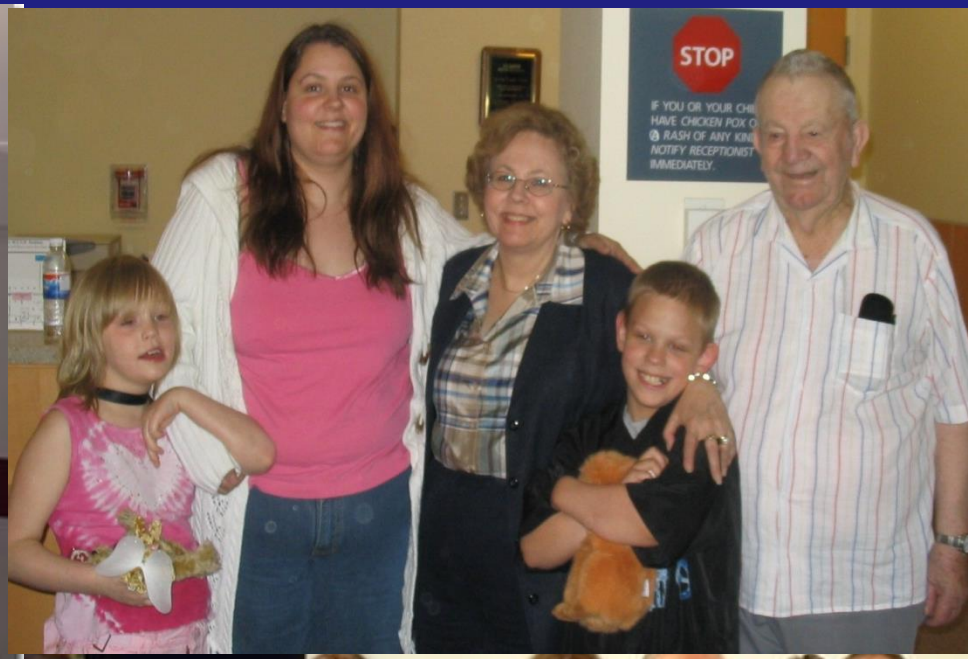
Most of the symptoms of premutation carriers are secondary to changes in the brain related to low level RNA toxicity influenced by background genetic effects and environmental influences ie depression, anxiety, tingling, migraines, mood instability etc. This is not FXTAS

FXTAS is a quantum leap in neuronal problems ie neurodegeneration associated with white matter disease and more brain atrophy and it can progress faster when combined with alzheimers, Parkinson's disease, LBD multiple sclerosis

# Life course of aging in carriers



# 100th birthday with FXTAS

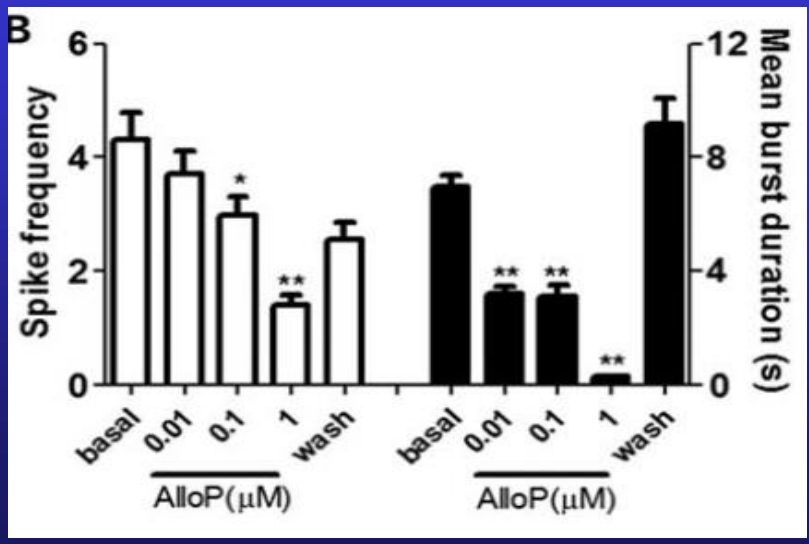

# Treatment of premutation problems including FXTAS

- Seritan et al 2014 J Cl Psychiatry; Controlled trial of memantine was not helpful for tremor, ataxia or executive function deficits in patients with FXTAS
- Subgroup of FXTAS patients underwent event related potential (ERP) studies (n=41) and treatment benefits in cued recall memory and N400 repetition effects were seen compared to placebo

# Allopregnanolone: a natural neurosteroid $GABA_A$ agonist

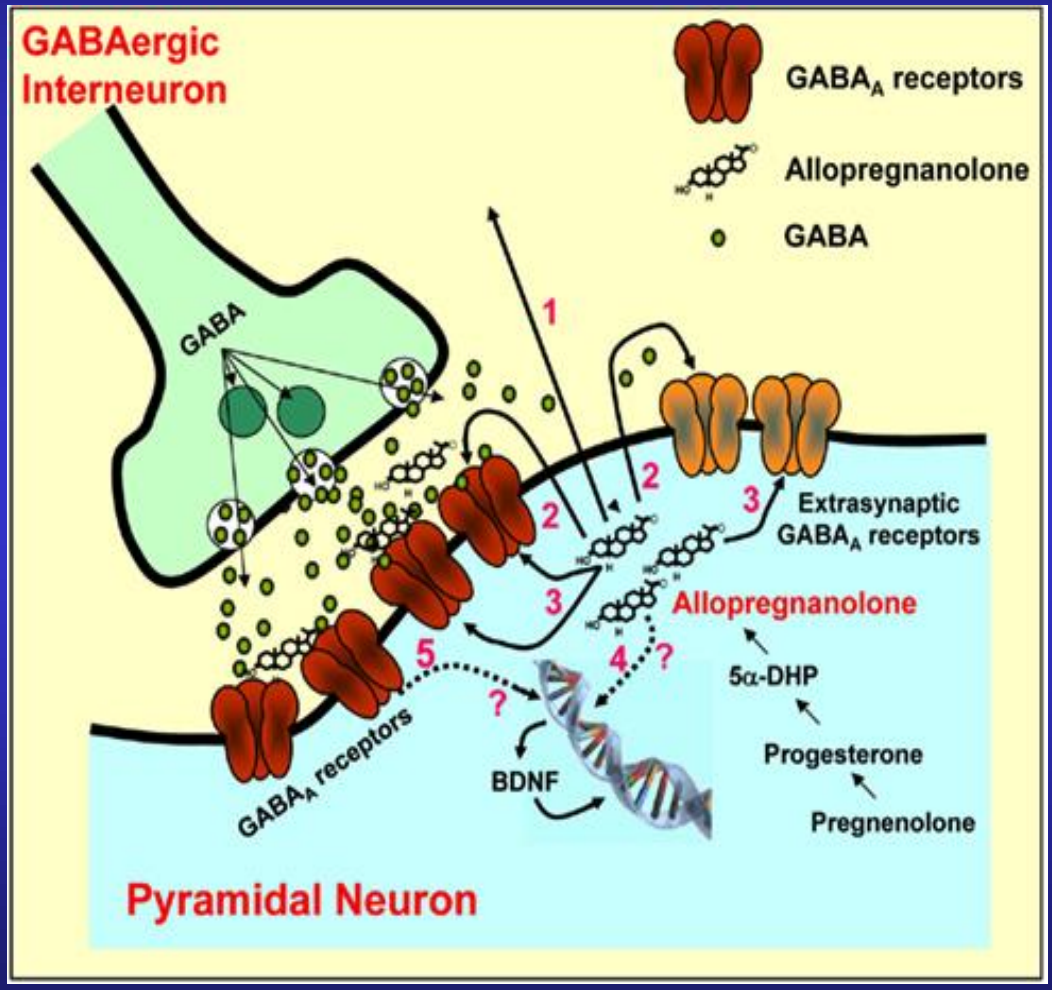
- AlloP is being studied in tramatic brain injury and in Alzheimer's Disease (Brinton et al 2013)
- AlloP reduced spike frequency and duration in premutation neurons (Cao et al 2012 HMG)
- Stimulates neurogenesis, and neuroregenerative

Open label trial (12 weeks) in FXTAS approved by FDA



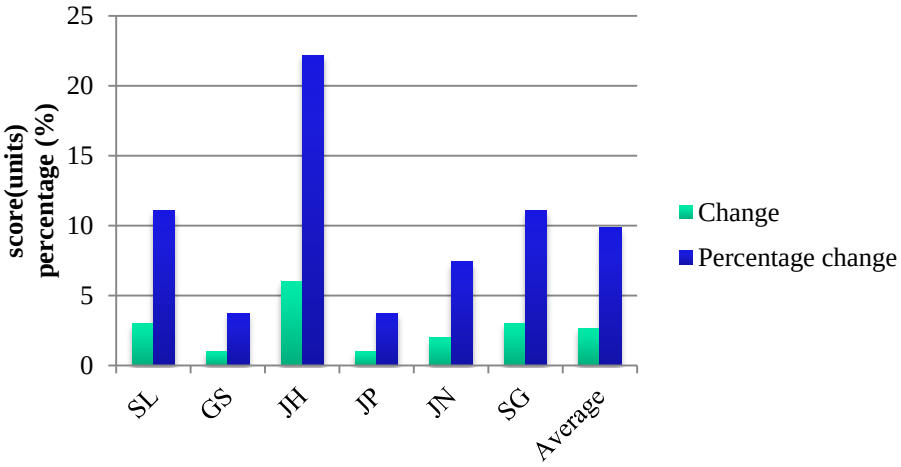
# Allopregnanolone

- Endogenous neurosteroid
- Produced by cortical and hippocampal pyramidal neurons
- Positive allosteric modulator
- GABA(A) Receptor
- Enhance inhibitory effect of GABA
- Neuroprotection (prevention of apoptosis)
- Neurogenesis

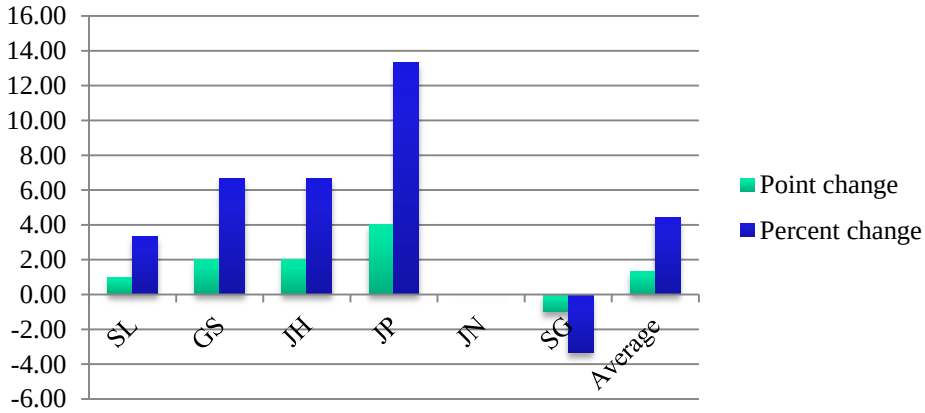


# Cognitive improvements with Allopregnanolone treatment

**BDS-2 score change post infusion**




**MMSE total score changes post infusion**




- **BDS-2 measures executive function, working memory**
- **Improvement in scores in all patients**
- **Frontal cortex involved**

- **Majority show improvements in scores post infusion**
- **No change in JN's scores; SG slight decrease**
- **Compare against a control for natural progression of disease**

# Collaborators

MIND Institute
- Norman Brule
- Mary Jae Leigh
- David Hessl
- Susan Harris
- Kushma Govindappa
- Gayatri Mahajdan
- Michele Ono
- Emma Hare
- Andrea Schneider
- Lindsey Partington
- Tasleem Chechi
- Jonathan Polussa
- Michele Ono
- Len Abbeduto
- Susan Rivera
- Alyssa Hamlin
- Louise Gane

Dept. Pathology
- Claudia Greco

NTRI Researchers
- Isaac Pessah
- Rob Williamson
- Rob Berman

Dept. Neurology
- Lin Zhang
- John Olichney
- Ricardo Maselli

Dept of Psychiatry
- Andreea Seritan

## UC Davis School of Medicine

Dept. Biochem & Molec. Medicine
- Paul Hagerman
- Flora Tassone
- Chris Iwahashi
- Anna Ludwig
- Dolores Garcia-Arocena
- Greg Mayeur
- Chris Raske

Dept. Biostatistics
- Danh Nguyen


University of Washington and UC Davis Fragile X Research Center NICHD Funded

Charles Laird  Mike Guralnick  Gwen Glew

University of Colorado Health Sciences Center (Denver)

Nicole Tartaglia  Maureen Leehey  James Grigsby ;  Karen Riley at DU

Rush University (Chicago)

Elizabeth Berry-Kravis  Meryl Lipton  Deb Hall  Christopher Goetz

*Latrobe University, Melbourne Australia*

Danuta Loesch  Richard Huggins

Support: NICHD, NINDS, NIA, NFXF,
Roche,  Novartis, Seaside Therapeutics, Forest