An updated review of the Fragile X Spectrum

Feliciano J. Ramos, MD PhD

Hospital Clínico Universitario "Lozano Blesa"
Facultad de Medicina. Universidad de Zaragoza
Zaragoza, España

Fragile X Spectrum

- Fragile X Syndrome (FXS)
- Fragile X Associated Tremor-Ataxia Syndrome (FXTAS)
- Fragile X Associated Premature Ovarian Insufficiency (FXPOI)

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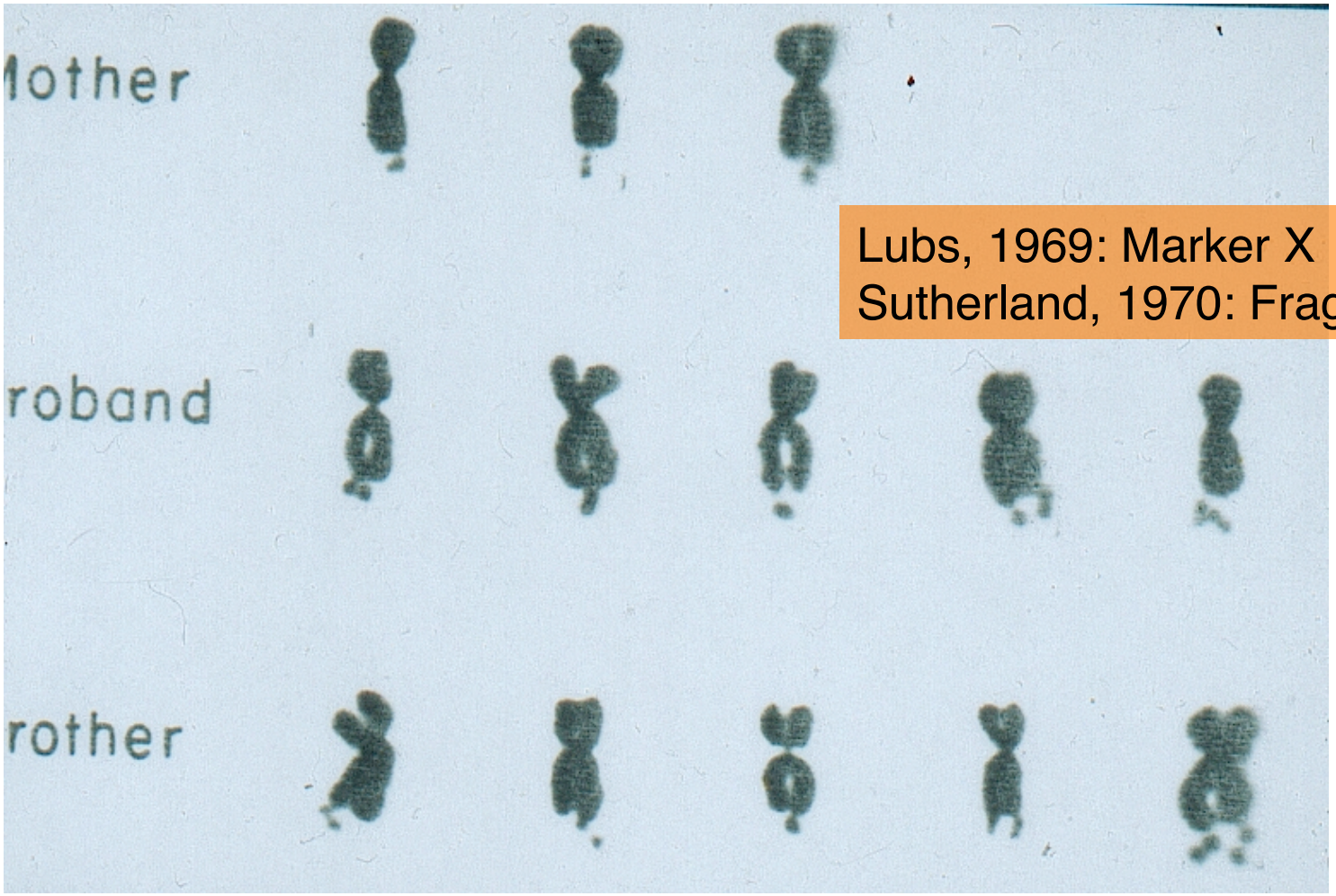
FXS: ¿Where the name comes from?



Lubs, 1969: Marker X
Sutherland, 1970: Fragile X

Fragile X Syndrome: *Epidemiology*

In the general population are affected:

≈ 1/4.000 males

≈ 1/8.000 females

… and are carriers:

≈ 1/250 females

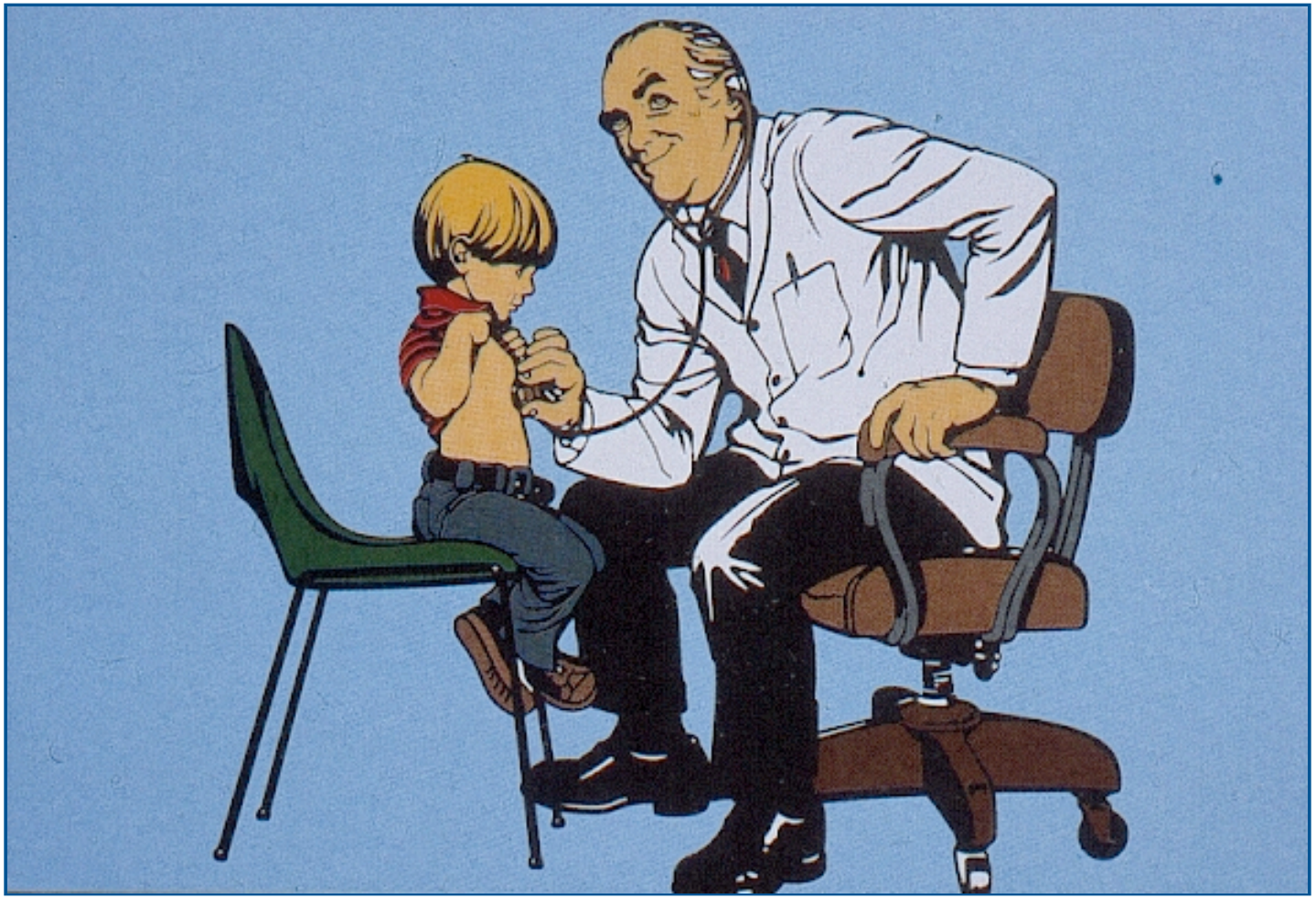
≈ 1/700 males

Fragile X Syndrome: *Clinical findings*

- Developmental delay / Intellectual disability
  - Speech delay (onset) (!)
  - Hyperactivity ± Attention Deficit Disorder
  - Behaviour problems
- Characteristic phenotype
  - Elongated face
  - Large (prominent) ears
  - Connective tissue dysfunction
  - Machroorchidism (at puberty, males)

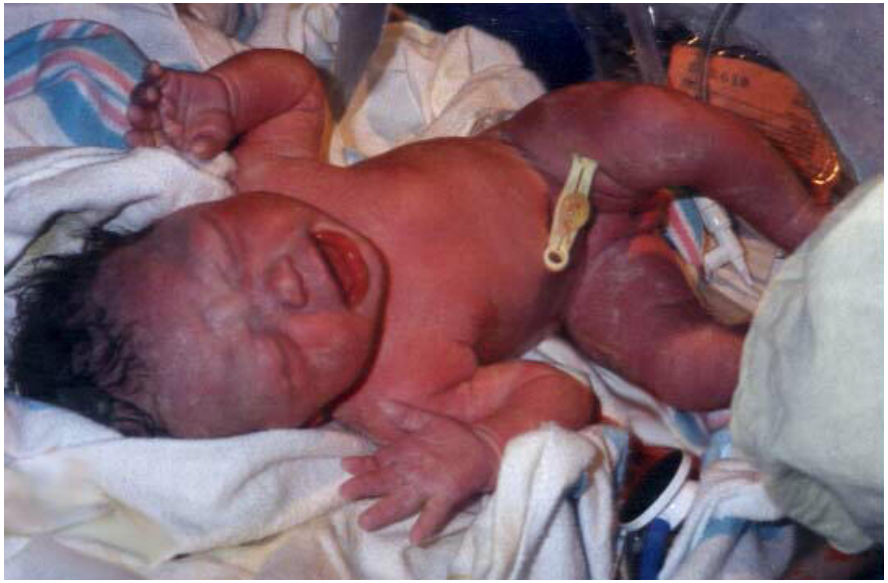
Fragile X Syndrome diagnosis:

It is a paediatrician job !



Fragile X Syndrome: Newborn

- No apparent physical findings!
- Clinical diagnosis not possible !



FXS: *Main clinical findings (I)*

1. Physical phenotype :

- ✓ Elongated face (broad forehead)
- ✓ Large and/or prominent ears
- ✓ Joint hypermobility
- ✓ Macroorchidism (after puberty in males)

FXS: *Main clinical findings (II)*

2. Intellectual function:
   - Developmental delay / Intellectual disability
   - Speech delay (onset)

3. Behavioural/Conductual anomalies:
   - Hyperactivity ± Attention Deficit Disorder
   - Stereotyped movements
   - Tactile defense and sight avoidance
   - Autism / Autistic-like disorders

FXS: *Hagerman´s Score*

	Not present (0 points)	Used to be present, not currently or mild (1 point)	Clearly present (2 points)
DD / Intelllectual disability			
Hyperactivity			
Attention Deficit Disorder			
Hand flapping			
Hands bitting			
Poor visual contact			
Repetitive speech			
Joint hypermobility			
Large prominent ears			
Macroorchidism (males)			
Tactile defense			
Simian crease			
Family history of intellectual disability			
TOTAL :			

Score system: <10: low risk; 10-16: moderate risk; >16 high risk

Hagerman et al. *Am J Med Genet, 1991*

Fragile X Syndrome:
Common medical conditions

- Recurrent otitis
- Strabismus
- Heart murmur (valvular anomaly)
  - Mitral valve prolapse (most common)
- Orthopaedic problems
  - Flat feet
  - Joint hyperlaxity (risk of luxations)
  - Scoliosis

Fragile X Syndrome:
Motoric problems

- Hand-writting difficulty
- Joint hipermobility
- Mild hypotonia
- Poor hand manipulation skills

Fragile X Syndrome:
Sensorial problems

- Tactile defense
- Hypersensitivity to stimuli
- Gravitational insecurity
- No discrimination

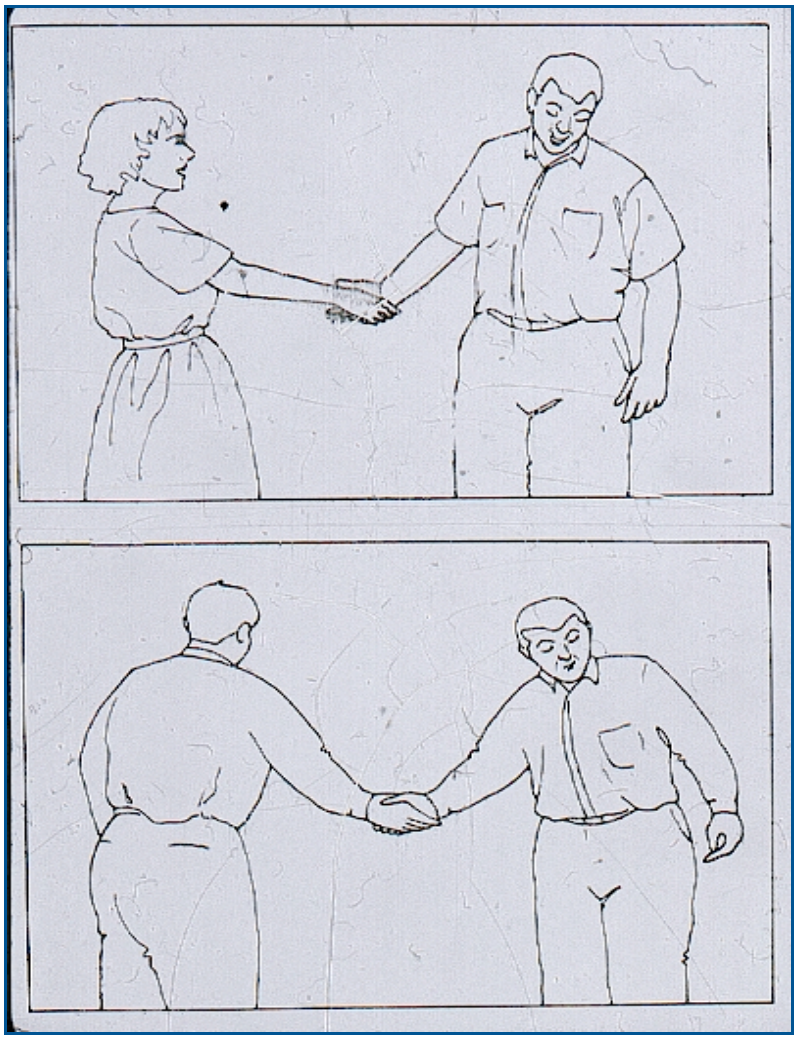
FXS: Speech problems

- Delayed onset
- Repetitive
- Echolalia
- No answers to questions
- Inadecuate expression of thoughts
- Inadecuate use

FXS: Behavioural problems

- Hyperactivity ± Attention Deficit Disorder
- Poor eye contact
- Stereotyped hand movements (flapping, etc.)
- Shyness or impulsivity
- Maladjustment to new situations
- Autism

FXS: Characteristic hand-shaking



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Fragile X Syndrome:
Clinical features in < 50% of cases

- Macrocephaly
- Seizures
- Heart murmur
- High palate
- Hypotonia (mild)
- Flat feet
- Autism
- Elevated birth weight

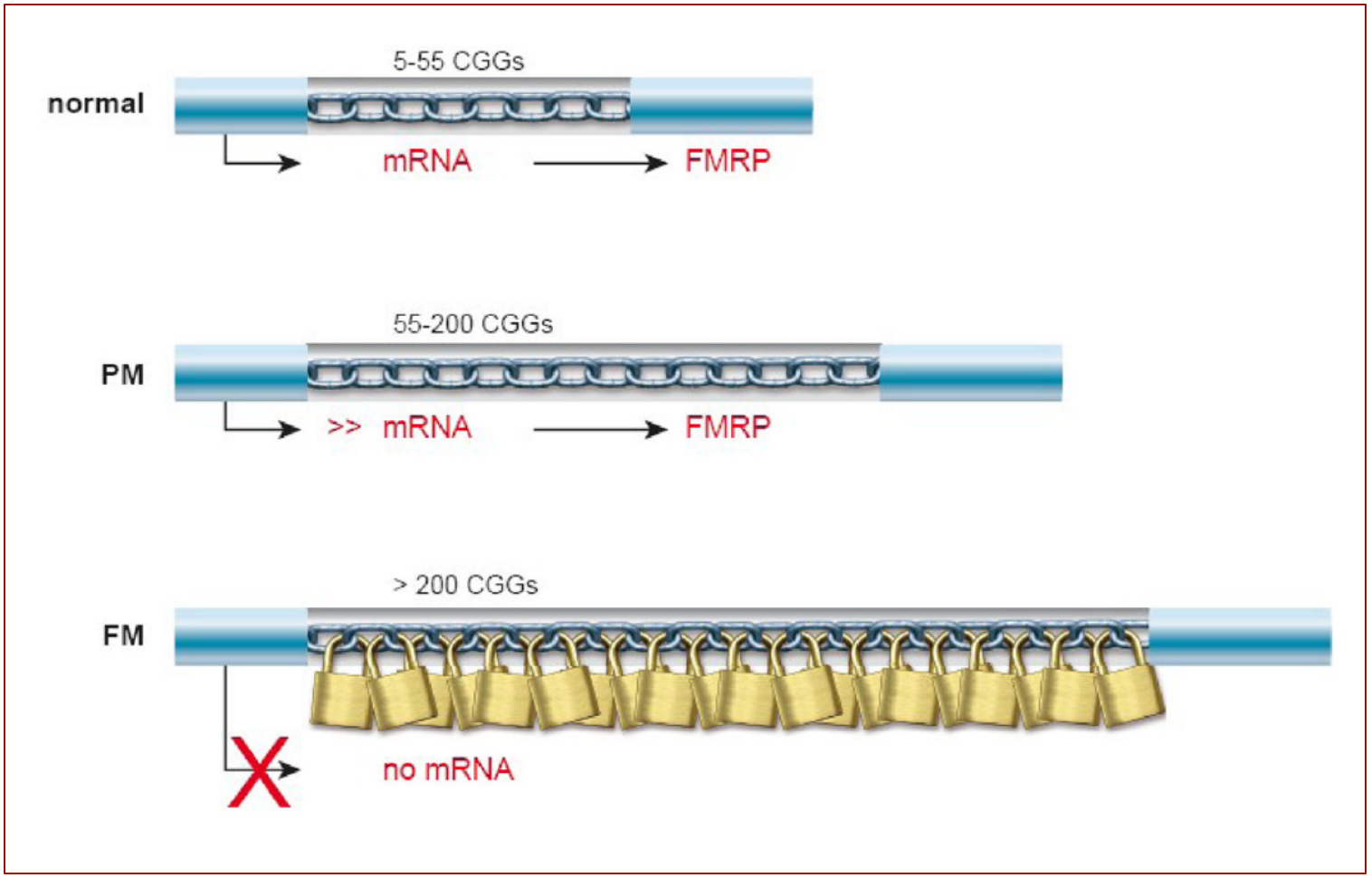
FXS: Clinical findings in females

- Affected:
  - Developmental delay / Intellectual disability
  - Similar phenotype than males
- Non affected (carriers)
  - No specific physical features
  - Difficulties with mathematics
  - Early menopause

FXS: Genetic mechanism

- *The number of repetitive CGG triplets in the FMR1 gene splits individuals in 3 groups:*
  - Normal individuals: 6-52 *CGGs* (mean 29-30)
    - Normal protein.
  - Premutation carriers: 55-200 *CGGs*
    - Protein transcribed. Normal or mildly affected phenotype.
  - Fully mutated: > 200 *CGGs*
    - Absent or very little protein. Typical FXS phenotype.

FXS: FMR1 gene, CGG expansions and mRNA

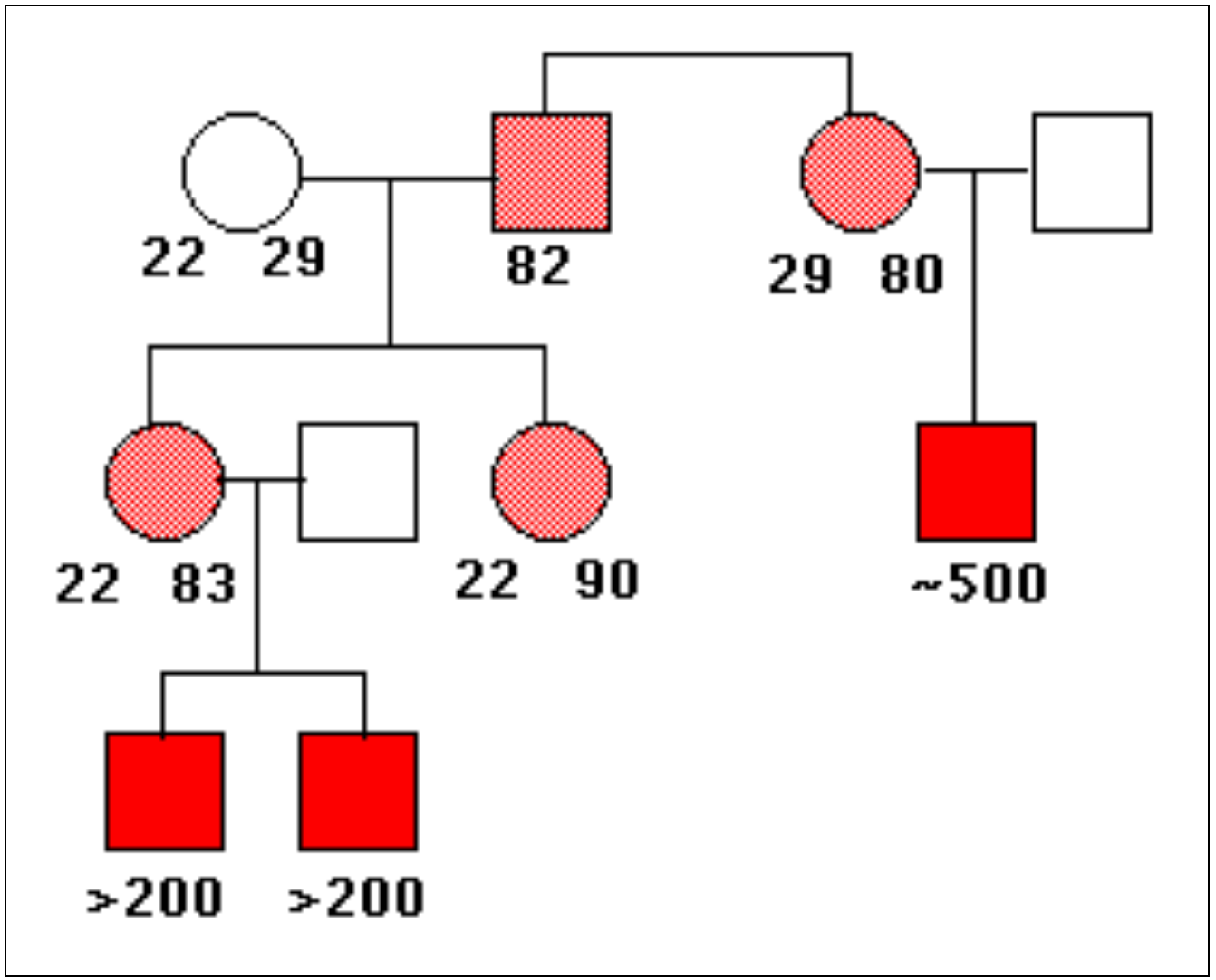


Oostra et al, 2009

Fragile X Syndrome: Diagnosis (I)

- Clinical:
  - Characteristic phenotype
  - Developmental delay / Intellectual disability
  - Behavioural problems
- Laboratory:
  - Karyotype: OBSOLETE !! (fragile site at Xq27.3)
  - Molecular: CGGs expansion in the FMR1 gene
    - NORMAL: 5-50
    - PREMUTATION: 50-200 --> carriers
    - FULL MUTATION: > 200 --> affected

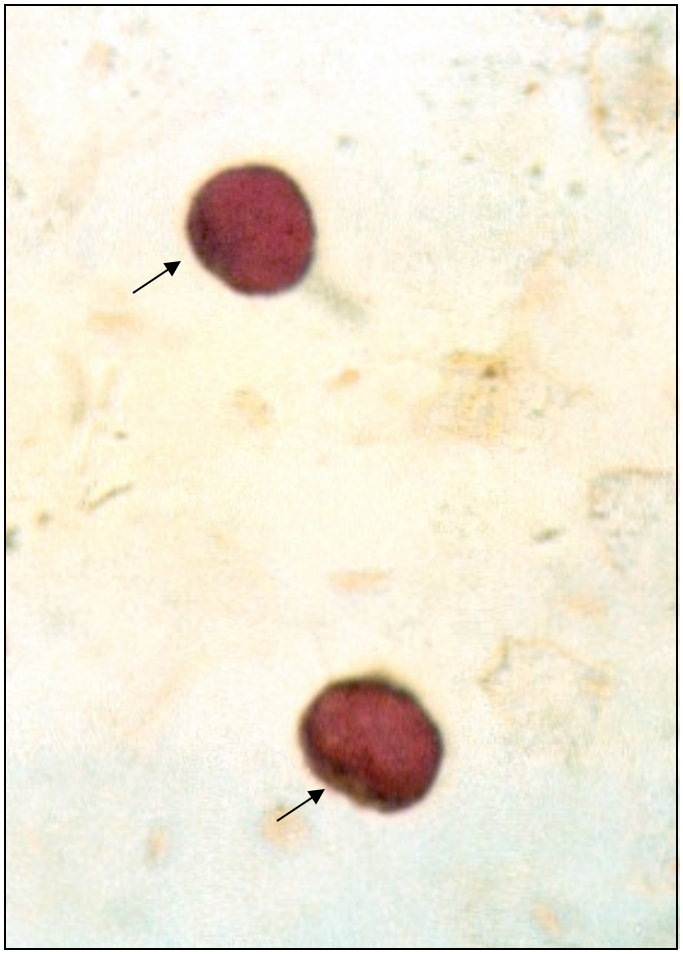
Fragile X Syndrome: Genetic anticipation



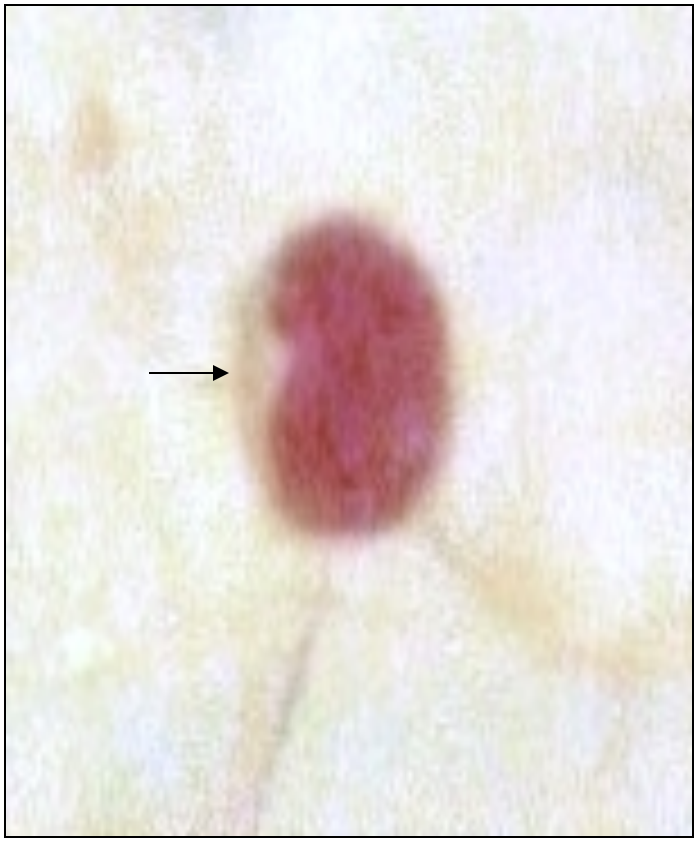
Fragile X Syndrome:
Alternative diagnostic method

- **FMRP protein analysis:**
  - Immunohistochemical test:
    - Specific monoclonal antibodies (anti-*FMRP)*
    - Visualization in cellular cytoplasm
    - Studied in blood (leucocytes) or hair roots

FXS: FMRP protein in blood cells

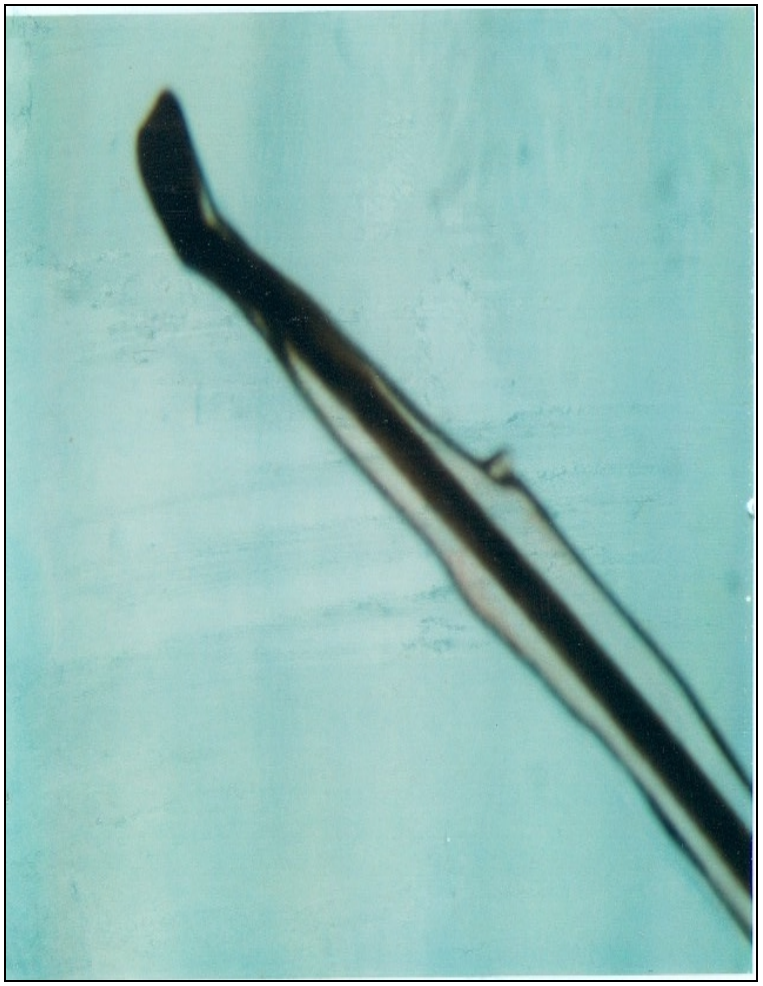


FMRP (+)



FMRP (-)

FXS: FMRP protein in hair roots



FXS: FMRP expression in hair roots

American Journal of Medical Genetics 95:105–107 (2000)

Screening for the Fragile X Syndrome Among Mentally Retarded Males by Hair Root Analysis

Ergül Tunçbilek,[1]* Mehmet Alikasifoğlu,[1] Dilek Aktas,[1] Funda Duman,[1] Hulya Yanik,[1] Burçu Anar,[2] Ben Oostra,[2] and Rob Willemsen[2]

[1]*Department of Pediatrics, Division of Medical Genetics, Hacettepe University, Ankara, Turkey*
[2]*CBG-Department of Clinical Genetics, Erasmus University, Rotterdam, The Netherlands*

A noninvasive antibody test was used to identify male fragile X patients in special education schools, on the basis of the lack of

tation carrier females was calculated to be as high as 1:259 [Rousseau et al., 1995]. The disease is caused by a dynamic mutation of a trinucleotide repeat (CGG)

- ***Studied 300 instituzionalized males with undiagnosed intellectual disability***

- ***FMRP test was useful as a screening test for FXS (5 individuals FMRP <2% -> FXS; 295 individuals FMRP >42% -> No FXS***

Fragile X Syndrome: Inheritance

- X-linked dominant
- Recurrence risk:
  - 50% in males (affected)
  - Depends on maternal premutation allele size

    (>100 CGGs: all will expand to >200 CGGs !)
  - All mothers of affected males are obligate carriers

No sporadic (de novo) FXS case reported ever !

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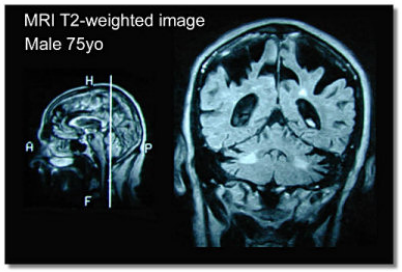
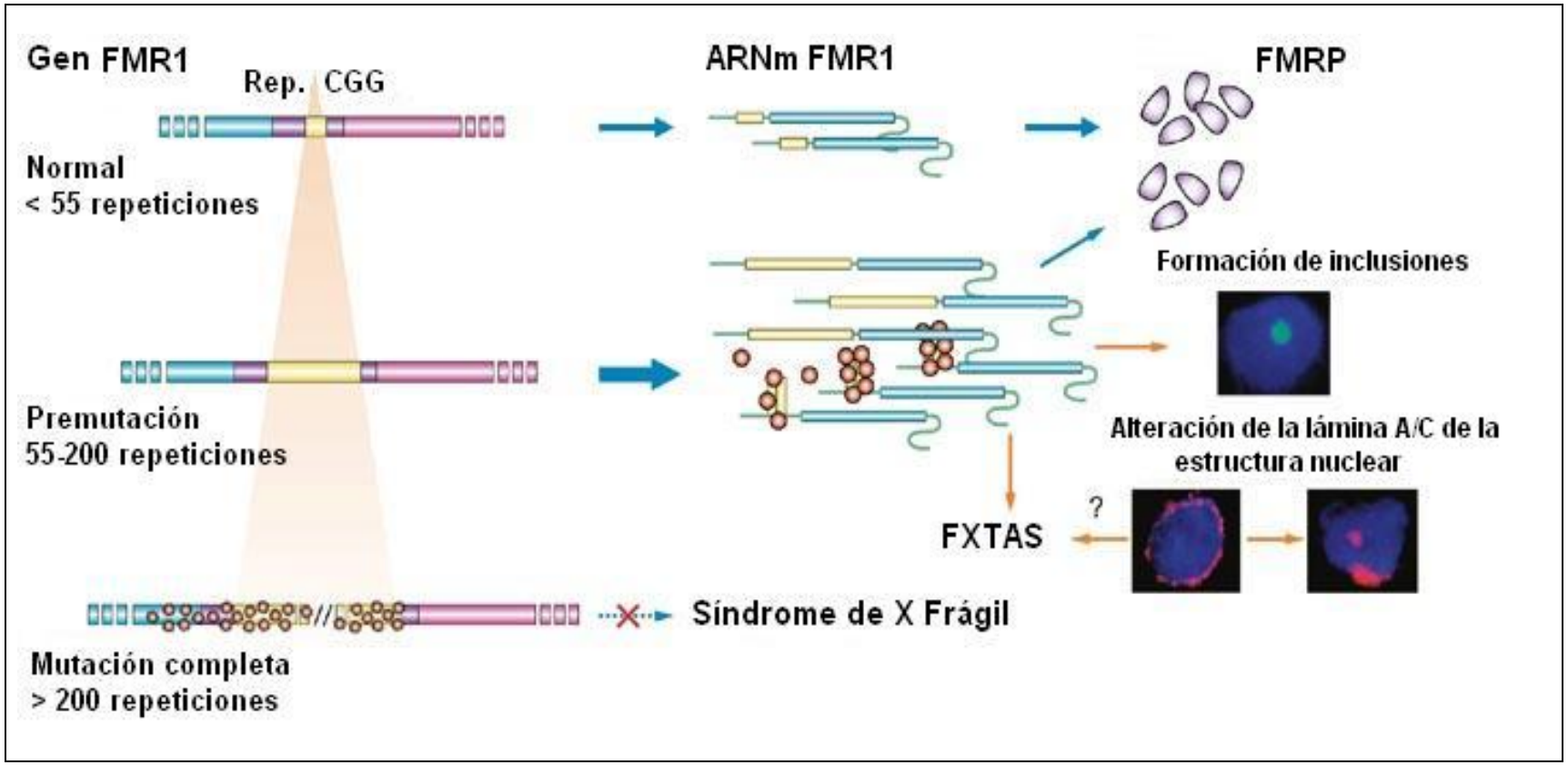
Fragile X-Associated Tremor Ataxia Syndrome (FXTAS)

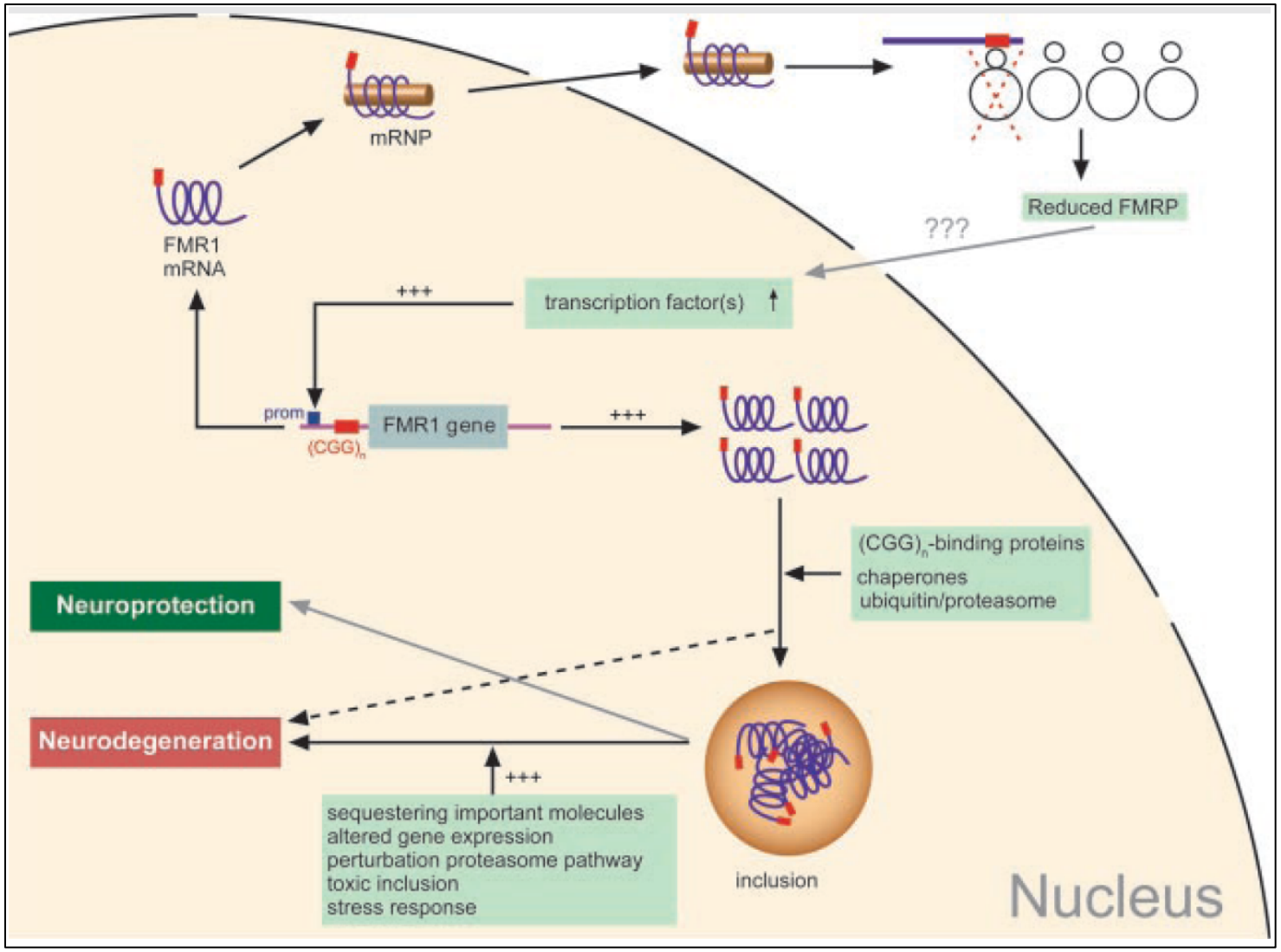
- ≈ 1/3.000 adult males >50 y.o. with FMR1 premutation and normal FMRP levels
- Normal childhood / adolescence
- Slowly progressive
- Tremor (writing difficulties, clumsy handling, etc.)
- Ataxia (frequent falls)
- Parkinsonism, stiffness, dystonia
- Elevated mRNA levels (intranuclear inclusions in cerebral neurons)



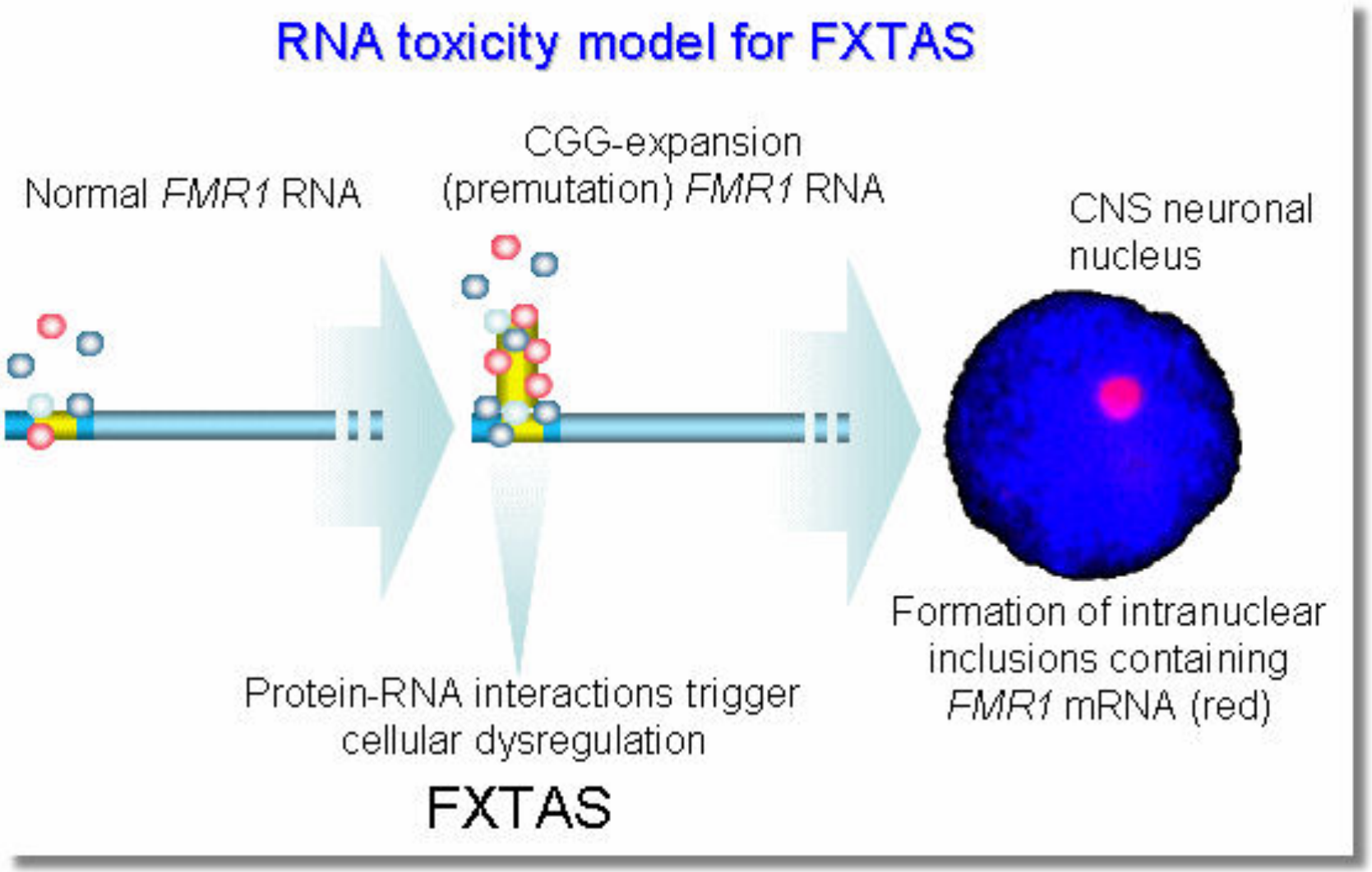
Fragile X Spectrum: *Genetics*



FXTAS: Pathogeny



Brouwer et al, 2008


RNA toxicity model for FXTAS
Normal FMR1 RNA
CGG-expansion (premutation) FMR1 RNA
CNS neuronal nucleus
Formation of intranuclear inclusions containing FMR1 mRNA (red)
Protein-RNA interactions trigger cellular dysregulation
FXTAS

FXTAS: Diagnostic criteria

Criteria	Major	minor
Radiological (Brain MRI)	Anomalies in cerebral peduncles Anomalies in brainstem	Generalized atrophy (moderate to severe) Anomalies in cerebral white matter
Clinical	Intentional tremor Ataxic gait	Parkinsonism Executive functions deficit Short-term memory loss (moderate to severe)

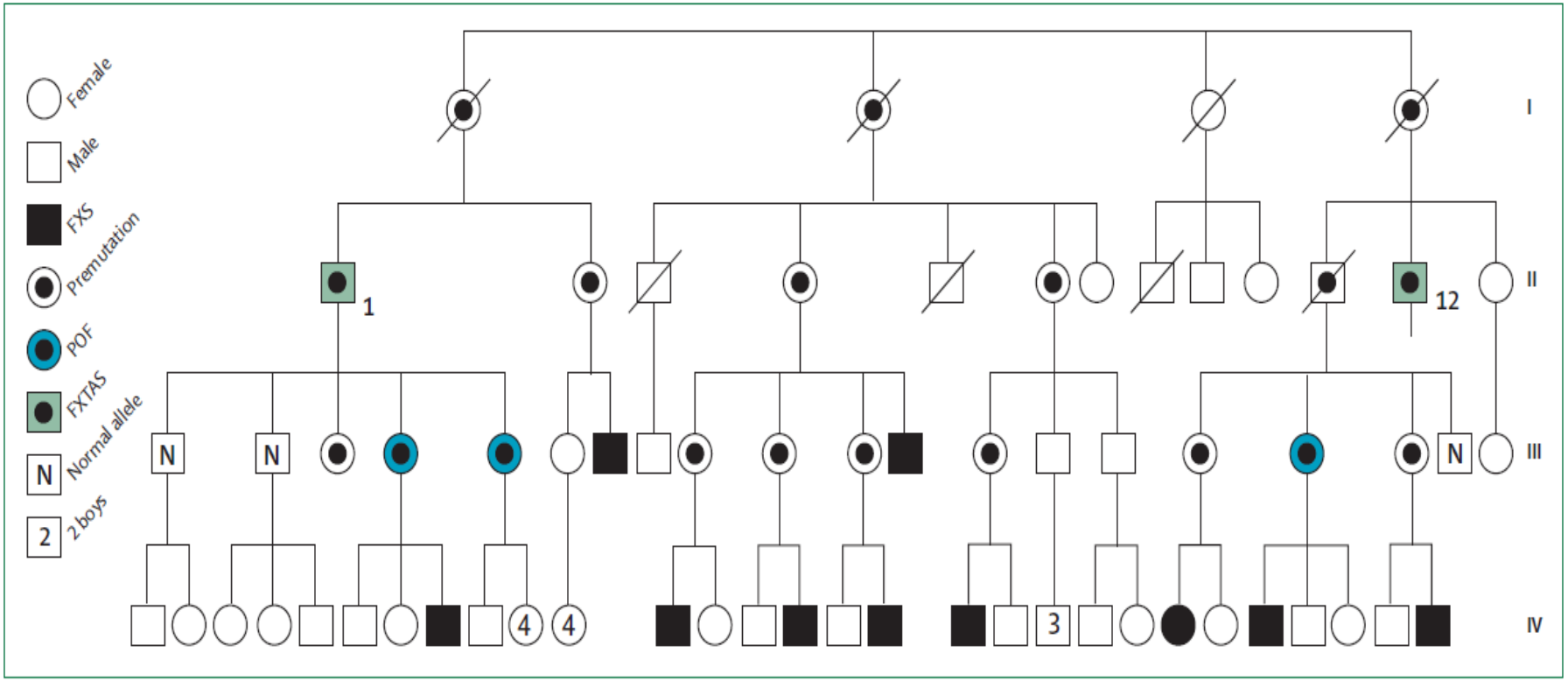
Jacquemont et al, 2003

FXTAS: Diagnosis

Diagnosis	Criteria: 55-200 CGG repeats
Certain	1 major radiological sign + 1 major clinical symptom or astrocytic inclusions
Likely	1 major radiological sign + 1 minor clinical symptom or 2 major clinical symptoms
Possible	1 minor radiological sign + 1 major clinical symptom

Jacquemont et al, 2003

Fragile X Spectrum: Affected family



Jacquemont et al, 2007

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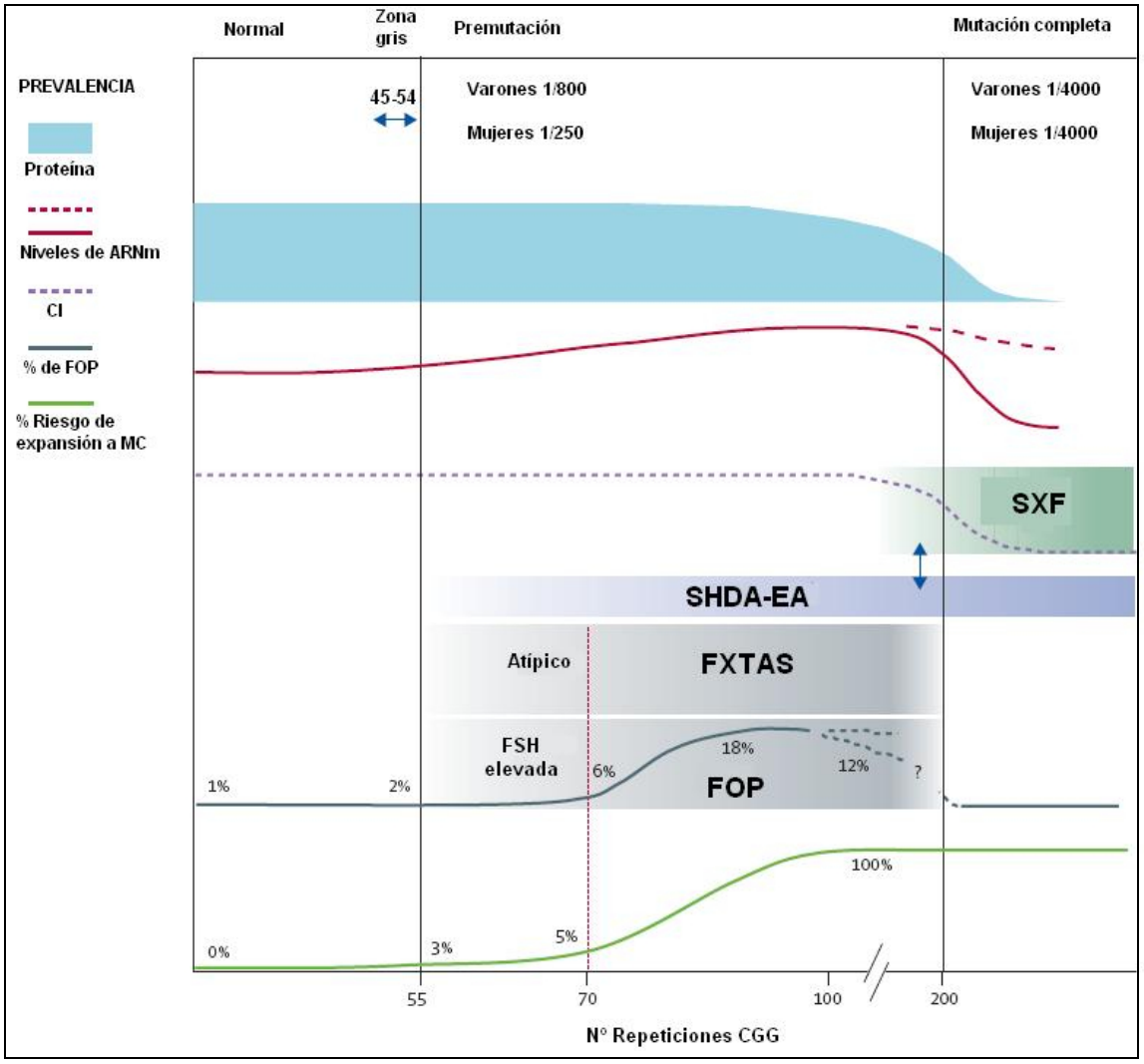
Fragile X Associated Premature Ovarian Insufficiency (FXPOI)

- Incidence of POI in general population ≈ 1%
- POI in 16-25% of females with FMR1 premutation
- POI definition:
  - Menopause ≤ 40 years of age
  - Sexual hormones deficiency (FSH/LH)
  - Elevated levels of serum gonadotropins
  - No influence of inactivation pattern of X chromosome
  - No increased risk of POI in women with FMR1 full mutation

Fragile X Associated Premature Ovarian Insufficiency (FXPOI)

- FMR1 premutation is the single genetic anomaly most frequently associated to POI in the general population
- No linear association between the number of CGG repeats and POI´s prevalence
- It is currently unknown why FMR1 premutation and POI are associated… Hypotheses:
  - Correlation with the woman´s initial number of ovocytes
  - Correlation with multiple ovulations
- No specific treatment available

Fragile X Spectrum



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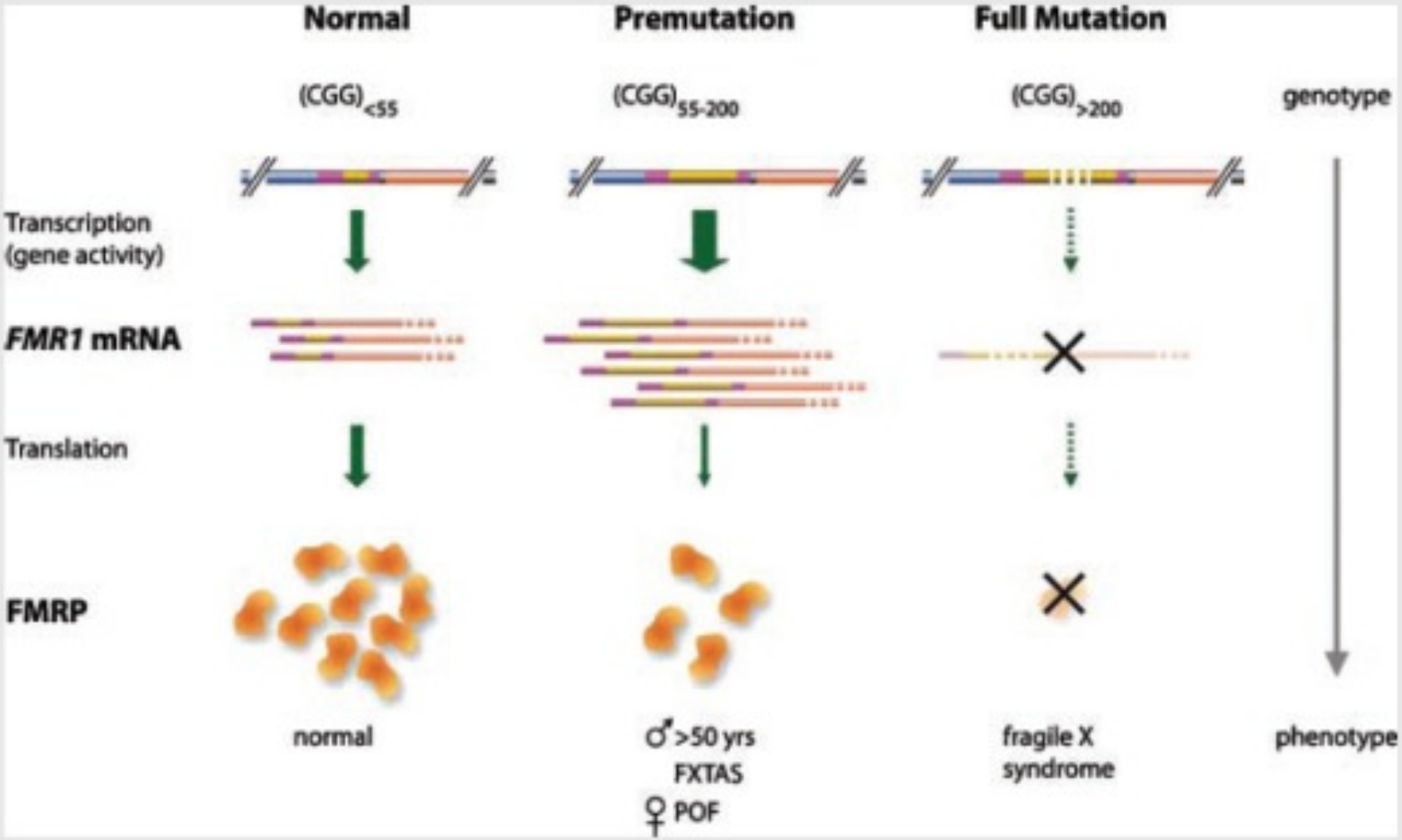
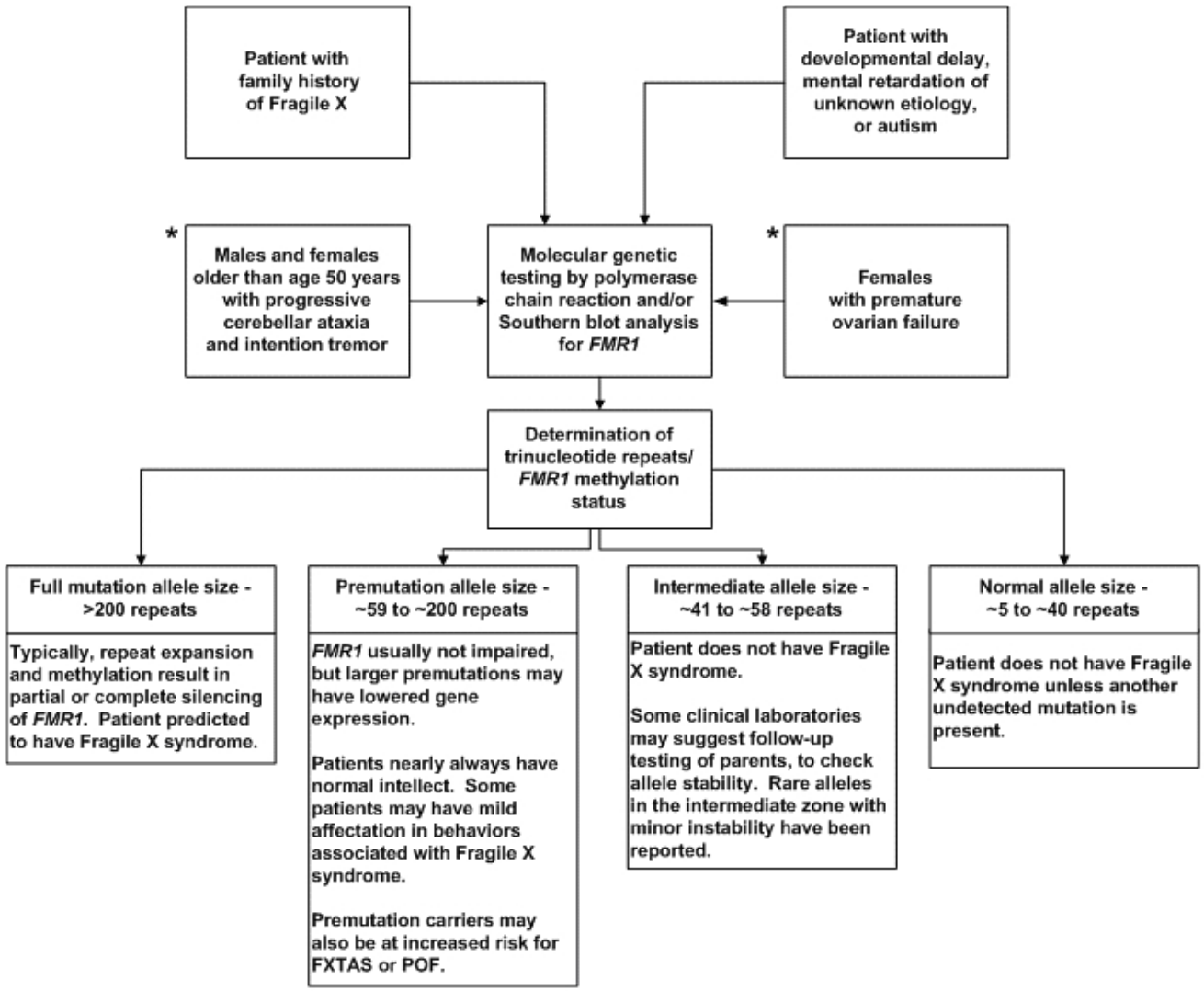


Brouwer et al, 2008

Fragile X Spectrum: Diagnostic flowchart



Sherman et al, 2005

BMC Neurology

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Systematic review of pharmacological treatments in fragile X syndrome

Jose-Ramon Rueda*†[1], Javier Ballesteros†[2] and Maria-Isabel Tejada†[3]

Address: [1]Department of Preventive Medicine and Public Health, University of the Basque Country, Barrio Sarriena S/N, Leioa 48940, Spain, [2]Department of Neurosciences, University of the Basque Country, Barrio Sarriena S/N, Leioa 48940 and CIBER in Mental Health (CIBERSAM), Spain and [3]Molecular Genetics laboratory, Department of Biochemistry, GIRMOGEN, Cruces Hospital, Plaza de Cruces s/n, Barakaldo 48903, Spain

Email: Jose-Ramon Rueda* - joseramon.rueda@ehu.es; Javier Ballesteros - javier.ballesteros@ehu.es; Maria-Isabel Tejada - mariaisabel.tejadaminguez@osakidetza.net

* Corresponding author †Equal contributors

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FXS: Current therapies (I)

- Non-pharmacological
- Pharmacological:
  - **ADHD**: Stimulants (Clonidine, Dextro-anphetamine, Methylphenidate, Guanfacin, L-Acetylcarnitine, Folic Acid)
  - **Anxiety**: Serotonin reabsorption inhibitors (Fluoxetine)
  - **Aggressiveness/Erratic behaviour**: Antipsychotics (Risperidone, Aripiprazol)

FXS: Current therapies (II)

- Pharmacological (cont.):
  - **Memory:** Amphakines (CX516)
  - **Sleep:** Melatonin
  - **Behaviour/Social and visual contact/Anxiety:** mGlu-receptor antagonists (Phenobam, Memantine), Acetyl-cholinesterase antagonists (Donepezil), GABA-B antagonists (Arbaclophen)
  - Behaviour: Lithium

FXS: Problems in clinical trials

- Few “double-blind” trials
- Small number of patients included
- Lack of control groups
- Dosification, presentation and time of the drug administration (children)
- Difficult monitorization of side effects
- Patients taking other drugs (i.e. antiepileptics)
- Problems with measurements (quantification) and interpretation of results

TRASTORNOS ASOCIADOS AL X-FRAGIL (TAXF)

Un manual para familias, profesionales de la salud, asesores y educadores

The National **Fragile X** Foundation

(Fundación Americana del **X-Frágil**)

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