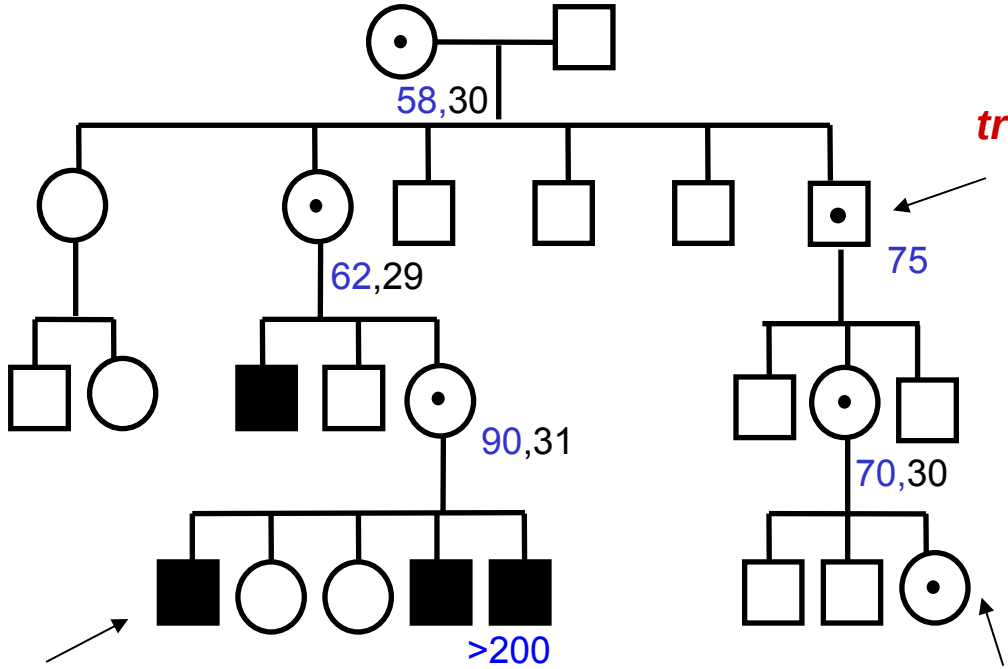
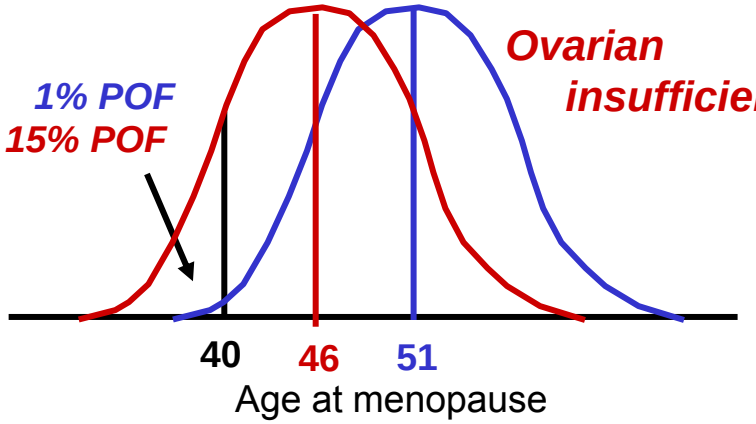
Fragile X syndrome and associated disorders

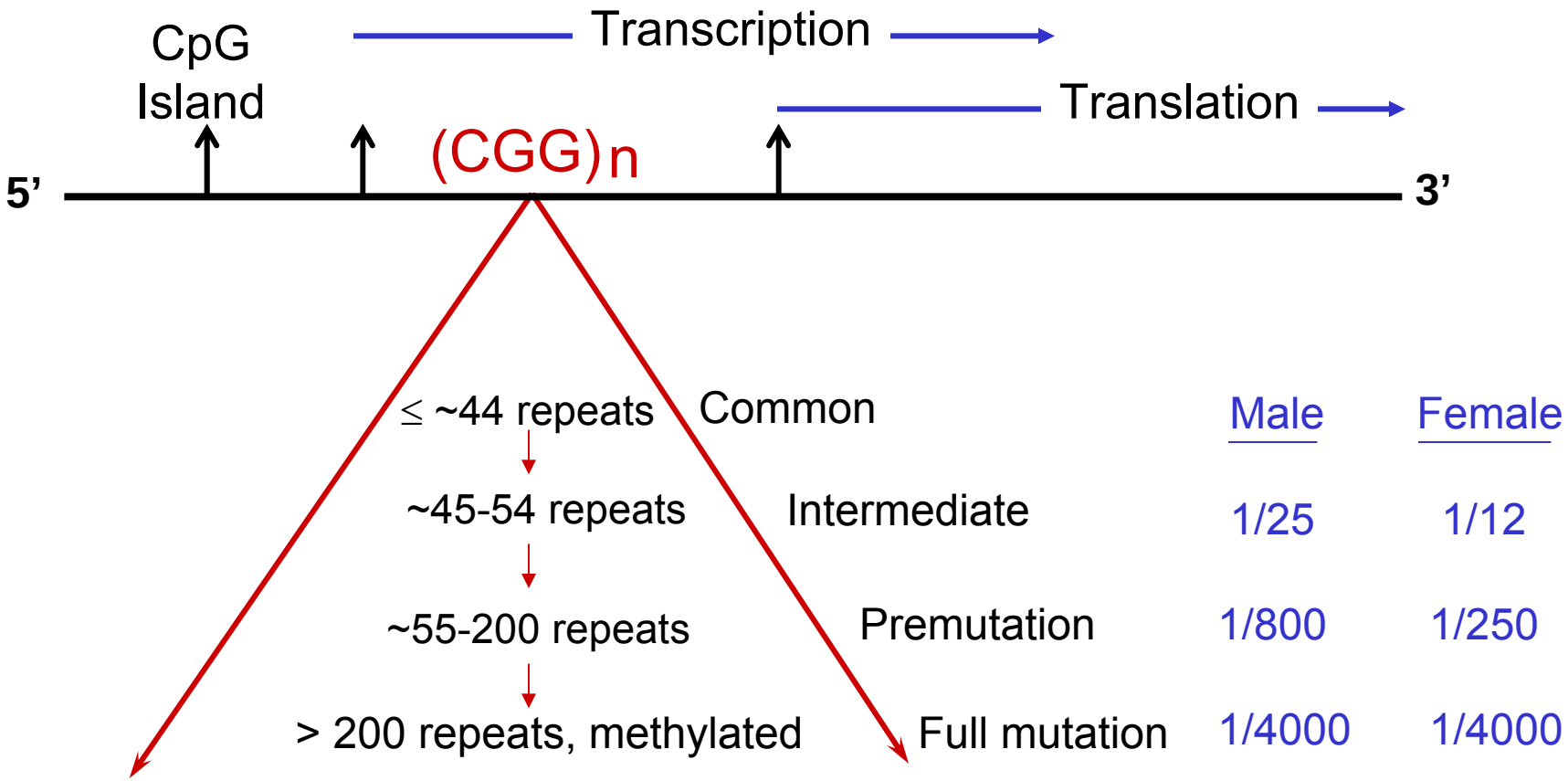


Fragile X related tremor/ataxia syndrome (FXTAS)

Fragile X syndrome



Fragile X Mental Retardation 1 (FMR1)



	Male	Female
Intermediate	1/25	1/12
Premutation	1/800	1/250
Full mutation	1/4000	1/4000

Fragile X-associated disorders: prevalence in general pop'n

MALES	Carrier Frequency	Fragile X syndrome	FXTAS
Premutation (~55-199 repeats)	1/800	~0	1/800*30% =1/2666
Full mutation (>200 repeats)	1/4000	1/4000	~0

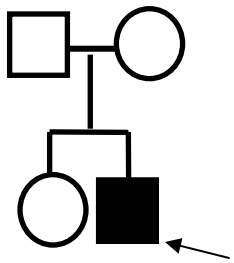
FEMALES	Carrier Frequency	Fragile X syndrome	FXTAS	Premature ovarian failure
Premutation (~55-199 repeats)	1/250	~0	1/250*1% =1/25000	1/250*15% =1/1666
Full mutation (>200 repeats)	1/4000	1/4000*50% =1/8000	~0	~0

Fragile X-associated disorders: prevalence in target pop'n

MALES	Carrier Frequency	Mental Retardation	Cerebellar ataxia
Premutation (~55-199 repeats)	1/800	~1/800	~2%
Full mutation (>200 repeats)	1/4000	2-3%	1/4000

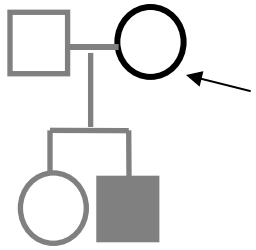
FEMALES	Carrier Frequency	Mental Retardation	Cerebellar ataxia	Premature ovarian failure
Premutation (~55-199 repeats)	1/250	1/250	~1/250	3%-10%
Full mutation (>200 repeats)	1/4000	<1%	1/4000	1/4000

Annual visit to pediatrician: at 12 months, mother is concerned that her son is hypersensitive to the environment and behaves badly in new settings; he is also not meeting some of his developmental milestones



Critical event	Age at event (months) Males	Females
Parents' first concern	13	18
Doctor confirmed concern	21	26
Eligible for services	25	26
FXS test ordered	30	40

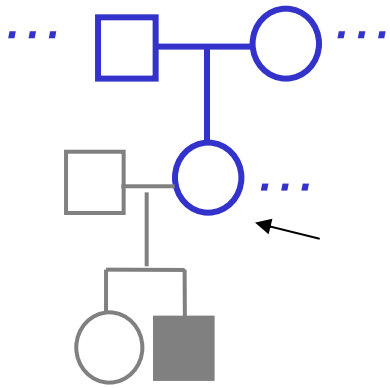
(Bailey et al, 2003)



Do you have a family history of:

- *fragile X syndrome*
- *mental retardation*
- *premature ovarian failure*
- *late onset tremor or ataxia*

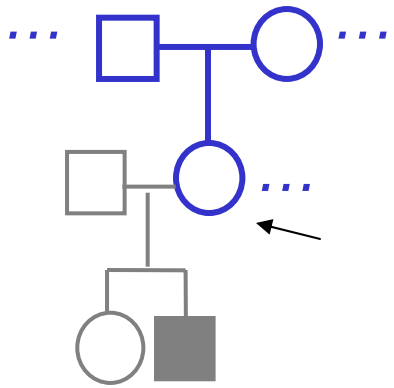
Has anyone in your family been diagnosed with mental retardation, autism, significant learning problems, learning disabilities ?



If yes, follow-up questions to increase validity:

Any specific diagnosis:	fragile X syndrome
Family relationship:	consistent with X-linked inheritance
Gender:	male
When did problems develop:	early in life
Any physical features:	none

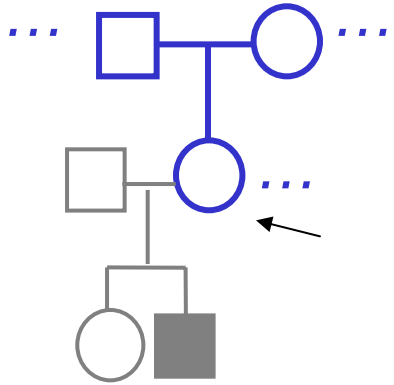
At what age did your mother or your sisters go through menopause?



If yes, follow-up questions to increase validity:

Age at menopause:	before age 40
Family relationship:	consistent with X-linked inheritance
Infertility problems:	yes, woman not responsive to ART

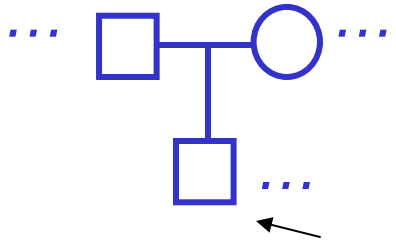
Have any of your older male relatives been diagnosed with tremor in their hands and have trouble walking without assistance ?



If yes, follow-up questions to increase validity:

Any specific diagnosis:	probably not helpful
Family relationship:	consistent with X-linked inheritance
Age of onset:	after age 50
Additional symptoms:	cognitive loss

How does this scenario change if the male is the proband?



Has anyone on your mother's side of the family been diagnosed with mental retardation, significant learning problems, learning disabilities ?

At what age did your mother or your sisters go through menopause? (little knowledge)

Have any of the older male relatives on your mother's side of the family been diagnosed with tremor in their hands and have trouble walking without assistance ?

Presymptomatic testing for a late-onset, neurodegenerative disease

Criteria for selecting a disease to use a family history tool

Substantial public health burden	MR: cost for special education, medication and intervention POF: cost for seeking diagnosis and intervention FXTAS: costs for seeking diagnosis
Well-defined case definition	MR: simple DNA test POF: DNA test, ↓ penetrance FXTAS: DNA test, ↓ penetrance
Awareness of disorder among relatives	increasing with education, but variable
Family history is established risk factor	yes, X-linked inheritance
Effective interventions	MR: prevention, knowledge of dx, behavioral intervention POF: smoking cessation, early reproduction FXTAS: no

Barriers for use of family history assessment in a primary care setting

- labor intensive for PCP
  - work up of MR
  - complicated inheritance and risk assessment

- diagnosis of carrier status leading to high risk for MR in offspring with prevention as only intervention

- pre-symptomatic testing for POF

- pre-symptomatic testing for FXTAS

Use of family history tool for fragile X-associated disorders: a “no-brainer” ???