Genetic Neurodegenerative Diseases

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Neurogenetic Diseases

- Huntington Disease
- Ataxias
- Charcot Marie Tooth
- Muscular Dystrophies
- ALS
- Dementias

Outline

1. Huntington Disease
2. Dementias
3. Genetic testing and counseling

Huntington Disease: The basics

- Autosomal Dominant
- Typically the disease first manifests in 30’s to 50’s (range is 1yr to 90+)
- The disease course is progressive
- Infrequently the gene change can transform dramatically and lead to early HD in offspring (anticipation)
- Juvenile HD (JHD) presents differently in children
- 10-13 per 100,000 individuals in the Western World develop HD

Symptoms of Huntington Disease

Movement and Coordination

- Chorea: involuntary movements
- Ballistic movements
- Dystonia
- Motor impersistence
- Impaired saccades
- Dyscoordinated breathing, swallowing

Cognitive

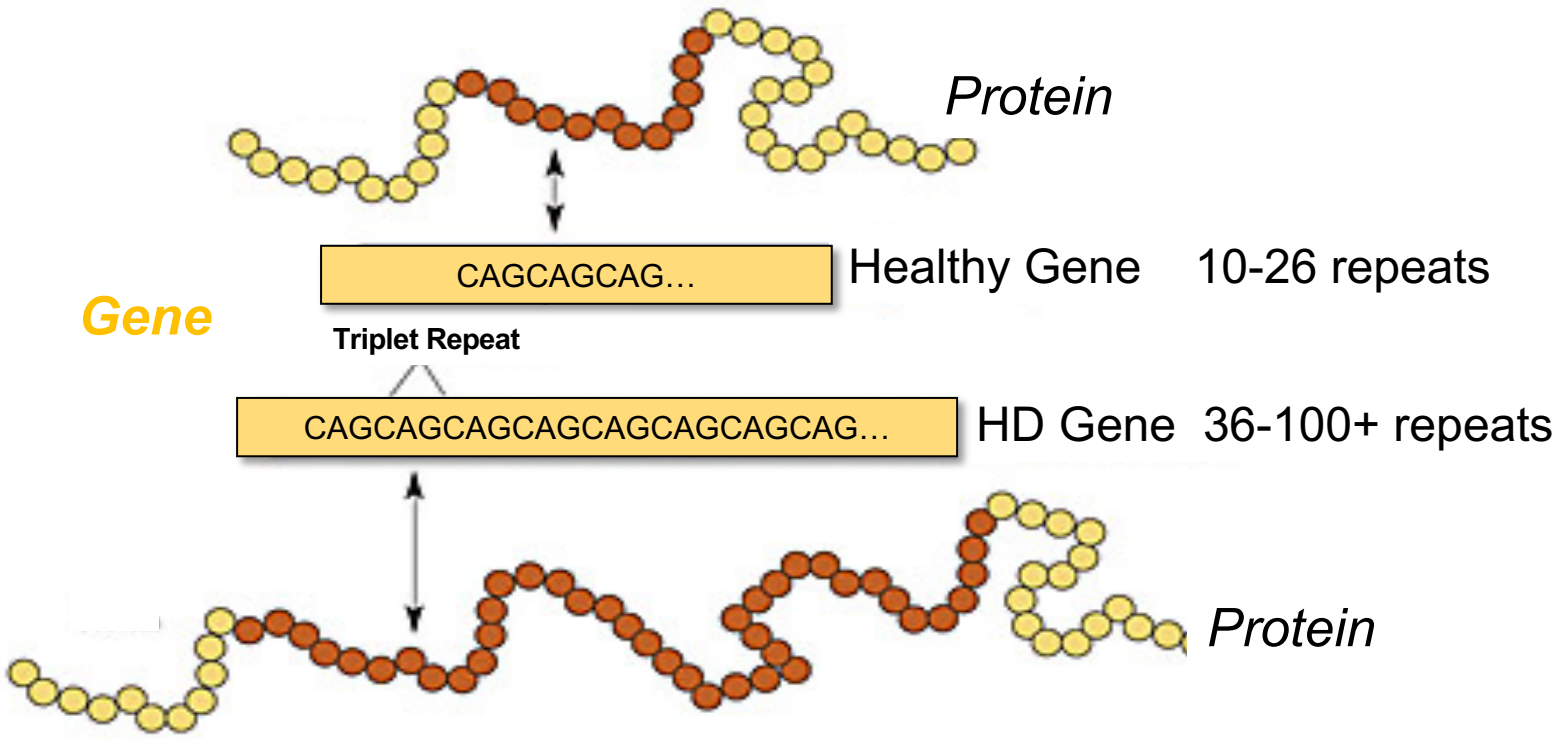
Executive dysfunction

- Impaired Judgment, multitasking
- Disinhibition
- Difficulty learning new things
- Poor concentration
- Apathy

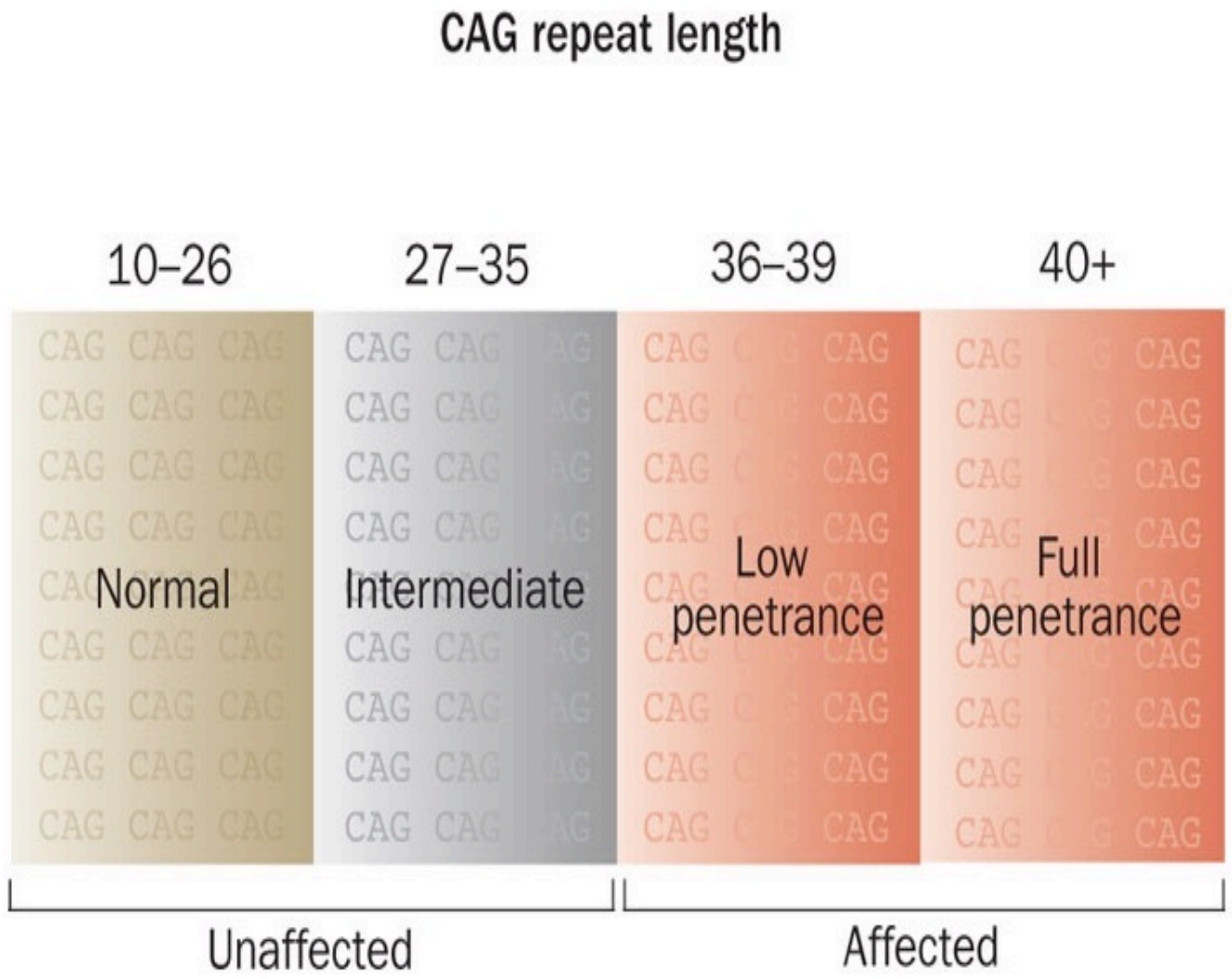
Psychiatric

- Depression
- Obsessive compulsive behaviors
- Agitation/Irritability
- Anxiety
- Perseveration
- Hallucinations/ Delusion

CAG Expansion in sequence causes longer gene, messenger RNA and Huntingtin protein



CAG triplet length in the *HTT* gene and penetrance



Squitieri, 2013 *Nat. Rev. Neurol.*
doi:10.1038/nrneurol.2013.128

Huntington Disease Challenges

- Patients face movement, psychiatric and cognitive dysfunction simultaneously
- Impacts individuals at most productive period of life with huge implications to family income
- Can be difficult to manage behavioral symptoms
- Can lead to legal troubles for patient and family
- Need social work assistance for disability, placement, counseling resources

Huntington's Disease Society of America Center of Excellence University of Washington

UW Huntington Disease Clinic

HD Center of Excellence

https://depts.washington.edu/hdcoe/

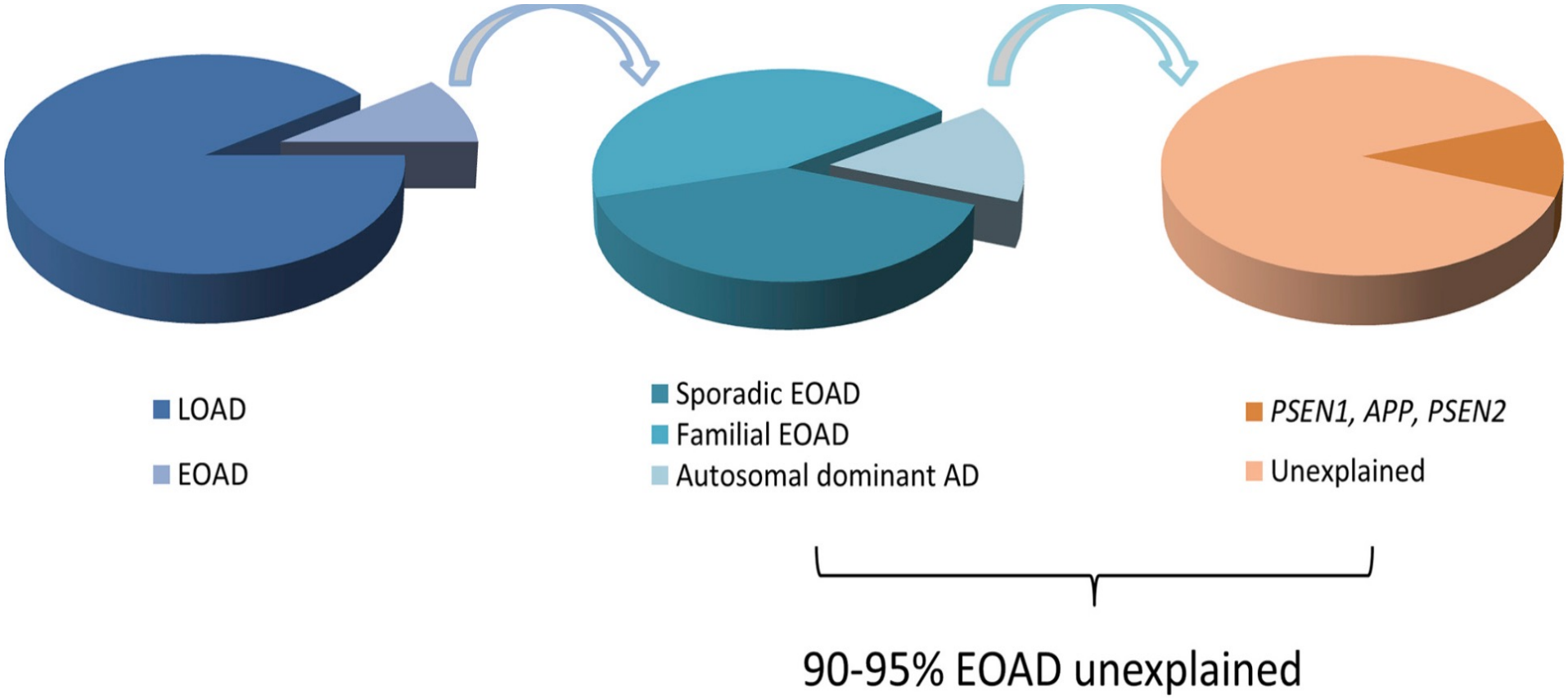
Part II

When to think zebra when you hear hoofprints…

When does genetic testing for dementia come to mind

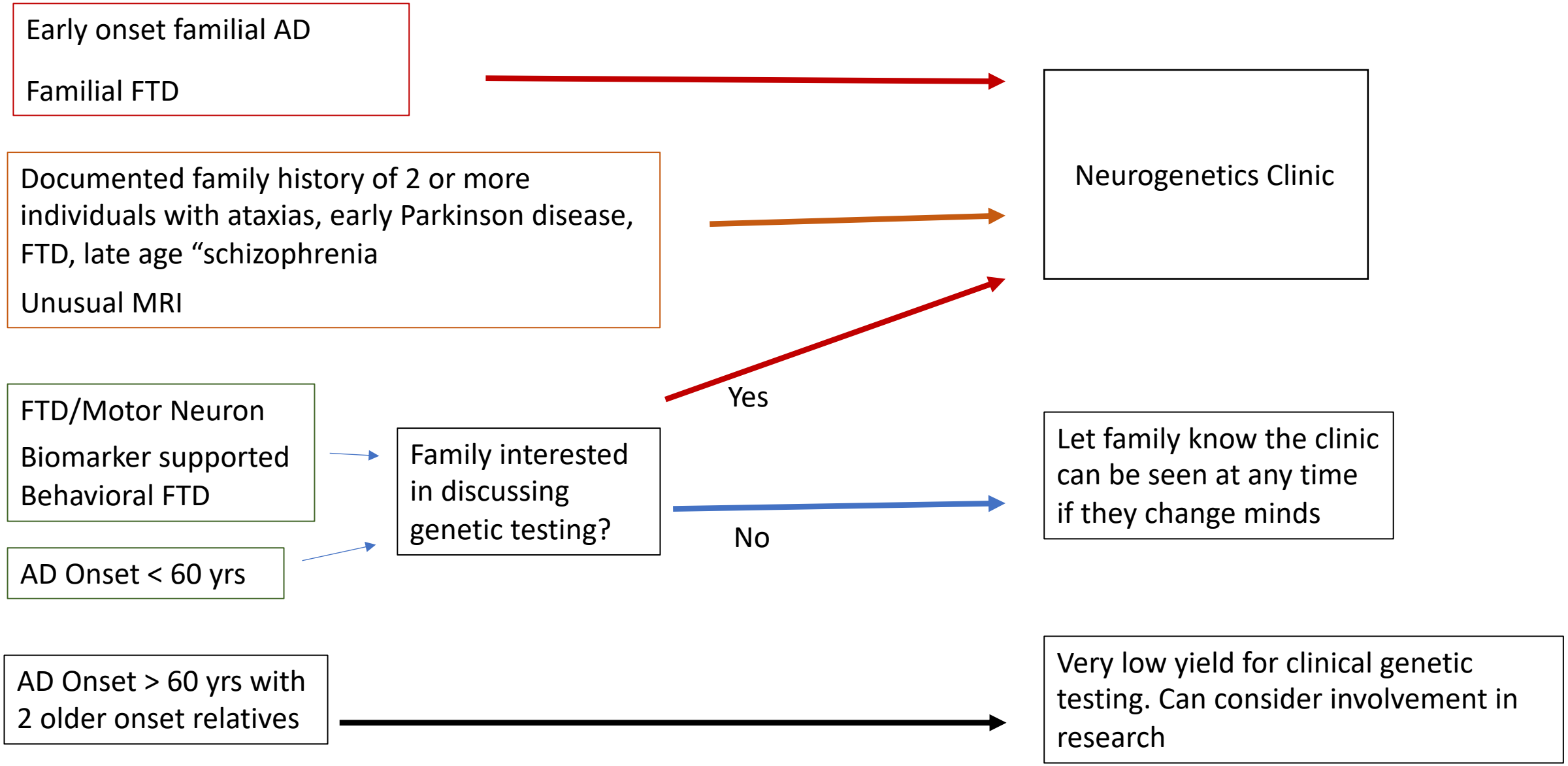
- Familial Early Onset Alzheimer
- Familial Frontotemporal Dementia
- FTD/Motor Neuron

Single gene Alzheimer Disease is Rare



Alzheimer Dem Cacace 2016

Suggested triage in dementia patient



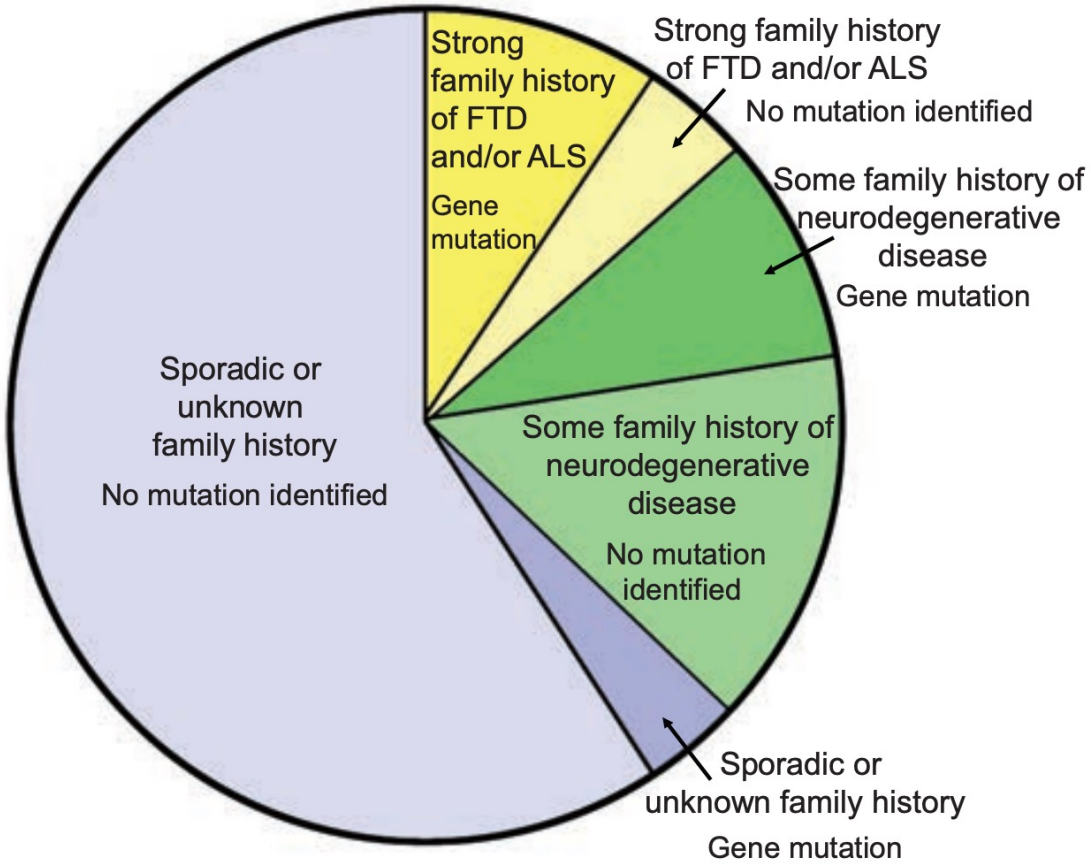
Sample Dementia/ALS Gene Panel

ALS2, ANG, ANXA11, APP, CHCHD10, CHMP2B, DCTN1, ERBB4, FUS, GRN, HEXA, HNRNPA2B1, ITM2B, KIF5A, MAPT, OPTN, PFN1, PRNP, PSEN1, PSEN2, SETX, SNCA, SOD1, SORL1, SPG11, SQSTM1, TARDBP, TBK1, TFG, TREM2, UBQLN2, VAPB, VCP

Alzheimer Disease, Frontotemporal Dementia, ALS, CADASIL, Prion Disease

AD like phenotype we start with Dementia Panel
FTD like phenotype we often start with C9orf72

Single gene Frontotemporal Dementia is Less Rare



10-15% of FTD have strong family history
Most have identifiable FTD gene

25% of FTD have some family history of neurodegenerative disease
Less than half of these will have identifiable FTD gene

60-70% of FTD have no or unknown family history
Less than 10% (6-8%) have identifiable gene

Part III

Choices in clinical gene testing

Single gene

MAPT ACTGCGTTACGGCTGAC**G**TT

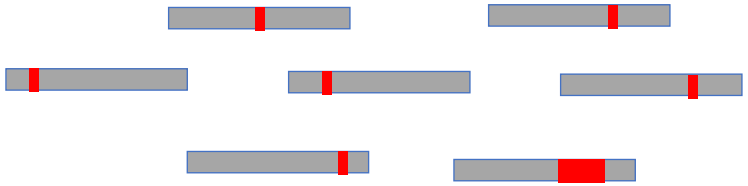
Single nucleotide mutation

C9orf72 ACTGCGTCAG**GGGGCCGGGGCC…GGGGCC**CAGCAGCAGCGTT

Nucleotide repeat

Gene Panels

Dementia panels
Hereditary Neuropathy
Limb-Girdle Muscular Dystrophy
Ataxia panels



Exons

*Does **not** get nucleotide repeat or duplication/deletion*
HD, C9orf72, DM, SCAs

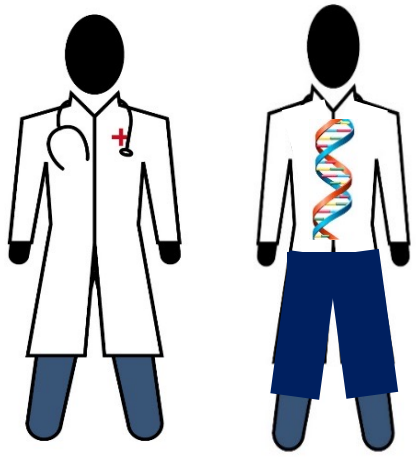
Whole Exome Sequencing

*Does **not** get nucleotide repeat or duplication/deletion*
HD, C9orf72, DM, SCAs

Chromosomes

What do we all want from genetic testing?

Diagnosis
Treatment
Understanding of Disease



Licensed Genetic Counselor

What do I have
How will this testing help me
Will I lose my job, my insurance
What about my kids, my family

Many individuals at risk for an autosomal dominant neurodegenerative disease choose NOT to do predictive testing

Things for patients to ponder

- How might testing influence my relationship with spouse/significant other? Relationships with friends and family?
- What are my coping strategies?
- Who is in my support network? Would it be helpful to meet with a professional counselor and/or spiritual support person?
- How might testing influence my short and long-term plans? Family planning decisions? Career decisions?
- What financial planning should be done prior to testing (such as life, disability, or long-term care insurance)?

What patients should know in advance

- Health insurance and employment protected by GINA
- Long term disability, life insurance NOT protected
- Implication to family members – children, siblings, parents
- Psychological consequences

- In neurodegenerative disease there is generally no significant change to medical management. (hopefully that changes!)

Genetic Counseling

Genetic Counselors earn Masters degree in Genetic Counseling and Licensure

- Important even in late adult-onset disease because of consequences to family
- Genetic counseling explores perceived risks/benefits to testing
- Counsels at results visit
- Very strongly recommended for predictive testing.

There is a current dearth of genetic counselors, but there are innovative genetic counseling services becoming more available if referral to a genetics clinic is not feasible

HD Genetic Testing Protocol

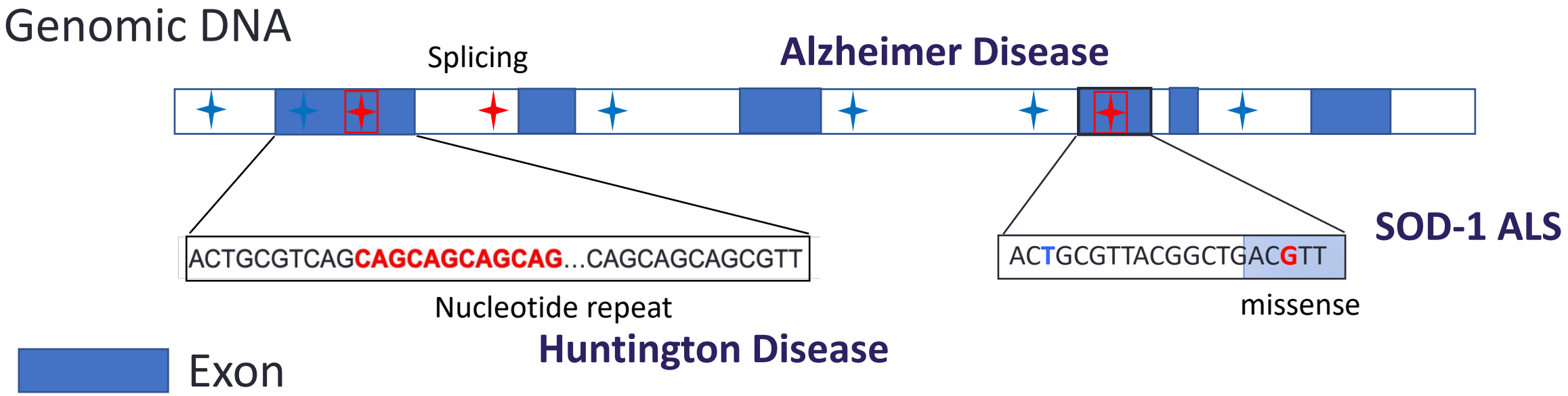
- Recommended Components of HD Predictive Testing Process:
  - **1. Telephone Contact**
  - **2. Visit 1**
    - Genetic Counseling
    - Sign Informed Consent Document
    - Mental Health Assessment
    - Neurological Exam
    - Draw Blood
  - **3. Visit 2**
    - Disclosure of Results in Person
    - Arrange Post-result Follow-up
  - **4. Follow-up**
    - Prearranged phone call or in-person visit

Thanks and call anytime!

Me: sumie@uw.edu

Debbie Olson, Clinic Manager: olsond@uw.edu

Genetic Variants



Rare disease variant

Typically found exome or linkage studies

Single Nucleotide Polymorphism (SNP): common

Substrate of Genome Wide Association Study (GWAS)

- **Exome variants are 1% of the genome:** single nucleotide, duplication, deletion variants in exons