Epidemiology of Huntington's Disease

Epidemiology 210
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Huntington's History

George Huntington's lecture and essay "On Chorea" is most credited and namesake of disorder. (1,2)

several physicians were describing similar hereditary disorders in the 1800's similar to Huntington's,

Chorea – Involuntary Movements

- Named “on account of the *dancing* propensities of those who are affected by it” (George Huntington 1872, “On Chorea”)(1)
- From ancient greek
- Later the disorder is further described more completely with cognitive and emotional disturbances that develop later in disease progression (2,12)

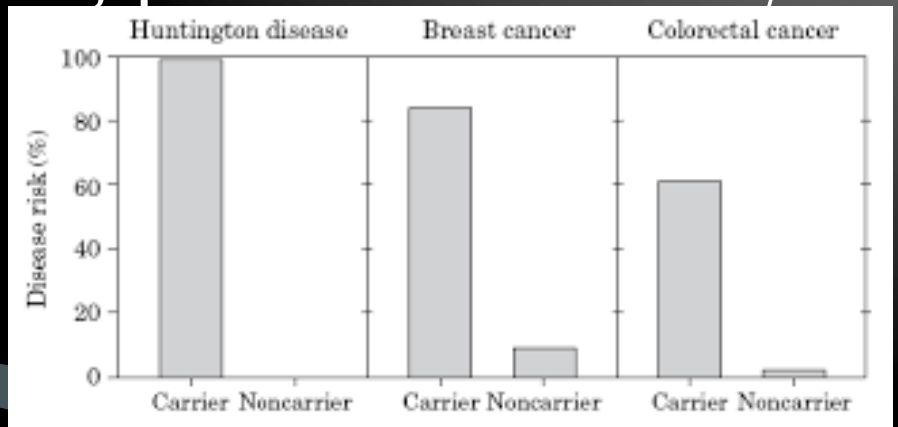
Definition of HD

- a hereditary disease marked by degeneration of the brain cells and causing chorea and progressive dementia.

- Gene for Huntington's discovered 1993. (12)

- Huntington's disease (HD)

autosomal dominant, parent to child 50/50



Descriptive Epidemiology

caused by a CAG repeat expansion
in the gene for
huntingtin protein
on chromosome 4 (8,13

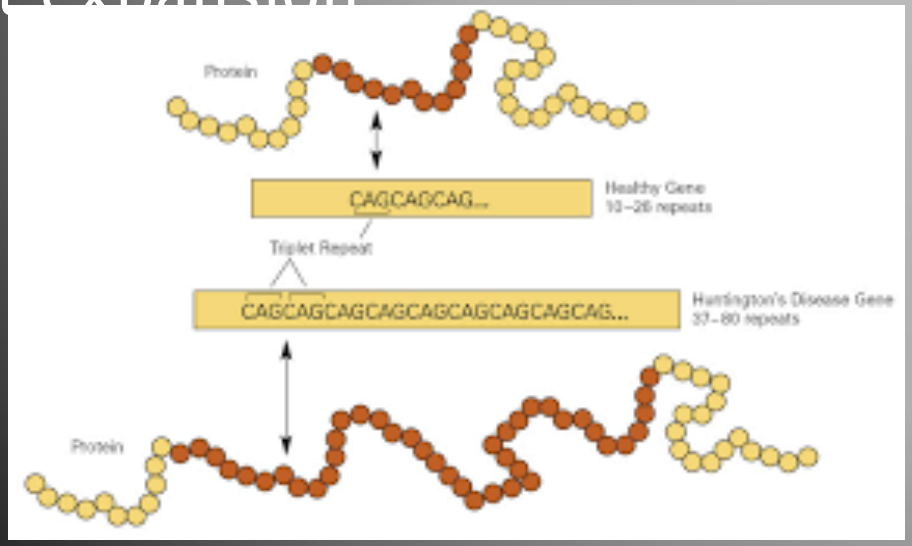


Image stanford HD blog

Prevalence is about 4-10 per 100 000 people in western countries, 1 in 25,000 at risk

About 50-70% of the variability in age of onset is due to CAG repeat lengths (12,13)

8% early onset (under 25) HD
4-25% late onset HD >65 years old
50-70% 25-50 (13)

Image stanford HD blog

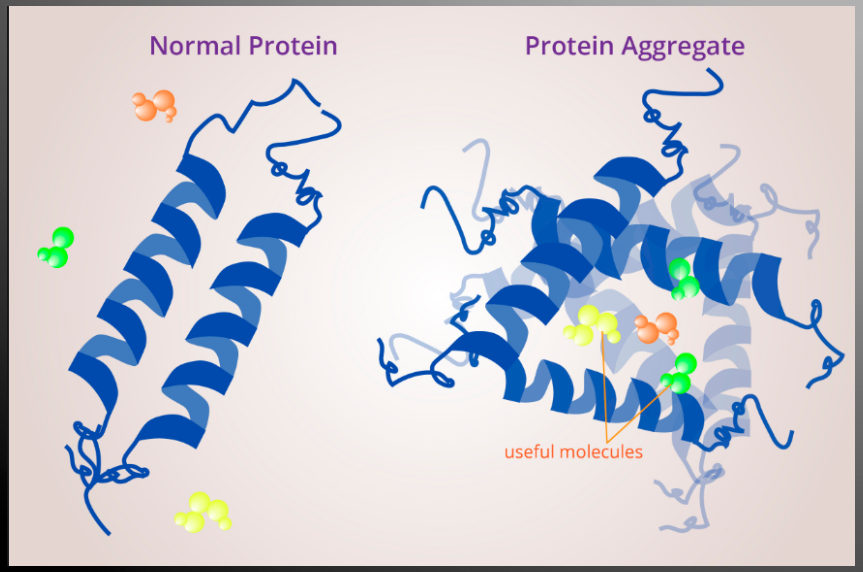
Molecular Epidemiology

- From protein aggregation blog

CAG repeat lengths of 40 and over are associated nearly 100% guarantee of symptom onset by age 65 years. (8)

Protein chains become to long and have exposed receptor Allowing aggregation of multiple HTT huntintin proteins

Neuronal death results



Stages of HD

Early / ProDromal – before symptoms and diagnosed through genetics only and sometimes family history. Late onset HD typically is missing family history (8, 13)

Manifest –motor cognitive and mood disorders apparent-

Late stage- severe impairment and institutionalization

Syptom Clusters of HD

Motor	Cognitive	Mood
Gait	Motor memory (driving, tying shoes)	Anger
Posture	Delayed recall	Depression
Tongue/mouth /chewing	Increased slowness	Suicidal Ideation
Incontinence	Attention	Anxiety
Eye tracking and pursuit	Executive tasks	Obsessiveness
Rigidity		Delusions
		Hallucinations
Reference 4,5,6,7		

Alzheimer's Disease Vs. Huntington's Disease Cognitive Skill Comparison

Table X-1: Comparison of Huntington's Disease & Alzheimer's Disease

Ability	Huntington's Disease	Alzheimer's Disease
Speed of processing	Slow, mostly accurate	Slow, often inaccurate
Speech output	Slurred & slow; accurate	Normal rate & clarity; often inaccurate
Learning new information	Disorganized & slow; can learn	Rapid forgetting; cannot store information
Free recall	Impaired: • cannot find the right words • can recognize with choices • benefits from cues	Impaired: • cannot recall memories • cannot recognize with choices • does not benefit from cues
Motor memory	Impaired: • cannot learn or recall motor memories	Impaired: • can learn & retain motor memories

1. Stevens at all and Stanford blog (1)

Method Issue: Assessment of Functional ability across all phases of HD

Why?

- To Test the effect of a medications and treatment
  - there needs to be a clear understanding of what early indicators of HD look like to show that symptoms can be changed across a population (5,6,10,16)
  - To predict onset of symptoms so families can plan after genetic testing. (3, 5,6,7)

General Problems

- Few cognitive tests or QOL "quality of life" assessments have been written and validated with large enough N (5,7)
- accuracy and reliability in HD versus other Neurodegenerative Diseases. (4,7)
- Relatively few longitudinal observational studies of HD but lately more registry and life course studies are ongoing (5)

Method Issue: Functional Assessments need more specificity

FAS 25: item scale example items found relevant to pre-HD symptomology

Could participant engage in gainful employment in his/her accustomed work?
Could participant engage in any kind of gainful employment?
Could participant manage his/her finances (monthly) without any help?
Could participant operate an automobile safely and independently?
Could participant engage in any kind of volunteer or non-gainful work?
Could participant shop for groceries without help?
Could participant use public transportation to get places without help?

TFC Total Functional Capacity 5 areas ranked 0-3

OCCUPATION: 3 = normal
2 = reduced capacity for usual job
1,0 = marginal work and unable
FINANCES: 3 = normal
2 = slight assistance
1,0 = major assistance and unable
ADL: 3 = normal
2,1,0 = minimal impairment and total care
DOMESTIC CHORES: 2 = normal
1,0 = impaired and unable
LEVEL OF CARE: 2 = normal

1 = minimal 0 = total care

Unified Huntington Disease Rating Scale (UHDRS)

stage I (least severe); 7–10, stage II; 3–6, stage III; 1–2, stage IV; and score of 0 is stage V (most severe).

- Assessments are great distinguishing stages of manifest HD in full onset -measurable change of .72 points /year in TFC) (6)

Problems with functional Assessment

- TFC and FAS pre symptom genetic carriers scored %88 on all longitudinal assessments (5,6)

- Length, specificity and training of test giver. Habituation and familiarity with test instrument (6,7)

Figure: Paulsen et al

Method Issue: Better prediction of onset after genetic testing

- Ceiling effect found
  - few indicators that correlated with approaching HD onset =occupational capacity and financial affairs(6)
- Solution? Other preHD assessment methods
- Biomarkers paired with functional deficit tests (Stout et al 2018) (7,14,10)
- Imaging – match structure to function (7,10)
- Better testing methods – caregiver vs. family vs. patient self report (7)
- More sensitive questions specific to HD (6,7)

Discussion

How would you improve functional assessment in HD?

What disorders could be mistaken for HD?

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