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HST.161 Molecular Biology and Genetics in Modern Medicine
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Lecture 13

Huntington's Disease

HD is a paradigmatic disease; affects more than just the strictly-HD population.

- not a huge public health problem, but in terms of clinical and basic research, this has been a very important disease in how it's illuminated various aspects of clinical and molecular neuroscience and genetics

Neurodegenerative disease: term reserved for disorders in which the brain starts out normally but gradually deteriorates. "Neurodegeneration" can occur after trauma, but this is not considered neurodegenerative disease.

- particular susceptibility of specific neuronal populations; in HD, is the medium spiny projection neurons of the caudate-putamen
- many ND diseases have familial forms
- common etiology may be misfolded proteins

History:

- 1872: George Huntington describes familial neurological disorder
- 1955: Amerigo Negrette graduated from medical school and sent to fishing village in Venezuela; found that everyone seemed to be stumbling around drunk. It was actually HD.
- 1972: Symposium in Columbus OH; someone showed a video of the people in Venezuela.
- 1979: Nancy Wexler leads expedition down to Venezuela.
- In the '80s and '90s, this population was used to isolate genes (and develop new techniques for doing so) involved in the disorder.
- 1999: first mouse model for *slowing* the progression of HD

Demographics:

- incidence: 4-10 / 100,000 (diagnoses of sporadic HD happen in about 10% of cases; usually, these patients are adopted or else there is some remote relation with HD; there are *very* few de novo cases)
- typically adult onset (but reports of onset much earlier and later)

Clinical Features

- triad of symptoms: movement, cognitive, psychiatric
- movement problems are most specific
- chronic: 15-20 years
- weight loss
- many die of aspiration pneumonia

Inheritance

- AD inheritance
- 10% of cases have juvenile phenotype (parkinsonian, rigid; often accompanied by seizures)
- Anticipation not common; when it does happen, about 90% is through paternal transmission

- New mutations seem to arise from “intermediate alleles”
- Homozygotes’ phenotype is no different from heterozygotes. Shows that this is a function-added mutation; one copy of the mutant protein does as much as all the proteins involved being mutant.

Pathology

(caudate putamen collectively known as striatum)

- death of the medium spiny projection neurons in the striatum → large cholinergic interneurons or medium aspiny neurons
- lesser involvement of other brain regions
- whole brain decreases in volume

Basal Ganglia circuitry:

Cortex projects to striatum, which loops back to cortex through the thalamus. Feedback loops go through basal ganglia, between striatum and thalamus – “direct” and “indirect” pathways. GABA is inhibitory; Glutamate is excitatory. [see “circuit” diagrams on slide – to note though, this diagram is wrong, somehow; we don’t know how, but it is. Overall though, it’s an OK first approximation for what’s going on]

Huntingtin protein isolated:

- chromosome 4, comprised of 67 exons
- ~350 kD
- No homology to other known proteins
- Function yet to be defined
- Huntingtin expressed in tissues throughout body; distribution in the brain not limited to striatum
- Knockout in mice causes embryonic lethality
- Heterozygote knockouts do not have HD (so again, this is **not** a loss-of-function disease). Some cell death reported in subthalamic nucleus and testes.
- Mutant versions of human huntingtin can rescue embryonic lethality in full knockouts

Mutant huntingtin has abnormally long polyglutamine moiety (CAG, or Q). Threshold effect of >39 CAG repeats required for pathology; number of repeats also helps determine age of onset (more repeats = younger onset).

- the larger the repeat, the harder it is to transmit in meiosis

HD fits into a family of CAG-repeat disorders

- all AD inherited disease
- all neurological
- adult-onset, progressive deterioration of particular neuronal subsets
- disease threshold repeat count is >37
- higher number of repeats correlates to earlier age of onset
- toxic mechanism of polyQ moiety is unknown
- the affected proteins are all different from each other; even the mutated forms don’t resemble each other, but they are caused by the same type of mutation

HD and aggregates

- neuronal intranuclear inclusions (NII)
- NII comprised of ubiquitinated N-terminal fragments of huntingtin, as well as heat shock proteins, proteasome subunits, and txn factors.
- Protein aggregates are hallmarks of all neurodegenerative disease, raising the possibility that ND disorders are disorders of protein catabolism.
- Role of NII unclear; seems like they would be bad for the neurons, but they could be a neuronal response to something else.

HD Pathological Mechanisms

(see slides for full list)

Ultimately, we don't know what's really going wrong in HD.

Dr. Cha studies transcriptional dysregulation in particular; not because he thinks it's the most likely suspect, but because he can only investigate so much at once.

- based on theory that huntingtin, like other Q-containing proteins, is a transcription factor and nuclear localization is altered in HD; so, does mutant huntingtin mess with transcription?
- Pattern of altered gene expression is more localized to neurons, rather than other parts of the body or any kind of systemic pattern.
- Nuclear aggregates in neurons might change transcription somehow, and/or free huntingtin, or huntingtin bound to transcription factors, might change transcription
- As to whether aggregates (inclusions) are good or bad, in his research he's found that neurons with inclusions don't seem to be any better or worse off than neurons without inclusions. There may be differences between large, useless inclusions and smaller inclusions that are actually interfering with things.

Histones can be "activated" by acetylation, which changes structure of chromatin, allowing genes to be transcribed. This is called "open DNA" – maybe there is an abnormality here, too?

Clinical: Initial workup

- take a detailed history; family history of HD? Behavioral history: depression, suicide, OCD, psychosis. Motor abnormalities. Cognitive difficulties like inability to multitask or concentrate.
- Motor exam: presence of involuntary movements, etc.

HD therapeutics

- currently, no effective therapies
- we do have treatments for the symptoms, like motor and mood symptoms
- motor: benzodiazepines
- psychiatric symptoms treated the same way as in non-HD patients
- cognition: difficult to treat; one of the most disabling symptoms.

Dr. Housman's lecture

Simple sequence repeats

Other repeat diseases:

- CGG repeat (Fragile X)
- CAG repeat (HD; Machado-Joseph; spinocerebellar ataxia, etc)
- GAA (Friedrich's ataxia)
- CTG (myotonic dystrophy)

Genetic anticipation: disease symptoms become worse or age of onset gets earlier as a disease gene is passed from generation to generation