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Huntington's Disease: A Timeline

Brian Kerlin

University of Nevada, Las Vegas, kerlin@unlv.nevada.edu

Brandon Polimeni

University of Nevada, Las Vegas

Michaelangelo Ortega

University of Nevada, Las Vegas

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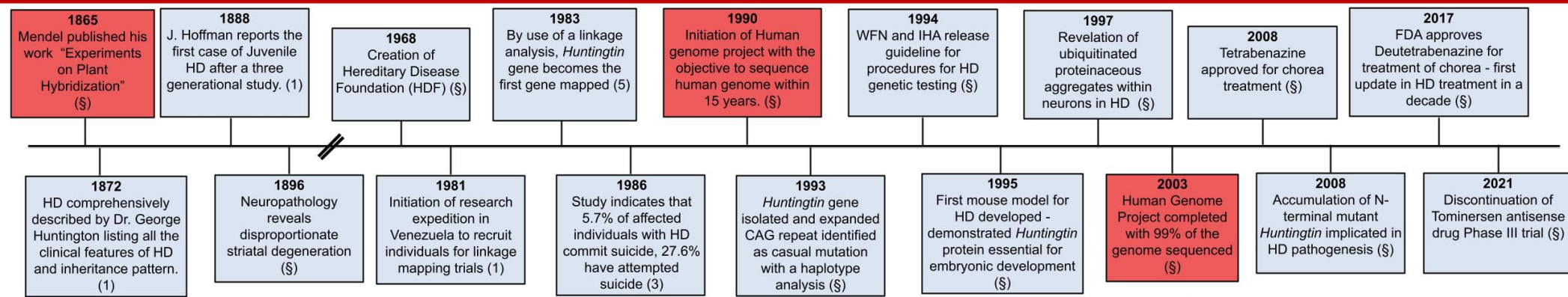
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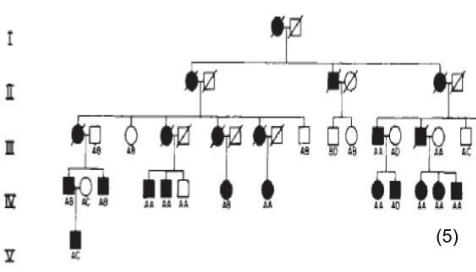
Huntington's Disease: A Timeline

Brian Kerlin, Michaelangelo Ortega, Brandon Polimeni



Inheritance of HD

- **Single-gene**, autosomal **dominant** disorder (1)
- **GOF** mutations of *huntingtin* gene on chromosome 4
- **Pedigree** used in **linkage analysis** during localization of HD gene locus (5)
- Males at elevated risk of transmitting **de novo mutation**
 - **high normal** (27-35 CAG Repeats) - between 1/1000 and 1/6000 chance having penetrant offspring (6)
- Complete **Penetrance** if more than 40 CAG Repeats
 - Partial Penetrance Between 36 and 40 Repeats



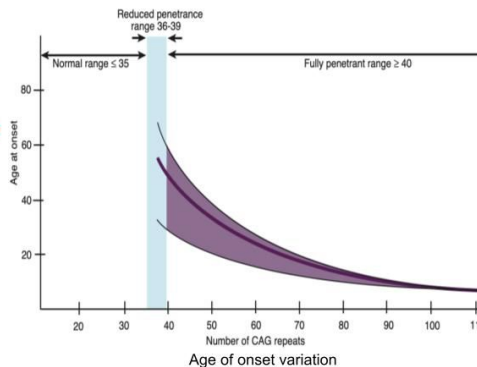
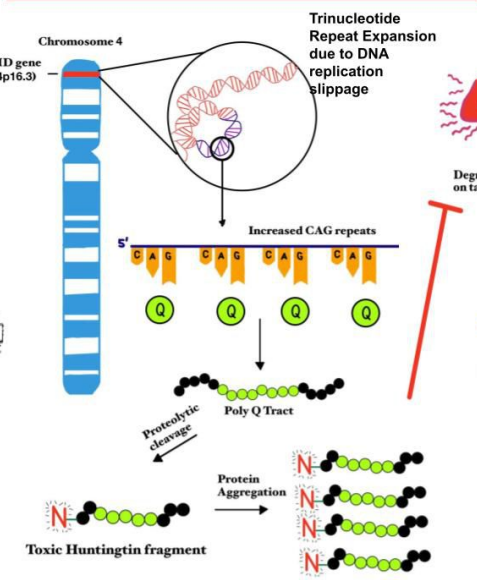
Population data

- **Prevalence** - globally 2.70 per 100,000 (8)
 - In USA, Australia, Europe - 5.40 per 100,000
 - compared to 0.40 per 100,000 in Asia
 - Lake Maracaibo, Venezuela - 700 per 100,000 (18)
- Average PolyQ region is larger in European vs. African and Asian populations leading to a higher **incidence**. (8)
- Distribution of Hardy-Weinberg: **Founder Effect Assortative Mating, Limited effect on fitness**

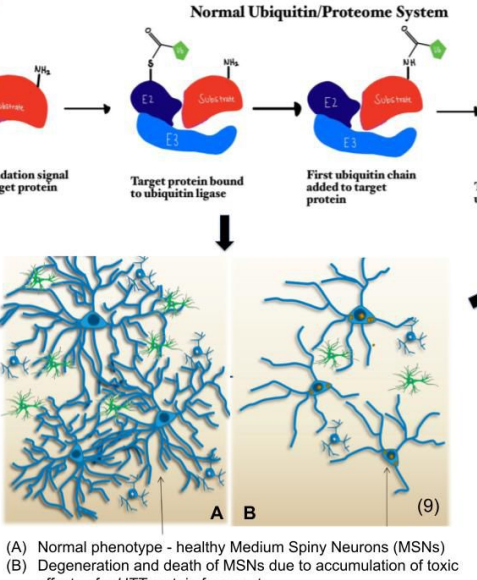
Variation of HD

- Most individuals with HD exhibit similar clinical symptoms
 - **Variable Expressivity**: variations with onset, progression, range in extent of psychiatric decline
- Number of CAG Repeats inversely correlated with age-of-onset
 - Juvenile HD - individual with > 70 Repeats
 - Notably, CAG Repeat Length accounts for ~56% of variability in age (20)
 - **Heterogeneity**: Variation in phenotype due to possible **modifier genes**, unquantified allelic heterogeneity, and environmental effects (2)

Molecular Mechanism

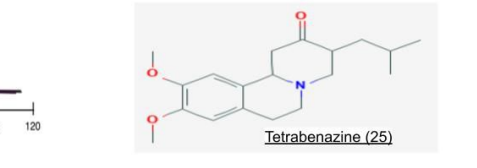


Cellular Mechanism

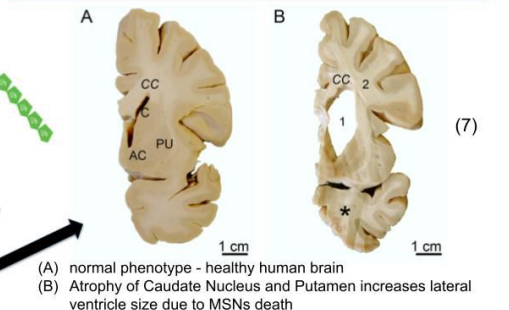


Treatment of HD

- The most common treatments:
 - palliative care, counseling, managing choreic motion, and treatment of depression (1)
 - FDA approved medication (subsides choreic motion)
 - tetrabenazine (Xenazine™) (11)
 - Monoamine vesicular reuptake inhibitor



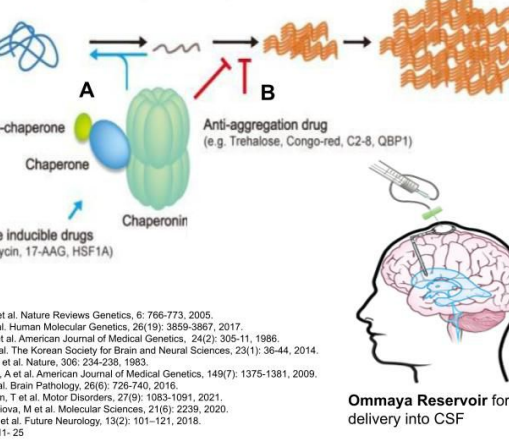
Neuropathology



Future Research Direction

- Mutant *huntingtin* aggregation prevention via **small molecule therapy** (4, 10)
 - **A** - Inducement of proper protein folding
 - **B** - anti-aggregation agent
 - Potential delivery via Ommaya Reservoir to lateral ventricle
- Main Funding Agencies: CHDI, NIH, HDSA (\$)

Protein Folding and Aggregation



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