From Guidelines to Action: Movement Disorders Care Through Regional & Multidisciplinary Collaboration

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International Parkinson and Movement Disorder Society Pan American Section

In collaboration with: Baptist Health



Updates in Huntington Disease

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curePSP | CENTER OF CARE

MSA CENTERS OF EXCELLENCE

Disclosures

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Overview

- HD discovery, epidemiology
- Features and diagnosis
- Genetics, pathophysiology
- Differential (look-alikes)
- Treatment: current and future



https://www.nytimes.com/2020/03/10/health/huntingtons-disease-wexler.html

HD Milestones



1872
George Huntington's paper published

Venzuela project initiated by Nancy Wexler
1981

1983
HD gene mapped to short arm Chr 4 (Gusella et al, 1983)

1993
HD gene isolated and CAG repeat mutation identified
(HDCR Group, Cell 1993)

1994
Htt protein identified

1996
First HD mouse model described
(Mangiarini et al, Cell 1996)

1997
Aggregates in mouse model and patient brains (Davies et al, DiFiglia et al)

2003
CARE-HD:
First phase III trial testing coenzyme Q10, remacemide

2006
PREDICT-HD:
Prospective observation HD study with DNA testing, MRI (Paulsen et al, Arch Neurol)
2006

2006
Tetrabenazine for chorea published by HSG (Neurology)

2010
CRISPR-Cas9 genome editing described (Ishino et al, 2009; Barrangou et al, 2010)

2015
ENROLL-HD:
Worldwide observational study, European HD registry

2016
2CARE: High-dose coenzyme Q10 in HD

2018
IONIS-HTTRX): First Phase 1/2 test of ASO targeting HTT

2020
ASO trials:
PRECISION-HD:
RG6042
(Roche/Genentech),
WAVE-001/2

AAV-miRNA:
uniCure,
Voyager Therapeutics

2022
HD-ISS:
staging system (Tabrizi et al.)

Small molecule inhibitors:
VIlBRANT-HD
PTVOT-HD
(PTC518/voltaplam)

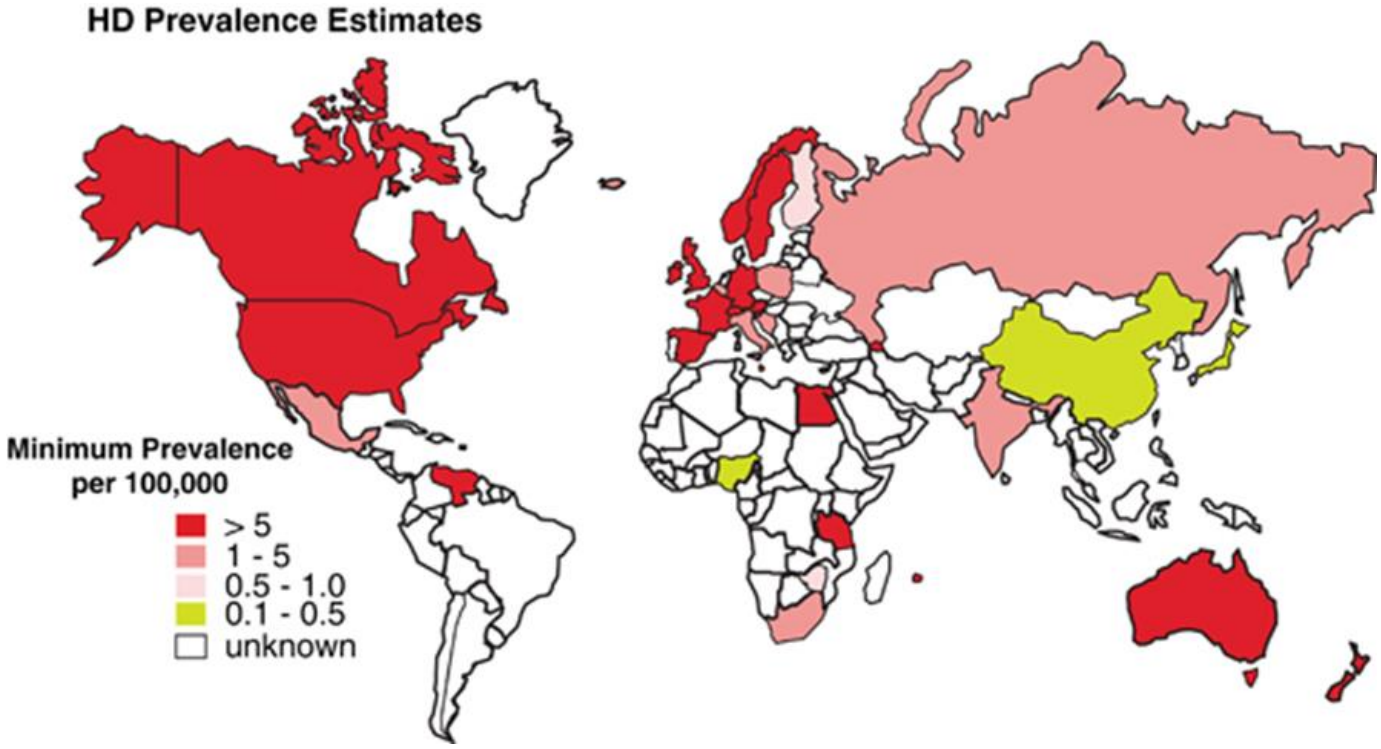
2025
ENROLL-HD 2.0:
based on HD-ISS cohorts

UFHealth | NORMAN FIXEL INSTITUTE for NEUROLOGICAL DISEASES

Modified: Bates, *Nature Rev* 2005

Epidemiology

- Multiple origins
  - Europe, Japan, Africa
  - Non-HD allele to HD
- Estimated prevalence
  - Worldwide 2.71 per 100,000
  - Mexico ~4 per 100,000
  - Lake Maracaibo, Venezuela – 560/100,000 (Harper, 1992)
- "Dancing mania" of Maracaibo in 1950s, led to discovery of HD gene



Warby et al, European Journal of Human Genetics (2011) 19, 561–566; doi:10.1038/ejhg.2010.229; published online 19 January 2011

Onset and Progression

- Typical onset in 30-50s (10% juvenile-onset, before 21)

Prodromal phase

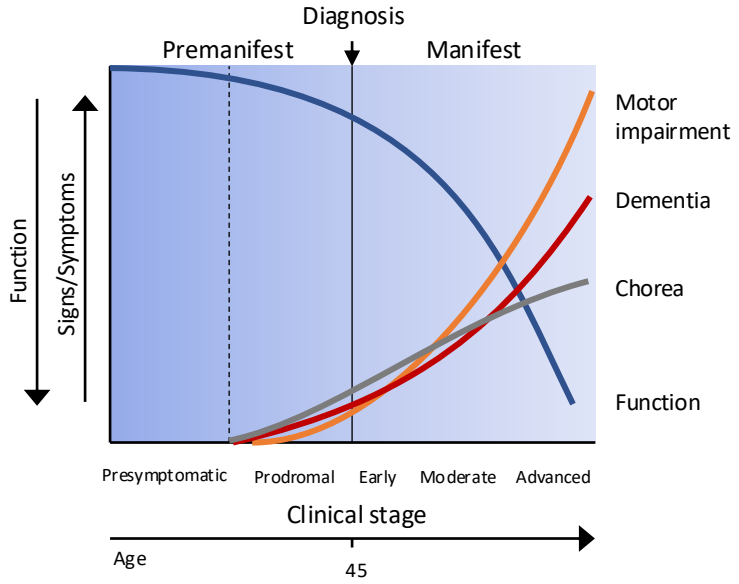
- mild neurobehavioral/cognitive changes, but able to work, perform all ADLs

Manifest disease

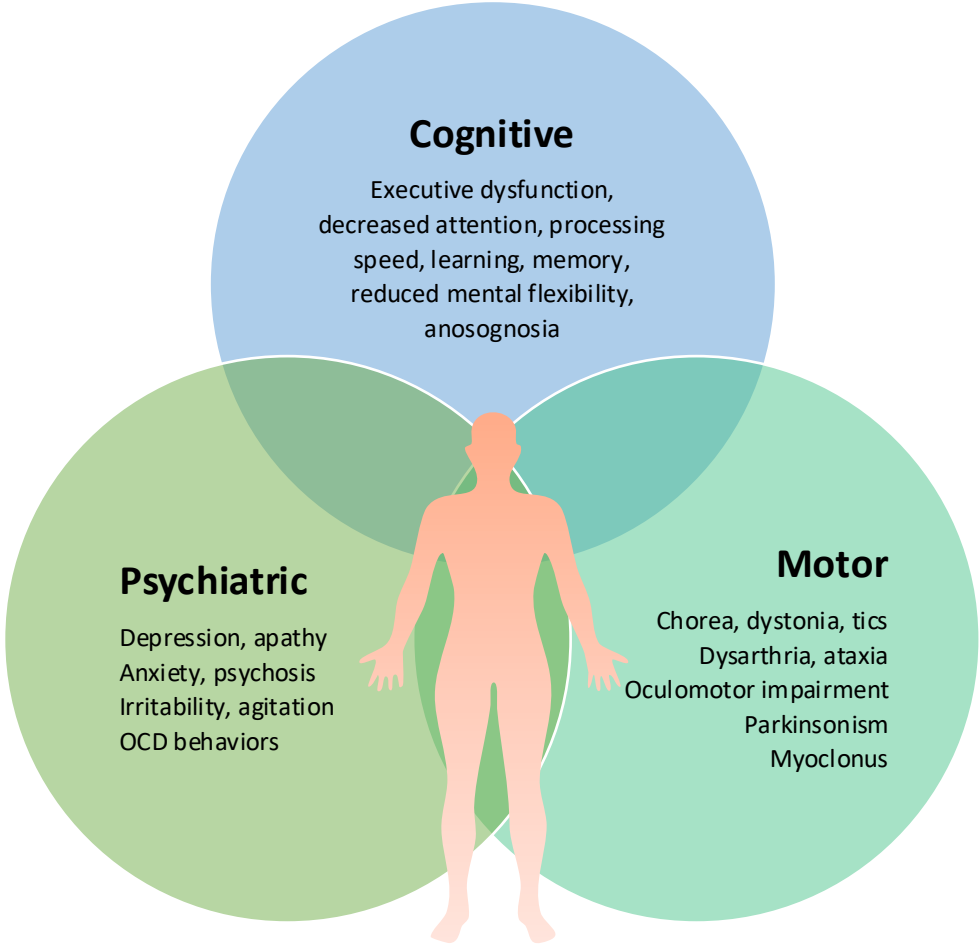
- Mild-moderate motor features (chorea, poor coordination, gait difficulty), mild impairment ADLs

Moderate-advanced disease

- marked motoric disability, functional dependence, dementia



From: Bates et al, Nat Rev 2015



HD Symptom Triad

HD Motor features

- Hyperkinesia
  - Chorea (adult-onset)
  - Dystonia, bruxism
  - Ataxia, incoordination
  - Myoclonus
  - Tics/Tourettism (rare)
- Rigidity, bradykinesia
- Motor impersistence – tongue protrusion, “milk-maid” grip
- Hung-up, pendular reflexes
- Gait imbalance, falls
- Dysarthria, dysphagia
- Impaired saccades, eye movements

Non-motor

Fatigue	Poor sleep
Muscle pain	Sexual issues
Weight loss	BP/HR variability

Juvenile(-onset) HD

- About 10% HD cases onset before age 21 (<5% childhood onset)
- Usually inherited from father (anticipation)
- 54% JHD have >60 CAG repeats
- JHD symptoms:
  - Developmental regression, dementia
  - Sleep difficulty, tics, pain, itching
  - Psychosis, visual hallucinations > delusions
  - Progressive rigid-bradykinesia (poor levodopa response)
  - Ataxia
  - Seizures >25% (presenting feature <15%)
- Motor onset 34.5%, psychiatric/behavioral 65.5%
- *LOMARS* – hypomorph compound heterozygous *HTT*

HUNTINGTON'S DISEASE YOUTH ORGANIZATION

Care for JHD

- Symptomatic treatment
- Focus on motor, cognitive, behavioral, functional
- Psychiatric care, counseling
- Supportive: PT, OT, SLP
- Involve school, develop IEP, educate

HD: Neurobehavioral/Neuropsychiatric

- Often precede motor sx's by years (prodromal)
- Challenging, overlap neurological and cognitive, vary in severity, frequency
- Comprehensive assessment
  - Medical history
  - Current symptoms
  - Medication use
  - Psychosocial factors

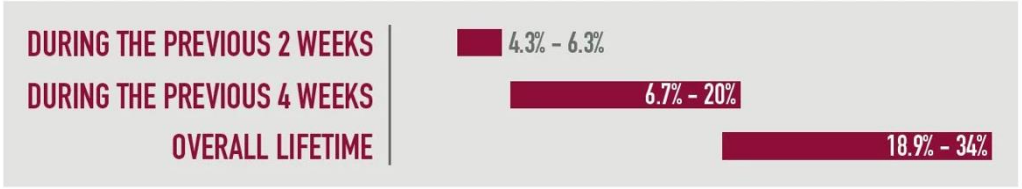


Fedoroff et al, 1994; Litvan et al, 1998; Paulsen et al, 2001

HD: Affective disorders

- Depression/bipolar,
  - One of the earliest symptoms, not related to CAG repeat
  - Estimated prevalence 9-63%, but most suggest 40-50%
  - Suicidality (5-10%) – 4-6X higher than general population!
  - Benzodiazepine use a independent risk factor for suicide
- Mania – less common (4.8%)
- Apathy, withdrawal – common (52-76%)
- Anxiety/panic disorder (17-61%)
- Obsessive-compulsive behavior (7-50%)
- Psychosis: delusions, paranoia, hallucinations, euphoria

Figure. Suicidal Ideation in Individuals With HD



HD: Psychotic Symptoms

- Delusions > hallucinations prevalent in HD (opposite in JHD)
- Differential diagnosis:
  - Comorbid schizophrenia or schizoaffective disorder
  - Infection
  - Metabolic
  - Drug/substance use
  - Other medical, SDH
  - Perseverative symptoms (fixated, repetitive, no tangible goal)

Risk factors:

- Lower CAG
- Lower socioeconomic status
- Lower TFC
- Prior psychiatric hx

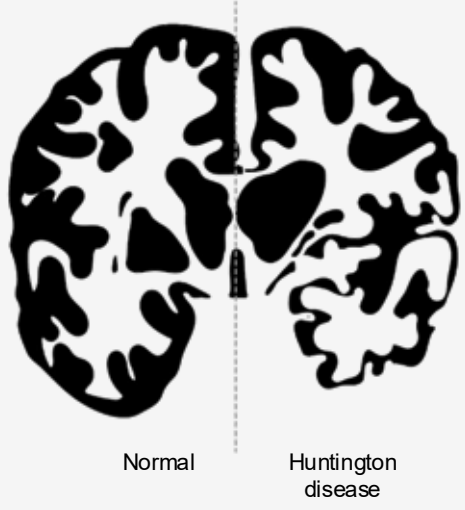
HD: Neurobehavioral changes

- **Dysexecutive syndrome**
- Personality change, mental inflexibility, perseveration, restlessness
- Social withdrawal, indifference, demoralization, sexual disorder (low vs high)
- Disinhibition, impulsivity
- Irritability/aggression
- Antisocial behavior, hostility
- Substance abuse, alcohol use disorder
- Lack of insight or self-awareness (anosognosia)
- Sleep disorders (~90%) – insomnia, nocturnal awakenings, EDS

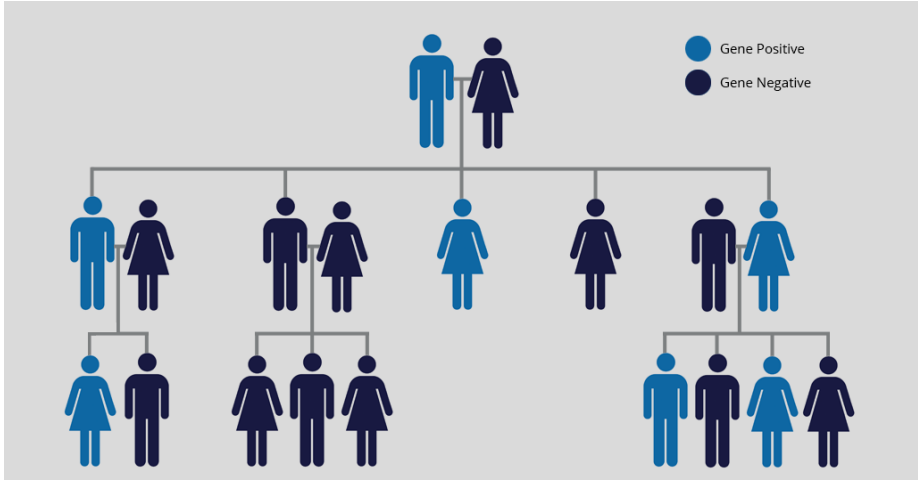
HD Genetics and pathophysiology

- Genes, protein aggregates, neuropathology





HD inheritance



Autosomal dominant w/ 100% penetrance

50/50 chance for all offspring

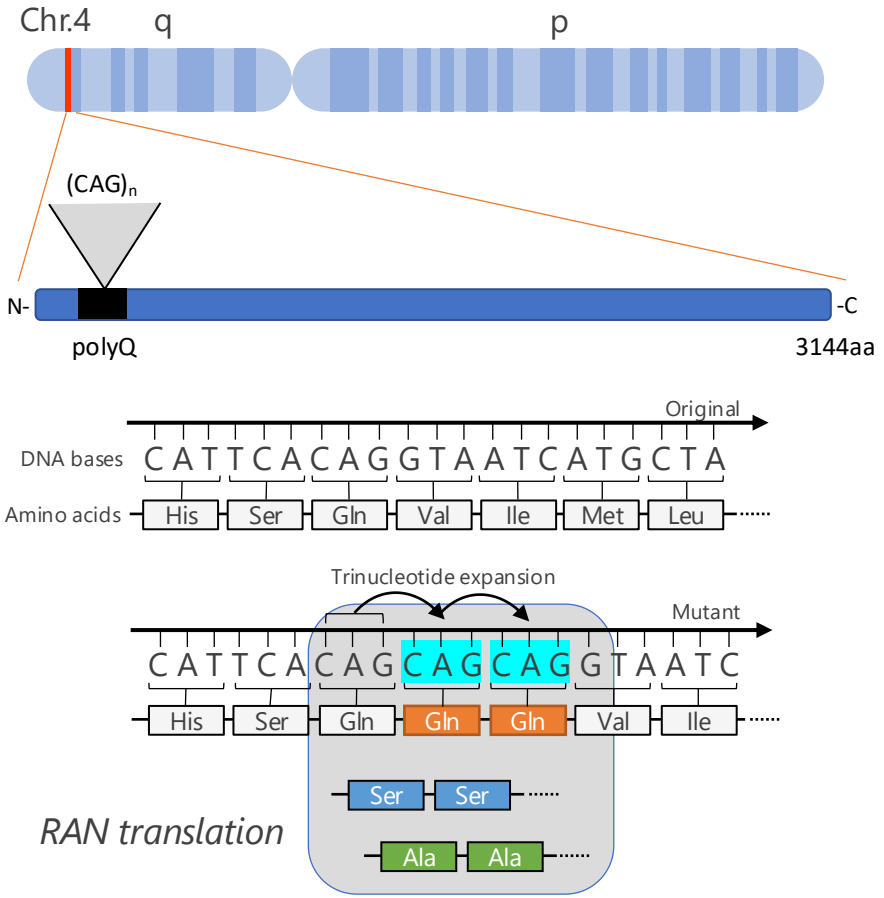
HD Genetics

HD gene (*HTT*) localized to Chr 4

Mutant gene cloned in 1993

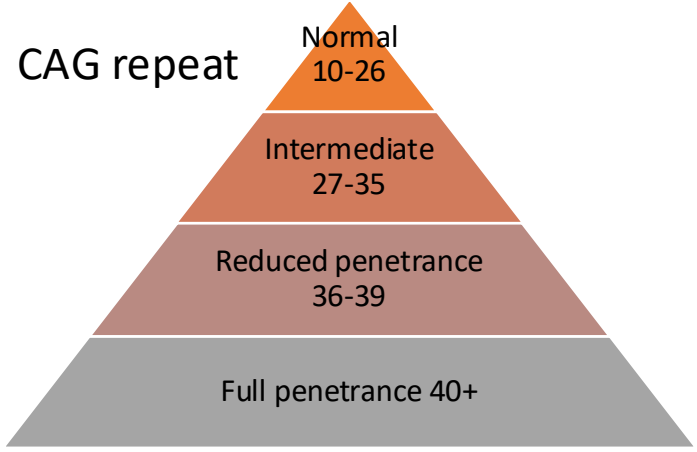
Large gene with 67 exons!

- HTT function unclear
- CAG repeat expansion in exon 1
- polyglutamine repeat



Genetics cont.

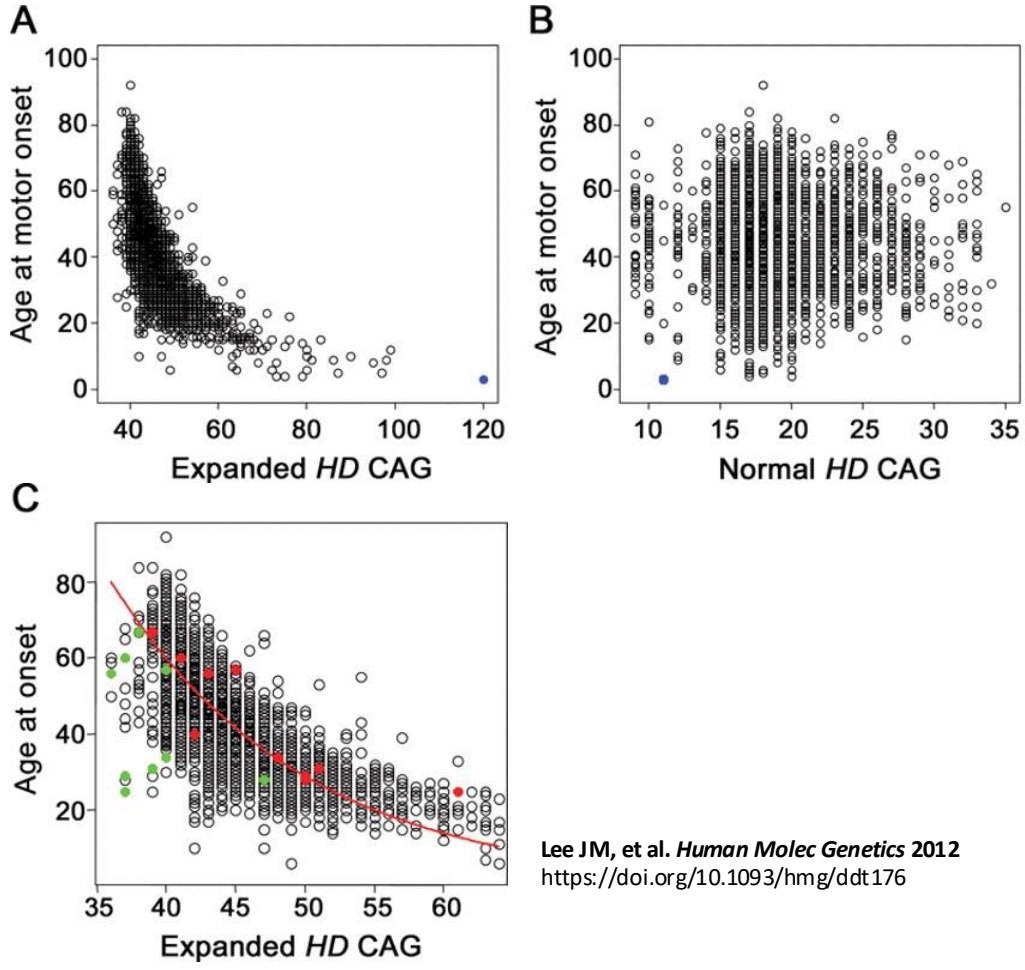
- CAG repeat



- Anticipation – paternal

	Paternal	Maternal
Age onset parent	41.2±11.9	41.5±11.2
Age onset offspring	33.5±13.3	40.0±11.1
CAG parent	45.0±3.5	46.4±4.8
CAG offspring	49.0±8.8	46.5±6.0
CAG change	**4.0±7.7**	**0.2±3.9**

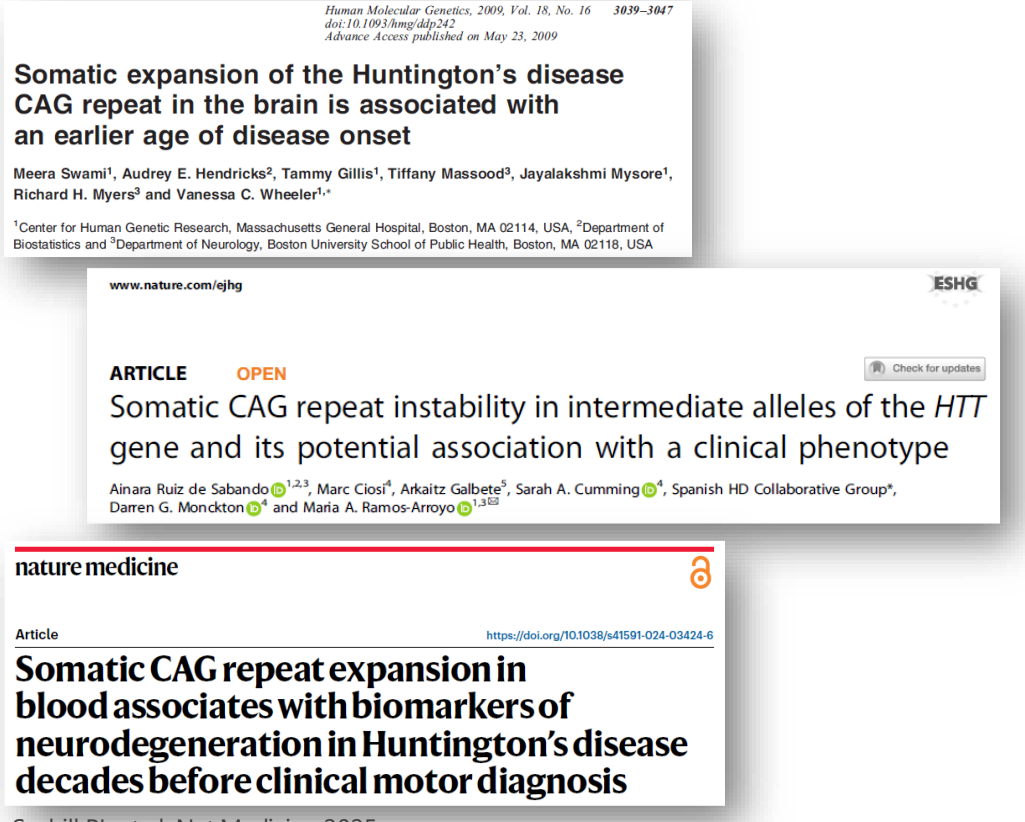
Ranen NG et al. Am J Hum Genet. 1995 Sep; 57(3): 593–602



Lee JM, et al. *Human Molec Genetics* 2012
https://doi.org/10.1093/hmg/ddt176

HD Genetic modifiers

- Age of disease onset has primarily been determined by the length of the CAG repeat expansion, but…
- Influenced by modifying factors:
  1. Stress, environmental exposures – none specific identified
  2. Genetic modifiers – multiple
  3. Somatic instability of the CAG expansion (that accelerates pathology)



Human Molecular Genetics, 2009, Vol. 18, No. 16 3039–3047
doi:10.1093/hmg/ddp242
Advance Access published on May 23, 2009

Somatic expansion of the Huntington's disease CAG repeat in the brain is associated with an earlier age of disease onset

Meera Swami[1], Audrey E. Hendricks[2], Tammy Gillis[1], Tiffany Massood[3], Jayalakshmi Mysore[1], Richard H. Myers[3] and Vanessa C. Wheeler[1,*]

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www.nature.com/ejhg ESHG

ARTICLE OPEN

Check for updates

Somatic CAG repeat instability in intermediate alleles of the *HTT* gene and its potential association with a clinical phenotype

Ainara Ruiz de Sabando[1,2,3], Marc Ciosi[4], Arkaitz Galbete[5], Sarah A. Cumming[4], Spanish HD Collaborative Group*, Darren G. Monckton[4] and Maria A. Ramos-Arroyo[1,3]

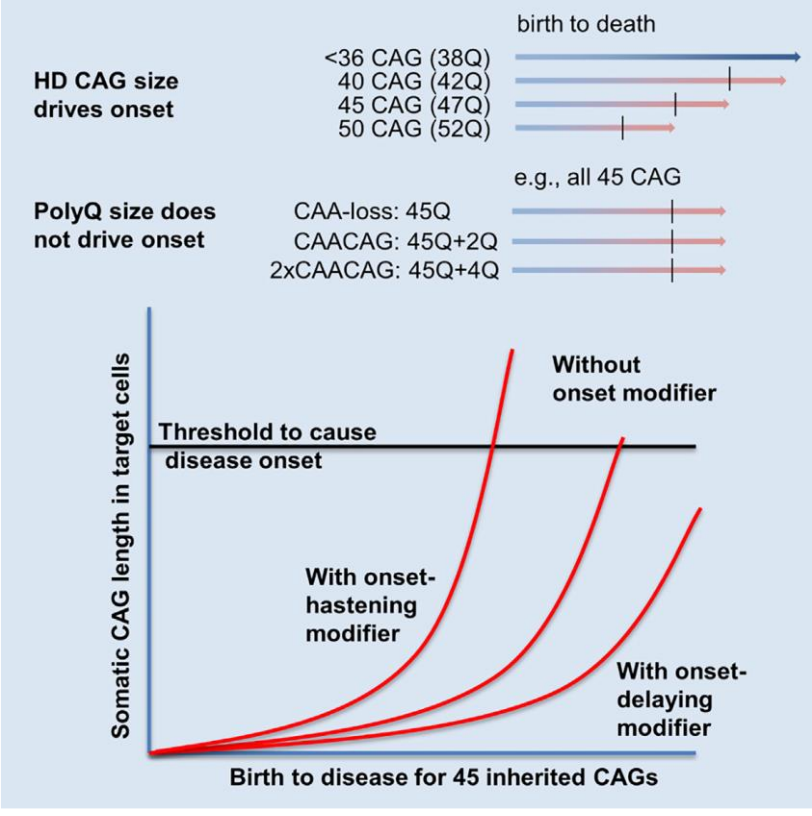
nature medicine

Article https://doi.org/10.1038/s41591-024-03424-6

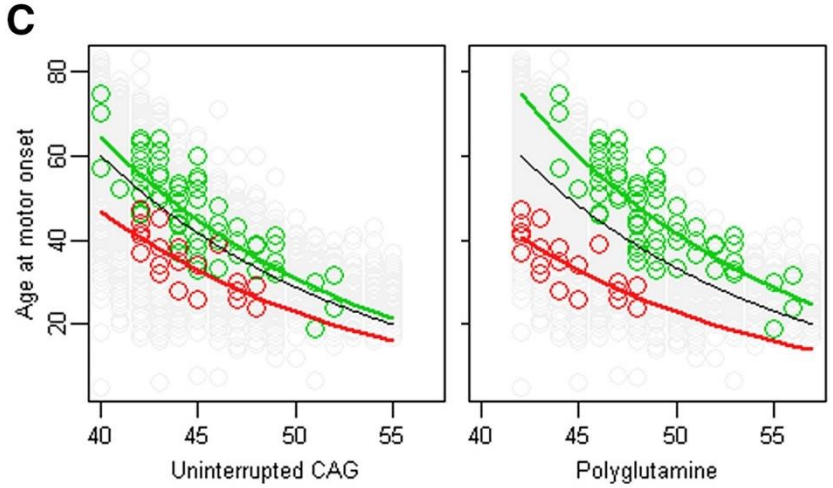
Somatic CAG repeat expansion in blood associates with biomarkers of neurodegeneration in Huntington's disease decades before clinical motor diagnosis

Scahill RI, et al. Nat Medicine 2025

HD: Genetic modifiers



- 95% carry an uninterrupted CAG repeat followed by CAACAG
- Loss of CAA-interruption (red): pure, unstable CAG tract, leading to symptom onset **up to 10 to 20.4 years earlier** than predicted
- CAACAG-duplication (green) can **delay onset by 5**



GeM-HD Consortium. Cell 2019. https://doi.org/10.1016/j.cell.2019.06.036

HD: Genetic modifiers

Expansion-promoting
(faster somatic CAG expansion, earlier onset)

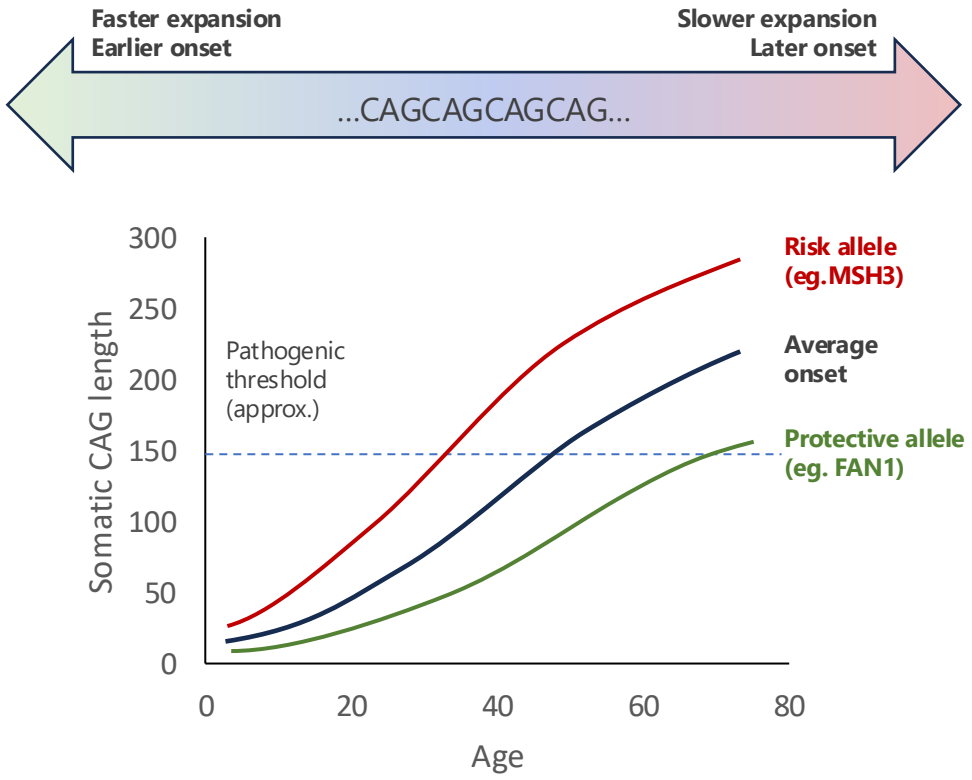
- **MSH3**
- **PMS2**
- **MLH1**
- PMS1
- MLH3
- MSH2
- MSH6

Protective modifiers
(slower somatic CAG expansion, later onset)

- **FAN1**

Other
(emerging/additional effects)

- TCERG1
- RRM2B
- POLD1
- RAB3B/ZFYVE9
- RRM2B
- LIG1



CAG somatic expansion

Cell

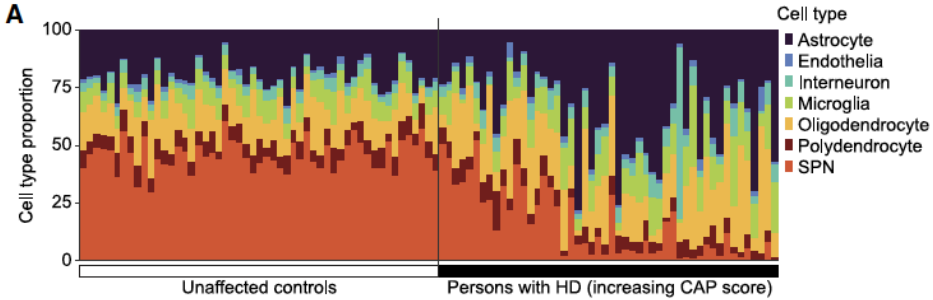
CellPress
OPEN ACCESS

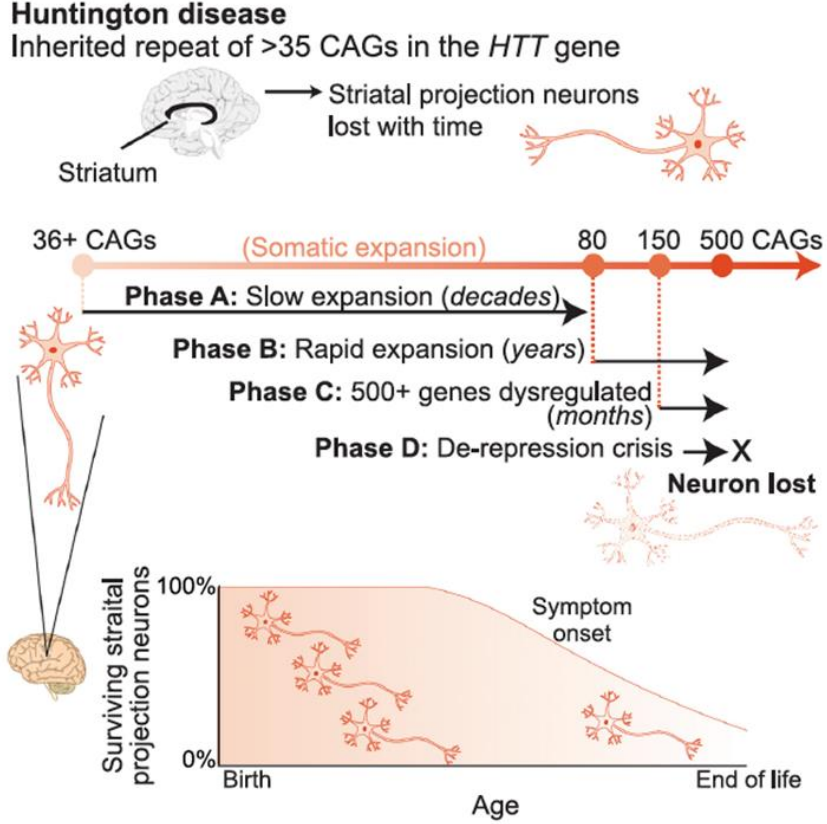
Article

Long somatic DNA-repeat expansion drives neurodegeneration in Huntington's disease

Robert E. Handsaker,[1,2,7,*] Seva Kashin,[1,2,7,*] Nora M. Reed,[1,2,7] Steven Tan,[1,2] Won-Seok Lee,[1,2] Tara M. McDonald,[1,2] Kiely Morris,[3] Nolan Kamitaki,[1,2] Christopher D. Mullally,[1,2] Neda R. Morakabati,[3] Melissa Goldman,[1,2] Gabriel Lind,[1,2] Rhea Kohli,[1,2] Elisabeth Lawton,[3] Marina Hogan,[1,2] Kiku Ichihara,[1,2] Sabina Berretta,[1,3,4,5,8,*] and Steven A. McCarroll[1,2,5,6,8,9,*]

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https://doi.org/10.1016/j.cell.2024.11.038





HD Diagnosis and treatment

- Diagnostic Criteria, look-alikes, testing



Clinical Evaluation

- Physical and neurological exam
- Unified HD Rating Scale developed in 1996 (HSG), updated UHDRS'99
  1. *Motor (eye movements, speech/swallow, chorea, dystonia, parkinsonism, gait) 0-4 rating
  2. Cognitive (verbal fluency, symbol-digit modalities, and Stroop interference tests)
  3. Behavioral (0-88 scale)
  4. Functional: Independence (0-100), ADLs (25 yes/no questions), TFC (0-13 scale)
- Short version (1997) by CAPIT-HD
- cUHDRS and video, vUHDRS validated

A. *Diagnostic confidence level (DCL)
0 – normal
1 – not quite normal, but nonspecific (<50%)
2 – possibly HD-related, but not sure (50-89%)
3 – probably HD, reasonably sure (90-98%)
4 – unequivocal HD (≥99% confidence)

B. Q80 diagnostic criteria
Based on entire UHDRS (Motor, Cognitive, Behavioral, and Functional) does the participant have manifest HD (0=no, 1=yes)?

Kieburtz K, *et al. Mov Dis* 1996, Schobel SA, *et al. Neurology* 2017, Frank S.. *Mov Dis (Suppl)* 2023

Genetic testing

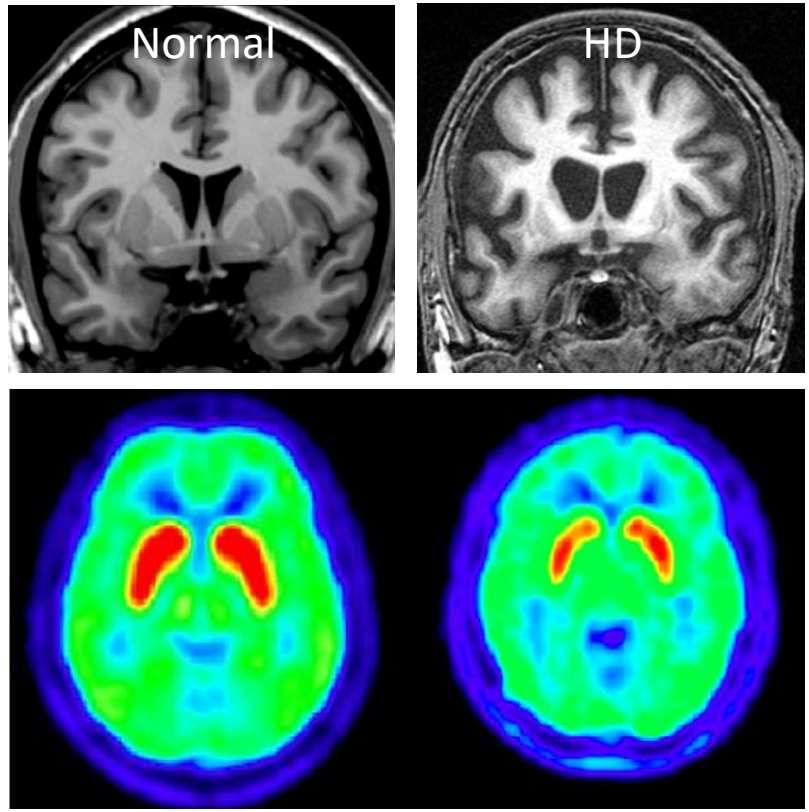
- Confirmatory vs Predictive HD testing
- Procedure and policy
  - Guidelines published by HDSA (1989, 1994, 2003)
  - Neurological exam and Mental health assessment
  - Support and Genetic counseling pre- and post-testing
  - Informed consent
  - Ensure confidentiality of test results
- Considerations (to test, or not to test)
  - No direct medical benefit
  - Planning for future needs
  - Privacy/confidentiality concerns
  - Discrimination: workplace, community, insurance, disability

GINA GENETIC INFORMATION NONDISCRIMINATION ACT (2008) protects individuals from genetic discrimination in health insurance and employment

Neuroimaging

- MRI - caudate, cortical atrophy
  - Striatal atrophy correlates with cognitive impairment (Bamford et al, 1995)
  - T2 striatal hyperintensity
  - DTI, progression gray matter atrophy presymptomatic HD mutation carriers
- PET – hypometabolism in cortex, basal ganglia

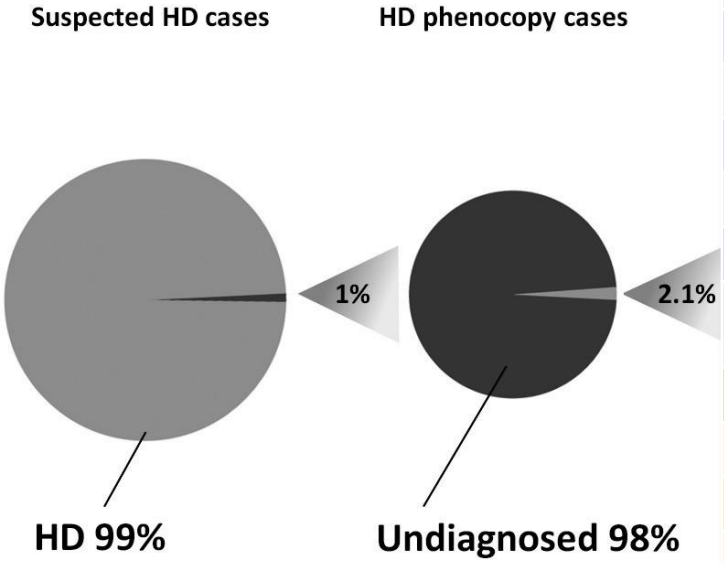
From: Radiopedia.org



[11-C]-RAC PET (D2 receptor antagonist). From: feinsteinneuroscience.org

Huntington-like diseases

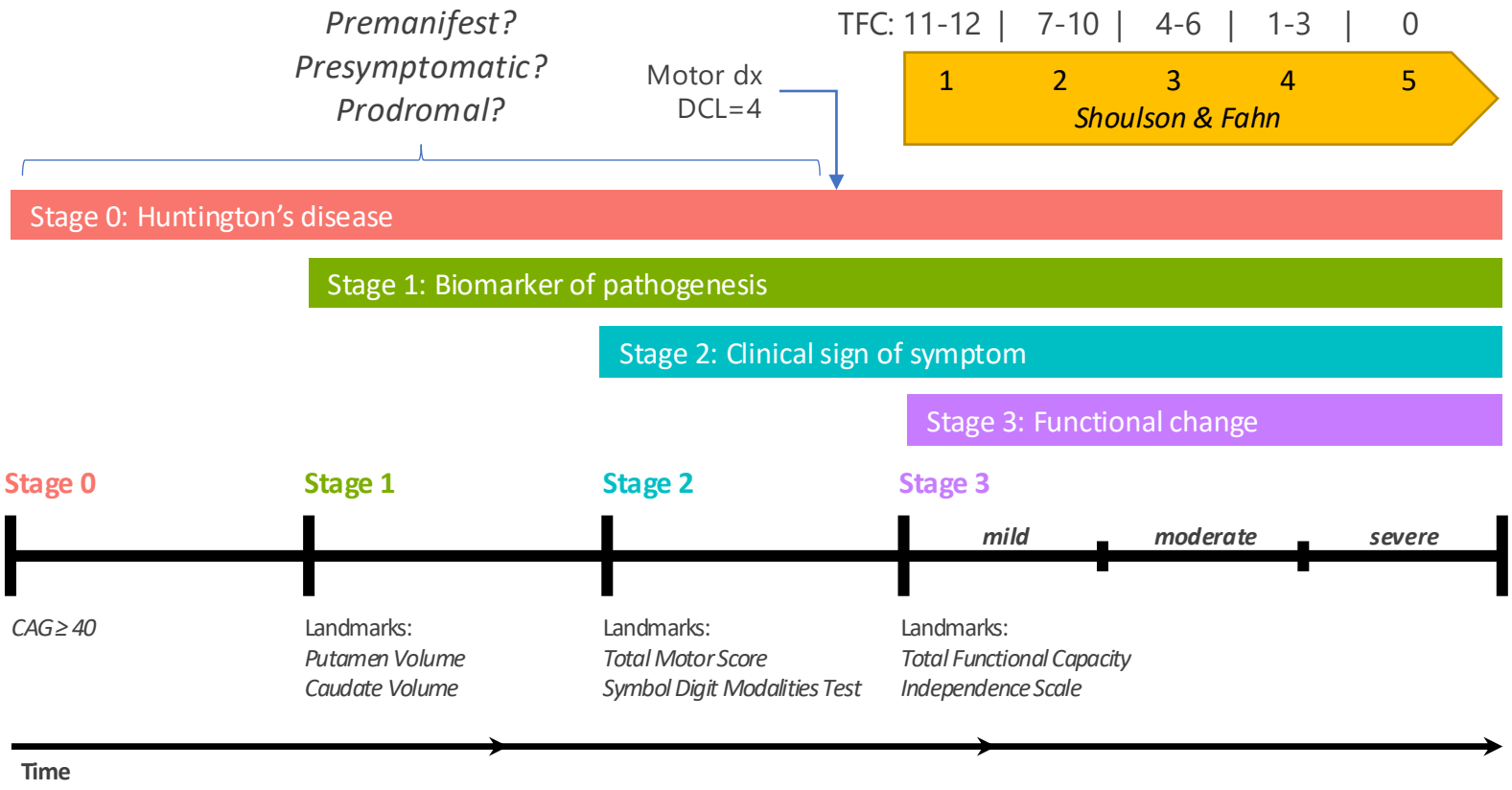
- HD phenocopies are rare



Schneider et al. Movement Disord Clin Pract. 3(4): 3
DOI: 10.1002/mdc3.12312

Disorder	Inheritance	Gene
HDL1 (prion disease)	AD	*PNRP*
HDL2	AD	*JPH3*
HDL4 (SCA17)	AD	*TPB1*
DRPLA	AD	*ATN1*
C9orf72 repeat disorders	AD?	*C9orf72*
SCAs (1,2,3,8,12)	AD	
Neuroferritinopathy	AD	*FTL1*
Benign hereditary chorea	AD	*TITF1* (type 1)
ADCY5-associated neurological dx	AD	*ADCY5*
Primary familial brain calcifications (Fahr's)	AD	*SLC20A2, PDGFRB, PDGFB, XPR1*
McLeod syndrome	XL	*XK*
Chorea-acanthocytosis	AR	*VPS13A*
Friedreich's ataxia (adult-onset)	AR	*FXN*
Ataxia telangectasia	AR	*ATM*
Wilson's disease	AR	*ATP7B*
FRRS1L-mediated chorea	AR	*FRRS1L*
HDL3 (childhood-onset)	AR	?
Aceruloplasminemia	AR	*CP*

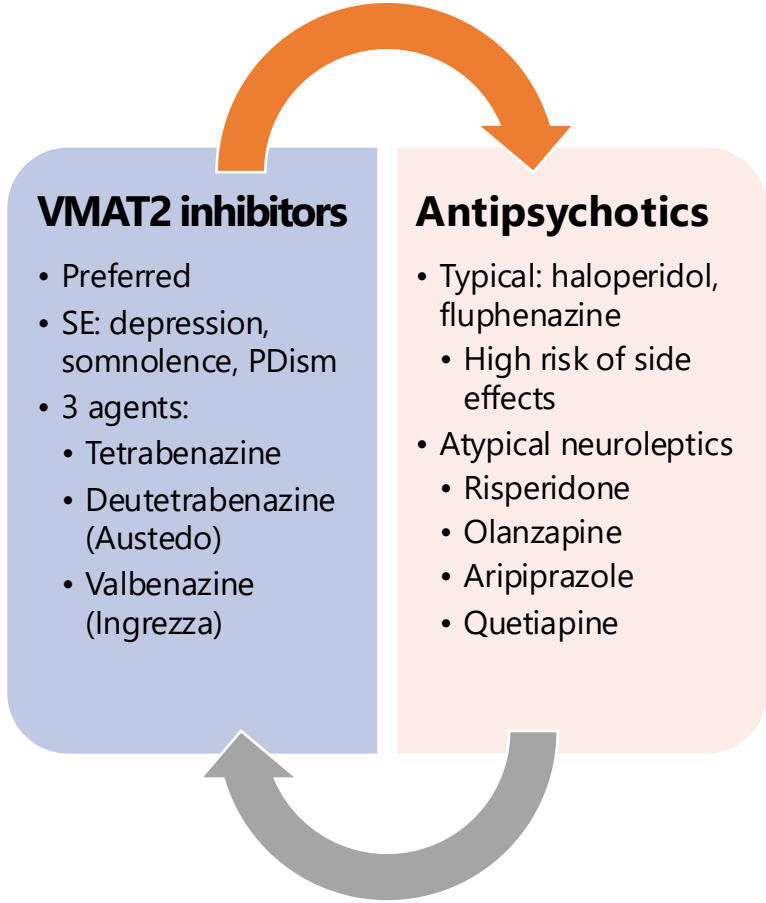
New HD-ISS Staging



Tabrizi SJ et al. Lancet Neurology 2022

Treatment of motor symptoms

- **Hyperkinesia, chorea most prominent**
- Current therapies focus on decreasing dopamine (DA) neurotransmission
- Alternatives include:
  - Amantadine – NMDA receptor antagonist (has indirect DA effects)
  - Riluzole – similar to amantadine, higher doses more effective, but no improvement in functional capacity, liver toxicity (reversible), and increased risk of suicide
  - Clonazepam – benzodiazepine, sedating
  - Levodopa – for rigidity and bradykinesia (limited data)



VMAT2 inhibitors

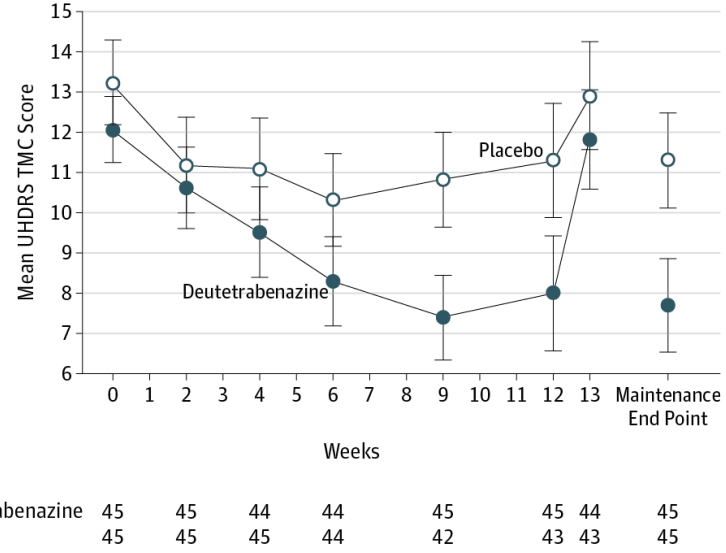
Tetrabenazine

- Originally developed for schizophrenia in 1950's and thousands treated, some with hyperkinetic mvt's

AEs (%)	Deutetrabenazine (n=45)	Placebo (n=45)
Somnolence	5 (11.1)	2 (4.4)
Dry mouth	4 (8.9)	3 (6.7)
Diarrhea	4 (8.9)	0
Irritability	3 (6.7)	6 (13.3)
Insomnia	3 (6.7)	2 (4.4)
Fatigue	3 (6.7)	2 (4.4)
Fall	2 (4.4)	4 (8.9)
Dysphagia	2 (4.4)	4 (8.9)
Depression	2 (4.4)	3 (6.7)

Deutetrabenazine

- FIRST-HD study
  - Safety/tolerability
  - AE's mild to moderate
  - One serious AE, resolved with drug suspension



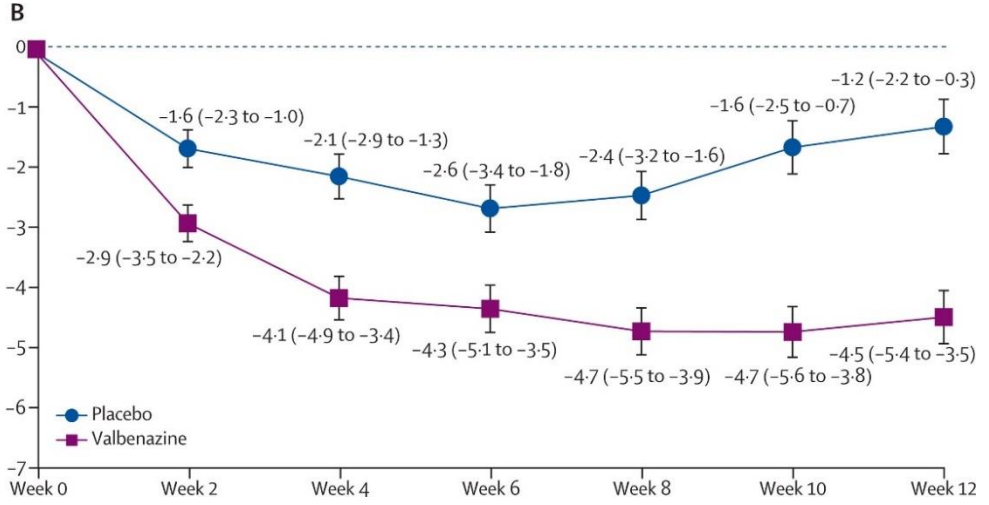
https://jamanetwork.com/journals/jama/fullarticle/2532012

Valbenazine

- Higher VMAT2 affinity, selectivity
- KINECT-HD trial
  - 46 HSG treatment sites
  - 12 week study of valbenazine (up to 80 mg/d) vs placebo with OLE (KINECT-HD2)
  - N=125 (127 for safety)
  - Endpoint: least square mean change in UHDRS TMS
  - Well tolerated: main AEs fatigue, headache
  - **FDA approved!**

Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled trial

*Erin Furr Stimming, Daniel O Claassen, Elise Kayson, Jody Goldstein, Raja Mehanna, Hui Zhang, Grace S Liang, Dietrich Haubenberger, on behalf of the Huntington Study Group KINECT-HD Collaborators**



Treatment: neuropsychiatric features

- Pharmacological and non-pharmacological
- Psychotherapy, CBT, family therapy, support groups, education
- Lifestyle modifications: diet, exercise, sleep hygiene, stress management
- Therapeutics

Antidepressants	Anxiolytics	Antipsychotics	Mood stabilizers
• fluoxetine, paroxetine CYP-2D6 effects, may reduce efficacy of VMAT-2 inhibitors • bupropion - dopamine effects + impact on chorea	• *Modify stressor* • SSRI/SNRI's • buspirone (weak) • Benzodiazepines	• help both mood, agitation, & chorea • Choose based on D2 activity • Second generation preferred • Quetiapine, clozapine rarely helpful	• divalproex • lamotrigine • oxcarbamazepine

Treatment: nonmotor



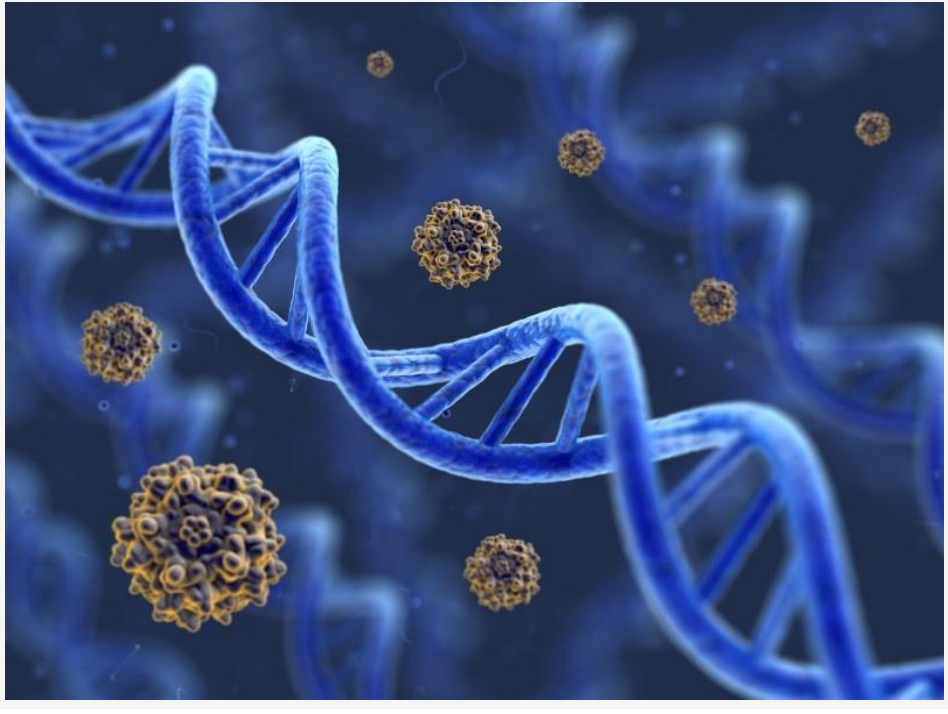
- Speech/communication
- Dysphagia - SLP to define problem
  - Large bolus, poor chewing, incoordinated breathing, tongue protrusion
- Weight loss
  - Out of proportion to nutrition and movements
  - Severe weight loss has negative impact on symptoms
  - Vicious cycle – involve nutritionist
- Sleep disorders – sleep study
- Autonomic dysf'n – heat intolerance, sweats, sexual sx
- Pain – ASK!

Clinical care and Treatment

- Motor features defining, but not all in HD
  - Treat nonmotor symptoms
  - Genetic/familial implications
  - Psychosocial aspects
- Functional outcomes vs symptoms (current drugs aren't cures)
  - Work, school, driving, home/ADLs, communication, nutrition…
- It takes a Team/Village
  - Multidisciplinary team (PT, OT, SLP)
  - Psychiatry, neuropsychiatry
  - Social work, palliative care

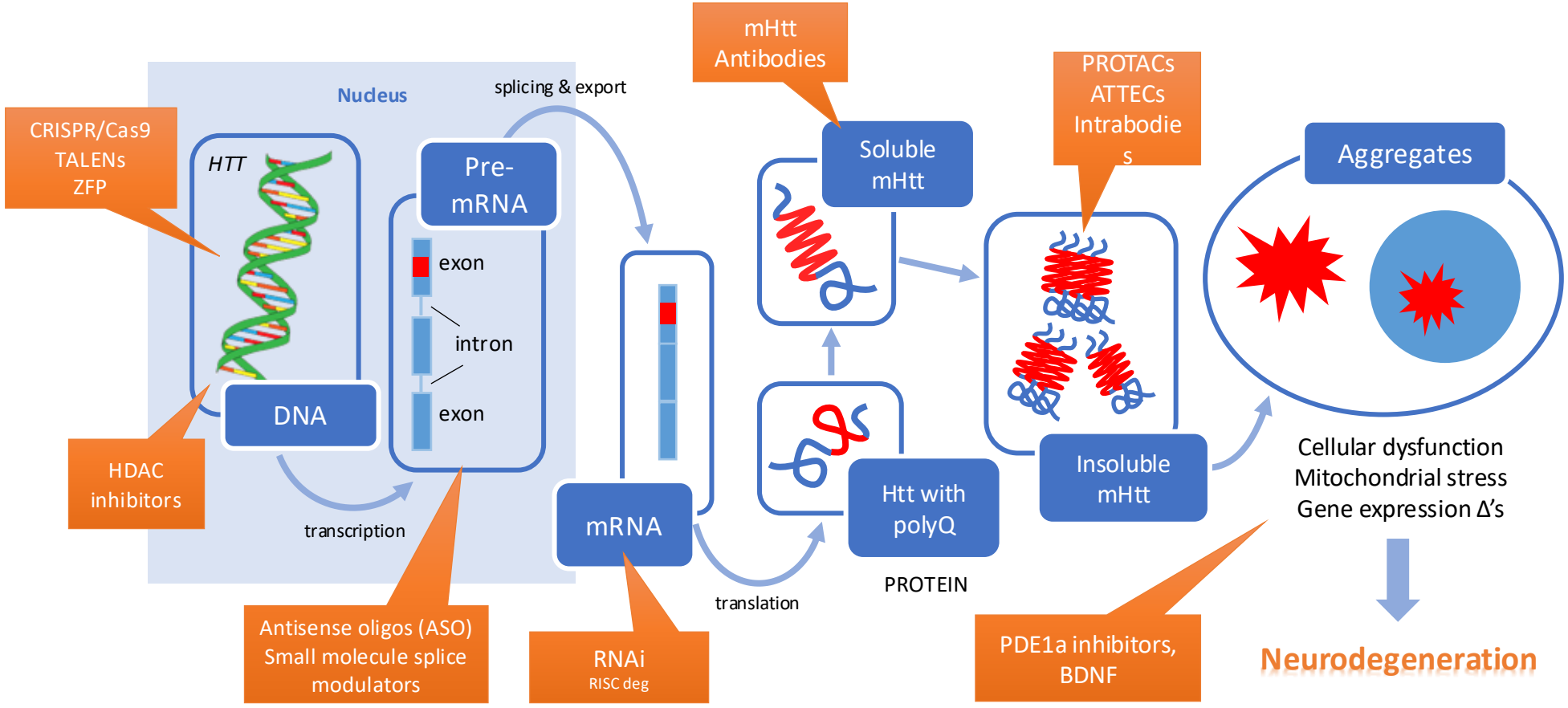
Huntington's Disease Society of America Center of Excellence University of Florida

Gene Therapy for HD



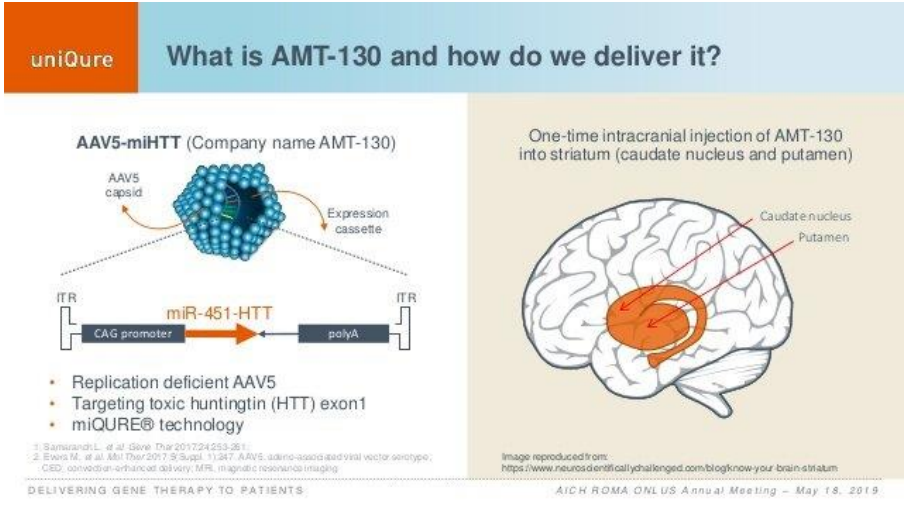
UFHealth | NORMAN FIXEL INSTITUTE *for* NEUROLOGICAL DISEASES

Targeting HD



uniQure AMT-130 – Top-Line results!

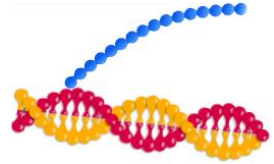
- **Phase I/II clinical trial**
- N=29, high dose 17 (*12*), low dose 12
- High dose group showed significant 75% slowing of disease progression (cUHDRS) compared to natural history "control" at 36 months!
- Also, slowed progression of TFC score
- Favorable trends for SDMT, SWRT, and TMS (p=0.174)
- Mean reduction in CSF NfL (-0.82, ~8%)
- *Well tolerated (after changes in administration procedure)*



- *Submitted Biologics Licensing Application (BLA) to FDA for accelerated approval*
- FDA denied app, but June 2026 agreed 30-yr data can serve basis for BLA

Gene Therapy for HD: RNAi

- SPK-10001
  - AAV-miRNA to lower mHTT protein and PMS1
  - One time MRI-guided injection
  - Phase 1/2 multicenter, randomized, sequential dose-escalation study
    - TEAEs: headache, psychosis - unclear related
    - *Significant mHTT protein lowering in blood (29-64%)*
  - Recruiting in 5 locations



- Brezosiran
  - Formerly ALN-HTT02
  - C16-siRNA to knock down mHTT in CSF (6-month dosing)
  - Phase 1b, HD patients aged 25-70, stage 2/3(early)
  - *60-64% reduction mHTT in high dose group at 3 months*

Jadhav *et al. Nature Biotechnol* 2024; 394-405.

Gene Therapy for HD: ASO's

Generation HD

- *Tominersen* – ASO, intrathecal delivery (q8-16 wks)
- 791 participants across 18 countries!
- Phase 3 study negative, stopped March 2021
- *Lower exposure may benefit younger patients with earlier disease*

Roche

Genentech
A Member of the Roche Group

Generation HD2

- Age 25-50, CAP 400-500 (n = 301)
- Primary outcome: reduction in mHTT in CSF from baseline to week 17, safety/tolerability
- Did not meet its efficacy objective
  - *Safety: well tolerated, no safety signals*
  - *Biomarkers: tominersin significantly lowered mHTT protein and NfL*

More HD Trials: Allele-Selective approach

- VO659
  - **ASO** targeting CAG repeat
  - Delivered by spinal injection
  - Phase 1/2a trial showed 26% reduction in HTT
- WAVE-003
  - **ASO** lowers mHTT > 30% (allele selective)
  - SELECT-HD – phase 1b/2a study, safe, well tolerated; no change in NfL but possible slowed caudate atrophy
- LETI-101
  - Advanced CRISPR platform, targets SNP rs362331 in Exon 50 to knock out mutant while retaining wild-type HTT expression

More trials: Oral splice inhibitors

Branaplam (VIBRANT-HD)

- Small molecule, splice modulator that lowers HTT
- Phase 2, multicenter study, double-blind, placebo-controlled, n=75 early HD
- *Stopped due to high incidence peripheral neuropathy!*

NOVARTIS

Votoplam (INVEST-HD)

- PIVOT-HD phase 2 study (PTC518), 5 and 10 mg dose, no placebo
- Durable, dose-dependent lowering Huntingtin protein (blood and CSF)
- NfL levels steady for up to 12 months
- Trend/hint of slowing HD progression!
- *INVEST-HD phase 3 trial now enrolling*

Skyhawk (SKY-0515)

- Oral RNA splicing drug, lowering mRNA for HTT
- May also affect PMS1 linked to CAG repeat expansion
- FALCON-HD Phase 1/2 results up to 15 months encouraging
- *Phase 2/3 study ongoing (Australia, New Zealand+)*

SKYHAWK THERAPEUTICS

Summary



HD is a complex, hereditary disease with motor, cognitive, and psychiatric features



Genetics and modifiers impact disease onset



Treatment is multi-modal and requires a multidisciplinary team approach



Novel therapeutics, including gene therapy show promise!



New clinical trials, hope!



Thank you!

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