Huntington's disease:

biomarkers of progression for clinical trials

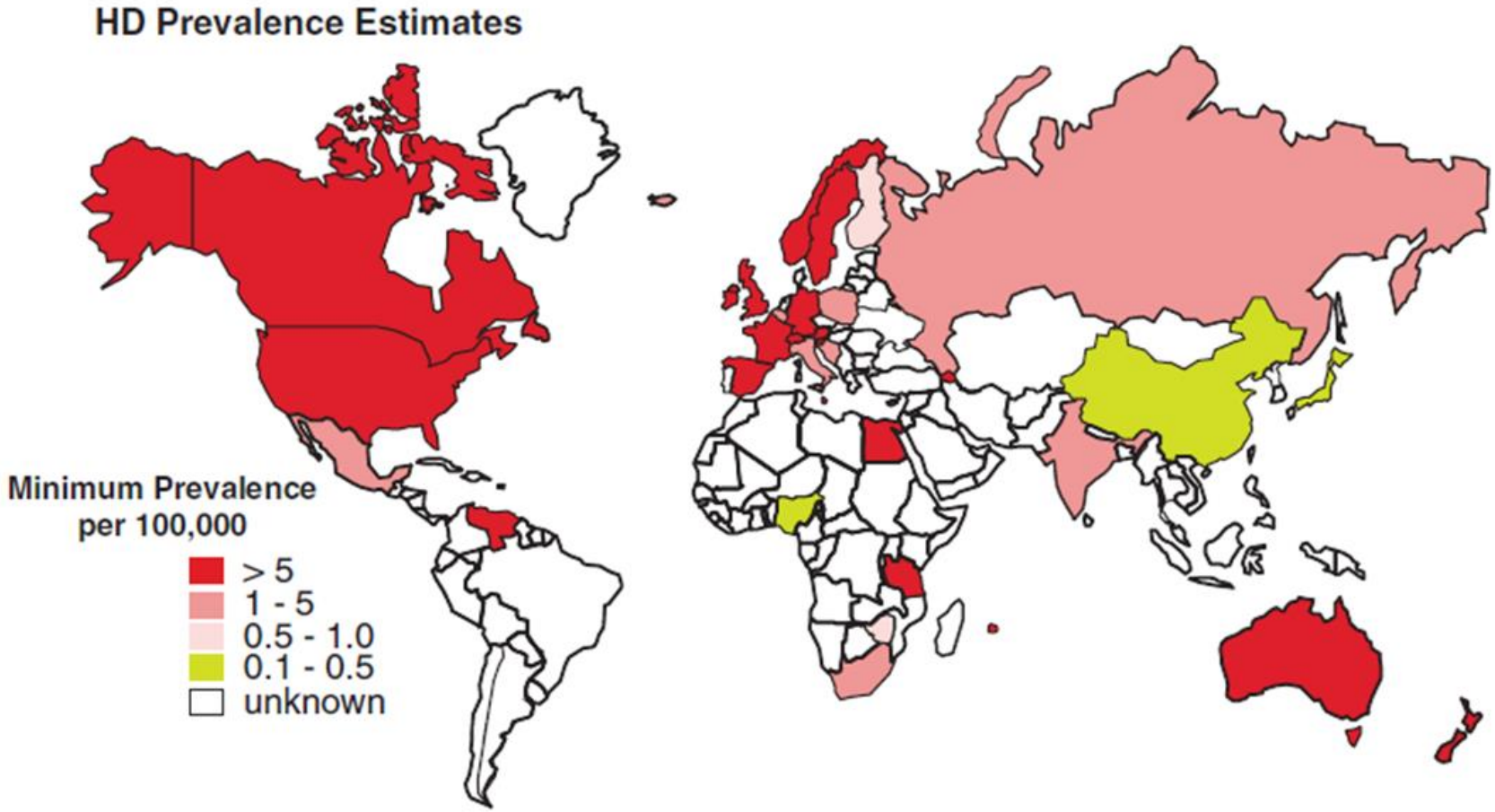
Lidia Sarro, MD

S.C. Neurologia

Ospedale Martini - ASL città di Torino

Dr. Sarro has nothing to disclose.

Epidemiology of HD

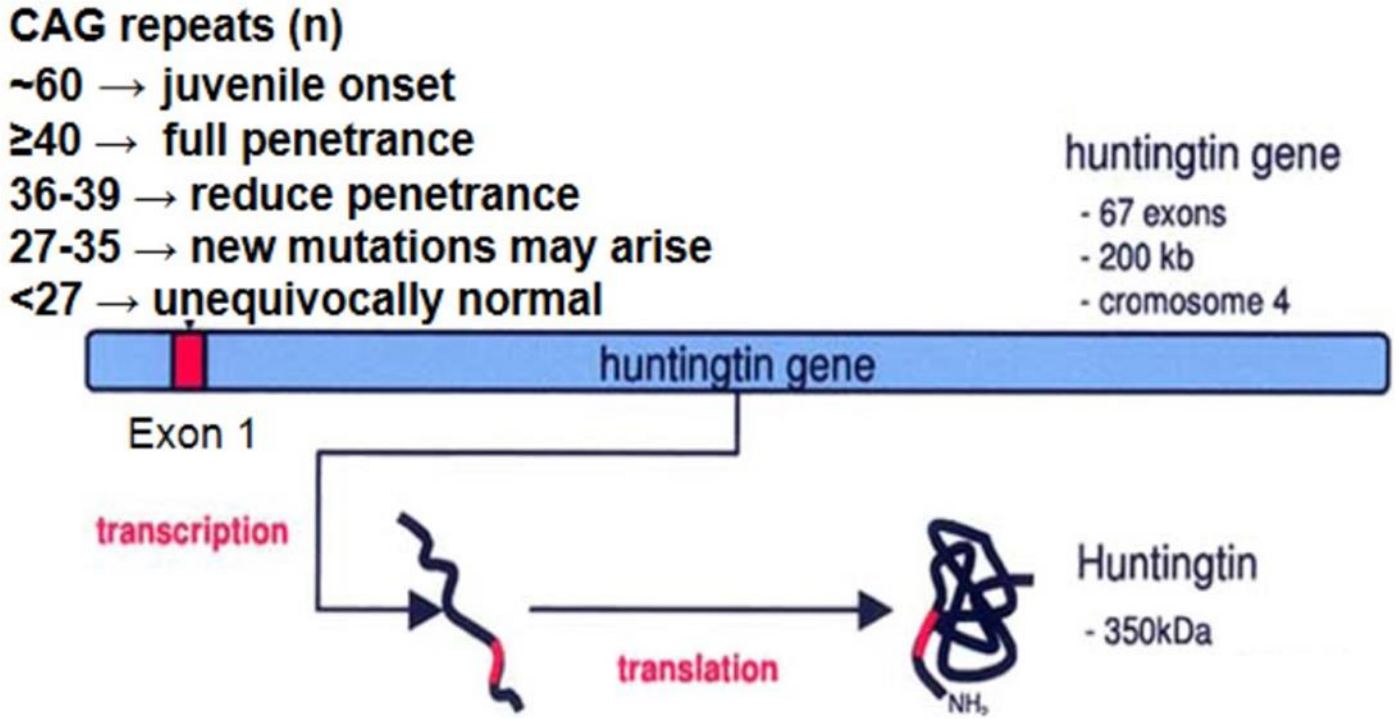


In Europe, North America and Australia an overall prevalence of 5.7 per 100,000 was reported

Pringsheim et al., *Mov Disord. 2012*

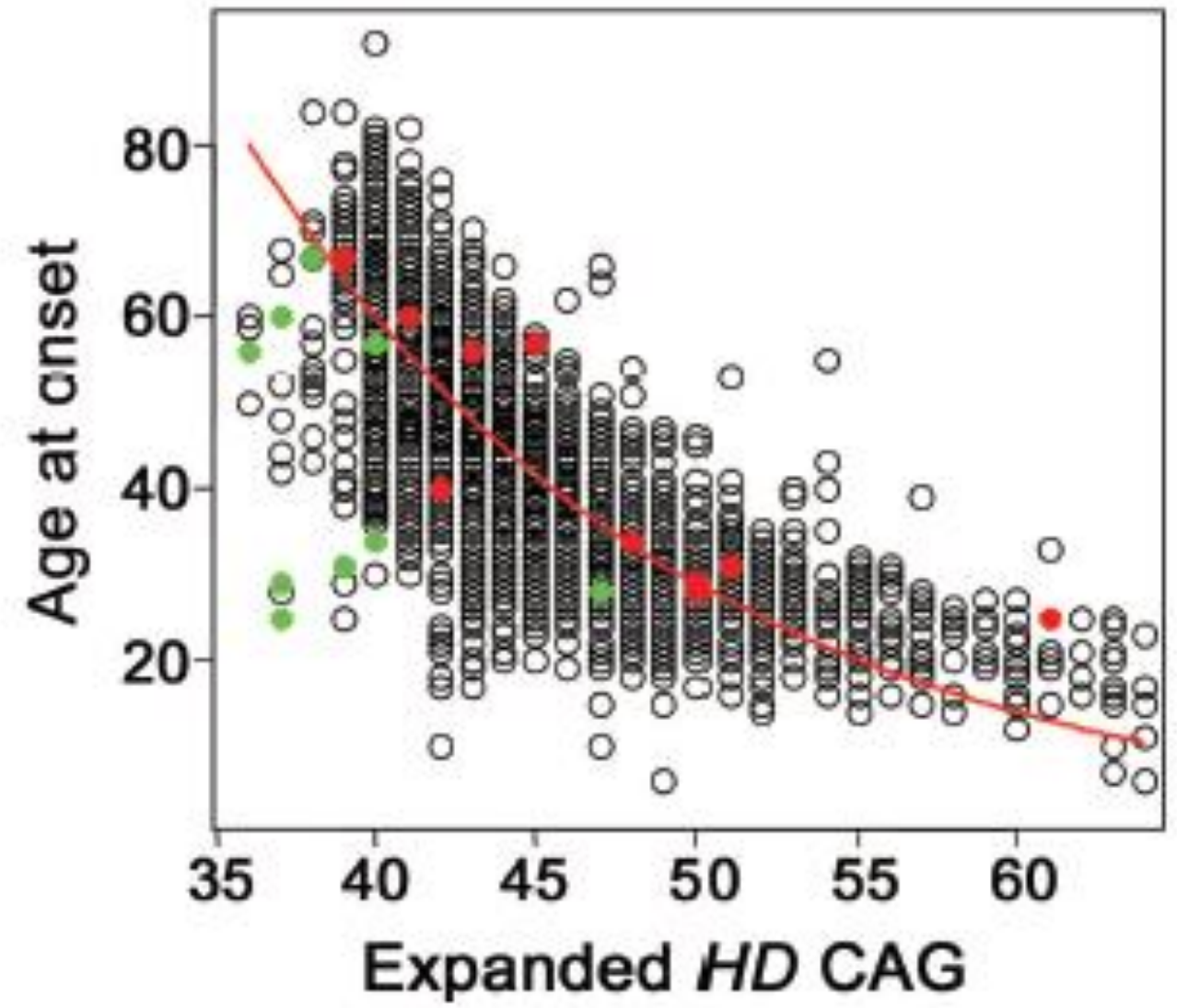
The genetics of HD

- Autosomal Dominant monogenic disorder, with full penetrance
- Caused by an expanded trinucleotide CAG sequence in exon 1 of the huntingtin gene (HTT)



CAG and age at onset

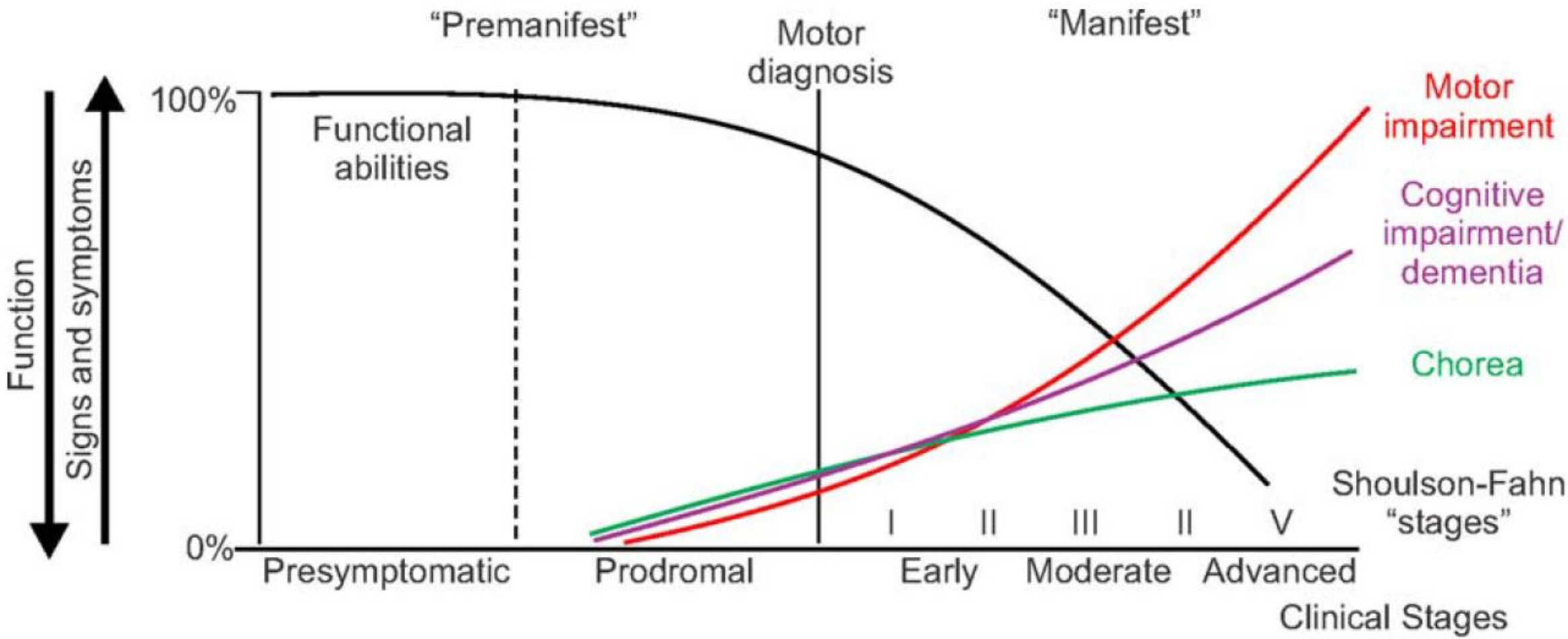
- CAG repeat expansion in HD determines age at onset in a fully dominant fashion



Lee JM et al. Neurology 2012

Diagnostic criteria of HD

HD Genetically Confirmed
(G10.1)



cognitive changes are significant AND there is evidence of progression)
– Symptomatic and disease-modifying treatment appropriate

Reilmann. Mov Disord. 2014

HD Predictive test in at-risk subjects

1993 HTT gene discovery

22 Years of predictive testing for Huntington's disease: the experience of the UK Huntington's Prediction Consortium

Sheharyar S Baig, Mark Strong, Elisabeth Rosser, Nicola V Taverner, Ruth Glew, Zosia Miedzybrodzka, Angus Clarke, David Craufurd, UK Huntington's Disease Prediction Consortium and Oliver W Quarrell

European Journal of Human Genetics (2016) **24**, 1515; doi:10.1038/ejhg.2016.81

At-risk individuals predictive

Regione Lombardia

Rete regionale per la prevenzione, la sorveglianza, la diagnosi, la terapia delle malattie rare ai sensi del d.m. 18 maggio 2001, n. 279

Percorso Diagnostico, Terapeutico e Assistenziale (PDTA) relativo a:

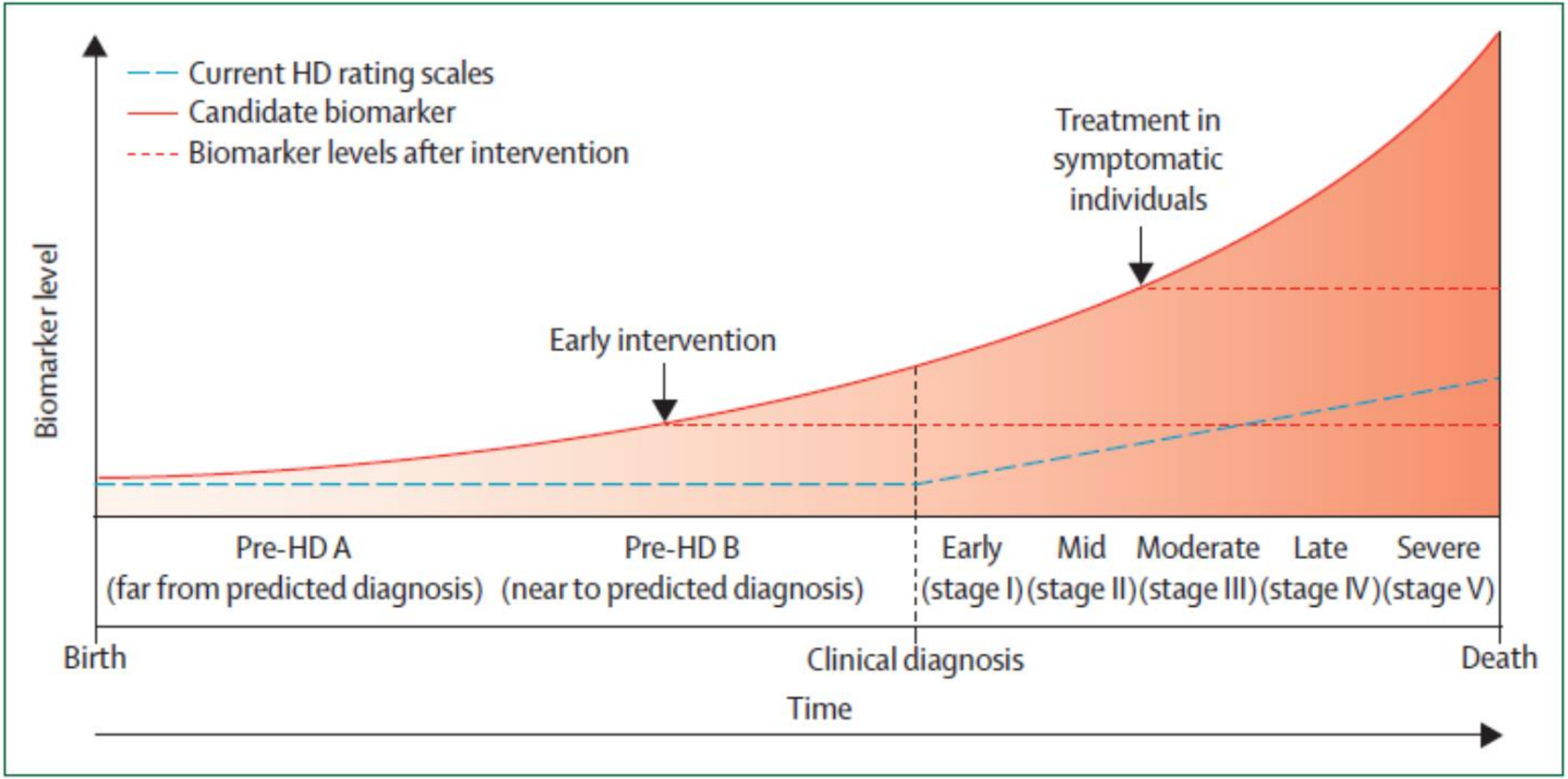
COREA DI HUNTINGTON

Codice di esenzione RF0080

f

PreHD)

Need for biomarkers for clinical trials:



Weier et al., Lancet 2011

Clincal biomarkers of progression:

Unified HD Rating Scale (UHDRS)

Motor function	Cognition	Behavior	Functional abilities
• Oculomotor function • Dysarthria • Chorea • Dystonia • Gait • Postural stability	• Phonetic verbal fluency test • SDMT • Stroop Interference Test	• Frequency and severity of symptoms related to affect, thought content, and coping styles	• HDFCS • Independence scale • Checklist of common daily tasks

HD Study Group. Mov Disord. 1996

UHDRS motor (Total Motor Score- TMS)

- Assessments
  - Ocular pursuit
  - Saccade
    - Initiation
    - Velocity
  - Dysarthria
  - Tongue protrusion
  - Maximal dystonia
  - Maximal chorea
  - Retropulsion pull test
  - Finger taps
  - Pronate/supinate hands
  - Luria
  - Rigidity in arms
  - Bradykinesia in body
  - Gait
  - Tandem walking
- Scoring
  - 0 = no abnormalities
  - 4 = most severe impairment

Maximal Chorea Score

- **Subset of UHDRS motor score**
- **Includes face, bucco-oro-lingual area, trunk, upper extremities (R & L) and lower extremities (R & L)**

HD Study Group. Mov Disord. 1996

Clincal biomarkers of progression:

Unified HD Rating Scale (UHDRS)

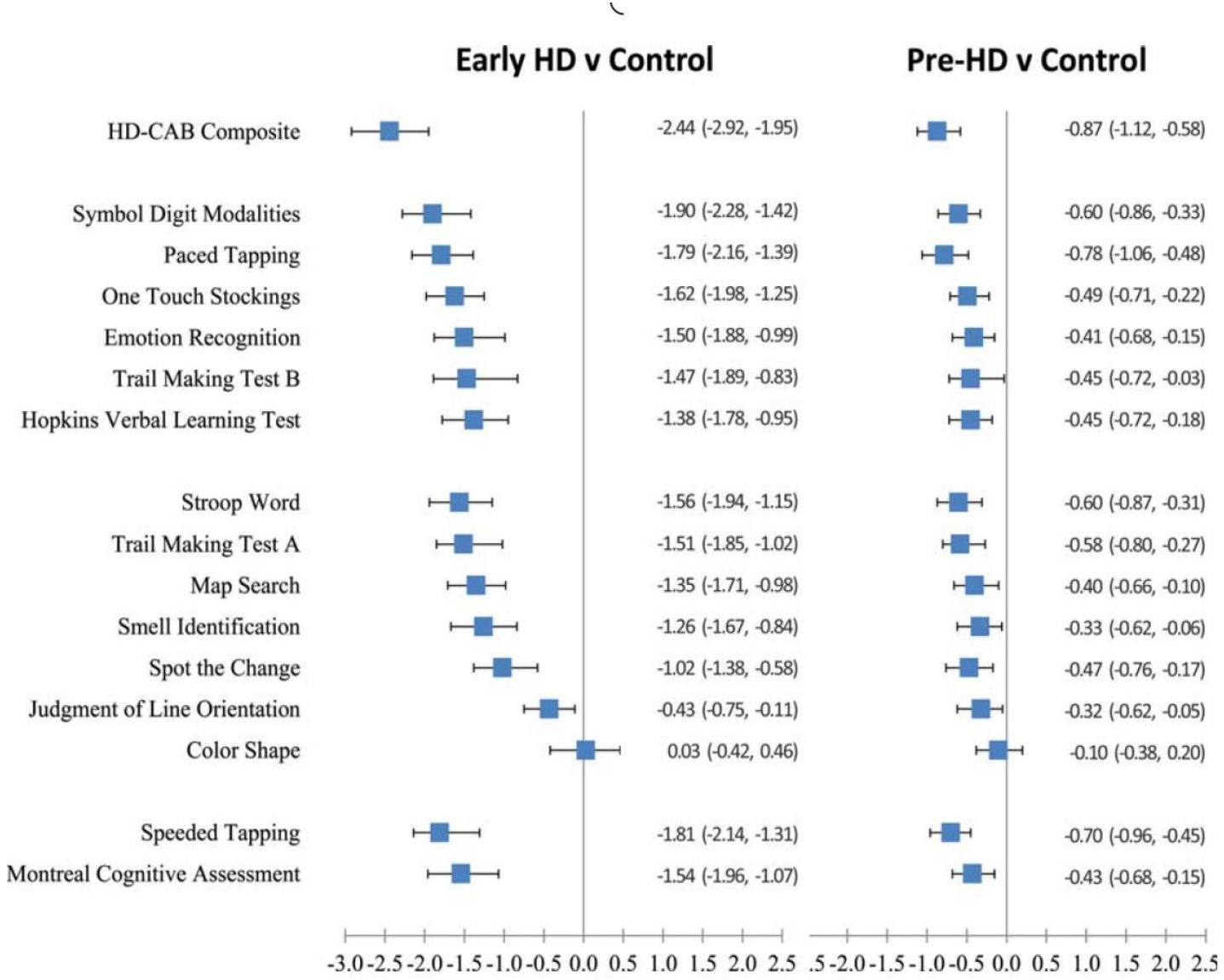
Motor function	Cognition	Behavior	Functional abilities
• Oculomotor function • Dysarthria • Chorea • Dystonia • Gait • Postural stability	• Phonetic verbal fluency test • SDMT • Stroop Interference Test	• Frequency and severity of symptoms related to affect, thought content, and coping styles	• HDFCS • Independence scale • Checklist of common daily tasks

HD Study Group. Mov Disord. 1996

A New Clinical biomarker for Cognitive Decline:

HD-CAB

- Symbol Digit Modalities Test
- Paced Tapping
- One Touch Stockings of Cambridge
- Emotion Recognition
- Trail Making test, part- B
- Hopkins Verbal LearningTest.



Stout et al., Mov Disord. 2014

Clincal biomarkers of progression:

Unified HD Rating Scale (UHDRS)

Motor function	Cognition	Behavior	Functional abilities
• Oculomotor function • Dysarthria • Chorea • Dystonia • Gait • Postural stability	• Phonetic verbal fluency test • SDMT • Stroop Interference Test	• Frequency and severity of symptoms related to affect, thought content, and coping styles	• HDFCS • Independence scale • Checklist of common daily tasks

HD Study Group. Mov Disord. 1996

Clinical biomarker for Behaviour:

PBA (problem behavior assessment for HD)

- Depressed mood
- Suicidal Ideation
- Anxiety
- Angry/aggressive behavior
- Apathy
- Perseverative thinking or behavior
- Obsessive-compulsive behaviors
- Delusion/paranoid thinking
- Hallucinations
- Disoriented behavior

Callaghan et al., J Neuropsychiarty Clin Neurosci. 2015

Longitudinal observational multicenter study

PREDICT-HD

AIM: *identifying biological and clinical markers in the Premanifest HD phase (PreHD) predicting onset of the Manifest HD phase*

RESULTS: strongest predictors of phenoconversion:

- **UHDRS-TMS (motor):** *+1 SD increased the risk of motor diagnosis by 3.07 times*
- **Putamen volume (MRI imaging):** *-1 SD increased the risk of diagnosis by 3.32 times*
- **Stroop word score (cognitive):** *-1 SD increased the risk of diagnosis by 3.32 times*

Paulsen et al., Lancet Neurol. 2014

Longitudinal observational multicenter study

TRACK-HD

AIM: *identifying sensitive and reliable biomarkers in PreHD and early HD to be applied in novel therapeutic interventions*

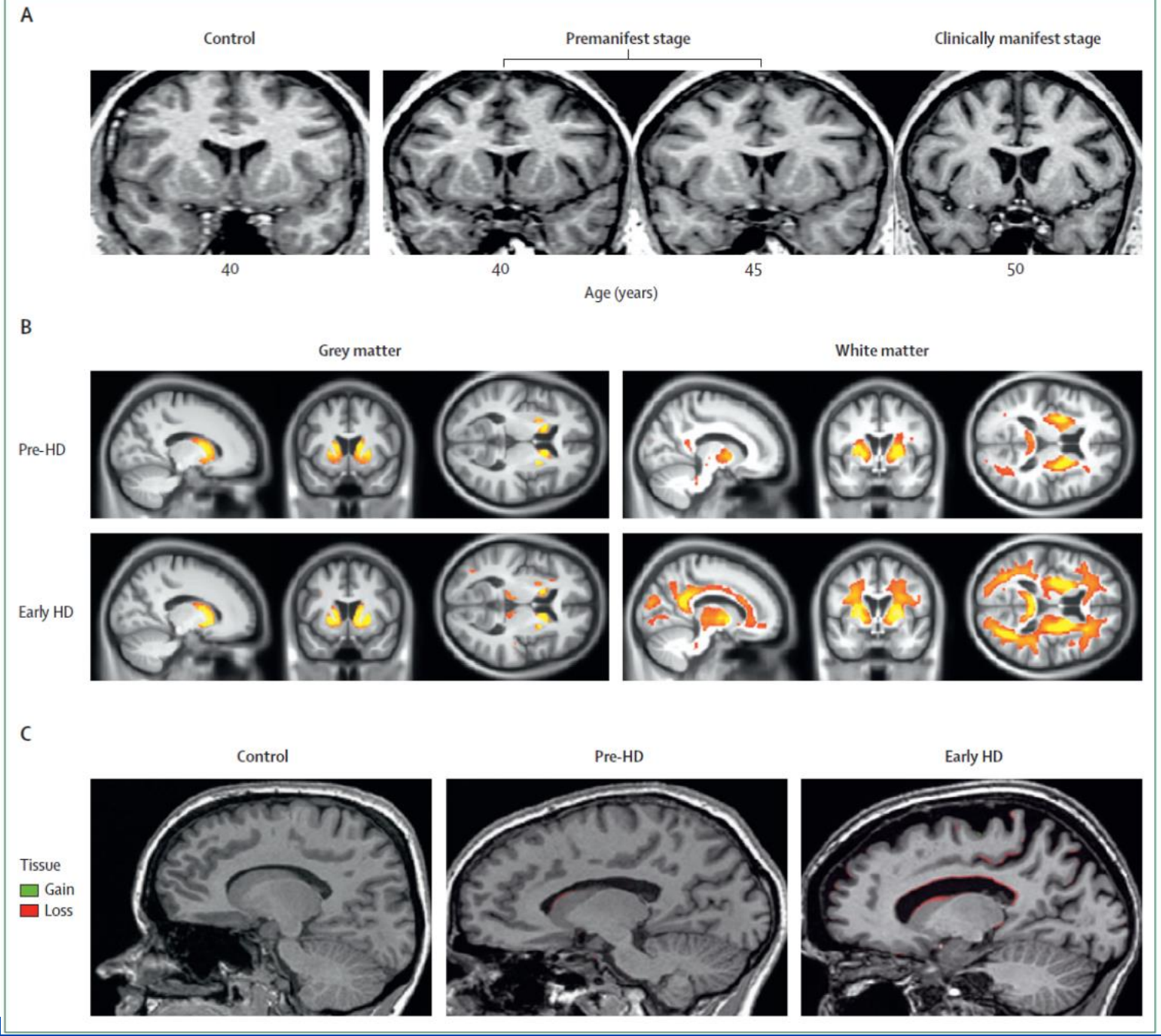
METHODS: *baseline, 12 months and 24 months 3T MRI data, clinical, motor, cognitive, oculomotor and neuropsychiatric assessments*

RESULTS:

- **Structural MRI imaging:** striatal (caudate, putamen) and whole brain volume loss, in premanifest HD up to 16 years from expected onset
- reduction in structural and functional brain connectivity as the disease progresses

Tabrizi et al., Lancet Neurol. 2012

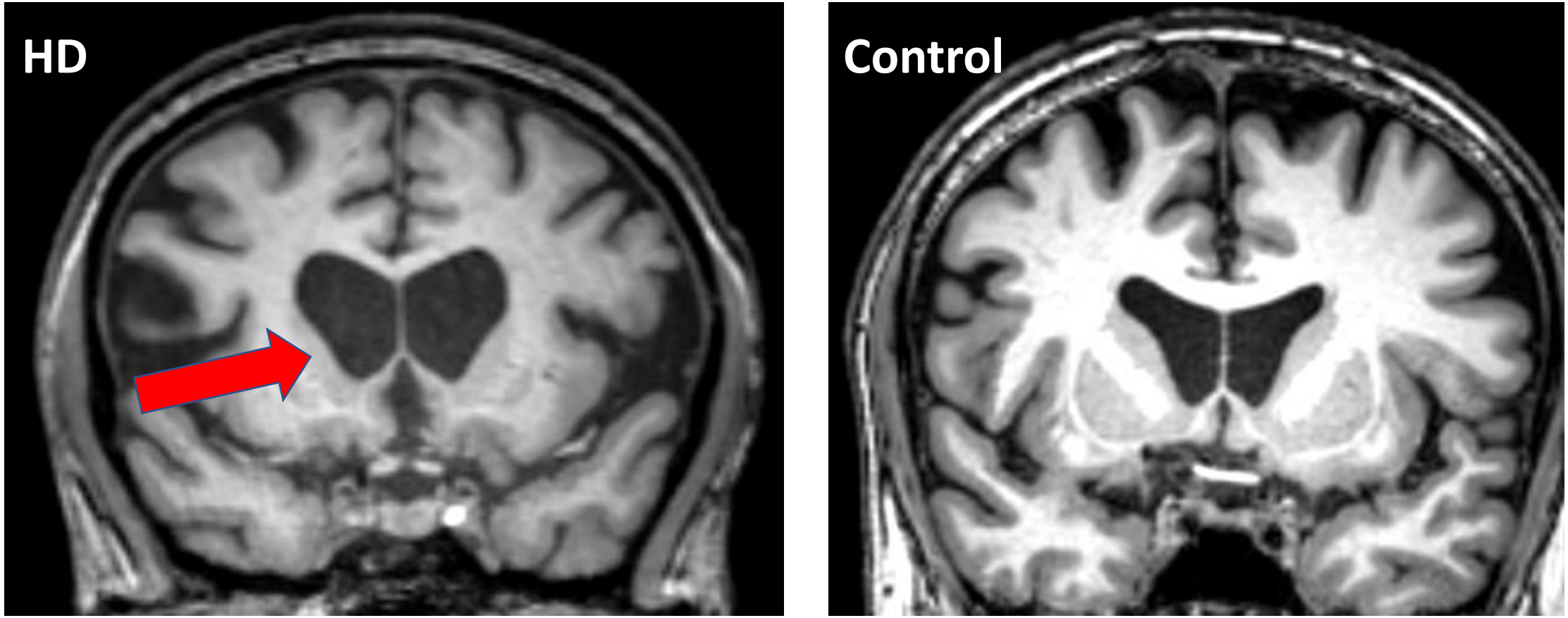
TRACK-HD



Tabrizi et al., Lancet Neurol. 2012

MR Imaging biomarkers of progression:

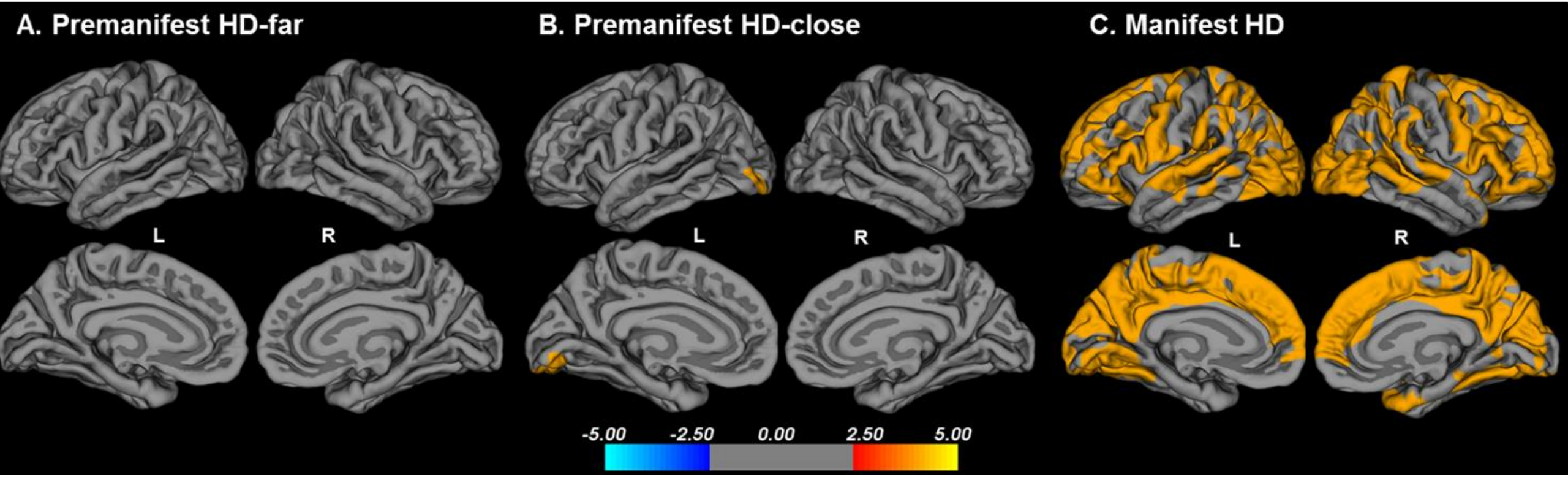
Caudate atrophy



Tabrizi et al., Lancet Neurol. 2012

MR Imaging biomarkers of progression:

Cortical thickness



Nanetti et al., Park Rel Disord. 2018

CSF biomarkers: dosing mutated huntingtin protein (mHTT)

HD-Clarity

Ultrasensitive single-molecule counting mHTT immunoassay to quantify mHTT levels in CSF samples

- *mHTT was detected in mutation carriers and not in control participant*
- *CSF mHTT concentration was higher in manifest than in PreHD subjects*
- *Correlations were found between CSF mHTT concentrations and UHDRS scores and cognitive tasks*

Wild et al., J Clin Invest. 2015

Thank you for your attention

The HD-like syndromes

what to consider in patients with a negative HD gene test?

Condition	Chromosomal location	Gene	Average age at onset (years)	Clinical characteristics
HD	4p15	*IT15/huntingtin/HD*	<30	Chorea, personality changes, dementia
HDL1	20p12	*PRNP*	20–40	HD phenocopy, prominent psychiatric features
HDL2	16q24.3	*JPH3*	25–45	HD phenocopy, most frequent in black South Africans
HDL4 (SCA17)	6q27	*TBP*	25–40	Ataxia, HD phenocopy
SCA1	6p23	*ATXN1*	30–40	Ataxia, parkinsonism, dystonia, chorea
SCA2	12q24	*ATXN2*	25–45	Ataxia, parkinsonism, dystonia, chorea, neuropathy, dementia
SCA3	14q32.1	*ATXN3*	20–50	Ataxia, parkinsonism, dystonia, chorea
DRPLA	12p13.31	*Atrophin 1*	<20 >40	Progressive myoclonus epilepsy Ataxia, chorea, dementia
Neuroferritinopathy	19q13	*FTL*	40	Chorea, dystonia, oromandibular involvement, parkinsonism, dysarthria
Benign hereditary chorea	14q13	*TITF-1* (and others)	Childhood	Non-progressive chorea (thyroid and pulmonary abnormalities)

Schenider et al., *Lancet* 2013