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A practical guide for clinical approach to patients with Huntington's disease in Korea

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PREFACE: Overview of Huntington's disease in Korea

Huntington's chorea was initially described in 1872 by Dr. George Huntington (1850-1916).[1] Roughly a century later, the first clinically diagnosed cases of Huntington's disease (HD) in Korea were reported in 1988.[2] Following the identification of the genetic cause of HD,[3] the initial genetic analysis of Huntington's chorea in Korea was published in 1996.[4]

In Korea, the gene test for HD has been covered by the National Health Insurance System (NHIS) since August 2005. Advancements in genetic testing and a greater understanding of the disease have made HD diagnosis easier compared to the past. A recent study examining the 10-year prevalence of HD in Korea, based on data registered between 2010 and 2019 in the NHIS database, reported an annual incidence of 0.29/100,000 and a 10-year prevalence of approximately 2.2 per 100,000.[5]

Despite advancements in understanding the disease, the clinical management and medical infrastructure for HD remain notably limited in Korea. Approximately one-third of individuals diagnosed with HD discontinue medical follow-up, and among those who continue to seek medical care, there is a tendency to incur substantial medical expenses in Korea.[5] The annual medical costs for an individual with HD are estimated to be around 6 million KRW or more, persistently sustained over a period of 9 years following diagnosis.[5] These statistics underscore the urgent need for significant improvements in various aspects of our medical system to provide effective support for patients with HD and their families in Korea. A recent analysis on caregiver burdens of HD patients in Korea, published at an opportune time, reveals that the caregiving burdens for HD are notably high and comparable to those expected in more common dementias.[6]

In an effort to enhance clinical practice and bolster the medical support system for HD in

Korea, the Korean Huntington's Disease Society (KHDS) was established in July 2022. This development comes approximately two years after the initiation of the first Korean Huntington's Disease Cohort (KHDC) study. [6] Initially, a total of 13 centers were involved in constructing the initial cohort. However, following the establishment of KHDS, the KHDC has expanded to include 30 sites and continues to actively recruit additional sites for participation (**Figure 1**).

This serves as preliminary groundwork for the development of clinical guidelines for HD in Korea. Under the subsequent headings, the taskforce of KHDS on the Clinical Management of HD has compiled fundamental and updated knowledge concerning the diagnosis and treatment of patients with HD. The initial draft originated from the taskforce and underwent meticulous review by a panel of esteemed experts from the Korean Movement Disorders Society. Our aim is that this comprehensive effort will assist clinical practitioners in Korea in making informed and efficient decisions based on the current resources available in the country. Moreover, we welcome any suggestions and proposals to further refine and advance the clinical guidelines for HD in Korea in the future.

EPIDMIOLOGY

Prevalence and incidence of HD

Throughout the years, numerous studies have endeavored to estimate the prevalence and incidence of HD across various countries and regions globally. A meta-analysis encompassing publications from 1985 to 2010 reported a pooled incidence of HD at 0.38 per 100,000 person-years, with a global overall prevalence of 2.71 per 100,000. [7] In a more recent meta-analysis covering studies from 2011 to 2022, there was a slight increase in both indices, with an annual HD incidence of 0.48 per 100,000 person-years and a global overall prevalence of

4.88 per 100,000.[8] Although these ratios demonstrated a marginal increase compared to previous meta-analyses, the difference was not statistically significant.[8] The improved case ascertainment, owing to wider availability of genetic testing, alongside aging populations and enhanced patient survival rates, might contribute to the observed rise in prevalence and incidence.

Significant variations in the prevalence and incidence of HD are observed between countries and regions, suggesting ethnic disparities. Europe and North America exhibit notably higher HD incidence rates compared to Asia. In addition, Europe, North America, and Oceania demonstrate higher prevalence rates than Asia and Africa (**Figure 2**). These discrepancies imply a less frequent occurrence of HD within the Asian population when contrasted with Western populations. However, a notable divergence in HD occurrence exists between the Middle East and East Asia, where prevalence and incidence rates in the Middle East closely resemble those in Europe, North America, and Oceania, while rates in East Asia are notably lower (**Figure 2**).[7, 8] These disparities in HD prevalence across distinct ancestral populations are believed to stem from genetic variations at the HTT locus.[9] Generally, populations with higher HD prevalence tend to exhibit longer average CAG repeats in the HTT gene. As illustrated in **Figure 3**, European populations typically display a range of 18.4–18.7 repeats, whereas most studied Asian populations exhibit a range of 16.5–17.8 repeats.[10-21] In addition to CAG repeat sizes, differences in the frequencies of haplotype and CCG polymorphism in the HTT gene may also be attributed to geographic and ethnic variations in HD epidemiology.[22]

A recent survey in Korea estimated the prevalence of HD to be approximately 2.22 per 100,000, with an annual incidence of 0.29 per 100,000 person-years.[5] These figures indicate lower rates compared to those reported in Western populations but are higher than previously

expected based on earlier reports.

Frequency of reduced penetrance and intermediate alleles in general populations

HD patients typically exhibit 36 or more CAG repeats within the HTT gene. However, 36–39 CAG repeats refer to reduced penetrance, resulting in a later age at onset and slower disease progression compared with full penetrance (≥40 CAG repeats). [9] In addition, CAG repeat numbers between 27 and 35 are classified as intermediate alleles, which are prone to genetic instability and might expand into the disease range within one generation. [9] A comprehensive analysis across three population-based cohorts from British Columbia, the United States, and Scotland revealed that among 7,315 asymptomatic individuals, 0.25% (with an allele frequency of 0.12%) possessed reduced penetrance, while 6.20% (with an allele frequency of 3.13%) had intermediate alleles. [11] This prevalence pattern was corroborated by another study involving five large European population-based cohorts,[14] which showed similar frequencies of reduced penetrance and intermediate alleles.

In the Korean population, among 941 asymptomatic individuals, reduced penetrance and intermediate allele frequencies were notably lower, at 0.11% (with an allele frequency of 0.05%) and 1.38% (with an allele frequency of 0.69%), respectively. [10] This mirrors the lower prevalence of HD in Korea compared to Western populations.

Regarding other Asian populations, intermediate alleles were found in 2.6% of 966 alleles among Chinese individuals[11] and in 0.5% of 430 alleles among Thai individuals. [13]

Interestingly, a recent study indicated that the East Asian population demonstrated the lowest prevalence of intermediate alleles (0%, 0/258) among diverse global populations. [18] However, inclusion of only a limited number of East Asian samples in these studies suggests the

necessity for a larger sample study to accurately determine the true prevalence in this population.

PATHOPHYSIOLOGY

Molecular pathogenesis

Extensive data supports the pivotal role of mutant huntingtin (mHTT) fragmentation in the pathogenic mechanism of HD. [23] mHTT fragments originate either from an abnormal splicing event leading to the formation of HTT exon 1 protein or through cleavage of the full-length HTT by enzymes such as caspases, calpains, and other proteases (see **Figure 4**). [24] These mHTT fragments instigate neuronal dysfunction and cell death through various pathways; mainly a direct effect from the exon 1 mHTT fragment, the tendency of mHTT to create abnormal aggregates, and its negative impacts on cellular proteostasis, axonal transport, transcription and translation, and mitochondrial and synaptic function. [25] Other potential pathogenic mechanisms have also been proposed, including reduced levels of brain-derived neurotrophic factor, glutamate excitotoxicity from cortico-striatal projections, and the deleterious effects of repeat-associated non-ATG translation proteins. [26, 27]

The differential expression levels of HTT across various cell types contribute to variations in the concentrations of mHTT fragments. Neurons typically exhibit higher HTT expression compared to glial cells, a factor likely contributing to the predominantly neuronal pathology observed in HD. [28] Among the neuronal cells, medium spiny neurons (MSNs) located in the striatum are particularly susceptible to the harmful effects of mHTT. [29] The striatal pathology in HD progresses through two phases: an early phase characterized by the loss of MSNs from the indirect pathway, leading to a hyperkinetic phenotype; and a late phase involving the loss of MSNs from the direct pathway, resulting in a hypokinetic phenotype. [30] The precise

mechanism behind the selective vulnerability of MSNs from the indirect pathway in the early phase remains incompletely understood. However, it is hypothesized that dopamine D_2 receptors, which are selectively expressed in indirect MSNs, may substantially contribute to the onset and development of HD. [31]

Macroscopic and microscopic pathology

Post-mortem investigations have revealed a diffuse pattern of atrophy primarily affecting the caudate and putamen in HD. This degeneration manifests along gradients on the caudo-rostral, dorso-ventral, and medio-lateral axes. While the globus pallidus and nucleus accumbens are also impacted, the effects are comparatively less pronounced. [32] A classification system has been proposed for the pathologic stages of HD, consisting of five grades (0–4): [33]

- Grade 0: Clinical signs of HD are present, yet no observable microscopic or macroscopic abnormalities related to the disease are evident.
- Grade 1: Microscopic observation reveals moderate fibrillary astrocytosis without macroscopic abnormalities in the caudate or putamen.
- Grade 2: Macroscopic changes become evident in the caudate and putamen, but not in the globus pallidus.
- Grade 3: Fibrillary astrocytosis is observed in the lateral segment of the globus pallidus without involvement of the medial segment.
- Grade 4: Macroscopic changes include a shrunken and yellow-brown caudate, an expanded anterior horn of the lateral ventricle, and a reduced nucleus accumbens. Additionally, changes may be present in other brain regions such as the thalamus, sub-thalamic nucleus, white matter, and cerebellum, particularly in Grades 3 and 4.

Previous studies employing magnetic resonance imaging have provided supportive evidence

for this pathological classification system of HD. [34]

CLINICAL SPECTRUM OF HD

Motor features

Chorea: Chorea is prototypical and the most common motor manifestation of HD, accounting for 90% of affected patients. [35] Chorea is more common in adult patients than in juvenile patients, and it typically initiates in the early stages, plateaus, and regresses during the late stages of the disease. In the early stages of HD, chorea is subtle in the extremities and either unnoticed (i.e., anosognosia) independent of cognitive dysfunction, or its presence is denied by the patient, who may camouflage it by semi-purposeful movements (i.e., parakinesia). Forehead chorea manifested by enlarged palpebral fissures with eyebrow elevation and frontalis contractions. Motor impersistence is one of the cardinal features of HD and is associated with insuppressible overactivity in HD. [36] It leads to an inability to maintain voluntary muscle contraction at a steady level when asking the patient to keep tongue protrusion ("flycatcher's tongue") or handshake ("milkmaid's grip"). [36] Symptoms of chorea in HD vary in severity affecting other motor and nonmotor symptoms, daily activities, hospitalization, and quality of life. [36, 37] As chorea progresses, patients experience recurrent injuries with falls due to postural instability and gait disturbance. [38] Moderate to severe chorea might lead to numerous non-motor symptoms, including pain, sleep disturbance, nutritional deficits, and weight loss, as well as social embarrassment and difficulties in communication. [35]

Dystonia: The prevalence of dystonia is reported as 91- 95% of adult patients, and the most affected body region is upper limb with internal rotation of the shoulder and sustained fist clenching. [39, 40] Dystonia worsens with the advancing disease, and the severity is correlated

with disease duration and the use of antidopaminergic agents. [39]

Myoclonus: Myoclonus is commonly seen in juvenile-onset HD[35] and rarely reported as a predominant and disabling motor feature in adult-onset HD. [41] Myoclonus in HD can be generalized, multifocal, or action-induced cortical myoclonus. [42]

Tourette syndrome: Tics in HD are reported in both juvenile-onset and adult HD patients. [43] However, the pathophysiology of the relationship between HD and Tourette syndrome (TS) needs further investigation to determine whether TS and HD coexist or whether TS is an atypical manifestation of HD.

Parkinsonism: As the disease progresses, chorea in HD patients often spontaneously subsides. Instead, parkinsonism develops and may advance to akinesia, severe rigidity, and mutism in the final stages. [35] As symptomatic treatment for chorea involves the reduction of dopaminergic transmission through either blocking dopamine receptors or depleting presynaptic dopamine, it may impair motor functions, leading to drug-induced parkinsonism in HD. [44] Therefore, hyperkinetic and hypokinetic motor symptoms in HD require a balanced treatment based on the functional consequence of those movement disorders in individual patients. Late-onset HD patients could be misdiagnosed as having atypical parkinsonism, due to their variable motor features such as dystonia, ataxia, and abnormal oculomotor findings, along with numerous non-motor symptoms including depression, dementia, and dysautonomia. [45]

Impaired voluntary motor controls: In HD, the progressive deterioration of voluntary motor control is prevalent in gait, balance, coordination, oculomotor function, swallowing, and speech. This deterioration is correlated with an acceleration of functional decline. [35]

Cognitive features

Cognitive dysfunction in HD can precede clinical diagnosis by 15 years, and gradual deteriorations of cognitive function is highly predictive of typical motor symptom development. [46] From the REGISTRY study, about 8% of the patients reported cognitive impairment as the first symptom, while 13% reported a mixed onset of motor, cognitive, and psychiatric symptoms. [47] Cognitive features of HD begin with non-amnestic MCI and progress into a broad range of cognitive deficits in executive, learning and memory, attention, perception, and language domains. [48] In South Korea, the prevalence of dementia in HD patients is approximately 40%, and gradually increases to 80% in patients over 80 years of age. [5] Cognitive performance could be poorer in the parkinsonism-dominant group than the chorea-dominant and mixed-motor phenotype groups independently from disease duration and severity. [49] Interestingly, patients often unaware their cognitive problems. Therefore, physicians should take history from caregivers and be alert to cognitive behavioral changes to share adaptive strategies with caregivers and maintain patients' functional capabilities. [35]

Executive function: Executive dysfunctions encompass slow cognitive processing speed, attentional deficits, and deterioration in decision-making, planning, organization, and sequencing. [50]

Learning and Memory: Difficulties in the retrieval of knowledge and the acquisition of procedural information are characteristic feature. [35] Compared to people with Alzheimer's dementia (AD), individuals with HD showed better performance on yes/no recognition testing but not on free delayed recall. [51] HD patients exhibit predominantly retrieval deficit, whereas AD patients have memory deficit primarily in encoding and storage. [50, 51] HD patients can show deficits in implicit memory, which are collections of coordinated movements and skills e.g. riding a bicycle, driving a car, chewing, and swallowing. [35] Manifest HD patients have shown impairments in encompassing verbal, episodic,

visuospatial, prospective, and echoic memory in a study. [52]

Perception: Both premanifest and very early manifest HD patients can show inability to perceive information. [35] This feature may be seen in recognizing facial emotional expressions, odors, understanding time, visuospatial perception, and overall awareness. [53]

Language: HD patients may show delay in initiating speech, decreased syllable rates, reduced number of words produced, diminished level of syntactic complexities, and increased paraphrasing errors with word-finding difficulties. [54] Metabolic imaging showed that impaired linguistic processing in HD was associated with the left striatum and specific portions of the striatum. [55]

Psychiatric features

Psychiatric features are highly prevalent in both premanifest and manifest HD. [35, 56] In adult-onset HD, the initial manifestation is more likely to be motor than psychiatric, while juvenile-onset HD are equally likely to present with motor, cognitive, or psychiatric features. [56] Psychiatric disturbances in HD are often underdiagnosed leading to inadequate treatment[57] despite their debilitating impacts on patients and their families, potentially causing financial exploitation and hospital admissions. [37, 58] Unlike the continuously worsening motor and cognitive functions, affective and behavior disorders show an irregular pattern of deterioration following the progression of the disease. [56] Among various psychiatric symptoms, depression, apathy, and irritability are prevalent across all stages of HD, while hallucinations and delusions occur more often in an advanced stage of the disease. [58]

Other non-motor features

Non-motor symptoms (NMS) and signs of HD include a range of metabolic alterations

(weight loss), disrupted circadian rhythm (sleep disturbance), and dysautonomia (cardiovascular, gastrointestinal, and genitourinary disorders). Patients with HD experienced weight loss, bowel problems, and vivid dreams even more frequently than those with Parkinson's disease[59] Non-motor symptoms in HD could start before the onset of motor symptoms and correlate with disease duration, total functional capacity, and disease stages. NMS in HD affect patients' quality of lives with a variable level of importance.

CLINICAL ASSESSMENT OF HD

Clinical diagnosis of HD

Diagnosis is based on the family history, personal history, neurological and psychiatric examinations, and genetic and any other appropriate testing. The diagnostic scheme of presymptomatic, prodromal and manifest HD is summarized in **Table 1**. Genetically confirmed HD is based on the CAG expansion of 36 or more of the Huntingtin gene (HTT). The full penetrance of HD in mutation carriers were >39 CAG repeats. Therefore, reduced penetrance is seen between 36–39 repeats, whilst 35 or below is considered normal. [26]

Evaluations of motor dysfunction and severity

Motor dysfunction and severity are evaluated with Unified Huntington's Disease Rating Scale (UHDRS) and total functional capacity, functional assessment scale, and independence scale. UHDRS-Total Motor Score (TMS), assesses eye movements, speech, alternating hand movements, dystonia, chorea and gait. UHDRS-TMS is sensitive to change in motor function over time. The details of these scales are explained below. [60] Of note, motor abnormalities in HD are rated as 'diagnostic confidence' scale (0~4) following the probability of manifestation, and not by the scores of TMS.

Evaluations of cognitive impairment

The screening test such as Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) may demonstrate only minor changes. MoCA is perhaps the simplest and most widely used screening test. The Symbol Digit Modalities Test and Stroop Word Reading Test are the best tools to evaluate cognitive function of HD. Moreover, verbal fluency test (category), Stroop color naming test, Stroop interference test, Trail making test (part A and B), and verbal fluency test (Letters) can be used to evaluate the cognition of HD. To diagnose individuals with 3 categories of HD (**Table 1**), presence of '***major cognitive disorder'*** in individuals with HD needs to be determined based on the DSM 5th criteria as follows; First, modest cognitive decline from a previous level of performance should be documented in one or more cognitive domains. Second, cognitive impairment interferes with independence in everyday activities. Comparatively, ***'minor cognitive disorder'*** in individuals with HD is defined if the cognitive decline does not interfere with independency but require greater effort, compensatory strategies, or accommodation. Secondary cognitive impairment due to depression has to be excluded. [61-63]

Evaluations of neuropsychiatric symptoms

The neuropsychiatric inventory (NPI) assesses the frequency (four-point rating scale) and severity (three-point scale) of 10 neuropsychiatric disturbances (delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior). The NPI offers advantages over previous psychiatric research in HD. Behavior symptoms can be assessed with problem behavior assessment (short), hospital anxiety and depression scale, Snaith irritable scale and Columbia suicide severity rating scale. [63]

The Unified Huntington's Disease Rating Scale (UHDRS)

UHDRS is developed to assess the clinical features of HD by the Huntington Study Group. [64] The UHDRS is composed of 6 sections (motor, cognitive, behavioral, functional assessment, independence scale, and total functional capacity). Korean version of UHDRS was available. [6, 65]

The UHDRS-TMS is formed of 15 items and has a maximum score of 124. The items of the UHDRS-TMS include chorea, dystonia, parkinsonism, motor performance, oculomotor function, and balance. The original version was published in 1996 and was updated and expanded in 1999 with the intention to increase its applicability. Different item combinations of the UHDRS-TMS have been used: 4 shortened versions were published 1 year later (TMS1–4); including a modified motor score as well as reported sub-item scores focused on gait, chorea, and dystonia or items related to bradykinesia. Internal consistency of the UHDRS-TMS has been reported to be very good in manifest HD (Cronbach' alpha 0.95 ~ 0.97). [64, 66] The test-retest reliability (0.96 and 0.97) seems to be also very good in patients with manifest HD, although studies used correlation coefficients. [66] Inter-rater reliability in manifest HD is very good with an intra-class correlation coefficient of 0.94, albeit in a small sample study (n = 24). [64] In the same study, the interclass correlation coefficient was lower for the chorea (0.82) and dystonia (0.62) sub-scores. [64] As expected, the UHDRS-TMS is negatively correlated with the UHDRS-Total Functional Capacity scale and disease stage, [65] as well as with other UHDRS functional and cognitive scales.

NATURAL COURSE

Natural course and progression of HD

After clinical manifestation, HD patients show neurological deterioration steadily. Many studies have tried to measure progression of HD. [67-70] The annual progression rate derived from the results of these studies are summarized in **Table 2**. One thing to note is that although most neurological symptoms have a steady deterioration course after onset, chorea progresses quickly in the early stages and reaches a plateau with more progression of the disease. [70]

Due to heterogeneity in the progression of diverse clinical symptoms in HD, simple functional staging is useful for clinical practice. The Shoulson and Fahn Staging Scale (SF scale) defines progression of HD into 5 stages based on the total functional capacity score of the UHDRS (**Table 3**). [71, 72] However, the SF 5-step classification is not based on the meaningful biological deterioration or clinical impact such as in cancer staging, there is an argue that it is better to use simple 3-step clinical stages (**Table 4**) than SF staging. [73]

Recently, the HD Integrated Staging System (HD-ISS) was introduced (**Figure 5**), which comprises a biological research definition and evidence-based staging centered on biological, clinical, and functional assessments. [74]

The most valid factors to be associated with the natural course of HD are 'age at onset' and 'CAG repeat length'. One study reported that younger age at onset is related to faster rates of motor, cognitive, and function progression. [75] Another study found that patients with late-onset HD had a much faster progression rate than patients with usual HD, reaching the severe stage an average of 2.8 years earlier. [76] The effect of CAG repeat length is rather complex than that of the onset age, and has shown controversial results. For example, one study reported that CAG repeat length was correlated with rapid progression, [77] while other study reported the opposite. [78] In 2019, a longitudinal study in which 443 HD patients were followed up for up to 6 years reported that motor-cognitive function and volumes of the caudate-putamen and the white matter-ventricle were associated with CAG repeat length and

age of patients. [79] Based on the evidence so far, the CAG repeat length are likely to be a most reliable predictor of progression rate in HD.

There is paucity of literature regarding HD patients in advanced stage. Patients with advanced HD present severe motor and cognitive impairments with nursing home placement in most cases. Therefore, neurologists cannot evaluate the patients properly at this stage. The caregivers are often unwilling to participate in research because they are exhausted in long-term care for this disastrous disease or became patients of manifest HD. Therefore, further studies on advanced and terminal stage of patients with HD remains to be unmet needs.

Survival of HD

The approximate life expectancy of HD patients is known to be about 15–20 years. In South Korea, one study analyzed the survival of 47 patients with genetically confirmed HD in 2016. [80] Mean age at onset was 46.1±14.0 years and mean age at death was 57.8±13.7 years. Median survival was 14.5 years. Median survival of HD is reported to be 15–18 years in Western population without genetic confirmation and European HD network cohort study showed median survival of 35 years from symptom onset. [81] The shorter survival in Korea may be explained by higher mean age at onset, differences in the HTT haplotypes and CCG polymorphisms, influence of other sociocultural factors, and population-specific comorbidities. [80]

As with disease progression, ‘age at onset’ is known as a predictor of survival in HD patients. Patients with juvenile onset (younger than 20 years) and with late onset (older than 50 years) were reported to have shorter disease duration than HD patients with common onset (20-50 years). [82] CAG repeat length was found to predict shorter survival in a study reported in 2022. [83] This study also reported that older age and male sex predicted shorter survival length. A

recent study in Korean patients also reported that survival after disease onset was shorter in patients with late-onset HD (age at onset ≥ 60 years) than in common-onset HD, and longer CAG repeats and higher age-at-onset were associated with shorter survival in Korean HD patients. [84]

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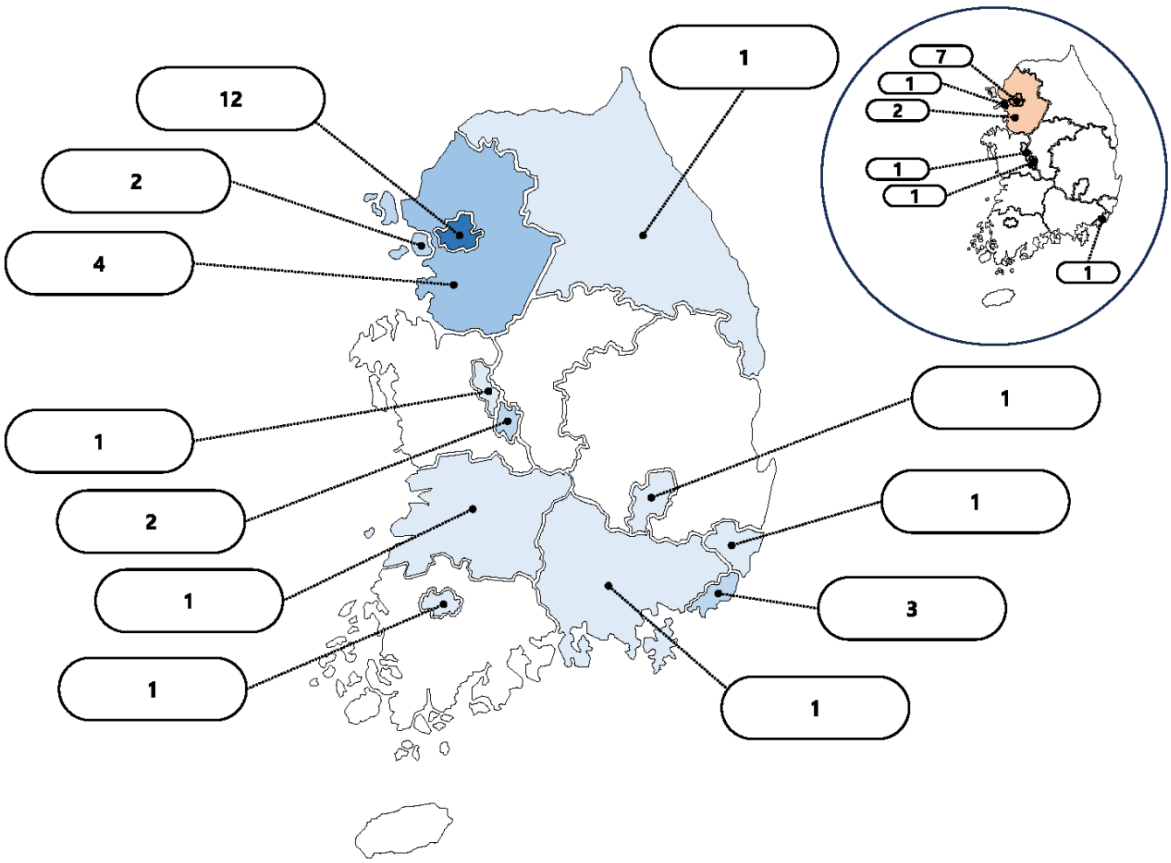

Figure 1. Number of participating sites within the Korean HD cohort study. Initially the first cohort study involved 13 sites (small circle), whereas the expanded KHD cohort currently encompasses 30 sites.

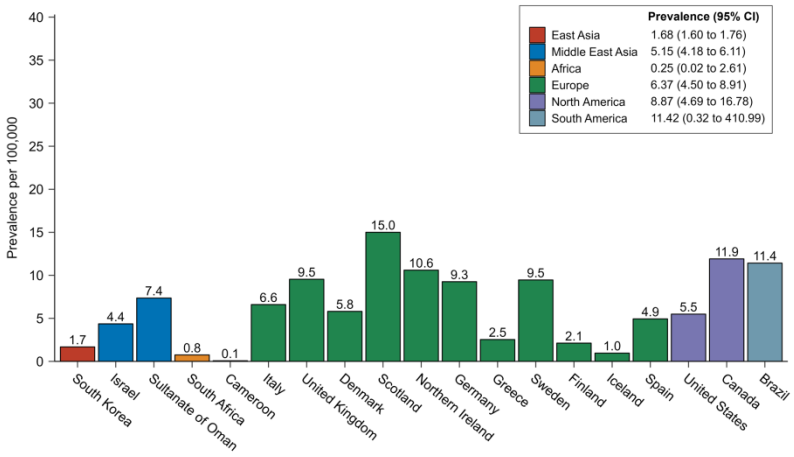

Figure 2. Prevalence of HD in various countries based on a systematic review and meta-analysis of studies published from 2011 to 2023. (modified from Medina et al.[5])

Abbreviations: CI=confidence interval; HD=Huntington's disease.

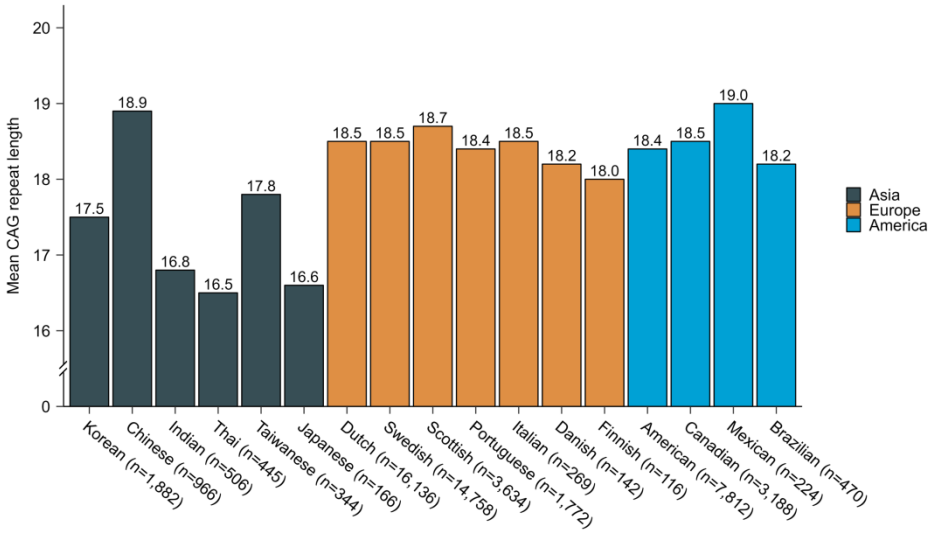

Figure 3. Ethnic diversity in mean CAG repeat length in the general population. The number next to ethnicity represents the allele count.

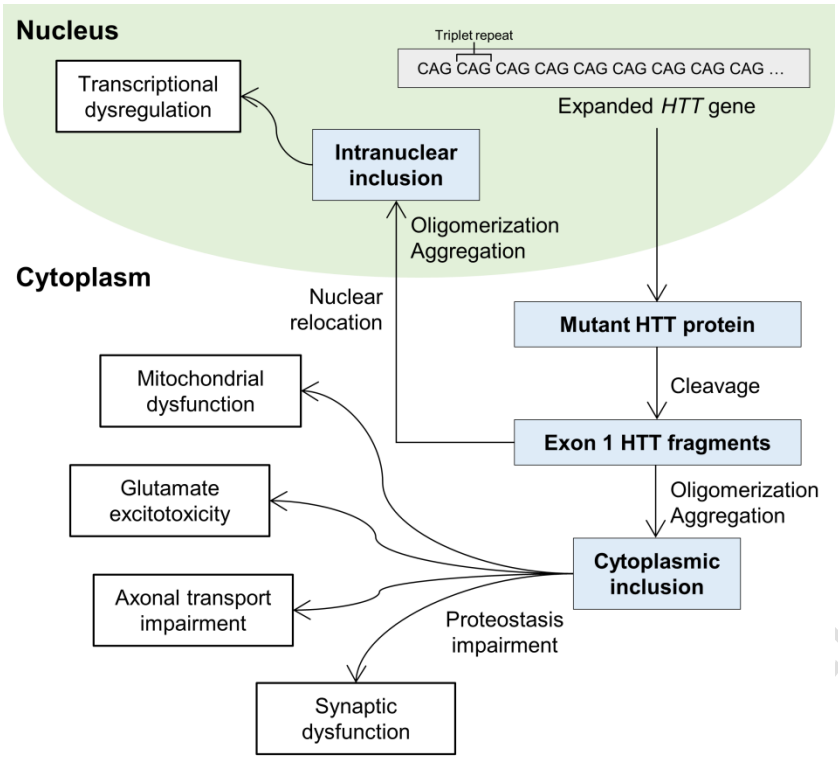

Figure 4. Molecular basis of pathogenesis of Huntington's disease.

Abbreviations: HTT, huntingtin.

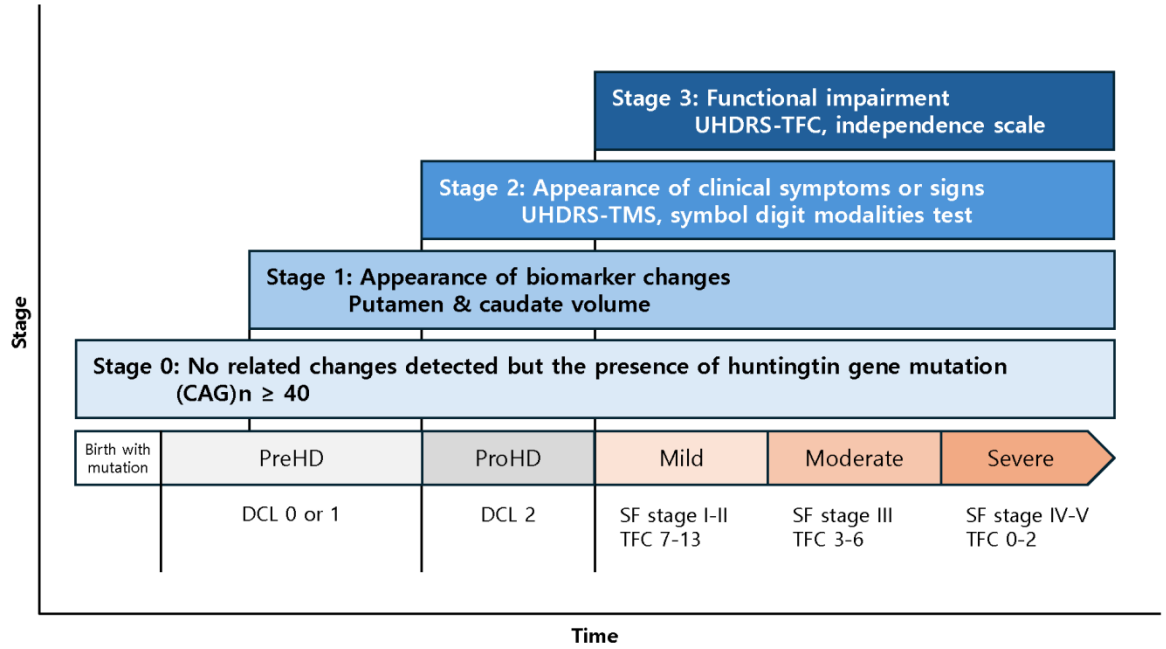

Figure 5. HD-ISS (Modified from Tabrizi et al. [74]). The HD-ISS characterizes individuals for research purposes. Stage 0: individuals with HD gene mutation without any pathologic changes starting from birth. Stage 1: only relevant biomarker changes are present. Stage 2: appearance of clinical symptoms or signs is measurable with UHDRS-TMS or symbol digit modalities test. Stage 3: Functional impairment starts in patients with manifest-HD. Abbreviations: HD-ISS, Huntington's Disease Integrated Staging System; HD, Huntington's Disease; PreHD, presymptomatic HD; ProHD, prodromal HD; DCL, motor diagnostic certainty level; UHDRS, unified Huntington's disease rating scale; TMS, total motor score; TFC, total functional capacity; SF, Shoulson–Fahn

Table 1. Criteria for diagnoses in individuals with an expanded CAG-repeats in Huntingtin

Diagnosis	Presymptomatic HD	Prodromal HD	Manifest HD
Motor (diagnostic confidence level)	0 or 1	2	3 or 4 2 (with significant progression in cognitive decline)
Cognition	No cognitive signs or symptoms	AND/OR minor cognitive disorder	AND/OR minor/major cognitive disorder

It is expected that the ability to define signs and symptoms would be enhanced by longitudinal follow-up and assessments. HD, Huntington's disease. (modified from Ross et al. 2019[1]). Following the diagnostic confidence level of the Unified Huntington's Disease Rating Scale (UHDRS), 0 = normal (no motor abnormalities); 1 = nonspecific motor abnormalities; 2 = motor abnormalities that may be signs of HD (50–89% confidence); 3 = motor abnormalities that are likely signs of HD (90–98% confidence); 4 = motor abnormalities that are unequivocal signs of HD (>99% confidence).

Table 2. Annual progression rate in selected motor, cognition, behavior, and function outcomes

Outcome category	Outcome	Sub-item	Annual progression rate
Motor outcome			
	Total motor score		2.9 — 6.4
	Chorea score		0.3 — 1
Cognition outcome			
	MMSE score		-0.7
	Verbal fluency score		-2.1 — 0.2
	SDMT score		-1.5 — -0.2
	Stroop score		
		Color naming	-4.8 — -1.8
		Word reading	-4.1 — 0.4
		Interference	-1.4 — -0.2
Behavior outcome			
	Frequency		-1.5 — 0.1
	Frequency × severity		0.6 — 1.2
Function outcome			
	Total functional capacity score		-1.4 — -0.4
	Functional checklist score		-1.8 — -1.0

The table modified Table 6. of Dorsey et al. 2013[2]

Abbreviations: HD, Huntington disease; MMSE, Mini-Mental State Examination; SDMT, Symbol Digit Modalities Test

Table 3. SF rating scale for assessment of progression of HD

SF stage	TFC Total score	Approximate years since motor diagnosis	Description
I	11-13	0-8	Only marginal decline in employment engagement and otherwise independence in basic functions, such as financial management, domestic responsibilities, and ADLs (eating, dressing, and bathing).
II	7-10	3-13	Work ability is typically lost and slight assistance in basic functions is required.
III	3-6	5-16	There is inability to engage in employment and major assistance in most basic functions is required.
IV	1-2	9-21	Major assistance in financial affairs, domestic responsibilities, and most activities of daily living is required. Care may still be provided at home but an extended care facility may better meet assistance needs.
V	0	11-26	Fulltime skilled nursing care is required.

Abbreviations: SF, Shoulson and Fahn; HD, Huntington's disease; TFC, total functional capacity; ADLs, activities of daily living

Table 4. Brief clinical stages for assessment of progression of HD

Clinical stage	Description	SF stage
Early	Patients are generally still active in most areas of functioning, and are often still working or driving	I
		II
Moderate	Patients become unable to perform complex functions such as work, driving or shopping independently, but still take care of ADLs and simple household tasks	III
Advanced	Patients can no longer take care of ADLs without help	IV
		V

Abbreviations: SF, Shoulson and Fahn; HD, Huntington's disease; ADLs, activities of daily living

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