

Genetic Profiling of Huntington's Disease: Insights from CAG Repeat Analysis for Precision Diagnosis and Management

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ABSTRACT

Introduction: Huntington's disease is a monogenic neurodegenerative disease that is inherited in an autosomal dominant manner and is characterized by motor, psychiatric and cognitive symptoms that progress within 15–20 years after diagnosis. In this study, we aimed to summarize our retrospectively compiled Huntington's disease diagnostic test results by correlating them with the patients' clinical findings.

Methods: We conducted an analysis on a cohort of 88 individuals and evaluated their clinical symptoms. The research included the sample collections, isolation of DNA, the polymerase chain reaction (PCR) step, and capillary electrophoresis for fragment analysis. The results were assessed and the Cytosine-Adenine-Guanine (CAG) repetition count was computed.

Results: The patients' CAG trinucleotide repeat (TNR) counts were determined. Individuals with a TNR of 39 and above were considered to have HD. Patients with increased clinical findings and pathogenic

TNR counts were evaluated in terms of detailed phenotypic features and family history. The ages of the patients ranged from 24 to 85, with a mean age of 50.12. The study suggests that the expansion of genetic repeats may affect the age of onset of the disease. The most common initial symptoms were chorea and psychiatric symptoms. Most patients had a family history of the disease and the transmission from the father occurred earlier.

Conclusion: It was emphasized that individuals with a TNR between 39 and above should be under the supervision of a physician. Prenatal diagnosis is recommended for those planning to have children. In addition, cases with a CAG trinucleotide repeat of 33 and 36 are recommended to inform the next generations about HD and to inform them about the possible effects in the future.

Keywords: Autosomal dominant, CAG repeats, Huntington's disease, Huntingtin gene

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INTRODUCTION

Huntington's disease (HD) is a progressive neurological disorder. Huntington's disease is characterized by choreiform movements, psychiatric disturbances, and cognitive decline (1). The autosomal dominant Huntingtin (HTT) gene on chromosome 4p has an increased cytosine-adenine-guanine (CAG) trinucleotide repeat (2). HD may be caused by mutant Huntingtin protein toxicity. Since no cure exists, treatment is symptomatic and supportive.

Worldwide, 4.88 people per 100,000 have HD. Europe (6.37 instances per 100,000) and North America (8.87 cases per 100,000) have the highest prevalence. HD impacts 0.48 per 100,000 (3).

Mental illness, dementia, and chorea are HD symptoms. First, subtle changes in movement and/or mental/cognitive skills appear. Motor symptoms become more prominent with disease progression. Cognitive and motor skills diminish (4).

Highlights

- Cytosine-adenine-guanine repeat length strongly correlates with Huntington's disease onset age.
- Psychiatric symptoms often precede motor dysfunction in HD patients.
- Paternal transmission of Huntingtin (HTT) gene shows earlier disease onset due to repeat instability.
- Lifestyle factors, such as exercise and smoking, influence HD progression.
- Intermediate CAG repeat alleles may cause HD-like symptoms in some individuals.

HD is a neurological condition characterized by motor symptoms such as chorea, hyperreflexia, dystonia, and motor instability (5,6).

Psychiatric symptoms include irritability, depression, and poor social connections, which may persist for years. Some late-onset HD patients only have motor symptoms due to their short life expectancy. Executive dysfunction is the main cognitive aspect of HD, impairing decision-making, multitasking, and goal switching. Some late-onset HD patients only have motor symptoms because their life expectancy is too short to develop cognitive symptoms (7–9).

In children with HD, symptoms like myoclonus, seizures, behavioral issues, and parkinsonism may be present before the age of 20. These symptoms are more noticeable in children than in adults when the illness first manifests (4).

Neuroimaging is used to assess the caudate head atrophy, a characteristic of HD, which is associated with volume reduction in the putamen. The caudate head atrophy can be evaluated using metrics like the ratio of frontal horn width to intercaudate distance and the ratio of intercaudate distance to inner table width. HD can also cause decreased T2 signal intensity on SWI sequences on head magnetic resonance image (MRI), associated with iron deposition in the basal ganglia. Cortical thinning and volume loss have been documented, regardless of age (10,15).

Diagnosis involves conventional clinical characteristics, family history, and genetic confirmation, with genetic molecular testing targeting pathogenic HTT gene duplications. Neuroimaging is commonly used to rule out structural abnormalities, but it no longer confirms HD diagnosis in the age of molecular testing.

HD is caused by a genetic process called “genetic anticipation” where individuals with 27–35 CAG repeats do not display symptoms but are at risk of passing the condition on to their children. This is due to greater spermatogenesis than oogenesis, resulting in longer CAG repeats and earlier symptoms. Individuals with over 40 CAG repeats develop HD earlier, while those with ≥ 60 CAG repeats experience juvenile-onset HD (16,20).

Effects of Post-Translational Modifications on Huntington's Disease

In HD, neuron loss specific to the striatum region of the brain is observed. The GABAergic (gamma-aminobutyric acid) medium-sized spiny projection neurons, which constitute 80% of the striatal neurons and project to the substantia nigra and globus pallidus, are the neuron group specifically affected in this disease (21). The initial clinical symptoms of the disease can be explained by the loss of 30–40% of striatal dopamine D1 and D2 receptors localized on these spiny neurons (22). In the advanced stages of HD, when more than 90% of the caudate-putamen neurons are lost, and atrophy and gliosis begin in the striatum, degeneration can also be observed in the cerebral cortex, globus pallidus, and to a lesser extent in the thalamus, subthalamic nucleus, nucleus accumbens, substantia nigra, cerebellum, and white matter (23,24). Sudden and uncontrolled movements result from disruption in the basal ganglia-thalamocortical pathways that control body movements.

HD is a neurodegenerative monogenetic autosomal dominant disorder that primarily affects spiny projection neurons in the striatum, leading to significant motor deficits.

These motor disorders are characterized by the appearance of involuntary movements and voluntary movement dysfunction, accompanied by neuropsychiatric symptoms such as depression (25) and cognitive

impairment (26). HD is caused by a mutation in the CAG repeat of the HTT gene, which encodes the Htt protein, a 348 kDa protein expressed in both the cytoplasm and nucleus of neurons (27). Htt is crucial for neural and embryonic development and is also involved in vesicular transport and transcription (28). When an expansion occurs in the CAG trinucleotide repeats in the HTT gene (polyglutamine –polyQ–stretch), a mutant form of the Htt protein (mHtt) is encoded, making this mHtt more prone to aggregation in both the cytoplasm and nucleus (29) and ultimately leading to neuronal death by disrupting mitochondrial and synaptic function, axonal transport, transcription, and translation processes (30,31).

Post-translational modifications (PTMs) are highly significant in HD, as they modulate the clearance and toxicity of polyQ-expanded Htt as well as the physiological functions of wild-type Htt (32). For instance, phosphorylation, acetylation, ubiquitination, and sumoylation of the first 17 amino acids of exon 1 of Htt, the smallest Htt fragment (Httex1), play critical roles in modulating cellular processes and functions.

SUMO-mHttex1 has recently been developed by (33) as region-specific, highly purified wild-type and mHttex1 proteins (34). These SUMO-Httex1 fusion proteins have been shown to enable Htt manipulation and modification and contribute to a better understanding of how Htt aggregation can be prevented.

Depending on which SUMO paralog is conjugated with Htt, different outcomes can be expected. Both SUMO-1 and SUMO-2/3 regulate HD via Htt modification and are thought to represent novel therapeutic targets for the development of neuroprotective treatments (35). However, SUMO-1 has been found to increase the solubility and toxicity of Htt (36) and SUMO-2 has been found to accumulate in the striatum, one of the most affected brain regions in HD, and is associated with pathogenic accumulation (37). Additionally, sumoylation is known to indirectly affect Htt and potentially contribute to neurotoxicity, as observed with the inflammatory kinase IKK, which activates mHtt clearance (quantity) (38).

METHODS

In this study, genetic analyses of a total of 88 Huntington's patients were performed with the experimental material and method procedure given below, and extra inferences were made from the total blood values of the patients. In addition to Huntington gene repeat results for genetic test analysis, the parameters examined in the patients were as follows: repeat number, age at onset, first symptom, current symptoms, family history, smoking, alcohol, education, weight, height, marital status, head trauma, cerebrovascular disease (CVD), hypertension (HTN), diabetes mellitus (DM), psychiatric symptoms, drugs, dementia and other findings. All these data were interpreted with statistical visualization and analysis using Python 3.13.0 version software language.

The molecular methods traditionally used in the diagnosis of HD are outlined below. The steps are provided in detail. DNA fragment analysis performed using gel electrophoresis is presented in the results section.

Subjects and Sample Collection

This research was conducted with permission obtained from the Umraniye Research and Training Hospital Ethical Committee, reference number 234072396. Patient blood samples related to this study were taken from the patients who were diagnosed with Huntington's disease after having applied to the neurology clinics. Each patient was informed about the study before blood sampling and was asked to sign an informed consent form. 5 mL blood samples were collected into EDTA tubes. After labeling, the tubes were stored at +4°C until isolation.

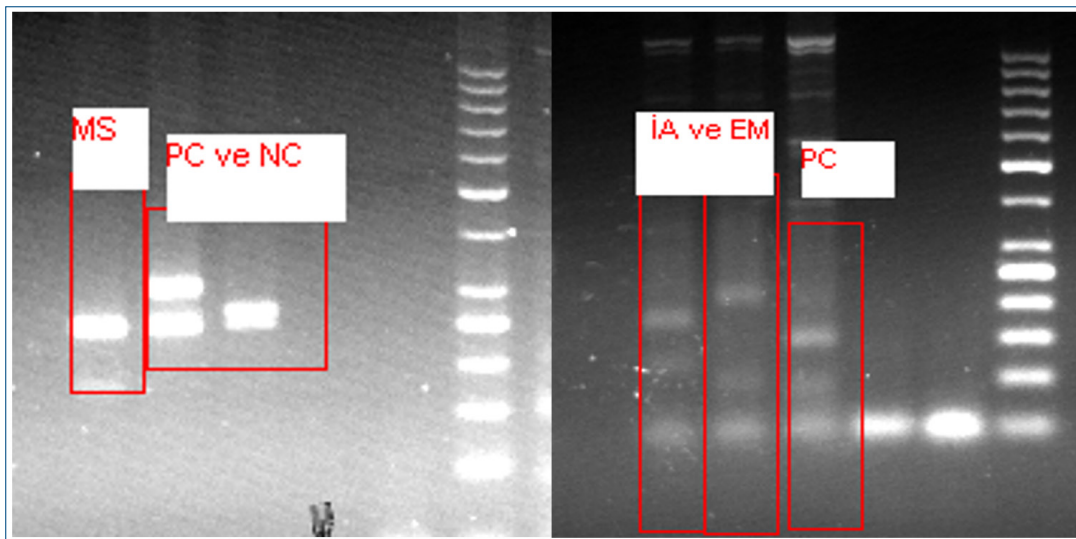


Figure 1. This gel electrophoresis image represents the genetic analysis results of a patient with Huntington's disease. The bands observed in the "IA" and "EM" regions correspond to the patient's DNA samples. The positioning of these bands at a higher location compared to the positive control (PC) indicates an increased number of CAG repeats, which is characteristic of Huntington's disease. This results confirms the presence of expanded CAG repeats, a genetic marker associated with Huntington's disease.

DNA Isolation

The goal of DNA isolation is to prepare contamination-free samples for subsequent tests. In this laboratory, the Lab-Aid 824 s Blood DNA extraction device and kit are used to automate DNA purification from whole blood using magnetic particle technology. The process yields high-quality DNA suitable for applications like PCR.

Preparation

- Sterilize the device under UV light for 15 minutes per 24-sample batch.
- Clean benches and micropipettes with alcohol.
- Label Eppendorf tubes with patient-specific codes.

Reagents and Sample Setup

- Reconstitute 0.45 g of DTT in 3000 μ L of water.
- Add 520 μ L of whole blood and 60 μ L of DTT to each labeled tube, vortex to mix.

Purification Procedure

1. Lysis: Add lysis buffer to release nucleic acids.
2. Binding: Mix lysates with binding buffer and magnetic particles to bind nucleic acids.
3. Washing: Remove contaminants with wash buffers while DNA remains bound to the particles.
4. Elution: Elute purified DNA into an elution buffer.

Post-isolation

- If magnetic particles remain, use a magnetic rack (e.g., DynaMag) to separate them.
- Transfer the DNA solution to a new tube.

The device processes up to 24 samples per run, yielding approximately 150 μ L of purified DNA per sample.

PCR Stage

PCR Sample Preparation

H₂O, PCR Mix, and Primer Mix were thawed at room temperature, while the Taq polymerase enzyme was kept on ice to preserve its activity. PCR Mix and Primer Mix were vortexed and spun down briefly. The polymerase enzyme was gently mixed by tapping and also spun down.

A master mix was prepared by multiplying the table quantities by half the number of samples. This mix was vortexed, spun down, and 4.7 μ L was

pipetted into 0.2 mL PCR tubes labeled with patient codes. DNA samples were vortexed, spun down, and 0.8 μ L of DNA was added to each tube containing the mix.

Gel Electrophoresis and Scanning

Total amount of 20–50 ng genomic DNA was used as an input material for amplifying the fragment of HTT gene which has the targeted CAG trinucleotide sequence. After amplification, samples were loaded into agarose gel concentrated 3%, 90 min for 110V. Gel visualization system was used to capture samples' fragmented products and they were measured in terms of their length quantitatively (Figure 1).

RESULTS

The genetic test results of 88 patients who applied to our department are stated according to the number of repeats on two alleles.

The geographic distribution of our patients is illustrated on the map below (Figure 2). No patients from the Aegean or Mediterranean regions have visited our clinic. Among the remaining regions of Türkiye, HD is most prevalent in the Eastern Anatolia region.

Our patients ranged in age from 24 to 85 years, with the average age being 50.12. The age at the onset of symptoms ranged from 15 to 78 years, with an average of 43.38. The average mutant allele CAG repeat length was 44.91, with the highest being 60. normal allele repeat length was on average 18.02, with a range between 12 and 26.

Among the 48 patients with heterozygous CAG repeats over 40, 50% were female and 50% were male (Table 1). The average age of the patients at the presentation was 47.9 years, irrespective of gender. The average age of presentation was 45.3 years for women and 50 for males. The average age upon diagnosis of the condition was 41.5 years for women and 45.6 for males. The mean age of diagnosis of the condition in our patient cohort was 43.6, irrespective of gender.

The most common first manifestations of the disease include chorea and psychiatric symptoms. In addition to the five presymptomatic individuals, chorea was identified as the first symptom in 10 patients, anxiety in three patients, and depression in three patients. Some family members were misdiagnosed as having Parkinson's disease, died before reaching the symptomatic stage/before being diagnosed, or displayed solely psychiatric symptoms. One of our patients fit the diagnostic criteria

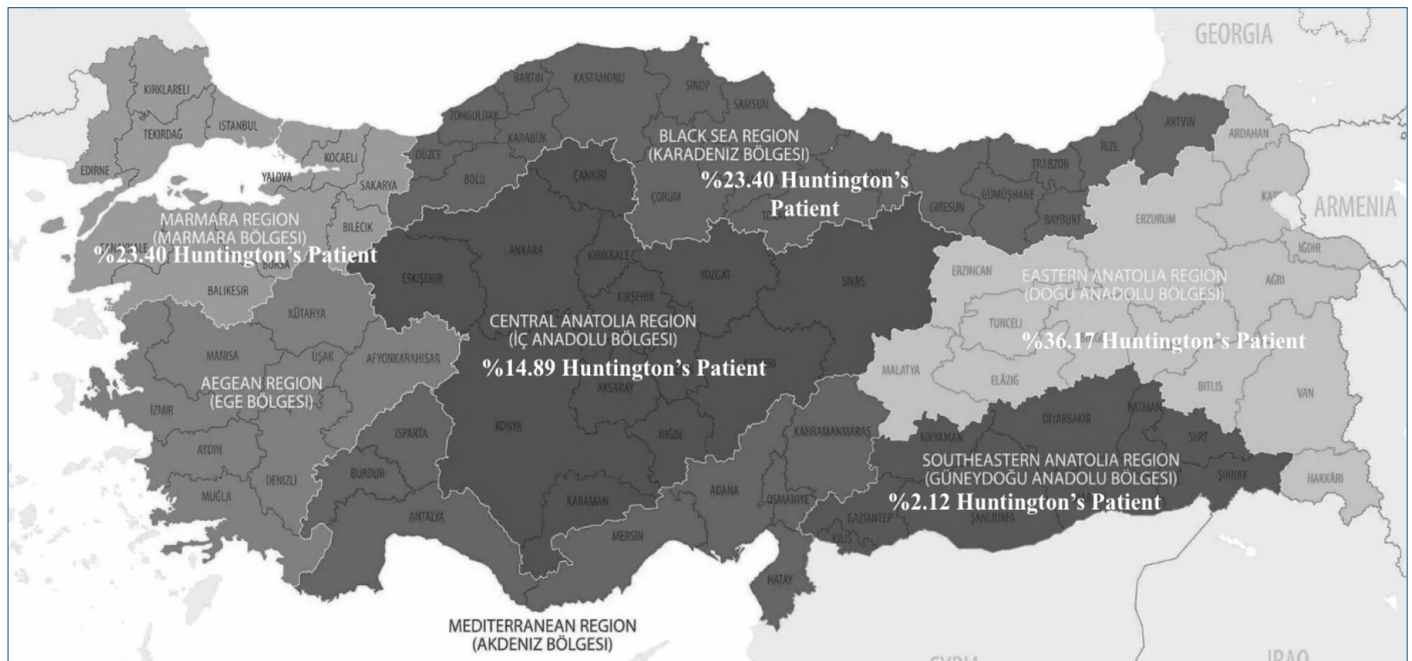


Figure 2. Geographic distribution map of Huntington's patients in our cohort.

Table 1. List of medications used by patients

Classification	Drug name	Prescription count
VMAT2 inhibitor (vesicular monoamine transporter 2)	Tetrabenazine	10
Typical antipsychotic	Haloperidol	7
	Risperidone	7
	Olanzapine	6
	Quetiapine	5
Atypical antipsychotic	Aripiprazole	3
	Sertraline	5
	Escitalopram	4
	Paroxetine	3
SSRI (selective serotonin reuptake inhibitor)	Fluoxetine	1
	Venlafaxine	2
SNRI (serotonin-norepinephrine reuptake inhibitor)	Mirtazapine	2
Atypical tetracyclic antidepressant	Clomipramine	1
Tricyclic antidepressant	Trazodone	1
SARI (serotonin antagonist and reuptake inhibitor)	Clonazepam	6
Benzodiazepine	Valproate	2
	Carbamazepine	1
	Gabapentin	1
Anticonvulsant	Donepezil	2
ACh inhibitor	Memantine	1
NMDA receptor antagonist	Piracetam	3
Racetam	Biperiden	2
Anticholinergic		

for juvenile HD, and demonstrated bradykinesia as one of her first signs, thus being closer to the Westphal variation. The largest number of CAG repeats we recorded was 60.

Additional initial symptoms encompass speech impairments, ambulation difficulties, depressive episodes, tics, bradykinesia, psychotic manifestations, movement disorders, polyneuropathy, balance loss, ataxia, suicide attempts, tremors, dystonia, paresthesia in the right arm, lower extremity atrophy, abrupt weight reduction, memory lapses, psychiatric disturbances, personality alterations, insomnia, and aggressive conduct.

The presenting symptoms and signs included speech abnormalities, ambulation difficulties, chorea, dysarthria, depression, muscular atrophy, loss of fine motor skills in the hands, dystonia, anxiety, psychosis, dementia, sleeplessness, and cognitive impairments. Patients exhibited tremors, dysphagia, stiffness, bradykinesia, psychosis, dementia, and cognitive impairments. Hemiparesis, tremors, chorea, cognitive impairments, personality alterations, speech difficulties, and motor dysfunctions were often noted.

Most patients had a family history suggestive of the disease as would be expected, though we were unable to reach some patients to confirm. In accordance with traditional knowledge and literature, anticipation appeared in paternally transmitted cases, with the sickness manifesting at an earlier age compared to maternally transmitted instances. The illness manifested at an earlier age in 13 paternally transmitted cases (28.9 years) than in 11 maternally transmitted cases (38.2 years). A notable age disparity existed regarding the beginning of the disease.

The majority of patients have a limited degree of schooling. To the best of our knowledge, just one patient had a high sociocultural level. The notable aspect about the patients' weight and height was that the majority exhibited normal weight before diagnosis but presented with a low body mass index after the onset of symptoms. The majority of the patients were married and had offspring.

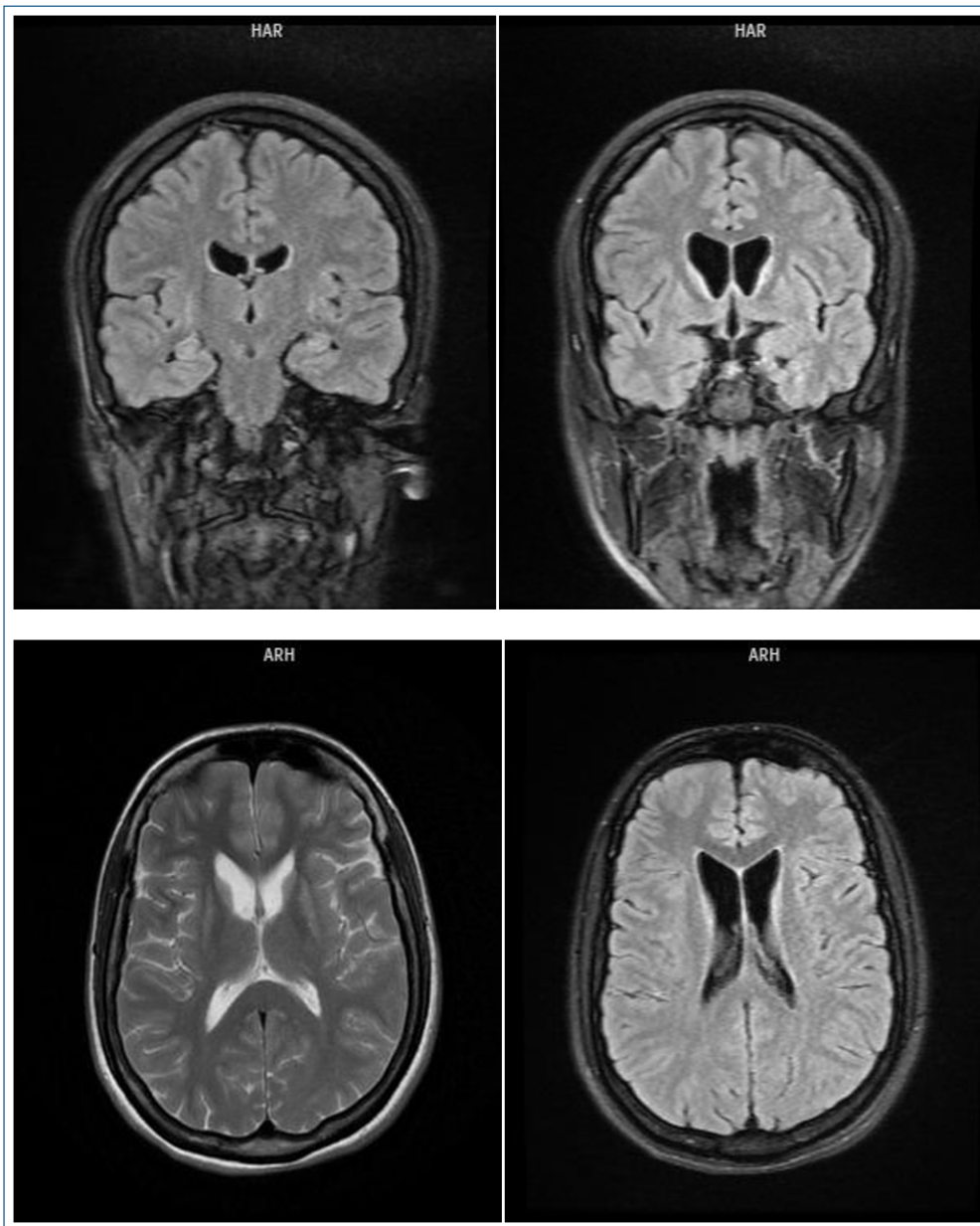


Figure 3. Magnetic resonance image of F7; Intercaudate distance (CC): 16.66 mm. Frontal horn width (FH): 33.66 mm. Inner table width (IT): 106.63 mm. FH/CC: 2.02. CC/IT: 0.15

Among the patients' medical histories, two had head trauma, three had cerebrovascular disease, six suffered from hypertension, and four were diagnosed with diabetes mellitus. The patients had mental symptoms such as adjustment problems, depressive episodes, anxiety, psychosis, suicidal thoughts, dementia, tense conduct, personality alterations, insomnia, aggressive behavior, night terrors, and mostly obsessive-compulsive disorder (OCD). Dementia was seen at a significant rate in the follow-up of the patients.

Ten patients used tetrabenazine at some point of their treatment, which made it the single most frequent drug in the list. In total, 12 patients used antipsychotics, with a total of 28 prescriptions, making it the most frequently used class of drugs, followed by antidepressants with 19 prescriptions and 12 patients. Patients also used other drugs for different health problems unrelated, or tangentially related, to HD (Table 1).

We have selected the MRI of three of our patients that best demonstrates the structural changes seen in HD, such as caudate atrophy and prominent lateral ventricular frontal horns (Fig. 3–5).

DNA Gel Electrophoresis Result Images

These images show the DNA fragment analysis of two HD patients. An increase in repeat numbers is observed.

DISCUSSION

Early in the 1990 s, innovative work by the Huntington's disease Collaborative Research Group revealed that CAG trinucleotide repeats expansions in the HTT gene on chromosome 4 constitute the genetic basis of HD, thus illuminating early understanding of the disorder. This finding represented a paradigm change and set the stage for further research on the molecular causes of CAG repeat instability (39).

Deepening knowledge of the association between CAG trinucleotide repeats expansions and HD has come from later studies, therefore clarifying the dynamic character of repeat expansion and its influence on disease phenotype (17,40,42). Research on how CAG repeat length influences disease onset and progression (43,44) and worldwide studies have shown environmental elements and genetic modifiers influencing CAG repeat dynamics, hence contributing to the variability seen in HD (45). These

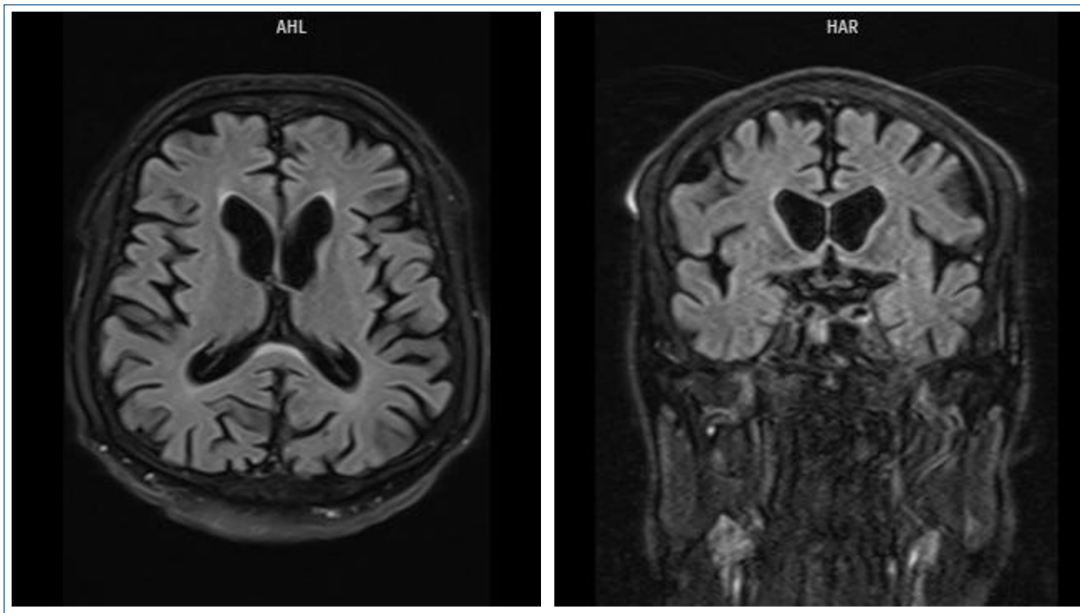


Figure 4. Magnetic resonance image of M4; Intercaudate distance (CC): 24.20 mm. Frontal horn width (FH): 38.78 mm. Inner table width (IT): 127.03 mm. FH/CC: 1.6. CC/IT: 0.18

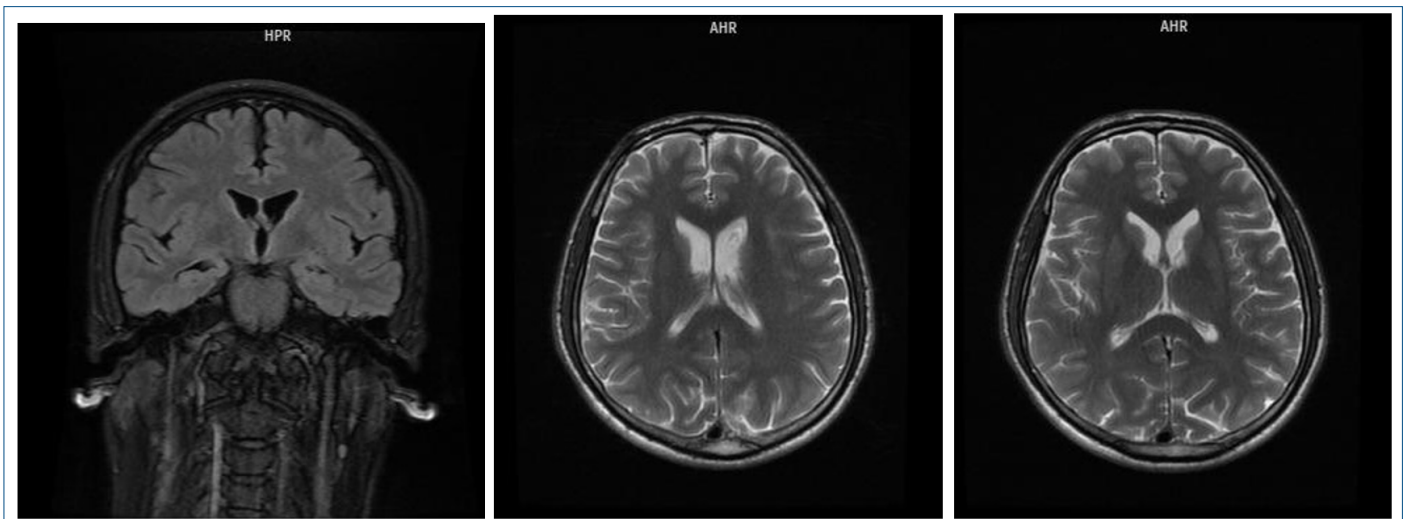


Figure 5. Magnetic resonance image of M7; Intercaudate distance (CC): 18.12 mm. Frontal horn width (FH): 36.22 mm. Inner table width (IT): 128.92 mm. FH/CC: 1.99. CC/IT: 0.14

results highlight the interdisciplinary character of HD research as well as the continuous attempt to enhance diagnosis and treatment plans (46,48).

Numerous recent studies on HD and CAG repeats has been published in the previous 15 years; one important change is the updated American College of Medical Genetics and Genomics (ACMG) recommendations for HD unveiled in 2014 (49). These recommendations define normal alleles as those with ≤ 26 CAG repeats and “mutable normal” or “intermediate alleles” for those with 27–35 repetitions. HD alleles with limited penetrance are those with 36–39 repetitions; those with ≥ 40 repetitions are linked with complete penetrance. Although no one with ≥ 40 CAG repeats has been identified without HD disease, a few asymptomatic carriers with 40–41 CAG repeats have been noted. Found in a young-onset patient (49), the biggest known HD allele had more than 250 CAG repeats.

Particularly for repetitions more than 50, the age of onset and CAG repeat length have an inverse relationship. Still, repetition duration makes it

difficult to forecast onset (49,50). Studies have shown that environmental and genetic elements affect HD onset; 40% of the effect comes from genes other than the HD gene and 60% from environmental elements. Contrary to the usual link, older people with intermediate CAG repeats had a greater chance of getting HD, according to a 2014 research (14).

Food restriction, phytochemicals, exercise, and intellectual stimulation may all help to improve cellular stress responses, therefore offering protection against HD and other neurodegenerative disorders. Aging processes compromise the neurocognitive scaffold, which enables intermediate CAG repeat length alterations (51,53) to arise. With alcohol and cigarette use associated to HD development, smoking is an environmental element accelerating neurodegenerative pathways (52,54).

Features of ovarian and breast cancer (55) and a non-linear connection between CAG size and lifetime depression risk have also been linked to CAG repeat length in HTT; both short and big alleles raise the risk (56).

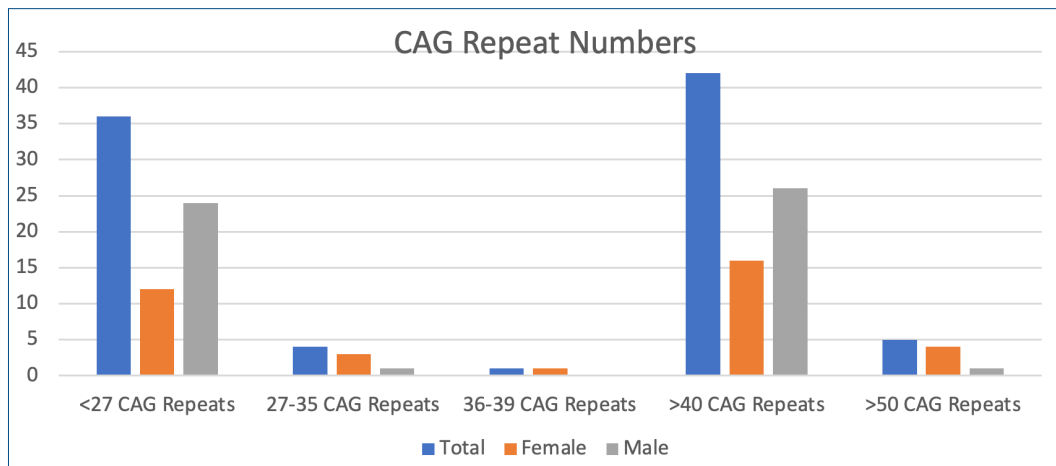


Figure 6. Cytosine-adenine-guanine (CAG) repeat numbers in our cohort: healthy and mutated repeat numbers.

Although HD is essentially a heterogeneous disorder, several homozygous examples have also been documented. For homozygous individuals, genetic counseling is very essential as kids of heterozygous parents have a 25% risk of getting a homozygous mutation and a 50% chance of receiving a heterozygous mutation (57).

With an inverted U-shaped pattern, J. K. Lee et al. (2018) discovered that the number of CAG repeats in HTT had a nonlinear influence on general intelligence; repeat lengths of 40–41 were connected to better General Ability Index (GAI) scores, while longer repetitions were linked to lower GAI scores (58). Given the numerous clinical presentations of HD make genetic discovery difficult, a 2019 review underlined the necessity of revised standards and appropriate psychological support during counseling (59).

While more unstable during paternal transfer, expanded CAG repeats are more stable during maternal transmission. Though they may point to a tendency toward CAG expansion during CCG10 germline transmission, CCG polymorphisms vary across various ancestral populations and have no effect on CAG instability (60).

A retrospective analysis of 6,316 HD patients from 161 sites within the European HD Network (REGISTRY) evaluated various symptoms, including motor, cognitive, and psychological aspects. The study emphasized that non-motor symptoms should not be relied upon for an HD diagnosis, as they are difficult to distinguish from underlying psychiatric conditions, particularly in younger individuals (4). Furthermore, another study found that clinical and neuroimaging results in patients with “intermediate range” CAG repeats were similar to those seen in HD cases, suggesting the need for further diagnostic investigation to determine whether HTT gene intermediate alleles (IAs) are causative in HD (61).

In a community study conducted in Mali, eighteen individuals from thirteen families were assessed for HD symptoms using the Total Motor Scale (TMS) and Mini-Mental State Examination (MMSE). The average CAG repeat length was 43.6 ± 11.5 , and the mean age of symptom onset was 43.1 ± 9.7 years. Common symptoms included choreic movements, cognitive impairment, and psychosocial issues (62).

Genetic testing results from 88 patients with HD in our cohort provide a detailed view of the clinical and molecular variability associated with CAG trinucleotide repeat expansions in the HTT gene. Comparing our findings with the literature presented here reflects several important trends documented in the past, while also providing new insights into the heterogeneity of the disease, particularly with respect to age of onset, clinical symptoms, and gender-related nuances in disease presentation.

The mean CAG repeat number in our study was 44.91, with the highest count reaching 60 repeats (Figure 6). This aligns with the well-established classification of HD alleles, where repeats exceeding 40 indicate full penetrance, as per the 2014 ACMG guidelines. Consistent with prior studies, we observed an inverse correlation between the length of the CAG expansion and the age at onset of symptoms, especially in patients with large repeat expansions (>50 repeats). Our data showed an average age of onset of 43.38 years, a finding consistent with the literature which suggests that HD typically manifests between the fourth and fifth decades of life (43–45).

Importantly, the phenomenon of anticipation –earlier onset of disease in successive generations– was apparent in our cohort, particularly in cases of paternal transmission. Thirteen patients with paternally inherited HD exhibited an earlier onset (mean age 28.9 years) compared to maternally inherited cases (mean age 38.2 years). This reflects the well-documented observation that paternal transmission tends to result in greater instability of the CAG repeat size, leading to earlier onset. The literature supports this, attributing the expansion during spermatogenesis as a key factor in this generational effect (60).

Clinically, our findings highlight the early motor and psychiatric manifestations typical of HD. Chorea was the most frequently reported initial symptom, present in 10 patients, consistent with HD's hallmark motor presentation. Psychiatric symptoms, including depression, anxiety, and psychosis, were also prevalent, supporting the growing recognition of HD as a neuropsychiatric disorder. Interestingly, we noted that psychiatric symptoms such as depression and obsessive-compulsive disorder (OCD) were present in several patients prior to the onset of motor symptoms. This echoes recent studies that emphasize the importance of psychiatric evaluation in patients at risk for HD, as psychiatric disturbances often precede motor signs (4).

One particularly noteworthy case in our cohort involved a patient diagnosed with juvenile-onset HD, characterized by bradykinesia and presenting with symptoms more aligned with the Westphal variant of the disease. Juvenile HD, while rare, is associated with a larger CAG repeat size and early motor symptoms that often mimic other neurodegenerative conditions, such as Parkinson's disease. This patient's bradykinesia and psychiatric symptoms are consistent with descriptions of juvenile HD in the literature, and highlight the diagnostic challenges this variant presents, particularly in differentiating it from other movement disorders early in the disease course (20).

The psychiatric burden in our cohort was significant, with symptoms ranging from anxiety and depression to more severe manifestations

such as psychosis and aggressive behavior. The prevalence of these psychiatric symptoms aligns with data from large-scale studies, such as the European HD Network's REGISTRY project, which highlighted the high frequency of non-motor symptoms in HD patients (4). This underscores the need for comprehensive psychiatric care and intervention as part of HD management, given the profound impact these symptoms have on patient quality of life and overall disease burden.

An important socio-economic observation in our cohort was the low educational level among most patients, with only one patient having a high socio-cultural background. Low educational attainment has been linked to poorer cognitive reserve, which may accelerate the cognitive decline observed in HD patients. This connection is supported by other research indicating that higher cognitive reserve may delay the onset of cognitive symptoms, although this remains an area for further investigation. Furthermore, many of our patients experienced significant weight loss following the onset of symptoms, which aligns with studies that link HD with metabolic dysfunction and cachexia. Weight loss in HD is thought to be associated with hypothalamic degeneration, and is a critical factor to monitor as the disease progresses (43-48).

Treatment strategies in our cohort were reflective of current pharmacological approaches to managing HD. Tetrabenazine, used to treat chorea, was the most frequently prescribed medication in our cohort, followed by antipsychotics and antidepressants. The high use of psychotropic medications in our patient population highlights the psychiatric morbidity associated with HD, reinforcing the need for a multidisciplinary approach to treatment. As studies have shown, treating psychiatric symptoms in HD not only improves quality of life but can also help manage the disease's overall progression.

From a genetic counseling perspective, our findings emphasize the complexities associated with intermediate CAG repeat alleles (27-35 repeats). Although none of our patients fell into this category, literature suggests that individuals with intermediate repeat lengths may still develop clinical features of HD, particularly in the presence of certain genetic modifiers or environmental factors. This has significant implications for genetic counseling, as these patients may be at risk for transmitting expanded alleles to future generations. Additionally, the recent work by Cheng et al. highlights the role of CCG polymorphisms

in modulating CAG repeat expansion, particularly in cases of paternal transmission, further complicating the genetic landscape of HD.

Our cohort also sheds light on the broader impact of environmental and lifestyle factors on HD progression. Research indicates that intellectual stimulation, physical exercise, and dietary restrictions may positively influence cellular stress responses, potentially delaying the onset of HD symptoms. Conversely, harmful habits such as smoking and excessive alcohol consumption have been linked to accelerated disease progression, particularly in those with longer CAG repeats. This suggests that lifestyle interventions may hold promise as part of a broader strategy for managing HD, although further research is needed to confirm these effects (47).

This study provides valuable insights into the complex genotype-phenotype correlations in HD, particularly focusing on CAG trinucleotide repeat expansions and their relationship with the onset and progression of clinical symptoms (Figure 7-8). Our findings reinforce established correlations between longer CAG repeat expansions and earlier disease onset, while highlighting the variability in clinical manifestations, which include motor dysfunctions, psychiatric disturbances, and cognitive impairments.

In line with previous research, our data underscore the role of genetic anticipation, particularly in paternally inherited cases, where disease onset occurred at significantly younger ages. The observation of distinct psychiatric symptoms, such as depression, anxiety, and obsessive-compulsive behaviors, even in presymptomatic individuals, emphasizes the importance of early psychiatric evaluation in HD management (16,18,20,60).

Interdisciplinary approaches are crucial in advancing our understanding of HD. From a genetic perspective, the dynamic nature of CAG repeat expansions necessitates further exploration into genetic modifiers and epigenetic factors that may influence disease penetrance and progression. Recent studies on environmental influences, such as intellectual stimulation, lifestyle, and epigenetic interactions, offer potential avenues for therapeutic interventions that go beyond the genetic mutation itself. These findings also highlight the need for personalized medicine approaches, integrating genetics with clinical and environmental factors (47,52,54).

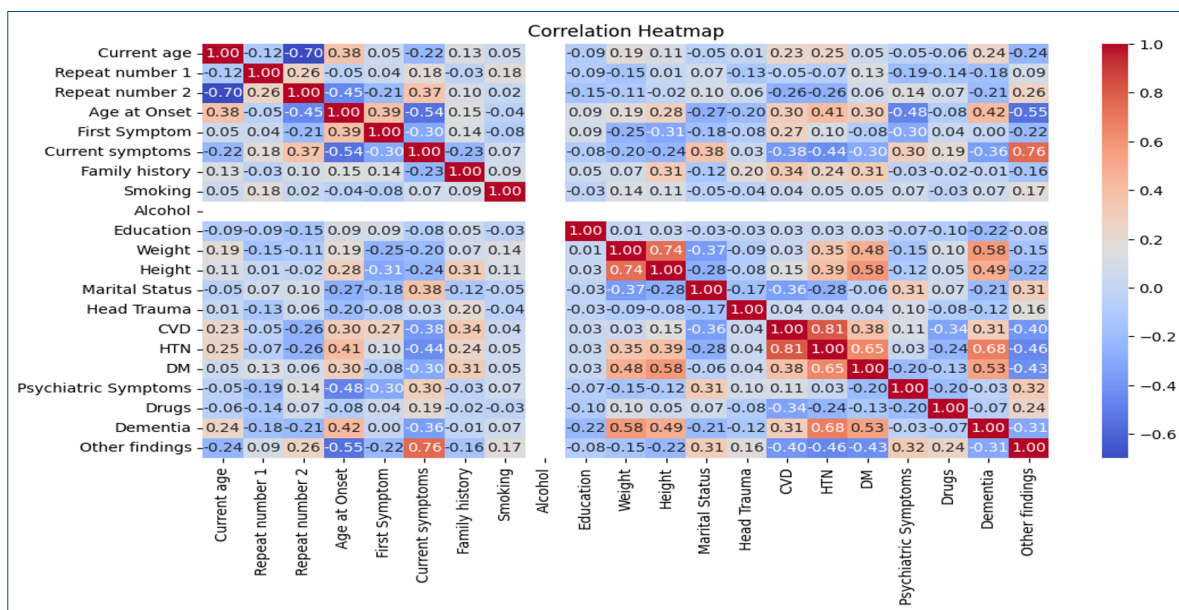


Figure 7. Correlation matrix and heatmap. The strong correlation between genetic repeat numbers may support genetic inheritance.

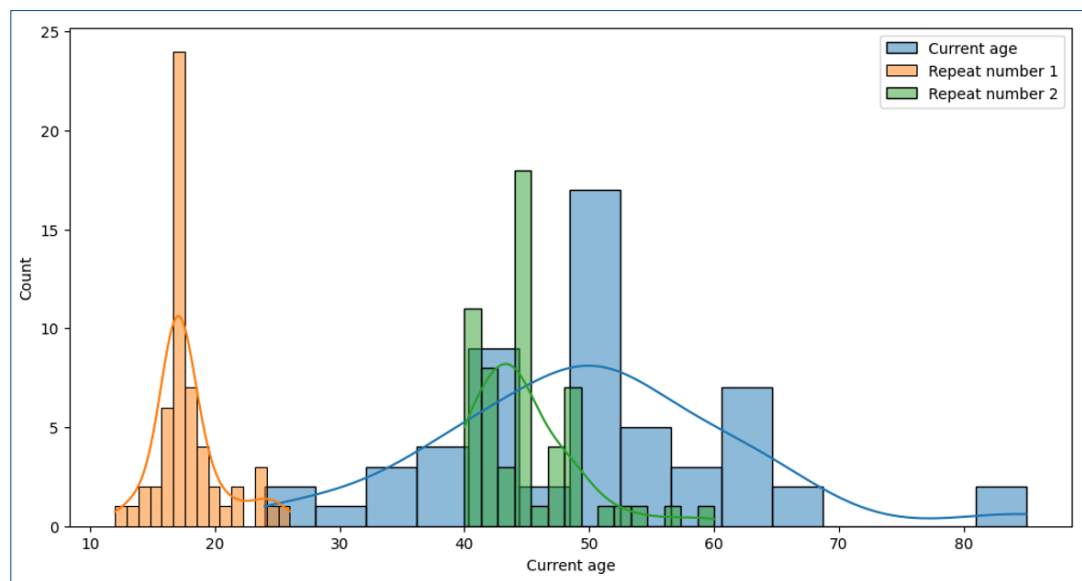


Figure 8. In Huntington's disease, the increase in genetic repeat numbers may influence the age of disease onset. The distributions in the figure indicate that lower genetic repeat numbers are predominant in younger individuals (lower age group), while an increase in repeat numbers is observed in the middle-age group. This supports the hypothesis that Huntington's disease is associated with the expansion of genetic repeats. It can be inferred that individuals with higher repeat numbers are more likely to exhibit symptoms of the disease at middle age.

Neurologically, our cohort exhibited the classical motor symptoms of HD, including chorea and bradykinesia, alongside cognitive decline, which have clear implications for both diagnosis and treatment. Advances in neuroimaging, such as magnetic resonance imaging (MRI), revealed characteristic caudate atrophy, supporting the role of neurodegeneration in the clinical trajectory of HD. These findings bridge molecular and clinical neurology, offering opportunities for biomarkers that could inform both early diagnosis and disease monitoring.

Psychiatrically, the overlap between HD-related neuropsychiatric symptoms and primary psychiatric disorders highlights the need for interdisciplinary collaboration between neurologists, psychiatrists, and genetic counselors. This collaboration is essential to provide holistic care for HD patients, ensuring that psychiatric manifestations are appropriately managed in the context of the overall disease burden.

In conclusion, this study underscores the value of integrating genetic, neurological, psychiatric, and molecular biology perspectives in HD research. A comprehensive, interdisciplinary approach to understanding HD not only advances our knowledge of disease mechanisms but also paves the way for novel therapeutic strategies aimed at improving patient outcomes. Future studies should focus on expanding genetic research to identify potential modifiers, while leveraging neuroimaging and psychiatric evaluations to develop more accurate predictive models for disease progression.

Ethics Committee Approval: This research was conducted with permission obtained from the Umraniye Research and Training Hospital Ethical Committee, reference number 234072396.

Informed Consent: Each patient was informed about the study before blood sampling and was asked to sign an informed consent form.

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