# Cranio-Facial Changes the in Patients with Huntington Disease, A Review Article

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*Abstract*— **Huntington's disease (HD) is a rare autosomal dominant sever and usually fatal chronic neurodegenerative illness with prevalence of 5.96 to 13.7 per 100000. The primary pathology is the precipitation of huntingtin protein in the neurons due to the presence of multiple CAG repeat in the N terminal of the HTT gene on the short arm of chromosome 4. Classically this is well known to primarily affect the caudate nucleus the largest of the basal ganglia. This manifests radiologically by shrinkage of the caudate nucleus with secondary dilatation of ventricular system. This however cannot explain the fact that the HD patients show a multitude of psychiatric and cognitive symptoms in addition to chorea. But it may be explained by the recent studies that show the basal nuclei are involved in limbic and emotional control in addition to their motor function. In order to review evidence of structural basal ganglia changes and their relation to clinical manifestations in patients with HD we conducted a web based search for published literature in the topic using pubmed and google scholar.**

**The review of the literature showed that the initial changes in HD happen in the caudate nucleus. Other parts of the striatum such as the putamen and globus pallidus are also affected, particularly following disease progression, with additional proof of thalamic changes. Such structural changes, in the striatum, for example, have been associated with specific cognitive deficits including attention, working memory and executive functions. Interestingly studies reported that MRIs are able to detect these changes long before clinical manifestation of HD.**

**We concluded that most of the components of the basal ganglia are reduced in size in HD. This volume reduction is evident years before the onset of the disease. The magnitude of volume reduction is directly related to the severity of the disease. These changes may be used to predict the onset and prognosis of disease and to monitor the response to treatment.**

*Index Terms*— **Basal Ganglia, Huntington Disease, Magnetic Resonance Images, Volumetric Changes.**

## I. Introduction

Huntington's disease (HD) is severe and usually fatal chronic neurodegenerative illness. The disease is inherited in a Mendelian dominant fashion with variable penetrance (Waldvogel, Kim, Tippett, Vonsattel, & Faull, 2015). Although it seems to be of mankind age the gene responsible for it was first identified on 1993 by the Huntington disease collaborative research group (Group, 1993) it is found to be on the short arm of chromosome 4 in a gene called HTT gene coding for a protein called huntigtin (Group, 1993). The gene defect is caused by something called trinucleotide expansion due to the presence of multiple (more than 40) CAG repeat in the N terminal of the gene. The specific mechanism by which this mutant protein causes the disease is not yet well understood. This may be due to the huntigtin protein intracellular aggregates which were identified by many researchers (Li et al., 2002). And they are assumed to cause cellular toxicity.

The disease is not common. The total global prevalence is estimated to be ranging from 5.96 to 13.7 per 100000. There is geographical and racial variation in the distribution of HD with the highest prevalence being reported in European, North American and Australian populations in comparison to Asian and African populations (Baig, Strong, & Quarrell, 20 July 2016).

The age at which the HD presented is ranging from 40 – 60 years (Ghosh & Tabrizi, 2015). And it is well known this is inversely related to the number of CAG repeats (Djousse et al., 2003). Patients with greater number have earlier onset of the disease. In contrary to what is expected being a disease of single gene etiology the HD has a very variable symptomatology. The spectrum of the symptoms ranges from motor, cognitive to behavioral and neuropsychiatric symptoms. Classically the well known symptom is the repetitive rapid alternating purposeless fliting writhing movement which is called chorea (Ghosh & Tabrizi, 2015). Other symptoms include: dementia, memory loss, depression, cognitive impairment, behavioral changes, irritability, aggression, anxiety and obsessions (Montoya, Price, Menear, & Lepage, 2006).

Classically the HD was thought to primarily affect the basal ganglia. Which are a group of subcortical grey matter nuclei derived from the telencephalon and include the caudate nucleus, the putamen and globus pallidus among others and they are involved in subcortical control of motor activity (Ali, 1993). This classical assumption is dared by the fact that the HD patients show a multitude of symptoms pertaining to other functions of the nervous system other than the motor function. And it is proved wrong by many histological studies that showed neuronal cell loss in the basal ganglia mainly the striatum (caudate and putamen) and all the following brain regions: prefrontal cortex, cingulated gyrus, orbital frontal cortex, temporal lobe, hippocampus, thalamus and cerebellum. So nowadays the HD is viewed as multi-system cortico-basal ganglia degenerative disease (Waldvogel et al., 2015).

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Structural images show shrinkage of the caudate nucleus with secondary dilatation of ventricular system (Osborn, Salzman, & Jhaveri, 2016). Other studies have shown diffuse cerebral atrophy mainly of the cerebral cortex, cingulated gyrus, hippocampus, thalamus and cerebellum (Gellersen et al., 2017). Moreover, these imaging studies are proved to detect brain changes years before the onset of the disease (Niccolini & Politis, 2014 ).

Although rare, Huntington disease has a major impact on the quality of life of the patients, their families and the communities. Moreover, it is associated with social stigma. This may cause delayed seeking of medical treatment. All these constraints in addition to the lack of specific biomarkers of disease progress led to the absence of disease modifying drugs till now. Furthermore, till now the diagnosis of HD is based in clinical history, physical examination and genetic analysis and there is no specific radiological or anatomical feature that is identified to be pathognomonic.

Studying and management of any disease need to have good knowledge of the natural history. And knowing the natural history is based on the knowledge of specific biomarkers that mark the stages of disease progression. In cases of neurodegenerative diseases, recent advances in the field of neuroimaging has facilitated the study and hence the identification of many structural and functional brain changes that may be used as biomarker for diagnosis and follow up. Many studies have been published identifying structural changes of many parts of the brain that is associated with HD. However none of them had been reported to be specific biomarker of HD. In this study we are reviewing the published literature focusing on the structural changes of the basal ganglia and their relation to the clinical manifestation in patients with HD. In order to achieve this, a web-based search for the published literature was done using PubMed and Google scholar.

## II. Development and General Topography of the Human Brain

All of the nervous system with its two parts the peripheral and central nervous systems is derived from the ectodermal germ layer (Sadler, 2015). It begins to develop at the beginning of the third week of intrauterine life as a thickening of the ectoderm termed neural plate subsequently this plate elevates to form neural folds and finally it closes to form neural tube (Moore, Persaud, & Torchia, 2013). Immediately before its closure a cluster of cells detaches from the neural folds these are called neural crest cells. The neural tube ultimately develops into the central nervous system while the neural crest cells form the peripheral nervous system.

The cranial part of the neural tube undergoes a complex change from neural tube to primary brain vesicles (prosencephalon, mesencephalon and rhombencephalon) then secondary brain vesicles (telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon) to finally become the adult brain which is composed of the cerebrum, cerebellum and brainstem. The brain can be defined as the part of the central nervous system that is housed within the cranial cavity. It is composed of the cerebrum, cerebellum and brainstem. The cerebrum is composed of two cerebral hemispheres which are connected in the midline by the corpus callosum and the diencephalic structures thalamus and hypothalamus. The cerebral hemisphere is composed of an outer layer of grey matter termed cerebral cortex and a core of white matter dispersed within this core of white matter are many nuclear masses composed of grey matter called basal ganglia (Moore et al., 2013; Sadler, 2015).

## III. Anatomy and Functional Circuits of the Basal Ganglia

Basal ganglia or more correctly they should be named basal nuclei are group of nuclear masses of grey matter embedded in the white matter of each cerebral hemisphere. Classically on anatomical basis the basal ganglia would include: the caudate, putamen, globus pallidus, amygdala and claustrum and even the thalamus. The thalamus has been excluded because of its unique structural and functional connectivity of its nuclei. The amygdaloid body is more concerned with limbic functions. Finally, the claustrum is regarded as an internally migrating part of the insular cortex. Some diencephalic and mesencephalic structures are intimately related to the basal nuclei and therefore they are included with them functionally these structures are the subthalamic nucleus and the substantia nigra (Ali, 1993).

Some confusing eponymous nomenclatures were used to describe different structures in the basal ganglia. The lentiform nucleus refers to the globus pallidus and putamen combined together. The corpus striatum is used to describe the caudate nucleus, putamen and globus pallidus. The neostriatum or sometimes just striatum is used to refer to the caudate and putamen (Ali, 1993; Snell, 2006).

Caudate nucleus is the largest of the basal nuclei. It is of comma shape with head, body and tail. All the parts of the caudate nucleus has a relation with the lateral ventricle with the head forming the lateral wall of the anterior horn, the body forms the floor of the body of the lateral ventricle and the tapering tail forming the roof of the inferior horn of the lateral ventricle. The head is partially fused with the putamen anteriorly and this grey matter is interrupted by the bundle of fibers of the anterior limb of internal capsule resulting in a stripped form from which the name striatum is derived(Ali, 1993; Snell, 2006).

The lentiform nucleus is somehow convex mass of grey matter situated between the head of caudate and the thalamus medially and the insular cortex laterally separated from the earlier by the internal capsule and from the later by the external capsule and the claustrum. It is composed of two anatomically and functionally separate components one of them is situated laterally which is the putamen and the other found medially and called globus pallidus. These two are separated by a narrow strip of white matter called external pallidal lamina and the globus pallidus is further subdivided by the internal pallidal lamina into external and internal parts (Ali, 1993; Snell, 2006).

The claustrum is serrated plate like mass of grey matter

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immediately below the insula. No known function has been ascribed to this structure although its sometimes regarded as submersed part of the insular cortex (Ali, 1993; Snell, 2006).

Amygdaloid body is almond shaped small mass of grey matter in the uncus of the temporal lobe that it is attached to the tip of the tail of the caudate nucleus. It is functionally related and considered part of the limbic system (Ali, 1993; Snell, 2006).

Substantia nigra is a functionally related part of the basal ganglia. It is found in the midbrain in between the crus cerebri and the tegmentum. It is composed of cells rich in melanin pigment. And is further subdivided into substantia nigra pars compacta and pars reticulata according to the density of the pigment (Ali, 1993; Snell, 2006).

Other functionally related nucleus is the subthalamic nucleus which is anatomically found in the diencephalon, specifically in the ventral thalamus caudal to the lateral thalamus related medially to the hypothalamus and inferiorly to the substantia nigra (Ali, 1993; Snell, 2006).

Till recent years the well-known and the only function of the basal nuclei was thought to be motor control via the extrapyramidal motor system. But now it is possible to characterize at least four functional circuits which start in the cerebral cortex go through the basal ganglia and return back to the cortex. These circuits are: a motor loop, concerned with learned movements; a cognitive loop, concerned with motor intentions; a limbic loop, concerned with emotional aspects of movement and an oculomotor loop, concerned with voluntary saccades (FitzGerald, Gruener, & Mtui, 2012).

## IV. Huntington disease

### A. Huntington disease

It's a progressive, disabling and usually fatal neurodegenerative disease with various motor, psychiatric and cognitive manifestations (Mehrabi, Singh-Bains, Waldvogel, & Faull, 2016). It was first described properly by George Huntington in 1872.

### B. Genetics of Huntington Disease

HD is inherited in mendelian autosomal dominant fashion. Huntington's disease is caused by an elongate CAG triplet repeat in exon 1 of the gene encoding Huntingtin protein (''HTT'' is the name given to the gene that encodes the protein ''HTT''), which is situated on the short arm of chromosome 4. The wild-type gene contains less than 36 repeats. Patients with more than 40 CAG repeats will contract HD sooner or later in their lives as the mutation is fully penetrant at these repeat lengths. Those patients who have 36–39 CAG repeats display a reduced penetrance—some may develop features of HD at an older age, others may never become symptomatic at all (RG, JC, & JP, 1993; Rubinsztein et al., 1996).

### C. Prevalence of Huntington Disease

The prevalence of HD is highly variable across the different regions in the world. With Japan, South Africa, and Finland have obviously very low rates of disease. It is prevalence was reported to be about 4–10 per 100,000 people in the Western hemisphere (Harper, Lim, & Craufurd, 2000). recent studies from UK showed high prevalence of 12.3 per 100,000 (Evans et al., 2013; M, 2010).For many causes, together with those rooted back to the seventeenth century when witchcraft was considered to be associated with HD, there has been a huge amount of stigma attached to this condition (A, 2010).

### D. Pathogenesis of Huntington Disease

The specific mechanism by which the mutation in HTT gene will culminate to produce the symptomatology of HD is till now not well understood. The most widely accepted theory is that the mutant gene will produce a faulty protein that is misfolded and precipitate in the cells of the nervous system. These precipitates are toxic to the cells and will result in their death and this finally result in the appearance of the symptoms (Waldvogel et al., 2015).

### E. Clinical presentation of Huntington Disease

Huntington's disease is classically distinguished by a triad of motor, cognitive and psychiatric symptoms, with slow but progressive deterioration over a 15–20 years period. Eventually, the reason of death is usually due to pneumonia (DJ, MJ, L, & Schoenberg, 1988). The mean age of the onset of the disease is at 40 years, but HD has been reported in very young children 2 years old and on the other hand up to the age of 87 years. If the disease onset happened at 20 years of age, the condition is called ''Juvenile HD'' (B, 2002).

The principal motor feature of HD is chorea (previously the disease was named Huntington chorea. Chorea can be defined as involuntary excessive movements which are short-lived and can appear to be semi-purposeful. Additionally, Dystonia may be observed in patients with HD —these are slower movements caused by increased muscle tone and sustained muscle contractions which lead to abnormal postures such as tilting or turning of the neck (torticollis) or arching of the back (opisthotonos).

The cognitive deficit in HD is of variable severity ranging from very mild deficit that goes unrecognized by the patient to a very severe prominent impairment. It usually occurs in the prodromal stage of the disease. The most commonly affected domain is the area of executive functioning.

The psychiatric features occur in about 33–76 % of patients (E, EM, & RC, 2007). The most common psychiatric manifestation is depression, followed by anxiety, and their presence is unrelated stage of disease (Julien et al., 2007).

Moreover, nowadays HD is being recognized as a multisystem disease this is because of the fact that the clinical presentation of the disease is not limited to the above mentioned neuropsychiatric and cognitive symptoms and signs. HD has been reported to be associated with a body wasting syndrome (cachexia) principally via the mutant HTT gene activity in skeletal muscle, bone, adipose tissue, and heart. Additionally, the mutant gene causes whole-organism effects including decline in systemic metabolic homeostasis through derangement of pancreatic, hepatic, gastrointestinal, hypothalamic-pituitary-adrenal axis and circadian functions

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(Julien et al., 2007).

Furthermore, HD patients when compared to controls were found to have significantly more decayed teeth and more plaques and overall worsening dental status even in pre-manifest gene carriers (Julien et al., 2007).

### *F. Treatment of Huntington Disease*

In spite of its very old history and well-known cause, HD remains incurable disease till date. Its management requires a multidisciplinary team approach. The team may include the following specialists: neurologists, psychiatrists, general practitioners, physiotherapists, occupational therapists, speech and language therapists, dieticians, and nurse specialists. In some regions in the world, they develop specialist HD clinics. The main target is symptomatic treatment and to optimize the function (RM & P, 2007; SL & RA, 2009). There is however much research in this field and trials of treatments that potentially alter the course of the disease are underway.

### *G. Cellular and molecular changes of the basal ganglia in Huntington disease*

The primary etiological cause underlying the pathophysiological mechanism of HD is the structural, cellular and chemical alterations of the basal ganglia (Mehrabi et al., 2016). Neurobiochemical studies have proven that both the motor and limbic functional circuits of the basal ganglia are affected in patients with HD. Following is a brief description of the pathological alterations in these neurotransmitters.

Many of the recent studies established the link between the disruption of basal ganglia striatal pathways and the development of hyperkinetic movement disorders that occur in early stages of HD and dyskinetic movement disorders that occur in advanced HD. Degeneration of "indirect" GABA/ENKEPHALIN striate-pallidal fibers, that project from the striatum to the Globus pallidus externus results in a decrease in the inhibitory action upon Globus pallidus externus, which cultivate in increased activation of the GABAergic neurons that project from the Globus pallidus externus to the subthalamic nucleus. This leads to the diminution of Globus pallidus internus inhibitory action over the thalamus, leading to hyperactivity of the cortical sensorimotor areas, consequently chorea will manifest (Crossman, Mitchell, Sambrook, & Jackson, 1988). On the other hand, degeneration of the "direct" GABA/Substance P striate-pallidal fibers results in lack of inhibition of the Globus pallidus internus. This, will consequently, causes more inhibition of the excitatory thalamic-cortical projection, and finally rigidity (Berardelli et al., 1999). The "indirect" GABA/ Enkephalin producing medium spiny neurons have been shown to be the most affected by the disease process, as their degeneration occurs before that of the "direct" GABA/Substance P producing medium spiny neurons. In fact, previous post-mortem studies have shown that decrease in Enkephalin staining of the Globus pallidus externus was a salient feature in early stages of HD, whereas Substance P staining in the Globus pallidus internus and Substantia nigra pars reticularis was affected only in later stages of the disease (Deng et al., 2004; Glass, Dragunow, & Faull, 2000).

Despite the fact that HD is classically regarded as a disease of motor system with a predominantly motor manifestations, patients with HD exhibit many behavioral, psychiatric and mood disturbances which are likely to be related to the dysfunction of the frontal cortical areas and/or the basal ganglia. Those non-motor symptoms of HD are hypothesized to be due to the disturbed functioning of the limbic circuit of the basal ganglia (Cummings, 1993, 2003). In fact, some previous studies connected between mood symptoms of HD, like depression for example, with disturbance of the cortico-basal ganglia limbic loop (Chamberlain & Sahakian, 2004, 2006).

Grossly post-mortem studies of HD human brains, in addition to the recent in vivo neuroimaging studies, showed prominent distinctive bilateral atrophy of the striatum (caudate nucleus and putamen) (de la Monte, Vonsattel, & Richardson, 1988; Vonsattel & DiFiglia, 1998). Most of the atrophic change of the striatum is due to the loss of GABA argic medium spiny projection neurons which form about 90-95% of the number of the neurons in the striatum, in addition to their dendritic arbors and heavily myelinated axons (Mehrabi et al., 2016).

### *H. Macroscopic changes of the basal ganglia in Huntington disease*

Characteristically, postmortem macroscopic studies of the brain of patients with HD revealed conspicuous bilateral atrophic changes of the striatum (Aylward et al., 1997; de la Monte et al., 1988; Vonsattel, 2008; Vonsattel & DiFiglia, 1998). Vonsattel and DiFiglia reported that this degeneration has specific ordered pattern by which it occurs starting at the tail of the caudate in the early stages of the disease and proceeds rostrally till it reaches the head in advanced stages. Furthermore, they also found that the degeneration progresses simultaneously from medial to lateral aspects and from dorsal to ventral aspects (Vonsattel & DiFiglia, 1998). Classically, it has been reported that the gross examination of HD brains showed that the volume of the caudate and putamen is decreased with the resultant change in their shapes this is also associated with reduction of the volume of the globus pallidus but to a lesser extent (Waldvogel et al., 2015). De la Monte et al studied 30 postmortem samples of brains of patients with HD they found that the cross-sectional area of the putamen and the caudate is averagely reduced by about 64% and 57% respectively (de la Monte et al., 1988). This progressive loss of the mass of the caudate nucleus results in a subsequent change of the characteristic convex shape of the caudate that mark the lateral boundary of the anterior horn of the lateral ventricle to become thinner and finally concave which causes enlargement of the lateral ventricle which is the most common radiological finding sought by clinicians in the brain scans of HD patients.

As mentioned above these gradual atrophic changes is primarily due to loss of the neurons in those nuclei mainly the medium spiny neurons along with their dendritic and and heavily myelinated axonal projections. Vonsattel grading system for HD uses the macroscopic degree of the ventricular dilatation and shape of the caudate in addition to the microscopic features of neuronal loss and gliosis to grade HD into five grades from 0 to 4 (Vonsattel, 2008; Vonsattel &

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DiFiglia, 1998).

*I. Structural neuroimaging modalities in Huntington disease*

In the recent years the world witnessed a huge advancement in many fields, of these neuroimaging modalities and its applications in the clinical and research fields is paramount. These neuroimaging techniques have enabled physicians in the clinic and researchers to identify the brain changes of almost all neurological diseases in living patients without using invasive procedures and furthermore to compare the patients with healthy control.

There are a number of accepted and safe imaging techniques used in hospitals and researches like; computed tomography (CT) scanning that builds up a picture of the brain based on the differential absorption of X-rays. CT scans reveal the gross features of the brain but do not resolve its structure well.

Positron emission tomography (PET) uses trace amounts of radioactive materials that are injected into bloodstream to map functional processes in the brain. Single-photon emission computed tomography (SPECT) is similar to PET and uses gamma rays and cameras to construct two- or three-dimensional images of active brain regions. Magnetic resonance imaging (MRI) uses strong magnetic fields and radio waves to produce high quality two- or three-dimensional images of brain structures without use of radioactive tracers. Functional magnetic resonance imaging (fMRI) relies on the paramagnetic properties of oxygenated and deoxygenated hemoglobin to see images of changing blood flow in the brain, so it can show which part of the brain is active or functioning, in response to a certain task performed by the patient through the recording of movement of blood flow (R & T, 2003; Wright, 2010).

*J. Structural neuroimaging changes of the basal ganglia in Huntington disease*

Structural neuroimaging techniques have opened the door to detect evidence of morphological changes of the brain of patients with HD. Stereology and automatic brain segmentation are recent and advanced methods that are very valuable in the analysis of in vivo obtained brain images that provide the researchers with data about the volume and surface area of the whole brain and all of the other parts of the brain and subcortical structures (Sahin & Elfaki, 2012). Most of the studies use CT or MRI scans of the brain of patients with HD to calculate the surface area and volume with the aid of computer software programs.

This volumetric analysis demonstrated progressive bilateral loss of volume of the striatum (Bamford, Caine, Kido, Cox, & Shoulson, 1995; Harris et al., 1992; Rosas et al., 2001; Tabrizi et al., 2009). Those atrophic changes are shown to be detectable in the earliest stages of HD and even to start before the clinical onset of the disease and then progress gradually over years (Aylward et al., 1994). Moreover, some studies reported detection of this volumetric loss in pre-manifest gene carriers about 15 – 20 years before the clinical onset of the disease (Aylward et al., 1996; Tabrizi et al., 2013). The average reduction of volume of the putamen has been reported to be in the range of 50%-54% while that of the caudate to be in the range of 28%-29% in patients with mild to moderate HD (Harris et al., 1996; Harris et al., 1992). Evidence from longitudinal Studies showed that earliest volumetric changes in HD to occur in the caudate nucleus (Harris et al., 1996). With advancement of the disease other parts of the striatum like the putamen and globus pallidus are also involved (Aylward et al., 1997; Harris et al., 1996). Furthermore, recent studies proved that those atrophic changes are not only restricted to the basal ganglia but other parts of the brain are also involved like: thalamus (Jernigan, Salmon, Butters, & Hesselink, 1991), frontal lobe (Aylward et al., 1994; Backman, Robins-Wahlin, Lundin, Ginovart, & Farde, 1997), temporal lobe (Dierks et al., 1999), hippocampus entorhinal cortex and brainstem volumes (Rosas et al., 2003), as well as reductions in cerebellum (Fennema-Notestine et al., 2004) and even the total brain volume (Rosas et al., 2003).

The degree of the volumetric changes of the striatum is found to be positively correlated with the number of the CAG repeats in the Huntingtin gene and the age of the onset of HD (Aylward et al., 1997; Rosas et al., 2001; Rosas et al., 2003). Furthermore, the degree of those structural changes is found to be directly related to the clinical manifestation of the HD. Harris et al in their study of 15 patients of HD and 19 controls found that the Motor symptoms and the findings of neurological examination correlates mainly with the atrophy of the putamen on the other hand the cognitive function and the score of the Mini-Mental status examination correlates with amount of caudate volume loss (Harris et al., 1996; Harris et al., 1992). Bamford et al found that the dgree of volume reduction of the caudate nucleus in patients with HD is significantly related to their impairement in the performance of the tests of complex psychomotor skills and tests of visuospatial processing (Bamford, Caine, Kido, Plassche, & Shoulson, 1989).

## Conclusion

From these studies and the above discussion, we can conclude that recent advances in neuroimaging techniques are very valuable in studying the structural changes of the brain in patients with HD. Furthermore, they allowed the researchers to study those changes in vivo without the need to dissect postmortem samples and to follow up the patients in order to study the natural history and the effects of therapeutic intervention.

Most of the components of the basal ganglia are affected by the atrophic changes during the disease process of HD which may occur decades before the clinical onset of the disease in gene carriers. Structural alterations are somewhat specific in the early stages of the disease, mainly affecting the caudate and putamen. The amount of the volume loss is correlated to the number of the CAG repeats, age of onset and the severity of the clinical symptoms.

There is an urgent need to identify specific disease biomarkers to monitor the disease and assess the effectiveness of therapeutic interventions. The use of modern neuroimaging techniques to study structural changes of the basal ganglia and also other parts of the brain will provide the opportunity to

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bridge this gap of knowledge.

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