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Biomarkers for Huntington's Disease

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1. Introduction

The core clinical features of Huntington's Disease (HD) were outlined by George Huntington in 1872 (Huntington 1872). Like nowadays, in George Huntington's time no cure for HD was yet available. However, genetic testing for HD that is now available can reliably predict the individuals at risk that will develop the disease. In such premanifest individuals slowing down the disease process may potentially delay the onset of disease symptoms. Therefore, there is an increasing need of finding the markers for the disease progression in premanifest HD individuals.

A biomarker is defined as an attribute of the disease that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention (Biomarkers definitions working group 2001). In adult HD mouse it has been demonstrated that stopping the expression of mutant Huntingtin may reverse the clinical and pathological phenotype (Yamamoto et al 2000). However, treatment trials expected to modify disease progression remain confined to population of manifest HD patients until reliable markers of disease process progression can be found for the premanifest HD gene carriers. Clinical measures may be used as primary endpoints and we will first focus on them. In our opinion, a comprehensive neurological and physical examination of premanifest HD gene carriers represents a reliable way towards identification of potential clinical biomarkers.

2. Clinical biomarkers for HD

A broad consensus exists among clinicians that a clinical diagnosis of HD can be made with certainty only in the presence of specific motor disorders. Thus, fixing the onset of the motor disorder in this way is a more or less reproducible method to conduct age at onset surveys or genotype-phenotype correlation studies (Kremer 2002). The most complete technique of assessing the early signs and symptoms of HD is to follow up a cohort of at risk individuals for an extended period of time. The most instructive follow-up study continues to be the one of the Venezuelan HD kindred (Penney et al 1990). It was performed prior to identification of the gene; nevertheless its conclusions are still valid. It demonstrated that patients pass through a transitional state from the normal presymptomatic phase to the time at which the diagnosis can clearly be made on neurological examination. The study revealed that there

was no single presenting sign or symptom in HD. In the earliest phases there was an insidious and slow deterioration of intellectual functions as well as mild personality change. The clear appearance of extrapyramidal signs such as chorea, hypokinesia, rigidity or dystonia indicates a phase on the disease progression, not the beginning of the disease. Prior to these signs however, most individuals will display minor motor abnormalities (Penney et al 1990). These minor abnormalities include general restlessness, abnormal eye movements, or impaired optokinetic nystagmus, hyperreflexia, impaired finger tapping or rapid alternating hand movements, and excessive and inappropriate movements of the fingers, hands, or toes during emotional stress as well as mild dysarthria. Minor abnormalities usually precede the obvious signs of extrapyramidal dysfunction by at least 3 years. Persons with a completely normal neurological examination have only a 3 per cent chance of being diagnosed as clinically manifest HD patients within the next 3 years (Penney et al 1990). A retrospective assessment of the affected individuals has revealed that minor involuntary movements are among the earliest symptoms experienced and that soon by those mental and emotional symptoms, including sadness, depression, irritability, and episodes of verbal and physical abuse may develop (Kirkwood et al 2001). Various research groups have revealed that so-called asymptomatic gene carriers statistically display subtle cognitive defects; such subtle cognitive deficits may precede motor abnormalities by years (Campodonico et al 1996, Lawrence et al 1998). However, it is important to realize that individuals with expanded repeats due to HD mutation may perform just as well or better than matched controls. Only when an individual is close to the estimated age of onset, as predicted by cytosine-adenine-guanine (CAG) repeat length (Brinkman et al 1997) that minor deficits in selected cognitive domain may become apparent (Campodonico et al 1996).

2.1 Unified Huntington's Disease rating scale

Clinical biomarkers are standardised clinical tests and rating scales that measure progression of HD phenotype. In order to provide a comprehensive assessment of motor performance, cognitive functioning, behavioral and psychiatric problems and functional status of an individual the United Huntington's Disease Rating Scale (UHDRS) was developed by the Huntington Study Group (Huntington Study group 1996). It enables a comprehensive, rapid, and efficient survey that is highly sensitive to disease progression over relatively short periods of time, such as 1 year. Using the UHDRS clinical score subtle motor abnormalities were found in premanifest HD subjects and were increasing with the proximity of the predicted time of clinical diagnosis (Biglan et al 2009). Although UHDRS is a standard assessment of disease progression it does not encompass every possible manifestation of HD. Special techniques have been developed to detect subtle premanifest clinical abnormalities that may lead to the development of new potential clinical biomarkers. HD progression may additionally be tracked by clinical techniques of oculomotor assessment (Klöppel et al 2008), tapping test (Andrich et al 2007), and gait analysis (Rao et al 2005).

2.2 Cognitive impairment

Subtle cognitive changes are present already in presymptomatic gene carriers (Kirkwood et al 2001, Craufurd & Snowden 2002); they become evident close to onset and early in the course of the disease and grow to be more severe as the disease evolves (Campodonico et al 1996; Brandt & Butters 1986). Cognitive changes therefore have the potential to identify

premanifest HD gene carriers close to the onset of the disease. Besides to Clinical psychological tests encompassed in the UHDRS (Verbal fluency, Symbol digit and Stroop test) other neuropsychological test batteries may be used for the purpose. However, the natural history of HD-related cognitive impairment is still not completely understood. Executive tests, combined with neuroimaging techniques have provided new evidence of cognitive abnormalities in HD; abnormal connectivity between basal ganglia and cortical areas has been suggested (Montoya et al 2006).

3. Positron emission tomography

Prior to HD gene identification the transitional state in HD development was proven to be accompanied by changes in metabolic rates of glucose as seen on positron emission tomography (PET) (Grafton et al 1992). After identification of the HD gene (Huntington's disease Collaborative Research Group 1993) longitudinal follow up studies of identified presymptomatic gene carriers were started. Using serial 11C-SCH 23390 and 11C-raclopride PET striatal dopamine D1 and D2 receptor binding was followed in a group of HD gene carriers of which 4 were in transitional state (Andrews et al 1999). The affected subjects showed mean annual reductions of 5.0 and 3.0 per cent loss of striatal dopamine D1 and D2 binding, respectively, while presymptomatic HD gene carriers showed mean annual reductions of 2.0 and 4.0 per cent, respectively. In mutation negative group no loss of dopamine binding was detected. The rate of loss of striatal dopamine D2 receptors correlated with CAG repeat length in presymptomatic HD gene carriers. Longitudinal studies have shown a mean annual decrease in dopamine D2 receptor binding of 5-6 per cent in HD patients and of around 4 per cent in premanifest HD gene carriers (Pavese et al 2003). Microglial activation was observed in the striatum of both HD patients and presymptomatic HD gene carriers by reduced binding of 11C-raclopride (Pavese et al 2006). The correlation with probability of time of onset was also shown in presymptomatic HD. (Tai et al 2007). Two-stage PET scanning method was applied to a cohort of presymptomatic and symptomatic HD individuals; this technique enables better visualization of anatomic structures and might potentially serve as a useful biomarker in the future. (Tomasi et al 2011).

PET scanning therefore shows promise for early visualization and quantification of pathological abnormalities in HD and therefore may be helpful in finding new potential biomarkers. There are however a number of weaknesses which limit usefulness of this technique. The cost is high and availability limited, scanning is time-consuming, radioactive ligands are difficult to manipulate. PET scanning also is susceptible to neuroleptic abuse which is common in HD patients.

4. Magnetic resonance imaging

Volumetric magnetic resonance imaging (MRI) enables estimation of brain region volumes. T1 volumetric MRI is the standard MRI technique most often used also in HD; however, other standard MRI techniques may provide useful information as well.

Longitudinal studies have shown significantly faster brain atrophy in early HD patients (Aylard et al 1997) and in presymptomatic gene carriers as far as 11 years from the predicted onset (Aylard et al 2004). Longitudinal assessment of striatal volumes thus seems to hold

capacity of providing potential biomarkers. The use of T1 weighted combined to diffusion-weighted scans seem to provide good information about the nature, and topographic specificity of brain changes in pre-HD individuals (Stoffers et al 2010). Basal ganglia are parts of the brain that are most affected by atrophy in HD patients, however, atrophy of other parts of the brain also takes place early in the course of the disease. Measurements of larger brain volumes may thus be more precise and less susceptible to local changes. Quantitatively, most of pathology in HD is extrastriatal and relative contributions to disease manifestation by striatal atrophy are not known. Without effective treatment techniques it is not possible to validate whether change in MRI striatal volumes can serve as an effective surrogate endpoint (Aylard 2007) Also, basal ganglia are closely interconnected to many parts of human brain and their atrophy may be contributed to different clinical pathology.

4.1 Brain volumes measurements

Using a semi-automated MRI volumetric technique Rosas et al proved that numerous extrastriatal brain areas are atrophied (Rosas et al 2002). Using an automated MRI technique they further managed to demonstrate regional cortical thinning in early HD patients (Rosas et al 2003). In premanifest HD gene carriers selective thinning of cortical parts was found that correlated positively with changes in cognition measured by the cognitive part of UHDRS (Rosas et al 2005). Further analyses revealed a significant association between regional cortical thinning and total functional capacity which is the leading primary outcome measure in neuroprotection trials (Rosas et al 2008). Progression of HD was evaluated by a longitudinal follow up volumetric MRI analysis and efficient measurement of the volume changes was performed within 15 years from the estimated onset of the clinical disease (Aylard et al 2011).

The boundary shift integral (BSI) is a semi- automated method by which changes in the brain volume can be calculated from registered 2-year interval scan pairs. Using BSI, Wild et al have demonstrated that whole-brain atrophy was significantly faster in early HD patients than in control subjects, and accelerated atrophy during the course of the disease was noted (Wild et al 2010).

Voxel-Based Morphometry (VBM) is an automated technique for analysis of series of MRI scans. VBM identifies variably affected brain regions in different stages of HD (Kassubek et al 2004) Longitudinal studies using this technique are promising (Tabrizi et al 2011).

The aforementioned MRI techniques are potentially useful in identifying the regions that may serve as biomarkers of disease progression in prevention trials.

4.2 Functional MRI

Functional MRI (fMRI) identifies subtle changes in regional blood flow during increased neuronal activity to identify brain regions active during performance of a specific task. Early abnormalities due to neuronal dysfunction can be detected. Neuronal dysfunction in early phase of the disease is potentially reversible which increases value of this technique. Thus, fMRI as a functional technique may reveal early functional pathology and may not require longitudinal measurements like morphometric methods. Several fMRI studies have demonstrated regional functional abnormalities in early HD (Georgiu-Karistanis et al 2007). A study conducted in presymptomatic HD gene carriers alterations in cortical functional

activity have been shown to correlate with the time of onset (Paulsen et al 2004) A study comparing data obtained from volumetric MRI and fMRI found that regions with altered activity were not those experiencing the most atrophy (Gavazzi et al 2007) While fMRI technique may represent a useful biomarker there are also weak points for its general use. Technical equipment is more demanding than conventional MRI and expertise of the technique is required.

4.3 Molecular MRI techniques

Diffusion tensor imaging (DTI) is an MRI technique developed from standard diffusion weight imaging (DWI) technique which applies the ability of water molecules to diffuse along axons and produces maps of white matter tracts. It can detect abnormalities in myelin which would appear normal on conventional MRI. In HD, the regions of decreased fractional isotropy (FI, measure of axonal organization) compared to controls were detected. Rosas et al found the regions that correlated to cognitive performance in presymptomatic HD gene carriers; more widespread lesions were detected in manifest HD (Rosas et al 2008). DTI shows promise to become a biomarker capable of detecting changes in HD earlier than other imaging techniques (Magnotta et al 2009) although not many studies have been performed and its potential remains to be tested.

MR spectroscopy is capable of noninvasive quantification of the biochemical composition of brain tissue. Lower neuronal markers (N-acetylaspartate) levels were shown in presymptomatic and early HD, whereas glial cell markers (myo-inositol) were increased (Surrock et al 2010). Elevated lactate and reduced creatine levels were shown in the striatum of presymptomatic HD gene carriers and early HD patients (Reynolds et al 2005). The technique is capable of detecting biochemical changes in the central nervous system and promises to be helpful in a potential biomarker discovery; its utility, however, is limited by long scan times, small number of molecules it can accurately detect, and comparatively low sensitivity.

5. Molecular biomarkers

Various molecular biomarkers can also be obtained from peripheral blood, urine and cerebrospinal fluid (CSF). Ideally, biomarkers obtained from body fluids would be expected to reflect pathologic changes in CNS. Such a substance is normally not present in the blood, but in HD gene carriers/patients it leaks across blood-brain barrier and becomes detectable. However, mutant huntingtin is expressed ubiquitously over all body tissues, therefore molecular changes detected in body fluids may reflect peripheral processes promoted by mutant huntingtin. In this way, biomarkers obtained from CSF could reflect CNS pathology more precisely (Huang et al 2011).

Candidate biomarkers obtained from body fluids can be divided in metabolic, endocrine, markers of oxidative stress, and markers obtained from signalling pathways.

5.1 Metabolic biomarkers

Due to ubiquitous expression of huntingtin in addition to neurological features peripheral deficits may be detected. HD-associated differences in metabolite levels in peripheral blood were detected by Underwood et al that identified a pro-catabolic pattern of metabolic

changes, present even in presymptomatic HD gene carriers (Underwood et al 2006). Another research group found decreasing levels of branched chain amino acids in presymptomatic HD gene carriers and clinically manifest HD patients in different stages of the disease compared to controls. The levels were found to correlate with CAG repeat length and UHDRS motor score (Mochel et al 2007). Uric acid, a known antioxidant agent that was found to be connected with the progression of Parkinson's disease has been investigated as a putative biomarker/modifiable agent that could slow down HD progression (Auinger et al 2010).

5.2 Endocrine biomarkers

Several features of early HD like weight loss, depression, disturbed sleep cycle could be due to hypothalamic dysfunction. Undeniably, loss of hypothalamic cells has been found in HD patients (Petersen et al 2006). Endocrine disturbances that may track disease progression have been identified. Urinary cortisol levels increase progressively with the advancing disease in HD patients (Bjorquist et al 2006). Still other potential endocrine biomarkers are under investigation in clinically expressed HD (Hult et al 2010).

Endocrine changes are of interest as potential biomarkers to track disease, yet endocrine features are susceptible to influence of drugs such as neuroleptics and antidepressants, and psychiatric pathology such as depression which may occur in early HD.

5.3 Oxidative stress biomarkers

Mitochondrial dysfunction has recently been shown in HD patients and presymptomatic HD gene carriers. (Saft et al 2005). Other markers of oxidative stress and metabolism are under investigation (Chen 2011). Mutant huntingtin and its cleavage products as the immediate cause of neuronal dysfunction and death in HD are being investigated as potential biomarkers (Moskovitch-Lopatin 2010).

5.4 Signalling pathways biomarkers

A significant decrease in brain-derived neurotrophic factor (BDNF), an agent that promotes survival of neurons was found in the serum of symptomatic HD patients (Ciammola et al 2007). Augmentation of neurotrophic gene products such as BDNF could present a potential therapeutic target in HD (Ross & Shoulson 2009). BDNF is an interesting potential biomarker of disease progression, however, it does not cross the blood-brain barrier. The balance of central and peripheral contributions to altered serum BDNF in HD requires further study.

Abnormalities of the endocannabinoid system were observed in premanifest HD gene carriers as well as in manifest HD patients (Fernandez-Ruiz et al 2009). Adenosine A2 receptors were found to increased density and affinity in different stages of manifest HD as well as in presymptomatic HD gene carriers (Varani et al 2007).

6. Autonomic nervous system function as a putative biomarker in HD

Our research started with the study of autonomic nervous system function (ANS) in presymptomatic HD gene carriers and symptomatic HD patients. Based on a standardized clinical ANS questionnaire (Turkka 1987) a group of 33 patients was enrolled, among them 8 presymptomatic HD gene carriers. Symptomatic patients were classified according to the

Shoulson and Fahn's HD disability scale (Shoulson & Fahn 1979) to mildly affected group and moderately /severely affected which were evaluated together. Mostly, an increase in the ANS function , especially of the sympathetic part, was observed in presymptomatic HD gene carriers and mildly affected HD patients, and a decrease in the ANS function in moderately/severely affected patients was observed (Kobal et al 2004). Our further research was modified by observing a presymptomatic HD gene carrier in whom choreatic movements appeared after suffering from chronic subdural hematoma that compromised the cerebral cortex, but not the basal ganglia (Kobal et al 2007) (Fig. 1).

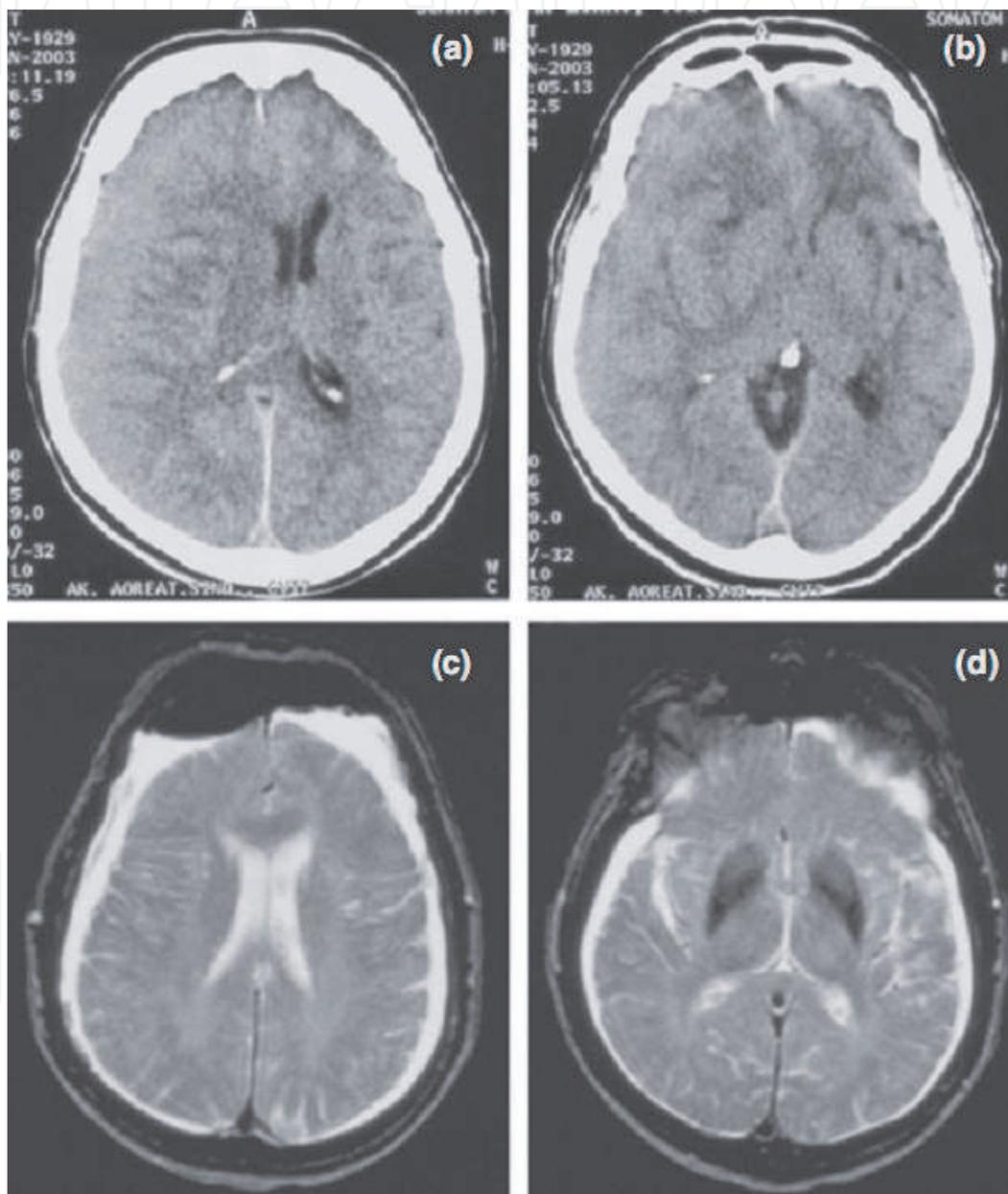


Fig. 1. Computed tomography scan of the head in a patient with chorea discovering isodense bilateral chronic hematomas expanding over the entire right hemisphere and over the left parietooccipitotemporal cortex (a, b). Proton density weighted Magnetic resonance imaging 6 days after surgical evacuation and after reappearance of the initially regressed chorea showed no structural abnormality in the basal ganglia (c, d).

We hypothesized that early autonomic dysfunction could be due to imbalance in the central ANS centres and conducted further research in this direction. In the next study we enlarged the number of presymptomatic HD gene carriers and early manifest HD patients, which were clinically evaluated by UHDRS clinical scale. ANS tests to challenge higher-order ANS centres like mental stress and the cold pressor test were introduced. Attenuated response to simple mental arithmetic test was shown in a group of 14 presymptomatic HD gene carriers and 11 early symptomatic HD patients (Fig. 2). The response to late phase of cold pressor test in the same patients was exaggerated (Fig. 3).

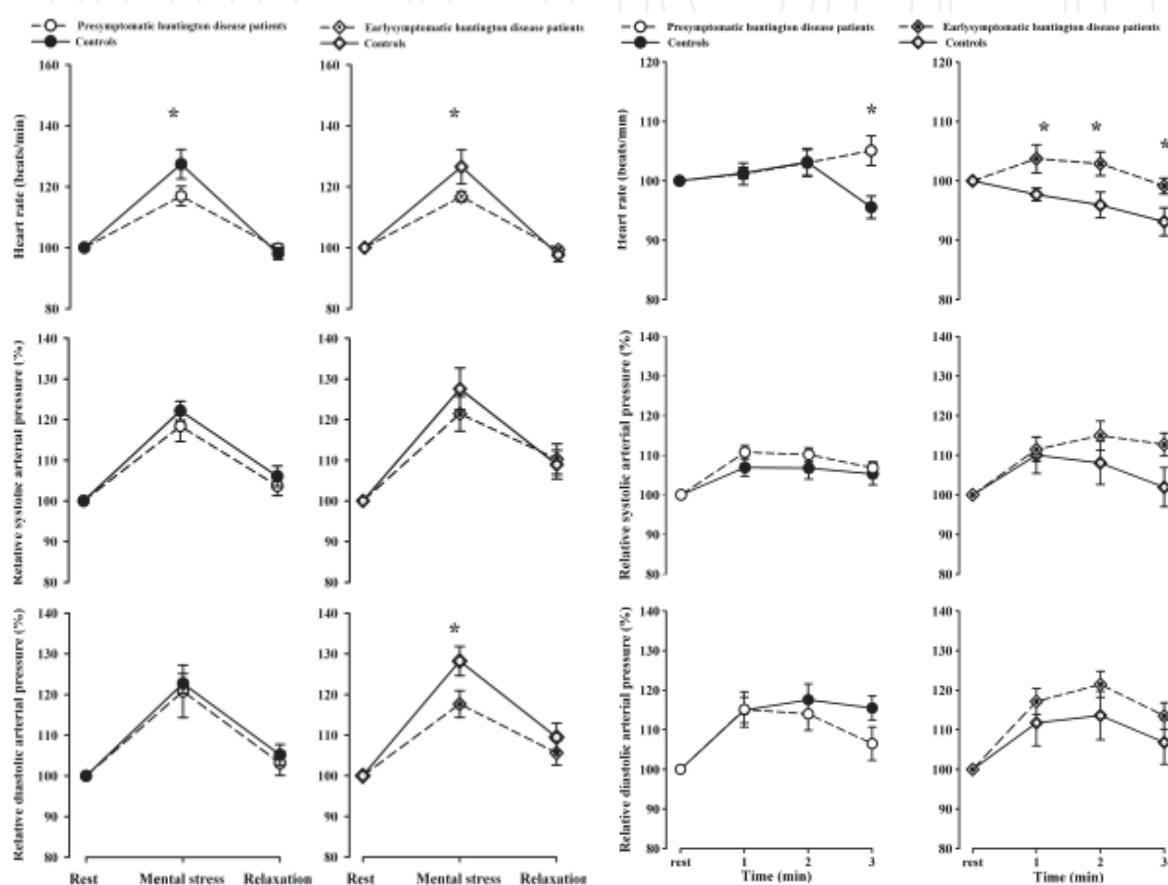


Fig. 2. (left): Arterial pressure and heart rate values during a simple mental arithmetic test. Values are expressed as percentage of resting arterial pressure and heart beat rates.

* statistically significant differences between the groups ($p < 0.05$). Fig. 2. (right): Heart rate and arterial pressure values during cold pressor test. Values are expressed as percentage of resting heart rate and arterial pressure values. * statistically significant differences between the groups ($p < 0.05$).

The results were in favour of highest-order cortical ANS centres hypofunction which, according to the concept of central autonomic network organization, could lead to hyperfunction of hypothalamus and lower order central autonomic centres (Kobal et al 2010, Melik et al-in print). Our findings were in line with the findings of a recent study on thalamic metabolism in preclinical HD. Thalamic metabolism was elevated at baseline, but fell to subnormal levels in the pre-HD subjects who developed symptoms (Feigin et al 2007). A recent survey found significantly more gastrointestinal, urinary cardiovascular and sexual

problems in group of HD patients. In premanifest HD group swallowing problems and light-headedness on standing up were prominent (Aziz et al 2010)

The ANS function could potentially represent a useful biomarker in HD however, further cross-sectional as well as longitudinal studies are needed. Drawbacks of these methods are that they are unspecific; they also may show variable intersubject response and are sensitive to use of drugs with anticholinergic effect such as neuroleptics which are commonly used in HD patients.

7. “Omic” biomarkers for HD

7.1 Use of “Omic” biomarkers in clinical practice

Complete sequencing of the human genome has launched a new era of systems biology referred to as »omics«. The term refers to the comprehensive analysis of biological systems and a variety of omics subdisciplines are acknowledged. Through genomics new approaches to monitor diseases are becoming available. New technologies are capable of defining large sets of biomarkers systematically in biological samples (Bell 2004), and provide an analytical approach to investigation of all the products of the genome at messenger RNA or protein level at once. These methodologies are capable of generating data on multiple biomarkers that vary quantitatively very early in the disease, in response to disease onset, progression or therapeutic intervention and may provide sets of prognostic factors (Schadt et al 2003). The development of biomarkers for prognostic use in diseases with asymptomatic phases is particularly challenging and can be time-consuming, as they must be validated and monitored in long-term clinical outcomes (Frank & Hargreaves 2003).

Microarray analysis has significantly augmented the throughput of genomic studies and haemogenomic approach has been proposed; several examples of potential microarray-based biomarkers in blood have already been described. Peripheral blood is an easily accessible tissue, and specific gene expression signatures have been shown to exist in a wide variety of diseases where no obvious clinical phenotype in blood is present, such as tuberous sclerosis, neurofibromatosis, Down syndrome, multiple sclerosis, etc (Tang et al 2004, Bomprezzi et al 2003, Achiron et al 2004).

Another two important goals of genomics and genetics in clinical practice, besides diagnosis and staging, are to improve therapeutic efficacy and reduce drug toxicity (Evans & Relling 2004). The field of pharmacogenomics encircles the role of genes in an individual's response to drugs and comprises a broad area of basic drug discovery research, the genetic basis of drug responses, pharmacodynamics, pharmacokinetics and metabolism. The implications for the development of new drugs and clinical patient management are huge. For example, in multiple sclerosis it has already been shown that differences in the gene expression profiles of treatment-responsive and treatment-non-responsive patients are present and detectable (Sturzebecher et al 2003). In cancer therapy, several studies have been published where expression signatures indicated the response to certain treatment (Glinsky et al 2005, Rosenwald et al 2002). In neurodegenerative diseases like HD, where no effective therapies are available and symptoms progression is relatively slow, biomarkers for therapy response monitoring are important.

7.2 Transcriptomic research in HD

The research on HD has mainly been focused on the nervous system, only few studies have reported on muscle or other tissues. Our previous results show (Borovecki et al 2005) that expression changes of many genes were present and detectable in blood of HD patients when compared to healthy controls. Not only were these changes present in HD patients with clinical symptoms but disturbances in gene expression were detected in presymptomatic mutation carriers as well (Figure 3). The analysis of gene expression changes was performed on 2 different microarray platforms (Affymetrix, Amersham) in 12 symptomatic patients and 10 healthy controls, as well as in 5 presymptomatic mutation carriers and 4 healthy controls. Ten times more probes were differentially expressed in symptomatic HD group than in presymptomatic HD group when compared to controls. Interestingly, Amersham detected up to 4 times more probes as differentially expressed in the symptomatic group than Affymetrix microarrays, whereas this was not the case in the presymptomatic group (Table 1).

Based on this study, in which we have shown that gene expression changes in HD are detectable in blood of HD patients, research in the field of disease progression and novel therapy response in human HD may focus on this easily accessible tissue as well. Further work in the proposed direction is needed to provide clues to these implications.

<i>p</i> -value	SYMPTOMATIC GROUP		PRESYMPTOMATIC GROUP	
	Affymetrix	Amersham	Affymetrix	Amersham
0.05	5267	12159	1369	939
0.01	3133	9685	392	490
0.005	2546	8678	223	314
0.001	1646	6579	58	75
0.0005	1366	5815	31	42
0.0001	884	4191	3	8
0.00005	740	3599	2	6

Table 1. Numbers of differentially expressed probes between HD group and healthy controls. Numbers of changed probes are shown for each microarray platform separately with respect to different *p*-values.

Only one study on gene expression changes in HD in human brain samples has been reported so far (Hodges et al 2006). The expression in three distinct brain regions from symptomatic HD patients was analyzed. We compared those with our expression results in blood of symptomatic HD patients on Affymetrix platform to compare expression changes in brain and blood (Table 2, Fig. 3). When using the same statistical measures ($p < 0.001$) the greatest expression changes were observed in the caudate nucleus, followed by blood > BA4 cortex > cerebellum. 30% of probe sets changed in blood were also significantly changed in caudate samples suggesting that HD specific changes might be detectable in blood. There was not a single probe set differentially expressed in all four tested tissues and 47 probe sets were significantly changed in blood, caudate and BA4 motor cortex, two of the more affected areas of brain in HD. These findings imply that similar cellular processes are disturbed in the caudate nucleus and blood cells, although there is no clinical phenotype in blood of HD patients. The latter may be due to the fact that unlike neurons, the life span of lymphocytes is short and the turn over rapid.

	Blood	Caudate	BA4 Cortex	Cerebellum
Number of changed probe sets	1646	5225	963	340

Table 2. Numbers of probe sets differentially expressed in blood and three brain regions in symptomatic HD patients ($p < 0.001$).

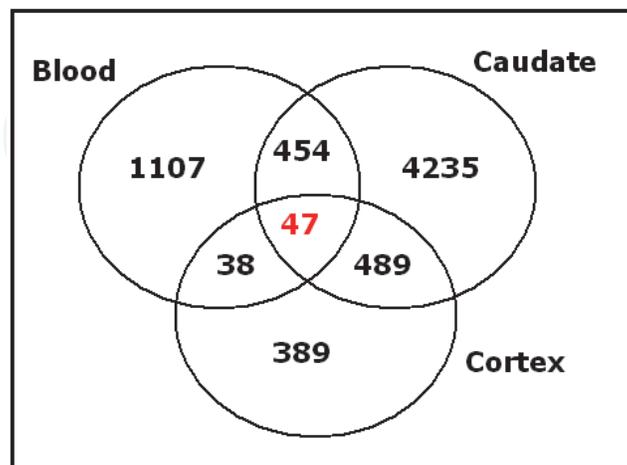


Fig. 3. Numbers of over-lapping differentially expressed probe sets in blood, caudate and BA4 cortex ($p < 0.001$).

7.3 Age-at-onset prediction

Since the gene expression changes were present already in presymptomatic stages, expression profiles might be used to refine the prediction of disease onset. There is a long time period before HD manifests itself through clinical symptoms. Due to available mutational testing, one can learn earlier about his/her gene mutation status. After the diagnosis, prediction of age at disease onset is most important information for mutation carriers and their relatives. Two ways to speculate about the age of onset have been accepted so far, both quite insensitive - number of CAG repeats and polymorphisms of modifier genes. Age of onset may presently only be given in a rather wide range - for example a mutation carrier with 42 CAG repeats will most probably develop symptoms between 35-57 years of age. Clearly, this is of no use to someone to plan the future. Brain-imaging studies have been trying to add some sensitivity to the prediction of disease onset. Study of basal ganglia volume showed that atrophy of basal ganglia occurred gradually, beginning years before symptoms onset (Aylard 2007). Mutation carriers who were close to the onset of HD as predicted by CAG repeat numbers had smaller volumes of basal ganglia than subjects far from onset for all structures except the caudate nucleus. Mutation carriers who were far from the onset had smaller basal ganglia volumes than healthy controls for all structures except the globus pallidus. A functional MR imaging (fMRI) study showed differences in the groups of mutation carriers far or close to the predicted age of onset when compared to healthy controls (Paulsen et al 2004). The group close to the onset had significantly less activation in subcortical regions than control subjects and the group far from the predicted onset had an intermediate degree of activation. Despite the mentioned findings there have not been any definite measurements or protocols for determining the age of onset proposed so far.

Our results suggest that gene expression in blood of HD mutation carriers is disturbed long before the onset of symptoms (some of tested mutation carriers were as young as 20 years with CAG repeat lengths of 41, suggesting the start of the disease between 40-50 years of age). These results imply that gene expression changes in blood might potentially be used not only to monitor the disease progression but to help predict the age of disease onset as well. Also, expression changes correlated with the disease progression in the symptomatic stages of HD, and they might be valuable in determining the progression of specific symptoms in the advanced stages.

7.4 Potential biomarkers of disease progression

Whole genome transcriptome analysis might define also biomarkers for disease progression. Using whole genome gene expression data from our study (Borovecki et al 2005) we have performed additional analysis to select a potential biomarker set – set of genes to be useful as a biomarker and test their expression with another independent method, quantitative RTPCR (QRT-PCR). To narrow down the list of differentially expressed genes, additional criteria for selecting genes of interest were implemented. We have selected top 12 candidate genes that had the best reproducibility of expression changes when tested with QRT-PCR in presymptomatic/symptomatic HD patients and healthy controls.

To make a study more stringent we validated the 12 gene set on an independent set of HD samples and controls (Fig. 4). Expression of individual genes increased with disease progression from the presymptomatic to advanced symptomatic stage, but the differences did not reach statistical significance. While only 6 genes, ANXA, MARCH7, CAPZA1, HIF1A, TAF7 and YPEL5, were significantly upregulated in the presymptomatic (P) group ($p < 0.05$), 10 genes were significantly upregulated in the symptomatic (S) group ($p < 0.05$) (PCNP and SF3B1 were not significant) and 11 genes were significantly upregulated in the late symptomatic (LS) group ($p < 0.05$) (SF3B1 was not significant).

This study provided confirmatory evidence of significant gene expression changes in blood of HD patients published by Borovecki et al. Expression of the 12 genes appeared higher in the advanced symptomatic group of patients compared to the presymptomatic group, but these stage-dependent differences in expression did not reach statistical significance. In order to investigate predictive performance of the gene set, we examined logistic regression machine learning algorithm on our dataset. Proposed classifier reached overall positive predictive value of 78% with 82% sensitivity and 53% specificity for HD with respect to healthy control. In addition, the potential of gene set to discriminate between presymptomatic and symptomatic patients was evaluated using the logistic regression algorithm. The results showed overall positive predictive value of 85% with relatively high sensitivity (83%), but with low specificity (50%). A possible explanation for low specificity may be the unequal distribution of cases in our dataset (14 presymptomatic and 47 symptomatic cases) and small set of training cases (Lovrecic et al 2009).

While high specificity and sensitivity are generally desirable for diagnostic biomarkers, these parameters are not essential in diseases such as HD where the diagnosis is already known and the intended use of biomarkers is to primarily monitor disease progression. As a potential marker of disease progression, the 12-gene set showed promising overall positive predictive value and sensitivity (85% and 83%, respectively), but with relatively low specificity (50%). Nevertheless, our results suggest that the 12-gene set may be of better

clinical value compared to individual genes as a marker of disease progression in HD. Moreover, we hypothesize that including more altered genes in the gene set may further enhance its clinical applicability.

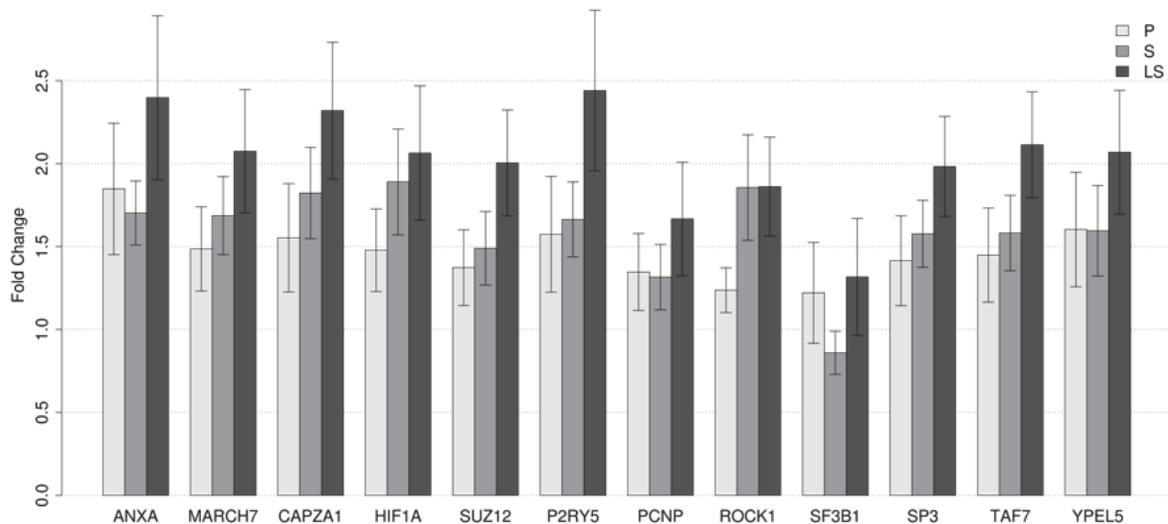


Fig. 4. Expression fold changes of 12 genes in different stages of HD.

The upregulation of expression of the 12 previously selected genes (8) was validated in the new cohort of HD patients. Bars represent fold increase in mRNAs in HD patients relative to healthy controls. Interval lines represent the (average fold change) $\times (2^{SEM-1})$. P-presymptomatic HD mutation carriers, S-symptomatic patients, LS-late symptomatic patients: ANXA-annexin A1; MARCH7-membrane-associated ring finger 7; CAPZA1-capping protein muscle Z-line, alpha 1; HIF1A-hypoxia-inducible factor 1, alpha subunit; SUZ12-suppressor of zeste 12 homolog; P2RY5-purinergic receptor P2Y, G-protein coupled, 5; PCNP-PEST proteolytic signal containing nuclear protein; ROCK1-Rho-associated, coiled-coil containing protein kinase 1; SF3B1-splicing factor 3b, subunit 1; SP3-Sp3 transcription factor; TAF7-TAF7 RNA polymerase II, TATA box binding protein (TBP)-associated factor; YPEL5-Yippee-like 5.

In addition, another study of global gene expression in lymphoblastic cell lines from HD patients failed to identify any significant changes in gene expression (Runne et al 2007) that were observed previously (Borovecki et al 2005). It is therefore evident that multiple independent validation studies will be required to evaluate potential clinical applicability of a putative biomarker. While development of novel hemogenomic approaches to non-invasively monitor disease progression showed promise, it remains unclear whether the observed changes in blood gene expression will be sufficiently robust to serve as biomarkers of disease. A combination of genomic, metabolomic and proteomic approaches may be required, in combination with neuroimaging, to successfully identify biomarkers of disease progression in HD and probably other neurodegenerative diseases.

7.5 Elucidation of pathophysiological processes in HD

Analysis of whole genome transcriptome might also give us insights into the disturbed pathways and processes involved in disease onset and progression. Although multiple

pathological mechanisms by which mutant htt causes neuronal dysfunction have been proposed and studied in detail (Harjes & Wanker 2003), the exact molecular mechanisms how mutant htt induces cell death are not understood.

Using whole genome gene expression data from our study (Borovecki et al 2005) we have performed additional bioinformatic analysis of microarray data with freely available Onto-Tools (Draghici et al 2003) and Gene set enrichment analysis (GSEA) (Subramanian et al 2005) software. Three separate comparisons were done: 1) all HD samples compared to healthy control samples (HDvsC); 2) symptomatic HD samples compared to healthy control samples (SvsC); 3) presymptomatic HD samples compared to healthy control samples (PvsC). When looking for enriched gene set with GSEA, additional comparison was done - symptomatic HD samples compared to presymptomatic HD samples (SvsP). Onto-Express was used to more thoroughly characterize the sets of functionally related differentially expressed genes (Draghici et al 2003, Khatri et al 2002). The tool classified genes according to two Gene-Ontology (GO) categories: biological process and molecular function (Fig. 5).

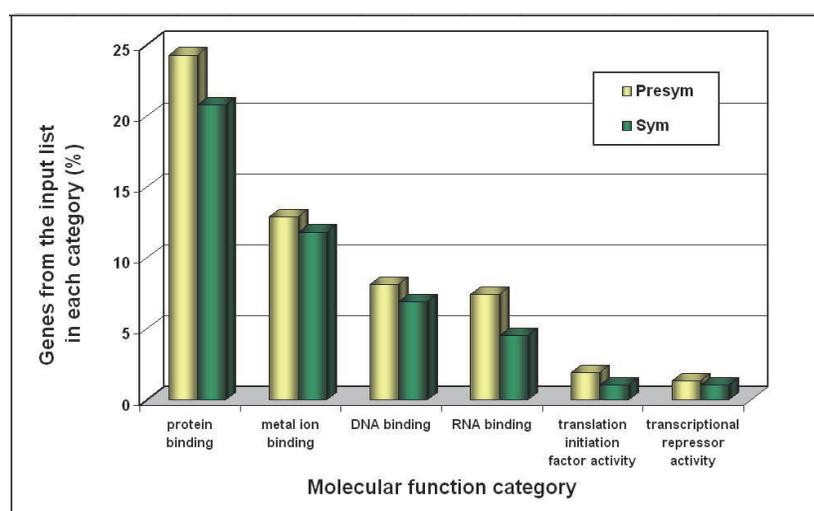


Fig. 5. Common molecular function categories changed in presymptomatic (Presym) HD mutation carriers and symptomatic (Sym) HD patients.

Molecular function category	Category rank*	Genes in category (%)
Structural constituent of ribosome	5	2.9
Unfolded protein binding	6	2.6
GTPase activity	7	2.3
Protein transporter activity	9	1.9
Protein heterodimerization activity	10	1.6
RNA polymerase II transcription factor activity	12	1.3
Hydrogen-transporting ATPase activity	13	1.3
Translation elongation factor activity	14	1
Helicase activity	15	1
Ubiquitin conjugating enzyme activity	16	1

* Category rank from PvsC comparison.

Table 3. Molecular function categories specifically changed only in presymptomatic HD mutation carriers.

Using Onto-tools we may propose that two novel mechanisms are disturbed in early stages of HD. Molecular function categories "metal ion binding" and "helicase activity" have been shown to be disrupted already in presymptomatic HD mutation carriers (Fig. 5, Table 3). Another interesting finding was that many more molecular function and biological process categories were disturbed at the gene expression level in presymptomatic than in symptomatic group (Table 3).

Using another method, Gene set enrichment analysis (GSEA) two additional mechanisms in terms of gene sets were significantly upregulated in the presymptomatic group - lipid metabolism with adipocyte function (Nadler et al 2000) and gene set linked to expression changes in major depressive disorder (Aston et al 2005). Also, our results have confirmed most of the previously described potential pathogenetic mechanisms to be disturbed at gene expression level using two completely different approaches.

Many hypotheses on HD pathogenesis have been investigated, but none has been able to decipher the basis of what goes wrong first. Since HD primarily affects the brain, majority of the research on the pathogenesis has been done on neuronal cells or tissue. We used a different approach in two aspects - we included presymptomatic mutation carriers that gave us an insight into the early changes in HD, and our analyses were done on blood cells which appear not to be affected in HD. Possibly, if their life span were longer, as is the case with neuronal cells, blood cells would also become affected. One study reported that lymphoblasts isolated from HD patients showed increased stress-induced apoptotic cell death, suggesting their abnormal function, but no apparent clinical phenotype was found present (Sawa et al 1999). These are more reasons to believe that the changes present in blood cells are early changes characteristic of HD. Moreover, the analysis of gene expression changes in presymptomatic mutation carriers separately might lead to explanation of some primarily disturbed mechanisms specific for HD.

Metal ion binding category was disturbed already in presymptomatic disease stage and only scarce data are currently available on metal ions in neurodegenerative diseases affecting basal ganglia (Dexter et al 1991, Moos & Morgan 2004). The results of previous studies have suggested that metal ions might contribute to neurodegenerative process. More studies are needed to elucidate the importance of metal ions in HD, but our results suggest that related mechanisms are disturbed already in presymptomatic disease stages. Interestingly, the analysis of molecular function and biological process GO categories have shown that many more categories are changed specifically in presymptomatic HD stages implying that many processes are active and changed in comparison to healthy controls before the onset of clinical symptoms. Since they are not present in symptomatic stages of HD they might exhibit the measures that cells are undertaking to counteract to mutation driven disturbances and efforts to execute normal processes appropriately.

In addition, expression results from our study showed that gene set consisting of genes controlling lipid metabolism and signal transduction (Nadler et al 2000) was specifically changed in the group of presymptomatic HD mutation carriers. Disturbed lipid metabolism and an adipocyte function have been previously reported in R6/2 mice, where a defect in fat breakdown by adipocytes was suggested (Fain et al 2001). No results on human samples have been available so far. Our results suggest that this might be one of the mechanisms disturbed early in the human HD pathogenesis. The second gene set significantly enriched

in presymptomatic group was previously defined in a study of expression changes in brain in major depressive disorder (Aston et al 2005) where a disruption in the expression of genes involved in neurodevelopment, signal transduction, synaptic function and cell communication was shown. Psychiatric symptoms usually precede motor impairment in HD for a few years and depression is one of them. Perhaps this might be the explanation for discovered enrichment of this gene set specifically in the presymptomatic HD group.

8. Conclusion

We conclude that identification of easily obtainable, reliable and robust biomarkers of Huntington's Disease progression will be important for development and evaluation of future therapies (Weir DW et al 2011). Specific pathogenic mechanisms can be readily proven by clinical, neuroimaging, and/or biochemical biomarkers. Peripheral blood due to its easy accessibility might be a representative tissue for genomic HD specific changes investigation and a potential tissue of choice for monitoring the course of the disease. However, without the effective treatment techniques it is not yet possible to validate which biomarker can serve as an effective surrogate endpoint for the disease process modification.

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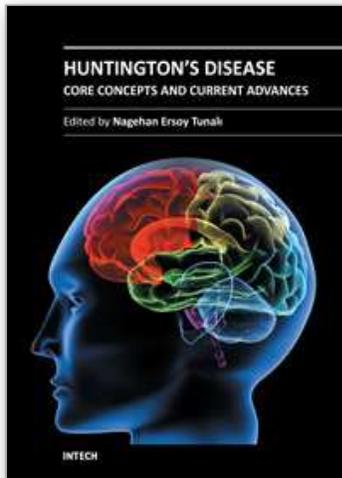
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Huntington's Disease - Core Concepts and Current Advances

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Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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