D Biomarkers

D.1 TRACK–HD TRACKING PROGRESSION IN PREMANIFEST AND EARLY HUNTINGTON'S DISEASE

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TRACK–HD is a multicentre, multinational, prospective, observational biomarker study of premanifest and early Huntington's disease (HD). The goal of the project is to contribute essential methodology that will provide unique insights into the neurobiology of premanifest and early HD and form the basis for neuroprotective trials in premanifest and early HD. TRACK–HD complements existing observational studies (Predict–HD, PHAROS, Registry and COHORT), sharing some features, but also having areas of unique emphasis, including extensive annual testing, implementation of multi-site 3T magnetic resonance imaging acquisition and novel assessment techniques. Premanifest subjects are stratified to focus on those close to motor onset. The use of a small number of sites allows flexibility for evaluating relatively complex and expensive techniques and dynamic modification of the study as promising new methodologies emerge. Here we give an update on recruitment and assessment to date. By the end of July all 360 subjects will have been enrolled and baseline assessments completed.

D.2 INCREASED ACTIVITY OF THE HYPOTHALAMIC–ADRENAL AXIS IN EARLY-STAGE HUNTINGTON'S DISEASE PATIENTS

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Background: Huntington's disease (HD) is a hereditary neurodegenerative disorder characterised by motor, cognitive, psychiatric and behavioural disturbances. Recently, progressive alterations of the hypothalamic–pituitary–adrenal (HPA) axis in the R6/2 mouse model of HD reminiscent of a Cushing-like syndrome were reported. However, no data are available on the diurnal cortisol secretory patterns in HD patients.
Aims: To perform a detailed functional analysis of the HPA axis in HD patients in relation to symptoms and signs.
Methods: Twenty-four hour pulsatile cortisol secretion was studied in eight early-stage, medication-free HD patients compared with eight age, sex and body mass index-matched control subjects. Blood sampling for the determination of cortisol concentration was performed at 10-minute intervals. Multiparameter autodeconvolution analysis was applied to study cortisol half-life, the number of secretory bursts, secretory burst half-duration, mean mass secreted per burst and basal, pulsatile and total production rates. Cosinor analysis was applied to assess 24 h variations in cortisol concentration while the orderliness of the concentration time series was evaluated by approximate entropy. The Unified Huntington's Disease Rating Scale (UHDRS) was used to assess clinical presentation in HD subjects. Statistical significance was set at $p<0.05$.
Results: The amplitude of the diurnal cortisol profile, the total number of cortisol secretory bursts as well as the pulsatile and total cortisol secretion rates were significantly higher in HD patients compared with controls (eg, total secretion in HD was 4781 versus 2658 (nmol/l per 24 h) in controls; $p = 0.016$). There was also a trend towards a higher basal cortisol secretion rate. In HD patients, UHDRS functional assessment score and total functional capacity scores both correlated inversely with the basal and total cortisol secretion rate.
Conclusion: HPA axis hyperactivity is an early feature of HD and is likely to have a central origin as the number of secretory bursts was increased. Increased cortisol levels might account for a number of disease signs such as mood disturbances and cognitive impairment.

D.3 DYSREGULATION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN HUNTINGTON'S DISEASE

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Background: Neurodegeneration in Huntington's disease (HD) is primarily found in the basal ganglia and cerebral cortex, but hypothalamic involvement in early disease stages has also been described. The hypothalamus is a major component of the hypothalamic–pituitary–adrenal axis (HPA) and previous studies report a hyperactivation of this axis in HD.
Methods: Presymptomatic ($n = 26$) and symptomatic ($n = 58$) HD mutation carriers were recruited from outpatient clinics and a specialised nursing home. Disease stage was defined with the confidence level of the motor section of the Unified Huntington's Disease Rating Scale. Verified non-mutation carriers ($n = 28$), who were at 50% risk for HD, were included as a comparison group. HPA axis functioning was measured in saliva with a cortisol awakening response (CAR), the area under the curve and a dexamethasone suppression test.
Results: The CAR and the area under the curve were significantly higher in presymptomatic mutation carriers compared with symptomatic mutation carriers. After adjusting for awakening time, sex and age, the differences remained intact for the CAR only. No significant differences were found between the three groups for the dexamethasone suppression test.
Conclusion: This study indicates a hyperactivation of the HPA axis in presymptomatic mutation carriers compared with symptomatic mutation carriers. This may reflect a decreased activation of the HPA axis after the onset of motor symptoms.

D.4 GROWTH HORMONE RESPONSE TO ARGININE INFUSION: PRELIMINARY RESULTS OF A STUDY OF HYPOTHALAMIC DYSFUNCTIONS IN HUNTINGTON'S DISEASE

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Introduction: There is increasing evidence pointing towards an early involvement of the hypothalamus and the endocrine system in Huntington's disease (HD). Investigating neuroendocrine changes in HD opens up the possibility of finding biomarkers for HD, as well as of identifying novel targets for therapeutic interventions. The aim of the study is to investigate hypothalamic dysfunctions in HD further through a detailed examination of the endocrinological changes in these patients. Here we present the preliminary results of the growth hormone (GH) response to arginine infusion in seven patients with a molecular diagnosis of HD. GH secretion from the pituitary gland is regulated by the hypothalamic peptides growth hormone-releasing hormone and somatostatin, which are modulated by various neuronal networks, especially the noradrenergic and cholinergic systems. Arginine,

through stimulation of hypothalamic alpha2-adrenoceptor, raises concentrations of GH in serum in healthy people.

Materials and Methods: Seven patients (five men, two women, mean age 45.14 ± 11.82 years and disease duration 7.40 ± 2.06 years) underwent the arginine test after a 12-h fast, between 08:00 and 08:30 hours. After subjects had rested in a supine position for at least 30 minutes, baseline samples (T0) were collected from a cannulated antecubital vein. Then 30 g arginine (arginine hydrochloride, 30% solution) was infused intravenously over 30 minutes and blood was sampled every 30 minutes for 1 hour (T30, T60, and T90). Serum GH was measured with a commercially available immunoradiometric kit. Disease severity was clinically evaluated with the United Huntington's Disease Rating Scale motor section. No patient had a history of endocrinological illness or was taking drugs acting on the central nervous system.

Results: In four patients we observed an absence of response (T0: 0.15 ± 0.06 μg/l; T30: 0.24 ± 0.02 μg/l; T60: 0.80 ± 0.25 μg/l; T90: 0.85 ± 0.11 μg/l), in two patients the GH peak was delayed at T90 (T0: 1.01 ± 0.29 μg/l; T30: 4.30 ± 0.12 μg/l; T60: 8.18 ± 0.32 μg/l; T90: 14.03 ± 0.32 μg/l), in one patient the peak was at T30 (T0: 0.71 μg/l; T30: 11.80 μg/l; T60: 11.30 μg/l; T90: 4.50 μg/l).

Discussion: The GH response to arginine was altered in most of the patients who performed the test. This may be due to an impairment of cholinergic hypothalamic systems in HD, confirming in vivo an involvement of the hypothalamus in the disease. No correlation was found between GH response and disease severity and disease duration.

D.5 NEUROENDOCRINE DISTURBANCES IN HUNTINGTON'S DISEASE: GROWTH HORMONE/INSULIN-LIKE GROWTH FACTOR 1 POSSIBLE BIOMARKERS

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Background: Huntington's disease (HD) is a severe inherited neurodegenerative disorder characterised, in addition to neurological impairment, by weight loss suggesting endocrine disturbances.

Aims: The aims of this study were to look for neuroendocrine disturbances in patients with HD and, should such disturbances be found, to determine whether they developed late, as a result of advanced neuron loss, or instead constituted an early effect of the mutant huntingtin protein.

Methods: We compared plasma levels of hormones from the five pituitary axes in 219 patients with genetically documented HD and in 71 sex and age-matched controls. Relationships between hormone levels and disease progression, including weight-loss severity, were evaluated.

Results: Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) were significantly higher in patients than in controls (0.25 (0.01–5.75) versus 0.15 (0.005–4.89) ng/ml, $p = 0.013$ and 0.06 ± 0.35 versus 0.04 ± 0.33, $p = 0.005$, respectively). Cortisol was higher ($p = 0.002$) in patients (397.3 ± 161.3 nmol/l versus 279.8 ± 130.1 nmol/l), whereas no differences were found for other hormone axes. In patients, elevations in GH and IGF-1 and decreases in thyroid-stimulating hormone, T3 and testosterone (in men) were associated with the severity of impairments (independence scale, functional score, total functional capacity, total motor score, behavioural score). Only GH was independently associated with body mass index ($\beta = -0.26$, $p = 0.001$).

Conclusion: Our data suggest that the thyrotropic and gonadotropic axes may undergo alterations over the course of HD. The somatotropic axis is overactive even in patients with early disease, and the GH increase may explain the weight loss seen in HD patients. Both GH and IGF-1 deserve further investigation as biomarkers for HD progression.

D.6 COGNITION IN RELATION TO METABOLIC CHANGES IN THE BRAIN OF PRECLINICAL MUTATION CARRIERS OF HUNTINGTON'S DISEASE

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Background: Mutation carriers of Huntington's disease (HD) who do not yet suffer from motor symptoms are considered preclinical mutation carriers (PMC). HD not only leads to progressive loss of motor functions but also causes cognitive, behavioural and emotional changes, eventually leading to subcortical dementia. However, it is unclear which of these domains is most informative in marking an individual's transition from healthy functioning to clinical HD. Alterations in the brain functioning of individuals with HD are thought to occur first and most severely in the striatum, but changes in other brain regions will also arise, resulting in widespread brain atrophy. It has not yet been clarified which specific pathological processes in the brain may be responsible for the diversity in cognitive dysfunction of PMC.

Aims: To explore the relationship between cognitive performance and biochemical alterations in the brain of PMC. This study is part of an ongoing follow-up project on the development of a reliable biomarker of neuronal dysfunction in preclinical HD.

Methods/Techniques: 22 PMC and 14 controls underwent neuropsychological assessment, neurological examination, 18F-fluorodeoxyglucose and 11C-raclopride positron emission tomography and magnetic resonance imaging scanning. All measures were repeated after 2 years.

Results/Outcomes: Our first results indicate normal cognitive functioning of all PMC at baseline, although biochemical abnormalities appeared in a considerable part of them, especially on 11C-raclopride positron emission tomography. However, relatively more PMC scored in the lower range of normal cognitive functioning compared with the control group. The imaging data are now being analysed and patterns of regional metabolic covariation will then be related to cognitive functioning measures.

D.7 CHANGES IN STRIATAL DOPAMINE D2 RECEPTOR BINDING IN PRECLINICAL HUNTINGTON'S DISEASE

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Objective: Carriers of the Huntington's disease (HD) mutation develop a progressive neurodegenerative disorder after a preclinical phase. The objective of this study is to examine the value of 11C-raclopride (RAC) positron emission tomography scans as a biomarker for HD pathophysiology before the onset of clinical motor HD.

Methods: We conducted a prospective cohort study with clinical and neuropsychological assessment and collected complete RAC data in 18 of 27 preclinical mutation carriers (PMC) and 11 of 14 controls. Follow-up was longer than 2 years in all subjects. We calculated RAC binding potential to measure dopamine D2 receptor availability in the putamen and caudate.

Results: No PMC had overt neuropsychological dysfunction. RAC binding potential was abnormal in up to 44% of PMC with the putamen more sensitive to changes than caudate. The rate of decline of RAC binding potential was 2.6% per year, which is not significantly higher than in controls (1.8% per year). Follow-up putaminal binding potential correlated weakly with predicted distance to onset of clinical HD ($p = 0.034$ for linear fit), but the rate of decline did not. Three PMC developed motor abnormalities suspect for HD during the study. They showed no increased rate of decline of putaminal RAC binding potential, but two had low RAC binding potential at baseline.
Conclusions: Many PMC have striatal abnormalities but we found no clearly increased rate of D2 receptor changes around the onset of clinical HD. In order to estimate a more reliable risk of clinical conversion from striatal D2 binding data, a longer follow-up of the present study cohort will be necessary.

D.8 MONITORING NEUROPROTECTIVE EFFECTS OF RILUZOLE IN HUNTINGTON'S DISEASE BY BRAIN AND PERIPHERAL BIOMARKERS

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Riluzole interferes with glutamatergic neurotransmission thereby reducing excitotoxicity, enhancing damaged neurite formation in motoneurons and increasing serum concentrations of brain-derived neurotrophic factor, involved in striatal degeneration in patients with Huntington's disease (HD). We set up a longitudinal prospective study to analyse the magnitude of volumetric and metabolic brain changes in riluzole-treated and untreated patients (100 mg/day versus placebo). All patients performed well in cognitive tasks, had a Mini-Mental State score above 25 and were matched for gender, HD duration, age of neurological onset, progression rate and mutation size. None of them had taken neuroleptic or antidepressant medications. Twenty-two patients were enrolled and underwent magnetic resonance imaging (MRI) and [fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography scanning, according to our fully automated protocols. Two MRI and positron emission tomography scans were obtained for each patient and a mean interval of 17 months elapsed between scanning sessions. Of 22 patients, 11 received blinded treatment with the neuroprotective agent. Follow-up MRI scans differed remarkably in the two groups. The repeated scan obtained in untreated HD subjects showed the considerably greater loss of functional grey matter volumes in patients who did not receive riluzole than in those who did. Coherently with structural MRI data, metabolic changes in all brain areas were greater in untreated patients than in riluzole-treated patients. Finally, mean serum brain-derived neurotrophic factor concentrations were higher in treated than in untreated subjects (Mann–Whitney U, $p = 0.012$). Riluzole therefore safely contributed to preserve HD patients' brains from progressive degeneration and dysfunction, thus confirming its potential beneficial neuroprotective effect in early or even presymptomatic HD.

D.9 CORRELATION BETWEEN BRAIN PARENCHYMA SONOGRAPHY FINDINGS AND CLINICAL STATUS IN PATIENTS WITH HUNTINGTON'S DISEASE

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Background: Brain parenchyma sonography (BPS) has become a new diagnostic tool in the evaluation of extrapyramidal disorders. Furthermore, recent studies report alterations of mesencephalic raphe structures in unipolar depression and in depressed Parkinson patients. The aim of this study was to evaluate BPS findings in patients with Huntington's disease (HD) in correlation with their neurological and psychiatric status.
Methods: Twenty-five patients with genetically confirmed HD were included (mean age 48.6 years, 16 women) following approval by the ethics committee. Neurological and psychiatric statuses including standardised scales were assessed by independent physicians. Echogenicities of basal ganglia including mesencephalic raphe structures were investigated according to previously described examination protocol for extrapyramidal disorders using a Siemens Sonoline Elegra system. The sonography examiner was blinded for clinical data.
Results: Six patients (24%) showed hyperechogenicity of the substantia nigra, two patients (8%) of the caudate nucleus and one patient (4%) of the lentiform nucleus. No correlation between these findings and the neurological status was seen. Twelve patients (48%) showed symptoms of depression at the time of evaluation, and of those, nine (75%) had hypoechogenic raphe structures. Nineteen patients (76%) had a history of depressive episodes, 13 (68.4%) of them with a hypoechogenic raphe region. All six patients without any history of depressive episodes showed normal echogenicity of raphe structures.
Conclusion: As a novel finding, a relationship between mesencephalic raphe echogenicity and depressive state could be identified in HD. An alteration of the serotonergic brainstem raphe might be involved in the pathogenesis of depression in HD.

D.10 7T MAGNETIC RESONANCE SPECTROSCOPY IN HUNTINGTON'S DISEASE

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Background: Gaining further understanding of the pathophysiology of brain changes in Huntington's Disease (HD) is crucial in the light of developing new interventions to be tested in clinical trials. To date, imaging techniques have shown structural and functional abnormalities in various brain structures in manifest gene carriers of HD and to a lesser extent in premanifest gene carriers. Magnetic resonance spectroscopy (MRS) provides a non-invasive in-vivo technique to measure alterations in brain metabolite concentrations as a reflection of functional changes. Low field MRS has shown generalised changes in the relatively large brain structures of premanifest gene carriers and manifest gene carriers. Ultra high field (7T) MRS has the potential to perform measurements in subregions, with greatly increased signal-to-noise ratio and spectral resolution. We expect to gain further insight into the underlying disease processes, even before structural changes can be demonstrated, essential in the search for a clear biomarker.

D.11 MAINLY AFFECTED CORTICAL BRODMANN AREAS AND CONSPICUOUS POWER CHANGES IN DIFFERENT STAGES OF HUNTINGTON'S DISEASE: A STUDY USING LOW RESOLUTION BRAIN ELECTROMAGNETIC TOMOGRAPHY

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Background: The EEG in Huntington's disease (HD) has been reported to be abnormal in several previous studies. By using EEG tomography such as three-dimensional low-resolution electromagnetic tomography (LORETA) we could already identify cortical

brain areas predominantly involved in our patients. The aims of the present study were to identify particularly affected Brodmann areas (BA) in daytime brain function in HD patients and to focus on power differences correlated with stages of disease.

Methods: In 71 patients and 71 healthy controls a 3-minute vigilance-controlled EEG was recorded during midmorning hours. Thereafter, EEG results were compared with controls within the whole group and within different subgroups by using LORETA for imaging of the regional brain electrical activity.

Results: Delta LORETA power was significantly increased, mainly over right frontal cortices with a maximum in the BA 11 of the inferior frontal gyrus. A decrease of theta, alpha and beta power, accentuated over the left frontotemporal brain areas with most often the maximal difference in the BA 20 of the inferior temporal gyrus, was found. The increase in delta power was not significant in the early stages of disease. Furthermore, with increasing disease severity the significant decrease of beta power became less. HD is not thought to be a lateralised disease; however, clear differences in the results between the right and the left hemisphere were found.

Conclusion: BA 11 belongs to the orbitofrontal cortex and is involved in planning, reasoning and decision making. BA 20 plays a part in high-level visual processing and recognition memory. Both areas are strongly connected to the basal ganglia. The caudate and thalamic activation of the orbitofrontal cortex may be relatively preserved in early HD, allowing this circuit to act in a compensatory fashion for the loss of dorsolateral prefrontal cortex function. The impaired recognition memory of patients with HD may be a result of damage to the ventrocaudal striatum, but the possibility of cortical atrophy, which might produce a similar deficit, can still not definitively be excluded. Contrary to our expectations with increasing disease severity, the decrease of beta power became less. Moreover, further analysis revealed an increase of frontal beta LORETA power with progressive worsening of the disease. These changes were also found in normal aging, so these results might be discussed as faster aging processes in HD patients.

D.12 PPARGC1A, ENCODING PGC-1A, IS A POTENTIAL MODIFIER GENE OF HUNTINGTON'S DISEASE

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Huntington's disease (HD) is one of the most common autosomal dominant inherited neurodegenerative disorders. HD is caused by an unstable CAG repeat expansion in the HD gene (HTT), localised on chromosome 4p16.3. The number of CAG repeats is the main predictor of disease onset, but the remaining variation is strongly heritable. Recent studies implicated PGC-1α (encoded by PPARGC1A) in the pathogenesis of HD. We therefore ascertained possible associations of PPARGC1A polymorphisms with disease onset in European HD patients. Initial studies in Italian patients suggested associations between PPARGC1A haplotypes located in the transcribed region and disease onset ($p = 0.0161$), whereas no such associations were observed with haplotypes located in the promoter region. Based on these studies, we identified associations of rs7665116, located in a conserved region of intron 2, with CAG adjusted age at onset in 449 Italian HD patients ($p = 0.0016$). If confirmed in other populations, these findings may have implications for the identification of therapeutic targets in HD and other neurodegenerative disorders.