Weight loss in Huntington disease increases with higher CAG repeat number
N. Ahmad Aziz et al., Neurology (2008), 71:1506–1513

This study shows that the rate of weight loss in Huntington’s disease is directly proportional to the length of the CAG repeat in the HD gene, and is likely to result from a hypermetabolic state.

Background
Huntington’s disease (HD) is a genetic neurodegenerative disorder caused by the expansion of the CAG repeat in the HD gene. It is characterised by a clinical triad of motor, behavioural and cognitive disturbances. Weight loss is also a hallmark of HD, and has been observed both in humans and HD transgenic mice. Interestingly, in HD, a lower body mass index (BMI) has been associated with a higher rate of disease progression.

The cause of weight loss has been attributed to the following:
• Difficulties with swallowing that might lead to a decreased intake of calories. Note however that weight loss is already seen in pre-manifest HD individuals, and previous studies have shown that, at early stages, caloric intake is increased both in HD patients and HD transgenic mice.
• Increased motor activity caused by chorea (involuntary movements) that might lead to higher energy expenditure. However, the severity of choreic symptoms does not correlate with weight loss.
• An increased metabolic rate. Mutant huntingtin (Htt) has been shown to perturb a number of molecular and cellular systems that could impact on energy homeostasis. This effect could vary with the length of the polyglutamine tract in mutant Htt.

Methods
The aims of this study were:
• To investigate weight loss in early stage HD over three years
• To assess whether there is a correlation between weight loss and clinical symptoms
• To determine whether CAG repeat length is directly related to the rate of weight loss and caloric intake.

Participants (517 early stage HD patients) were recruited from the European Huntington’s Disease Initiative, a phase III interventional clinical trial. Riluzole, the drug tested in this trial, does not affect body weight. Patients taking neuroleptic drugs were excluded. Clinical symptoms were assessed with the Unified Huntington’s Disease Rating Scale (UHDRS) subscales for motor, behavioural, cognition and functional capacity. Data analysis was performed using linear mixed-effects models. The relationship between CAG repeat length, body weight and caloric intake was also studied in the R6/2 mouse model of HD.

Results
In HD patients, BMI significantly decreased by 0.15 units per year on average (normal BMI lies between 18–25). The rate of weight loss was greater in patients with a longer CAG repeat (see figure), although none of the symptoms assessed by the UHDRS correlated with weight loss. A correlation between weight loss and CAG repeat length was also observed in HD mice, despite the fact that mice with longer CAG repeats had increased caloric intake.

Conclusion
Weight loss in HD is directly correlated to CAG repeat length and likely to result from a hypermetabolic state. This correlation suggests that mutant Htt interferes directly with cellular energy homeostasis. Hypothalamic pathology, changes in the innate immune response and mitochondrial disturbances have all been described in HD, and could contribute to this process.