

## Effect of CAG repeat length on psychiatric disorders in Huntington's disease

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### Abstract

There is strong evidence that the length of CAG repeats, in patients with Huntington's disease (HD), govern the age of onset and the rate of clinical progression of neurological symptoms. However, psychiatric manifestations of the disease have not been examined as comprehensively. Seventy two Greek patients with Huntington's disease had DNA testing and were clinically assessed by means of a semi-structured interview (SCID) and four self-rated questionnaires. Genotype–phenotype correlations were examined. The CAG repeat length had a significant negative association with the age of onset of psychiatric disorders, the total level of functioning and the MMSE. However, the probability of developing a psychiatric disorder and the severity of psychiatric symptoms were not determined by the trinucleotide expansion, after controlling for the duration of illness, sex, and age of the subjects. The factors that determine the development of psychiatric symptoms in HD patients seem not to be limited to a dose related toxicity of the expanded Huntington. It is hypothesized that alternative genetic or environmental factors underlie the pathogenesis of the psychiatric phenotype.

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### 1. Introduction

Huntington's disease (HD) is a progressive, autosomal dominant, neurodegenerative disease, characterized by motor disorder (usually chorea), dementia and psychiatric symptoms. An increased number of CAG repeats in the 5' region of the IT15 gene, on chromosome 4p16.3 is the responsible mutation. The psychiatric disorders reported in patients with HD include affective disorders, schizophrenia-like states, behavioural and personality disorders, obsession-like symptoms, irritability and aggression (Berrios et al., 2001). The prevalence of psychiatric disorders ranges from 35% to 73%, depending on the study design (Craufurd et al., 2001). The wide variation in the prevalence most likely results from definitional and ascertainment problems. Single symptoms, rarely amounting to

official DSM-IV or ICD-10 diagnoses, are very frequent in HD (Berrios et al., 2001).

Motor and cognitive impairment have been investigated more extensively than behavioural and psychiatric aspects (Paulsen et al., 2001; Soliveri et al., 2002).

Psychiatric signs and symptoms have been unrelated to the length of CAG repeats (Anderson and Marder, 2001; Naarding et al., 2001). However, most of the studies on psychiatric symptomatology have methodological controversies. The majority have, so far, been retrospective (based only on medical chart reviews), the psychiatric symptomatology has not been defined with precision, using valid diagnostic instruments, and on many occasions psychiatric and cognitive disorders were analyzed jointly (Andrew et al., 1993; Claes et al., 1995; MacMillan et al., 1993; Tsuang et al., 2000; Weigell-Weber et al., 1996). The only study with direct psychiatric examination of the patients, to our knowledge (Zappacosta et al., 1996), has limited number of patients ( $n = 29$ ) and focuses only on depression.

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The strong inverse relationship between the age of onset of HD and the number of CAG repeats is unequivocal (Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993). A number of studies define the age of onset as the first time motor signs representing a permanent change from the normal state are identified in a patient (Langbehn et al., 2004). Other studies consider the age at which the first clearly defined abnormality, including involuntary movements, psychiatric or cognitive abnormalities, is apparent (Brinkman et al., 1997). However, only few studies exist that examine the relationship between the age of psychiatric onset, particularly, and the CAG expansion (Andrew et al., 1993; Squitieri et al., 2001; Tsuang et al., 2000).

The gross pathology of HD is limited to the brain, with atrophy most prominent in the caudate, putamen and cortex (Margolis and Ross, 2003). The rate of deterioration and the severity of neuropathological impairment appear to depend on the number of CAG repeats (Furtado et al., 1996; Penney et al., 1997). This is reflected in the earlier onset and the faster clinical decline of patients at the upper end of CAG repeat length (Brandt et al., 1996; Illarionov et al., 1994; Mahant et al., 2003; Rosenblatt et al., 2006). Although this is supported regarding motor and cognitive symptoms, to our knowledge no studies have looked specifically at the relation between the trinucleotide expansion and the severity of psychiatric symptoms. Previous research has indicated that neuropsychiatric symptoms in HD are relatively independent of cognitive and motor aspects of the disease (Paulsen et al., 2001).

The aim of the present study was to investigate the association between CAG repeat length and psychiatric disorders in HD. We looked specifically at the relation between the trinucleotide expansion and the prevalence, the age of onset and the severity of psychiatric disorders.

## 2. Materials and methods

### 2.1. Subjects

The subjects potentially to be included in the study were consecutively referred to the Clinical and Molecular Genetics Unit, Department of Neurology, “Eginition Hospital”, University of Athens. This is the unique reference centre in Greece with facilities for molecular genetic testing for HD and, consequently, patients were referred from across the country. Between 2002 and 2006, 101 consecutive adult patients with probable clinical diagnosis of HD at the time of referral were invited to participate to the study. Eleven patients were not able to attend the clinic for interview and 10 patients with severe cognitive impairment were unable to cooperate for the interview and were excluded. Out of the 80 remaining individuals, 75 agreed (by giving informed consent) to participate in the study and underwent the psychiatric interview. No obvious differences related to the study design were identified among the 5 subjects who refused to participate. Seventy two of the participants (43 males and 29 females) had positive DNA testing

and three subjects tested negative. The sociodemographic profile of the patients is summarized in Table 1.

### 2.2. Neuropsychiatric assessment

All patients with a probable clinical diagnosis of HD were interviewed by a psychiatrist (EV) and motor symptoms were assessed by a neurologist (MP) who ascribed a clinical diagnosis, according to the criteria suggested by Folstein (Folstein et al., 1986). With a view to avoid selection and ascertainment bias, the clinical assessment was carried out blindly to the results of genetic testing. A semi-structured clinical interview (SCID) (First et al., 1996), leading to DSM-IV diagnoses, was used. Information was also collected from medical records, referral letters and in 85% of cases from interviews with relatives or carers and the investigator used all available information in rating each item, according to his clinical judgement. SCID was employed to provide present and lifetime “formal” as well as subthreshold diagnoses of axis I disorders of DSM-IV. As, in most cases, patients did not come in for examination of psychiatric symptoms, but mainly for their motor symptoms, the analysis of lifetime psychiatric disorders was considered more appropriate than the analysis of current disorders. Taking into account that symptoms in HD often do not amount to “formal” DSM diagnoses, subthreshold disorders, as defined by the manual of SCID, were included in post-hoc analyses.

Age of onset of neurological symptoms was defined as the age at which involuntary movements, or other motor abnormalities representing a clear and permanent change from the normal state, occurred. Age of onset of psychiatric disorders was defined as the age of the first presentation of a psychiatric diagnosis, as determined by the SCID.

In order to quantify the severity of the disorder, the General Assessment of Functioning scale (GAF) was estimated, as a measure of psychological, social and occupational functioning, and the Mini Mental State Examination (MMSE) (Folstein et al., 1975) was used to provide information on the level of cognitive decline of patients. To employ a dimensional approach to the psychopathology, four self-rated questionnaires were used, when patients were capable to complete those (53 patients). The Symptom Checklist 90-R (SCL-90-R) (Derogatis, 1977), which has been standardized in Greek population, evaluated general mental health, as well as nine dimensions

Table 1  
Sociodemographic characteristics of the participants

Characteristic	Number
Sex: male	43 (59.7%)
Sex: female	29 (40.3%)
Age: mean (sd)	50.64 (15.0)
Duration of illness <sup>a</sup> : mean (sd)	5.62 (5.7)
Years of education: mean (sd)	10.9 (4.4)
MMSE: mean (sd)	24.9 (4.0)

<sup>a</sup> Time between onset of motor symptoms and assessment.

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