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# Late-onset Huntington disease with intermediate CAG repeats: true or false?

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► Supplemental files: Videos of case 1 and case 2 are published online only at <http://journal.bmj.com/content/vol81/issue2>

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## ABSTRACT

Huntington disease (HD) is a neurodegenerative disorder associated with an expanded CAG trinucleotide repeat length in the huntingtin gene. 'Intermediate alleles' with 27 to 35 CAG repeats generally do not cause HD but are unstable upon germ-line transmission. Insights in CAG repeat mosaicism and enhanced trinucleotide expansion in postmitotic neurons indicate that in the intermediate range, other factors than the CAG repeat length in diagnostic tests have to be considered. Here, we report two patients with mild, late onset HD and an intermediate repeat allele. The authors anticipate that intermediate repeats can cause late-onset HD due to disease modifiers and may be more common than previously stated.

## INTRODUCTION

Huntington disease (HD) is a progressive autosomal dominant neurodegenerative disorder characterised by movement disorders, psychiatric symptoms and cognitive dysfunction. HD is associated with expansion of CAG trinucleotide repeats in the coding region of the huntingtin gene (OMIM 143100) on chromosome 4. In the general population, the CAG repeat length varies from 6 to 35 trinucleotides in the HD gene. A proliferation of 40 or more is invariably associated with HD, but at a lower CAG repeat range (36 to 39), reduced penetrance is present.<sup>1</sup> Alleles with 27 to 35 CAG repeats are generally considered 'intermediate.' The CAG repeats in this range show instability and have the potential to expand into the disease range within one generation through the paternal line.<sup>2</sup> A small number of cases with the HD phenotype and an intermediate repeat number have been reported.<sup>3–5</sup> In the present report, we present two additional patients with late-onset HD and an intermediate CAG repeat number. In light of recent insights in somatic CAG trinucleotide expansion and instability,<sup>6</sup> we hypothesise that intermediate repeat alleles may cause late-onset HD.

## CASE REPORTS

### Case 1

This 72-year-old man noticed involuntary movements of abdomen, chest and throat at age 68. This resulted in walking problems and difficulties with speech. Continuous restlessness was present and worsened in stress situations. Gradually, unwanted movements developed in the hands, abdomen and face. His short-term memory and concentration were impaired, and his wife noticed behavioural changes. A sister of the patient died while diagnosed

as having olivo-ponto-cerebellar atrophy. This diagnosis is postmortem changed into HD, as her symptoms were identified by several family members as identical to the symptoms of her three children all having genetically confirmed HD (43 CAG repeats). One brother suffers from late-onset Parkinson disease with normal CAG repeats in the HD gene (17/18). The history of the parents was not suspect for HD.

Neurological examination showed chorea of the abdominal wall, spreading to the trunk, which affected breathing and speech. There is an interrupted ocular pursuit and increased latency of saccade initiation in both directions. Choreatic restlessness is present in the upper extremities. The signs did not improve with tiapride, sulpiride, levodopa/carbidopa and amitritypyline. A postural tremor was present in both hands. Motor impersistence was not observed. The Mini Mental Status Examination score was 26 out of 30. Neuropsychological examination revealed memory impairment and increased irritability. Polymyography showed irregular bursts of muscle activity in the rectus abdominis muscle, consistent with chorea. MRI scan of the brain showed mild generalised atrophy. An [11C]-raclopride PET scan showed no abnormalities. Genetic testing for HD revealed 31 CAG repeats on one allele and 18 repeats on the other. Test results were confirmed in an independent sample.

### Case 2

This 68-year-old woman complained of involuntary movements of her mouth starting after the death of her husband 3 years ago. The restless movements worsened with stress and emotion, and were progressive, resulting in speech problems and neck pain. Her husband noticed frequent blinking. No abnormal movements of the tongue or other parts of the body were noticed. Except for a loss of interest, no psychiatric symptoms were present. The family history revealed a sister with psychiatric disease of unknown origin and possible jerky movements in both arms. Her mother suffered from Parkinson's disease. The father did not show any neurological or psychiatric symptoms.

On examination, she had dysarthria and chorea, especially around the mouth, and an increased latency of saccade initiation with mild slowing of saccade velocity. Chorea is present in all extremities with mild dystonia of the upper extremities. Furthermore, cervical dystonia with slight rotation (10°) and lateroflexion (20°) was detected. She had 30 CAG repeats on one huntingtin allele and 17 repeats on the other. This finding was confirmed in an independent sample.

Genetic tests for HD like-2, dentatorubropallidoluysian atrophy and spinocerebellar ataxia 3, 14 and 17 were all normal.

Both patients are of Caucasian origin. There was no history of neuroleptic medication. Laboratory tests for thyroid function, vitamins B<sub>1</sub>, B<sub>6</sub>, B<sub>12</sub> and folic acid, syphilis, *Borrelia burgdorferi*, plasma copper, ferritin, ceruloplasmin, antiphospholipid antibody and ANA were normal, and the ESR was low. No acanthocytes were seen in the blood smear, creatine kinase was normal, and MRI scans in both cases were normal, revealing no signs of neurodegeneration with brain iron accumulation. During follow-up by a movement disorder specialist (RMAB and MAJT), both patients slowly deteriorated over a course of 4 and 3 years, with a present UHDRS motor rating of 19 and 22, respectively.

## DISCUSSION

Here we describe two patients with an intermediate number of CAG repeats in the huntingtin gene and late-onset HD. Most of the currently known HD-phenocopies or HD-like disorders have been excluded.<sup>7</sup> In the first patient, family history proved to be positive for HD, and in the second patient, family history is suggestive for HD. The stringent cut-off point for disease causing repeat numbers (36 repeats or more) is under discussion, as recently published reports<sup>3–5</sup> of mild, late-onset HD with an intermediate CAG repeat length suggest that such cases, although rare, do occur. In the report of Kenney *et al*, the authors present a case with autopsy-proven HD and 29 repeats. This claim, however, was discussed critically, as known HD phenocopies and HD-like syndromes were not excluded. Furthermore, no huntingtin inclusions were detected in the brain of this patient with autopsy.<sup>8–9</sup> In literature, a number of HD-phenotype cases with normal CAG alleles (<27 triplets) have been reported. In these reports, the authors attribute the cases to HD-phenocopies and discuss the possibility of a mutation in as-yet unidentified genes. Furthermore, misdiagnosis and mistakes in sample processing were considered.<sup>10–12</sup> In contrast to normal alleles, the instability of intermediate repeat tracts is shown by anticipation. Therefore, we place the intermediate repeats with late-onset HD at the end of the phenotype spectrum of HD and suggest that such cases have to be considered clinically and in genetic counselling.

The frequency of intermediate alleles (27–35 CAG repeats) in a selected population of patients and their partners was estimated to be as high as 3.9%,<sup>2</sup> whereas the study by Kremer *et al* shows a much lower prevalence of 30–35 repeats (0.75%).<sup>13</sup> Intermediate alleles have been categorised in ‘general population intermediate alleles’ and ‘new mutation intermediate alleles’ based on how the allele is ascertained within the context of a family. New mutation intermediate alleles are prone to repeat expansion in following generations. The likelihood of proliferation of general population intermediate allele carriers has been shown to be very low.<sup>14</sup> The proven positive family history of the first patient indicates susceptibility to anticipation of the intermediate CAG allele. Whether genetic factors resulting in anticipation are similar to the factors leading to enhanced somatic CAG repeat expansion is not known.

The length of the CAG repeats accounts for about 70% of the variation in age of onset.<sup>15</sup> The late age at onset (65 and 68 years) observed in both patients is consistent with the inverse correlation between the age of onset and the number of CAG repeats. Laboratory and animal studies show that, besides the CAG trinucleotide expansion, other genetic factors modulate the pathogenicity of the HD gene. In humans, intermediate repeats on some specific ‘HD-haplotypes’ are prone for CAG expansion,<sup>16</sup> and association studies revealed various disease

modifiers.<sup>17–19</sup> In mouse models, different genetic backgrounds influence intergenerational and somatic instability, as well as nuclear accumulation of mutant huntingtin.<sup>20</sup> In polyglutamate disorders, the expanded CAG sequence serves as a template for synthesis of an increasingly toxic HD protein in neurons. Based on the observation that somatic CAG trinucleotide expansion is dependent on a DNA glycosylase (OGG1), a ‘toxic oxidation cycle’ model causing neurodegeneration was proposed.<sup>21</sup> Interestingly, recent studies show that a striking somatic mosaicism of CAG repeats is present in the brain, with prominent cell-specific expansion in the neuronal cells in the striatum.<sup>6</sup> Further studies of the factors which play a role in the somatic changes in repeat tracts and modulate toxicity in striatal neurons are required. However, the enhanced trinucleotide expansion in postmitotic neurons emphasises that factors other than CAG repeat number have to be considered and indicates that a CAG repeat number of 35 or less, extracted from peripheral blood samples, does not necessarily reflect the length and toxicity of the repeat tracts in neurons. Therefore, accurate neuropathological assessment of the symptomatic carriers of intermediate CAG repeats will be of great value.

The present cases illustrate the difficulties in diagnostics and counselling in patients with intermediate CAG repeats in the HD gene and chorea. In light of recent insights in the age-dependent somatic instability and mosaicism, we suggest that the development of HD—typically with a late age of onset—can occur with an intermediate CAG repeat number and should be considered in patients with mild and late-onset chorea. We treated both patients as such and offered them and their family members genetic counselling.

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**Competing interests** None.

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**Patient consent** Obtained.

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## Short report

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