

SHORT REPORT

Maternal transmission in sporadic Huntington's disease

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Abstract

Huntington's disease is an autosomal dominant neurodegenerative disorder caused by the expansion of a (CAG)_n repeat in the *IT15* gene. Three per cent of cases are sporadic and in those in which family studies have been performed, the origin of the mutation was always paternal. The first sporadic case of Huntington's disease is presented in which a premutated maternal allele of 37 CAG repeats was transmitted expanded to the proband (43 CAG repeats). Molecular analysis of the *IT15* gene is extremely important in sporadic cases of Huntington's disease, providing correct diagnosis of the disorder and facilitating genetic counselling to the family members.

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Huntington's disease is an autosomal dominant neurodegenerative disorder, which presents usually in the fourth decade of life. Its approximate prevalence is 1/10 000 and it is characterised by motor and personality disturbances and dementia, caused by selective cell death of the basal ganglia.¹ The molecular defect in the gene responsible for Huntington's disease (*IT15*) consists of a (CAG)_n trinucleotide repeat expanded and unstable on chromosomes with the disease.² This (CAG)_n triplet is polymorphic in normal chromosomes (11 to 34 CAG repeats), whereas it is expanded (mutated) when it has 37 or more repeats.³ Alleles overlapping between these two ranges of (CAG)_n repeats (30 to 38) have been designated as intermediate or premutated.⁴

The frequency of new mutation in Huntington's disease is extremely low with a mutation rate estimated as the lowest known in inherited neurological diseases.⁵ Clinical diagnosis of Huntington's disease is difficult when neither of the parents are affected, making it necessary to follow very strict criteria to consider a case of Huntington's disease as truly sporadic. The classic criteria for defining a

case of Huntington's disease due to new mutation⁴ are (1) clinical confirmation of Huntington's disease features in the patient, (2) unaffected parents beyond the sixth decade of life, (3) exclusion of non-paternity, and (4) transmission to the offspring. Due to the stringency of these criteria the Huntington's disease mutation rate has probably been underestimated. After the discovery of the molecular defect responsible for Huntington's disease, several de novo mutations have been reported.¹⁻⁶ In those sporadic cases in which the parental origin of the pre-mutation was proved, this was always of paternal origin. We present here the first sporadic case of Huntington's disease with demonstrated maternal origin.

Case report

A 42 year old man was referred for molecular analysis of Huntington's disease. He started at the age of 35 years with behavioural and personality changes, which were initially attributed to alcohol misuse. One year later, he initiated choreic movements, unquietness, and hypomania. At that time, brain MRI showed no alterations. He was the first son of three children from a non-consanguineous marriage. His two brothers and his parents (aged 69 and 71) did not show any clinical sign of the disease. The interview did not disclose other family members affected with neurodegenerative disease in the preceding five generations. Several neurological diseases, such as cerebrovascular or autoimmune diseases and neuroacanthocytosis, were disregarded as the cause of the symptomatology. The patient was not treated with neuroleptic drugs. Although a clinical diagnosis of Huntington's disease was not initially considered due to the lack of family history, a molecular analysis for Huntington's disease was indicated.

DNA samples for molecular analysis were obtained from both parents, the affected patient, and the two clinically unaffected brothers. The familial genetic analysis was performed following the rules for Huntington's disease of the International Huntington Association and the World Federation of Neurology Research Group on Huntington's chorea.⁷ Molecular analysis of the (CAG)_n repeat of the *IT15* gene was per-

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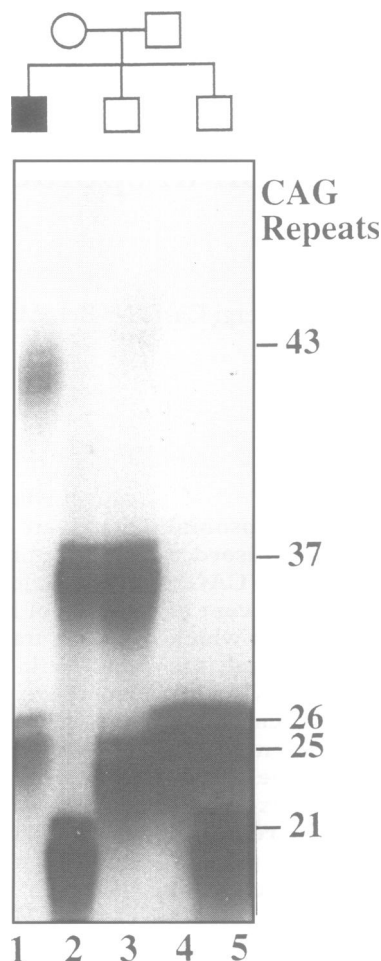
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Polymerase chain reaction analysis of the (CAG)_n repeats in the *IT15* gene in a sporadic case of Huntington's disease of maternal origin. The mother (lane 2) has a premutated allele (37 CAG repeats) that has been transmitted expanded (43 CAG repeats) to the proband (lane 1) and with the same unexpanded length (37 CAG repeats) to the second son (lane 3); the third son (lane 5) has inherited the normal maternal allele (21 CAG repeats).



formed as previously described.⁸ Paternity and maternity were analysed using five microsatellite markers located in different chromosomes.⁹

Molecular analysis of the (CAG)_n repeat of the *IT15* gene showed that the father of the patient had two alleles of 25 and 26 CAG repeats, his mother had 21 and 37 (premutated allele) CAG repeats, and the index patient inherited the allele with 26 CAG repeats from his father and an expanded allele of 43 CAG repeats from his mother. One of his brothers (clinically normal) inherited the allele of 25 CAG repeats from his father and the premutated allele of 37 CAG repeats from his mother, and the other brother showed two alleles of 26 and 21 CAG repeats (fig).

Discussion

To our knowledge, this is the first report of a sporadic case of Huntington's disease with maternal origin. In this patient the carrier of the premutated allele was the mother, with an allele of 37 CAG repeats, who transmitted to her kindred the normal, premutated, and expanded alleles. Although this segregation analysis already shows the maternal origin of the expanded CAG allele, paternity and maternity were confirmed with microsatellite markers with a probability higher than 99%. The possibility that the maternal premutated allele (37 CAG repeats) was by itself a disease allele and that the mother could have a late

onset cannot be disregarded, but she was 71 years old and totally free of symptoms of Huntington's disease.

In all the previously reported sporadic cases of Huntington's disease the father was the carrier of the premutated allele.¹⁻⁶ One explanation for the paternal transmissions in such disease could be a higher mutation rate in males due to a greater number of germ cell divisions and the advanced parental age, as was shown in some reported Huntington's disease paternal transmissions and in other autosomal dominant disorders.⁴ Our patient does not fit with this proposal due to the maternal transmission and the fact that the mother was only 30 years old when the patient was born. In this case the increase of the (CAG)_n repeat transmitted to the next generation was of six repeats, whereas in seven sporadic cases reported by Golberg *et al*⁴ the inferred mean increase in parent-sibling transmission was of 14 CAG repeats (range 4-25).

This is the first reported case of a premutated woman transmitting the Huntington's disease allele. It has been shown that the Huntington's disease mutation undergoes a smaller expansion when transmitted by females than when transmitted through the male germ line.³ This could also account for premutated alleles, explaining the exceptional occurrence of maternal transmission in sporadic Huntington's disease. Due to the inverse correlation that exists between the age of onset of Huntington's disease and the number of (CAG)_n repeats,³ it is possible that when the sporadic cases are diagnosed the parents are already deceased, this being more likely for those of maternal origin, which should have undergone smaller expansions of the (CAG)_n repeat. The 3% frequency of sporadic cases of Huntington's disease reported⁴ is similar to that in our patients (four cases in 98 families). Only in the case presented here were samples from the parents available for analysis.

Molecular analysis of the *IT15* gene plays an important part in the clinical diagnosis of Huntington's disease in familial cases, but especially in the sporadic ones. In addition to providing correct diagnosis of the disease, it facilitates genetic counselling to other family members about a severe disease that they were not previously aware of.

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