New mutation to Huntington’s disease

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SUMMARY We report a large family with an isolated case of Huntington’s disease (HD), which is probably the result of a new mutation. The patient developed clinical signs typical of HD at the age of 36. The clinical course of the patient’s disease is documented by several clinical admissions over a period of 14 years at present. The family history is strikingly negative with the parents having been clearly unaffected into their 80s and with 13 older and two younger, living, healthy sibs. Extensive testing of polymorphic markers (blood groups, red cell and serum proteins, HLA antigens) showed no indication of non-paternity, but rather gave strong support to the hypothesis that the proband is a full sib. In addition, DNA typing for several RFLPs known to be closely linked to the HD gene locus indicated that several clearly unaffected sibs share one or the other or both of the patient’s haplotypes. This is further evidence in favour of the hypothesis of a new mutation at the HD locus.

The posterior probability of a new mutation to HD in the patient exceeds 99%, even if an a priori probability of non-paternity of 10% and a mutation rate of HD of $10^{-7}$ is assumed.

Huntington’s disease (HD) is an autosomal dominantly inherited neurodegenerative disorder with a variable age at onset but full penetrance by old age. The defect causes specific neuronal loss, leading to progressive motor disturbance, psychological manifestations, and intellectual deterioration. The mutation rate is among the lowest known for human disorders, the estimated number of mutants per million gametes varying between $0.13 \times 10^{-6}$ and $9.6 \times 10^{-6}$. Calculated mutation rates using the ‘direct’ method, based on the proportion of cases without a detectable family history, are clearly maximum estimates owing to the inherent difficulties in defining a mutant case.6 Wendt and Drohm,7 in their study of 4024 HD patients, found no mutant case after having tested for paternity by examining blood groups of all living unaffected parents and after having excluded those cases where the parents died before outliving their risk.

In a review of data on mutation rates to HD, Shaw and Caro8 came to the conclusion that new mutants make up only around 0.1% or less of all cases.

Twelve possible cases of new mutation to HD, in which the parents were living or died healthy at advanced age, have been reported to date, but none of them meets all of the criteria suggested by Stevens and Parsonage16 to designate a case of a new mutation: (1) clinical cardinal features in the proband and similarly affected offspring; (2) both parents having outlived most of their risk; (3) sufficient information about the health status of the parents; and (4) proof of paternity.

Not surprisingly, there is no definite proof of a new mutation in HD. It seems impossible that a specific case will meet all the postulated criteria. Clinical symptoms being unspecific with a wide differential diagnosis, late onset, and the difficulty in most sporadic cases of establishing a convincing negative family history, cause inherent problems, which led Reed and Neel15 to the conclusion that specific instances of mutation in this disorder will not be demonstrable.

However, proving a new mutation in a sporadic case may be of great importance to the family, that is, healthy relatives other than offspring who other-

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New mutation to Huntington's disease

wise would carry a substantially increased risk for HD too.

Most of the diagnostic problems in HD can be overcome by careful documentation of clinical observations in combination with a panel of paraclinical tests over a period of several years, thus corroborating the diagnosis of HD even in a living, isolated case.23, 24

Gusella et al25 identified highly informative RFLPs closely linked to the HD locus on the short arm of chromosome 4. Since then, additional probes detecting various RFLPs at this and neighbouring loci have been found.26, 27 These RFLPs can be used to identify gene carriers with high probability in most familial cases of HD, but this method cannot be used in sporadic cases to identify other possible gene carriers. However, typing for closely linked DNA markers in healthy relatives of an isolated case, together with serological paternity testing, allows the probability of a new mutation to be defined more precisely.

We show that the results of these methods subjected to a rigorous statistical analysis of family data can lead to decisive probabilistic statements concerning the underlying cause of the disease in a specific isolated case of HD, even if the parents of the patient are already dead.

Results of our investigations in a unique family with 17 sibs add further evidence to the existence of new mutations in HD.

Case report

The female patient was born in 1937 as the 15th of 17 brothers and sisters, when her father and mother were aged 55 and 42, respectively (fig 1). The pregnancy, birth, and psychomotor development were normal as reported by the older sibs. She finished primary school with average results and worked as a housemaid and later as a factory worker. She married twice and has borne two healthy girls, now 10 and 23 years old. Both marriages ended in divorce.

Her medical history was unremarkable until the age of 36, when she was referred to a peripheral psychiatric clinic after repeated shoplifting. During the following years she was caught shoplifting another 10 times. Because of additional compulsive washing behaviour a compulsive disorder was diagnosed at that time. From the age of 41 she has suffered from recurrent attacks of a depressive illness with severe depressive mood, vital symptoms such as sleep disturbance and loss of appetite, and despair. Five admissions to a peripheral psychiatric clinic were necessary because of kleptomania and paranoid depression. She had been treated several times with neuroleptics and antidepressants.

![Figure 1: Pedigree of the family.](http://jmg.bmj.com/)

<table>
<thead>
<tr>
<th>Huntington's disease</th>
<th>Serological testing and DNA typing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died at 81 years</td>
<td>Aged 30 years after investigation</td>
</tr>
<tr>
<td>Born in 1920</td>
<td></td>
</tr>
</tbody>
</table>
The patient was first referred to our psychiatric department at the age of 46 when she was caught shoplifting again and the legal question of compulsory psychiatric placement had to be decided. At that time she suffered from agitated depression. Her mental condition was found to be normal with a low intelligence and a low score in the Benton test. Additionally, she had slight choreic or fidgety movements of her fingers and hands. Some disturbance of fine movements, like writing, eating, etc, and slight dysdiadochokinesia were found. Under an appropriate mental load some truncal hyperkinesia could be observed. Apart from that, neurological examination was normal. Her body weight was 56 kg and her height 175 cm.

Somatosensory evoked potentials, electrically elicited long latency reflexes of thenar muscles following median nerve stimulation (fig 2), and electronystagmography were normal. CT scan showed a slight enlargement of the right temporal horn. The bicaudate diameter was enlarged (fig 3). As the family history was negative, the diagnosis of HD was rejected and a depressive syndrome with a compulsive disorder was assumed. The hyperkinesia was suspected to be the result of tardive dyskinesia.

During the following four years her mental state deteriorated and she was no longer able to work or even look after her house. The dyskinesia worsened and she was again referred to our neurological department at the age of 50.

At general examination she looked older than she was and she was underweight (weight 50 kg, height 175 cm). The chest, lungs, heart, blood vessels, and abdomen were found to be normal.

At that time she was moderately depressed with reduced drive and had a pronounced amnesic syndrome. Neuropsychological examination showed corresponding severe deficits of short term verbal memory, visuospatial and constructional disturbances, and intellectual deficit. She had severe choreic movements of the extremities and trunk with disturbance of everyday activities like eating and writing. Facial and tongue muscles as well as the diaphragm were involved in the choreic movement disorder. Her gait was unsteady owing to the choreic leg and trunk movements. Tendon reflexes were brisk and patellar tendon reflexes displayed the 'hung up' tendon jerk. Coordination tests of legs and arms were disturbed by frequent choreic movements. All laboratory tests including calcium, parathormone, copper, caeruloplasmin, and haematological parameters were in the normal range. Thyroid function tests were normal too, and immunological tests for lupus erythematosus proved to be negative. Cerebrospinal fluid was normal including gamma-globulins and oligoclonal bands. The MR showed

![Fig 2](http://jmg.bmj.com/)

**FIG 2** Somatosensory evoked potentials (SEP) and electrically elicited long latency reflexes (LLR) to median nerve stimulation recorded in October 1983 and June 1987 (right hand). The cortical SEP (C3-Fz) was reduced in amplitude and the probably transcortically mediated LLR completely disappeared during the observation period. In contrast, the subcortical N13 (C7-Fz) and the spinal Hoffmann reflex (HR) remained unaffected. This pattern of abnormality is frequently found in HD.
New mutation to Huntington’s disease

Clear atrophy of the caudate nucleus and slight cortical atrophy (fig 4). Compared with the earlier CT scans, the enlargement of the frontal horns as well as parietal cortical atrophy was slightly advanced. The EEG was flat with frequent muscle artefacts. Early cortical somatosensory potentials were diminished bilaterally to a third of the amplitudes found four years earlier with normal potentials at C7 as before (fig 2). Electrically elicited long latency reflexes in both hands were now absent with preserved Hoffmann reflexes. All electrophysiological investigations were performed during a medication free period of three months. Unfortunately, the patient and her family refused positron emission tomography which is not available at our clinic and would have required long distance transport to another clinic.

Family history

The pedigree is shown in fig 1. As reported by the patient’s healthy sibs and the family doctor, the parents were physically and mentally healthy all their life. They died from cardiac failure at the age of 87 and 81, respectively. They were hard working farmers and innkeepers, the father having carried on commerce until his death.

All 13 sibs of the parents reached an age of over
70 years. None of these is known to have had any physical, mental, or behavioural disturbances evoking suspicion of HD. The grandparents of the proband are said to have been healthy throughout their life and to have died at an advanced age of at least 60 to 70 years.

At the time of investigation, 15 of 16 brothers and sisters of the proband were still alive and healthy. Their mean age was 57.9 years (range 46 to 67). Altogether they have 46 children with a mean age of about 25 years (range 7 to 40). One brother (III.4) was healthy until he died during the second world war at the age of 22.

All living sibs could be contacted personally, except the sister, III.3, who lives in Poland but is said to be as healthy as the others. We had detailed interviews with all of them and no signs suggesting HD were observed in any case. None of them consented to a detailed neurological examination, but nine of them (III.1, 3, 6, 7, 9, 10, 12, 15, and 17) agreed to have blood sampling for serological investigations and DNA typing for scientific purposes.

Material and methods

**SEROLOGICAL INVESTIGATIONS**

Blood group and HLA typing and serum marker examinations were performed using blood collected from the patient and eight healthy sibs, according to standard methods using commercial reagents.

**MOLECULAR STUDIES**

For RFLP analysis, DNA was prepared from isolated leucocytes. Restriction, digestion, electrophoresis, transfer, and hybridisation were performed according to the methods of Southern,28 Feinberg and Vogelstein,29 and Vandenplas et al.30 DNA probes and restriction enzymes detecting different RFLPs at the locus D4S10 which segregate informatively in this family are listed in table 1. Three polymorphisms do not segregate informatively in this family: the BglII RFLP detected by probe pKO82, the EcoRI RFLP detected by probe pKO83 at locus D4S10, and the HincII RFLP detected by probe p8 at locus D4S62 (not shown in table 1).

<table>
<thead>
<tr>
<th>Probe</th>
<th>Enzyme</th>
<th>III.1</th>
<th>III.3</th>
<th>III.6</th>
<th>III.7</th>
<th>III.9</th>
<th>III.10</th>
<th>III.12</th>
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<td>C</td>
<td>B</td>
<td>C</td>
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<td>C</td>
<td>B</td>
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<td>1</td>
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</tr>
<tr>
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<td>2</td>
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<td>b</td>
<td>a</td>
<td>c</td>
<td>a</td>
<td>c</td>
<td>a</td>
</tr>
</tbody>
</table>

Pedigree numbers refer to fig 1: patient is III.15.

**FIG 4** Follow up of parietal cortical atrophy with little progression between 1981 (a), 1985 (b), and 1987 (c).
**New mutation to Huntington's disease**

**Statistical analysis**
Likelihoods regarding paternity/non-paternity using phenotypic data from blood group, serum proteins, and HLA typing were calculated according to Ihm and Hummel\(^1\) and Conradt and Hummel.\(^2\) Allele frequencies of all polymorphic marker systems tested (table 2) were taken from Hummel\(^3\) and are appropriate for a population from south-western Germany. All other likelihood calculations were performed by using a modified version of the computer program LIPEP V.3.\(^4\)

The frequency of a mutant allele at the HD locus was calculated at about 1.165 \times 10^{-7} according to an estimated heterozygote frequency of 2.33 \times 10^{-4}.\(^5\) Using an HD gene frequency as high as this is in favour of all hypotheses not assuming a new mutation as the cause of the proband's disease, and thus results in a conservatively low estimate of the posterior probability of the mutation hypothesis.

Conditional probabilities (likelihoods) of phenotypic observations regarding the main (HD) locus, the closely linked DNA marker loci, and the blood group, serum protein, and HLA loci were calculated under the hypothesis of (1) non-paternity, and (2) true paternity. The hypothesis of true paternity is further split into the hypothesis (2a) a new mutation in a parental germ cell and (2b) assuming one parent to be a carrier of a defective HD gene, notwithstanding the healthy phenotype up to an advanced age, skewed segregation of the corresponding wild type gene of this parent in most of the offspring, and recombination between the HD locus and the linked DNA marker loci to account for haplotype sharing of the proband and her healthy sibs.

Obviously, in unaffected sibs the genotype assignments have to be weighted according to phenotype and age. We used the age at onset distribution of Newcombe\(^6\) with a penetrance of 0.9990 at age 80 or over. The recombination rate between the HD locus and the DNA marker gene complex was assumed to be 0.04 in both sexes;\(^7\) other values (0.00 to 0.50) were taken in a separate run and showed a moderate effect on posterior probabilities.

Posterior probabilities of the three hypotheses were calculated starting from different prior prob-
abilities. Prior probabilities of non-paternity were in the range 0.01 to 0.50, the latter value being an inadmissible overestimate, whereas 1 or 2% is considered arguable. The mutation rate was considered as a parameter of the problem, following the design of Baraitser et al., and calculations were done using a set of values in the range $10^{-5}$ to $10^{-8}$.

**Results**

**Paternity testing**

Results of the blood group and HLA typing as well as the serum markers are shown in table 2. From our personal knowledge of the family, true paternity was considered to be very likely and this view is supported by the results of serological testing. The odds are $1.3 \times 10^5$ in favour of true paternity, that is, our patient being a full sib of her tested brothers and sisters. This rate corresponds well with the respective odds of the other sibs, thus virtually excluding non-paternity for each tested sib.

**DNA analysis**

For six RFLPs detected by four different probes at the locus D4S10, there is informative segregation in this family. Results of DNA typing are shown in table 1. Under the plausible assumption of no crossover between the different RFLPs in the parental meioses, four unique haplotypes can easily be assigned to the genotypes of the parents. Two each of these haplotypes can unambiguously be assigned to each parent. Each sib tested shares at least one haplotype with the affected sister, one sib sharing both haplotypes.

**Statistical analysis**

Results of the statistical analysis are shown in table 3.

It is evident that posterior probabilities are in favour of the new mutation hypothesis. Even under the most unfavourable assumptions of an a priori probability of non-paternity of 10% and a mutation rate of $10^{-8}$, this hypothesis has a final probability exceeding 95%.

Assuming a plausible 1% non-paternity rate a priori and a mutation rate of $10^{-6}$, the posterior probability of the new mutation hypothesis is higher than 99.99%. Table 4 shows the contribution of the various conditional probabilities to the different hypotheses. The main contribution of odds against the segregation/recombination hypothesis comes from the improbability of one parent being a carrier of the HD gene ($4.68 \times 10^{-6}$), followed by the improbability of the parents being healthy at the age of over 80 ($10^{-3}$), and the improbability of segregation of the HD gene in this family ($1.17 \times 10^{-3}$).

A contribution is made by the necessity of recombination between the marker locus and the HD locus (0.71) under hypothesis 2b. Interestingly, even if we had a marker which showed no recombination at the HD locus this conditional probability would not be lower than 0.54 (the normalised conditional probability equals the lod score of the pedigree given the recombination frequency).

The conditional probability of only one family

<table>
<thead>
<tr>
<th>Phenotypes at</th>
<th>Conditional probabilities</th>
<th>Hypothesis 1</th>
<th>Hypothesis 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New mutation</td>
<td>Segregation/recombination</td>
<td></td>
</tr>
<tr>
<td>Pedigree</td>
<td>Hypothesis 1 Non-paternity</td>
<td>0.99990912</td>
<td>0.000000912</td>
</tr>
<tr>
<td>Pedigree</td>
<td>Hypothesis 2 True paternity</td>
<td>0.99990912</td>
<td>0.000000912</td>
</tr>
</tbody>
</table>

TABLE 3 Posterior probabilities of the three hypotheses regarding the origin of the HD gene in the patient.

<table>
<thead>
<tr>
<th>Mutation rate</th>
<th>Hypothesis 1 Non-paternity</th>
<th>Hypothesis 2 True paternity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New mutation</td>
<td>Segregation/recombination</td>
</tr>
<tr>
<td>$1 \times 10^{-5}$</td>
<td>(i) 0.00000997</td>
<td>0.99999891</td>
</tr>
<tr>
<td></td>
<td>(ii) 0.00001062</td>
<td>0.99998026</td>
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<tr>
<td>$1 \times 10^{-6}$</td>
<td>(i) 0.00000965</td>
<td>0.9999915</td>
</tr>
<tr>
<td></td>
<td>(ii) 0.000010618</td>
<td>0.99980266</td>
</tr>
<tr>
<td>$1 \times 10^{-7}$</td>
<td>(i) 0.00000945</td>
<td>0.99899239</td>
</tr>
<tr>
<td></td>
<td>(ii) 0.00010589</td>
<td>0.99802983</td>
</tr>
<tr>
<td>$1 \times 10^{-8}$</td>
<td>(i) 0.00095579</td>
<td>0.99001450</td>
</tr>
<tr>
<td></td>
<td>(ii) 0.01041420</td>
<td>0.98041519</td>
</tr>
</tbody>
</table>

(i) Prior probability of non-paternity 0.01, (ii) prior probability of non-paternity 0.10.
New mutation to Huntington's disease

member being affected with HD owing to a new mutation is twice the mutation rate assumed for the HD gene. As there are no reliable estimates of the mutation rate in our population, we calculated posterior probabilities for different mutation rates in the range 10⁻³ to 10⁻⁸. The conditional probability of non-paternity in this family is remarkably low despite the fact that both parents are dead. This is because of the large number of sibs tested and the large number of polymorphic systems used, including HLA.

The resulting posterior probability is influenced by the a priori probability of non-paternity and by the mutation rate. For example, a ‘neutral’ a priori probability of non-paternity of 33.3% together with a mutation rate of 10⁻⁴ results in a posterior probability of new mutation of about 95%.

Discussion

The first question that has to be addressed is whether the patient is really suffering from HD or another choreic disorder. The clinical course of the disease is characterised by a prodromal phase of about five years with psychiatric symptoms of deviant behaviour and depressive mood, followed by a typical progressive movement disorder, dementia with predominant amnesic syndrome, and recurrent paranoid depression with kleptomania. Initially predominant psychiatric disturbances are well documented and quite common in the prodromal phase of clinically manifest HD.2 38-40 The cardinal symptoms developed slowly in our patient with progression over about six years. Furthermore, she suffered striking weight loss during that time. Weight loss has been suggested to be the third cardinal feature in HD.2

The development of the full blown disease could be directly observed over a four year period, with the typically slow progressive worsening of the symptoms. This course substantially reduces the number of possible differential diagnoses of choreic movement disorders.

A second line of reasoning comes from paraclinical investigations of the patient. There is general agreement that enlargement of the ventral horns on CT or MR imaging with some cortical atrophy is a hallmark of clinically manifest HD.41-44 The patient displays both findings. The progression of these abnormalities, which are not specific in general, can be interpreted as a confirmation of the clinical diagnosis.

Electrophysiological investigations showed a flat EEG which is clearly non-specific but often seen in HD.45-47 More specific is the finding of a decrease in the amplitude of the cortical N20 component with preserved N13 neck potential within the four year observation period. This finding was first described by Oopen et al48 and has been confirmed by others.49-51 Another finding frequently seen in HD is the absence of long latency reflexes (LLR) in the hand muscles.52-54 In the patient, the LLR disappeared within the four year observation period. A correlation between the absence of LLR and diminishing of cortical SEP has been proposed previously.52 To our knowledge this is the first follow up study in which the development of these parameters from the normal to the pathological state has been shown.

In conclusion, the clinical and paraclinical tests strongly support the diagnosis of HD. The remaining few differential diagnostic possibilities,22 such as hypoparathyroidism, thyroid dysfunction, Wilson’s disease, choreoacanthocytosis, and metabolic and inflammatory diseases including lupus erythematosus, have been excluded by the results of laboratory tests. Tardive dyskinesia can be disregarded as it is not associated with progressive dementia and caudate atrophy.

The diagnosis of HD in the patient is at variance with the lack of other cases in her family, and, hence, a new mutation as well as illegitimacy have to be considered. However, the genetic data are strongly in favour of a new mutation because of the results of paternity testing. Segregation data, the phenotype of the parents, and recombination at the marker locus are other sources of conditional probabilities in favour of the mutation hypothesis.

Former calculations of probabilities of a sporadic HD case being a new mutation did not consider a segregation hypothesis. In their review on the mutation rate to HD, Shaw and Caro5 calculated probabilities of specific isolated cases of HD being new mutations considering only the conditional probability of the parents being clinically unaffected at an advanced age but carriers of the HD gene.

In a recent report, Baraitser et al59 evaluated the non-paternity/new mutation hypothesis only. However, neglecting the segregation sub-hypothesis leads to an overestimate of the posterior probability of the new mutation hypothesis. This is the reason why they estimated a higher probability of their case being a new mutation than we did with ours. Therefore, we did a reanalysis of their data with our probabilistic design assuming the four older sibs of their sporadic case were healthy at the age of over 50 years, an a priori probability of non-paternity of 10%, and a mutation rate of 10⁻⁸, and taking the results of blood group typing as stated. A substantially lower posterior probability of 0.55 is obtained regarding the new mutation hypothesis.

Disregarding the phenotypic information which
might be provided by grandparents and other members of the pedigree will result in an over-estimation of the segregation hypothesis, and so we are on the safe side regarding new mutation. Sufficiently reliable information about legitimacy and phenotypes is lacking in either case, and thus we did not attempt to incorporate this information into the analysis.

In only three other cases of possible new mutation in HD was illegitimacy excluded by serological paternity testing. The most plausible case is that of Wallace. In this family, the unaffected father died at the age of 74, the mother being alive at the time of investigation as well as seven older and two younger, unaffected sibs. This observation suggests advanced parental age at the birth of the patient, as in our case. It is well established that advanced age increases the risk for dominant mutations in parental germ cells leading to severe inherited diseases in the offspring.

In the case of Baraitser et al, the father and mother were aged 37 and 38 years, respectively. In their case, as well as in those of Pleydell and Wallace, the patient had several older sibs. This could be a pointer to advanced paternal age at the time of the patient's birth. In three other of the more recent cases of possible new mutation to HD, the parental ages at birth are known, but well below 25 years. Thus, despite the observation in our family, no definite conclusion can be drawn with respect to a possible parental age effect on mutations to HD.

Definite proof that a patient carries the dominant mutation to HD would come from similarly affected offspring. In the past, this observation could be made only in families in which the parents were dead, as in the families of Pleydell, and Wallace, and in some of the very old pedigrees. However, in these families the question of true paternity remains open. The offspring of our patient are healthy at the ages of 24 and 13 years. At this age, no definite statement about their potential HD carrier status can be made, but as the results of clinical investigations led to the unambiguous diagnosis of HD in the patient there is a substantial risk for both offspring. Until the precise molecular defect of the mutation is defined, there will be no way to make a preclinical risk assignment by molecular methods, which are useful in other instances.

We thank J Gusella for the probes pKO82, pKO83, and R7, P Pearson for the probes F5.52 and F5.53, L Carlock for the probe pTV20, and R Thayer for the probe p8.

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28. Southern EM. Detection of specific sequences among DNA

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