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A Huntington Disease–Like Neurodegenerative Disorder Maps to Chromosome 20p

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Summary

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor disturbance, cognitive loss, and psychiatric manifestations. The disease is associated with a CAG trinucleotide–repeat expansion in the Huntington gene (IT15) on chromosome 4p16.3. One family with a history of HD was referred to us initially for predictive testing using linkage analysis. However, the chromosome 4p region was completely excluded by polymorphic markers, and later no CAG-repeat expansion in the HD gene was detected. To map the disease trait segregating in this family, whole-genome screening with highly polymorphic dinucleotide-, trinucleotide-, and tetranucleotide-repeat DNA markers was performed. A positive LOD score of 3.01 was obtained for the marker D20S482 on chromosome 20p, by two-point LOD-score analysis with the MLINK program. Haplotype analysis indicated that the gene responsible for the disease is likely located in a 2.7-cM region between the markers D20S193 and D20S895. Candidate genes from the mapping region were screened for mutations.

Introduction

Huntington disease (HD; MIM 143100) is an autosomal dominant neurodegenerative disorder with a disease frequency of 1/10,000 individuals and onset usually in midlife. The mutation responsible for HD is an expansion of a CAG repeat >35 repeats, at the 5′ end of the HD gene (The Huntington's Disease Collaborative Research Group 1993). Although this mutation has been identified in most patients diagnosed with HD, there is a small minority of the patients in whom no CAG amplification in the HD gene can be detected. In a large study of 1,007 patients with a clinical diagnosis of HD, no CAG-repeat expansion was found in 12 patients (Kremer et al. 1994). In at least three families, linkage studies excluded changes in the HD gene as being associated with this phenotype (Andrew et al. 1994).

One of these families was referred to us for linkage analysis in the predictive-testing program for HD in 1991. This family comprises 21 individuals in three generations. Seven of the family members were affected, and their condition was diagnosed as HD because of its clinical and neuropathological similarities to HD. The region containing the HD gene was, however, completely excluded by linkage analysis using polymorphic markers on chromosome 4p. Later, no CAG-repeat expansion in the HD gene was detected in the affected individuals (16–22 CAG repeats). Taken together, the data indicated that changes in the HD gene are not associated with the neurodegenerative disease in this family. Therefore, the family might have an HD-like neurodegenerative disorder. To map the genetic locus of the disease, a whole-genomic screen was undertaken.

Subjects, Material, and Methods

Patient Material

All members of the family that we studied originate from Sweden. Genomic DNA was isolated from peripheral blood and from Epstein-Barr virus (EBV)–transformed lymphoblastoid cell lines for all living individuals. Paraffin-embedded material was collected from deceased individuals.

Genotype Analysis

A total of 391 microsatellite markers from Cooperative Human Linkage Center (CHLC) Human Screening Set/Weber version 6 and additional markers from Research Genetics, Inc. (Dib et al. 1996) were used. Genotypes were determined by PCR amplification using ^{33}P-

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Table 1

Clinical and Neuropathological Features of the Affected Family Members

	Status of Subject[a]						
	I-2	II-2	II:6	III-1	III-3	III-8	III-10
Age at HD onset (years)	41	28	29	23	29	29	29
Age at death or present age (years)[b]	52	42	43	46	39	36	32
Duration (years)	11	14	14	23			
Clinical features:							
Motor disturbances:							
Rigidity	+	+	ND	+	+	+	ND
Choreic movements	+	+	+	+	−	−	−
Coordination problems	+	+	+	+	+	+	+
Dysarthria	+	+	+	+	+	+	+
Ataxia	ND	+	+	ND	ND	ND	ND
Psychiatric disturbances:							
Depression	ND	ND	+	+	−	+	ND
Aggressiveness	+	+	+	+	+	ND	ND
Personality changes	ND	+	+	ND	+	ND	ND
Cognitive impairment	+	+	+	+	+	+	ND
Epileptic seizures	ND	+	+	NA	+	ND	ND
Neuropathology:							
Basal-ganglia atrophy	+	+	+	NA	NA	NA	NA
Frontal-lobe atrophy	−	ND	+	NA	NA	NA	NA
Temporal-lobe atrophy	−	+	−	NA	NA	NA	NA
Cortical atrophy	−	+	−	NA	NA	NA	NA
Occipital-lobe atrophy	−	ND	+	NA	NA	NA	NA
Plaques and tangles	−	−	ND	NA	NA	NA	NA
Neuroimaging (CT/MRI)	NA	NA	NA	Large ventricles	Temporal-lobe atrophy	Wide sulci	NA
EEG	NA	NA	Encephalopathy	Encephalopathy	Abnormal	NA	NA

[a] A plus sign (+) denotes presence of feature, and a minus sign (−) denotes its absence. ND = not described/unknown, and NA = not available.

[b] Ages at death are underlined.

labeled primers. PCR reactions were performed on 96-well microtiter plates in 10-μl reaction volumes: 50 ng of genomic DNA, 2 pmol of each primer, and 0.5 unit of DynaZyme (Finnzymes Oy). The PCR cycle conditions were 95°C for 1 min, 55°C–60°C for 1 min, and 72°C for 1 min, with a final extension of 72°C for 7 min. The PCR products were separated on 6% denaturing polyacrylamide gels, and the alleles were visualized by autoradiography.

Two-Point Linkage Analysis

Two-point LOD scores were calculated by the MLINK program as implemented in the FASTLINK software package, version 3.0P (Lathrop and Lalouel 1984; Cottingham et al. 1993; Terwilliger and Ott 1994). The frequency of this disease gene was assumed to be 1/10,000 in the population, and the inheritance pattern was considered to be autosomal dominant with a 100% penetrance.

Sequence Analysis

PCR amplifications were performed on either genomic DNA (if the exon/intron boundaries were known) or cDNA. PCR products were used for heteroduplex analysis and sequencing. Heteroduplex analyses were performed by an MDE heteroduplex kit (FMC Bioproducts). DNA from both strands was sequenced by a cycle sequencing kit (Perkin-Elmer, Amersham Life Science), according to the manufacturer's instructions.

Results

Clinical Features of the Affected Family Members

Clinical and neuropathological findings are summarized in table 1. Subject I-2 became aggressive, anxious, and restless at age 41 years. Four years later, he was admitted to a hospital because of intellectual dysfunction, delusional thoughts, an unstable gait, and elements of chorea, rigidity, grimacing, and slurred speech. No tremor was noted. Anticholinergic medication had no effect. At the age of 51 years, his choreic movements increased, and 1 year later he died. Autopsy and histopathology showed chronic encephalitis with cell loss and gliosis in the basal ganglia, but no pathological changes in the cerebrum, cerebellum, pons, medulla oblongata, or cortex were seen.

Subject II-2 presented with personality changes, aggressiveness, and dementia at age 28 years. Two years later, she had an unsteady gait, expressionless face, and dysarthria with some features of rigidity. Her condition was diagnosed as "atypical HD." Later she developed epileptic seizures, and her choreic movements became worse. She died at age 42 years. "Brain atrophy" in the cerebral cortex, caudate nuclei, and globus pallidus and more extensive atrophy in the temporal lobe were found, and her brain weight was 960 g. The remaining neurons showed a pronounced accumulation of lipofuscin pigment. The thalamus and substantia nigra were intact, whereas the cerebellum showed a slight loss of Purkinje cells and mild gliosis in the molecular layer. However, no signs of advanced degeneration of the cerebellum were found, and no senile plaques or fibrillary degeneration was found. Extensive muscle atrophy and myelopathy (degeneration of the nerve cells in the ventral horns of the spinal cord) were noted. A diagnosis of HD with some atypical features was made.

Subject II-6 was assessed at age 30 years for problems of coordination, dysarthria, depression, and aggressiveness. Psychology tests showed "global cognitive impairment." An electroencephalogram (EEG) yielded pathological findings, probably due to encephalopathy. Within the next couple of years, she developed ataxia, an unsteady swaying gait, and jerky, clumsy movements, and her condition was diagnosed as probable HD. Later she developed epileptic seizures, and she died at age 43 years. Autopsy showed loss of body weight (27 kg) and brain weight (950 g). Her brain atrophy was diffuse and symmetric, particularly in the frontal and occipital lobes, with a thin cortex and atrophy of caudate nuclei. The substantia nigra, cerebellum, and brain stem were normal. Microscopic examination revealed gliosis and foci of extensive degeneration in the basal ganglia.

Subject III-1, who was depressed and disoriented at age 23 years and who was assessed for cognitive decline, was diagnosed as having possible HD, on the basis of cognitive impairment and family history of HD. An EEG showed mild or moderate diffuse encephalopathy. Six years later, however, an unsteady gait and obvious jerks in the arms and legs were noted. Over time the choreic movements worsened, and they were accompanied by further intellectual dysfunction and aggressiveness. A computed tomographic (CT) scan showed bilaterally widened ventricles but no other pathological findings.

Subject III-3 developed personality changes (apathy and difficulties with daily activities) and aggressiveness at age 29 years. Three years later, this person was admitted to a hospital because of increasing memory problems and signs of speech disturbances. A CT scan showed central and peripheral atrophy of the brain and reduction of the temporal lobes. The subject's condition was diagnosed as presenile dementia of unknown cause (no family history of HD was known to the foster parents). Over time, subject III-3 showed significant deterioration, including muteness, a stiff gait, dysphagia, and occasional epileptic seizures.

Subject III-8 requested predictive testing for HD in 1991, at age 30 years. No obvious dystonia or chorea was observed. Muscular tone, tendon reflexes, cerebellar functions, eye movements, and sensory functions were normal. However, this patient had noted difficulties in walking down stairs and increasing problems with coordination. Subject III-8 was mildly depressed, and cognitive performance was significantly impaired. Drawing, writing, and calculation tests were poorly performed. A magnetic-resonance imaging (MRI) scan of the brain revealed widened sulci of the convexity, but the neostriatum was normal (fig. 1). The symptoms showed significant progression, with worsening of speech and deterioration in fine motor abilities. This individual is now in extended home care and can say only a couple of words.

Subject III-10 has had symptoms similar to those of subject III-8 (poor handwriting, gait disturbances, and speech problems) for ~3 years, although no diagnosis has been made.

Review of Neuropathological Material

Autopsy material, preserved as slides for subjects I-2, II-2, and II-6, was reviewed again by an experienced neuropathologist and a neurologist, and previous findings were confirmed. In summary, pathological changes consistent with HD were found—namely, pronounced neuronal loss and gliosis in the basal ganglia and cortical atrophy. However, both the generalized cortical atrophy with very low brain weight in subjects II-2 and II-6 and the temporal-lobe atrophy in subjects II-2 and III-3 are more atypical findings, as is the myelopathy seen in subject II-2. The substantia nigra was preserved in all cases, and no senile plaques or fibrillary tangles were found. There were no pathological changes consistent with dentatorubral-pallidoluysian atrophy (DRPLA; MIM 125370). Multisystem atrophy with striato-nigral degeneration was also excluded, since the substantia nigra was intact.

Other diagnoses that have significant clinical similarities to HD, such as spinocerebellar ataxia 3 (SCA-3; MIM 109150), spinocerebellar ataxia 2 (SCA-2; MIM 183090), and DRPLA, were excluded by DNA testing. Chorea-acanthocytosis (CHAC; MIM 200150) was excluded by cytological analysis of the red blood cells. No diagnostic alternative to HD could be suggested.

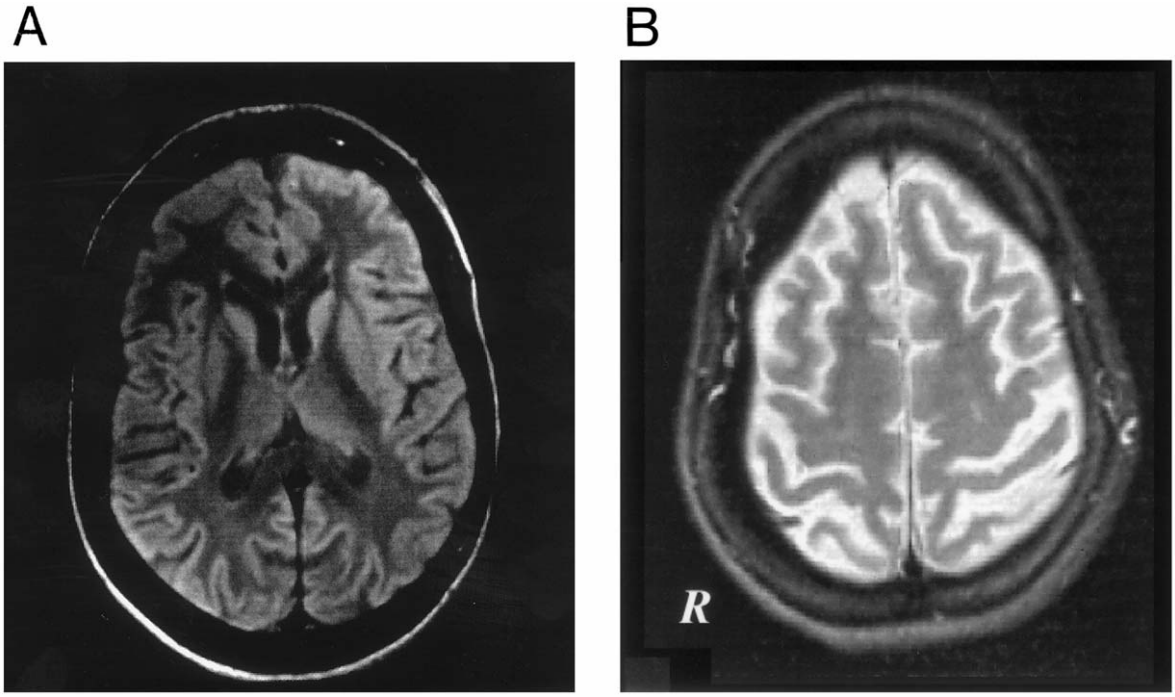

Figure 1 MRI of subject III-8. *A*, Normal neostriatum. *B*, Widened sulci of convexity, indicating cortical atrophy.

Genetic Analysis of the Family, and Exclusion of the HIP1 Gene

Whole-genome screening using the CHLC Human Screening Set/Weber version 6 was performed. The screening set consists of 391 markers with an average interval of 10 cM. Most chromosomes were completely excluded by haplotype and linkage analysis (LOD score <-2). A few regions on chromosomes 7–9 and 12 were not excluded, since the markers were not informative enough. A weak positive LOD score was obtained with marker D7S1816. The huntingtin interacting protein–1 (HIP1; MIM 601767) gene, which interacts with huntingtin, was mapped close to D7S1816 (Kalchman et al. 1997). The genomic structure and exon/intron boundaries of HIP1 were determined, and all the exons of the HIP1 gene were analyzed by sequencing and heteroduplex analysis (A. H. M. M. Huq, K. Nichol, L. R. Osborne, S. W. Scherer, E. W. Almqvist, F. Squitieri, M. Anvret, T. S. Ross, L.-C. Tsui, and M. R. Hayden, unpublished data). No mutation in the HIP1 gene was detected in the affected family members. Additional highly informative markers from these regions were used in order to either confirm or exclude the respective region. Haplotype analysis of these regions on chromosomes 7–9 and 12 also excluded them as candidates.

Mapping to Chromosome 20p

Haplotype analysis showed that affected individuals in the family shared the same haplotype for several markers on chromosome 20p. However, a normal individual (subject II-8) who is still unaffected at the age of 50 years inherited the same haplotype as was seen in the affected individuals. An individual at this age and with this haplotype would be expected to show some symptoms, since the disease is considered to be fully penetrant. The origin of the identical haplotype shared by the affected individuals and normal individual II-8 cannot be determined, since the affected grandfather was homozygous for several markers in this region. Therefore, an additional 30 highly polymorphic markers at high density in the region were employed. Haplotype analysis indicated that all the affected individuals share the same haplotype for markers from loci D20S97 through D20S892 (fig. 2), which originated from the affected grandfather (subject I-2). Subject II-8, who is normal, shares, between markers D20S895 and D20S892, the same haplotype as is seen in the affected individuals, suggesting that recombination has occurred close to marker D20S895. The only common region shared by affected individuals should be from D20S97 to D20S889. Linkage analysis shows that the LOD score reached 3.01, at a recombination fraction of .0, for the most informative marker, D20S482 (fig. 3 and table 2). This is the highest LOD score predicted by simulation test. The variation in LOD scores for markers D20S181, D20S116, D20S97, D20S482, and D20S889 was due to the uninformativeness of the markers in some family members. The disease locus in the family is likely to be

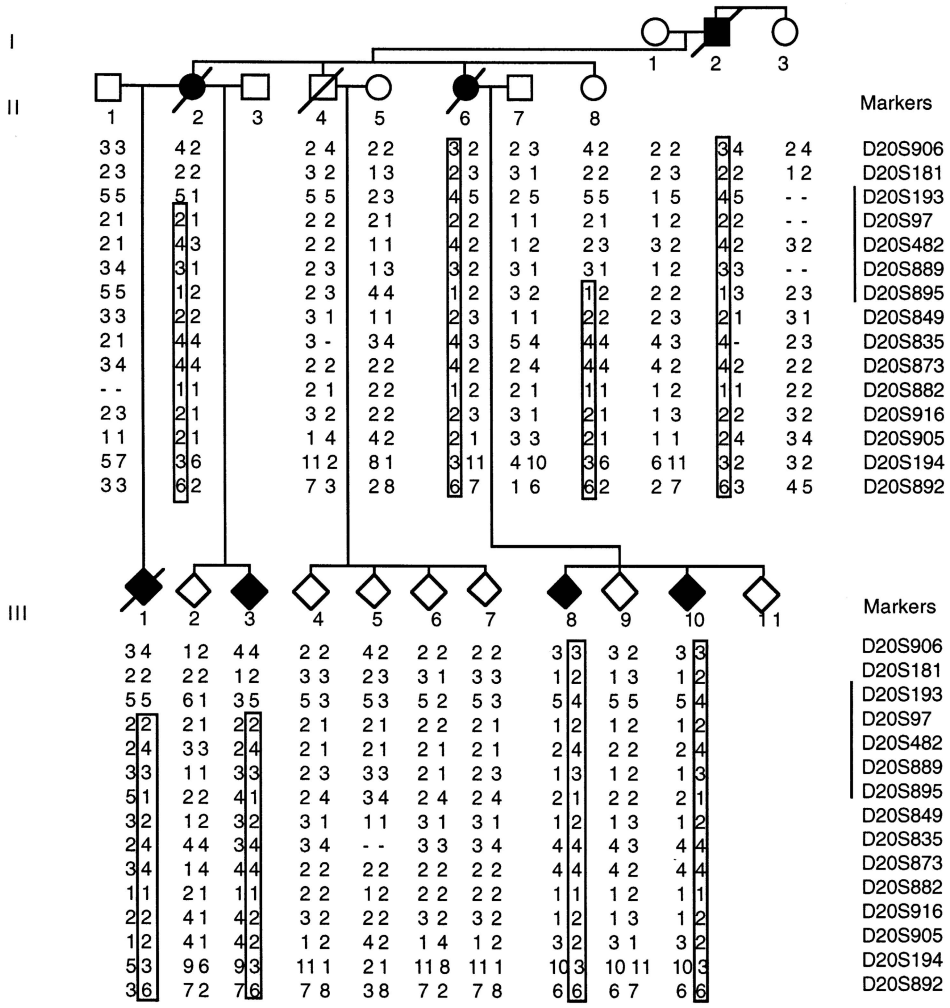

Figure 2 Pedigree and haplotypes of family studied. The haplotype associated with the disease is boxed. The pedigree has been changed to protect confidentiality. Subject I-3 is still unaffected at 91 years of age.

located in the chromosomal region from D20S193 to D20S895, spanning only 2.7 cM (fig. 4).

Evaluation of Candidate Genes on 20p

In the mapped region of chromosome 20, there are several genes that play critical roles in normal neural function and can be implicated as possible candidate genes for this condition, such as the prion gene, SNAP25, CCA12, preproenkephalin B, and the transglutaminase 3 gene.

The prion gene consists of two exons, and the protein is coded by the second exon (Puckett et al. 1991). The whole coding region was completely sequenced by PCR amplification, and no mutation or abnormal repeat in the gene was detected.

The SNAP25 gene encodes a 25-kD protein and was first investigated as a neuron-specific gene preferentially expressed in CA3 pyramidal neurons of mouse hippocampus. The human SNAP25 and mSNAP25 showed perfect amino acid sequence conservation (Zhao et al. 1994). The whole coding sequence (nucleotides 206–823) was completely sequenced by reverse transcription–PCR, but no mutation was found.

The human preproenkephalin B gene is known to contain the determinants for neoendorphin, dynorphin, and leumorphin. These opioid peptides, each with a leucine-enkephalin structure, act on the kappa receptor (Horikawa et al. 1983). No changes were found in the coding region of this gene, by sequencing of cDNA from EBV-transformed lymphoblastoid.

The CCA12 transcript contains a CCA repeat and maps to this region (The Human Gene Map). No variation in the repeat size between affected and normal individuals in this family was detected by PCR ampli-

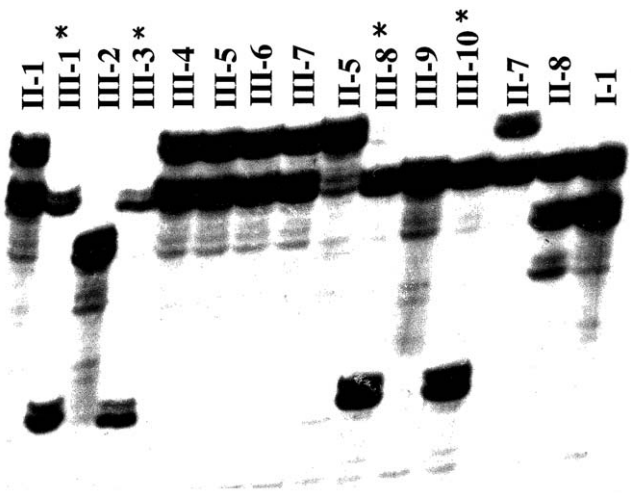

Figure 3 Genotype of marker D20S482. Affected individuals are marked with an asterisk (*).

fication. Other candidate genes, such as transglutaminase 3 and bone morphogenetic protein–2, are in the process of being screened.

Discussion

The diagnosis of HD in this family was first made in the 1960s, in two sisters (subjects II-2 and II-6). The rapid progression of dementia early in the disease, which is atypical of HD, could be consistent with early-onset familial Alzheimer disease (MIM 104311). However, this diagnosis could not be confirmed by neuropathological changes such as senile plaques or neurofibrillary tangles. The clinical features in the affected family members are similar to those of frontotemporal dementia (FTD; MIM 601630). However, FTD usually has a slower progression, with preserved spatial orientation (The Lund and Manchester Groups 1994). In addition, in contrast to the family in the present study, atrophy of the striatum is usually not seen, and the substantia nigra shows neuronal loss. In some families, FTD maps to chromosome 17 (Yamaoka et al. 1996; Heutink et al. 1997), but linkage to this region could not be verified in this family. All affected individuals presented with dysarthria and problems with coordination at onset and, later, with both choreic movement, seen in the classic presentation of HD, and neuropathological findings consistent with HD. However, some subjects presented with epileptic seizures, which is unusual for adult-onset HD, and they do not show the CAG expansion in the HD gene. It is clear that in this family there is no other HD-gene mutation causing this disease, since the HD locus was excluded by linkage analysis. The positive LOD score of 3.01 on chromosome 20p suggests, instead, that in this family the mutation that is responsible for this phenotype is likely in another gene.

Affected individuals in this family show some features of anticipation (i.e., decreasing age at onset in successive generations). Thus far, >12 human diseases that are caused by trinucleotide-repeat expansions in the respective gene have been identified (Reddy and Housman 1997; Ross 1997), most of them associated with anticipation. It could therefore be possible that the causative mutation in this family is a trinucleotide expansion. PCR analysis was performed to assess possible variation in the size of the CCA repeat (human transcript CCA12) that is located in this region. However, no variation in its size was observed among affected and normal individuals, and it can be excluded as the disease-associated mutation in this family.

The prion diseases are a group of unusual degenerative diseases affecting both humans and animals, which involve the CNS and always result in a fatal outcome (Prusiner 1996). The human prion diseases are caused by mutations in the prion gene on chromosome 20p. The majority of the mutations are missense mutations, a 144-bp insertion or an extra-tandem repeat (octapeptide coding repeat) between codons 51 and 91. The clinical features of the prion diseases do vary to a great extent from one individual to the next. To a certain degree, the clinical picture in this family overlapped with that of prion diseases. The prion gene is located to the same region (from marker D20S97 to marker D20S95; The Human Gene Map) as in the family in which we mapped the disease locus. However, no substitution, insertion, or extra-tandem repeat in the coding sequence of the prion gene was identified in the affected individuals. Therefore, the prion gene is unlikely to be a candidate gene for the disease.

Table 2

Pairwise LOD Score of Markers on Chromosome 20p

	LOD Score at Recombination Fraction of						
Marker	.0	.01	.05	.10	.20	.30	.40
D20S906	−∞	.37	.93	1.05	.96	.72	.40
D20S181	1.00	.98	.92	.83	.65	.46	.24
D20S193	−∞	.67	1.21	1.30	1.16	.87	.47
D20S97	.78	.77	.72	.66	.52	.37	.20
D20S482	3.01	2.96	2.74	2.47	1.87	1.24	.58
D20S889	1.81	1.78	1.67	1.53	1.22	.88	.48
D20S895	−∞	.96	1.47	1.51	1.29	.92	.48
D20S849	−∞	.07	.63	.75	.68	.48	.25
D20S835	.48	.50	.55	.55	.44	.28	.12
D20S873	−∞	−.53	.05	.19	.18	.08	.01
D20S882	.90	.89	.82	.73	.54	.36	.18
D20S916	1.89	1.86	1.74	1.58	1.25	.89	.48
D20S905	−∞	.96	1.47	1.51	1.29	.92	.48
D20S194	−∞	−.01	.73	.98	1.01	.80	.46
D20S892	−∞	.96	1.47	1.52	1.30	.93	.49

Recently, Hallervorden-Spatz syndrome (HSS; MIM 234100) was mapped to the same 20p region by homozygosity mapping (Taylor et al. 1996). HSS is an autosomal recessive neurodegenerative disorder characterized by increasing dysarthria, progressive dementia and rigidity, and involuntary movements, with onset in childhood. Mental deterioration and epilepsy are also seen in some cases, and histologic study has shown massive iron deposits in the basal ganglia. Pathological brain iron accumulation occurs in several common disorders, such as Parkinson disease, Alzheimer disease, and HD. Although the affected individuals in this family do share several common symptoms with HSS, in HSS the inheritance is recessive, whereas it is clearly dominant in this family. It is possible that a heterozygous mutation in the HSS gene could cause a milder, late-onset neurodegenerative disorder. An example would be porphyria catanea tarda (PCT; MIM 176100), a late adult–onset disorder due to a heterozygous mutation in the uroporphyrinogen decarboxylase gene, whereas a homozygous mutation in the same gene causes hepatoerythropoietic porphyria (HEP; MIM 176100), which is a more severe disorder and has onset of symptoms in infancy (de Verneuil et al. 1988; Garey et al. 1989). Thus, different mutations in the same gene could be responsible for both HSS and the HD-like neurodegenerative disorder in this family.

Although the mutation causing HD has been identified as a CAG expansion in the HD gene, the mechanism by which CAG expansion leads to neurodegeneration is not clearly understood. It has been proposed that the expanded glutamine repeats in huntingtin could result in the precipitation of the huntingtin protein in specific neurons, causing the observed selective neuronal loss (apoptosis) (Igarashi et al. 1998; Martindale et al. 1998). Identification of the genes that are responsible for HD-like neurodegenerative disorders may provide useful additional information for understanding the molecular mechanisms and pathways underlying this disorder associated with selective neuronal loss in the basal ganglia.

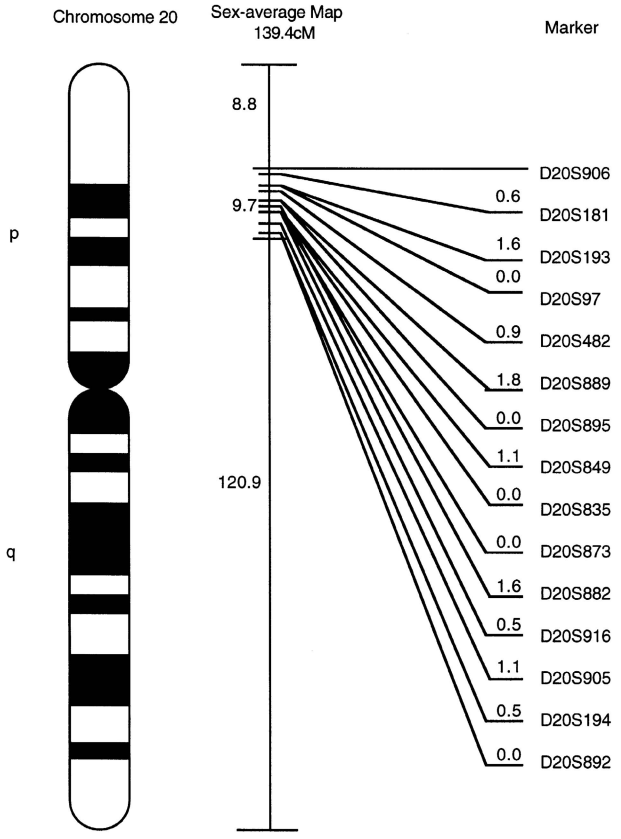

Figure 4 Map of chromosome 20 and localization of markers. The order and distance (in cM) are based on the data from Généthon.

Acknowledgments

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Généthon, http://www.genethon.fr
Human Gene Map, http://www.ncbi.nlm.nih.gov/science96/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for HD [MIM 143100], DRPLA [MIM 125370], SCA-3 [MIM 109150], SCA-2 [MIM 183090], CHAC [MIM 200150], HIP-1 [MIM 601767], early-onset familial Alzheimer disease [MIM 104311], FTD [MIM 601630], HSS [234100], and PCT and HEP [MIM 176100])

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