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Benign Hereditary Chorea of Early Onset Maps to Chromosome 14q

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Summary

Benign hereditary chorea (BHC) is an autosomal dominant disorder characterized by an early-onset nonprogressive chorea. The early onset and the benign course distinguishes BHC from the more common Huntington disease (HD). Previous studies on families with BHC have shown that BHC and HD are not allelic. We studied a large Dutch kindred with BHC and obtained strong evidence for linkage between the disorder and markers on chromosome 14q (maximum LOD score 6.32 at recombination fraction 0). The BHC locus in this family was located between markers D14S49 and D14S1064, a region spanning ~20.6 cM that contains several interesting candidate genes involved in the development and/or maintenance of the CNS: glia maturation factor-β, GTP cyclohydrolase 1 and the survival of motor neurons (SMN)-interacting protein 1. The mapping of the BHC locus to 14q is a first step toward identification of the gene involved, which might, subsequently, shed light on the pathogenesis of this and other choreatic disorders.

Introduction

Choreatic disorders are common neurological entities that can be either acquired or inherited. A well-known familial entity is Huntington disease (HD [MIM 143100]), an autosomal dominant form of progressive chorea associated with mood and personality changes, usually presenting in adult life and leading to early death. In contrast to HD, benign hereditary chorea (BHC [MIM 118700]) has its onset in childhood and is nonprogressive. This autosomal-dominant disorder usually starts before age 5 years, reaching its maximum severity between at age 10–20 years. Generally, BHC patients have normal intelligence, and dementia, as in HD, is not seen. The early onset of symptoms, frequently before 1 year of age, suggests a developmental disturbance. In some BHC families, the choreic movements tend to decrease in adulthood. A nearly complete penetrance in males and a 0.75 penetrance in females were reported by Harper (1978). The disorder occurs less often than HD (Harper 1978).

Since the identification of BHC in 1966 (Haerer et al. 1966, 1967), more than 30 families have been reported to have this disorder (reviewed by Bruyn and Myrianthopoulos [1986] and Wheeler et al. [1993]). The disorder demonstrates both intra- and interfamilial variability. Some BHC families show atypical additional features, such as dysarthria and gait disturbances (Chun et al. 1973), mental impairment (Leli et al. 1984), or axial dystonia and progression in adulthood (Schady and Meara 1988). The latter report could describe a variant of the disorder, but might as well be an entirely separate entity, considering the progressiveness of the chorea in that family (Wheeler et al. 1993). Other variants have been described as well, such as BHC associated with sensorineural deafness (Damasio et al. 1977) and BHC with intention tremor (Pincus and Chutorian 1967). These studies also reflect the interfamilial variability. Although treatment with haloperidol, chlorpromazine, and prednisone led to improvement for some patients (Wheeler et al. 1993), a general curative treatment is not available. Besides HD, BCH should be differentiated from a number of other diseases, such as familial cerebellar ataxia, Sydenham chorea, and Friedreich ataxia (Bruyn and Myrianthopoulos 1986; Wheeler et al. 1993). However, the benign clinical course of the chorea and the family history in BHC generally facilitate the correct diagnosis.

In 1993, the gene for HD, *IT15,* was identified on chromosome 4p16.3 (The Huntington's Disease Collaborative Research Group 1993). The *IT15* gene contains a highly polymorphic CAG repeat at the 5′ end in the range of 10–35 copies. In HD patients, the CAG repeat is expanded beyond 36 repeats (The Huntington's Disease Collaborative Research Group 1993; Kremer et al. 1994). Although an expanded CAG repeat in the 5′ end of the IT15 gene has been found in one atypical BHC family (MacMillan et al. 1993), several reports show

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that BHC is not allelic to HD (Quarrell et al. 1988; Yapijakis et al. 1995; Hageman 1996). We performed a genomewide linkage study in a large BHC family with ataxia and found evidence for a gene defect responsible for BHC localized on chromosome 14q.

Subjects, Material, and Methods

Subjects

Thirty-three relatives from a four-generation Dutch family with BHC were included in the study. The pedigree is shown in figure 1. Informed consent was obtained from each subject. The study was approved by institutional review by the Medical Ethical Committee of Erasmus University and University Hospital Dijkzigt, Rotterdam. All individuals, except for spouses and subject III-14, were examined by a neurologist (W.F.M.A.) and medical records from the past were reviewed, if available. Children with obvious clinical features of BHC were included in the study only after informed consent was given by the parents. Apparently unaffected children younger than 18 years of age were excluded from the study because of nonpenetrance of the disorder reported in other families. Blood samples were collected from 30 individuals.

DNA Analysis

Genomic DNA was isolated from peripheral blood, as described by Miller et al. (1988). Short-tandem-repeat polymorphisms from the Marshfield screening set 6A (see Electronic-Database section) were used for genotyping. Genomic DNA (25 ng) was amplified in 10-μl PCR reactions containing GeneAmp PCR Gold Buffer, 1.5 mM $MgCl_2$, 25 ng of fluorescent forward primer, 25-ng unlabeled reverse primer; and 0.4 U of Ampli*Taq* Gold DNA polymerase. Initial denaturation was 15 min at 95°C, followed by 32 cycles of 30 s denaturation at 95°C, 30 s annealing at 55°C, and a 90 s extension at 72°C. Reactions were prepared by using a Beckman Biomeck 2000 robot system and done in 384-well plates covered with sealing lids (Costar 6557; 6555). Amplification was done by using a dual 384-well-equipped GeneAmp PCR System 9700 (PE Biosystems). PCR products were pooled and loaded on an ABI377 automated sequencer (filterset C; 5% denaturing FMC LongRanger acrylamide gel) and data were analyzed by using ABI GeneScan3.1 and ABI Genotyper2.1 software. Binning of the alleles and preparation of prelinkage files was done by using Linkage Designer 1.0 (Van Camp et al. 1997).

Oligonucleotide primers were used to amplify the trinucleotide repeat for HD, spinocerebellar ataxia 1 (SCA1), SCA2, Machado Joseph disease (SCA3), SCA6, and dentatorubropallidoluysian atrophy (DRPLA) (Gellera et al. 1996).

Linkage Analysis

Two-point linkage analysis was done by using the MLINK and ILINK programs of the LINKAGE package (version 5.1). Maximum LOD and location scores were calculated for each marker by using two different models because of uncertainty of penetrance values reported in other families. In model 1, an "affected-only analysis," unaffected persons were typed as unknown. In model 2, all available clinical diagnoses of pedigree members were included, and 100% penetrance was assumed. For both models, a gene frequency of 1:10,000, no phenocopies, and equal allele frequencies of the genotyped markers were used in the calculations. Changing allele frequencies of the polymorphic markers did not significantly alter the LOD and location scores.

Results

Clinical Analysis

The affected persons in the pedigree showed a generally mild neurological disorder with a benign course (fig. 1). Clinical data are shown in table 1. During childhood, the affected subjects had considerable problems, such as choreatic movements of the hands, feet, and head, sometimes accompanied by a slight ataxia of gait. No further abnormalities were found in the first three generations, except for psychosis in subject III-14. Because of his psychosis, the latter patient was not available for physical examination; however, he was shown to be affected by history. A mild pyramidal syndrome was observed in the proband (subject IV-1). She had a mild spastic-ataxic diplegia. Extensive studies in many affected relatives excluded other known causes, and a diagnosis of BHC was made. The course in this family was benign. The luxury movements usually did not subside completely, but they abated considerably by early adulthood, as did the ataxia. Sydenham's chorea had been diagnosed in some children, but this diagnosis evidently had to be revised because of the familial nature of the affection. There was a suggestion of anticipation in this family, because the children in the fourth generation were clearly more severely affected than their parents and grandparents and showed cerebellar and pyramidal signs in addition to the involuntary movements. However, at this moment, the ultimate development of these children is still unknown.

At age 3 mo, the proband (subject IV-1) was already hyperkinetic, with superfluous movements of the extremities and later, the face. At a later age, her speech was unclear. At age 2.5 years, an analysis of her developmental delay and deterioration of her walking ability was done. She fell repeatedly and had uncoordinated movements of the extremities, with a dysmetric gait and a slight intention tremor. The legs were extended while walking, with a tendency to go on tiptoes. Reflexes were

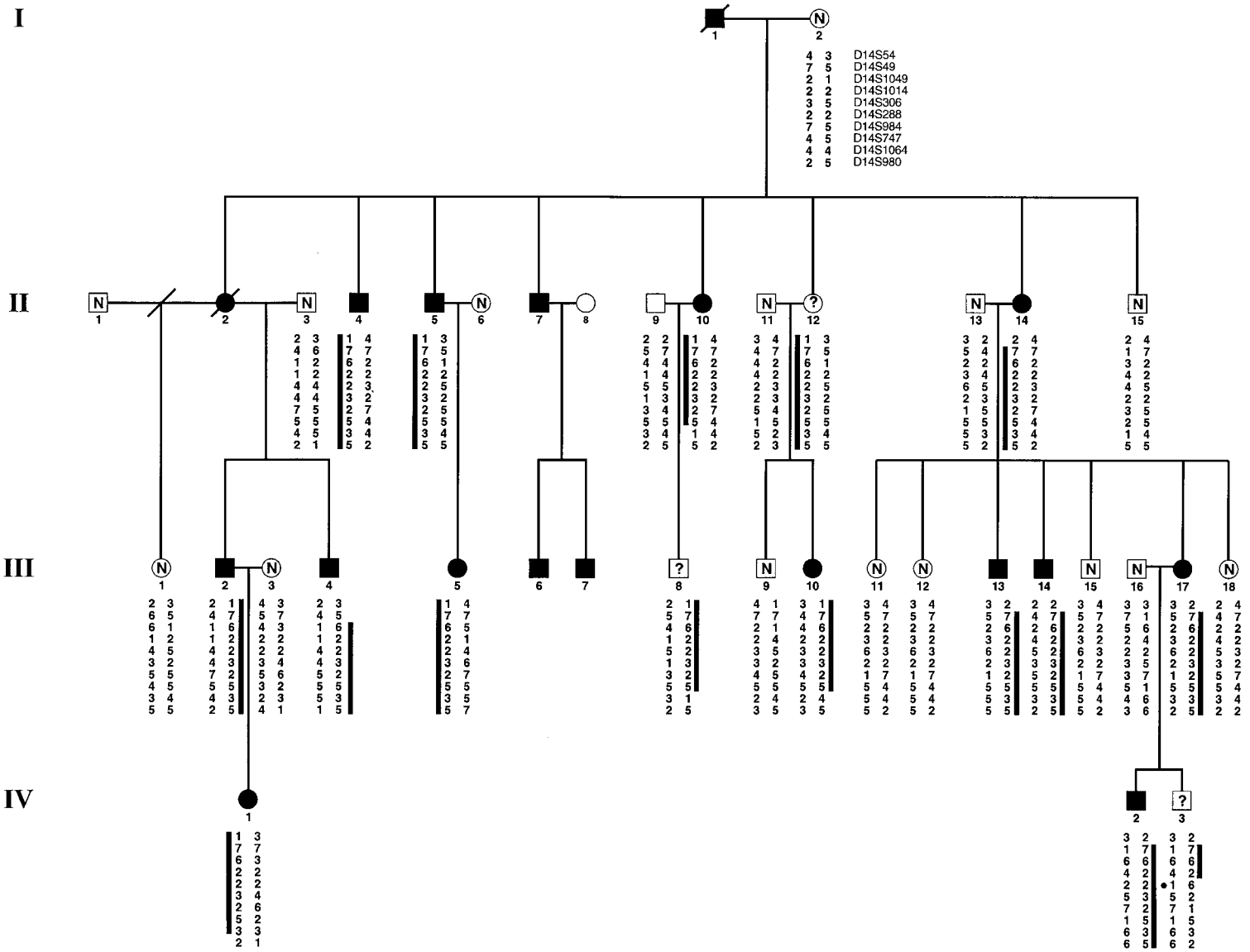

Figure 1 Pedigree of Dutch BHC family with haplotypes for chromosome 14q12–q22 markers (ordered from centromere to telomere). Blackened symbols represent affected subjects. Symbols with N represent unaffected subjects. ? = diagnosis unknown. Bars next to haplotypes indicate a shared-risk haplotype. Blackened circles (•) indicate inconsistent genotype (subject IV-3).

Table 1

Clinical Findings of BHC Family

Subject	Age (years)	Choreatic Movements		Ataxia	Pyramidal Signs	Improvement in Adolescence
		By History	By Examination			
II-4	61	+	+	+/−	−	+
II-5	65	+	−	−	−	+
II-7	62	+	−	−	−	+
II-10	56	+	−	−	−	+
II-12	50	+(?)	−	−	−	+
II-14	53	+	−	−	−	+
III-2	33	+	+	+/−	−	+
III-4	29	+	+	+/−	−	+
III-5	28	+	−	−	−	+
III-6	28	+	+	−	−	+
III-7	27	+	+	−	−	+
III-8	29	+/−(?)	−	−	−	+
III-10	26	+	−	−	−	+
III-13	31	+	+	+/−	−	+
III-14	29	+				
III-17	24	+	−	−	−	+
IV-1	4	+	+	+	+	NA
IV-2	5	+	+	+	?	NA
IV-3	3	−	−(?)	+	+	NA

Note.—The affected subjects are shown and subjects II-12, III-8, and IV-3, who are classified as unknown (?). Subject III-14 was not available for neurological examination. NA = not available.

brisk and the plantar responses were extensor. The head was titubating frequently. There were no signs of luxury movements, and the fine motor skills were better preserved than the gross motor skills. Intellectual development seemed to be normal without intellectual decline. Magnetic resonance imaging (MRI) investigation of the brain had normal findings. Other causes for cerebellar and extrapyramidal syndromes at this age were excluded. DNA studies for SCA (types 1, 2, 3, and 6), HD, and DRPLA were normal (data not shown). At age 5 years, her gait problems were unchanged. She showed choreatic movements in the arms.

A typical example of a patient now in his twenties is III-6. He showed delayed motor development, walking alone at age of 2 years. He remained clumsy, with a walking pattern suggesting ataxia, without other signs of ataxia. His speech was slightly dysarthric. At age 5 years, he developed involuntary movements later diagnosed as chorea. They increased in severity during the next 2 years and then stabilized, interfering with his school performance. Choreatic movements increased with physical exertion. At age 12 years, the walking pattern was no longer considered ataxic, and, a few years later, the choreatic movements had almost completely vanished. At age 19 years, his motor capabilities were considered normal, and he was working as a metal assembly worker. His brother, III-7, had similar symptoms, signs, and clinical course.

Three relatives (II-12, III-8, IV-3) were classified as unknown (table 1 and fig. 1). Sydenham's chorea had been diagnosed in childhood in subject II-12, but this diagnosis evidently has to be revised, considering the course of the affection and its familial nature. Subject III-8 did not show abnormalities on physical examination and the history of choreatic movements was unclear. He had problems with walking until age 18 years; however, these difficulties seemed more related to weakness in the legs than to abnormal movements. Subject IV-3 had ataxic diplegia without obvious signs of chorea. Seven relatives were unaffected, on the basis of history as well as physical examination by a neurologist (W.F. M.A.).

Linkage Analysis

Several candidate loci for trinucleotide-repeat elongation—HD, SCA 1, SCA2, Machado Joseph disease (SCA3), SCA6, and DRPLA—were tested on the proband (subject IV-1). No repeat elongation beyond that found in the general population was found (data not shown).

To determine whether the BHC phenotype was linked to the HD gene region, 10 polymorphic markers on the short arm of chromosome 4 were subsequently tested. Two different linkage models, as described earlier, were used to demonstrate that none of the markers showed evidence for linkage, making chromosome 4p an unlikely site for BHC (data not shown).

Subsequently, a genomewide search with polymorphic markers was started. A total of 95 markers were used

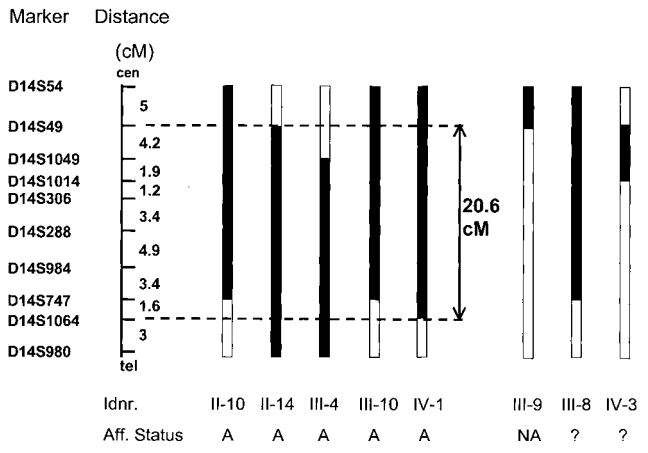

Figure 2 Haplotype sharing of subjects of the Dutch BHC family. Dark bars represent maximal extension of BHC "risk" haplotype in each subject. Dotted lines delineate the maximal critical region of 20.6 cM from recombinational events. Chromosome 14q12–q22 linkage map plus intermarker distances are indicated. A = affected; NA = nonaffected; ? = diagnosis unknown.

until marker D14S306 showed a positive LOD score. A maximum two-point LOD score of 4.20 was found by using the affected-only analysis (model 1) and a score of 6.32 by using model 2 (100% penetrance). Additional markers flanking D14S306 were tested (table 2). The order of all markers was taken from the Marshfield comprehensive linkage map chr.14 (see Electronic-Database section). No recombination was observed between the phenotype and D14S1049, D14S1014, D14S306, D14S288, D14S984, and D14S747. The highest LOD scores were obtained with markers D14S984 and D14S306; LOD 6.32 at recombination fraction (θ) 0 by using model 2 (100% penetrance), indicating strong evidence for linkage between these markers and the BHC locus. The closest recombination events in affected persons were seen between the phenotype and D14S49 proximal and D14S1064 distal (fig. 1 and fig. 2). Pairwise LOD scores were calculated for different values of θ for all markers by use of the two different models and are summarized in table 2. Additional haplotype analysis by using clinical diagnosis of all persons in the pedigree did not reduce the genomic interval, so that the most likely location of the BHC locus in this family is between D14S49 and D14S1064, a region spanning ~20.6 cM (fig. 1 and fig. 2).

Discussion

BHC is one of the choreic disorders that should be differentiated clinically from HD. In children with BHC, the most characteristic presenting symptom is the motor delay associated with the choreic movements. Later on in childhood, their inability to write legibly hampers schooling. A correct diagnosis at a young age will avoid unnecessary investigations and enable the parents to be reassured. Although the clinical signs in all patients in this Dutch family with BHC ameliorate in adolescence, a minority remained choreatic into adulthood. Several patients had (minor) ataxia, two adult patients had psychosis (one not shown in the pedigree), and a child had pyramidal signs. These additional features suggest a more general involvement of the brain than the basal ganglia alone. The early onset of clinical features presuppose a disturbance of development. The clinical course with improvement in time is, to some extent, similar in the patients of this family. However, some adults still showed choreatic and/or slight ataxia, even beyond age 60 years. The latter reflects the intrafamilial variability, as has been reported in other families with BHC (Bruyn and Myrianthopoulos 1986; Wheeler et al. 1993). Additional features also reported in other families with BHC include dysathria and ataxia (Chun et al. 1973; Harper 1978; Schady and Meara 1988). Schady and Meara (1988) reported a family with, in addition to the dysarthria, elements of an axial dystonia. However, these symptoms were progressive in the latter family, which is uncharacteristic for BHC and therefore might indicate a different disorder. Also, other BHC families with additional manifestations have been reported, suggesting clinical heterogeneity.

Several loci, such as the HD gene region, were excluded as the location of the BHC locus in this large Dutch family. In addition, the SCA1, SCA2, SCA3, SCA6, and DRPLA-related CAG-repeat elongations were excluded. Subsequently, the BHC locus was located on chromosome 14q12–22 in a 20.6-cM interval defined by the markers D14S49 and D14S1064. This shows the heterogeneity of genes and loci involved in the development of movement disorders, and the changing effects of some mutations over time: BHC ameliorates and HD aggravates.

A candidate-gene search of this region identified large numbers of expressed-sequence tags, most with unknown function, and three interesting candidate genes that are expressed in the nervous system. The first, the glia maturation factor-β, is a small, 142-amino acid polypeptide expressed in the brain of vertebrates (Kaplan et al. 1991). This endogenous brain protein is involved in the differentiation, maintenance, and regeneration of the nervous system and expressed in neurons as well as astrocytes (Wang et al. 1992). The protein's level increases slowly prenatally and plateaus shortly after birth, as studied in rat brain (Zaheer et al. 1993). Because the clinical features in BHC patients appear before the first year, a disturbance in maturation of glia cells might be part of the pathogenic process, although, so far, no major cerebral abnormalities, as detectable by

Table 2

Pairwise LOD Scores for Different Values of θ between BHC and Chromosome 14 Markers

	LOD Score at θ =							
Marker	.00	.01	.05	.10	.20	.30	.40	θ
Model 1[a]								
D14S54	−3.50	.16	1.31	1.61	1.55	1.16	.60	.14
D14S49	−.40	1.26	1.75	1.80	1.54	1.08	.50	.08
D14S1049	4.20	4.14	3.87	3.51	2.75	1.88	.91	.00
D14S1014	2.05	2.01	1.87	1.68	1.27	.82	.34	.00
D14S306	4.20	4.14	3.87	3.51	2.75	1.88	.91	.00
D14S288	3.30	3.24	3.01	2.71	2.07	1.36	.61	.00
D14S984	4.20	4.14	3.87	3.51	2.75	1.88	.91	.00
D14S747	2.56	2.51	2.34	2.10	1.60	1.05	.45	.00
D14S1064	−.40	.04	1.04	1.36	1.34	1.01	.53	.14
D14S980	−2.04	−0.49	0.06	.20	.19	.10	.03	.14
Model 2[b]								
D14S54	−∞	.24	2.00	2.45	2.38	1.82	.97	.14
D14S49	−∞	.16	1.32	1.62	1.56	1.16	.56	.13
D14S1049	5.86	5.77	5.41	4.94	3.90	2.71	1.36	.00
D14S1014	2.36	2.32	2.16	1.95	1.49	.98	.41	.00
D14S306	6.32	6.23	5.83	5.31	4.19	2.91	1.47	.00
D14S288	4.53	4.45	4.15	3.75	2.90	1.96	.93	.00
D14S984	6.32	6.23	5.83	5.31	4.19	2.91	1.47	.00
D14S747	4.08	4.01	3.74	3.39	2.64	1.79	.85	.00
D14S1064	−∞	1.64	2.72	2.90	2.58	1.89	.98	.10
D14S980	−∞	−.93	−.22	.04	.19	.16	.08	.22

[a] Affected persons only.
[b] Affected and unaffected persons.

MRI studies, were found in BHC (Bruyn and Myrianthopoulos 1986; Wheeler et al. 1993). At a later patient age, the delayed maturation might be (partially) overcome by other factors consistent with the reduction of symptoms. Another candidate is GTP cyclohydrolase 1 (GCH1). Mutations in GCH1 were found in hereditary progressive dystonia with diurnal variation (HPD [MIM 128230]) (Ichinose et al. 1994). Remarkably, the course of HPD and BHC is slightly similar, with onset in the first decade, progression in the first two decades, and amelioration, at a later age in BHC and subsided progression in HPD. However, HPD shows mainly dystonic movements that increase during the day and are responsive to l-DOPA, suggesting that its pathogenesis is restricted to the nigrostriatal dopaminergic system. Moreover, in HPD a marked female predominance is noted (Segawa et al. 1986), whereas in BHC the penetrance is reported to be lowered in females (Harper 1978) or similar between the sexes, as in the current family (see following).

The survival of motor neurons (SMN)–interacting protein 1 (SIP1), which is associated with the SMN gene product (Liu et al. 1997), might be another candidate. The SMN gene product is deleted or mutated in 98% of the spinal muscular atrophy patients. SIP1 and SMN forms a complex with spliceosomal small nuclear ribonucleoproteins (snRNP) (Liu et al. 1997). Although the consequences of genetic abnormalities in SMN are known, a clinical phenotype from an SIP1 mutation is unknown.

The candidate region might be narrowed down when subject IV-3, who had been characterized as unknown at age 3 years, eventually turns out to be affected later in life. One recombinant event in subject IV-3 between markers D14S1014 and D14S288 falls in the middle of the critical region (fig. 2). The exact position of this recombination could not be determined because the genotype of this person is inconsistent with the haplotype of the father. Because no other inconsistent genotypes were detected, the most likely explanation is that in the father one allele has elongated one repeat unit from 206 to 210 bases. Unfortunately, this recombination is of little help for defining the critical region of BHC, because the precise diagnosis of subject IV-3 is still uncertain.

Two other subjects that had been classified as unknown (II-12 and III-8) carried the risk haplotype (fig. 2). The clinical diagnosis in II-12 was uncertain because of a history of Sydenham chorea. However, she had an affected daughter, which made her an obligate carrier, and which also made the diagnosis of BHC most likely. The second relative, III-8, might be the only case of lowered penetrance in the family, because all other 13 clinically diagnosed relatives have the risk haplotype. Assuming III-8 as a nonpenetrant case will still give a nearly complete penetrance (>0.90) in this family without a (significant) difference between males and females. This contrasts reports by others suggesting a lowered penetrance in females (Harper 1978).

As shown in the current family and reported by others (Bruyn and Myrianthopoulos 1986; Wheeler et al. 1993), there is an obvious intrafamilial variability in BHC. Also, considerable interfamilial differences can be observed. However, it is unknown whether this reflects genetic heterogeneity. Further linkage studies in other BHC families will give insight into this issue.

The improvement of choreatic movements in adolescence makes the BHC an intriguing disorder. Cloning of the BHC gene and functional studies of the BHC protein might reveal the mechanism(s) involved in choreatic disorders and the interaction of various molecular mechanisms in their pathogenesis.

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Electronic-Database Information

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

Center for Medical Genetics, Marshfield Medical Research Foundation, http://www.marshmed.org/genetics
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nim.nih.gov/omim

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