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# Chorea-Acanthocytosis: Genetic Linkage to Chromosome 9q21

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## Summary

**Chorea-acanthocytosis (CHAC) is a rare autosomal recessive disorder characterized by progressive neurodegeneration and unusual red-cell morphology (acanthocytosis), with onset in the third to fifth decade of life. Neurological impairment with acanthocytosis (neuroacanthocytosis) also is seen in abetalipoproteinemia and X-linked McLeod syndrome. Whereas the molecular etiology of McLeod syndrome has been defined (Ho et al. 1994), that of CHAC is still unknown. In the absence of cytogenetic rearrangements, we initiated a genomewide scan for linkage in 11 families, segregating for CHAC, who are of diverse geographical origin. We report here that the disease is linked, in all families, to a 6-cM region of chromosome 9q21 that is flanked by the recombinant markers GATA89a11 and D9S1843. A maximum two-point LOD score of 7.1 ($\theta$ = .00) for D9S1867 was achieved, and the linked region has been confirmed by homozygosity-by-descent, in offspring from inbred families. These findings provide strong evidence for the involvement of a single locus for CHAC and are the first step in positional cloning of the disease gene.**

## Introduction

Chorea-acanthocytosis (CHAC) is a rare autosomal recessive disorder that is described, with at least two other syndromes, as "neuroacanthocytosis" (Hardie 1989; Brin 1993). The core symptoms of the neurological syndromes that comprise neuroacanthocytosis are difficult to distinguish clinically and occur with aberrant red-cell morphology (Hardie 1989; Brin 1993). Acanthocytosis was derived from the Greek "akantha," or thorn, and is used to describe the spiky appearance of erythrocytes occurring at elevated levels, in affected individuals. The significance of abnormal red cells in a neurological context is unclear, as are the molecular events required for acanthocyte formation. However, alterations in membrane lipids and cytoskeletal proteins have been implicated (Sakai et al. 1991). Bassen and Kornzweig (1950) first associated acanthocytosis with neurological abnormalities when they described the rare, autosomal recessive syndrome abetalipoproteinemia. A defect in lipid-loading of apolipoprotein B initiates a series of events leading to fat intolerance and fat-soluble vitamin deficiency (Narcisi et al. 1995).

McLeod syndrome is an X-linked disorder characterized by weak expression of Kell blood-group antigens (Marsh 1983; Redman and Marsh 1993). The XK gene, disrupted in this condition, codes for a novel protein with structural features characteristic of prokaryotic and eukaryotic membrane-transport proteins (Ho et al. 1994). Its exact role in the pathogenesis of neurological symptoms (Witt et al. 1992) is still unknown.

CHAC, like McLeod syndrome, is characterized by involuntary movements and progressive neurodegeneration (Hardie et al. 1991; Brin 1993). Chorea, which is the most characteristic associated movement abnormality, is defined as random, abrupt, irregular involuntary movements of variable severity. In most cases, symptom onset is delayed until 25–45 years of age. Motor or vocal tics also are observed in CHAC, as are dystonia, Parkinsonism, progressive supranuclear palsy, and apraxia of the eyelid opening (Jankovic 1986; Peppard et al. 1990; Hardie et al. 1991; Brin 1993). Degeneration of the basal ganglia, closely resembling that seen in Huntington disease, results in atrophy of the putamen and the caudate nucleus (Bird et al. 1978; Alonso et al. 1989; Hardie et al. 1991; Malandrini et al. 1993). Cognitive impairment and psychosis manifest as dementia, para-

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noia, and/or personality change and even may lead to suicide (Aguilar i Bascompte et al. 1988; Alonso et al. 1989; Kartsounis and Hardie 1996). Chorea, orofacial dyskinesia, and epileptic seizures underlie the commonly found tongue and lip biting (Hardie et al. 1991; Schwartz et al. 1992). An axonal neuropathy leading to the depression of reflexes and muscle atrophy is shared by both CHAC and McLeod syndrome (Kito et al. 1980; Hardie et al. 1991; Witt et al. 1992). There is no effective long-term treatment for either condition. Verapamil has been found to be of only temporary help (Brenes et al. 1990).

Genetic heterogeneity appeared to be a feature of CHAC, since both autosomal dominant (Levine et al. 1968) and recessive (Vance et al. 1987) transmission have been reported. However, an autosomal recessive mode of transmission seemed most likely, given that a number of studies have reported the disease in inbred families (Bird et al. 1978; Alonso et al. 1989). Clinical studies have used a variety of different terms for what was quite likely the same disorder—for example, "familial amyotrophic chorea with acanthocytosis," "CHAC," and "Levine-Critchley syndrome" (Kito et al. 1980; Sakai et al. 1985). It also is likely that disease prevalence has been underestimated because the disease can be mistaken easily for Huntington disease or may have been diagnosed as so-called subchorea or atypical chorea (Lange et al. 1976; Serra et al. 1986; Vance et al. 1987; Alonso et al. 1989; Brin 1993).

We performed linkage studies on 11 families, segregating for CHAC, who are of diverse geographical origin. The results of these studies were confirmed, by homozygosity-by-descent (HBD) analysis, in offspring from consanguineous marriages and, together, provide strong evidence for the CHAC gene being located on chromosome 9q21.

## Subjects and Methods

The clinical features of the neuroacanthocytosis syndromes are very similar. In order to reduce the risk of misdiagnosis, a protocol was designed for ascertainment of putative CHAC families, at the clinical, biochemical, and molecular levels. CHAC was diagnosed if a neurological syndrome was associated with acanthocytosis and if abetalipoproteinemia and McLeod syndrome were excluded through assessment of blood lipids or lipoproteins, as well as through Kell blood-group typing or mutation analysis of the XK gene (Ho et al. 1994).

The neurological syndrome could consist of movement disorders (chorea, tics, vocalizations, tongue/lip biting, dystonia, or Parkinsonism), caudate-nucleus atrophy, myopathy, neuropathy, epilepsy, or abnormalities in the neuropsychological or psychopathological examination. The severity and number of neurological symptoms (listed above) seen in affected individuals varied significantly (see Hardie et al. 1991) but, when considered together with the molecular and biochemical information, were deemed sufficient for a correct diagnosis.

### *CHAC Families*

*Family CHAC1.*—This family, from the United Kingdom, was ascertained by Hardie et al. and was termed "family H" in their original report (Hardie et al. 1991; Kartsounis and Hardie 1996). Two affected females (individuals II-8 and II-9) and 12 unaffected relatives (individuals II-4, II-5, II-6, II-7, III-1, III-2, III-4, III-5, III-6, III-7, III-8, and III-10) were available for study (see Hardie et al. 1991).

*Family CHAC2.*—Originally from France, this family is the result of a consanguineous marriage between second cousins. Seven unaffected and two affected members were available for study (fig. 1). Individual IV-5 had been studied previously (Ferrer et al. 1990).

*Family CHAC3.*—From Italy, this family had two affected brothers, who died at 29 and at 37 years of age. The latter individual and four unaffected members of his family were available for study. The proband had been reported in a previous study (case 2 in Malandrini et al. 1993).

*Family CHAC4.*—This family, from the United States, provided one affected individual and 13 unaffected individuals, from three generations, for analysis.

*Family CHAC5.*—From the United States, this family provided an affected brother and sister, an unaffected sister, and both parents for study (family A in Vance et al. 1987; case 1 in Kaplan et al. 1986).

*Family CHAC6.*—From this family of Turkish origin, both parents, one affected sib, and three unaffected sibs were studied. Individual II-4 (born in 1978) was recorded as "phenotype unknown," for linkage analysis (fig. 1).

*Family CHAC7.*—A Mexican family of an unknown degree of consanguinity had given rise to a sibship with five affected and four unaffected individuals. Three of the affected individuals, who were unavailable for genetic analysis, had been studied elsewhere (Alonso et al. 1989).

*Family CHAC8.*—An Italian family, derived from a first-cousin marriage, had one affected and three unaffected individuals available for study.

*Family CHAC9.*—From the United Kingdom, both parents and both affected sibs were tested (family B in Hardie et al. 1991; also see Kartsounis and Hardie 1996). Interestingly, the male and female sibs developed symptoms at 8 and 12 years of age, respectively.

*Family CHAC10.*—From this Italian family, one parent, one affected sib, and four unaffected sibs were studied.

*Family CHAC11.*—From this English family, both parents, one affected sib, and one unaffected sib were available for study.

### *Isolated Cases*

DNA from 13 affected individuals, received without data from relatives or as data from single-child families (with data from both parents, which was uninformative for linkage analysis), was tested for HBD across the linked region. Cases 13, 16, 18, and 19 from the study by Hardie et al. (1991) (also see Kartsounis and Hardie 1996) and nine other cases were studied.

### *Genotyping*

DNA from available family members was isolated from fresh blood samples or from permanent B-lymphocyte cell lines, by use of a Nucleon™ Biosciences DNA-extraction kit. A panel of 280 microsatellite markers for fluorescence-based detection were selected for the genome scan (Reed et al. 1994). PCR reactions were performed in 96-well Costar (Thermowell™) plates in a 15-μl volume, on 40 ng of genomic DNA, with MJ 225 PCR machines. Products were detected with a model 373A DNA sequencer (Applied Biosystems), and data were analyzed by use of Genescan™ (version 2.0.2) and Genotyper™ (version 1.1).

### *Linkage Analysis*

Data was analyzed under the assumption that CHAC is a fully penetrant, autosomal recessive disorder. In the absence of any published estimates of the prevalence of CHAC, in the general population, a disease-gene frequency of .003 (~1/100,000) was estimated. Because of the potential for age-dependent penetrance, unaffected individuals under the age of 25 years were considered to be "phenotype unknown," for linkage analysis. Power calculations were performed by use of SLINK (Weeks et al. 1990). Genotyping data was converted to LINKAGE format by use of the GAS package (version 2.0) (©1993–1995 by Alan Young, Oxford University), and inbreeding loops were broken by use of MAKEPED, in order to perform the linkage analysis using MLINK from the LINKAGE package (Lathrop et al. 1984). Heterogeneity was assessed by use of the HOMOG program (version 3.3) (Ott 1991), and multipoint linkage analysis was performed by use of LINKMAP (Lathrop et al. 1985). No sex difference was assumed, and the existence of phenocopies could not be ruled out.

### *Fine Mapping and Haplotyping*

In total, 26 polymorphic microsatellite markers were used for the fine mapping of chromosome 9q. The following dinucleotide-repeat markers were obtained from a number of sources (markers are listed in chromosomal order, proximal to distal): D9S147E, D9S15, and D9S175 (Reed et al. 1994); D9S1844, D9S1837, D9S175, D9S1860, D9S1807, D9S1834, D9S1674, D9S153, D9S1780, D9S1785, D9S1867, D9S1843, D9S167, and D9S152 (Dib et al. 1996); and AFM207vb8, AFMa101xd1, AFMb358xe9, and AFM273vb1, which are genetically unmapped Généthon CA-repeat markers that have been mapped onto the Whitehead Institute/CEPH mega-YAC maps. The following tetranucleotide-repeat markers from the Cooperative Human Linkage Center were chosen according to their location as defined by the Whitehead Institute/CEPH mega-YAC maps: GATA89a11, GGAT-13b07, GATA89c08, GATA21f05, and GATA3d04 (Sheffield et al. 1995). Haplotypes were constructed manually by use of the 15 most informative markers, by minimization of recombination events between markers, and were confirmed by use of SIMWALK2 (Sobel and Lange 1996).

## Results

### *Two-Point Evidence for Linkage to Chromosome 9q21*

A genomewide search for linkage was initiated for 11 families, after power calculations indicated a statistically significant likelihood of detection of linkage, given the density of the markers to be used and the families available for study (fig. 1). Two-point LOD scores were generated for 70 markers corresponding to various chromosomes, before a two-point LOD score $>1$ was calculated for D9S15 (1.81 at $\theta = .00$; table 1), which is tightly linked to the Friedreich ataxia locus (FRDA) at 9q13-q21 (Fujita et al. 1990). Flanking markers D9S147e and D9S175, which were in the genome-scan set, gave LOD scores of .90 ($\theta = .20$) and 2.70 ($\theta = .05$), respectively (table 1). Since D9S167, which is 14 cM distal to D9S175 (Dib et al. 1996), achieved a LOD score of 2.74 ($\theta = .05$), the region between D9S175 and D9S167 was studied in the CHAC families with a greater marker density (table 1 and fig. 2).

### *Haplotype Analysis and Fine Mapping*

Cumulative two-point LOD scores for the most informative markers tested are shown in table 1. Haplotype analysis indicated that CHAC is linked, in all families, to this region of chromosome 9 and that no unaffected members received the disease haplotype on both chromosomes (table 1 and fig. 1). Correspondingly, homogeneity was not rejected in a HOMOG test (data not shown). The markers (cen-qter) GATA89c08, D9S1674, D9S153, D9SS1780, D9S1867, and GATA21f05 were nonrecombinant and defined a critical region of 6 cM for the CHAC disease locus (fig. 1, fig. 2, and table 1). The proximal recombination event was observed in affected individual CHAC2 IV-7, positioning the CHAC

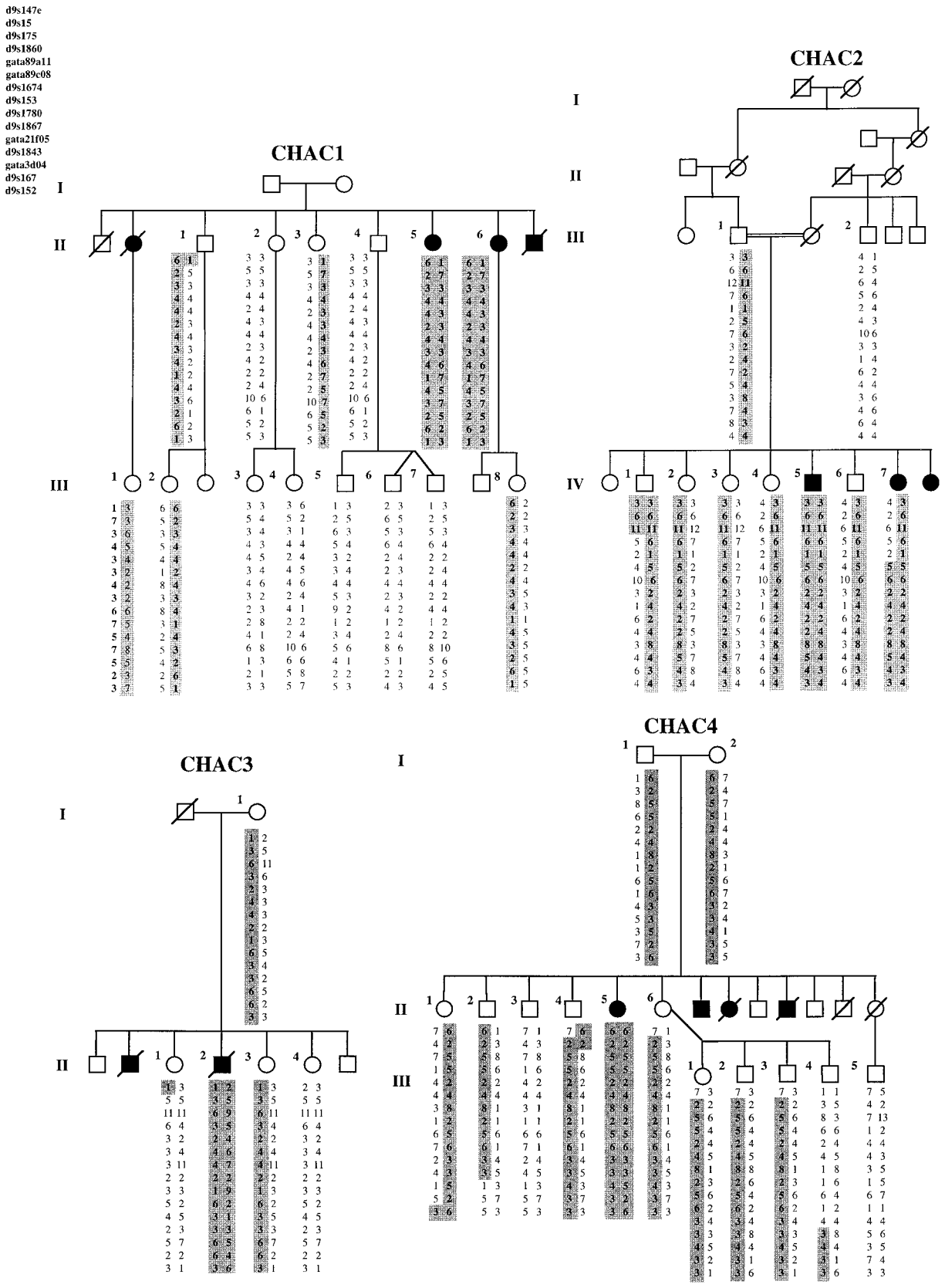
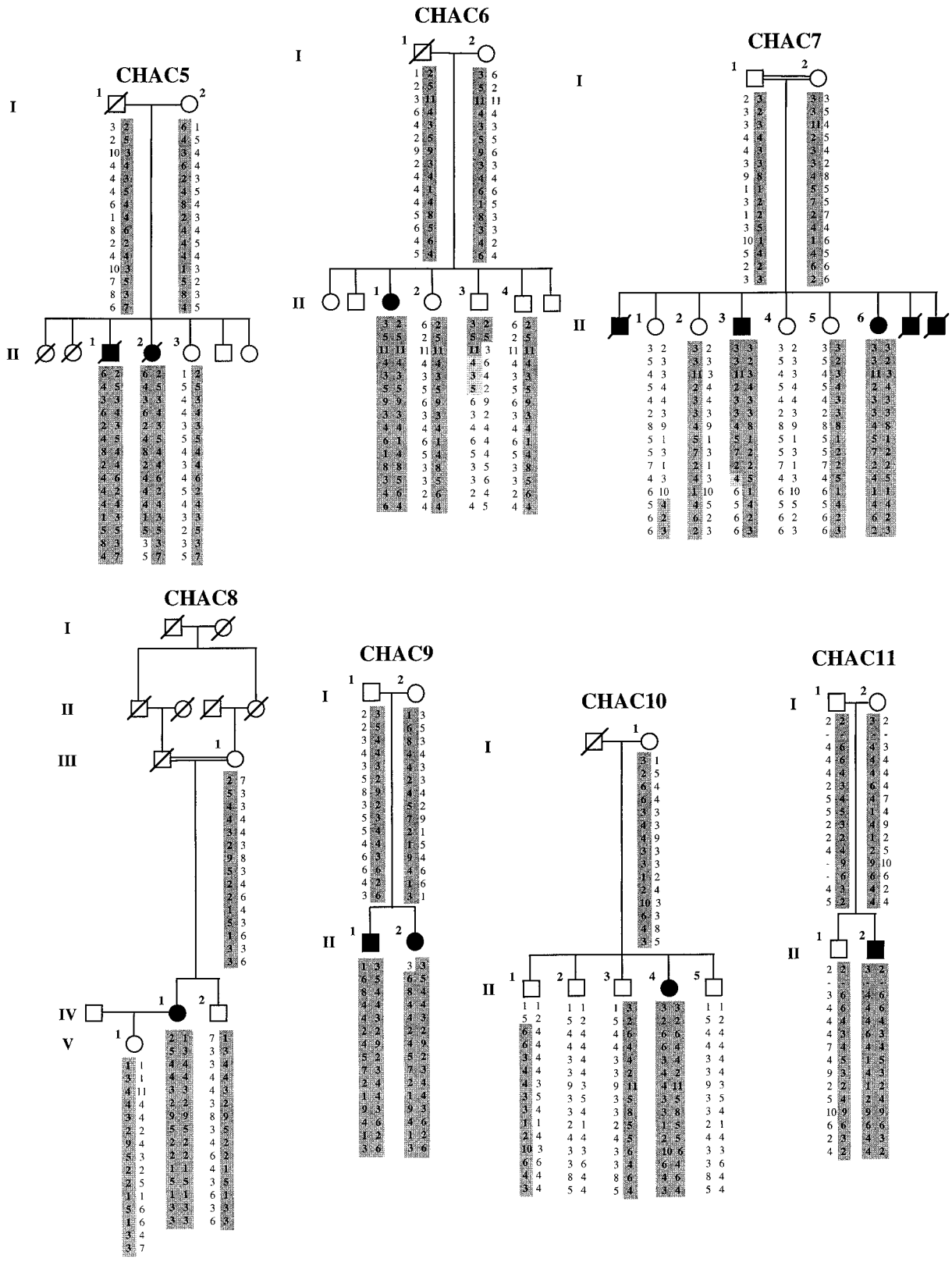



**Figure 1** Haplotype analysis of 11 CHAC families. CHAC family members were analyzed for 15 polymorphic marker loci from chromosome 9q. The order of these genetic markers reflects their order, proximal (top nos.) to distal (bottom nos.), on chromosome 9 (based on Dib et al. 1996 and the Whitehead Institute/CEPH mega-YAC maps). The disease-associated haplotype is indicated by boldface type in the darker-shaded boxes. Haplotypes were assigned minimizing numbers of crossover events in each family. Proximal and distal recombination events that define the critical region for the CHAC disease locus have occurred in affected individuals CHAC2 IV-7 and CHAC7 II-3, respectively.




These recombination events identified GATA89c08, D9S1674, D9S153, D9S1780, D9S1867, and GATA21f05 as nonrecombinant markers. Close scrutiny of the maternal haplotype for individual CHAC7 II-3 revealed that phase cannot be assigned for GATA21f05. This implies that a recombination event may have occurred proximal to GATA21f05 (between GATA21f05 and D9S1867), which would exclude it from the CHAC critical region. Light shading indicates markers for which phase cannot be assigned.

**Table 1**

**Cumulative Two-Point LOD Scores between the CHAC Locus and Chromosome 9q Markers**

| | LOD Score at θ = | | | | | | |
|---|---|---|---|---|---|---|---|
| Marker | .00 | .01 | .05 | .10 | .20 | .30 | .40 |
| D9S147e | −∞ | −2.94 | −.12 | .72 | .90 | .55 | .16 |
| D9S15 | −∞ | −.64 | 1.40 | 1.81 | 1.49 | .82 | .23 |
| D9S175 | −∞ | 2.00 | 2.70 | 2.46 | 1.57 | .75 | .21 |
| D9S1860 | −∞ | 1.78 | 2.04 | 1.80 | 1.09 | .49 | .13 |
| GATA89a11 | −∞ | 2.29 | 2.56 | 2.33 | 1.59 | .82 | .24 |
| GATA89c08 | 5.67 | 5.50 | 4.81 | 3.98 | 2.44 | 1.19 | .36 |
| D9S1674 | 6.57 | 6.36 | 5.55 | 4.56 | 2.74 | 1.28 | .35 |
| D9S153 | 4.46 | 4.32 | 3.77 | 3.08 | 1.84 | .84 | .22 |
| D9S1780 | 6.25 | 6.06 | 5.33 | 4.43 | 2.74 | 1.33 | .38 |
| D9S1867 | 7.01 | 6.81 | 6.00 | 5.01 | 3.12 | 1.52 | .42 |
| GATA21f05 | 4.84 | 4.94 | 4.64 | 3.96 | 2.48 | 1.19 | .32 |
| D9S1843 | −∞ | 4.44 | 4.92 | 4.40 | 2.88 | 1.45 | .42 |
| GATA3d04 | −∞ | 3.46 | 3.81 | 3.41 | 2.20 | 1.05 | .28 |
| D9S167 | −∞ | 2.24 | 2.73 | 2.50 | 1.62 | .75 | .19 |
| D9S152 | −∞ | −.40 | .97 | 1.24 | .99 | .52 | .15 |

locus telomeric to GATA89a11 (table 2 and fig. 1). The distal recombination event in CHAC7 II-3 positioned the CHAC locus centromeric to D9S1843.

HBD has provided strong evidence that GATA21f05 can be excluded from the CHAC critical region (table 3 and fig. 2). Conventional haplotype analysis was unable to conclusively exclude or include GATA21f05 in the critical region, since phase could not be assigned for this marker, owing to maternal homozygosity in family CHAC7 (fig. 1). Haplotype analysis of offspring from a consanguineous marriage (CHAC2 IV-5 and CHAC2 IV-7) suggested that ancestral recombination events have occurred, thereby excluding this marker from the CHAC disease region, owing to loss of HBD in both individuals (table 3).

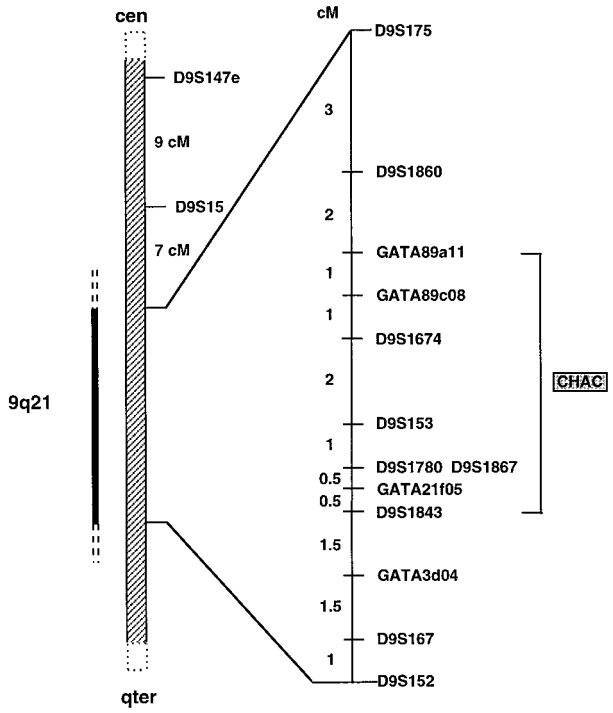



**Figure 2** Genetic map of chromosome 9q21, showing the CHAC critical region. Genetic distances between adjacent markers are sex-averaged recombination fractions, in centimorgans (cM). The order of and distances between markers are based on data from a number of sources (Dib et al. 1996 and the Whitehead Institute/CEPH mega-YAC maps).

The highest two-point LOD score was 7.01 at θ = .00, for D9S1867 (table 1). Multipoint analysis across the disease region, with the 15 polymorphic microsatellites, confirmed the critical region for CHAC and yielded a multipoint LOD score of 8.53, for D9S1867 (data not shown).

## Discussion

We have found linkage of CHAC to a 6-cM region on chromosome 9q21, in 11 families of distinct geographical origin. These results indicate that the affected family members suffer from a homogeneous, autosomal recessive disorder.

It is widely recognized that rare recessive traits occur more frequently in offspring of consanguineous marriages than in the general population (Lander and Botstein 1987; Farrall 1993). Homozygosity mapping relies on the use of multipoint linkage analysis to identify HBD regions shared by inbred affected children and inherited from a recent ancestor common to both the maternal and paternal lineages (Lander and Botstein 1987; Farrall 1993).

## Table 2

**Two-Point LOD Scores between the CHAC Locus and Three Chromosome 9q Marker Loci, for the 11 CHAC Families**

| Marker and CHAC Family | LOD Score at θ = .00 | .01 | .05 | .10 | .20 | .30 | .40 |
|---|---|---|---|---|---|---|---|
| GATA89a11: | | | | | | | |
| 1 | 1.16 | 1.14 | 1.02 | .88 | .58 | .30 | .08 |
| 2 | −∞ | −1.40 | −.73 | −.46 | −.21 | −.08 | −.01 |
| 3 | .37 | .37 | .33 | .28 | .19 | .10 | .03 |
| 4 | −.15 | −.15 | −.12 | −.10 | −.05 | −.02 | −.01 |
| 5 | .73 | .71 | .62 | .51 | .31 | .14 | .03 |
| 6 | −.05 | −.05 | −.04 | −.03 | −.02 | −.01 | −.00 |
| 7 | 1.10 | 1.08 | .97 | .83 | .55 | .29 | .08 |
| 8 | .37 | .35 | .29 | .22 | .12 | .05 | .02 |
| 9 | .30 | .29 | .26 | .21 | .13 | .06 | .02 |
| 10 | −.04 | −.04 | −.03 | −.03 | −.01 | −.01 | −.00 |
| 11 | .00 | .00 | .00 | .00 | .00 | .00 | .00 |
| D9S1867: | | | | | | | |
| 1 | 1.40 | 1.37 | 1.25 | 1.09 | .74 | .40 | .12 |
| 2 | 1.65 | 1.60 | 1.40 | 1.15 | .69 | .31 | .08 |
| 3 | −.01 | −.00 | .00 | .01 | .01 | .01 | .00 |
| 4 | .75 | .72 | .61 | .48 | .26 | .10 | .02 |
| 5 | .43 | .42 | .37 | .32 | .20 | .10 | .03 |
| 6 | −.05 | −.05 | −.04 | −.03 | −.02 | −.01 | −.00 |
| 7 | 1.10 | 1.08 | .97 | .83 | .55 | .28 | .08 |
| 8 | .51 | .49 | .41 | .32 | .17 | .08 | .03 |
| 9 | .60 | .58 | .52 | .43 | .27 | .13 | .03 |
| 10 | .50 | .48 | .42 | .34 | .20 | .09 | .02 |
| 11 | .12 | .12 | .10 | .08 | .05 | .02 | .01 |
| D9S1843: | | | | | | | |
| 1 | 1.40 | 1.37 | 1.25 | 1.09 | .74 | .40 | .12 |
| 2 | 1.69 | 1.63 | 1.43 | 1.19 | .74 | .36 | .11 |
| 3 | −∞ | −1.16 | −.51 | −.27 | −.09 | −.02 | −.00 |
| 4 | .75 | .72 | .61 | .48 | .26 | .10 | .02 |
| 5 | .73 | .71 | .62 | .51 | .31 | .14 | .03 |
| 6 | .25 | .24 | .21 | .17 | .10 | .05 | .01 |
| 7 | −∞ | −.91 | −.27 | −.05 | .07 | .06 | .02 |
| 8 | .68 | .65 | .56 | .45 | .25 | .12 | .04 |
| 9 | .60 | .58 | .52 | .43 | .27 | .13 | .03 |
| 10 | .50 | .48 | .42 | .34 | .20 | .09 | .02 |
| 11 | .12 | .12 | .09 | .07 | .03 | .01 | .00 |

Note.—GATA89a11 and D9S1843 are the closest markers flanking the proximal boundary and the distal boundary, respectively, of the critical region (fig. 1). Familial LOD scores for D9S1867 are shown, since it is located in the critical region and yields the highest two-point LOD score (7.01 at θ = .00) for the markers analyzed (table 1).

In our study, it was known prior to the genome scan that families CHAC2, CHAC7, and CHAC8 were consanguineous (fig. 1); however, these families alone would provide insufficient power to conclude linkage solely by use of homozygosity mapping in a genomewide search. Interestingly, haplotype analysis of affected individuals (including isolated cases), for the region studied, has provided strong evidence of consanguinity in family CHAC4 and in a family from which an isolated case was studied (table 3). Inferred HBD in these individuals could be due to chance; however, this is unlikely given the high rate of heterozygosity for the markers studied (table 3). Despite the consanguinity in family CHAC7, an extended region of homozygosity across the CHAC critical region was not seen in affected individuals (fig. 1). This could be due to the fact that the parents (CHAC7 I-1 and CHAC7 I-2) were related through a distant marriage, making the HBD in the offspring more difficult to detect, given this density of polymorphic markers. Further analysis for HBD in the affected individuals from family CHAC7, with more closely spaced markers, may help to reduce the candidate region.

**Table 3**

**HBD in CHAC-Affected Individuals**

| Marker[a] | Haplotype for[b] | | | | | No. of Alleles[d] | Average Heterozygosity[d] |
|---|---|---|---|---|---|---|---|
| | CHAC2 IV-5[c] | CHAC2 IV-7[c] | CHAC4 II-5 | CHAC8 IV-1[c] | Isolated Case | | |
| D9S147e | 3 3 | 4 3 | 6 6 | 2 1 | 2 2 | 7 | . . . |
| D9S15 | 6 6 | 2 6 | 2 2 | 5 3 | 2 5 | 7 | . . . |
| D9S175 | 11 11 | 6 11 | 5 5 | 4 4 | 3 13 | 13 | 84 |
| D9S1860 | 6 6 | 5 6 | 5 5 | 4 4 | 6 6 | 7 | 50 |
| GATA89a11 | 1 1 | 2 1 | 2 2 | 3 3 | 3 3 | 4 | . . . |
| GATA89c08 | 5 5 | 5 5 | 4 4 | 2 2 | 4 4 | 6 | . . . |
| D9S1674 | 6 6 | 6 6 | 8 8 | 9 9 | 8 8 | 11 | 73 |
| D9S153 | 2 2 | 2 2 | 2 2 | 5 5 | 5 5 | 6 | 76 |
| D9S1780 | 4 4 | 4 4 | 5 5 | 2 2 | 3 3 | 9 | 71 |
| D9S1867 | 2 2 | 2 2 | 6 6 | 2 2 | 6 6 | 8 | 82 |
| GATA21f05 | 2 4 | 2 4 | 3 3 | 1 1 | 2 2 | 10 | . . . |
| D9S1843 | 8 8 | 8 8 | 3 3 | 5 5 | 8 8 | 5 | 80 |
| GATA3d04 | 5 4 | 5 4 | 4 5 | 1 1 | 4 4 | 7 | . . . |
| D9S167 | 4 3 | 4 3 | 3 2 | 3 3 | . . . | 8 | 87 |
| D9S152 | 3 4 | 3 4 | 3 6 | 3 3 | 7 7 | 9 | 83 |

[a] The polymorphic marker loci that are nonrecombinant with the CHAC locus (fig. 1 and table 1) are underlined. For individuals CHAC2 IV-5 and CHAC2 IV-7, the region that reduces the critical region to exclude GATA21f05 lies between GATA89c08 and D931867.

[b] Contiguous regions of homozygosity that overlap with the CHAC disease interval (fig. 1 and table 1) are indicated by shading.

[c] Offspring from a known consanguineous marriage.

[d] Determined across all CHAC families (Dib et al. 1996).

Autosomal dominant familial dilated cardiomyopathy (FDC) was mapped recently to chromosome 9q13-q22 in the interval between D9S153 and D9S152 (Krajinovic et al. 1995), which overlaps with the CHAC critical region (fig. 2). Krajinovic et al. cite two genes as candidates for the FDC gene, which also are attractive candidates for the CHAC gene: The gene for Friedreich ataxia (9q13-q21.1) (Carvajal et al. 1996), a severe neurodegenerative disease with autosomal recessive transmission and heart involvement, is a good candidate, but recombination events in families CHAC2, CHAC4, and CHAC6 exclude D9S15 (table 2 and fig. 1), a marker tightly linked to FRDA (Fujita et al. 1990). Another candidate for the CHAC gene is tropomodulin (TMOD) (9q22), a tropomyosin regulatory protein that inhibits actin filaments binding to tropomyosin, which is believed to interact with the membrane cytoskeleton (Sung et al. 1992). Recent physical mapping studies of 9q22, however, located TMOD outside the CHAC critical region (Lench et al. 1996).

So far, it has been difficult to distinguish between subtypes of the neuroacanthocytosis syndromes (Faillace et al. 1982; Marsh 1983; Takashima et al. 1994; Ho et al. 1996). Therefore, analysis of the CHAC and the McLeod genes has immediate consequences for differential diagnosis. This may be compared with the clinical benefit that testing for the Huntington disease mutation provided for choreatic syndromes in general.

Functional characterization of the CHAC gene will contribute to the much-needed understanding of the pathophysiology involved in basal ganglia degeneration and in chorea. Given the similarities of Huntington disease, McLeod syndrome, and CHAC, at the clinical and the neuropathological levels, it appears quite likely that these three choreatic syndromes share a common final pathogenetic pathway, resulting, for example, from the accumulation of neurotoxic amino acids in striatal neurons (Lipton and Rosenberg 1994). Elucidation of the mechanism may help to design effective therapies for these as yet untreatable disorders.

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