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Localization of Disinhibition-Dementia-Parkinsonism-Amyotrophy Complex to 17q21-22

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Summary

Disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) is defined by familial adult-onset behavioral disturbance, followed by frontal lobe dementia, parkinsonism, and amyotrophy in variable proportions. A genetic etiology of DDPAC was suspected because of the familial clustering in family Mo, despite their wide geographic distribution. We have mapped the DDPAC locus to a 12-cM (sex averaged) region between *D17S800* and *D17S787* on chromosome 17q21-22. The basis for the variability of the clinical findings and pathology in DDPAC is unknown but suggests that the DDPAC locus should be screened as a candidate locus in family studies of conditions with behavioral abnormalities and neurological degeneration.

Introduction

The power of family studies to elucidate the biochemical basis of conditions that are considered sporadic is unpredictable. Conditions that occur sporadically may be clustered in families. For practical reasons, there is a bias toward these families in gene-mapping studies. The positive linkage results found in some families with schizophrenia have not been shown to be relevant to schizophrenia as it occurs in the general population and are considered to be spurious by some (Kennedy et al. 1988; Sherrington et al. 1988; Weeks et al. 1990*a*). In contrast, the identification of the *DYT1* locus in a large non-Ashkenazi Jewish family with idiopathic torsion dystonia (ITD) has clarified the etiology of ITD among most Ashkenazi Jewish patients (Ozelius et al. 1989, 1992). In familial forms of amyotrophic lateral sclerosis (ALS) and Alzheimer disease, linkage analyses have led to the identification of mutations in specific genes involved in their etiology (Goate et al. 1989, 1991; Siddique et al. 1989; Chartier-Harlin et al. 1991; Murrell et al. 1991; Mullan et al. 1992*a;* Corder et al. 1993; Rosen et al. 1993). It is in this context that we began studying the family Mo, whose members are affected with an intriguing spectrum of behavioral and neurodegenerative problems.

When viewed in isolation, the clinical features in individual Mo family members suggested a variety of unrelated clinical diagnoses (fig. 1). Two Mo family members who died prior to the initiation of this study were institutionalized and carried the functional diagnosis of schizophrenia. Five family members had depression or alcoholism as young adults. A clinical diagnosis of amyotrophy was made in another. In retrospect, when all the cases were viewed as a group, there was a common theme. Disinhibition occurred early in the disease course. This was manifested by alcoholism, hyperreligiosity, inappropriate sexual behavior, excessive eating, and shoplifting. Curiously, many exhibited a pattern of hording and craving of sweets. Eventually, all affected family members developed frontal lobe dementia (affecting behavior and judgment more than language and praxis) and parkinsonism. The premise that affected Mo family members were affected by the same disease was supported by pathologic, and now genetic, analysis. We named this condition "disinhibition-dementia-parkinsonism-amyotrophy complex" (DDPAC) (Lynch et al., in press).

Neuropathological examination of six affected family members revealed fronto-temporal atrophy and neuronal loss with superficial (layer 2) spongiform change and neuronal loss with gliosis in the substantia nigra and amygdala (authors' unpublished data). Anterior horn cell loss was found in both of the spinal cords examined. One of these was from a person with signs and symptoms of amyotrophy. The coexistence of frontal lobe dementia, parkinsonism, and amyotrophy, as well as the pathological involvement of the substantia nigra, amygdala, and frontal and temporal lobes, with no Lewy bodies, amyloid plaques, or neurofibrillary tangles, distinguishes DDPAC from Alzheimer disease, Parkinson disease, and ALS.

To verify that this clinically heterogenous disorder is due to a single genetic locus, we screened simple-sequence-repeat markers for linkage to DDPAC. We began this study with the hope that conclusions reached would be generally applicable. A locus capable of causing a wide spectrum of signs and symptoms may be involved in the etiology of more common conditions. There are many

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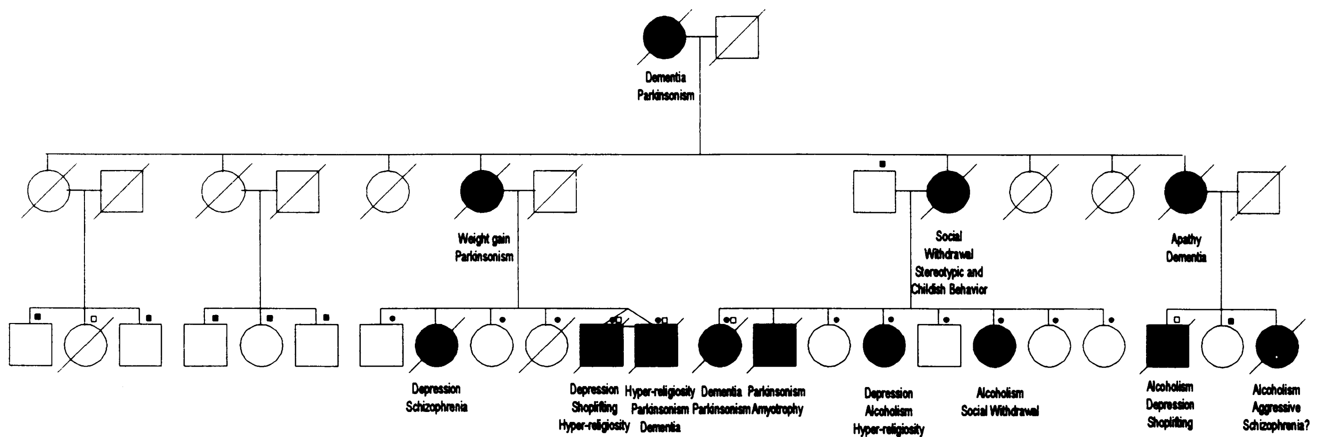

Figure 1 First three generations of family Mo. To protect patient confidentiality, some of the sexes and birth orders have been changed. A blackened circle (●) over the right-hand corner of individual symbols indicates individuals who were used in the initial marker screen; a blackened square (■) indicates individuals who were genotyped for markers in candidate regions; and an unblackened square (□) indicates individuals who had progeny genotyped who are not shown. All affected individuals (blackened symbols) eventually developed some parkinsonism and dementia. Below each affected individual are their prominent early clinical features.

pathological and clinical studies of both sporadic and familial cases of neurodegenerative disease that may be etiologically related to DDPAC (Caidas et al. 1966; Boudouresques et al. 1967; Bonduelle et al. 1968; Hughes et al. 1973; Bonduelle 1975; Shiraki and Yase 1975; Burnstein 1981; Cummings and Duchen 1981; Hudson 1981; Mata et al. 1983; Horoupian et al. 1984; Schmitt et al. 1984; Mitsuyama et al. 1985; Brun 1987; Morita et al. 1987; Gilbert et al. 1988; Rosenberg et al. 1989). Notably, each of these reports gave different names to these overlapping syndromes. The identification of a locus for DDPAC allows the testing of the hypothesis that these conditions are etiologically related.

Methodology

Pedigrees and Diagnosis

After informed consent was obtained, neurological examination and phlebotomy were performed on Mo family members (fig. 1). Other family members, who were unavailable for examination, were interviewed by telephone. For a final determination of "definite DDPAC," an affected member had to have at least two of the following: (1) personality change (aggression; change in sexual habits; alcohol abuse; hyperreligiosity; disinhibited "childish" egocentric behavior; withdrawn apathetic and stereotyped behavior; emotional blunting; or impaired judgment, including shoplifting, irritability, callousness, or excessive eating); (2) profound memory loss with relative preservation of language; (3) parkinsonism progressing to akinetic mutism; or (4) clinical or pathological evidence of motor-neuron disease. The diagnosis was deferred in individuals who met only one of the criteria and were designated as "unknown" for linkage analysis. All of the affected individuals were easily identified by untrained examiners.

Linkage Analysis Model

The DDPAC trait appears to be transmitted in an autosomal dominant manner (fig. 1). Since all affected individuals were definitely affected by age 50 years and since 11 of 22 (2 at-risk individuals in fig. 1 died prematurely) children of affected parents were affected, we estimated the penetrance of gene carriers to be 95% for individuals >50 years of age, 75% for individuals 40–50 years of age, and 10% for individuals <40 years of age. Because the phenotype is very unusual but may be variable, we estimated that the phenocopy rate was 0.1% for individuals >50 years of age and 0.01% for individuals <50 years of age. The model used for linkage calculations was determined in advance and has not been modified. We assumed a disease allele frequency of .00001.

Marker Selection and Genotyping

DNA was isolated from lymphoblastoid cell lines or whole blood. Simple-sequence-repeat polymorphisms (SSRPs) were determined by the length of amplified PCR products on a 6% acrylamide gel (Lasser et al. 1993). Oligonucleotide primer pairs were synthesized, using a Cyclone DNA synthesizer (Milligen-Biosearch), and were purified by reverse-phase column chromatography. Immediately prior to PCR, one primer from each pair was end-labeled with γ^{32}-ATP, using polynucleotide kinase. To maximize coverage of the genome, 300 markers were selected. For the initial screen, genotypes were determined with the knowledge of phenotypes. When the candidate region was identified, all relevant markers were retyped, and genotypes were determined blind to phenotype.

Linkage Analyses

Two-point lod scores were calculated for all markers, by assuming equal allele frequencies and with allele frequencies estimated by their occurrence in the family by using Ilink (from LINKAGE programs, version 5.03) (Lathrop and Lalouel 1988). The identical twins were coded as one person with two spouses. We constructed a multipoint map of the region containing DDPAC locus by using MultiMap/CRI-MAP (Green 1992) and the three-generation versions of LINKAGE. Multipoint analysis was performed with "fastlinkage," an adaptation of LINKAGE on a SPARC 10-40 with 1 gigabyte of swap space (Cottingham et al. 1993).

Results

Clinical Characteristics

The detailed clinical characteristics of family Mo have been described elsewhere (Lynch et al., in press). In summary, we identified 6 affected individuals among the 38 family members examined. We interviewed 10 other unaffected family members and obtained information about 7 other affected individuals. Prior diagnoses among affected individuals included dementia, Parkinson disease, schizophrenia, and amyotrophy (fig. 1). A long history of insidious personality and behavioral change were the initial symptoms in all 12 (there was insufficient history available on 1). Although family members estimated the mean age at onset to be 45 years, all were aware of earlier behavioral changes in the affected members. Preliminary work suggests that neuropsychological testing can identify carriers in this early period. The progression of the disease appeared to follow a regular course. All affected individuals eventually had features of dementia (memory impairment with anomia) and parkinsonism (bradykinesia and postural instability). One also had prominent muscle wasting and weakness (a feature of amyotrophy). In contrast to the dementia of Alzheimer disease, there was relative preservation of language and praxis. In the terminal stages, the patients were akinetic and mute. The mean duration from recognized onset to death was 13 years.

Linkage Analysis

Initially, 12 individuals (fig. 1) were selected for screening of markers for linkage to the DDPAC locus. These individuals were selected on the basis of both our confidence in the diagnosis and simulations made using SLINK (Weeks et al. 1990*b*). The average maximum lod score for a linked simulated marker (five equally frequent alleles, simulated with a true θ of .05; 100 replicates) was >1.0. The maximum observed simulation lod score was 2.56. A simulated unlinked marker gave an average maximum lod score of 0.08 and was >1 <1% of the time. We planned to genotype an additional 21 unaffected individuals (fig. 1), for any marker with a maximum lod score >0.8. All of the additional individuals are young, but they contributed information about the genotypes of individuals who were unavailable for analysis. With simulated genotypes available for 33 individuals, the average maximum lod score for a linked simulated marker (five equally frequent alleles,

Table 1

DDPAC Locus Two-Point Lod Scores for Family Mo

Locus	Primer-Pair Name	No. of Alleles Observed	Equal Allele Frequencies		Estimated Allele Frequencies	
			Lod_{Max}	cM[a]	Lod_{Max}	cM[a]
D17S783	026vh7	8	.00	50.0	.00	50.0
D17S798	179xg11	6	.00	50.0	.00	50.0
D17S800	200zf4	5	1.75	9.2	1.83	7.7
D17S791	155xd12	12	3.96	.0	4.06	.0
HOX2B	Pyg-1,8	5	2.59	.0	3.03	.0
GP3A	GPIIIa-1,2	4	3.18	.0	3.28	.0
D17S806	234td2	8	4.18	.0	4.17	.0
D17S787	095tc5	5	1.81	.0	2.10	.0
D17S788	095zd11	4	2.26	.0	2.50	.0
D17S790	151xa11	8	2.88	.0	2.74	.0
D17S809	248tb9	6	2.13	.0	2.33	.0
D17S808	238yf8	4	.94	20.0	.90	21.6
D17S792	158xc3	4	.93	20.0	.93	20.5
D17S794	168xd12	4	.92	18.4	1.15	15.2
D17S789	107yb8	7	.00	17.3	.02	18.6
D17S807	234xc9	9	.95	19.4	1.01	17.3

[a] Sex-averaged Kosombi map units F/M ratio 5.4.

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simulated with a true θ of .00; 100 replicates) was 2.14. The maximum observed simulation lod score was 4.17.

We genotyped 12 members of the family with 300 markers and calculated two-point lod scores. Negligible amounts of the genome were excluded using a lod-score threshold of −2. The cumulative region with a lod score <−1 was 951 cM. The twin pair had identical genotypes for all markers tested. Only two markers had a calculated maximum lod score >1. Markers for loci *GP3A* and *HOX2B* had calculated maximum lod scores of 2.4 and 2.61, with no obligate recombinants. In the extended family, the markers have calculated lod scores of 2.6 and 3.2 (when alleles were assumed to be equally frequent; table 1). *GP3A* and *HOX2B* have both been localized to 17q21-22 (Deinard et al. 1992; Stoffel and Bell 1992). On the basis of the genotypes of these markers for the CEPH reference pedigrees (Dausset et al. 1990), we estimated that *GP3A* and *HOX2B* are separated by ~0.7 cM (sex averaged). We concluded that these markers are probably linked to the DDPAC locus.

To confirm and precisely determine the probable location of the DDPAC locus, we constructed a linkage map for the region. In the CEPH version 6 database, we identified 14 microsatellite polymorphisms that are linked to *GP3A* and *HOX2B* (Weissenbach et al. 1992). Because there are data for only eight reference pedigrees for the majority of these, we supplemented the CEPH data by typing additional CEPH families for microsatellites at loci *D17S790, D17S791,* and *D17S800.* These data and CEPH database data were used to construct a linkage map (fig. 2). The estimated female:male recombination ratio for the region is 5.4.

The maximum multipoint lod score for the DDPAC locus is 4.2, in the region containing *D17S791, GP3A, D19S806,* and *HOX2B* (fig. 2 and table 1). The support interval (region where lod ⩾ $\text{lod}_{\text{Max}}-1$) is a 10.9-cM (sex averaged) region between *D17S800* and *D17S787.* Because we do not know the true age-adjusted penetrance, caution must be taken in identifying the most probable location of the DDPAC locus. All affected individuals have inherited the same haplotype for markers between *D17S798* and *D17S808.* The reduction of the multipoint lod at *D17S800* and *D17S787* is due to two normal individuals (>50 years of age) who have inherited different portions of the haplotype associated with DDPAC. The calculated multipoint lod score for the region, when all clinically normal individuals are treated as diagnosis unknown, is ~1.8.

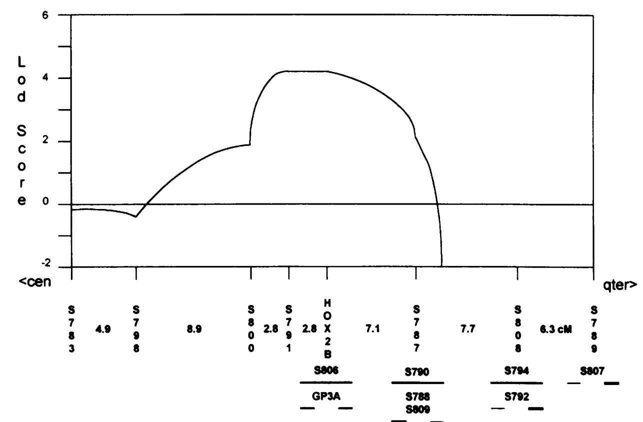

Figure 2 Composite four-point lod-score analysis for the DDPAC locus in family Mo. Four-point lod-score calculations were performed using permutations of markers from the linkage map at the bottom of the figure. The sex-averaged Kosambi map units are indicated between each of the markers on the map. Likelihood calculations were made assuming a constant sex-specific recombination fraction. Based on CEPH reference pedigree data for the region, the estimated sex-specific recombination fraction is 5.4. Markers that could not be placed in specific intervals with >1,000:1 odds are indicated below the linkage map. Solid lines indicate markers that segregate with markers on the map. Broken lines indicate markers that map to an interval on either side of a marker. Thicker lines indicate the most probable interval for the position of markers.

Discussion

This is the first genetic localization of a frontal lobe dementia-disinhibition syndrome and of a dementia-parkinsonism-amyotrophy complex. Linkage analysis supports the concept that DDPAC is a heritable trait, and not a simultaneous occurrence of more common neurodegenerative diseases. Further work is needed to determine the relationship of DDPAC to other syndromes and whether these results can be replicated in other families.

In studies of other behavioral disorders, initial positive linkage results were found to be spurious when more informative markers became available for the same families (Baron et al. 1987, 1993; Egeland et al. 1987; Law et al. 1992). In DDPAC, it is unlikely that lack of informative markers has contributed to a false-positive result. Eight tightly linked highly polymorphic microsatellites show linkage without recombination (table 1). These results still need to be interpreted cautiously, because more than half of the maximum lod score comes from assigning a normal status to at-risk individuals. Although very conservative criteria were used to determine affection status, it is more difficult to define criteria for normal status. A false-positive linkage result could be caused by errors in the estimate of the penetrance values. Because the mode-of-inheritance model was determined prior to any linkage analysis and has not changed, it is unlikely that this linkage result is due to an unintentional bias. Identification of either distantly related affected relatives in family Mo or a second family with DDPAC will be necessary to corroborate linkage of DDPAC to 17q21-22.

The DDPAC locus is genetically distinct from other known loci for dementing illnesses (Hsiao and Prusiner

1990; Mullan et al. 1992*b;* St George-Hyslop et al. 1992; Van Broeckhoven et al. 1992; Corder et al. 1993), inherited parkinsonism (Wilhelmsen et al. 1991; Nygaard et al. 1993), and motor-neuron disease (Deng et al. 1993; Rosen et al. 1993). The dementia-parkinsonism-ALS complex of Guam is clinically similar but differs pathologically from DDPAC (Rodgers-Johnson et al. 1986). Other sporadic and familial forms of dementia-parkinsonism-ALS have been described with varying pathology (Caidas et al. 1966; Boudouresques et al. 1967; Bonduelle et al. 1968; Hughes et al. 1973; Bonduelle 1975; Shiraki and Yase 1975; Burnstein 1981; Cummings and Duchen 1981; Hudson 1981; Mata et al. 1983; Horoupian et al. 1984; Schmitt et al. 1984; Mitsuyama et al. 1985; Morita et al. 1987; Gilbert et al. 1988; Rosenberg et al. 1989). Some of these overlap the heterogeneous clinical and pathological findings in family Mo (Haberlandt 1964; Caidas et al. 1966; Boudouresques et al. 1967; Bonduelle et al. 1968; Bonduelle 1975; Horoupian et al. 1984; Brun 1987; Gilbert et al. 1988; Yoshida et al. 1992). Indeed, there may be a common pathway leading to neurodegeneration (Appel 1981; Stewart and Appel 1988). The identification of a disease locus responsible for DDPAC will allow testing of the hypothesis that these clinically related conditions are due to mutations in the same locus. The DDPAC locus may be important in behavioral and psychiatric disorders, in view of the initial alcoholism and disinhibition noted in some of the affected members. It is possible that mutations in the DDPAC locus exist that cause behavioral changes without neurodegenerative progression.

In the genome database, >100 genes and a folate-sensitive fragile site (Kormann-Bortolotto et al. 1992) have been localized to the 17q21-23 region. Very few of these genes would be predicted to have any relationship to DDPAC. Two are of particular interest as candidate genes: microtubule-associated protein τ(tau) and low-affinity nerve growth-factor receptor ($p75^{NGFR}$). A marker for the homeobox B gene cluster was one of the markers that supplied the initial evidence of linkage for DDPAC. These genes are expressed in the nervous system and have a clear role in embryologic development (Acampora et al. 1991). It is unknown whether they could be responsible for an adult-onset disorder.

τ Protein is the subject of intense research because of its role in the formation of neurofibrillary tangles in Alzheimer disease (Kosik 1990). τ Protein is the product of a single gene from 17q21 (proximal to *GP3A* and distal to markers at 17q11.2) (Abel et al. 1993) that is expressed predominantly in neurons. The τ transcript undergoes a complex series of alternative splicing and posttranslational modifications. Some of these modifications lead to the formation of the paired helical filament, which is a major component of neurofibrillary tangles. The physiological role of τ appears to be in the maintenance of axonal cytoskeletal structure. Although τ is suspected to participate in neuronal damage, no change in the primary coding sequence has been associated with a pathological state. Although we do not see neurofibrillary tangles in DDPAC, it is plausible that a mutation in τ could have diffuse effects on CNS function and morphology.

The gene for $p75^{NGFR}$ has been physically linked to the homeo box B gene cluster (Bentley et al. 1989) (the DDPAC locus is linked to the microsatellite marker for *HOX2B*) and is expressed in many cell types (Raffioni et al. 1993). $p75^{NGFR}$ binds several related nerve growth factors (NGF, brain-derived neurotrophic factor, neurotrophin 3, and neurotrophin 4/5), but its physiological role is controversial. $p75^{NGFR}$-deficient mice are viable but have abnormal sensory neurons (Davies et al. 1993). This suggests that $p75^{NGFR}$ has a role in at least some neurons. Rabizadeh et al. (1993) demonstrated in neuronal cultures that expression of $p75^{NGFR}$ leads to apoptosis, unless NGF is present. It is plausible that a mutation in $p75^{NGFR}$ could lead to a neurodegenerative process.

Additional families with DDPAC will be required if we are to further resolve the location of the DDPAC locus, address issues of locus heterogeneity, and make the transition to positional cloning. Ultimately, a knowledge of the normal function of the DDPAC locus will contribute to our understanding of the pathogenesis and pathophysiology of neurodegenerative diseases.

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