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Linkage Studies in Alcohol-Responsive Myoclonic Dystonia

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Summary: A large German family with “myoclonic dystonia with lightning jerks responsive to alcohol” was identified. Eleven affected pedigree members and six obligate gene carriers from five generations were identified. A description of one branch of this pedigree was published in 1964. Our examination 30 years after the initial report confirms the clinical syndrome of a nonprogressive movement disorder characterized by myoclonic jerks affecting the proximal muscles and the muscles of the trunk, accompanied by mild dystonic features in some affected family members. Segregation analysis favors autosomal dominant inheritance with high, but incomplete, penetrance in males and much lower penetrance in females. Linkage analysis was performed using simple sequence repeat polymorphisms (CA repeats) closely associated with or spanning the chromosomal regions contain-

ing 15 candidate genes: the gene for early-onset generalized torsion dystonia, *DYT1* (chromosome 9q34); the genes for subunits $\alpha 2$, $\beta 1$, and $\gamma 1$ (chromosome 4p12–4q13); for $\alpha 1$, $\alpha 6$, $\beta 2$, and $\gamma 2$ (chromosome 5q31.1–5q31.3); for $\alpha 4$, $\alpha 5$, $\beta 3$, and $\gamma 3$ (chromosome 15q11–15q13); for $\rho 1$ and $\rho 2$ (chromosome 6q14–6q21) of the gamma-aminobutyric acid A receptor; and for the alpha subunit of the glycine receptor (chromosome 5q31). By a combination of pairwise and multipoint linkage analysis, it could be excluded that any of these candidate gene-bearing chromosomal regions contain the disease gene in this family. We also excluded major portions of three chromosomal regions syntenic with mouse chromosome 3, which carries the murine beta subunit of the glycine receptor. **Key Words:** Linkage analysis—Myoclonic dystonia—Candidate gene.

Abnormal movements in dystonic syndromes range from slow, sustained dystonic postures to fast, repetitive, rhythmical or arrhythmical jerks (1). Based on clinical features, several distinct hereditary dystonic syndromes, such as Dopa-responsive dystonia, paroxysmal dystonia, and myoclonic dystonia, have been identified (2,3). Although myoclonic movements may also occur in the classic form of idiopathic torsion dystonia (ITD), a subtype of autosomal dominantly inherited myo-

clonic dystonia has been described that is characterized by a predominance of very brief (lightning-like) myoclonic jerks, a relatively benign course, and temporary relief after the ingestion of alcohol. This form has been termed “hereditary dystonia with lightning jerks, responsive to alcohol” (4–6) and may be identical to other forms of hereditary myoclonus (7–9).

The gene for early-onset generalized ITD has been mapped to the *DYT1* region on the long arm of chromosome 9 in Ashkenazi Jewish and non-Jewish families (10–12). Genes for some variants of ITD have also been mapped (X-linked dystonia-parkinsonism [13]) or identified (Dopa-responsive dystonia [14,15]).

In recent years, many disease genes have been mapped without prior knowledge of the encoded gene product by a random genomic search using polymorphic DNA markers. An alternative ap-

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proach is to target the search at specific candidate gene loci, i.e., chromosomal regions bearing genes that, based on our knowledge of the pathophysiology and pathogenesis of the disease, may play a role in the etiology of the disorder under investigation. This candidate gene approach has been used successfully in the identification of several genes for neurologic disorders (16,17).

The molecular and cellular basis for dystonia and myoclonus is unknown, but hyperactive neuronal circuits within the basal ganglia and/or the brain stem can be hypothesized to play a role. Therefore, genes encoding receptor subunits of inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA) and glycine, may be considered to be candidate genes for myoclonic dystonia. This suggestion is supported by the observation that benzodiazepines, which enhance GABAergic function, have been found to be beneficial in myoclonic syndromes. Furthermore, myoclonus in this condition is typically sensitive to alcohol. In low concentrations, ethanol is thought to exert some of its effects by acting on the GABA receptor/chloride channel complex (18).

Hyperreflexia (hereditary startle syndrome), another hyperkinetic movement disorder, has been shown to be caused by a mutation in the alpha subunit of the glycine receptor (19), and mutations in both the alpha and beta subunits of this receptor cause neurologic disorders in mice (20,21). It is con-

ceivable that myoclonic dystonia is an allelic variant of one of these disorders. Last, *DYT1*, the gene causing generalized torsion dystonia, may be implicated in myoclonic dystonia, since the two disorders share many clinical features and the phenotype associated with mutations in the *DYT1* gene is highly variable.

Here we report clinical and molecular genetic studies on a large German family with myoclonic dystonia. We have performed linkage analysis using highly polymorphic markers from the genomic regions containing *DYT1*, the $\alpha 1$ subunit of the glycine receptor, as well as 13 subunits of the GABA A receptor. Based on pairwise and multipoint linkage analysis, all of these genes could be excluded as candidate genes in our family.

METHODS

Neurologic examination was carried out by three of the authors (T.G., R.P.S., G.D.) in nine affected and 25 unaffected family members. Only those affected were videotaped, and the diagnosis was confirmed by an independent reviewer. Medical records were reviewed on one additional affected person. One deceased individual (III:3 in Fig. 1) was confirmed to have been clinically affected by family history. Blood was obtained by venipuncture from all 10 living affected and 25 unaffected family members after informed consent. DNA was isolated

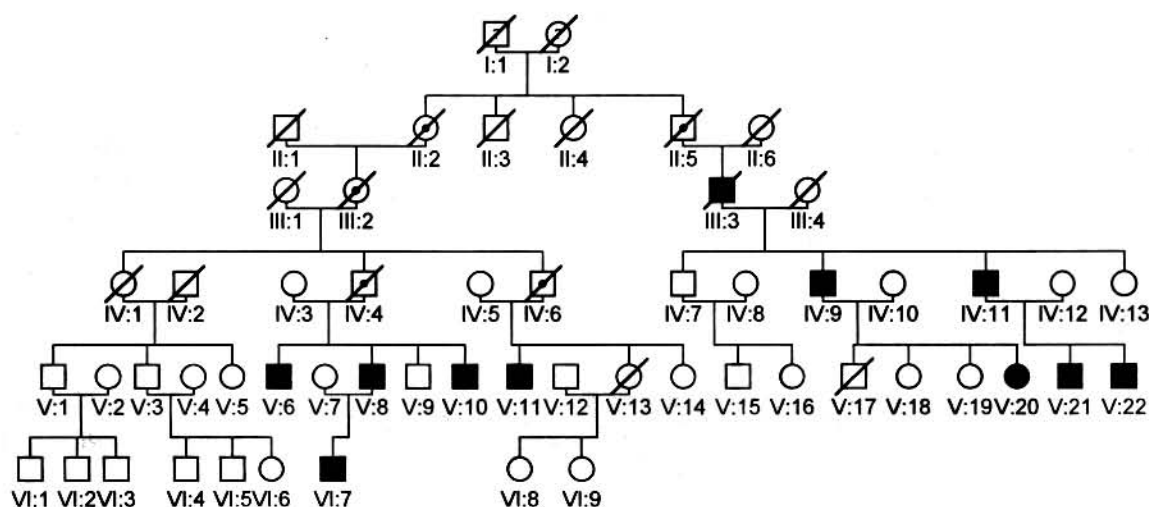


FIG. 1. Portion of a family with myoclonic dystonia with lightning jerks responsive to alcohol is shown. Filled symbols indicate affected individuals, and open symbols indicate unaffected pedigree members. Dots inside symbols show presumed obligate gene carriers; slashed symbols represent deceased individuals.

from peripheral blood leukocytes by standard methods (22).

The allele status for CA repeats was determined by amplifying the repeat-containing region using the polymerase chain reaction (23). Reactions were carried out in a volume of 10 μ l containing 0.2 mM each of dATP, dCTP, dTTP, and dGTP; 0.05 μ l *Taq* polymerase (Boehringer Mannheim); and $\times 1$ reaction buffer containing 2–4 mM magnesium chloride. The reverse primer was end-labeled using 32 P ATP (3,000 mCi/mmol; Amersham) and T4 polynucleotide kinase; 32 cycles of 94°C for 1 min, 52–59°C for 1 min, and 72°C for 1.5 min were routinely used, followed by a final extension for 10 min at 72°C. Amplified fragments were separated by acrylamide gel electrophoresis. Gels were dried and exposed to Kodak XAR film for 4 to 24 h.

GABA receptor subunits are tightly clustered on chromosomes 4, 5, 6, and 15 (24). The alpha subunit of the glycine receptor also maps to chromosome 5q31 (20). Markers spanning the regions that bear these candidate genes (Table 1) were chosen from the Genethon linkage map (for oligonucleotide sequences, see Gyapay et al. [25]). Map positions and primer sequences for the CA repeat polymorphisms spanning the *DYT1* locus (12) and for intragenic polymorphisms within the genes for the $\alpha 1$, $\alpha 5$, $\beta 1$, and $\beta 3$ subunits of the GABA A receptor have also been published (26–28).

The beta subunit of the glycine receptor has not been mapped in humans. The murine gene maps to mouse chromosome 3 (29). We therefore also stud-

ied chromosomal regions syntenic with this mouse locus. Seventeen CA repeat polymorphisms spanning a total of 174 centiMorgans (cM) of the respective portions of chromosomes 1 (1p21–1q31), 3 (3q21–3q28), and 4 (4q24–4q28) were also analyzed by pairwise and multipoint linkage analysis.

The following CA repeat polymorphisms were investigated (Table 1):

- Chromosome 1p12–1q31: 1ptel-D1S248-(13 cM)-D1S252-(19 cM)-D1S305-(15 cM)-D1S194-(4 cM)-D1S196-(19 cM)-D1S191-(2 cM)-D1S238-1qtel

- Chromosome 3q21–3q28: 3cen-D3S1303-(16 cM)-D3S1309-(14 cM)-D3S1279-(17 cM)-D3S1282-(18 cM)-D3S1262-(12 cM)-D3S1314-3qtel

- Chromosome 4p13–4q28, bearing the gene cluster for subunits $\alpha 2$, $\beta 1$, and $\gamma 1$ of the GABA A receptor: 4ptel D4S418-(13 cM)-D4S405-(9 cM)-D4S428-(10 cM)-D4S398-(23 cM)-D4S395-(8 cM)-D4S414-(20 cM)-D4S406-(17 cM)-D4S422-(19 cM)-D4S424-(12 cM)-D4S413-qtel. A tetranucleotide repeat polymorphism within *GABRB1* was also investigated.

- Chromosome 5q31.1–5q31.3, bearing the gene cluster for subunits $\alpha 1$, $\alpha 6$, $\beta 2$, and $\gamma 2$ of the GABA A receptor and the alpha subunit of the glycine receptor: 5cen-D5S393-(15 cM)-D5S410-(19 cM)-D5S400-5qtel. An intragenic CA repeat within *GABRA1* was also analyzed.

- Chromosome 6q13–6q21, bearing the genes for the subunits $\rho 1$ and $\rho 2$ of the GABA A receptor: 6qcen-D6S286-(19 cM)-D6S283-(23 cM)-D6S262-6qtel

- Chromosome 9q34, bearing the gene for early-onset generalized dystonia (*DYT1*): 9cen-D9S63-DYT1-(1.5 cM)-ASS-9qtel

- Chromosome 15q11.2–15q12, bearing the gene cluster for the $\alpha 5$, $\beta 3$, and $\gamma 3$ subunits (probably also containing subunit $\alpha 4$) of the GABA A receptor: 15 cen-D15S128-(26 cM)-D15S118-15qtel. Intragenic CA repeats within *GABRA5* and *GABRB3* were placed between *D15S128* and *D15S118* (27,28).

Two-point linkage analysis was performed using the program MLINK from the LINKAGE program package in its FASTMAP implementation (30,31). Multipoint lod scores were approximated using FASTMAP (32). Only individuals who were rated as being definitely affected or unaffected by two independent investigators and who were >25 years old, and thus well beyond the average age of onset in this pedigree, were included in the analysis. Au-

TABLE 1. Candidate genes for myoclonic dystonia and their chromosomal locations

| Gene | Location |
|--------------------|--------------------|
| <i>DYT1</i> | 9q34 |
| GABA A receptor | |
| $\alpha 1$ subunit | 5q31–5q35 |
| $\alpha 2$ subunit | 4p13–4q11 |
| $\alpha 3$ subunit | Xq28 |
| $\alpha 4$ subunit | 15q11.2–15q12 |
| $\alpha 5$ subunit | 15q11.2–15q12 |
| $\alpha 6$ subunit | 5q31–5q35 |
| $\beta 1$ subunit | 4q12 |
| $\beta 2$ subunit | 5q31–5q35 |
| $\beta 3$ subunit | 15q11.2 |
| $\gamma 1$ subunit | 4p12–4q13 |
| $\gamma 2$ subunit | 5q31 |
| $\gamma 3$ subunit | 15q11.2–15q12 |
| δ subunit | 1p |
| $\rho 1$ subunit | 6q4–6q21 |
| $\rho 2$ subunit | 6q14–6q21 |
| Glycine receptor | |
| $\alpha 1$ subunit | 5q31 |
| β subunit | Mouse chromosome 3 |

tosomal dominant inheritance of a rare gene (frequency of 0.01%) was assumed. Calculations were based on equal recombination rates in males and females. Segregation ratios were calculated as 0.7 in males and 0.0 in females (see Results). Because there was at least one case of nonpenetrance in a male gene carrier (IV:4 in Fig. 1), penetrance was set at 0.9 in males. Because of the low numbers, penetrance in females can only be estimated and was set to 0.3.

RESULTS

Clinical Findings

The ancestors of this German family were traced back to the geographic region of Ostfriesland, in the coastal area of northern Germany. Ten living individuals in three generations have been identified as being clinically affected by personal examination ($n = 9$) or by review of hospital charts ($n = 1$, V:10). One deceased individual (III:3) was clearly affected, as confirmed by family history. In addition, six deceased family members (I:1 or I:2, II:2, II:5, III:2, IV:4, and IV:6 in Fig. 1) have to be considered carriers of the disease gene, if autosomal dominant inheritance is assumed. Individual IV:4, who is an obligate gene carrier based on the pedigree structure, did not ever exhibit any abnormal movements as far as living family members could recall. He died in 1976 at 75 years of age. It is likely that he represents true nonpenetrance. No information on clinical status was available on the other deceased obligate gene carriers.

Transmission of the disease from parent to child suggests autosomal dominant inheritance. Twenty-four at-risk individuals from seven sibships were identified, for whom sufficient clinical information was available for segregation analysis. Eleven of them were affected clinically, resulting in an overall segregation ratio of 0.41 (95% confidence limit 0.17–0.65) as calculated by the singles method (33). There is, however, a striking predominance of males ($n = 10$) over females ($n = 1$) among those affected, which cannot be explained by the slight predominance of male at-risk individuals (13 of 24) in these sibships.

In fact, the deviation from the expected number in the male to female ratio is statistically significant ($p < 0.002$, Fisher's exact test). The segregation ratio for males is calculated to be only 0.70 (95% confidence interval 0.39–1.00), compatible with autosomal dominant inheritance with high penetrance.

Because of the low number of females affected, penetrance cannot be calculated with precision and was set at 0.3 for the purpose of linkage analysis. (Calculated by the singles method, the segregation ratio for females would be 0 with no estimation of a 95% confidence interval possible.) Therefore, variable penetrance, nearly complete in males and much lower in females, is a likely explanation.

The index patient (V:6; Fig. 1) met the diagnostic criteria for "myoclonic dystonia with lightning jerks, responsive to alcohol" set forth by Mahloudji and Pikielny (7). He had bilateral, asymmetric, myoclonic jerks affecting predominantly the upper extremities, with the right side more affected than the left. No dystonic features were noted, and neurologic examination was otherwise unremarkable. The age of onset was 6 years. Electromyography showed spontaneous rhythmical bursts of muscle activity lasting 90–250 ms. Electroencephalography and cranial computed tomography results were normal. Myoclonic jerks improved markedly following ingestion of alcohol.

Action-provoked bilateral, asymmetric, alcohol-responsive myoclonus was present in all other affected relatives (Table 2), except for individual V:11, who had only action-induced torticollis and writer's cramp with some superimposed myoclonic jerks. He was scored as possibly affected and not included in the linkage analysis. The average age of onset of myoclonus was 8.7 years, ranging from 4 to 12 years. Dystonic features, if present, evolved after the onset of myoclonus, were mild, and did not progress significantly over many years.

The index patient (V:6) underwent unilateral (left hemisphere), stereotactic surgery in 1972, resulting in improvement of right-sided myoclonus. On ex-

TABLE 2. Clinical characteristics in those affected with myoclonic dystonia who are alive

| Individual | Age at onset | Mc | Tc | Wc | Remarks |
|------------|--------------|-----|-----|----|--|
| III:3 | ? | + | | | By family history |
| IV:9 | ? | + | + | + | |
| IV:11 | ? | + | | | |
| V:6 | 10 | + | | | Left stereotactic thalamotomy |
| V:8 | 12 | + | | | |
| V:10 | 9 | + | | | Bilateral stereotactic thalamotomy |
| V:11 | ? | (+) | + | + | Not considered to suffer from "family condition" |
| V:20 | 4 | + | (+) | + | |
| V:21 | 9 | + | | | |
| V:22 | 11 | + | + | + | |
| VI:7 | 6 | + | | | |

Mc, myoclonus; Tc, torticollis; Wc, writer's cramp.

amination in 1994, action-induced myoclonus was present on the left side, and mild, functionally irrelevant hemiparesis was noted on the right. Another individual (V:10) underwent bilateral stereotactic surgery, which relieved myoclonus but resulted in marked and persistent dysarthria.

In order to relieve myoclonic movements, most affected family members regularly consume moderate to large amounts of alcohol, which has resulted in several charges of drunk driving. However, except for one individual, all those affected remained employed and reasonably integrated socially, possibly reflecting the tightly knit familial support in this rural area. The clinical characteristics of the affected family members are summarized in Table 2.

Molecular Analysis

Thirty of 34 CA repeat polymorphisms analyzed were sufficiently informative in our family to pro-

vide exclusion (lod scores ≤ 2) of the marker locus and a region between 1 and 10 cM on either side (see Table 3 for polymorphisms on chromosomes 4, 5, 6, 9, and 15). Using published map information, multipoint linkage analysis allowed us to exclude large portions of chromosomes 4, 5, 6, and 15, which bear the genes for 13 subunits of the GABA A receptor (Table 1, Fig. 2). Likewise, the region bearing the *DYT1* locus on chromosome 9q34, which is flanked by marker loci *D9S63* and *ASSGT* (12), could be excluded by multipoint analysis (Table 3, multipoint data not shown). Intragenic CA repeats within the genes for the $\alpha 1$, $\alpha 5$, $\beta 1$, and $\beta 3$ subunits of the GABA A receptor also excluded the respective genes (Table 3). The gene for the alpha subunit of the glycine receptor, which maps to chromosome 5q31, is also excluded by multipoint linkage analysis (Fig. 2B).

Seventeen CA repeat polymorphisms, spanning a total of 174 cM on chromosomes 1, 3, and 4, were

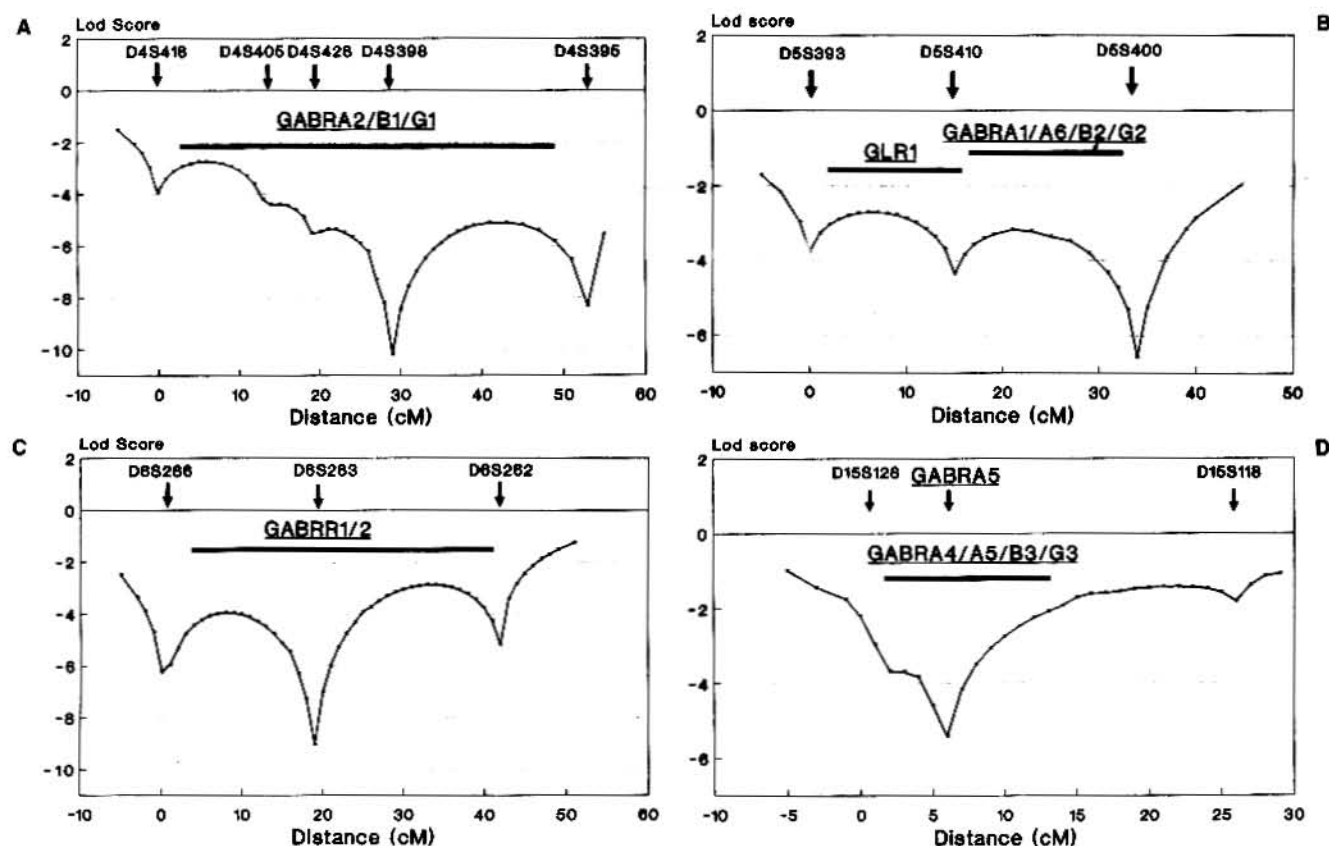


FIG. 2. Results of multipoint analysis of polymorphic markers spanning the chromosomal regions containing candidate genes for myoclonic dystonia. A: Subunits $\alpha 2$, $\beta 1$, and $\gamma 1$ of the GABA A receptor on chromosome 4p12-4q13. B: Subunits $\alpha 1$, $\alpha 6$, $\beta 2$, and $\gamma 2$ of the GABA A receptor and the alpha subunit of the glycine receptor on chromosome 5q31.1-5q31.3. C: Subunits $\rho 1$ and $\rho 2$ of the GABA A receptor on chromosome 6. D: Subunits $\alpha 4$, $\alpha 5$, $\beta 3$, and $\gamma 3$ of the GABA A receptor on chromosome 15. The most likely locations of the candidate genes are symbolized by horizontal bars. Genetic distances between markers are taken from published maps and given in centiMorgans (cM). Marker names are given at the top of the figure.

TABLE 3. Two-point lod scores obtained with markers on chromosome 4, 5, 6, 9, and 15

| Locus | Lod scores at Theta values of | | | | | | |
|---------|-------------------------------|-------|-------|-------|-------|-------|-------|
| | 0.0 | 0.01 | 0.05 | 0.1 | 0.2 | 0.3 | 0.4 |
| D4S18 | -7.72 | -2.70 | -1.22 | -0.60 | -0.1 | 0.06 | 0.08 |
| D4S405 | -7.95 | -2.73 | -1.20 | -0.55 | -0.06 | 0.04 | 0.01 |
| GABRB1 | -2.10 | -1.84 | -0.85 | -0.41 | -0.11 | -0.05 | -0.04 |
| D4S428 | -3.36 | -3.33 | -2.54 | -1.68 | -0.82 | -0.40 | -0.15 |
| D4S398 | -10.78 | -6.55 | -4.15 | -2.67 | -1.24 | -0.54 | -0.17 |
| D4S395 | -10.77 | -6.26 | -3.90 | -2.48 | -1.15 | -0.50 | -0.16 |
| D4S414 | -6.21 | -3.17 | -1.26 | -0.56 | -0.10 | -0.03 | -0.05 |
| D4S406 | -2.91 | -0.79 | -0.10 | 0.14 | 0.26 | 0.21 | 0.13 |
| D4S424 | -7.91 | -2.17 | -0.89 | -0.41 | -0.03 | 0.07 | 0.05 |
| D4S413 | -10.11 | -2.67 | -0.76 | -0.1 | 0.30 | 0.29 | 0.12 |
| D5S393 | -3.62 | -1.72 | -0.87 | -0.49 | -0.17 | -0.06 | -0.02 |
| D5S410 | -7.57 | -3.19 | -1.60 | -0.91 | -0.33 | -0.11 | -0.03 |
| GABRA1 | -11.58 | -4.49 | -2.32 | -1.41 | -0.61 | -0.25 | -0.07 |
| D5S40 | -6.87 | -4.50 | -2.50 | -1.61 | -0.78 | -0.36 | -0.13 |
| D6S286 | -6.63 | -3.52 | -1.78 | -1.02 | -0.42 | -0.18 | -0.06 |
| D6S283 | -10.72 | -6.83 | -3.53 | -2.15 | -0.94 | -0.40 | -0.13 |
| D6S262 | -11.71 | -4.97 | -2.32 | -1.29 | -0.47 | -0.19 | -0.10 |
| D9S63 | -2.89 | -1.02 | -0.38 | -0.16 | -0.02 | 0.01 | -0.00 |
| ASS | -6.66 | -1.98 | -0.72 | -0.30 | -0.05 | -0.02 | -0.01 |
| D15S128 | -7.38 | -1.91 | -0.57 | -0.09 | 0.20 | 0.21 | 0.11 |
| GABRB3 | -2.18 | -0.45 | 0.16 | 0.33 | 0.35 | 0.23 | 0.09 |
| GABRA5 | -9.80 | -4.25 | -2.90 | -1.18 | -0.41 | -0.12 | -0.03 |
| D15S118 | -3.74 | -1.11 | -0.41 | -0.15 | 0.03 | 0.05 | 0.03 |

also analyzed by pairwise and multipoint linkage analysis. These regions are syntenic to mouse chromosome 3, which bears the murine homolog of the beta subunit of the glycine receptor. Approximately 70% of these chromosomal regions could be excluded as bearing the disease gene in this family (data not shown). Thus, all mapped autosomal subunits of the inhibitory neurotransmitter receptors for GABA and glycine could be excluded as candidate genes for myoclonic dystonia by our study. We were able to exclude a total of ~450 cM of genomic DNA, equivalent to ~15% of the human autosomal genome.

DISCUSSION

The classification of hyperkinetic movement disorders, such as ITD, myoclonic syndromes, and essential tremor, is based on clinical criteria, but the exact relationship of these syndromes is unclear. Frequently, autosomal dominant inheritance is found, but phenotypes may be highly variable. Both myoclonic jerks and postural tremor can be found in patients with torsion dystonia (34,35). On the other hand, dystonic features diagnosed as hereditary essential myoclonus may occur in patients, and a similar disorder has also been designated as benign hereditary chorea (reviewed Quinn et al. [9]). Owing

to this overlapping range of phenotypes, it may often be difficult to classify an individual patient based on clinical features alone.

Recently, Quinn has suggested a nomenclature, subsuming the entities of hereditary essential myoclonus and myoclonic dystonia as "myoclonic dystonia with lightning jerks, responsive to alcohol" (9). The clinical spectrum of abnormal movements observed in our family confirms this clinical entity as an autosomal dominant disease with early onset, exhibiting predominantly proximal, asymmetric myoclonic jerks exquisitely sensitive to alcohol. Dystonic features are mild and present in some, but not all of those affected. Symptoms are socially stigmatizing but do not result in a significant degree of physical disability.

A report concerning a portion of this pedigree (descendants of III:2) was published by Feldmann and Wieser in 1964 (36), allowing a 30-year follow-up in this part of the family. Those affected in these sibships were in their teens and twenties at the time of the first report. Compared with this early description, symptoms have fluctuated slightly over the years, but they generally have not changed significantly. Interestingly, individual V:3 was described as possibly affected in the original publication. Examined at age 29 in 1964, he did not show

any spontaneous myoclonic jerks, but he had myoclonic contractions predominantly affecting the muscles of the trunk in response to acoustic and sensory stimuli. This individual was never aware of any neurologic dysfunction and now, at age 59, is neurologically completely normal, as are his three children aged 21–27. Only the identification of the genetic defect will allow us to determine whether this individual is now a nonmanifesting gene carrier.

The low number of females affected in our family possibly reflects a variable penetrance of the mutation in males and females. This phenomenon has not been observed in other published reports of families with myoclonic dystonia (5,6,8), which may be due either to genetic or allelic heterogeneity. The reverse finding, a higher penetrance in females compared with males, has been reported for Dopa-responsive dystonia (37).

Genetic linkage studies can be helpful in classifying the spectrum of hereditary hyperkinetic movement disorders as well as in delineating the underlying molecular defect. Since many of the components of intercellular electrochemical communication are known and the genes encoding the respective proteins have been mapped within the human genome, it became feasible to investigate these "candidate genes" in large families. In fact, this approach has recently helped to identify the mutations causing several inherited disorders characterized by abnormal neuronal or neuromuscular signal transduction, such as periodic paralyses (38,39), episodic ataxia (40), and the familial startle syndrome (19).

Alcohol-responsive myoclonic dystonia shares some characteristics with these disorders. It is an early-onset disease, characterized by intermittent abnormal movements, which can be influenced by a number of centrally acting drugs, such as benzodiazepines and alcohol. The disease shows little or no progression during life and is not associated with any known degenerative changes. Therefore, by analogy, a mutation in one of the components of central nervous system signal transduction, particularly within the inhibitory circuits of the basal ganglia and/or the brain stem may be suspected to be the underlying defect in this disorder. Increasing evidence suggests that the specificity of neurotransmitter function may be predominantly the result of differential expression of a number of receptor subunits, resulting in a highly diversified profile of receptors on a given population of neurons. An inherited defect in one of the receptor subunits could

therefore cause a very distinct motor disorder because functions mediated by other receptor subtypes would remain intact.

Our study excludes a causative role of mutations of 13 subunits of the GABA A receptor ($\alpha 1$, $\alpha 2$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\beta 1$, $\beta 2$, $\beta 3$, $\gamma 1$, $\gamma 2$, $\gamma 3$, $\rho 1$, and $\rho 2$) and of the $\alpha 1$ subunit of the glycine receptor. The X-chromosomal $\alpha 3$ subunit of the GABA A receptor is excluded by virtue of male-to-male disease transmission in our family. Earlier studies have excluded the chromosomal region bearing the *DYT1* gene in one Swedish pedigree with alcohol-responsive myoclonic dystonia (41). Here we demonstrate the exclusion of the *DYT1* region on chromosome 9q34 in a German family.

Further studies are aimed at the $\beta 1$ subunit of the glycine receptor as another candidate gene for this disease. This subunit has been mapped to chromosome 3 in the mouse. So far, linkage analysis with polymorphisms spanning three syntenic chromosomal regions in humans (chromosomes 1, 3, 4) have been negative. Furthermore, a systematic search of the entire genome is presently under way to identify the underlying genetic defect in this family.

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