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# Chromosomal localization of glutamate receptor genes: Relationship to familial amyotrophic lateral sclerosis and other neurological disorders of mice and humans

PAUL GREGOR[a,b], ROGER H. REEVES[c], ETHYLIN W. JABS[d], XIAODONG YANG[a], WILLIAM DACKOWSKI[e], JULIE M. ROCHELLE[f], ROBERT H. BROWN, JR.[g], JONATHAN L. HAINES[h], BRUCE F. O'HARA[i], GEORGE R. UHL[a,j], AND MICHAEL F. SELDIN[f]

[a]Molecular Neurobiology Section, Addiction Research Center, National Institute on Drug Abuse, National Institutes of Health, P.O. Box 5180, Baltimore, MD 21224; Departments of [c]Physiology, [d]Pediatrics and Medicine, and [j]Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205; [e]Integrated Genetics, Framingham, MA 01701; [f]Departments of Medicine and Microbiology, Duke University, Durham, NC 27710; [g]Day Neuromuscular Research Center and [h]Molecular Neurogenetics Unit, Massachusetts General Hospital, Boston, MA 02129; and [i]Department of Biological Sciences, Stanford University, Stanford, CA 94305

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**ABSTRACT** **Receptors for the major excitatory neurotransmitter glutamate may play key roles in neurodegeneration. The mouse *Glur-5* gene maps to chromosome 16 between *App* and *Sod-1*. The homologous human *GLUR5* gene maps to the corresponding region of human chromosome 21, which contains the locus for familial amyotrophic lateral sclerosis. This location, and other features, render *GLUR5* a possible candidate gene for familial amyotrophic lateral sclerosis. In addition, dosage imbalance of *GLUR5* may have a role in the trisomy 21 (Down syndrome). Further characterization of the murine glutamate receptor family includes mapping of *Glur-1* to the same region as neurological mutants spasmodic, shaker-2, tipsy, and vibrator on chromosome 11; *Glur-2* near spastic on chromosome 3; *Glur-6* near waltzer and Jackson circler on chromosome 10; and *Glur-7* near clasper on chromosome 4.**

L-Glutamate is the major excitatory neurotransmitter of the mammalian central nervous system. Its action is mediated by ionotropic and metabotropic glutamate receptors (GluRs). The ionotropic GluR channels are further classified into *N*-methyl-D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA) receptors (e.g., ref. 1). Glutamate and related excitatory amino acids are also known to be powerful neurotoxins. This phenomenon, often called excitotoxicity, has been well-documented *in vitro* and *in vivo* (for reviews, see refs. 2 and 3). Thus, in addition to the physiological functions of the glutamate neurotransmitter network, a primary involvement in neurodegenerative disorders and epilepsy has long been suspected. The function of NMDA, kainate, and AMPA receptors in mediating this excitotoxicity raises the possibility that mutations in genes encoding GluR subunits could cause mouse and human neurogenetic diseases.

The recent cloning of cDNAs encoding the ionotropic GluRs has revealed a substantial family of related genes (4–16). We have isolated partial or full-length cDNAs encoding several GluR subunits and have undertaken to localize the respective GluR genes on mouse chromosomes. The initial focus of this work was to assess the possibility that these GluR genes could represent sites of mutation in mice with inherited neurological disorders. Here we report the chromosomal localization of eight GluR genes in mice (designated *Glur-1* through *Glur-7* and *Nmdar-1*) and identify several candidates for neurological mutations. The combination of mouse and human mapping localized the human *GLUR5* gene to human chromosome 21, in the same region as the locus for a familial form of amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease; motor neuron disease; ref. 17, k), a common and fatal disease of unknown etiology with no effective treatment (18).

## MATERIALS AND METHODS

**GluR Probes.** GluR cDNA probes, except for GluR3 and NMDAR1, were isolated by PCR (19) with sets of degenerate oligonucleotides based on sequences of the kainate-binding proteins (5, 6) and GluR1 (4). Rat cortex or rat cerebellum cDNAs were used as template in PCRs. Gel-purified DNAs were subcloned into pKSII Bluescript plasmid (Stratagene) and sequenced from both ends with the Sequenase kit (United States Biochemical). The partial cDNA encoding rat GluR1 corresponds to nt 1177–1738 of GluR1 cDNA (4). The rat GluR2 cDNA probe corresponds to nt 918–1353 of GluR-B sequence (7). The plasmid containing rat GluR3 cDNA (8) was digested with *Apa* I and *Sac* I to generate a 0.7-kb DNA probe. The rat GluR4 cDNA fragment corresponds to nt 1394–1641 (7). PCRs and screening of a mouse brain cDNA library (Stratagene) resulted also in isolation of a 3.4-kb GluR5 cDNA (GenBank accession no. X66118), a 3.1-kb GluR6 cDNA (GenBank no. X66117), and a 0.5-kb cDNA that has been identified as the mouse homolog of GluR7 (ref. 13; amino acids 375–507). The probe for mapping GluR5 locus in mouse was a 0.6-kb *Eco*RI–*Xho* I restriction fragment (nt 2706–3383 of mouse GluR5 cDNA); for human mapping, a 2.7-kb *Eco*RI fragment was used (nt 1–2706). The GluR6 probe was a 2.1-kb cDNA that contained a portion of GluR6 coding region from amino acid 253 and included the entire 3′ end of the cDNA. Finally, the mouse *Nmdar-1* locus was mapped with a partial cDNA (ref. 16; nt 1469–1934) that was obtained by PCR and encoded the human *NMDAR1* homolog (G. M. Durand and P.G., unpublished data).

**Mouse Chromosome Localization.** Interspecific backcross mice [(C3H/HeJ-*gld* × *Mus spretus*)$F_1$ × C3H/HeJ-*gld*] (cross 1) were used as described (20). Informative restriction fragment length variants (RFLVs) of clones used as probes in the current study are listed in Table 1. Previous studies have defined the location of the following reference loci used in these studies: *Il-3* (21, 22), *Gas-3* (23), *Mme* (24), *Cd1* (25),

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Abbreviations: ALS, amyotrophic lateral sclerosis; GluR, glutamate receptor; cM, centimorgan; RFLV, restriction fragment length variant; lod, logarithm of odds.

[b]To whom reprint requests should be addressed.

[k]Figlewicz, D. A., McInnis, M. G., Goto, J., Haines, J. L., Warren, A. C., Krizus, A., Brown, R. H., Jr., Khodr, N., Antonarakis, S. E. & Rouleau, G. A., Third International Workshop on Chromosome 21, April 20–21, 1992, Baltimore, p. 19 (abstr.).

Table 1. List of clones used for linkage analysis

| Locus | Clone | Enzyme | C3H/HeJ-*gld* RFLV(s), kb | *M. spretus* size(s), kb |
|---|---|---|---|---|
| *Glur-1* | pPCR550 | *Msp* I | 8.6, 4.6 | 5, 3.6 |
| *Glur-2* | pPCR30-7 | *Eco*RI | 6, 1.9 | 6.4, 1.5 |
| *Glur-3* | Rat cDNA | *Taq* I | 6.8, 4.5, 4, 3.2 | 6.8, 5.2, 4 |
| *Glur-4* | pPCR36-5 | *Msp* I | 2.8 | 4.1 |
| *Glur-5* | pmGluR5 | *Taq* I | 1.8 | 3.4 |
| *Glur-6* | pSKGR4 | *Taq* I | 3.5, 3.3, 1.5 | 6.5 |
| *Glur-7* | pSKGR3 | *Bam*HI | 9.5, 5.4, 4.1 | 7.4, 2.3 |
| *Nmdar-1* | pfNMDAR1 | *Taq* I | 4.5 | 2.4 |

*DxPas3* (26), *Gdx* (27), *Ldlr* (28, 29), *Thy-1* (30, 31), *D21S16h* and *App* (32, 33), *Sod-1* and *Ets-2* (34, 35), *Myb* (36, 37), *Col10a-1* (38), *Minta* (39), *Lmyc-1* (40, 41), *Lck* (40, 42), *Il1rn* (43), and *Spna-2* (44). Gene linkage was determined by segregation analysis (45). Gene order was determined by haplotype analysis that minimizes crossover frequency between all genes that were determined to be within a linkage group. This method resulted in determination of the most likely gene order (46). Other backcrosses utilized for *Glur-5* mapping studies were as described (female parent is indicated first): BALB/cJ × (BALB/cJ × MOLD/Rk)$F_1$ (cross 2; ref. 47), (BALB/cJ × MOLD/Rk)$F_1$ × BALB/cJ (cross 3; ref. 47), and (MOLD/Rk × DW/J)$F_1$ × DW/J (cross 4; ref. 48). Interval mapping was as described (47).

**Human Chromosome Localization.** Two complete somatic cell hybrid panels were screened to determine the chromosomal localization of the human *GLUR5* locus. Southern blot hybridization was carried out with the murine GluR5 cDNA probe under high stringency. The panels were from National Institute of General Medical Sciences (NIGMS; Coriell Institute for Medical Research, Camden, NJ). Panel 1 consisted of 17 mouse–human hybrids and 1 CHO–human hybrid. Each hybrid cell line contained one or more human chromosomes. Panel 2 consisted of 5 mouse–human hybrids and 19 CHO–human hybrids, the majority of which contain only one human chromosome. Discordancy (in percent) was calculated as the number of discordant hybrids divided by total number of hybrids.

***In Situ* Hybridization.** Human genomic clones (HGLUR5-5a and HGLUR5-1m) encoding portions of the *GLUR5* gene were isolated by screening a human genomic library in phage λ EMBL-3 (Clontech). The identity of the 12-kb HGLUR5-5a insert was confirmed by sequencing an exon and aligning it with human GluR5 cDNA (X.Y. and P.G., unpublished data). Metaphase spreads were prepared from short-term blood cultures. Probe labeling, hybridization under suppression conditions, detection, and photography were performed as described (49), with the following exceptions. Clone HGLUR5-5a was labeled with biotin-11-dUTP (Sigma) and detected with Cy3-streptavidin (Jackson ImmunoResearch). The chromosome 21 cosmid contig was labeled with digoxigenin-11-dUTP and detected with fluorescein isothiocyanate-conjugated anti-digoxigenin (Boehringer Mannheim). The concentration of probes and competitor DNA used was 20 μg/ml, 1 μg/ml, and 500 μg/ml for HGLUR5-5a, the chromosome 21 cosmid contig, and COT1 DNA, respectively.

**Mapping of *GLUR5* on Human Chromosome 21.** Linkage of *GLUR5* to chromosome 21 was tested in the Venezuelan Reference Pedigree (ref. 50; [1]). A two-allele dinucleotide CA repeat polymorphism was developed from a genomic λ clone HGLUR5-1m. The PCR primers were 5′-GATAAAGCCACATGACTACTTGG-3′ and 5′-AGTGACCTCAGTCTTCTGTTTCC-3′. The frequencies of the two alleles estimated from 48 unrelated Caucasians were 0.53 (133-bp allele) and 0.47 (127-bp allele). The chromosome 21 data set has been used to define the recombination events on each chromosome in 17 sibships. To confirm linkage to chromosome 21, *GLUR5* was tested in one sibship of 14 children, and a logarithm of odds (lod) score of 3.9 was generated with *D21S223*. Examination of the recombination events in this family suggested that *GLUR5* mapped between *D21S210* and *D21S224*, spanning ≈10 centimorgans (cM). *GLUR5* was then tested against an additional panel of recombination events specific to that region.

## RESULTS

**Mouse Chromosomal Localization.** Partial cDNAs encoding GluR subunits were isolated by PCR with degenerate oligonucleotide primers. The PCR products were subcloned, sequenced, and compared with sequences of other cloned GluR cDNAs (4–16). cDNAs corresponding to portions of rodent GluR subunits were thus identified. GluR genes were mapped initially using a panel of DNA samples from an interspecific cross that has been characterized for >400 genetic markers throughout the genome. The genetic markers included in this map span between 50 and 80 cM on each mouse autosome and the X chromosome (51). DNA from the two parental mice [C3H/HeJ-*gld* and (C3H/HeJ-*gld* × *M. spretus*)$F_1$] were digested with various restriction endonucleases and hybridized with the GluR cDNA probes to determine RFLVs and allow haplotype analyses. Informative RFLVs were detected for each GluR clone (Table 1). Each of the digested DNAs from the [(C3H/HeJ-*gld* × *M. spretus*)$F_1$ × C3H/HeJ-*gld*] interspecific backcross mice displayed the homozygous or heterozygous $F_1$ pattern when hybridized with the GluR cDNA probes.

Comparison of the haplotype distribution of the GluR RFLVs allowed each to be mapped to specific regions of mouse chromosomes with respect to reference loci by haplotype analysis (Fig. 1). The probability of linkage for each locus was >99% and indicated the following mouse chromosome assignments: *Glur-1*, chromosome 11; *Glur-2*, chromosome 3; *Glur-3*, X chromosome; *Glur-4*, chromosome 9; *Glur-5*, chromosome 16; *Glur-6*, chromosome 10; *Glur-7*,

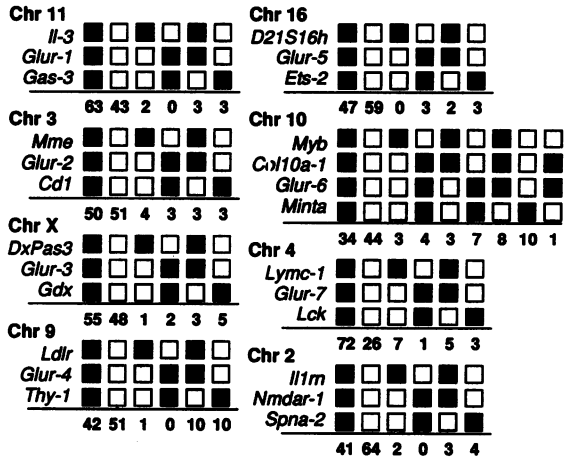


FIG. 1. Segregation of GluR loci on eight mouse chromosomes in [(C3H/HeJ-*gld* × *M. spretus*)$F_1$ × C3H/HeJ-*gld*] interspecific backcross mice. ■, Homozygous C3H pattern; □, $F_1$ pattern. The informative RFLVs that were used are designated in Table 1. The larger number of mice typing as C3H homozygotes on mouse chromosome 4 represents a phenomenon of segregation distortion that has been described for another region of the mouse genome in this cross (52).

[1]Haines, J. L., Guillemette, W., Brown, R. H., Rosen, D. R., Patterson, D., Donaldson, D. & Tanzi, R. E., Third International Workshop on Chromosome 21, April 20–21, 1992, Baltimore, p. 23 (abstr.).

chromosome 4; and *Nmdar-1*, chromosome 2. The best gene order (46) [±SD (45)] indicated the following gene orders from most proximal to distal on each chromosome: *Il-3*–1.8 ± 1.2 cM–*Glur-1*–5.3 ± 2.1 cM–*Gas-3; Mme*–6.1 ± 2.2 cM–*Glur-2*–5.3 ± 2.1 cM–*Cd1; DXPas3*–2.6 ± 1.5 cM–*Glur-3*–7.0 ± 2.4 cM–*Gdx;Ldlr*–0.9 ± 0.9 cM–*Glur-4*–17.5 ± 3.8 cM–*Thy-1; D21S16h*–2.6 ± 1.5 cM–*Glur-5*–4.4 ± 1.9 cM–*Ets-2; Myb*–7.0 ± 2.4 cM–*Col10a-1*–8.8 ± 2.8 cM–*Glur-6*–16.7 ± 3.5 cM–*Minta; Lmyc-1*–7.0 ± 2.4 cM–*Glur-7*–7.0 ± 2.4 cM–*Lck; Il1rn*–1.8 ± 1.2 cM–*Nmdar-1*–6.1 ± 2.2 cM–*Spna-2*.

**High-Resolution Mapping of *Glur-5* Locus on Mouse Chromosome 16.** Localization of *Glur-5* on chromosome 16 was refined using interval mapping to analyze three intersubspecific backcrosses (crosses 2–4). Since only a subset of the progeny from a given cross demonstrate recombination across a specific region, accurate mapping results can be obtained by typing only those animals that recombine in the previously defined reference interval to which the marker under study is localized (27, 47, 53). Digestion with *Eco*RI and analysis with the GluR5 probe detected a 7.9-kb fragment in BALB/cJ and DW/J DNAs and a 4.9-kb fragment in MOLD/Rk. By using this polymorphism, *Glur-5* was mapped on the equivalent of 484.3 intersubspecific backcross progeny with the interval-mapping procedure (Fig. 2). Previous analysis of these crosses identified all recombinations in the reference intervals *D21S16h–App*, *App–Sod-1*, and *Sod-1–Ets-2* (47). When *Glur-5* was typed on four of seven recombinant DNAs from the *D21S16h–App* interval panel of cross 2, the *Glur-5* parental type was always the same as that of *App* (all progeny showed recombination between *Glur-5* and *D21S16h*), indicating that *Glur-5* is close or distal to *App*. Originally, 197 progeny from cross 2 were typed to identify seven recombinants in this interval; i.e., there was on average one crossover per 28.1 animals typed; thus, the four recombinants typed are approximately equivalent to 112.4 randomly chosen DNAs from this cross. Twenty-six DNAs from the *Sod-1–Ets-2* interval of cross 2 (the equivalent of 198 backcross progeny) were typed with *Glur-5* with the result that *Glur-5* was always of the same type as *Sod-1*, indicating that it is proximal to *Sod-1*. Analysis of the *App–Sod-1* interval panel identified 5 animals that recombined between *Glur-5* and *App* and five recombinants with *Sod-1*. A similar analysis was carried out using the corresponding interval panels from crosses 3 and 4 with consistent results (Fig. 2). Combining results from all three crosses, the gene order and distances *App*–2.1 cM–*Glur-5*–3.5 cM–*Sod-1* were determined on the equivalent of 484.3 backcross progeny. The analysis required 71 DNAs, 27 of which provided all the information about the position of *Glur-5* within this interval.

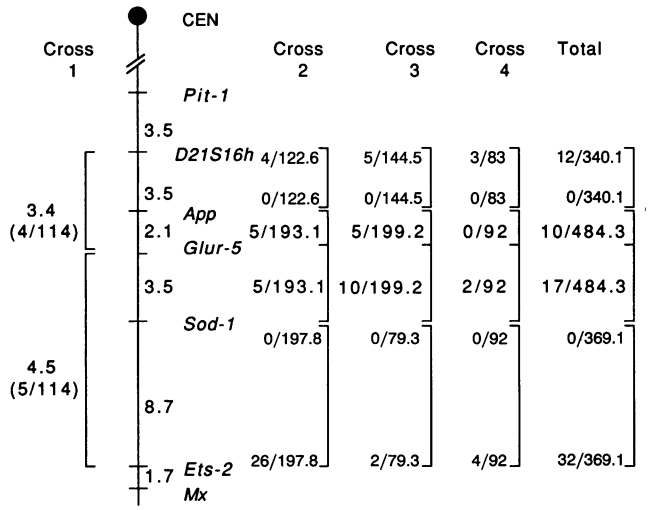


FIG. 2. Backcross mapping of the murine *Glur-5* gene. Chromosome 16 reference markers are shown adjacent to the chromosome. The position of *Glur-5* relative to *D21S16h* and *Ets-2* determined on the interspecific cross is shown to the left. Species-specific compression of the chromosome 16 map has been demonstrated for this region (32, 47). Average distances between genes (in cM) calculated by interval mapping are given to the right of the diagrammatic chromosome. The number of recombinants divided by the equivalent number of animals typed is given for each interval of each cross. Totals represent the sum of recombinants from crosses 2–4 divided by the equivalent number of animals typed. The number of animals typed for each reference interval (*D21S16h–App*, *App–Sod-1*, and *Sod-1–Ets-2*) is the same as the number of recombinants. For example, 12 DNAs from animals that recombined between *D21S16h* and *App* were typed for *Glur-5*. These 12 were identified originally by typing the equivalent of 340.1 animals. Of these, all 12 showed recombination between *Glur-5* and *D21S16h*, whereas *Glur-5* never recombined with *App*. Since the only crossover on each of these 12 chromosomes occurs proximal to *App*, *Glur-5* is distal to *App* (54). Crossovers between *Glur-5* and both the proximal and distal reference markers (*App* and *Sod-1*) occur within the interval where *Glur-5* is located and are emphasized with a larger font.

**Human Chromosomal Localization of the *GLUR5* Gene.** The human *GLUR5* gene was mapped using two complete somatic cell hybrid panels (data not shown). In the first panel, NIGMS 1, there was 100% concordance between chromosome 21 and the presence of human-specific *Hin*dIII restriction fragments of 14.5, 9.6, 7.4, 5.4, 3.9, 3.1, and 2.75 kb. There was >6% discordance between the human hybridization pattern and all other chromosomes. The localization of *GLUR5* on chromosome 21 was confirmed using NIGMS panel 2. There was complete concordance between the presence of human-specific *Hin*dIII restriction fragments and chromosome 21. Hybrids containing other human chromosomes were negative for the human-specific *GLUR5* restriction fragments.

The human *GLUR5* gene was also mapped to chromosome 21 by fluorescent *in situ* hybridization of human metaphase chromosomes. A differentially labeled cosmid contig at *D21S71* (49) was cohybridized with clone HGLUR5-5a and dual-color detection of the two probes was employed. This assay confirmed that HGLUR5-5a hybridizes exclusively to chromosome 21 at a locus proximal to *D21S71* (Fig. 3).

A two-allele polymorphism of *GLUR5* was tested for linkage to chromosome 21 in the Venezuelan Reference Pedigree (50) by using a set of meiotic breakpoints defined by

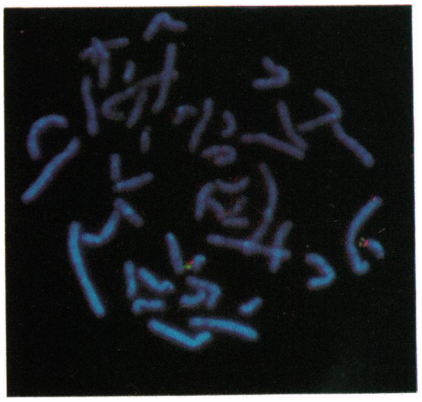

FIG. 3. Fluorescent *in situ* hybridization of HGLUR5-5a (red) and the chromosome 21q22.3 contig (green) on human metaphase chromosomes counterstained with 4′,6-diamidino-2-phenylindole. The photograph is a double exposure, which allows simultaneous visualization of the fluorescent hybridization signals and the chromosomes. The signals on the right provide evidence that *GLUR5* is located on the long arm of chromosome 21 at a locus proximal to 21q22.3.

reference markers.[l] Six recombination events placed *GLUR5* distal to *D21S210 (APP)*, and two recombination events placed it proximal to *D21S223*. These markers span a region of 7 cM. A single recombination event with *D21S213*, which maps in between *D21S210* and *D21S223*, places *GLUR5* proximal to *D21S213*, in a 4-cM region.

## DISCUSSION

In this study, eight GluR subunit genes were mapped in the mouse by using a well-characterized interspecific backcross and cloned cDNA probes. The GluR genes segregated independently and showed linkage to previously mapped loci on eight mouse chromosomes. The localization of the GluR subunit genes to mouse chromosomes allows prediction of the chromosomal location of human homologues. The conservation of linkage groups over 100 million years of mammalian evolution and the efforts of many groups in defining linkage maps and the chromosomal locations of genes in mice and humans have defined many of these relationships (51, 55). The predicted positions of human homologues are summarized in Table 2.

**Relationship of *GLUR5* to Familial ALS and Other Neurological Loci on Chromosome 21.** The localization of murine *Glur-5* was further refined by interval mapping, which provides a rapid and efficient means of determining gene position on high-resolution backcross panels. This procedure allowed assignment of *Glur-5* to 2.1 cM distal to *App* and 3.5 cM proximal to *Sod-1*. The strong conservation of linkage between human chromosome 21 and mouse chromosome 16, which extends from *D21S16* to *MX1* (32), allowed the prediction that the human *GLUR5* gene will localize to 21q21–q22.1. This location of *GLUR5* was confirmed using (*i*) somatic-cell hybrids, (*ii*) fluorescent *in situ* hybridization, and (*iii*) genetic linkage analysis with the Venezuelan Reference Pedigree. The later method has allowed the assignment of *GLUR5* to the region between *APP* and *SOD1* genes. The precise positioning of *GLUR5* with respect to *D21S213* is provisional. A single recombination event in the Venezuelan pedigree suggests that *GLUR5* might be proximal to *D21S213*. However, the calculated lod score for this positioning is 1.4; this is considerably less than the 1000:1 odds (lod score = 3) usually taken as conventional confirmation of genetic position mapping.

This position of the *GLUR5* locus is at or near an autosomal dominant form of ALS (17). About 5–10% of cases of ALS are familial. The majority of these show linkage to *D21S58, APP*, and other markers on the distal arm of chromosome 21 (17). The position of the familial ALS locus has recently been confirmed with the aid of six highly polymorphic simple sequence repeat markers[k]; highly significant lod scores were obtained with *D21S213*/GT05 and *D21S210*/GT12 (*APP*) markers. In one family there was a single crossover based on reconstructions, suggesting that the familial ALS locus may be distal to *D21S213*.[k] However, in the absence of clear cut data firmly localizing *GLUR5* proximal to *D21S213* and the familial ALS locus distal to *D21S213, GLUR5* remains a candidate gene for chromosome 21-linked familial ALS.

Table 2. Assignment of the human GluR genes

| Locus | Putative chromosomal locations | Defined position(s) |
|---|---|---|
| *GLUR1* | 5q23–31; 4p16–15; 17p13–12 | 5q33*; 5q31–33.3†‡ |
| *GLUR2* | 1q21–cen; 3q21–27; 4q32–33 | 4q25–34†; 4q32–33‡ |
| *GLUR3* | Xq26; Xp11.4–11.2 | Xq25–26‡ |
| *GLUR4* | 19p13, less likely 11q23.3 | 11q22–23‡ |
| *GLUR5* | 21, *APP–SOD1* | 21, *APP–SOD1* |
| *GLUR6* | 6q21–22; 10q22; 21q21–22 | 6§ |
| *GLUR7* | 1p32–34 | |
| *NMDAR1* | 9q33–34 | |

*, Ref. 56; †, ref. 57; ‡, ref. 58; §, data not shown.

Glutamatergic mechanisms have been proposed as the cause of Guamanian and sporadic ALS (e.g., refs. 59–61) and represent one of the major current theories about the etiology of ALS (for review, see refs. 3, 62, 63). The chief clinical signs of ALS are progressive muscular weakness and atrophy usually in combination with spasticity; the corresponding pathological findings are loss of motor neurons in spinal cord and brainstem and degeneration of the corticospinal tracts. These observations generally correlate with the expression of GluR5 in the rodent central nervous system (11, 76).

Several other neurological disorders are associated with chromosome 21. Trisomy 21 is the cause of Down syndrome, in which the brain is markedly hypocellular. A major effort in Down syndrome research is the attempt to correlate dosage imbalance of specific genes on chromosome 21 with specific aspects of the phenotype. Since Down syndrome is the most frequent genetic cause of mental retardation, genes expressed in the central nervous system are of special interest in this type of analysis. During embryogenesis, murine GluR5 is strongly expressed in areas of neuronal differentiation and synaptogenesis (11). Overexpression of GluR5 could alter the subunit composition and properties of heteromeric GluR-associated ion channels and have a detrimental effect on the developing central nervous system.

Familial Alzheimer disease has been associated by linkage with markers on proximal 21q (e.g., refs. 64 and 65). In addition, the gene for amyloid precursor protein, a cleavage product of which is the major constituent of the amyloid plaques, the histopathological hallmark of Alzheimer disease, is also located on chromosome 21q. Mutations in this gene have been described in several cases of early-onset familial Alzheimer disease (65). Nevertheless, evidence for the association of late-onset familial Alzheimer disease with chromosome 21 markers has also been described and is not related to *APP* (66). The chromosomal location of *GLUR5* would not exclude it as a cause of this association.

**GluR Genes in Neurologically Mutant Mice.** Several of the murine GluR genes map close to loci that are defined by neurologic mutations. The *Glur-1* locus is localized to a region of mouse chromosome 11 in which the recessive vibrator (*vb*), shaker-2 (*sh-2*), tipsy (*ti*), and spasmodic (*spd*) mutations have been mapped (67–70). *Glur-2* maps to the region of mouse chromosome 3 that contains the spastic (*sp*) mutation; and *Glur-7* maps to the region of mouse chromosome 4 that contains the clasper (*cla*) mutation (69, 71–74). As indicated by their distinct names, these mice exhibit motor signs, such as various tremors and spasms. In the spastic mouse, a large decrease in glycine receptors may be the primary cause of the disease (75). Spasmodic is a very similar phenotype, but it does not manifest changes in glycine receptor numbers (68). The *Glur-6* gene maps close to circling mutants Jackson circler (*jc*) and waltzer (*v*) on mouse chromosome 10.

**Note added in proof.** Eubanks *et al.* (77) have also mapped *GLUR5* to chromosme 21q21.1–22.1 and, citing converging evidence from a number a studies, suggested that a mutated *GLUR5* gene may be responsible for familial ALS. Recently, we have carried out segregation analyses of polymorphic *GLUR5* markers in families with chromosome 21-linked ALS and found two recombinations suggesting that the familial ALS locus is distinct from *GLUR5* (P.G., J.L.H., and R.H.B., unpublished work).

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(*DxPas3*, *Gdx*), J. Ihle (*Il-3*), R. Perlmutter (*Lck*), D. Russell (*Ldlr*), F. Alt (*Lmyc*), M. Taketo (*Minta*), M. Shipp (*Mme*), N. Sheiness (*Myb*), K. Huppi (*Thy-1*), A. S. Whitehead (*Il1rn*), and C. S. Birkenmeier (*Spna-2*). This work was supported by National Institute of Drug Abuse intramural grant (G.R.U.); U.S. Public Health Service Grants HG00101 (M.F.S.), HG00465 (R.H.R.), HG00324 (J.L.H.), and HG00373 (E.W.J.); and ALS Association, Muscular Dystrophy Association, P. L. de Bourghknecht ALS Foundation, and MacLellan ALS Research Foundation (R.H.B.).

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