Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 11849–11853, December 1994
Neurobiology

The genes encoding the glutamate receptor subunits KA1 and KA2 (*GRIK4* and *GRIK5*) are located on separate chromosomes in human, mouse, and rat

(ligand-gated ion channels/human chromosomes 19q13.2 and 11q22-23/mouse chromosomes 7 and 9/rat chromosomes 8 and 1)

CLAUDE SZPIRER*, MONTSE MOLNÉ†, RACHELE ANTONACCI‡, NANCY A. JENKINS§, PALMA FINELLI‡, JOSIANE SZPIRER*, MICHELE RIVIERE*, MARIANO ROCCHI‡, DEBRA J. GILBERT§, NEAL G. COPELAND§, AND VITTORIO GALLO†¶

*Departement de Biologie Moleculaire, Université Libre de Bruxelles, B-1640 Rhode-St.-Genese, Belgium; †Laboratory of Cellular and Molecular Neurophysiology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892; ‡Istituto di Genetica, University of Bari, 70126 Bari, Italy; §Mammalian Genetics Laboratory, Advanced BioScience Laboratories–Basic Research Program, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, MD 21702

Communicated by E. Costa, August 10, 1994

ABSTRACT **The chromosomal localization of the human and rat genes encoding the kainate-preferring glutamate receptor subunits KA1 and KA2 (*GRIK4* and *GRIK5*, respectively) was determined by Southern analysis of rat × mouse and human × mouse somatic cell hybrid panels and by fluorescence *in situ* hybridization. The localization of the mouse genes (*Grik4* and *Grik5*) was established by interspecific backcross mapping. *GRIK4* and *GRIK5* are located on separate chromosomes (Chrs) in all species. *GRIK4* mapped to human Chr 11q22.3, mouse Chr 9, and rat Chr 8. *GRIK5* mapped to human Chr 19q13.2, mouse Chr 7, and rat Chr 1. The genes encoding the (*R*,*S*)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-preferring subunit GluR4, or GluRD (*GRIA4*), the neural cell adhesion molecule (*NCAM*), the D2 dopamine receptor (*DRD2*), and the Thy-1 cell surface antigen (*THY1*) have all been previously mapped to the human Chr 11q22 region. The mapping of the human *GRIK4* and *GRIK5* genes confirms and extends the relationship between human Chr 11 and mouse Chr 9 and also human Chr 19 and mouse Chr 7. *GRIK4* is the fifth gene shared by human Chr 11 and rat Chr 8, whereas *GRIK5* is 1 out of the 12 genes that are located on both human Chr 19 and rat Chr 1. Our data extend the conserved synteny established between certain human, mouse, and rat Chrs.**

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS) (1). Its physiological action is exerted through the activation of ligand-gated ion channels and guanine nucleotide-binding protein (G-protein)-coupled membrane receptors (1). Besides their central role in excitatory synaptic transmission, glutamate receptors are also thought to be involved in long-term potentiation, learning, Alzheimer disease, and epilepsy (1, 2). Glutamate-gated ionic channels are broadly classified into *N*-methyl-D-aspartate (NMDA) and non-NMDA types (1, 3). cDNAs for subunits belonging to both classes of receptors have been cloned and characterized in their molecular and functional properties (3). The expression of the individual subunits and of their splice variants has been analyzed in different CNS regions (4, 5).

The cDNA sequences of non-NMDA receptor subunits show a high degree of similarity with each other but derive from distinct genes that are differentially expressed in the mammalian CNS (3). Three related non-NMDA receptor subunit gene families have been defined (3): the (*R*,*S*)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-preferring family (GluR1–4, or GluRA–D; *GRIA* gene family) and the two kainate-preferring families (GluR5–7 and KA1 and KA2; in the two *GRIK* gene families). The kainate-preferring subunits KA1 and KA2 display 68% identity in their amino acid sequence and code for proteins that do not form functional homomeric ionic channels but bind kainate with affinities in the nanomolar range (6, 7). Studies performed in transfected mammalian cells (7), in oocytes (8), and in cultured CNS glial cells (9) have indicated that KA1 and KA2 form functional heteromeric kainate-preferring ionic channels with the GluR5–7 subunit family but not with GluR1–4.

KA1 and KA2 display a strikingly different expression pattern in the rat brain. KA1 mRNA expression is restricted to the CA3 region of the hippocampus, whereas KA2 mRNA can be detected in almost all regions of the brain (6, 7). This differential distribution has been detected as early as embryonic day 14 (7), suggesting that different transcriptional factors may regulate and segregate the expression of the genes encoding the KA1 and KA2 receptor subunits in the CNS. Altered levels of KA1 or KA2 expression, as well as synthesis of mutated proteins, could have serious functional consequences in several classes of CNS cells and possibly be linked to neurologic and/or psychiatric disorders. We have, therefore, analyzed the chromosomal localization of the genes encoding KA1 and KA2 in human (*GRIK4* and *GRIK5*), mouse (*Grik4* and *Grik5*), and rat (*GRIK4* and *GRIK5*). We report here that *GRIK4* and *GRIK5* genes are localized on different human chromosomes (Chrs), 11 and 19, respectively. This localization extends the synteny conservation between human Chr 11, mouse Chr 9, and rat Chr 8 (10–12) and between human Chr 19, mouse Chr 7, and rat Chr 1 (11, 13).

MATERIALS AND METHODS

Interspecific Backcross Mapping. Interspecific backcross progeny were generated by mating (C57BL/6J × *Mus spretus*)F_1 females and C57BL/6J males as described (14). A total of 205 N_2 mice were used to map the *Grik4* and *Grik5* loci. Southern blot analysis was performed as described (15). The probe for *Grik4* was a 415-bp *Nco* I/*Dra* I fragment of the rat

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Abbreviations: Chr, chromosome; AMPA, (*R*,*S*)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; FISH, fluorescence *in situ* hybridization; NMDA, *N*-methyl-D-aspartate; CNS, central nervous system; RFLP, restriction fragment length polymorphism; DAPI, 4′,6-diamidino-2-phenylindole.

¶To whom reprint requests should be addressed at: Laboratory of Cellular and Molecular Neurophysiology, National Institute of Child Health and Human Development, National Institutes of Health, Building 49, Room 5A-78, Bethesda, MD 20892.

cDNA, labeled with [α-^{32}P]dCTP; washing was done to a final stringency of 0.8× standard saline citrate phosphate (SSCP)/0.1% SDS at 65°C. Fragments of 6.2, 3.8, and 0.5 kb were detected in *Taq* I-digested C57BL/6J (B) DNA, and fragments of 4.2, 3.8, 3.3, 2.4, and 0.5 kb were detected in *Taq* I-digested *M. spretus* (S) DNA. The presence or absence of the 4.2-kb *M. spretus*-specific fragment was followed in backcross mice. The probe for *Grik5* was a 507-bp *Bam*HI fragment of the rat cDNA, which detected *Sca* I fragments of 15.0 kb (B) and 8.7 and 5.7 kb (S). The presence or absence of the *M. spretus*-specific fragments, which cosegregated, was followed in backcross mice.

A description of the probes and restriction fragment length polymorphisms (RFLPs) for the loci linked to *Grik4*, including the *Ets1* protooncogene (*Ets1*), thymus cell antigen 1 (*Thy1*), and dopamine receptor 2 (*Drd2*), has been reported (16). A description of the probes and RFLPs for the loci linked to *Grik5*, including transforming growth factor β1 (*Tfgb1*), glucose phosphate isomerase 1 (*Gpi1*), and ras-related oncogene (*Rras*), has been reported (17, 18). Recombination distances were calculated as described (19). Gene order was determined by minimizing the number of recombination events required to explain the allele distribution patterns.

Cell Hybrids. Two panels of somatic cell hybrids were used to localize the genes in human and rat (13, 20, 21). In addition, a human × Chinese hamster cell hybrid (GM10449; line 5HL9-4) characterized by the presence of only human chromosome 19 (22) was used.

Southern Blot Analysis and Hybridization Probes. Genomic DNAs from hybrids and parental control cells were examined by Southern blot analysis (13). Sequences encoding *GRIK4* were identified by hybridization to a 413-bp *Nco* I/*Dra* I fragment (nucleotides +100 to +513, relative to the ATG) that was isolated from the rat KA1 cDNA (6). *GRIK5* genomic sequences were identified by hybridization to a 507-bp *Bam*HI fragment (nucleotides −58 to 449, relative to the ATG) that was derived from the rat KA2 cDNA (7).

***In Situ* Hybridization.** Human metaphase spreads were obtained from phytohemagglutinin-stimulated peripheral blood lymphocytes from a human donor. Chr preparations were hybridized *in situ* with probes labeled with biotin by nick-translation (23). The rat cDNA-derived probes used for hybridization were a *Nco* I/*Ava* I fragment (2.6 kb) for *GRIK4* and a *Xba* I/*Stu* I fragment (3.0 kb) for *GRIK5*. Biotin-labeled DNA was detected with fluorescein isothiocyanate (FITC)-conjugated avidin. Chr identification was obtained by simultaneous 4′,6-diamidino-2-phenylindole (DAPI) staining. Digital images were obtained using a Zeiss Axioplan epifluorescence microscope equipped with a cooled charge-coupled device camera (Photometrics, Tucson, AZ). FITC and DAPI fluorescence, detected using Pinkel no. 1 specific filter set combinations (Chroma Technology, Brattleboro, VT), were recorded separately as gray-scale images. Pseudocoloring and merging of images were performed using GENEJOIN software (T. Rand and D. C. Ward, Yale University).

RESULTS

Chr Assignment of the Rat *GRIK4* and *GRIK5* Genes. We determined the chromosomal localization of the rat *GRIK4* and *GRIK5* genes by using rat × mouse hybrids that segregate rat Chrs. The rat *GRIK4* cDNA-derived probe detected three rat genomic *Bam*HI fragments (10.5, 6.7, and 2.9 kb) that were easily distinguishable from three mouse fragments (data not shown). The three rat fragments were detected in the three clones that possess rat Chr 8 and only in these clones (Table 1). At least four discordant clones were counted for each of the other Chrs (Table 1). The rat *GRIK5* cDNA-derived probe detected four rat-specific *Eco*RI restriction fragments. The signal arising from two fragments (21 and 4.5 kb) was sufficiently strong to be followed in the hybrid clones that possess rat Chr 1 (data not shown). These fragments clearly cosegregated with rat Chr 1 (Table 1). At least three discordant clones were counted for each of the other Chrs (Table 1). It can be concluded, therefore, that the rat *GRIK4* and *GRIK5* genes reside on rat Chrs 8 and 1, respectively.

Chromosome Assignment of the Human *GRIK4* and *GRIK5* Genes. The rat *GRIK4* and *GRIK5* cDNA-derived probes were found to cross-hybridize with human sequences. This is consistent with previous studies reporting a high degree of similar-

Table 1. Rat chromosome constitution of the rat × mouse hybrids and segregation of the rat *GRIK* genes

	Rat *GRIK* genes*		Rat chromosome†																				
Hybrid	4	5	X	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
LB20	−	−	+	−	(+)	(+)	−	−	−	+	−	−	−	−	+	+	−	−	+	(+)	+	+	−
LB150-1	−	−	+	−	−	+	+	−	−	+	−	+	(+)	+	+	+	−	−	(+)	(+)	+	+	−
LB161	−	−	+	−	+	+	+	+	+	+	−	+	+	−	(+)	+	+	+	+	+	+	+	(+)
LB210-I	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	+	−	−
LB251	−	+	+	+	+	−	+	−	(+)	+	−	−	+	−	+	+	−	−	−	+	−	+	−
LB330	−	−	+	−	+	+	+	−	+	−	−	−	+	−	+	−	−	−	−	+	−	−	−
LB360B	+	ND	+	−	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
LB510-6	−	−	+	−	+	+	+	−	−	+	−	−	−	−	+	+	+	+	+	+	+	−	−
LB630	−	+	+	(−)	−	+	+	(+)	+	+	−	+	−	+	+	+	(+)	+	+	−	+	+	(−)
LB780	−	−	+	−	+	+	+	+	−	+	−	−	+	+	−	+	−	−	−	+	+	−	+
LB810	+	−	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+	(+)
LB860	−	−	+	−	+	+	+	−	−	+	−	+	−	+	+	+	−	+	+	+	+	−	(+)
LB1040	−	−	+	−	−	+	+	(−)	+	+	−	−	+	+	+	−	−	+	+	−	+	−	+
BS511	+	−	+	−	+	+	+	(−)	+	+	+	−	−	+	−	+	−	+	+	+	−	+	−
GRIK4‡			11	4	8	9	9	4	6	9	0	7	7	5	10	9	5	5	7	8	11	5	5
GRIK5‡			10	0	8	10	8	3	4	8	3	4	7	6	8	8	5	6	8	9	9	4	6

ND, not determined.

*+ and − indicate the presence and absence of the rat gene, respectively.

†+ indicates that the rat chromosome is present in >55% of the metaphases; (+) indicates that the rat chromosome is present in 25–55% of the metaphases; (−) indicates that the rat chromosome is present in <25% of the metaphases; − indicates that the rat chromosome is absent.

‡Independent discordant clones. Independent hybrid clones are derived from distinct fusion events. All hybrids presented in this table are independent clones. When a chromosome was present in <25% of the metaphases [(−)], the hybrid in question was not taken into account to establish the number of discordancies for that particular chromosome.

Table 2. Human chromosome constitution of the human × rodent cell hybrids and segregation of the human *GRIK* genes

Hybrid	Human *GRIK* genes*		Human chromosome†																						
	4	5	X	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Y
HA11	+	−	−	−	−	−	+	+	+	−	+	−	−	+	−	−	−	−	−	−	−	−	+	+	−	−
HA13	+	−	+	+	−	−	+	+	+	−	+	−	−	+	+	−	−	−	+	−	−	−	+	+	−	−
HA212	+	+	−	+	−	+	−	−	−	−	−	−	−	+	−	−	−	+	−	+	−	−	−	+	−	−
HA221	+	−	+	−	−	−	+	−	+	+	−	−	−	+	−	−	−	+	−	−	−	−	−	+	−	−
HA232	+	+	−	−	−	+	+	−	+	−	−	−	−	+	−	−	(+)	+	+	−	−	−‡	−	+	+	−
HB25	ND	−	−	−	+	+	+	+	(−)	+	+	(+)	(+)	+	(+)	(+)	+	+	(+)	+	+	−	+	+	+	−
HB26	+	+	+	−	+	+	−	−	+	+	−	−	+	(+)	−	+	+	+	+	+	+	(+)	+	+	+	−
HB33	+	−	−	−	−	(+)	(+)	−	+	−	+	−	−	(+)	−	−	+	−	−	(+)	−	−	−	−	+	−
HB43	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	−
HB111	+	−	−	−	−	+	(+)	−	−	−	(−)	−	−	+	+	−	+	−	−	+	−	−	−	+	−	−
HB142-2	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	+	+	−	+	−	−	+	−	−	−
HB181	+	+	−	−	+	+	−	−	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	−
JVO1	+	ND	−	−	−	+	−	+	−	+	−	−	+	+	−	+	+	−	−	+	−	−	−	−	−	+
JV211	+	ND	−	(+)	+	+	(−)	+	+	+	+	−	+	+	+	(+)	+	−	+	+	−	−	+	−	+	−
HR40C8	−	+	+	−	−	−	−	−	−	+	−	(−)	+	−	+	+	+	+	(−)	+	+	+	(+)	+	(+)	−
GM10449	ND	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
GRIK4§			8	7	4	2	5	5	3	5	3	9	7	0	6	6	4	6	6	4	7	7	6	4	5	8
GRIK5§			5	6	4	5	11	8	6	4	7	6	5	7	6	4	6	4	5	6	3	0	5	5	4	6

ND, not determined.

*+ and − indicate the presence and absence of the human gene, respectively.

†+ indicates that the human chromosome is present in >55% of the metaphases; (+) indicates that the human chromosome is present in 25–55% of the metaphases; (−) indicates that the human chromosome is present in <25% of the metaphases; − indicates that the human chromosome is absent.

‡HA232 lacks intact human chromosome 19, but contains genetic material derived from 19q (*CEA*, *PSG1*, and *LHB* genes; see ref. 13).

§Independent discordant clones. Independent hybrid clones are clones derived from distinct fusion events. They are identified by unrelated numbers (nonindependent clones are HA11 and HA13, or HA212, HA221, and HA232, or HB25 and HB26). When a chromosome was present in <25% of the metaphase [(−)], the hybrid in question was not taken into account to establish the number of discordancies for that particular chromosome.

ity between rat and human glutamate ionotropic receptors in their coding sequences (24). Using human × rodent cell hybrids (Table 2), we then determined the chromosomal localization of the human *GRIK4* and *GRIK5* genes. When hybridized with the *GRIK4* probe, a *Hin*dIII digest of human genomic DNA generated two restriction fragments at 23.0 and 5.0 kb, respectively (data not shown). These could be distinguished from the homologous rodent fragments and were found to cosegregate with each other and with human Chr 11 (Table 2). Several discordant clones were counted for all the other Chrs (Table 2). The *GRIK4* gene thus resides on human Chr 11.

The *GRIK5* cDNA-derived probe hybridized to a 7.2-kb *Bam*HI human restriction fragment, which could be distinguished from the rodent homologues (data not shown) and was found to segregate with human Chr 19 (Table 2). The *GRIK5* gene thus resides on human Chr 19. The hybrid HA232, which lacks intact human Chr 19 but possesses material from 19q (13), was positive for the human *GRIK5* gene, indicating that this gene resides on 19q.

Subchromosomal Localization of the Human *GRIK4* and *GRIK5* Genes by Fluorescence *in Situ* Hybridization (FISH). To define the subregional localization of *GRIK4* and *GRIK5* genes in human Chrs, FISH experiments were performed. The results obtained confirmed the mapping of *GRIK4* and *GRIK5* on human Chrs 11 and 19 and allowed the regional localization of *GRIK4* to band 11q23 and *GRIK5* to 19q13.2 (Fig. 1).

Chr Assignment of *Grik4* and *Grik5* Genes in the Mouse. The murine chromosomal locations of the *Grik4* and *Grik5* genes were determined by interspecific backcross analysis using progeny derived from matings of [(C57BL/6J × *M. spretus*)F_1 × C57BL/6J] mice. This interspecific backcross mapping panel has been typed for over 1600 loci that are well distributed among all the autosomes as well as the X chromosome (14). C57BL/6J and *M. spretus* DNAs were ana-

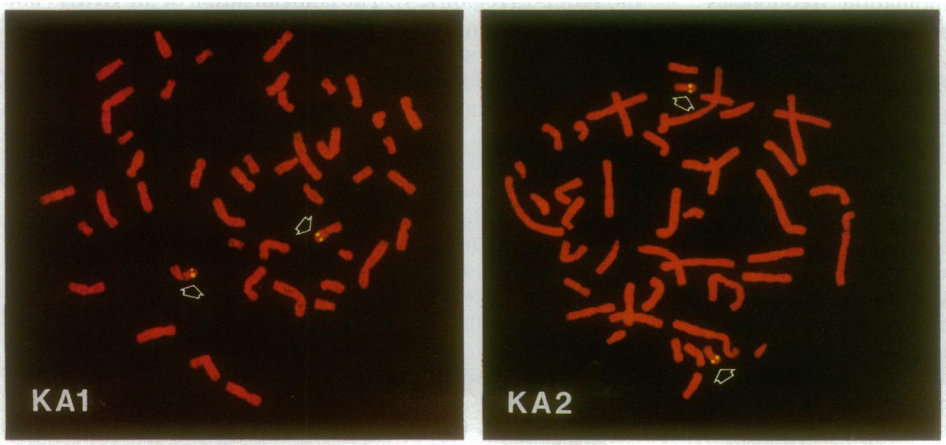

FIG. 1. FISH of pKA1 and pKA2 probes to metaphase spreads of human chromosomes counterstained with DAPI. KA1, *GRIK4* gene; KA2, *GRIK5* gene. Hybridization signals are shown in yellow (arrows). Double exposures of the same fields are shown, which allow simultaneous visualization of the fluorescent hybridization signals and the chromosomes. The DAPI counterstain was pseudocolored in red to provide greater contrast with the hybridization signals. Paired fluorescence spots derived from the diploid are observed on chromosome 11q23 (*Left*) and 19q13.2 (*Right*) for *GRIK4* and *GRIK5* probes, respectively.

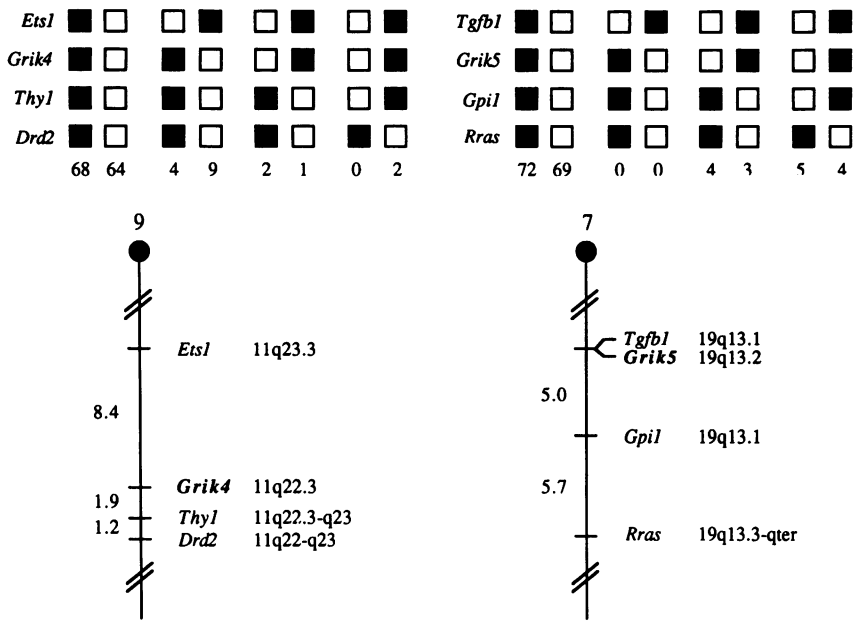

FIG. 2. Chromosomal locations of *Grik4* and *Grik5* in the mouse genome. The loci were mapped by interspecific backcross analysis. The segregation patterns of these loci and flanking genes in backcross animals that were typed for all loci are shown above the chromosome maps. For individual pairs of loci, more animals were typed (see text). Each column represents the chromosome identified in the backcross progeny that was inherited from the (C57BL/6J × *M. spretus*)F_1 parent. The black boxes represent the presence of a C57BL/6J allele, and white boxes represent the presence of a *M. spretus* allele. The number of offspring inheriting each type of chromosome is listed at the bottom of each column. Partial chromosome linkage maps showing the location of *Grik4* and *Grik5* in relation to linked genes are shown. Recombination distances between loci in centimorgans are shown to the left of the chromosome, and the positions of loci in human chromosomes, where known, are shown to the right. References for the map positions of loci mapped in human chromosomes can be obtained from the Genome Data Base, a computerized data base of human linkage information maintained by The William H. Welch Medical Library of The Johns Hopkins University (Baltimore).

lyzed by Southern blot hybridization for informative RFLPs. A 4.2-kb *Taq* I *M. spretus*-specific RFLP was used to follow the segregation of the *Grik4* locus in backcross mice. The mapping results indicated that *Grik4* is located in the central region of mouse Chr 9 linked to *Ets1*, *Thy1*, and *Drd2*. Although 150 mice were analyzed for every marker and are shown in the segregation analysis (Fig. 2), up to 162 mice were typed for some pairs of markers. Each locus was analyzed in pairwise combinations for recombination frequencies using the additional data. The ratios of the total number of mice exhibiting recombinant Chrs to the total number of mice analyzed for each pair of loci and the most likely gene order are centromere–*Ets1* (13/155)–*Grik4* (3/160)–*Thy1* (2/162)–*Drd2*. The recombination frequencies [expressed as genetic distances (in centimorgans) ± SE] are *Ets1* (8.4 ± 2.2)–*Grik4* (1.9 ± 1.1)–*Thy1* (1.2 ± 0.9)–*Drd2*.

The *Grik5* locus was defined by 8.7- and 5.7-kb *Sca* I *M. spretus*-specific RFLPs. In this case, 157 mice were analyzed for every marker and are shown in the segregation analysis (Fig. 2), and up to 180 mice were typed for some pairs of markers. The results indicate that *Grik5* is located in the proximal region of mouse Chr 7. Also in this case, each locus was analyzed in pairwise combinations for recombination frequencies using the additional data. The ratios of the total number of mice exhibiting recombinant Chrs to the total number of mice analyzed for each pair of loci and the most likely gene order are centromere–*Tgfb1* (0/172)–*Grik5* (9/180)–*Gpi1* (10/175)–*Rras*. The recombination frequencies [expressed as genetic distances (in centimorgans ± SE] are [*Tgfb1*, *Grik5*] (5.0 ± 1.6)–*Gpi1* (5.7 ± 1.8)–*Rras*. No recombinants were detected between *Tgfb1* and *Grik5* in 172 animals typed in common, suggesting that the two loci are within 1.7 centimorgans of each other (upper 95% confidence level).

DISCUSSION

Native non-NMDA glutamate receptors consist of distinct homo- or heterooligomeric combinations of AMPA- or kainate-preferring subunits. The subunit composition confers different biophysical properties to the resulting membrane channels (3). The expression of functional non-NMDA ionic channels in the brain requires coordinated transcription of genes encoding AMPA- or kainate-preferring subunits at critical times during development. A tandem arrangement of members of the AMPA or the kainate gene family in a single chromosomal locus could, therefore, be necessary to regulate their coordinate expression, as previously hypothesized for some muscle (25) and neuronal (26) acetylcholine receptor genes and for two γ-aminobutyric acid A receptors (27).

In the present study, we mapped the two genes encoding the kainate-preferring subunits KA1 and KA2 to determine (*i*) if they are localized in a single locus and/or (*ii*) if they are contiguous to other glutamate receptor subunit genes. We found that *GRIK4* and *GRIK5* map on two separate Chrs in mouse, human, and rat and that they are not colocalized with any of the genes encoding other kainate-preferring subunits. The subunits KA1 and KA2 do not assemble to form functional homomeric channels, but they are hypothesized to form heterooligomeric ionic channels with the GluR5–7 family (5, 7). Our chromosomal localization of *GRIK4* and *GRIK5* suggests, therefore, that their coordinated expression in the CNS with the genes encoding the subunits GluR5–7 (*GRIK1–3*) does not require linkage on a particular Chr.

The chromosomal localization of all the AMPA-preferring (24) and some of the kainate-preferring (28–30) subunit genes has been reported in mouse and human, showing that all members of both glutamate receptor gene families are located on different Chrs. In our analysis, the chromosomal localization of *GRIK5* on 19q13.2 does not correspond to any of the previously mapped GluR genes, whereas *GRIK4* is colocalized with the AMPA-preferring subunit *GRIA4* gene in the 11q22-23 region (24). The colocalization of the *GRIK4* and *GRIA4* genes on the same region of Chr 11 does not appear to be linked to a requirement for coordinated expression of these two subunits in the CNS. Kainate- and AMPA-preferring subunits do not combine with each other to form native receptor channels (8, 31), and *in situ* hybridization analysis of KA1 and GluR4 expression in rat brain showed that the distribution pattern of their mRNAs is markedly different (6, 32).

From a viewpoint of comparative mapping between species, our data extend the conserved synteny previously established between certain human, mouse, and rat Chrs. While most human homologues of rat Chr 8 genes are located on human Chr 3, *GRIK4* is the fifth gene shared by human Chr 11 and rat Chr 8. The other genes previously mapped on these Chrs are *APOC3*, *ES6*, *NCAM*, and *THY1* (10–12). The localization of *GRIK5* extends the synteny conservation

between rat Chr 1 and human Chr 19 (11, 13). It is remarkable that, with one exception (*C3*), all localized rat genes homologous to human Chr 19 genes (12 genes, including *GRIK5*) are located on Chr 1 (33). Finally, the central region of mouse Chr 9 and the proximal region of Chr 7 display conserved synteny with human Chr 11q and 19q, respectively. The placement of *GRIK4* on mouse Chr 9 and *GRIK5* on Chr 7 confirms and extends the relationship between these pairs of mouse and human Chrs.

GRIK4 and *GRIK5* are not located near chromosomal regions associated with any human neurogenetic disorders mapped so far. Several genes highly expressed in the CNS have been previously mapped in the q22-23 region of human Chr 11, where *GRIK4* is localized. These include the *DRD2* and the *NCAM* genes encoding the dopamine receptor subtype D2 and the cell surface glycoprotein N-CAM, which is thought to play an important role during neural development (34). The *THY1* gene, encoding the cell surface antigen Thy-1, which is shared by neurons and astrocytes in the CNS (35), was also mapped in the same chromosomal region (36). The q22-23 region of Chr 11, as well as regions of human Chrs 3, 6, 15, and 19, are homologous to mouse Chr 9 (37). The gene *El1*, the major gene responsible for an epileptic mouse phenotype, was previously localized by linkage analysis on mouse Chr 9 (38). The *El* mouse is considered a genetic model for human temporal lobe epilepsies and complex partial seizures (39); therefore, an altered *Grik4* gene appeared to be a good candidate for this phenotype. In fact, the mRNA for the subunit KA1 is prominently expressed in the CA3 region of the hippocampus, an area known to be responsible for the precipitation and pacing of epileptiform activity in a variety of animal seizure models (2). CA3 hippocampal neurons are also the cell population most vulnerable to kainate-induced neurotoxicity (2). A recent study has, however, indicated that a partial duplication in the ceruloplasmin gene, localized in mouse Chr 9 and human Chr 3q, is associated with the epileptic phenotype in the *El* mouse (40). These findings, however, do not completely rule out the possibility that, because of its highly restricted expression in the brain, mutations in *GRIK4* may be linked to other forms of epilepsy. Finally, the localization of *Grik5* on mouse Chr 7 places this gene in the vicinity of several mutations, one of which (*nv*, Nijmegen waltzer; ref. 41) affects the neurological behavior of mice. Our chromosomal localization analysis of *GRIK4* and *GRIK5* in three different species will provide tools for future linkage studies of the KA1 and KA2 kainate receptors in various human diseases or neuropathologic states.

We thank Dr. Peter Seeburg for generously supplying the KA1 and KA2 cDNA plasmids. We thank Drs. Lynne Hudson, David Ledbetter, Chris McBain, and Steve Scherer for critically reading the manuscript and for discussion. This work was partially supported by the Fund for Medical Scientific Research (Fonds de la Recherche Scientifique Médicale, Belgium), the Belgian Program on Interuniversity Attraction Poles, by grants from Associazione Italiana per la Ricerca sul Cancro and Telethon, and by the National Cancer Institute, Department of Health and Human Services, under contract NO1-CO-74101 with Advanced BioScience Laboratories. C.S. is Research Director of the National Fund for Scientific Research (Fonds National de la Recherche Scientifique, Belgium).

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