

Chromosomal localization of genes encoding guanine nucleotide-binding protein subunits in mouse and human

(recombinant inbred strains/restriction fragment length polymorphisms/gene mapping/syntenic/somatic cell hybrids)

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ABSTRACT A variety of genes have been identified that specify the synthesis of the components of guanine nucleotide-binding proteins (G proteins). Eight different guanine nucleotide-binding α -subunit proteins, two different β subunits, and one γ subunit have been described. Hybridization of cDNA clones with DNA from human-mouse somatic cell hybrids was used to assign many of these genes to human chromosomes. The retinal-specific transducin subunit genes *GNAT1* and *GNAT2* were on chromosomes 3 and 1; *GNAI1*, *GNAI2*, and *GNAI3* were assigned to chromosomes 7, 3, and 1, respectively; *GNAZ* and *GNAS* were found on chromosomes 22 and 20. The β subunits were also assigned—*GNB1* to chromosome 1 and *GNB2* to chromosome 7. Restriction fragment length polymorphisms were used to map the homologues of some of these genes in the mouse. *GNAT1* and *GNAI2* were found to map adjacent to each other on mouse chromosome 9 and *GNAT2* was mapped on chromosome 17. The mouse *GNB1* gene was assigned to chromosome 19. These mapping assignments will be useful in defining the extent of the $G\alpha$ gene family and may help in attempts to correlate specific genetic diseases with genes corresponding to G proteins.

Guanine nucleotide-binding proteins (G proteins) mediate intracellular responses to a wide variety of extracellular stimuli. They are generally found as heterotrimers composed of an α , β , and γ subunit and are associated with transmembrane receptors. G proteins respond to the activation of specific receptors by ligand (e.g., hormone, neurotransmitter) or by physical stimuli (e.g., light absorption) and participate in the process of transducing these signals into changes in the intracellular level of second messengers. The activated receptor stimulates the exchange of guanosine diphosphate (GDP) bound to the α subunit of the G protein for guanosine triphosphate (GTP), resulting in the disassociation of $G_{\alpha-GTP}$ from the β - γ complex. The G_{α} nucleotide complex and perhaps the $G_{\beta\gamma}$ complex as well are able to interact with effector molecules such as adenylate cyclase, phosphodiesterases, phospholipases, and transmembrane channels to evoke a cellular response (1-5).

On the basis of both molecular cloning and biochemical characterization, it has become clear that there are multiple genes that encode a variety of homologous α -subunit proteins. These can be divided into a number of subgroups based both on their function and on their similarities in amino acid sequence and cellular localization. Some of the α -subunit proteins, for example, are found only in specific terminally differentiated cells. Thus, the transducin $\alpha 1$ ($T_{\alpha 1}$) protein is found only in retinal rod photoreceptor cells, while the

transducin $\alpha 2$ ($T_{\alpha 2}$) subunit is present only in cone cells (6). Other G_{α} subunit proteins are found to be expressed ubiquitously. For example, $G_{s\alpha}$ is found in a large variety of cells; it functions to couple the activation of certain receptors to adenyl cyclase stimulation (1). Another group of G_{α} subunits is represented by the $G_{i\alpha}$ proteins. They include a small subfamily of polypeptides $G_{i\alpha 1}$, $G_{i\alpha 2}$, and $G_{i\alpha 3}$ (2, 7, 8). These proteins differ from each other by only 10-20% in their amino acid sequences and from the other G_{α} proteins by 30-60% in amino acid sequence. Transcripts corresponding to all three $G_{i\alpha}$ cDNAs have been found in cloned cell lines in tissue culture. However, it is clear that each member of the G_i subfamily represents a distinct gene product since the amino acid sequence of a particular $G_{i\alpha}$ protein is almost identical in different mammals. Thus, for example, $G_{i\alpha 1}$ in rats and humans shows 98% amino acid sequence identity. On the other hand, while the $G_{o\alpha}$ protein, which is found ubiquitously in brain tissue, has sequence similarity to the G_i subgroup, it can be clearly distinguished as representing a different family (for review, see ref. 9). Finally, another G protein encoding gene was identified by cDNA cloning and called $G_{z\alpha}$. The corresponding protein differs strikingly from other G_{α} subunits in amino acid sequences in a number of regions and it appears to be highly enriched in neural tissue (10, 41). Considering the great diversity of interactions that appear to be mediated by G proteins, it is not surprising to find a variety of subunits, and we may anticipate that other homologous genes encoding other G_{α} subunit families will be found.

The other components of the G protein heterotrimer also show diversity. It has been reported that there are two distinct β subunits (β_1 and β_2), and both are expressed in a variety of different tissues (11, 12). Furthermore, there is clearly diversity in the γ subunits, since the only cDNA that has been cloned and sequenced thus far is found to be restricted to retinal tissues; yet γ subunits are found associated with β in all tissues that have been examined (13). If G_{α} subunits can interact combinatorially with β and γ subunits, a large variety of complexes with different functional properties could be formed. It is necessary, therefore, to determine the limits of diversity in members of the G-protein family. One way to further examine the organization of this multigene family is to classify individual genes by their relative chromosomal locations. In this paper, we report the relative map positions of a number of G-protein-determining genes.

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Abbreviations: G protein, guanine nucleotide-binding protein; $T_{\alpha 1}$ and $T_{\alpha 2}$, transducin $\alpha 1$ and $\alpha 2$ protein subunits; RI, recombinant inbred; RFLP, restriction fragment length polymorphism; SDP, strain distribution pattern.

MATERIAL AND METHODS

Nomenclature. Probes of cDNA clones and polypeptides are referred to as they have been in the literature (14). Thus, the transducin α subunits are $T_{\alpha 1}$ and $T_{\alpha 2}$. The members of the G_i subfamily are $G_{i\alpha 1}$, $G_{i\alpha 2}$, $G_{i\alpha 3}$, etc. However, the corresponding genes are referred to by the nomenclature adopted at the Ninth International Workshop on Human Gene Mapping (1987). The letters GN refer to the guanine nucleotide-binding protein product. The third letter refers to the nature of the α -subunit subfamily. Thus, the two transducin α genes would be *GNAT1* and *GNAT2*. The members of the G_i subfamily are *GNAI1*, *GNAI2*, and *GNAI3*. The genes that encode the β_1 and β_2 subunits are referred to as *GNB1* and *GNB2*.

Genomic DNA Isolation and Digestion. Mouse DNA from parental and B \times D recombinant inbred (RI) strains were purchased from The Jackson Laboratory; A \times B/B \times A RI DNA was prepared from liver and kindly donated by M. Nesbitt (University of California, San Diego). Microcell hybrid clones retaining various mouse chromosomes in a rat or hamster background were grown and DNA was extracted as described (15–17). The human \times mouse somatic cell hybrid lines were the same as described (18) and DNA was prepared as described (18). High molecular weight DNA was digested with a 4- to 6-fold excess of restriction enzyme (Bethesda Research Laboratories). DNA fragments were separated by agarose gel electrophoresis and transferred to GeneScreenPlus (DuPont) by the method of Southern or by the alkaline method (19, 20).

DNA Probes. cDNA probes were obtained as follows: *GNAT1* and *GNAT2* were isolated from bovine retina and were provided by M. Lochrie (California Institute of Technology, Pasadena, CA) (21); *GNAI1*, *GNAI2*, *GNAI3*, and *GNAS* were isolated from rat olfactory epithelium by Jones and Reed (7). *GNB1* and *GNB2* were isolated from human HL-60 myeloid leukemia cells by T. Amatruda (California Institute of Technology) (11).

Probe DNA was labeled by nick-translation or by the random oligonucleotide priming method (22) and hybridization was carried out at 65°C in 6 \times SSC (1 \times SSC = 0.15 M sodium chloride/15 mM sodium citrate)/2% bovine serum albumin/2% Ficoll 400/2% polyvinylpyrrolidone/1% sodium dodecyl sulfate (SDS)/10% dextran sulfate for restriction fragment length polymorphism (RFLP) analysis, or in 0.5 M sodium phosphate, pH 7/1 mM EDTA/7% SDS/1% bovine serum albumin at 52°C–68°C for somatic cell hybrid analysis. Membranes were washed at 55°C–65°C with 0.1 \times –0.2 \times SSC/0.1% SDS and autoradiographed with Kodak XAR-5 x-ray film with an intensifying screen at –70°C. The methods for the use of RFLPs and RI strains of mice for mapping in our laboratory have been described (23).

RESULTS

Mapping with RFLPs in Recombinant Inbred Mice. To demonstrate that we could clearly follow each gene that corresponded to a specific cDNA probe without apparent cross-hybridization with other G protein-determining genes, the restriction fragment patterns for heterologous probes were examined. Each of the probes derived from either bovine, rat, or human was hybridized and washed at high stringency (0.1 \times SSC, 65°C) with DNA from A/J mice that was digested with a variety of restriction enzymes. Fig. 1 shows that each $G_{i\alpha}$ subunit probe gave a unique pattern of restriction fragments that could easily be distinguished. In addition, the hybridization pattern of probes isolated from human cells (HL60 myeloid cells) corresponding to $G_{i\alpha 2}$ (T. Amatruda, personal communication) was essentially the same as the pattern found with the $G_{i\alpha 2}$ cDNA probe derived

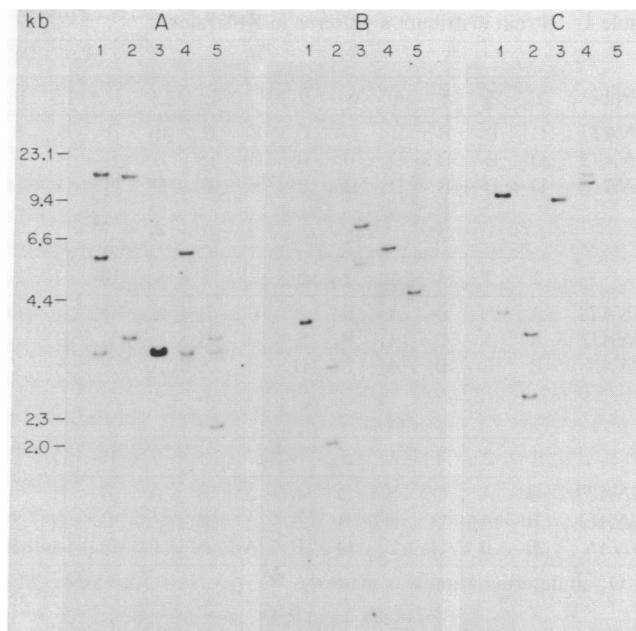


FIG. 1. Southern blot comparison of *GNAI1*, *GNAI2*, and *GNAI3*. Mouse A/J DNA was digested with *Bam*HI (lane 1), *Bgl* II (2), *Hind*III (3), *Pst* I (4), and *Xba* I (5), transferred to GeneScreenPlus, and probed with $G_{i\alpha 1}$ (A), $G_{i\alpha 2}$ (B), or $G_{i\alpha 3}$ (C).

from rat olfactory epithelial cells. Homologous cDNA probes corresponding to a specific isoform of G_{α} from rat, human, and bovine tissue each hybridized with the same set of restriction fragments in the mouse. This demonstrates that each probe detects a unique set of restriction fragments. Thus, while there is a great deal of similarity in the amino acid sequences of the α subunits, high stringency hybridization with mouse DNA distinguishes between them. These results support the assumption that each probe from the different sources is characteristic for at least one gene in the mouse genome.

To use the probes to map the corresponding genes, parental mouse DNAs (A/J, C57BL/6J, and DBA/2J) were digested with a battery of restriction endonucleases and inspected for polymorphism after hybridization with specific probes. When a polymorphism was found by using a particular restriction enzyme, then DNA from the appropriate RI strains digested with the same enzyme was hybridized to the probe and the polymorphic pattern was scored for resemblance to one parental strain or the other. This procedure was followed with all of the available probes and the resulting strain distribution pattern (SDP) of polymorphisms is shown in Table 1. Linkage was determined by comparing these newly determined SDPs to the SDPs determined for previously mapped genes. Linkage results are summarized in Table 2 and Fig. 2. Linkage and statistical analysis were calculated as described (24).

Several RFLPs were associated with the $T_{\alpha 1}$ probe. SDPs were determined in the B \times D RI strains for polymorphisms found by using *Kpn* I and *Xba* I; the SDPs were identical. Comparison of this SDP with other markers indicates linkage on chromosome 9 to the LTW-3 (a liver protein variant) gene and the FV-2 (Friend virus insertion) locus. The SDP was also obtained for an *Eco*RI polymorphism found in the A \times B and B \times A RI strains. Although conclusive linkage to a known marker was not established in this system, weak linkage [>8 centimorgans (cM)] to the β -galactosidase gene on chromosome 9 was indicated. Interestingly, the SDP for a *Pst* I polymorphism identified with *GNAI2* was identical to that of *GNAT1* in 42 of 42 A \times B and B \times A strains. Thus,

Table 1. Strain distribution patterns in RI strains

Probe	B × D RI strain																															
	1	2	5	6	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	27	28	29	30	31	32						
<i>GNAT1</i>	D	B	B	B	D	B	B	B	B	B	B	B	D	D	D	B	D	B	B	D	B	B	B	B	D	D						
<i>GNAT2</i>	D	B	D	D	B	B	D	D	B	B	B	B	D	B	B	B	D	B	D	D	B	D	B	D	D	D						
<i>GNB1</i>	D	B	B	D	D	B	B	B	D	B	B	D	D	B	D	B	B	O	D	B	D	O	B	D	B	D						

Probe	A × B RI strain																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
<i>GNAT1</i>	A	A	B	A	B	B	B	B	B	B	B	O	A	A	A	O	B	A	A	A	A	A	A	B	B
<i>GNAI2</i>	A	A	O	A	B	B	B	B	B	B	B	A	A	A	A	O	B	A	A	A	A	A	A	B	B
<i>GNAS</i>	B	B	B	A	B	B	B	A	A	A	A	O	B	B	A	O	B	B	B	B	B	A	A	A	B

Probe	B × A RI strain																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
<i>GNAT1</i>	O	A	O	B	O	A	A	B	A	B	B	A	A	B	O	A	B	A	A	B	O	A	B	B	A
<i>GNAI2</i>	B	A	O	B	B	A	A	B	A	B	B	A	A	B	O	A	B	A	A	B	O	A	B	B	A
<i>GNAS</i>	B	B	O	B	O	B	A	A	B	B	A	B	B	B	O	B	A	B	O	B	O	B	B	B	A

O, no determination was made.

these two genes are tightly linked and are probably within 1 cM of each other. They are both on chromosome 9.

A polymorphism was also detected by *Pvu* II digestion and hybridization with $T_{\alpha 2}$ in the B × D system. The *GNAT2* gene was found to map adjacent to Hba-ps4 (a hemoglobin α pseudogene) on chromosome 17 (see Table 2; Fig. 2). A SDP was found using $G_{\beta 1}$ as a probe with *Bam*HI restriction of DNA from the B × D RI strains. The *GNB1* gene was found to be weakly linked to the *POMC* gene on chromosome 19. To make a clearer assignment, somatic cell hybrid lines containing different mouse chromosomes in a rat or hamster background were used. After *Hind*III digestion and hybridization with the $G_{\beta 1}$ probe, the pattern of hybridization to the cell lines that was found was consistent with the assignment of *GNB1* to chromosome 19. The mouse-rat and mouse-hamster somatic cell hybrids were also used to confirm the location of *GNAI2* on chromosome 9 (data not shown).

A polymorphism was found using the $G_{S\alpha}$ probe to hybridize to *Eco*RI- or *Pst* I-digested A × B RI DNA. The SDP determined was clearly dissimilar to those of the other α subunits, but no statistically significant linkage to other markers was found. However, using somatic cell hybrids we could show a *GNAS*-specific band that segregated with chromosome 2 (data not shown). The map positions found are summarized in Table 2. No RFLPs were detected using $G_{\beta 2}$, $G_{\alpha 1}$, $G_{\alpha 3}$, or $G_{Z\alpha}$ with the three parental strains digested with 24 different restriction enzymes.

Mapping in Human-Mouse Somatic Cell Hybrids. The *G* protein cDNAs were used to probe Southern blots of mouse and human DNA to assay for interspecific differences. A

panel of mouse-human somatic cell hybrid clones (18) was probed and discordancies between the presence or absence of a human chromosome and a hybridizing human-specific band(s) were scored. *GNAT1*, *GNAT2*, *GNAI1*, *GNAI3*, *GNB1*, *GNB2*, and *GNAS* were found to map to human chromosomes 3, 1, 7, 1, 1, 7, and 22, respectively, each showing no discordancies with these assignments. *GNAS* appears to map to chromosome 20, although the analysis indicates that the assignment is not completely concordant. The low level of discordancy is most likely due to the inability to detect a human band in one hybrid cell line with low levels of retention of human chromosome 20. The chromosomal locations of these genes in both mouse and humans are summarized in Table 3.

In some of the hybridization experiments with human-mouse somatic cell hybrids, it was possible to identify more than one human-specific restriction fragment that could be followed through the analysis. In most cases, the same chromosome assignment was found for each fragment. In the case of the mapping of *GNAI2* (using the rat $G_{\alpha 2}$ probe) three human chromosome-specific bands were found after digestion with *Hind*III and hybridization at low stringency ($0.1 \times$ SSC, 55°C). They corresponded to 9.2 kilobase pairs (kbp), 4.3 kbp, and 2.6 kbp. The chromosome assignment derived from the pattern of hybridization to two of the restriction fragments (9.2 and 2.6 kbp) was chromosome 3. However, the pattern of hybridization with the 4.3-kb band resulted in an assignment to another chromosome. To further test the chromosomal assignment of *GNAI2*, the mapping procedure was repeated at high stringency ($0.1 \times$ SSC, 65°C) using two

Table 2. Map position in RI strains

Gene	Probe	RFLP	RI strain	Linkage	Chromosome
<i>GNAI1</i>	$G_{\alpha 1}$	*			
<i>GNAI2</i>	$G_{\alpha 2}$	<i>Pst</i> I	A × B	$T_{\alpha 1}$ 0.0 (0–2.4) cM	9
<i>GNAI3</i>	$G_{\alpha 3}$	*			
<i>GNAS</i>	$G_{S\alpha}$	<i>Eco</i> RI, <i>Pst</i> I	A × B	No significant linkage to known markers	2
<i>GNAT1</i>	$T_{\alpha 1}$	<i>Eco</i> RI	A × B	$G_{\alpha 1}$ 0.0 (0–2.4) cM	9
		<i>Xba</i> I	B × D	LtW-3 3.7 (0.7–14.7) cM	
				FV-2 3.8 (0.7–15.7) cM	
				BGL 5.2 (1.2–19.6) cM	
<i>GNAT2</i>	$T_{\alpha 2}$	<i>Pvu</i> II	B × D	Hba-Ps4 2.3 (0.2–10.7) cM	17
<i>GNAS</i>		*			
<i>GNB1</i>	$G_{\beta 1}$	<i>Bam</i> HI	B × D	No significant linkage to known markers	19
<i>GNB2</i>	$G_{\beta 2}$	*			

*No RFLP detected using 24 restriction enzymes.

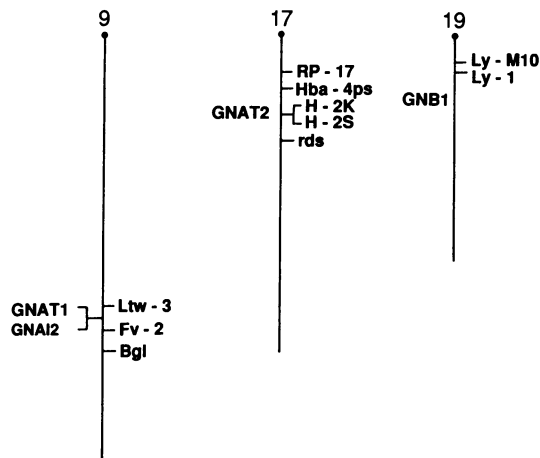


FIG. 2. Localization of G protein genes on mouse chromosomes relative to neighboring genes. The position for *GB1* is an approximation as only weak (>6–8 cM) linkage was detected. *GNAS* was mapped to chromosome 2, although a specific location was not identified.

other enzymes (*Bgl* II and *Pst* I). Two restriction fragments were followed in the *Bgl* II digest and both could be unequivocally assigned to chromosome 3. One fragment was used for analysis with the *Pst* I digest and it also was assigned to chromosome 3. Southern hybridization using the $G_{i\alpha 2}$ cDNA probe with human DNA revealed a more complex pattern of restriction fragments than the pattern seen when mouse DNA was used. Therefore, it is possible that there are multiple *GNAI2* genes or pseudogenes in human chromosomes that are not present in the mouse genome.

DISCUSSION

The exact number of genes encoding α subunits of G proteins is not known (1–8, 10, 21). There are at least eight α genes, two β genes, and more than one γ gene based on molecular cloning studies and hybridization experiments in mammals. It is likely that additional genes exist. Recently, a number of groups have reported the independent isolation of *GNAI*-like genes. Jones and Reed (7) isolated three distinct forms of *GNAI* from rat corresponding to *GNAI1*, *GNAI2*, and *GNAI3*, while Beals *et al.* (25) obtained the corresponding cDNA clones from human B-cell libraries. Based on nucleotide sequence homology, *GNAI1* appears to correspond to the cDNAs isolated by Sullivan *et al.* (26) and Itoh *et al.* (27), while *GNAI2* corresponds to those of Nukada *et al.* (28) and Michel *et al.* (29). *GNAI3* is distinct from the other genes and appears to correspond to the human cDNA isolated by Didsbury and Snyderman (30). Southern blot comparisons show that these three cDNAs are clearly different (Fig. 1). Neer *et al.* (31) have cloned two cDNAs, which they call α_i

Table 3. Comparative map positions in mouse and human

Probe	Chromosome	
	Mouse	Human
$GN_{\alpha 11}$	9	3
$GN_{\alpha 12}$	17	1
$GN_{\alpha i1}$	—	7
$GN_{\alpha i2}$	9	3
$GN_{\alpha i3}$	—	1
$GN_{\alpha z}$	—	22
$GN_{\alpha s}$	2	20
$GN_{\beta 1}$	19	1
$GN_{\beta 2}$	—	7

and α_h . Based on the Southern blot banding patterns and chromosome assignments, α_h appears to be *GNAI2*, and α_i is probably *GNAI1*. Neer and coworkers have mapped the *GNAI1* gene to human chromosome 7. However, they found that α_h hybridized to two human-specific bands in *Eco*RI-digested DNA, which segregates to different human chromosomes. Neer *et al.* (31) scored one of these bands, assigning it to chromosome 12. In *Hind*III-digested DNA we observe these bands with *GNAI2*, two of them are concordant with chromosome 3 and one segregates with chromosome 12. Repeating the experiment using two other restriction enzymes we confirmed the chromosome 3 assignment. Thus, in humans there may be two genes with significant cross-reactivity to *GNAI2*; alternatively, the chromosome 12 assignment may correspond to a pseudogene with a sequence that is similar to *GNAI2*.

We have shown that the *GNAI2* gene in mouse maps adjacent to the *GNAT1* gene on chromosome 9. Recently, Ashley *et al.* (32) have mapped a *GNAI* gene to chromosome 9 in the mouse. In the human, *GNAT1* maps to chromosome 3 in a region that shows syntenic relationships with the distribution of markers on mouse chromosome 9. Thus, it is reasonable to suggest that *GNAT1* and *GNAI2* may be closely linked on chromosome 3 in humans as they are on chromosome 9 in mice.

Although several members of the G protein multigene family are closely related (e.g., *GNAT1* and *GNAT2*; *GNAI1*, *GNAI2*, and *GNAI3*; *GNB1* and *GNB2*), these relationships are not observed at the level of chromosomal organization. Some clustering of related genes is found on chromosome 9 in mouse; however, the genes that are potentially clustered are not those that are most closely related in DNA sequence. It is difficult at this point to assign any significance to this arrangement. Recently, Nakafuku *et al.* (33) found a G protein in yeast with a great deal of conserved sequence that was homologous to $G_{i\alpha}$. This suggests that the G protein family may be very ancient. Some genes may have remained tightly linked through evolution (34). The syntenic group in which *GNAT1* and *GNAI2* are found also contains *Acy-1* (aminoacylase-1) and *Bgl* (β -galactosidase) and extends over a region >10 cM (35). *GNAS* may also lie in a human–mouse synteny group, as several human chromosome 20 markers are also found on mouse chromosome 2. Ashley *et al.* (32) also found that *GNAS* mapped to mouse chromosome 2. The genes mapped thus far do not necessarily account for all the members of the *GNA* gene family, and we expect that more members of this group will be found.

The *GNB1* and *GNB2* proteins share 90% protein sequence homology within a species, while between species each of these proteins is identical. This suggests that divergence of each gene has been constrained and implies that these two genes may interact with different effector or receptor molecules to elicit potentially different responses in signal transduction. The two β genes map to different human chromosomes. While no position has yet been determined for *GNB2* in mouse, on the basis of studies with somatic cell hybrids, it clearly does not lie on chromosome 19 adjacent to *GNB1* (data not shown).

G proteins have been implicated in the etiology of at least one human disease, pseudohypoparathyroidism type Ia (36). Decreased levels of G_s , observed in erythrocytes, result in a partial uncoupling of receptor-bound parathyroid hormone and intracellular adenylate cyclase levels. Other hormones also appear to be affected. It is likely that G proteins are involved in other diseases (2, 37, 38). An examination of the genes mapped in this study reveals at least one G protein gene in the vicinity of a known retinal marker. *GNAT2* maps on mouse chromosome 17 near the locus corresponding to retinal degeneration slow (*rds*) (39, 40). The extent of diversity among the G_{α} -subunit genes is not known; eventually

some of them may be found to be associated with diseases that result from defects in sensory transducing systems.

Note Added in Proof. Kaziro and coworkers (41) isolated a human genomic clone and a rat cDNA clone designated G_{α} that corresponds in sequence to the G_{α} clone (10).

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