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INHERITED DISEASES INVOLVING G PROTEINS AND G PROTEIN–COUPLED RECEPTORS*

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■ **Abstract** Heterotrimeric G proteins couple seven-transmembrane receptors for diverse extracellular signals to effectors that generate intracellular signals altering cell function. Mutations in the gene encoding the α subunit of the G protein–coupling receptors to stimulation of adenylyl cyclase cause developmental abnormalities of bone, as well as hormone resistance (pseudohypoparathyroidism caused by loss-of-function mutations) and hormone hypersecretion (McCune-Albright syndrome caused by gain-of-function mutations). Loss- and gain-of-function mutations in genes encoding G protein–coupled receptors (GPCRs) have been identified as the cause of an increasing number of retinal, endocrine, metabolic, and developmental disorders. GPCRs comprise an evolutionarily conserved gene superfamily (1). By coupling to heterotrimeric G proteins, GPCRs transduce a wide variety of extracellular signals including monoamine, amino acid, and nucleoside neurotransmitters, as well as photons, chemical odorants, divalent cations, hormones, lipids, peptides and proteins. Following a brief overview of G protein–coupled signal transduction, we review the growing body of evidence that mutations in genes encoding GPCRs and G proteins are an important cause of human disease.

OVERVIEW OF G PROTEIN–COUPLED SIGNAL TRANSDUCTION

G Protein–Coupled Receptors

All members of the GPCR superfamily share a common structural feature: seven membrane-spanning helices connected by three intracellular loops and three extracellular loops with an extracellular amino terminus and an intracellular carboxy terminus (2). This basic structure has now been verified by X-ray crystallography for rhodopsin (3). Superimposed on the basic structure of GPCRs are a number of

variations relevant to differences in ligand binding, G protein coupling, and interaction with other proteins. Sequence alignment, especially of the transmembrane helices, allows one to divide the superfamily into subfamilies (1, 4). Of these, family 1 is the largest and includes opsins, odorant receptors, and receptors for monoamines, purines, opiates, chemokines, some small peptide hormones, and the large glycoprotein hormones, thyroid stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Family 2 shows essentially no sequence homology to family 1, even within the transmembrane helices. Members include receptors for peptide hormones, such as parathyroid hormone (PTH), parathyroid hormone–related protein (PTHrP), and calcitonin. Family 3 members include the metabotropic glutamate receptors, an extracellular Ca^{2+}-sensing receptor, and putative taste and pheromone receptors. Family 3 GPCRs form dimers, and this may be true of other GPCRs as well.

A general model of GPCR activation postulates that GPCRs are in equilibrium between an activated state and an inactive state (5). These states presumptively differ in the disposition of the transmembrane helices, and in turn, the cytoplasmic domains that determine G protein coupling. Agonists, according to this model, stabilize the activated state. For some family 1 GPCRs, agonists activate the receptor by binding directly within the seven-transmembrane domain and altering the disposition of the helices. For other GPCRs in families 1, 2, and 3, agonist binding involves portions of the receptor's extracellular domain, and the mechanism whereby this signal is transmitted to the seven-transmembrane domain remains to be clarified.

All GPCRs act as guanine nucleotide exchange factors (6). In their activated (agonist-bound) conformation, they catalyze exchange of guanosine diphosphate (GDP) tightly bound to the α subunit of heterotrimeric G proteins for guanosine triphosphate (GTP) (Figure 1). This in turn leads to activation of the α subunit and its dissociation from the G protein $\beta\gamma$ dimer. Both G protein subunits are capable of regulating effector activity. Identified G protein–regulated effectors include enzymes of second-messenger metabolism such as adenylyl cyclase and phospholipase C-β, and a variety of ion channels. Agonist binding to GPCRs thus alters intracellular second-messenger and ion concentrations with resultant rapid effects on hormone secretion, muscle contraction, and a variety of other physiologic functions. Longer-term changes in gene expression are also seen as a result of second messenger–mediated phosphorylation of transcription factors.

G Proteins

The G protein subunits are encoded by distinct genes (7). The α subunit binds guanine nucleotides with high affinity and specificity and possesses intrinsic GTPase activity. The β and γ polypeptides are tightly but noncovalently associated in a functional dimer subunit. There is considerable diversity in G protein subunits, with multiple genes encoding all three subunits. There are at least 16 distinct α subunit genes in mammals. These vary widely in range of expression. Some, such as $G_s\alpha$, which couples many GPCRs to stimulation of adenylyl cyclase and cAMP formation (Figure 1), are ubiquitous; others, such as $G_{t1}\alpha$ (transducin),

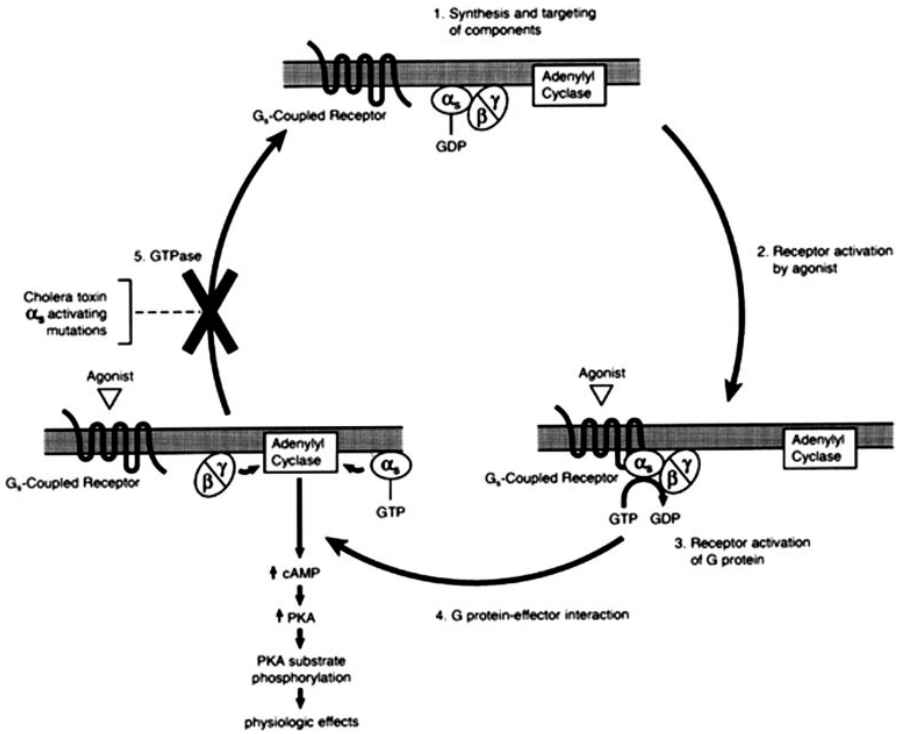

Figure 1 The G protein GTPase cycle (described in text). Potential sites for disease-causing abnormalities are numbered. In each panel, the stippled region denotes the plasma membrane with extracellular above and intracellular below. Under physiologic conditions, effector regulation by G protein subunits is transient and is terminated by the GTPase activity of the α subunit. The latter converts bound GTP to GDP, thus returning the α subunit to its inactivated state with high affinity for the $\beta\gamma$ dimer, which reassociates to form the heterotrimer. The figure shows the G protein G_s with its effector, adenylyl cyclase. Activation of adenylyl cyclase generates the intracellular second messenger, cAMP, which activates protein kinase A (PKA). The latter enzyme phosphorylates a variety of proteins that mediate the physiologic effects of agonists for G_s-coupled receptors. Cholera toxin covalently modifies the $G_s\alpha$ subunit blocking its GTPase activity. Somatic mutations of the $G_s\alpha$ subunit likewise block GTPase activity. In both cases, constitutive activation and agonist-independent cAMP formation result.

which couples the GPCR rhodopsin to cGMP phosphodiesterase in retinal rod photoreceptor cells, are highly localized. There are 5 distinct mammalian β subunit genes and at least 11 γ subunit genes. Within any given cell, multiple distinct GPCRs, G proteins, and effectors are expressed, but there is relative specificity in G protein coupling to GPCRs and to effectors based on unique sequence determinants of the respective components (8).

GENERAL FEATURES OF DISEASES CAUSED BY MUTATIONS IN G PROTEIN AND GPCR GENES

Mutations in genes encoding GPCRs and G proteins can cause loss of function by impairing any of several steps in the normal GPCR/GTPase cycle (Figure 1) (9). G protein and GPCR loss-of-function mutations block signaling in response to the corresponding agonist(s). Gain-of-function mutations in either GPCRs or G proteins lead to constitutive, agonist-independent activation of signaling. In endocrine signaling, loss-of-function mutations cause hormone resistance, mimicking hormone deficiency, whereas gain-of-function mutations mimic states of hormone excess. Defective G protein–mediated signaling can also lead to neoplasia and developmental and sensory abnormalities. The phenotype caused by GPCR and G protein mutations depends on the range of expression of the involved gene and on whether the mutation is somatic or germline. For germline mutations, the phenotype will be pleiotropic for widely expressed genes and more focal for genes expressed more narrowly. In contrast, somatic mutation of even a ubiquitously expressed gene can cause focal manifestations.

G PROTEIN GENE DISORDERS

To date, mutation of two Gα subunits (transducin and $G_s\alpha$) have been associated with human disease. The Nougaret form of autosomal dominant stationary night blindness is associated with a transducin mutation that uncouples it from its effector (10). No Gβ or Gγ mutations have been associated with monogenic human disorders, but a polymorphism of the β_3 subunit has been implicated in several common multigenic disorders.

Activating $G_s\alpha$ Mutations

Activating $G_s\alpha$ mutations encode substitutions of either Arg^{201} or Gln^{227}—two residues that are critical for the GTPase reaction—and lead to constitutive activation by disrupting the intrinsic GTPase activity, which prolongs the active state (Figure 1). These dominant, somatic mutations are present in ~40% of growth hormone–secreting pituitary adenomas (11) and infrequently in nonsecreting and adrenocorticotropic hormone (ACTH)–secreting pituitary tumors, as well as in thyroid, parathyroid, and adrenal tumors (11, 12). In growth hormone–secreting tumors, the mutation is almost always in the maternal allele, presumably because $G_s\alpha$ is expressed almost exclusively from the maternal allele in pituitary cells (13).

Somatic $G_s\alpha$ Arg^{201} mutations are also present in fibrous dysplasia (FD) of bone (14) and in a more widespread tissue distribution in the McCune-Albright syndrome (MAS) (15, 16). MAS is classically defined by the triad of polyostotic FD, café-au-lait skin lesions, and gonadotropin-independent sexual precocity (15), although these patients may also develop tumors (or nodular hyperplasia)

of pituitary somatotrophs, thyroid, or adrenal cortex with associated hormonal oversecretion and other nonendocrine abnormalities (e.g., cardiomyopathy, sudden death, liver abnormalities) (16). It is believed that the somatic mutation in MAS patients occurs early in development, and therefore the clinical spectrum in each individual is determined by the tissue distribution of mutant-bearing cells (15). Although MAS is generally not inherited, presumably because $G_s\alpha$-activating mutations are lethal in the germline, one patient with severe skeletal, endocrine, and developmental abnormalities was reported to possibly have a germline Arg^{201} Leu mutation (17). $G_s\alpha$-activating mutations have also been identified in intramuscular myxomas, both those that occur alone and those that present with accompanying FD (Mazabraud syndrome) (18).

Most, if not all, of the clinical manifestations associated with $G_s\alpha$-activating mutations result from increased intracellular cAMP level. In many endocrine organs, growth and hormone secretion are stimulated by trophic hormones that activate G_s/cAMP pathways, and constitutive G_s activation leads to endocrine tumors and hormonal hypersecretion in the absence of circulating trophic hormones. FD is a focal bone lesion consisting of immature mesenchymal cells with interspersed woven bone spicules and cartilaginous islands. This lesion results from excess cAMP within bone marrow stromal cells, which stimulates their proliferation and alters their differentiation (19). The hypophosphatemia often associated with MAS appears to result from hypophosphatemic factors secreted from FD lesions (20). Hyperpigmentation in MAS results from excess cAMP in melanocytes, which stimulates the expression of tyrosinase, the rate-limiting enzyme for melanin production (21). The cardiac manifestations occasionally associated with MAS likely reflect the effects of G_s/cAMP overstimulation in cardiomyocytes.

Inactivating $G_s\alpha$ Mutations

ALBRIGHT HEREDITARY OSTEODYSTROPHY Patients who inherit a heterozygous $G_s\alpha$ null mutation develop Albright hereditary osteodystrophy (AHO), a syndrome characterized by one or more of the following clinical features: short stature, brachydactyly, subcutaneous ossifications, centripetal obesity, depressed nasal bridge, hypertelorism, and mental or developmental deficits (22, 23). The severity of the AHO phenotype is variable, and some patients with $G_s\alpha$ mutations have few or no symptoms. Although the ectopic ossifications in AHO are generally subcutaneous and limited, some patients develop progressive osseous heteroplasia, a severe form of ossification that invades the deep tissues (24).

PSEUDOHYPOPARATHYROIDISM TYPE 1a In addition to the AHO phenotype, patients who inherit $G_s\alpha$ mutations from their mother also develop resistance to various hormones (PTH, TSH, LH, and FSH) that stimulate G_s/cAMP in their target tissues, a condition referred to as pseudohypoparathyroidism type 1a (PHP1a) (22, 23). In contrast, patients who inherit the same mutations from their father develop only the AHO phenotype, a condition also referred to as

pseudopseudohypoparathyroidism (PPHP). This is because $G_s\alpha$ is imprinted in a tissue-specific manner. Although $G_s\alpha$ is biallelically expressed in most tissues, it is expressed primarily from the maternal allele in various hormonal target tissues, including renal proximal tubule, thyroid, and pituitary (13, 25). Null mutations in the active maternal allele lead to $G_s\alpha$ deficiency and hormone resistance, whereas mutation of the inactive paternal allele has little effect on $G_s\alpha$ expression or hormonal signaling. In fact, the $G_s\alpha$ gene *GNAS* at 20q13 has multiple gene products owing to the use of alternative promoters that are also imprinted (22). In most other tissues, $G_s\alpha$ is not imprinted, and therefore its expression is similarly reduced by ~50% in both PHP1a and PPHP (23). $G_s\alpha$ haploinsufficiency probably leads to the AHO phenotype (22). One mutation (Ala366Ser) produces both PHP1a and gonadotropin-independent precocious puberty in males. This mutation leads to increased GDP dissociation, which at core body temperature denatures the protein, resulting in PHP1a. At the lower temperature of the testis, the mutant protein is stable but is activated because it can bind GTP in the absence of receptor stimulation (26).

$G_s\alpha$ Imprinting Defects: Pseudohypoparathyroidism Type 1b

Patients with pseudohypoparathyroidism type 1b (PHP1b) have renal PTH resistance in the absence of AHO or resistance to other hormones (except mild TSH resistance in some cases). Most cases of PHP1b are sporadic, but it can be familial. In these families, PTH resistance only occurs when the disease is inherited maternally, similar to the parental inheritance pattern of PTH resistance within AHO kindreds (27). Familial PHP1b has been mapped to 20q13 in the vicinity of *GNAS* (27). However, erythrocyte G_s function is normal in PHP1b patients (23), ruling out $G_s\alpha$ null mutations.

Within *GNAS* is an imprinted region (the exon 1A region) located just upstream of the $G_s\alpha$ promoter in which the DNA is methylated on the maternal allele (28). In virtually all PHP1b patients, the maternal-specific methylation of exon 1A is absent, consistent with failure to establish a maternal imprint in the oocyte (28). In one case, PHP1b was associated with paternal uniparental disomy of chromosome 20, which results in the same imprinting pattern (29). Familial PHP1b presumably results from mutations that disrupt the establishment of the maternal imprint, although no specific mutations have been identified to date (27, 29).

In PHP1b, both *GNAS* alleles have a paternal-specific imprinting pattern. In renal proximal tubules, this probably results in $G_s\alpha$ deficiency and PTH resistance because $G_s\alpha$ is normally expressed primarily from the maternal allele (22). In most other tissues, $G_s\alpha$ expression would be unaffected by the imprinting defect because in these tissues it is normally expressed equally from both parental alleles. This would explain the lack of $G_s\alpha$ haploinsufficiency in erythrocytes or the AHO phenotype in PHP1b patients (23). The exon 1A region appears to be important for the tissue-specific imprinting of $G_s\alpha$, although the specific mechanisms have not been delineated (22, 28). In one kindred, three affected siblings had a $G_s\alpha$

mutation that deletes residue Ile^{382} within the carboxyl terminus, which results in selective uncoupling of $G_s\alpha$ from the PTH receptor (30).

Role of $G\beta_3$-C825T Polymorphism in Multigenic Disorders

A single base substitution (C825T) polymorphism within the $G\beta_3$ subunit was identified and initially shown to be associated with hypertension (31). More recent studies link the C825T allele to other features of the metabolic syndrome, including obesity and insulin resistance (32, 33), although these associations have not been confirmed in all studies (34). The C825T polymorphism generates a shortened $G\beta_3$ through alternative splicing, which enhances signaling through G_i pathways (31). The mechanisms by which this variant affects G_i signaling or human phenotypes are presently unknown.

DISEASES CAUSED BY MUTATIONS OF GPCR GENES

GPCR Gene Loss-of-Function Mutations

Clinically significant impairment of signal transduction generally requires loss of function of both alleles of a GPCR gene; thus, most such diseases are autosomal recessive, but there are several exceptions (Table 1). Loss-of-function

TABLE 1 Diseases caused by GPCR loss-of-function mutations

Receptor	Disease	Inheritance
Cone opsins	Color blindness	X-linked; autosomal recessive
Rhodopsin	Retinitis pigmentosa	Autosomal dominant; recessive
V2 vasopressin	Nephrogenic diabetes insipidus	X-linked
ACTH	Familial ACTH resistance	Autosomal recessive
LH	Male pseudohermaphroditism	Autosomal recessive
Ca^{2+} sensing	Familial hypocalciuric hypercalcemia	Autosomal dominant
Ca^{2+} sensing	Neonatal hyperparathyroidism	Autosomal recessive
Endothelin-B	Hirschsprung disease	Complex
FSH	Hypergonadotropic ovarian failure	Autosomal recessive
TSH	Congenital hypothyroidism	Autosomal recessive
TRH	Central hypothyroidism	Autosomal recessive
GHRH	Growth hormone deficiency	Autosomal recessive
GnRH	Central hypogonadism	Autosomal recessive
Melanocortin 4	Extreme obesity	Codominant
PTH/PTHrP	Blomstrand chondrodysplasia	Autosomal recessive

mutations may be missense as well as nonsense or frameshift mutations that truncate the normal receptor protein. They may involve any portion of the receptor, although the membrane-spanning helices are a particularly frequent site (35). Loss-of-function mutations of receptors for ACTH, TSH, FSH, and the hypothalamic hormones—gonadotropin-releasing hormone (GnRH) (36), thyrotropin-releasing hormone (TRH), and growth hormone–releasing hormone (GHRH)—mimic deficiency of the respective hormones. Subjects with heterozygous loss-of-function mutations of the TSH receptor gene are generally euthyroid with compensatory elevated serum TSH, but homozygous mutations result in congenital hypothyroidism associated with a hypoplastic or even absent thyroid gland (37, 38).

Loss-of-function mutations in LH, endothelin B, and PTH/PTHrP receptors cause developmental anomalies, reflecting the critical role of the respective hormones in normal development. Hirschsprung disease, congenital intestinal obstruction, is caused by lack of enteric ganglia secondary to defects in development of neural crest–derived cells. Loss-of-function mutations of the endothelin type B receptor can lead to Hirschsprung disease, but inheritance is complex (39). As many as 20% of subjects with heterozygous endothelin B receptor mutations may show the disease, but even when homozygous mutations are present, penetrance for Hirschsprung disease is not complete. Homozygotes may also show pigmentary defects (Shah-Waardenburg syndrome), presumably because melanocytes are also neural crest–derived. Loss-of-function mutations of the RET gene encoding a tyrosine kinase receptor for several neurotrophic factors can also cause Hirschsprung disease, and evidence in humans and mice supports genetic interactions between mutations in the RET gene and endothelin B receptor gene in the complex inheritance of this disease.

Loss-of-function mutations of both copies of the LH receptor gene cause a rare form of 46,XY male pseudohermaphroditism known as Leydig cell hypoplasia (40). Absence of functional PTH/PTHrP receptors causes a rare, lethal form of dwarfism known as Blomstrand chondrodysplasia (41). Defects in breast and tooth formation in affected subjects show that this receptor is important for normal development of bone, teeth, and breast.

X-linked nephrogenic diabetes insipidus (renal vasopressin resistance) is caused by loss-of-function mutations in the V2 vasopressin receptor gene located on the X chromosome (42). Males inheriting a mutant gene develop the disease, whereas most females do not show overt disease because random X inactivation results, on average, in 50% normal receptor genes. Identification of the mutation in carrier females facilitates early treatment of affected male neonates to avoid hypernatremia and brain damage. In familial hypocalciuric hypercalcemia, there is relative resistance to extracellular Ca^{2+} action caused by loss-of-function mutation of one copy of the gene encoding the Ca^{2+}-sensing receptor that controls PTH secretion from the parathyroid and reabsorption of Ca^{2+} by the kidney (43). If two defective copies are inherited, extreme Ca^{2+} resistance causing neonatal severe primary hyperparathyroidism results. Loss-of-function mutations in the gene encoding the melanocortin 4 receptor, which regulates hypothalamic pathways controlling

appetite and energy metabolism, result in a distinct obesity syndrome characterized by hyperphagia and increased linear growth (44). Inheritance is codominant, with homozygotes showing a more severe phenotype than heterozygotes. Autosomal dominant retinitis pigmentosa is an exceptional case in which certain mutations in one copy of the rhodopsin gene impair normal folding and synthesis of rhodopsin (45). This ultimately leads to degeneration of retinal rod photoreceptor cells in which rhodopsin synthesis accounts for a high proportion of total protein synthesis.

GPCR Gene Gain-of-Function Mutations

Given the dominant nature of activating mutations, most diseases caused by GPCR gain-of-function mutations are inherited in an autosomal dominant manner (Table 2). Unlike loss-of-function mutations, GPCR gain-of-function mutations are almost always missense mutations. Activating missense mutations are thought to disrupt normal inhibitory constraints that maintain the receptor in its inactive conformation (5). Mutations disrupting these constraints mimic the effects of agonist binding and shift the equilibrium toward the activated state of the receptor. Germline gain-of-function mutations in the LH and TSH receptor genes may mimic states of hormone excess, familial male precocious puberty (40), and familial nonautoimmune hyperthyroidism (38), respectively. Women inheriting gain-of-function mutations in the LH receptor gene do not show precocious puberty because, unlike in males, the combined action of LH and FSH is required for female pubertal development. As discussed above for activating $G_s\alpha$ mutations, increased cAMP in many endocrine cells leads to increased proliferation and hormone hypersecretion. Thus, somatic gain-of-function mutations of the LH and TSH receptor genes cause sporadic tumors of Leydig cells and the thyroid cells, respectively.

Most germline activating mutations of the Ca^{2+}-sensing receptor gene are not truly constitutively activating. Instead, they increase the receptor's sensitivity to agonist stimulation (43). Because the agonist, extracellular Ca^{2+}, is always present, such mutations lead to suppression of PTH secretion and increased urinary Ca^{2+} excretion at inappropriately low concentrations of serum Ca^{2+}. This results in

TABLE 2 Diseases caused by GPCR gain-of-function mutation

Receptor	Disease	Inheritance
Rhodopsin	Congenital night blindness	Autosomal dominant
LH	Familial male precocious puberty	Autosomal dominant
LH	Sporadic Leydig cells tumors	Somatic
TSH	Familial nonautoimmune hyperthyroidism	Autosomal dominant
TSH	Sporadic hyperfunctional thyroid adenomas	Somatic
Ca^{2+} sensing	Familial hypocalcemia	Autosomal dominant
PTH/PTHrP	Jansen metaphyseal chondrodysplasia	Autosomal dominant

hypocalcemia and relative hypercalcuria. The latter may become clinically significant if calcium supplements and vitamin D are used aggressively to raise the serum Ca^{2+}. Activating mutations of the PTH/PTHrP receptor gene cause Jansen's metaphyseal chondrodysplasia (46). The phenotype includes hypercalcemia and hypophosphatemia mimicking the effects of PTH hypersecretion, but also abnormal bone development (short-limb dwarfism), reflecting the critical role of PTHrP in endochondral bone formation. A mutant PTH/PTHrP receptor has also been identified in human endochondromatosis, a condition characterized by abnormal proliferation and differentiation of growth-plate cartilage cells (47). Normal sensitivity to light depends on constraining rhodopsin tightly in its inactive state under dark conditions. Activating rhodopsin mutations cause congenital night blindness by disrupting normal constraints (45).

GPCR Gene Polymorphisms

Variations in GPCR gene sequence can have important consequences beyond causing Mendelian diseases. Homozygous loss-of-function mutations of the type 5 chemokine receptor confer resistance to HIV infection because this receptor serves as a coreceptor for HIV entry into cells (48). As more polymorphisms are discovered in the human genome, many examples of variations in GPCR gene sequence will be found (35). The challenge will be to elucidate their possible functional significance, for example, whether such differences are important in individual variation in drug response (pharmacogenomics) or whether they could confer susceptibility to disease (complex disease genes). Specific polymorphisms in adrenergic GPCR genes have already been shown to confer susceptibility to congestive heart failure (49).

CONCLUSIONS

By careful study of the phenotypic consequences of naturally occurring mutations in genes encoding G proteins and GPCRs, we can learn a great deal about the normal function of these genes. These mutations also help define critical structure-function relationships. Artificial knockouts of G protein and GPCR genes in mice reveal many nonredundant, functionally important G proteins and GPCRs for which no human disease-causing mutations have yet been identified. There are, moreover, multiple GPCRs (so-called orphans) for which the endogenous agonist is unknown (1). This suggests that further search for disease-causing mutations, informed by careful analysis of relevant phenotypes, is likely to be fruitful. Even more likely is the identification of additional polymorphisms in genes encoding G proteins and GPCRs that play a role in complex inheritance of common diseases.

Identification and study of diseases caused by mutations in G proteins and GPCRs should also lead to advances in novel forms of treatment for such diseases, including development of inverse agonists (5) and "pepducins" (50) to inhibit

constitutively activated GPCRs, and methods to rescue function of misfolded or truncated GPCRs (42).

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