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Human RAS Superfamily Proteins and Related GTPases

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Abstract

The tumor oncoproteins HRAS, KRAS, and NRAS are the founding members of a larger family of at least 35 related human proteins. Using a somewhat broader definition of sequence similarity reveals a more extended superfamily of more than 170 RAS-related proteins. The RAS superfamily of GTP (guanosine triphosphate) hydrolysis–coupled signal transduction relay proteins can be subclassified into RAS, RHO, RAB, and ARF families, as well as the closely related Gα family. The members of each family can, in turn, be arranged into evolutionarily conserved branches. These groupings reflect structural, biochemical, and functional conservation. Recent findings have provided insights into the signaling characteristics of representative members of most RAS superfamily branches. The analysis presented here may serve as a guide for predicting the function of numerous uncharacterized superfamily members. Also described are guanosine triphosphatases (GTPases) distinct from members of the RAS superfamily. These related proteins employ GTP binding and GTPase domains in diverse structural contexts, expanding the scope of their function in humans.

Introduction

GTPases, together with their associated regulators and effectors, participate as central control elements in signal transduction pathways that touch on virtually every aspect of cell biology. Most of these proteins fall within a superfamily named for the RAS oncoprotein. Research into the biochemistry and function of RAS-related GTPases has focused on a relatively small subset of proteins. Genome analysis and gene expression results from multiple sources were used to create an extensive accounting of the genes and proteins that constitute the human RAS superfamily and some more distantly related GTPases (1). Sequence comparison analysis (2) revealed insights into the relationship among members of this signal transduction superfamily.

RAS Biochemistry and Function

RAS superfamily proteins share a basic biochemical activity: GTP (guanosine triphosphate) binding and hydrolysis (Fig. 1). This commonality is directly reflected in the presence in each protein of several characteristic “G box” sequences (3,4). The G1 box [aaaaGxxxxGK**(**S or T**)**, where a = L or I or V or M, and x = any amino acid**]**, also known as a P-loop or Walker A motif (5), is a purine nucleotide binding signature. The G3 box (blbbDxxGl, where l = hydrophilic and b = hydrophobic), which overlaps with the Walker B motif at the invariant aspartic acid residue, is involved in binding a nucleotide-associated Mg^{2+} ion and is also well conserved among superfamily members. Residues of the G4 box [bbbb(N or T)(K or Q)xD] make hydrogen bond contact with the guanine ring (conferring specificity to GTP over ATP) and provide stabilizing interactions with G1 box residues. Amino acids in the G5 box [bbE(A or C or S or T)SA(K or L)] primarily make indirect associations with the guanine nucleotide

and are less well conserved among supergroup members. The G2 box (YDPTIEDSY for HRAS and several other RAS subfamily members) is located in one of two segments that reorient as a function of GDP or GTP binding and provide major components of the effector binding surface. Of all RAS superfamily G2 box sequences, only the threonine residue is highly conserved, but several other residues recur within subfamilies. Mutations in this domain can block association of HRAS with one or more of its downstream effectors (6–8).

RAS proteins share a common mechanism of operation that is tied to nucleotide-regulated conformational shifts [reviewed in (9)]. In the GTP-bound state, they display a binding surface with high affinity for downstream effector proteins [for example, HRAS-GTP has a K_d (dissociation constant) of 18 nM for the protein kinase RAF1 (10)]. The structural changes are confined primarily to two loop regions called switch 1 and switch 2 (11). However, the high-affinity effector-binding conformation of RAS proteins is transient; GTP hydrolysis and release of the γ-phosphate leads to reorientation of effector binding residues, the release of effector proteins (due to reduced affinity), and attenuation of downstream signaling.

The rate-limiting step in RAS protein activation is the exchange of bound GDP for GTP. In most cases this is a slow step (3.4×10^{-4} s^{-1} for HRAS) (12), favoring an inactive steady-state conformation of RAS even in the presence of a high cellular GTP/GDP ratio [~10-fold (13), although this may not be uniform throughout the cell]. This kinetic limitation is the basis for stimulus-induced mechanisms of RAS protein regulation. Guanine nucleotide exchange factors (GEFs, also called guanine nucleotide–dissociation stimulators or GDSs) catalyze the release of GDP (Fig. 1), thus promoting GTP loading and activation of RAS (~sixfold stimulation for HRAS by the exchange factor SOS1) (14). Several GEFs may act on a particular RAS protein [reviewed in (15)], with each GEF responding to distinct upstream stimuli (for example, growth factor receptor phosphorylation or diacylglycerol production), providing multiple avenues for signal regulation. GEF-mediated regulation is also a point of vulnerability for RAS function: RAS mutants that bind GEFs unproductively (e.g., $HRAS^{S17N}$) can dominantly block the activation of endogenous RAS (16,17).

Guanine nucleotide dissociation inhibitors (GDIs) act in opposition to exchange factors. GDIs bind specifically to GDP-bound GTPases and inhibit the release of GDP (18), thus prolonging the inactive state. GDI binding also serves to emulsify some lipid-modified GTPases, allowing them to dissociate from membrane surfaces. Multiple GDIs have been identified for RHO and RAB proteins (19,20) but, to date, not for other subfamilies. GDI-bound, cytoplasmic RHO and RAB proteins are effectively sequestered from membrane-associated effectors as well as regulators.

The intrinsic GTPase activity of RAS-related proteins is typically low (4.2×10^{-4} s^{-1} for HRAS) (12), which would tend to prolong signal transduction. GTP hydrolysis is greatly enhanced, however, by the intervention of GTPase activating proteins (GAPs) (Fig. 1) (21). As with GEFs, there are often multiple GAPs that function on a given RAS protein (22), allowing for a variety of input sources at this stage of regulation.

Many RAS family proteins are subject to multiple lipid modifications (23), which promote association with cellular membranes. Covalent posttranslational modif ication of C-terminal cysteine residues by isoprenylation (attachment of a farnesyl or geranylgeranyl group) is observed for most RAS, RHO, and RAB family members. This modification has also been implicated in determining subcellular membrane localization, which in turn can influence effector binding or activation and regulatory protein interactions (24–29). Cysteine palmitoylation (covalent attachment of a palmitate fatty acid) also occurs near the C terminus of some RAS and RHO proteins.

At the N terminus of many ARF (ADP ribosylation factor) and Gα subfamily proteins, cotranslational modification of glycine by myristoylation occurs. For some Gα proteins, myristoylation is combined with palmitoylation of a neighboring cysteine (30,31). In other cases, palmitoylation of cysteines near the N terminus appears to be independent of other modifications (32). As with the modifications at the C terminus, the N-terminal lipid additions likely play a role in membrane localization but may well contribute in other ways to RAS protein structure or function.

RAS Proteins and Cancer

RAS (rat sarcoma) genes were first identified and characterized as transduced oncogenes in the Harvey and Kirsten strains of acutely transforming retroviruses (33,34) (note: early publications use the name $p21^{src}$ for these genes). Mutationally activated forms of *HRAS* (also called *H-Ras*), *KRAS* (also called *K-Ras*), and *NRAS* (also called *N-Ras*) were subsequently isolated from human tumor cells using transfection-based assays (35–37). Tumor-derived RAS mutations, such as $HRAS^{G12V}$, disable GTPase function and GAP responsiveness (38). Mutations that enhance guanine nucleotide exchange (e.g., $HRAS^{N116H}$) also enhance the basal activation state of RAS proteins (39,40).

High rates of KRAS-activating missense mutations have been detected in non–small cell lung cancer (15 to 20% of tumors) (41), colon adenomas (40%) (42), and pancreatic adenocarcinomas (95%) (43), making it the single most common mutationally activated human oncoprotein. In some tumors, HRAS- or NRAS-activating mutations are also seen. More than half of the most malignant thyroid tumors, characterized as poorly differentiated or undifferentiated, harbor a mutation in KRAS, HRAS, or NRAS (44). In addition to mutational activation, RAS genes are amplified or overexpressed in some tumors (45). In the case of breast cancer, the incidence of RAS-activating mutations is low, but RAS activity is elevated due in part to increased upstream signaling from the receptor tyrosine kinase ERBB2 (also called Her2) (46). Other mechanisms leading to RAS overactivation in tumor cells include the deletion of genes encoding negative regulators (for example NF1, a GAP for RAS, in neurological tumors) (47–50) and overexpression of positive regulators (such as SOS1, a GEF for RAS, in renal cancer cells) (51). Taken together, these data illustrate the critical and pervasive role played by RAS in cell transformation.

Activating mutations in other members of the RAS superfamily are much less common in human tumors, and the known examples are generally restricted to neoplasias of relatively low frequency. In vitro systems, however, provide compelling evidence that several members of the RAS superfamily, aside from KRAS, HRAS, and NRAS, can enhance or facilitate cell transformation.

RAS Protein Subfamily (35 members)

RAS subfamily members show high conservation within the G1, G3, G4, and G5 boxes (Fig. 2). Most proteins in this group are relatively small (183 to 340 amino acids in length) and show no prominent functional motifs outside of those defining their RAS relatedness.

Most of the RAS subfamily proteins localize predominantly to the plasma membrane. Membrane localization results in part from C-terminal prenylation. Prenylation signals mostly conform to the Caax (a = aliphatic, x = terminal amino acid) motif that directs cysteine farnesylation (except when x = L or F, which instructs geranylgeranylation as occurs on RRAS proteins and some RAP proteins). The prenylation reaction is followed by proteolysis of the three C-terminal residues (aax) and methylation of the lipid-modified cysteine [reviewed in (23,52)]. The later two posttranslational processing steps take place in the endoplasmic reticulum (ER) before transport to the plasma membrane (53). RAL proteins contain the

geranylgeranylation signal CCaa. Some RAS subfamily members lack either type of isoprenylation motif and are not subject to any known lipid modification.

Some RAS subfamily proteins contain fatty acid acylation signals. Notably, HRAS, NRAS, ERAS, RRAS1 and RAP2A, RAP2B, and RAP2C have palmitoylated cysteine residues proximal to their C-terminal prenylated cysteines. This modification requires transit through the Golgi compartment (54). Endomembrane localization of RAS proteins may be more than just a posttranslational modification detour, however. Several lines of evidence suggest that RAS proteins are functional signal transducers in the ER-Golgi complex (55–57).

N-terminal lipidations may contribute to the localization of other RAS subfamily members such as ARHI (Ras homolog member I), which has a potential myristoylation site (MetGly) at its N terminus, and NKIRAS1 and NKIRAS2 (NF-κB inhibitor–interacting Ras-like 1 and 2) proteins, which have putative myristoylation or palmitoylation modification signals (MGxxCxxxxC) .

An additional factor in RAS protein trafficking and localization is the presence of a C-terminal polybasic region, as seen on the predominant KRAS splice variant KRAS2B. This protein lacks a palmitoylation site but has a strong polybasic region immediately upstream of the C-terminal farnesylation site. In contrast, HRAS and NRAS have palmitoylation sites but no polybasic regions. These differences are believed to underlie the distinct membrane localization characteristics (58) and signaling properties (59) of these otherwise close paralogs. In the 2A isoform of KRAS (N terminus = KTPGCVKIKKCIIM), the polybasic sequence is replaced with a palmitoylation site. As a result, the KRAS2A isoform may be more similar to HRAS and NRAS in its subcellular localization. Interestingly, RAP1 (prenylation + polybasic) and RAP2 (prenylation + fatty acylation) proteins appear to have a relationship similar to that of KRAS2B and HRAS. The RIT1 and RIT2 proteins encode C-terminal polybasic sequences (6 of 10 residues are R or K) but lack both prenylation and fatty acylation signals. RERG (Ras-related and estrogen-regulated growth inhibitor) appears to be devoid of all standard lipid membrane localization signals and displays cytosolic localization, suggesting that it functions outside the context of cellular membranes (60).

Other posttranslational modifications have been described for RAS subfamily proteins. These include serine phosphorylation (61) and nitrosylation (62–64) of HRAS and tyrosine phosphorylation of RRAS1 (65,66); the functions of these modifications are still under investigation.

Variation at the level of alternative splicing has been described for some RAS genes. For KRAS (67,68) and HRAS (69), the primary function of alternate splicing may be to generate isoforms with distinct subcellular localizations.

A comparison of RAS subfamily sequences from *Homo sapiens*, *Drosophila Melanogaster*, and *Caenorhabditis elegans* (Fig. 3) shows strong conservation through evolution, with most branches of the dendrogram containing representatives from each species. This analysis also illustrates a notable expansion of RAS subfamily proteins (human = 35, fly = 14, worm = 12) and suggests 12 structural or functional branches.

RAS oncoprotein branch (HRAS, KRAS, and NRAS)

HRAS, KRAS, and NRAS (H, K, NRAS) proteins are perhaps best known for their mitogenic properties. As discussed above, mutationally activated forms of these proteins can efficiently transform cells in vitro and in vivo, and such mutations are common in a broad spectrum of human tumors. There is also strong evidence from cell culture experiments (70) and model organisms (71,72) that H, K, NRAS proteins contribute to cell differentiation and organ

development. These same proteins have more recently been implicated in neuronal plasticity in the central nervous system (73–78).

The protein kinase RAF1 (also called c-Raf) was the first identified RAS effector (79–83) and, together with the closely related ARAF (also called A-Raf) and BRAF (also called BRaf), has been the most intensively studied [reviewed in (84)]. Activated RAS binds with high affinity to the "Raf-like Ras–binding domain" (Interpro IPR003116), as well as an adjacent cysteine-rich domain, and leads to activation of the kinase activity of RAF and initiation of the MEK-ERK mitogen-activated protein kinase cascade, which affects transcription and other cellular functions. The precise mechanism of RAS-mediated activation is complex and not yet fully elucidated, but seems to involve enhanced membrane association, as well as allosteric derepression (deletion of the RAS binding domain results in constitutive kinase activity) (85) and promotion of RAF phosphorylation by serine-threonine and tyrosine kinases. Hyperactivation of the RAF effector pathway alone can transform immortalized rodent fibroblast cells, but appears to be insufficient for transformation of some other cell types (86, 87). The frequent occurrence of dominant BRAF mutations in some human cancers (88) further suggests that this effector pathway has a major role in tumorigenesis. Other human proteins with "Raf-like Ras–binding domains" include TIAM1, which functions as a RAS-controlled GEF-type activator of RAC (a member of the Rho subfamily) (89). Mice deficient in TIAM1 function develop normally but are impaired in carcinogen-induced, RAS-mediated, tumorigenesis (90), consistent with a role for this effector in RAS-mediated growth regulation.

The catalytic subunits of phosphotidylinositol 4,5 bisphosphate 3-kinase (PI3K) constitute another well-established class of RAS effectors (91). RAS binds to a consensus "phosphoinositide 3-kinase Ras binding domain" (Interpro IPR000341) found in seven distinct human proteins (PIK3CG, PIK3C2A, PIK3C2G, PIK3CB, PIK3CA, PIK3C2B, and PIK3CD). This interaction promotes PI3K catalytic activity (92), resulting in increased production of membrane-associated PIP_3 (phosphatidylinositol 3,4,5-trisphosphate) and the subsequent plasma membrane recruitment of PIP_3-binding PH domain proteins such as the protein kinases AKT1 and PDPK1 (3-phosphoinositide–dependent protein kinase 1, also called PDK1). RAS-mediated activation of PI3K is also an important component of cell transformation (8).

Several GEFs for RAL proteins are RAS effectors (93–97). RALGDS, RGL1 (Ral GDP dissociation stimulator–like; also called ARHGAP9), RGL2 (also called Rab2L), and RGL3 each encode a Ras association (RA) domain (Interpro IPR000159), a third type of RAS-effector interaction motif. RAS proteins stimulate the nucleotide-exchange activity of RALGDS (98), and this appears to have a critical role in human cell transformation (99,100).

RIN1 is another RA domain–containing RAS effector protein (101,102). The RIN1 protein functions as a RAS-responsive GEF for RAB5 (103) and also stimulates the catalytic activity of the ABL tyrosine kinase (104,105). RIN1 has a restricted expression pattern (78) and, because of its high-affinity binding to RAS proteins (101), may function in part as a physiological competitor of other effectors. The related proteins RIN2 and RIN3 have discernable RA domains but have not been functionally connected to any RAS protein. Another RAS effector, NORE1 (novel Ras effector 1; also called RASSF5 and RapL), is a positive regulator of cell death through association with the proapoptotic kinase STK4 (106). NORE1 is itself part of a family of related proteins (RASSF1 through RASSF6) that all contain RA domains but have not all been functionally connected to RAS. The RA domain–containing enzyme phospholipase C epsilon (PLCE1; also called PLCε) has also been described as a RAS effector (107). However, RA domains show affinity for RAP as well as RAS proteins. In the case of the RA protein MLLT4 (also called AF6), Rap1 proteins may be the preferred physiological binding partners (108). Finally, another RA domain–containing protein, RASIP1 (Ras-interacting protein 1, also called RAIN), is an effector of RAS and RAP (109). Systematic

analysis of RAS family GTPases and multiple effectors has demonstrated binding specificity that often correlates with biochemical and biological activation (110).

BRAP (also called IMP, impedes mitogenic signal propagation) is another protein that binds specifically to activated RAS (111), although BRAP has no RA or other recognizable RAS-interaction domain. BRAP appears to function as a dedicated inhibitor of signaling between RAF and MEK.

RRAS (Related to RAS) branch

RRAS1, RRAS2 (also called TC21), and MRAS (also called RRas3) appear to be involved in control of mitogenesis and the cytoskeleton. RRAS1 localizes to focal adhesions where it promotes cell adhesion and activates integrins (112,113). Activating (GTPase-defective) mutants of all the RRAS proteins can transform cultured fibroblast cells, with RRAS2 being the most potently transforming (114–117). Activating mutations and overexpression of RRAS2 are found in some human tumors (118–120). Effectors implicated in the function of RRAS family members include PI3K (121,122), RALGDS and related proteins (97,122,123), and RAF kinases (124,125), but RRAS1 appears to work primarily through PI3K (121). This overlap with effectors of the H, K, NRAS family likely reflects the complete conservation of G2 box (switch 1) sequences among members of both branches. The differences between the physiological consequences of RRAS activation versus that of H, K, NRAS activation may reflect quantitative differences in effector engagement, as well as the contribution of some unique effectors for each protein.

RAP (Ras-Proximal) branch

RAP proteins are activated by mitogenic stimuli and function as regulators of integrin-mediated cell adhesion and cell spreading (126,127). In cultured cells, RAP proteins do not show transforming activity. Rather, overexpression of RAP1A inhibits RAS-mediated transformation (128). However, RAP1A has been reported to bind and activate BRAF (129), suggesting that it has the capacity to promote mitogenesis and perhaps transformation in some contexts but not others (130). Two observations suggest contributions of RAP proteins in tumorigenesis, but with possible tissue-type specificity. Activation of a RAP-directed GEF (131) or inactivation of a RAP-directed GAP (132) promotes hematopoietic tumor formation. Conversely, the loss of an activator of RAP1 proteins has been found in a mouse osteosarcoma and in several nonhematopoietic human cancer cell lines (133).

RAP proteins may function through activation of RALGDS and related proteins, but not in the same way that RAS does (134), and through associations with PLCE1 (135). In lymphoid cells, RAP1 proteins promote integrin activation through NORE1 (136).

RAL (RAS-Like) branch

RALA and RALB have been implicated in a broad spectrum of functions including mitogenic responses, differentiation, protein trafficking, and cytoskeleton dynamics [reviewed in (137)]. As discussed above, H, K, NRAS, RRAS2, MRAS, and RAP proteins all appear to work in part through RALGDS-type effectors that are expected to stimulate RAL functions. Although mutationally activated RAL proteins are not themselves oncogenic, they can enhance transformation of cultured cells by RAS and EGFR (epidermal growth factor receptor) (98, 138). The two RAL proteins appear to have distinct and complementary roles in cell transformation; RALB is required for tumor cell survival, whereas RALA promotes anchorage-independent cell proliferation (139). Each RAL also has a distinct role in epithelial cell polarization (140).

Several RAL effectors have been identified but, to date, these do not include members of the RAF-PI3K-RALGDS triumvirate. This may seem surprising because RAL proteins show high overall relatedness to H, K, N-RAS proteins. However, the two subfamilies diverge appreciably in their Switch 1 regions (Fig. 2). The sequence YDPTIED is completely conserved in H, K, N-RAS proteins as well as in RRAS1 RRAS2, MRAS, and all RAP proteins, all of which share many effectors. In RALA and RALB the equivalent sequence is YEPTKAD.

The RAL effector RALBP1 (also called RLIP), which has a RAC- and CDC42-directed GAP domain (141–143), regulates endocytosis (144–146). RAL is also a component of the exocyst complex. RAL directly binds to both SEC5L1 (also called Sec5) and EXOC8 (also called EXO84), promoting exocyst complex assembly and membrane trafficking (147–149).

RIT (RAS-like Protein in All Tissues) branch

RIT1 and RIT2 (also called Rin) are positive factors for neuronal cell survival as well as for the initiation, elongation, and branching of neu-rites in culture (150–152). The enhanced expression of RIT1 and RIT2 in developing and mature neurons (153) supports the biological relevance of these properties. RIT2 includes a Ca^{2+}-calmodulin binding site (153), which appears to be required for its neurite outgrowth function (150). Although an activated (GTPase-deficient) mutant of RIT1 can transform a fibroblast cell line (154,155), there is no evidence that either RIT gene functions in tumorigenesis.

On the basis of protein interaction experiments, RALGDS (and related proteins) and AF6 are potential effectors of RIT1 and RIT2 (156), but no RIT-specific effectors have been characterized. Several lines of evidence indicate that RAF and PI3K are not direct effectors of RIT proteins (150,154,156).

ERAS (Embyonic Stem Cell–Expressed Ras) branch

ERAS is an unusual subfamily member in several respects. As indicated in Fig. 3, ERAS occupies a branch with no human paralogs and no fly or worm orthologs. ERAS expression is restricted to undifferentiated embryonic stem (ES) cells (157).

Ectopic expression of wild-type ERAS transforms cultured fibroblast cells (157). This unusual property likely reflects the effect of sequence differences at residues that regulate the GTP/GDP binding equilibrium in other RAS proteins (that is, the amino acid corresponding to Gly^{12} in H, K, NRAS). ERAS may be an important factor in the propensity of ES cells to form teratomas. A strong candidate effector of ERAS is PI3K (157).

DIRAS (Distinct Subgroup of RAS) and ARHI branches

The DIRAS1 (also called Rig) and DIRAS2 proteins, like RHEBs, show reduced GTPase activity compared to that of most RAS superfamily GTPases, and DIRAS proteins remain predominantly in the GTP-bound state (158). DIRAS and ARHI proteins may have tumor suppressor functions. Overexpression of DIRAS1 antagonizes Ras-mediated signaling and transformation, and DIRAS1 is silenced or down-regulated in many neural tumors and tumor-derived cell lines (159). The ARHI (also called Noey2) protein has been implicated as a tumor suppressor in breast and ovarian cancer (160,161).

Ectopic expression of DIRAS1 or DIRAS2 can induce the formation of large vacuolar structures (158), but downstream effectors have not been identified for these proteins.

RASD (Ras Induced by Dexamethasone) branch

RASD1. (also called dexRas) was identified as a transcript that shows strong, rapid, and transient induction after treatment of cells with dexamethasone (162), and RASD2 (also called

RHES, for Ras homolog enriched in striatum) was identified as a protein expressed in pancreatic beta cells in response to efaroxan, an imidazoline that functions as an α_2-adrenergic receptor antagonist and insulin secretagogue (163). There is no evidence to support involvement of RASD1 or RASD2 in transformation or tumorigenesis. RASD1 appears to function as a negative regulator of peptide hormone secretion (164) and as a cell growth suppressor (165). RASD2 has the capacity to activate PI3K and may interfere with G protein–coupled receptor signaling (166).

The uncharacterized gene products RASL10A and RASL10B are the closest related proteins to RASD1 and RASD2.

NKIRAS (NFKB Inhibitor–interacting RAS-like, also called kB-Ras) branch

NKIRAS1 and NKIRAS2 were discovered as proteins that interact with NFKBI (usually called IκB), an inhibitor of the transcription factor NFKB (usually called NF-κB) (167). Binding of NKIRAS to NFKBI-NFKB complexes prevents nuclear translocation of the complex in resting cells, suggesting that NKIRAS proteins participate in the negative regulation of NFKB (168).

REM (Rad and Gem–related) branch

REM1, REM2, RRAD (also called Rad), and GEM (also called Kir) were identified primarily on the basis of their restrictive and regulated expression patterns (169–172). They share a conserved C-terminal cysteine (position –7), but this is not within a context recognized for lipid modification. REM subfamily proteins show no transforming or tumorigenic properties. REM1, RRAD, and GEM function in part as negative regulators of calcium currents through a direct interaction with the β subunit of a voltage-gated Ca^{2+} channel (173,174). Overexpression of GEM produces cytoskeletal changes marked by cellular processes. These changes may result from a direct interaction of GEM with the kinesin-like protein KIF9 (175) and RHOA inactivation [reviewed in (176)], perhaps through GMIP (Gem interacting protein), a RHOGAP (177).

RERG (RAS-related and Estrogen-Regulated Growth inhibitor) branch

RERG was identified during a search for genes whose expression in breast tumors correlates with prolonged survival (60). As its name implies, transcription of the RERG gene is increased in response to estrogen, perhaps through direct estrogen receptor binding to the RERG gene promoter. RERG shows no binding to H, K, NRAS effectors tested (RAF, RALGDS, PI3K, and RIN1), and RERG neither transformed cultured fibroblasts nor enhanced HRAS-mediated transformation (60). Ectopic expression of RERG actually blocked transformation and tumorigenesis in a breast tumor cell line (60).

Three gene products—RASL11A, RASL11B, and RASL12—show relatedness to REM. Abundance of *RASL11A* transcripts is decreased in some prostate tumors (178), but its function is uncharacterized. The RASL11A, RASL11B, and RASL12 gene products have no lipid modification signals, suggesting functions that are not restricted to membrane surfaces. Further analysis of these proteins will determine if they are best considered as a separate branch of RAS proteins.

RHEB (Ras Homolog Enriched in Brain) branch

RHEB proteins are involved in the control of cell cycle and cell growth (179). Although early studies found that RHEB proteins block MAPK (mitogen-activated protein kinase) signaling and inhibit RAS-mediated transformation of cultured fibroblasts (180,181), it is not yet clear whether these observations represent physiological activities.

RHEB proteins have low intrinsic GTPase activity and exist predominantly in the GTP-bound form. RHEBs are subject to negative regulation, however, by the GAP activity of a TSC1-TSC2 complex. The best-characterized downstream effector of RHEB is the Ser-Thr kinase FRAP1 (also called mTOR, target of rapamycin) (179,182–186), which in turn regulates translation through its substrates RPS6K (ribosomal protein S6 kinase 1) and EIF4EBP1 (eukaryotic initiation factor 4E–binding protein). Loss-of-function mutations in TSC genes are associated with tuberous sclerosis complex, a benign tumor syndrome, suggesting that RHEB may have tumor promoter functions in vivo.

RHO Protein Subfamily (23 members)

The RHO (*R*as *ho*molog) subfamily of proteins is closely related to the RAS subgroup [reviewed in (187–188)], and members of this family show strong conservation among their G1 to G5 boxes (Fig. 4). However, most members of this subfamily have an insert sequence that is not found in other RAS superfamily GTPases. Mounting evidence supports the involvement of RHO proteins in cancer (189). They appear to be primarily collaborators in, rather than initiators of, cell transformation. The unconventional RHO protein RHOBTB2 [named after the BTB (Broad-complex Tramtrack, and Bric a brac) domain; and also called DBC2] is reported as a potential tumor suppressor (87), and overexpression of a RAC1 splice varient, RAC1B, has been reported in colorectal tumors (190).

RHO subfamily proteins segregate into six branches based on sequence similarity (Fig. 5). Effectors for RHOA, B, and C branch proteins include ROCK1 (Rho-associated protein kinase 1) (and probably ROCK2) (191) and the formin protein DIAPH (also called mDia, mammalian homolog of Diaphinous) (192). RHO proteins bind to and activate PKN proteins, serinethreonine kinases that have been implicated in cell stress responses (193,194). PLCE is another demonstrated effector of RHO proteins (195). The RHO-binding proteins Rhophilin (194), Rhophilin2 (196), and Rhotekin (197) may also serve as effectors. RAC [Ras-related C3 botulinum toxin substrate (198)] branch proteins appear to function primarily through direct activation of PAK (p21-associated protein kinase) family kinases (199). Other RAC effectors include phospholipase C–β (PLCB) (200). Some effects of CDC42 branch proteins are mediated by WAS (Wiscott-Aldrich syndrome protein; also called WASP) (201–203) together with TOCA1 (transducer of Cdc42-dependent actin assembly), another CDC42 effector (204). CDC42 proteins also participate in the function of a multiprotein complex that includes PAR6, PAR3, and atypical protein kinase C isoforms (205). RND proteins are RHO family members that are constitutively active due to extremely low GTPase activity. They have been reported to antagonize RHOA function, in part through the activation of RHOGAPs (206) or through blocking ROCK activity (207). No effectors have been identified for members of the more distal branches of the RHO family, RHOT1 and RHOT2 (also called Miro for mitochondrial Rho), and RHOBTB1 and RHOBTB2.

RHO proteins have been directly implicated in multiple aspects of cytoskeletal remodeling and cell polarity (208,209), and activated forms of representative RHO proteins demonstrate that certain aspects of remodeling segregate with particular branches of this subfamily (208,210). The cytoskeletal changes reported include formation of lamellipodia (RAC1 to RAC3 and RHOG), filopodia (CDC42, RHOJ, RHOQ), or stress fibers (RHOA, RHOB, and RHOC) and the disruption of stress fibers (RND1 to RND3).

The majority of RHO subfamily proteins are subject to the same Caax-signaled prenylation and posttranslational modifications as those seen on RAS subfamily members. Some RHO proteins (most notably RAC1, RAC4, RHOA, and RHOC) also include C-terminal polybasic sequences, whereas others are modified by palmitoylation.

RHOT1 and RHOT2 are distinct in several ways from members of the RHO family and might best be considered as a unique subfamily. First, the RHOT proteins show notable sequence divergence from most RHO family members. This includes a lack of C-terminal cysteines, implying that RHOT proteins do not undergo lipid modification, and an absence of the "RHO insert" sequence following the G4 box. Second, RHOT1 and RHOT2 are more than twice as large as other RHO family members. Third, RHOT proteins contain two EF hand (EFh) motifs that may confer calcium binding, a function not associated with other family members. Each RHOT protein also includes a putative GTP-binding motif at the C terminus, but no functional significance has been assigned to these sequences. RHOT proteins localize to mitochondria, and expression of mutationally activated RHOT1 or RHOT2 leads to disruption of the mitochondrial network and to increased rates of apoptosis (209,210).

An interspecies comparison of RHO subfamily proteins (Fig. 5) shows that they have been highly conserved through evolution and that, as with the RAS subfamily, there has been a notable expansion of the RHO protein subfamily (human = 23, fly = 8, worm = 10).

RAB and RAN Protein Subfamily (71 members)

The RAB proteins were first identified as Ras-related genes expressed in rat brain (211). RABs represent the largest subfamily of the RAS superfamily, and the close relatedness of some members (RABL2A to RABL2B; RAB1A to RAB1B; and RAB11A to RAB11B) suggests that recent duplications may have occurred (Fig. 6). Although most RAB proteins include C-terminal prenylation signals, these are distinct from those found in RAS and RHO GTPases. One subfamily member (RAB35) has an adjacent polybasic motif. Several RABs have potential N-terminal myristoylation sites. Sequences of two RABs (RAB6C and RABL4) diverge from the G1 box consensus (otherwise universal in the RAS superfamily) and may not be functional GTPases. RAB44 and RASEF are the largest of the RAB subfamily proteins (predicted molecular masses of 108 and 83 kD, respectively). Each encodes a calcium binding EF hand motif (Interpro IPR002048). In addition, RAB44 encodes a spectrin repeat motif (Interpro IPR002017) and a proline-rich motif (Interpro IPR00064). The RAS domains of RAB44 and RASEF are located at their C termini.

Only one member of the RAB family has been reported to exhibit transforming potential; the RAB8A (also called Mel) gene was first isolated in an NIH3T3 cell transformation assay (212).

RAB proteins function in protein trafficking pathways, regulating vesicle formation, movement, and fusion [reviewed in (213–215)]. Several RAB effectors have been identified. These include rabphilin (also called RPH3A), an effector for the exocytosis function of RAB3 proteins (216). RAB5 proteins regulate endosomal vesicle transport through EEA1 (early endosome antigen 1) (217), early endosome fusion through RBEP1 (rabaptin) (218), and affect nuclear functions through APPL1 (adaptor protein containing PH domain, PTB domain, and leucine zipper motif; also called DIP13α) and APPL2 (also called DIP13β) proteins (219). The participation of RAB7 in lysosomal transport has been attributed in part to the effector protein RILP (Rab7-interacting lysosomal protein) (220,221). RAB9 proteins interact with the effector M6PRBP1 (also called TIP47) to mediate receptor recognition and cargo selection (222). Rabphilin-11 serves as an effector for RAB11 proteins in their vesicle recycling function (223). RAB27A works through MLPH (melanophilin) to regulate the movement of secretory vesicles along actin filaments (224).

Although the RAN protein has been considered to define a separate family, comparative sequence analysis suggests that RAN resides on a branch of the RAB subfamily. RAN is a regulator of nuclear import and export [reviewed in (225)]. This function is tied directly to the guanine nucleotide status of RAN, with both RAN-GTP and RAN-GDP showing specific

interactions with nuclear transport factors. Nuclear RAN is maintained in the GTP-bound state through sequestration of GAP and GEF regulators. RAN-GTP binds importins and exportins but with opposite consequences (promoting import into the nucleus with the former or export from the nucleus with the latter), leading to directed protein transport. RAN binding to importins has also been implicated as a requisite step in mitotic spindle assembly (226,227). The RAN branch of the RAB subfamily includes four less well-characterized proteins: RABL2A, RABBL2B, RABL3, and RABL5. It remains to be determined if these proteins are functionally similar to RAN.

Most branches of the RAB subfamily appear to be well conserved through evolution (Fig. 7) and show notable expansion (human = 71, fly = 32).

ARF (and SARA) Protein Subfamily (30 members)

The first identified proteins in this subfamily were named for their role as ADP ribosylation factors (228–230). ARFs and related proteins are regulators of trafficking of intracellular proteins and membranes and of cytoskeletal remodeling [reviewed in (231)]. ARF proteins lack C-terminal lipid modification signals (Fig. 8) but in most cases are subject to N-terminal myristoylation.

Effectors mediating ARF functions include the Arfaptins (ARFIPs) (232) and Arfophilin (RAB11FIPs) (233). ARF1 interacts directly with the vesicle coat protein COPI (234) and regulates disassembly (235). At the plasma membrane, ARF6 can regulate endocytic recycling through direct interaction with SEC10L1 (also called Sec10), a subunit of the exocyst complex (236).

ARF proteins also function in part through their ability to regulate phospholipid metabolism by directly activating phosphatidylinositol 4-phosphate 5-kinase (237,238). ARF1 and ARF3 also bind to GGA (Golgi-localized, gamma-adaptinear–containing, Arf-binding) proteins (239,240) and function in trans-Golgi network membrane trafficking (241).

The SARA proteins (note that the HGNC name for these proteins overlaps with the common acronym for Smad anchor for receptor activation, a distinct signaling protein) are an off-shoot of the main ARF subfamily. SARA1 (also called Sar1) functions as a component of the COPII complex that mediates export from the ER [reviewed in (242)]. Eight additional ARF-related proteins are located on the same branch as SARA1 and SARA2. There are currently no data, however, on the function of ARL9, ARL10A, ARL10B, ARL10C, ARFRP2, LOC339231, LOC344988, and DKFZp761H0.

Two additional proteins (ENSG00000127917, GI:37538730; ENSG00000185829, GI: 7706177) show similarity with ARFs but have major G box motif disruptions that would likely compromise G protein function.

Analysis of ARF and related proteins from human, fly, and worm (Fig. 9) indicates that this is a well-conserved family with a degree of expansion similar to that of other RAS subfamilies (human 30, fly 12, worm 13).

Gα Protein Subfamily (16 members)

The α subunits of G proteins were among the first well-characterized mammalian GTPases. When aligned with other RAS superfamily proteins, the 16 Gα proteins show multiple sequence insertions (Fig. 10) [reviewed in (243)]. The largest of these additional sequence elements, located between the G1 and G2 boxes, is believed to account for the high intrinsic GTPase activity and low intrinsic nucleotide exchange rate of Gα subunits relative to those of RAS

[(244), and reviewed in (243)]. Most Gα proteins undergo N-terminal lipid modification by myristate and/or palmitate fatty acids.

Mutant Gα proteins are associated with several diseases including cancers. Activating mutations in $G\alpha_s$ are found in some pituitary tumors, and $G\alpha_i$ mutations have been reported in tumors of the adrenal cortex (245).

The functions of Gα-type G proteins are inextricably linked to their association with βγ heterodimer subunits and with proteins of the large family of G protein coupled receptors (GPCRs). The inactive (GDP-bound) G protein heterotrimers are typically "parked" on the C-terminal domains of GPCRs. Receptor activation leads to a conformational change that facilitates both GTP loading and reduced affinity for βγ dimers [in some cases, however, the heterotrimer remains intact (246)]. Downstream effectors of Gα include multiple adenylyl cyclase isoforms, several ion channels and transporters, and various other cell regulatory components [reviewed in (247)].

The Gα subfamily of proteins is well conserved in evolution (Fig. 11). The main branches of the Gα tree (the branches containing G_s and G_l, G_i and G_t, G_{12} and G_{13}, and G_q and G_{11}) are represented in mammals, flies, and worms, but there is an expansion of *C. elegans* genes in the branch containing G_i, G_t, and G_o.

The RAS Superfamily of Proteins

Sequence comparison analysis of all RAS superfamily members (GTPase domains only) highlights the relationship among the subfamilies (Fig. 12). The RAS, RHO, RAB, ARF, and Gα groupings are apparent, and the proximity of the RAS subfamily to the RHO and RAB subfamilies is noteworthy. The close relationship of the ARF and Gα subfamilies is also revealed. The RABL3 and RABL5 proteins segregate outside of the RAB subfamily and are not clearly positioned within any of the other subfamilies. This may reflect an unusual evolutionary origin for these sequences, which also do not have any apparent orthologs in *Drosophila* (Fig. 7). RABL4 and RAB28 fall slightly outside the main RAB cluster. In addition, the RHOT proteins appear to be only marginally within the RHO family.

Other Human GTPases

GTPases outside the RAS superfamily

There are at least 50 additional proteins that have demonstrated or predicted GTPase function, but that fall outside the RAS superfamily. These proteins were, in many cases, identified on the basis of genetic or biochemical analyses of function and only subsequently revealed to be GTPases. Each protein includes recognizable G1, G3, and G4 boxes (Fig. 13). They are generally larger than the RAS superfamily proteins, due to the presence of additional functional domains. These "distant" GTPases also do not include the lipid modification signals seen in most RAS subfamily proteins, and they function in multiple subcellular regions.

GTPases outside the RAS superfamily are diverse in structure and function. Sequence alignment of their GTPase domains, however, reveals the existence of subfamilies that may also reflect functional characteristics (Fig. 14). One of the largest groups is composed of the septins (SEPT1 to SEPT11), which play a critical role in the constricting ring structure required for cytokinesis. Septins have also been implicated in the formation of focal adhesion complexes and in cell polarity [reviewed in (248)]. Association of septin with the plasma membrane is guanine nucleotide regulated. Specifically, GDP enhances binding to the membrane lipid PIP2 (249).

The dynamin family members DNM1 to DNM3 and DNM1L regulate vesicle and organelle dynamics through their participation in a constricting ring structure that requires GTP [reviewed in (250)]. OPA1 (optic atropy 1), MX1 (myxovirus resistance 1), MX2, and the closely related mitofusin proteins (MFN1 and MFN2) are also members of the dynamin family, but their biological functions are not well understood.

Initiation and elongation factors (EIF2S3, EEF1A1, EEF1A2, and TUFM) are perhaps the first class of protein for which GTP binding and hydrolysis were studied in structural and biochemical terms [reviewed in (251,252)]. During initiation, GTP hydrolysis is coupled to the stepwise assembly of the mRNA-ribosome-tRNA $^{Met}_{i}$ complex. For elongation, conformational changes associated with GTP binding or hydrolysis are used to drive cycles of recruitment and release of aminoacylated elongator tRNAs.

Signal recognition peptide receptor complex components SRPRA (also called SRPR, SRPRα), SRPRB (also called SRPRβ), and SRP54 also utilize GTP hydrolysis to regulate the formation and function of a protein translocation complex (253). However, although the GTPase domains of SRPRA and SRP54 are closely related, the sequence of SRPRB is sufficiently divergent to be placed in a distinct branch.

The centaurin gamma proteins CENTG1 (also called GGAP2), CENTG2 (also called GGAP1), and CENTG3 (also called MRIP1) have GTPase domains that are closely related to those of RAS, RHO, and RAB proteins, but do not fit well into any of these RAS subfamilies. CENTGs are unusual because they also include a GAP domain that appears to function intramolecularly to promote GTP hydrolysis (254). Each CENTG protein also encodes a PH (pleckstrin homology) domain (Interpro IPR001849) and an ANK (ankyrin) domain (Interpro IPR002110). The XAB1 GTPase, implicated in the nuclear translocation of a DNA repair factor (255), is structurally similar to members of this branch, raising questions about possible functional similarities.

The RRAG proteins (RRAGA, RRAGB, RRAGC, and RRAGD) are sometimes described as members of the RAS superfamily because they show some similarity with the ARF and Gα proteins. RRAGs have been implicated as factors in the nuclear import and export functions of RAN (256).

Three groups of GTPases were identified because their transcription is induced after treatment of cells with IFNG (also called interferon gamma or IFN-γ) (257). The proteins share an IIGTP (interferon-inducible GTPase) domain (Interpro IPR007743). The first group is represented by IIGP5 in humans but appears to have undergone notable expansion in mice, where they were first discovered and characterized (mouse orthologs are Irg47, Tgtp, Iigp, Lrg47, Igtp, and Gtpi). Some evidence suggests a critical role for IIGTP proteins in normal immune responses, perhaps through participation in vacuolar trafficking (258). Members of the second IFN-inducible group (the guanylate-binding proteins GBP1 through GBP5) are relatively large G proteins. They show unusual GTP binding characteristics (259) that may explain their capacity to generate both GDP and GMP. A closely related gene product is SPG3A (atlastin), mutations in which are associated with hereditary spastic paraplegia (260). The third group of IFN-inducible G proteins are represented by VLIG (very large inducible GTPase 1) and, in mice, by several VLIG paralogs (261).

GTPBP proteins (GTPBP1 to GTPBP5) show some relatedness to the initation/elongation factor branch proteins (262,263). These genes also show IFN-inducible expression. Although their physiological function remains unclear, GTPBP4 may be identical to NGB (also called Nog1), a nucleolar protein involved in ribosome biogenesis (264). ERAL1 (Era-like 1, also called H-Era, for *Escherichia coli* Ras-like protein) is named for its structural relationship with Era, an essential bacterial GTPase (265). The ERAL1 protein also includes a KH domain

(Interpro IPR004087) involved in RNA binding. ERAL1 is a potential regulator of apoptosis (266).

DRG genes (DRG1 and DRG2) were identified as Developmentally Regulated G proteins (267,268). *Xenopus laevis* orthologs of DRG have RNA binding activity (269), but little else is known about their function.

The major histocompatibility complex class II transactivator, MHC2TA (also called CIITA) functions as a master coactivator of MHC class II gene expression. MHC2TA has only weak intrinsic GTPase activity, but GTP binding regulates its nuclear localization (270,271). The nucleotide-binding domain of MHC2TA has been grouped in the NACHT family (named for founding members NAIP, CIIA, HETE, and TP1) (272). Other mammalian proteins in this large family—which includes BIRC1 (baculovial IAP repeat-containing 1); CIAS1 (cold autoinflamitory syndrome 1); CARD (caspase recruitment domain family) 4, 6, 12, and 15; and NALP (NACHT, leucine rich repeat, and PYD containing) 1, 2, and 4 to 14—that have been tested show greater binding affinity for ATP than for GTP.

TUBB, the β subunit of tubulin, is an established GTP-binding and GTP-hydrolyzing protein, but its structure diverges to such a large extent from those of the other GTPases (273), that it has not been included in sequence comparisons. The identification of other human proteins with GTPase function but relatively low G box sequence conservation will require a deeper understanding of the structure and function relationships for these versatile enzymes. A database of human GTPases can be found at http://www.doe-mbi.ucla.edu/~sievers/gproteins.

GTP-binding proteins

The human genome encodes many proteins with demonstrated or predicted GTP-binding properties, but no apparent GTPase enzymatic function. These include GNL1 (guanine nucleotide binding protein–like 1, also called HSR1), which encodes a likely GTP binding domain that, together with a mouse ortholog (Mmr1) and several bacterial proteins, appears to form a structural subclass of proteins (PFAM domain PF01926) (274). The brain-enriched RING finger protein ZNF179 (also called BFP, brain finger protein) shows close relatedness to the GBPs, but no guanine nucleotide biochemistry has yet been described for BFP.

The dozen or more human RHOGAP protein family members include several with putative GTP-binding domains. RHOGAP5 (also called p190-B or ARHGAP5) and GRLF1 (also called p190A) have the most conserved such domains (275), but even in these cases they have not been demonstrated to have GTPase activity or to play any role in RHO regulatory function. Two other RHOGAP proteins, ARHGAP21 and CHN1 (also called RHOGAP2), have putative GTP-binding domains that are more divergent.

A GTP-binding domain also appears within DAPK1 (death-associated protein kinase), a cell death–associated protein kinase with ankyrin repeats and a death domain (276,277). Two other DAPK proteins do not include recognizable GTPase domains. Other enzymes with reported GTP-binding domains include transglutaminase, phosphoenolpyruvate carboxy kinase, and glutamate dehydrogenase.

AGTPBP1 (also called NNA1) has an unusual binding site that accommodates either GTP or ATP (278). Other reported GTP-binding proteins of interest include TSN (also called translin or TB-RBP, testis brain RNA-binding protein) (279), ANXA6 (human annexin A6) (280), and MEN1 (multiple endocrine neoplasia 1) (281).

Each of the RHOT proteins has a potential GTP binding site downstream of their RHO-type GTPase domains. The uncharacterized gene product MGC10731 (ENSG00000132881; GI: 34147392) also includes a putative GTP binding site.

Conclusions

A survey of all human RAS superfamily GTPases, and analysis of structural and evolutionary relatedness among family members, represents only the end of the beginning of our efforts to understand these pervasive signal transduction regulators. It is likely, for instance, that we have only scratched the surface of variation resulting from alternate splicing and posttranslational modifications of GTPases. Much attention has also turned to determining the specificity of GTPase regulators such as the large family of GAPs and GEFs, as well as continuing efforts to identify downstream effectors. Continued research in these areas should provide a more accurate picture of human GTPase functions in normal and pathological conditions.

References and Notes

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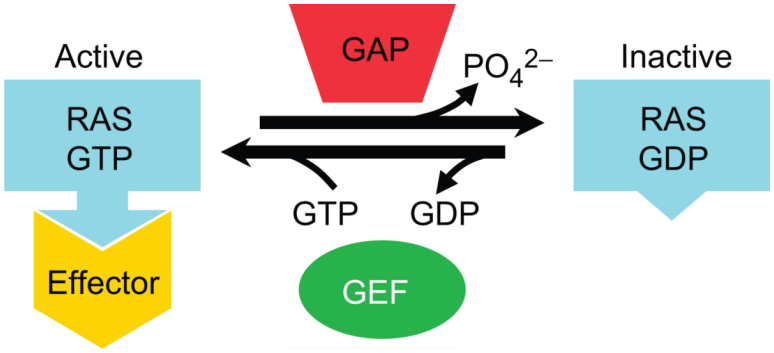


Fig. 1.
RAS proteins exist in equilibrium between GTP- and GDP-bound forms. GEFs and GAPs regulate the relative amounts of each form. The GTP-bound conformation of RAS shows high-affinity interactions with effector proteins that propagate downstream signaling.

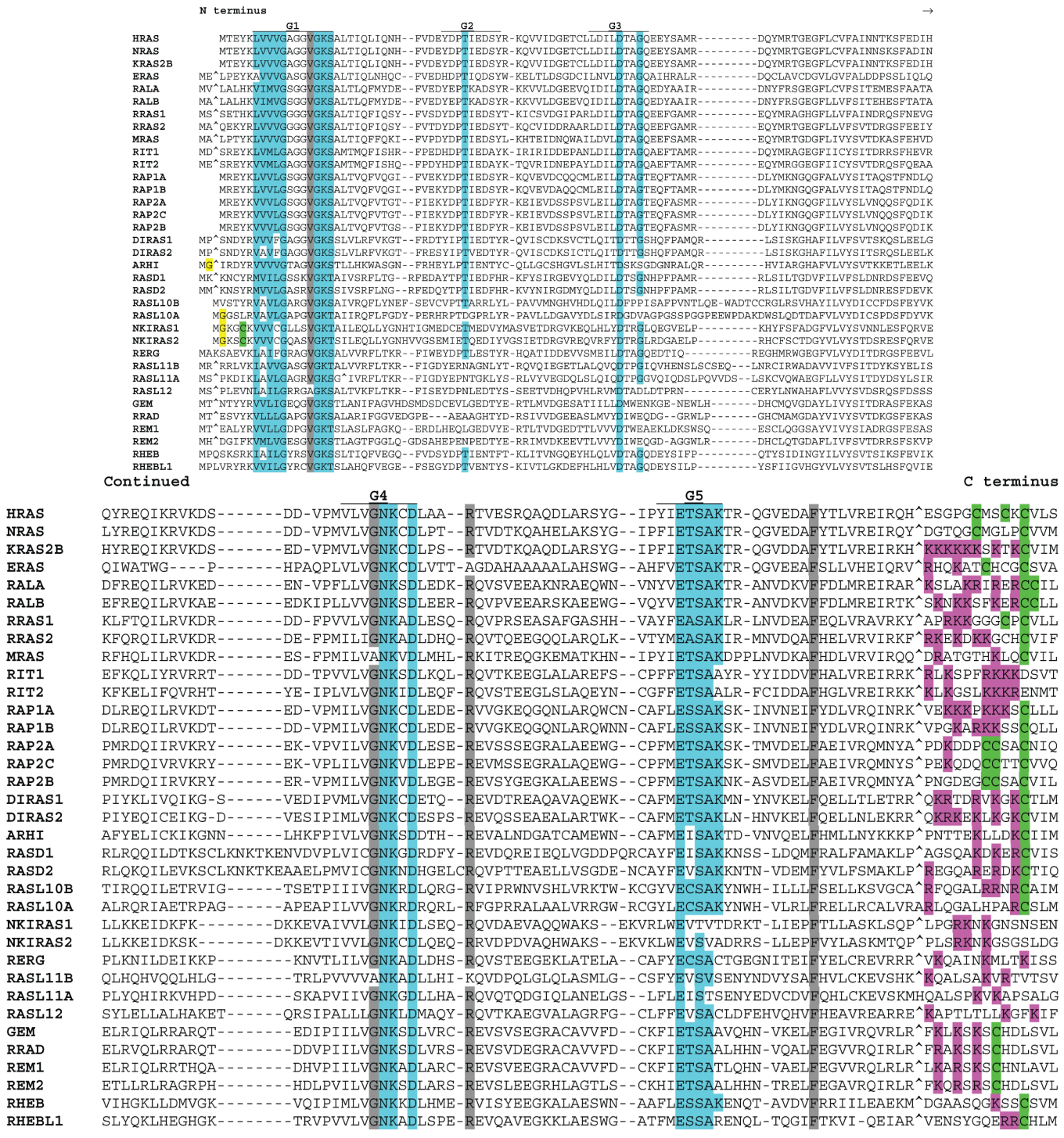


Fig 2.

Alignment of human RAS subfamily members. G box consensus residues are highlighted in blue. N- and C-terminal region cysteines, some of which are substrates for prenylation or fatty acid modification, are highlighted in green. N-terminal glycines in positions favoring myristoylation are highlighted in yellow. C-terminal basic residues are highlighted in pink. Gray highlighting indicates residues that are highly conserved in 90% of members. Amino

acids omitted for optimum alignment are indicated with the "^" symbol. For KRAS, the KRAS2B isoform sequence is presented. See Table 1 for alternate gene symbols.

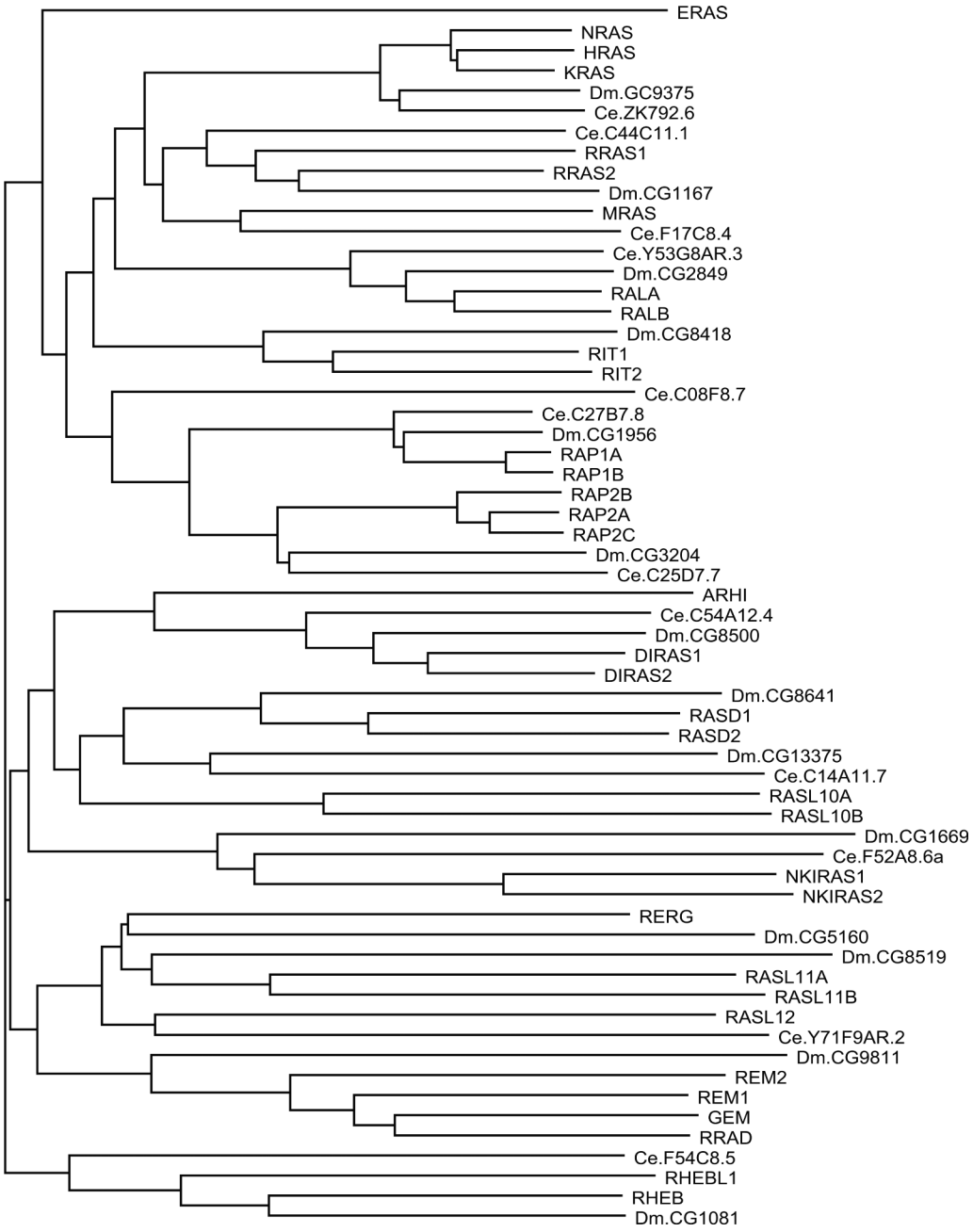


Fig. 3.

Dendrogram of RAS subfamily members from *H. sapiens*, *D. melanogaster* (Dm), and *C. elegans* (Ce). Human protein names are in uppercase letters. Branch lengths are directly proportional to the number of differences between sequences compared. See Table 1 for alternate names for human protein.

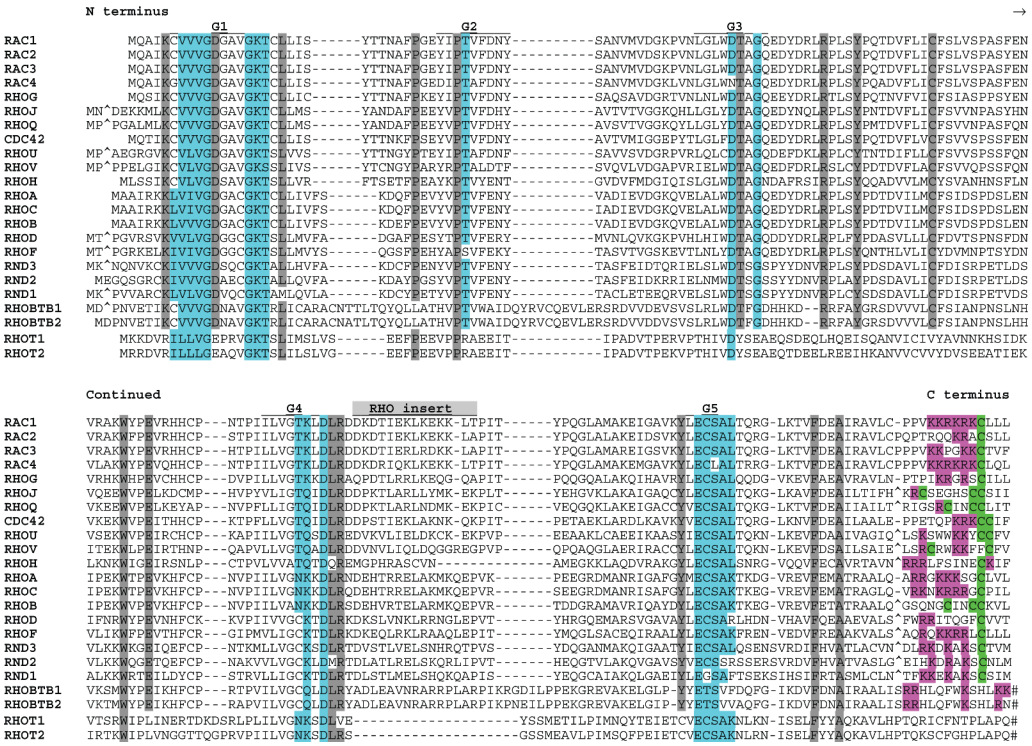


Fig 4.

Alignment of human RHO subfamily members. Highlighting and symbols are as in Fig. 2. Large C-terminal sequence extensions for RHOBTB and RHOT proteins have been removed (indicated by the “#” symbol). See Table 1 for alternate gene symbols.

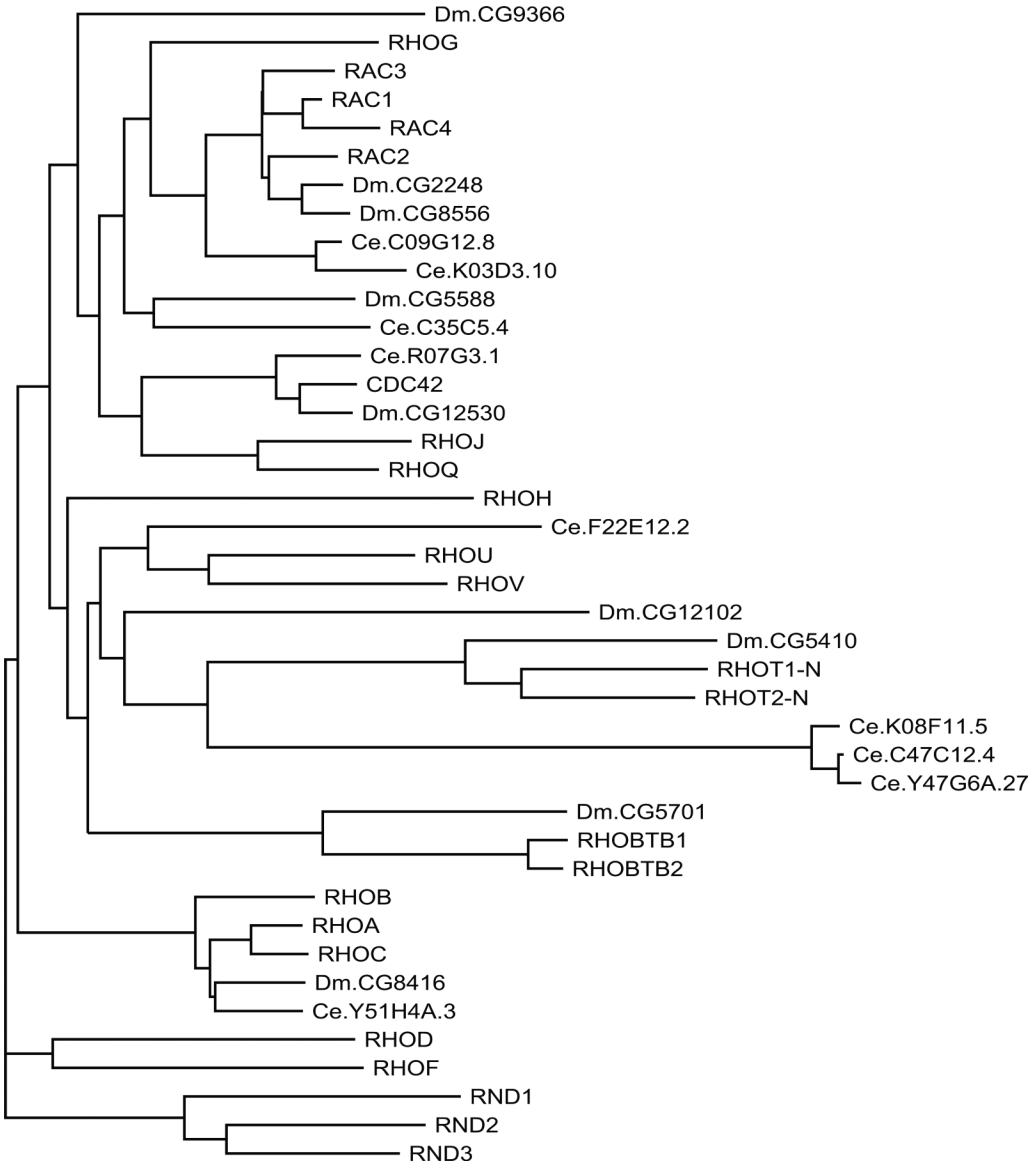
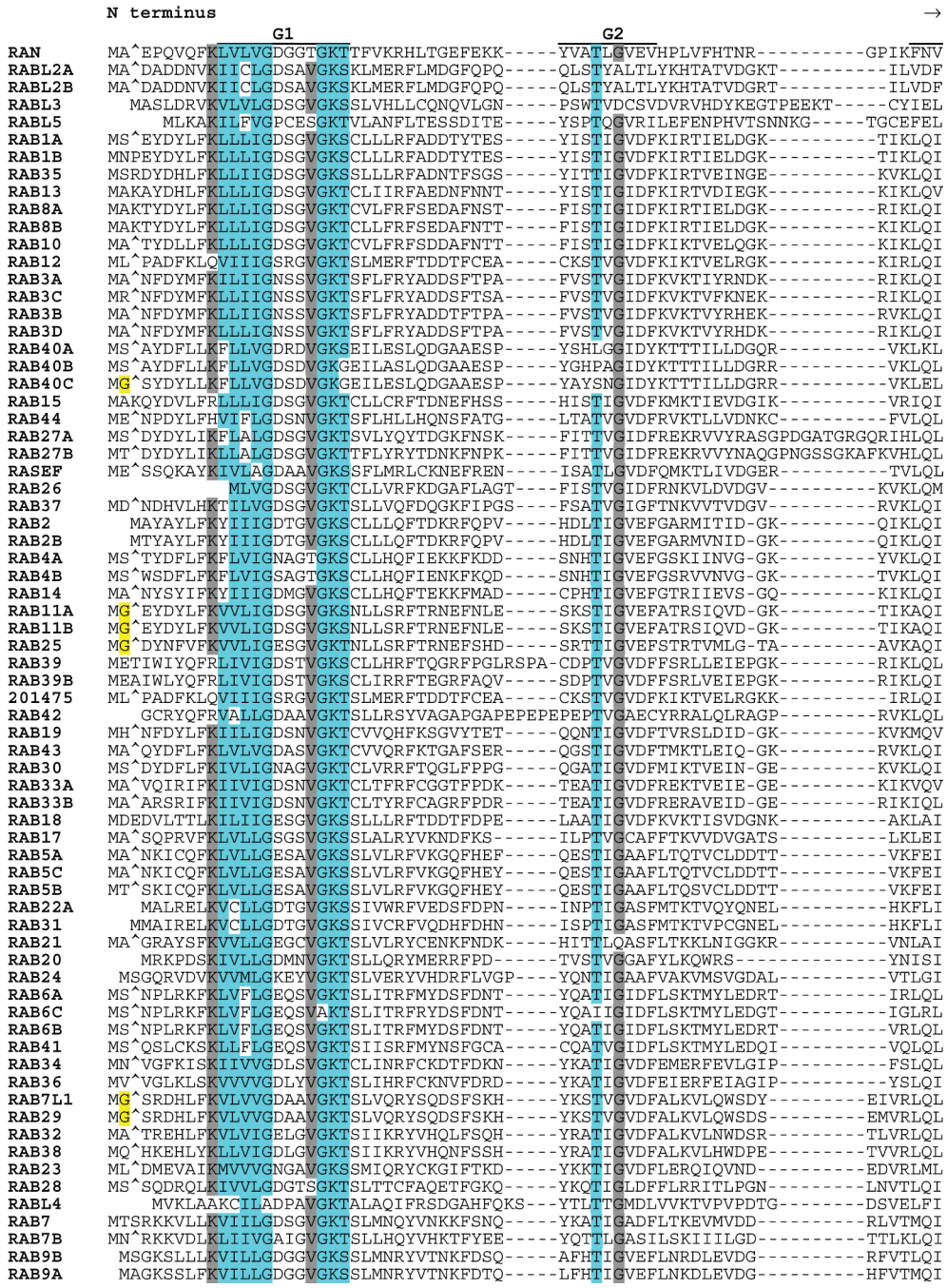
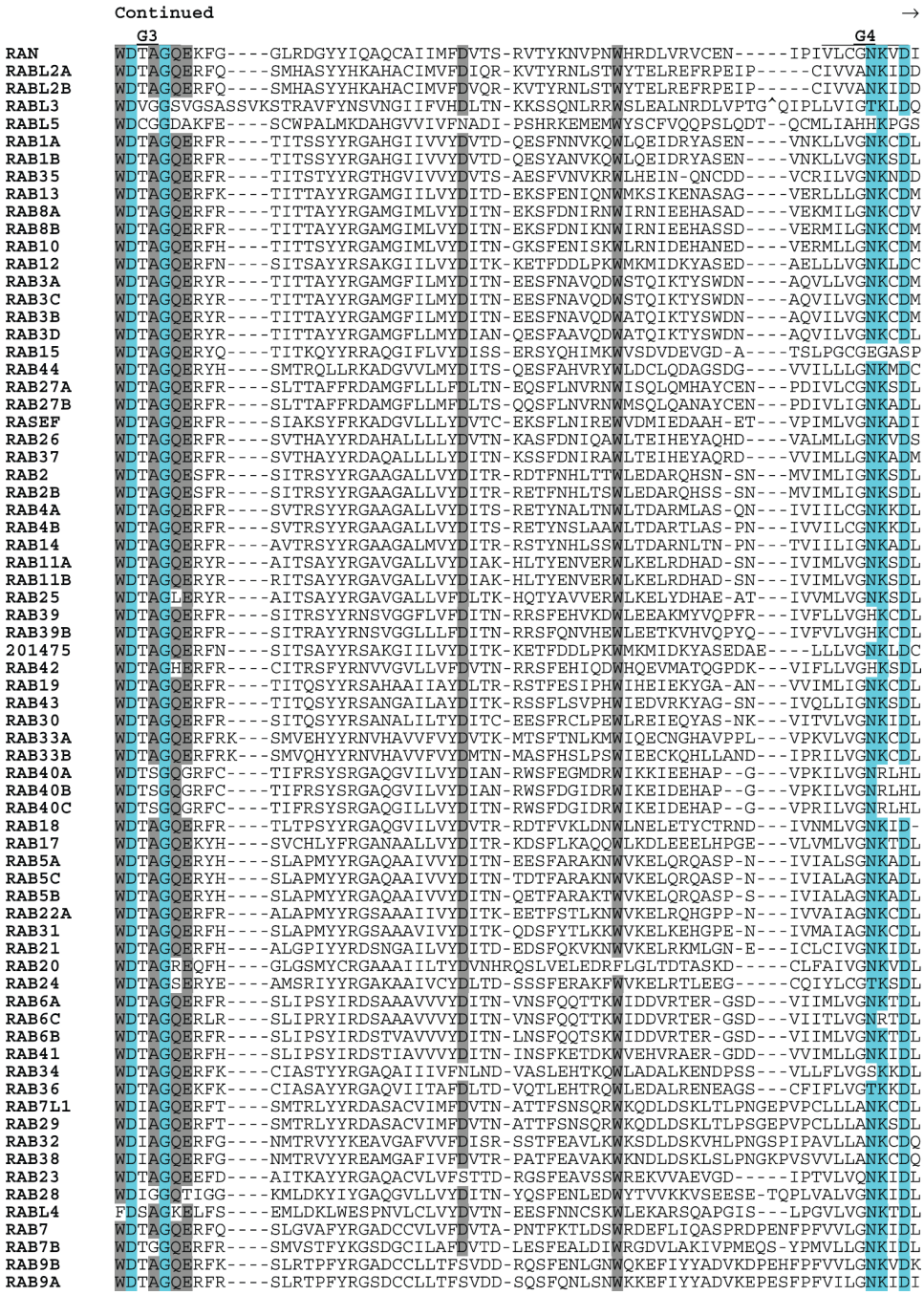


Fig. 5.

Dendrogram of RHO subfamily members from *H. sapiens*, *D. melanogaster*, and *C. elegans*. RHOT1-N and RHOT2-N represent the N-terminal GTPase domains of RHOT1 and RHOT2. Human protein names are in uppercase letters.





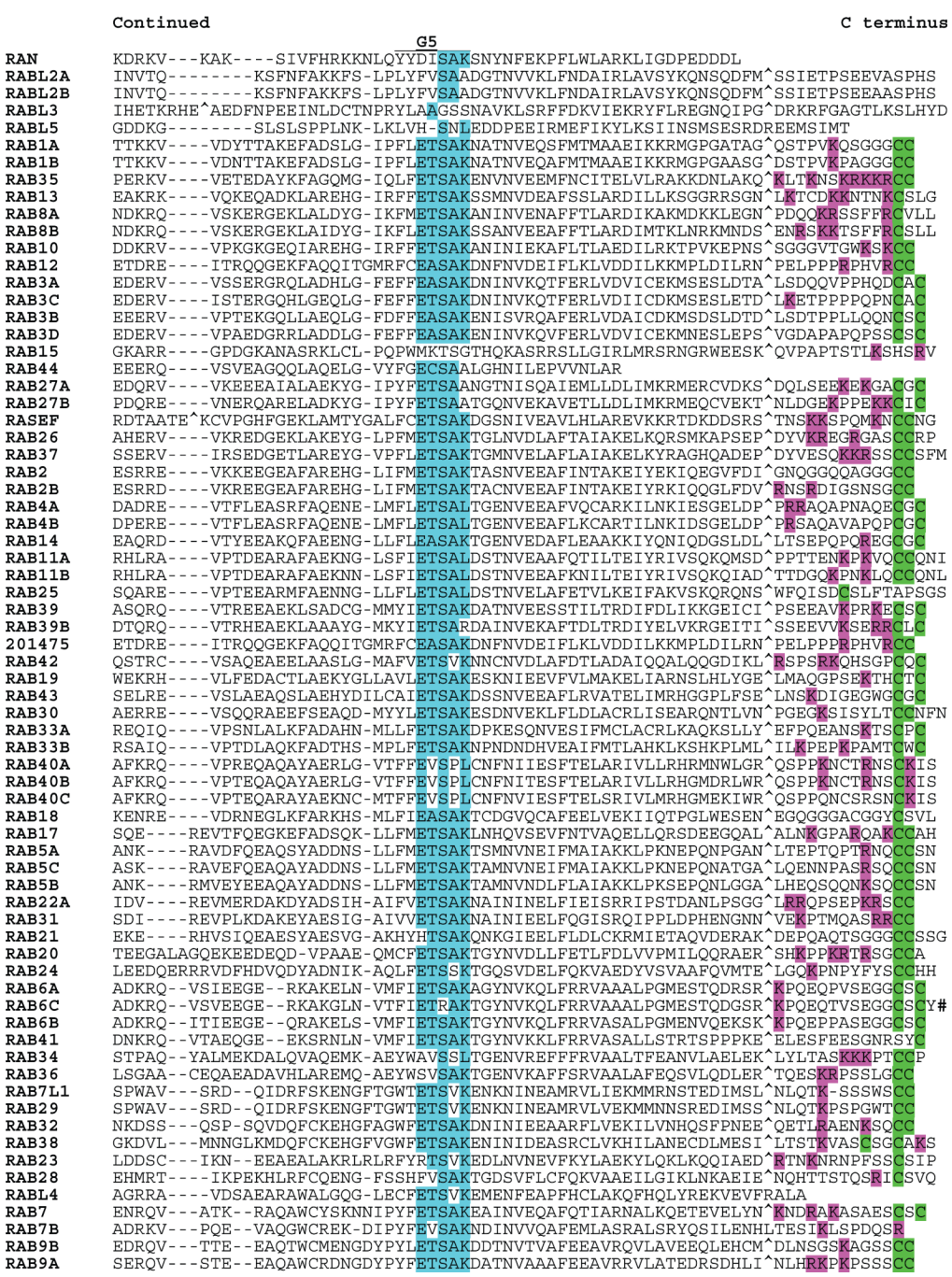


Fig. 6.

Alignment of human RAB subfamily members. Highlighting and symbols are as in Fig. 2. See Table 1 for alternate gene symbols. 201475 (LOC201475, gi41150884) represents an unannotated gene and matching cDNA. The RAB42 sequence is derived from an N-terminal truncated message.

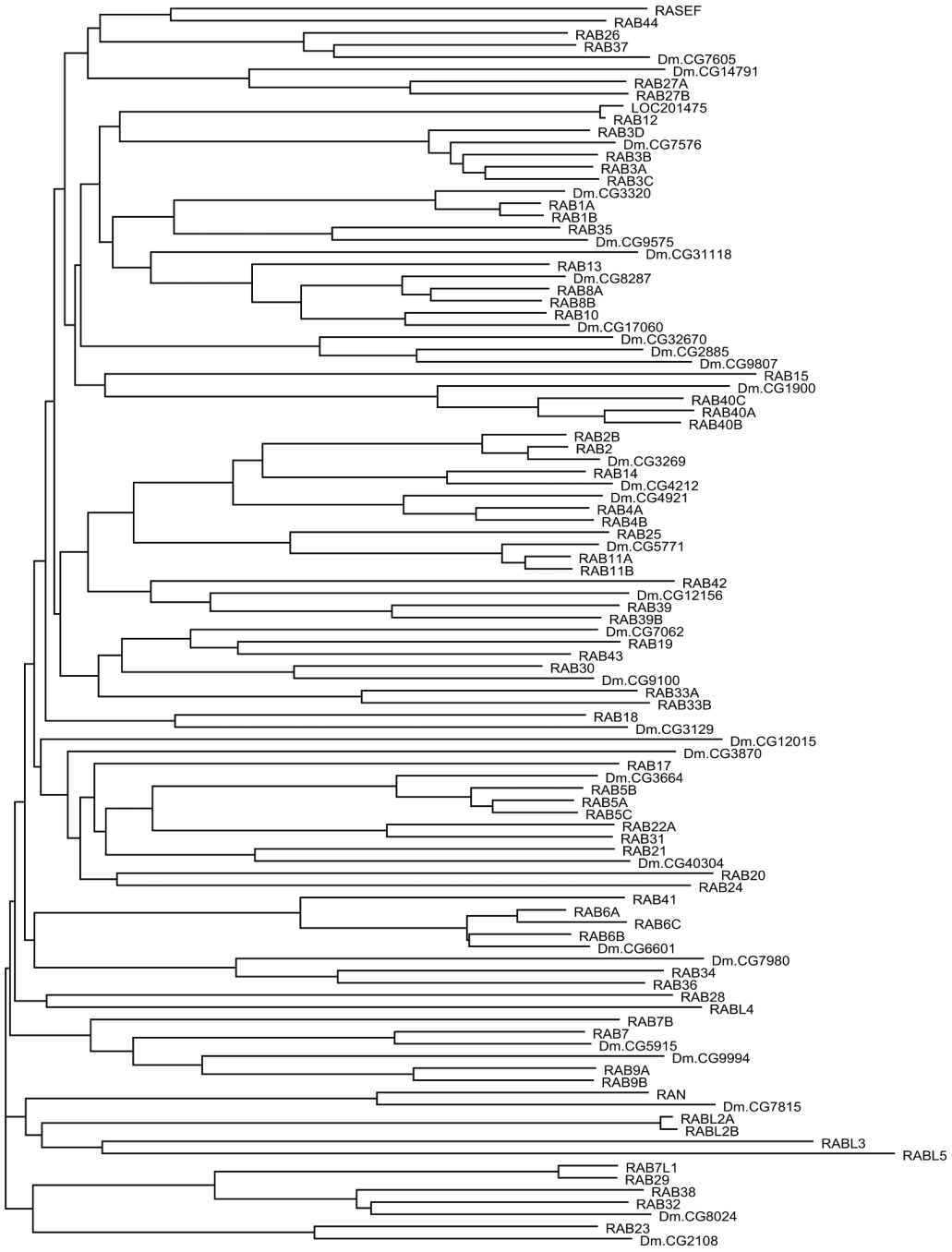


Fig. 7.

Dendrogram of RAB subfamily members from *H. sapiens* and *D. melanogaster*. Human protein names are in uppercase letters.

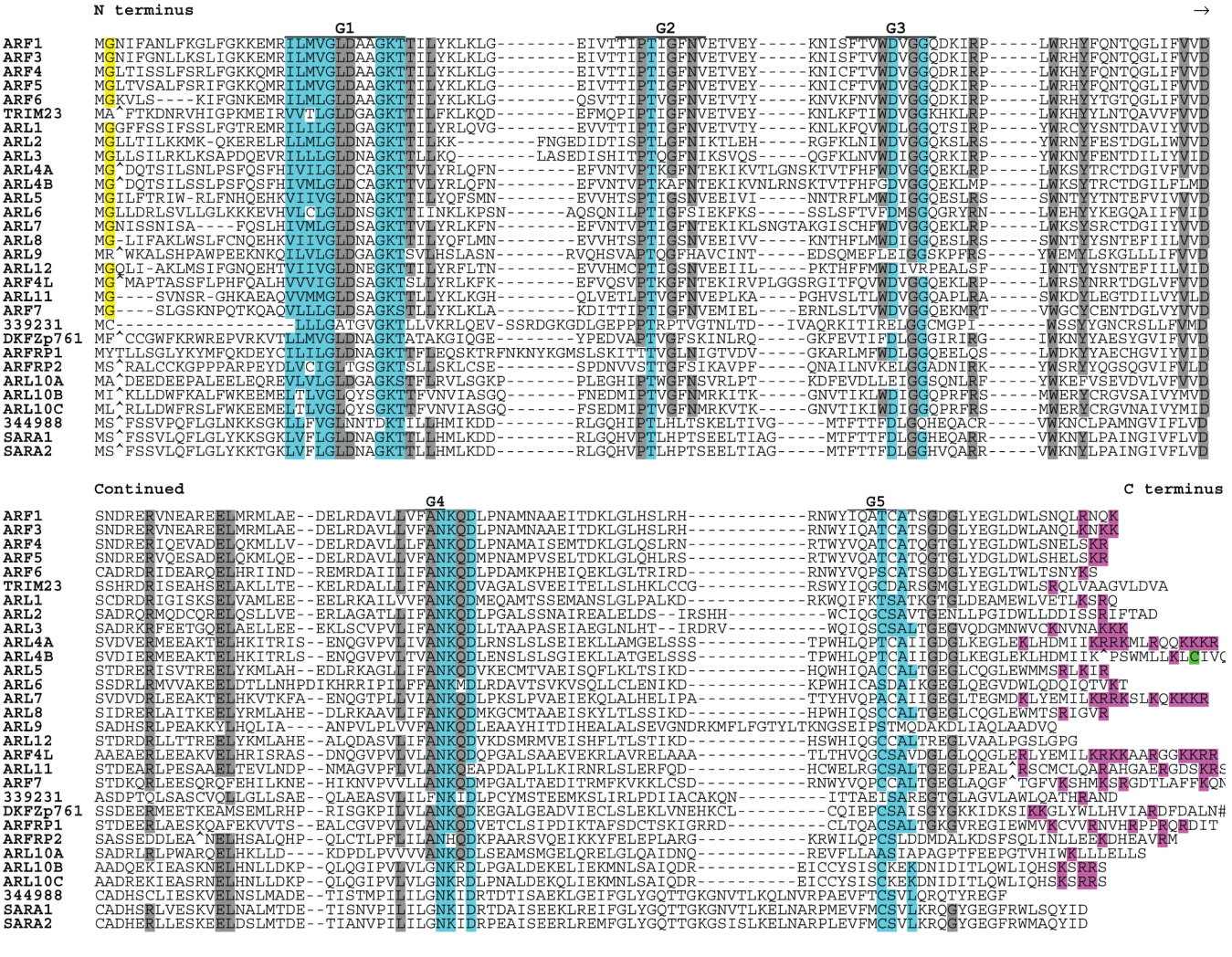


Fig. 8.

Alignment of human ARF subfamily members. Highlighting and symbols are as in Fig. 2. See Table 1 for alternate gene symbols. The following are unannotated genes with matching cDNAs: 339231 (LOC339231, gi 42661282), 344988 (LOC344988, gi 37539816), and DKFZp761 (DKFZp761H079, gi 33598955).

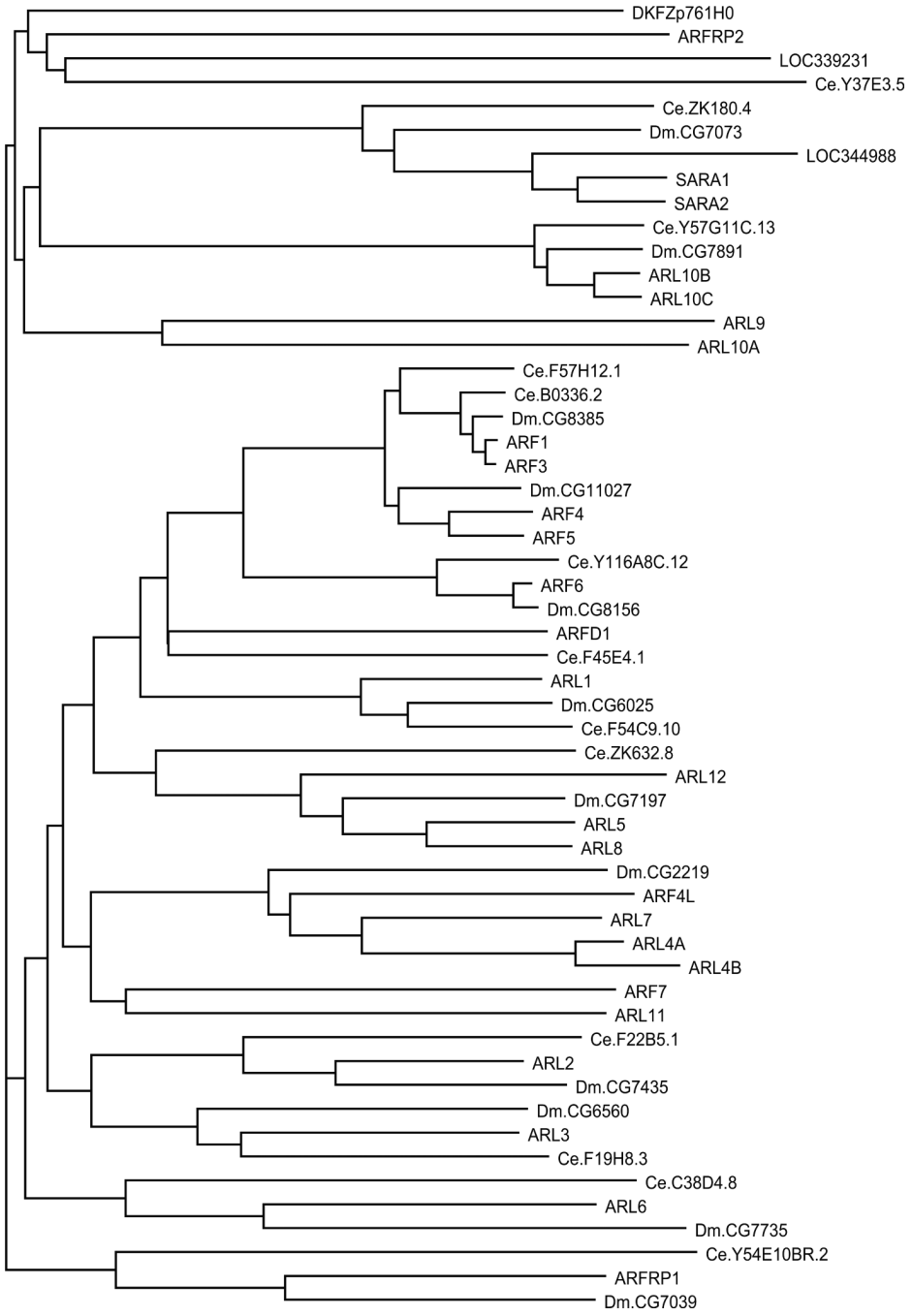


Fig. 9.

Dendrogram of ARF subfamily members from H. sapiens, *D. melanogaster*, and *C. elegans*. Human protein names are in uppercase letters.

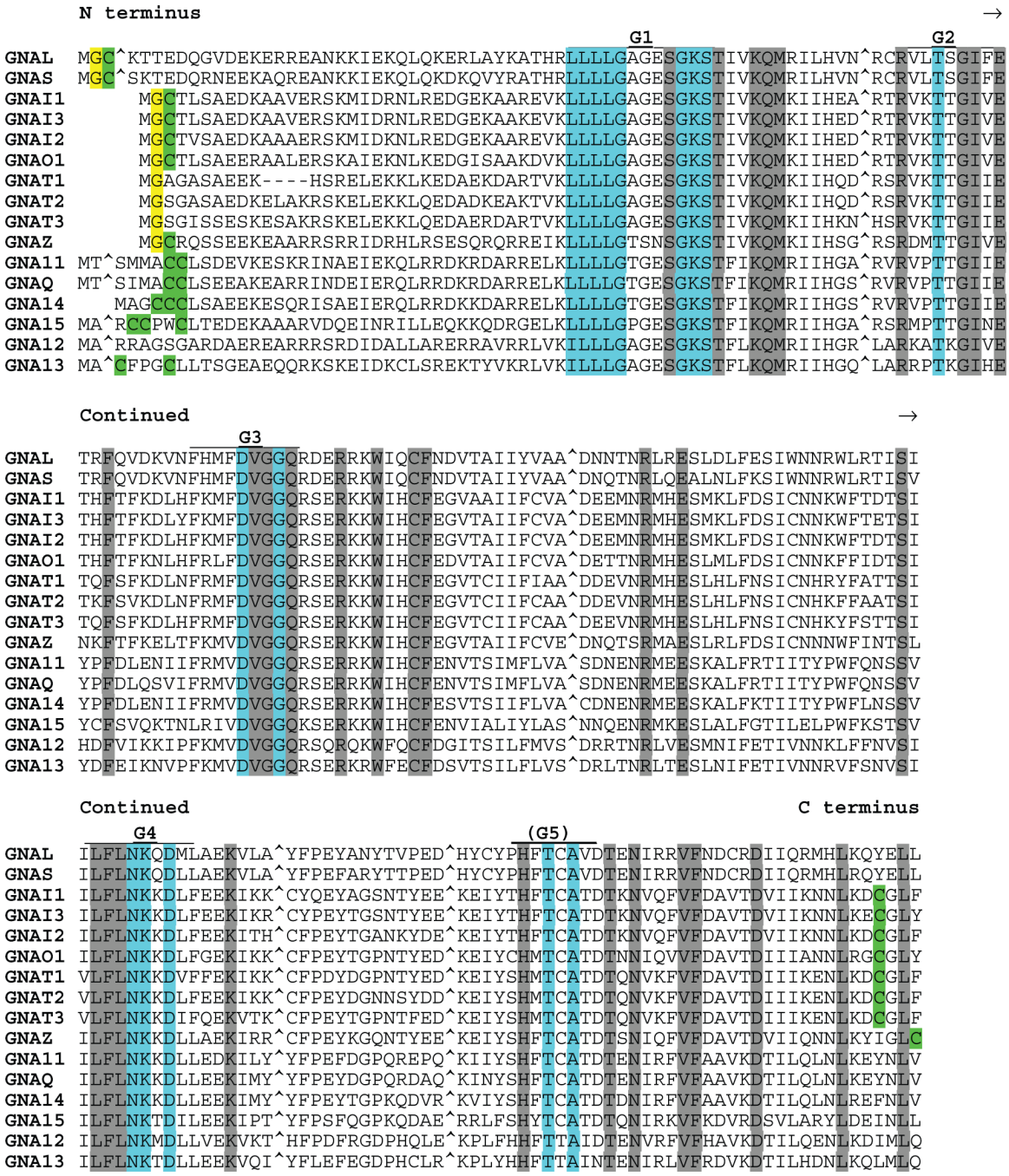


Fig. 10.

Alignment of human Gα subfamily members. Highlighting and symbols are as in Fig. 2. Insert sequences (relative to RAS subfamily proteins) have been removed and are indicated with "^". See Table 1 for alternate gene symbols.

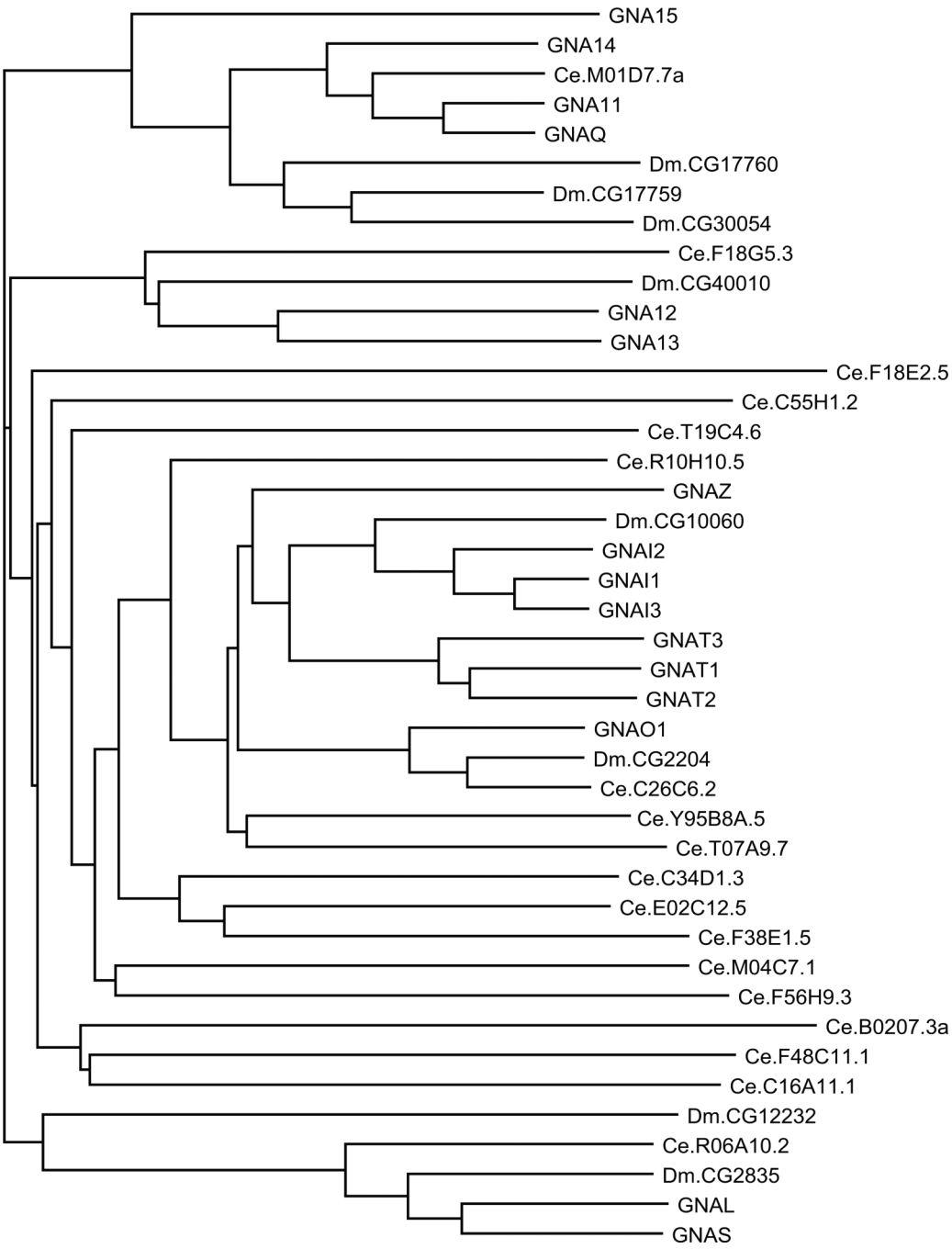


Fig. 11.

Dendrogram of Gα subfamily members from *H. sapiens*, *D. melanogaster*, *and C. elegans*. Human protein names are in uppercase letters.

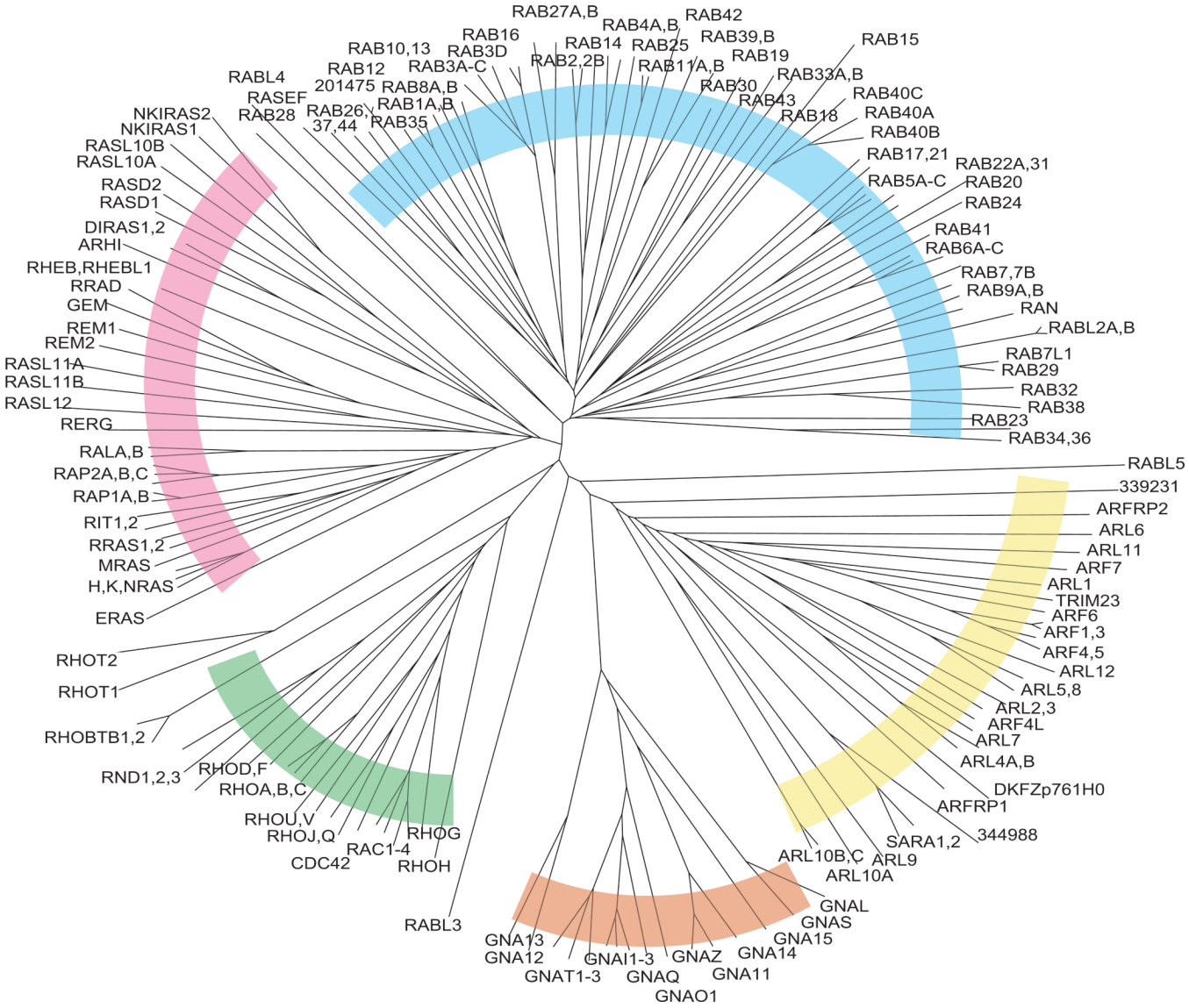


Fig. 12.

Unrooted tree of human RAS superfamily members. As with dendrograms in previous figures, branch lengths are directly proportional to the number of differences between sequences compared. Subfamilies of proteins are indicated by colored arcs: RAS (red), RHO (green), Gα (orange), ARF (yellow), and RAB (blue).

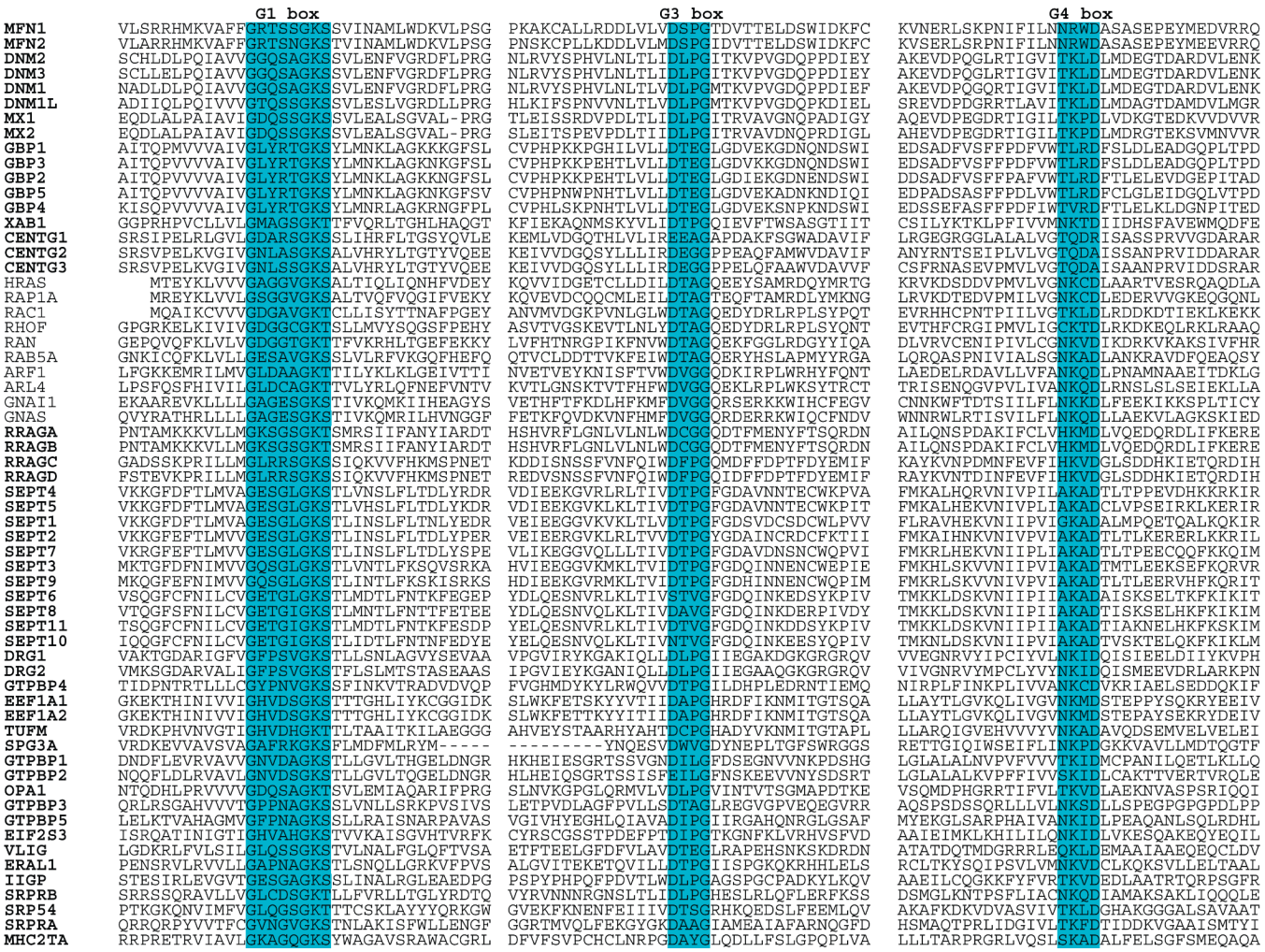


Fig. 13.

Alignment of human G proteins with representative members of the RAS superfamily. The G1, G3, and G4 box motifs and surrounding sequences are presented. See Table 1 for alternate gene symbols.

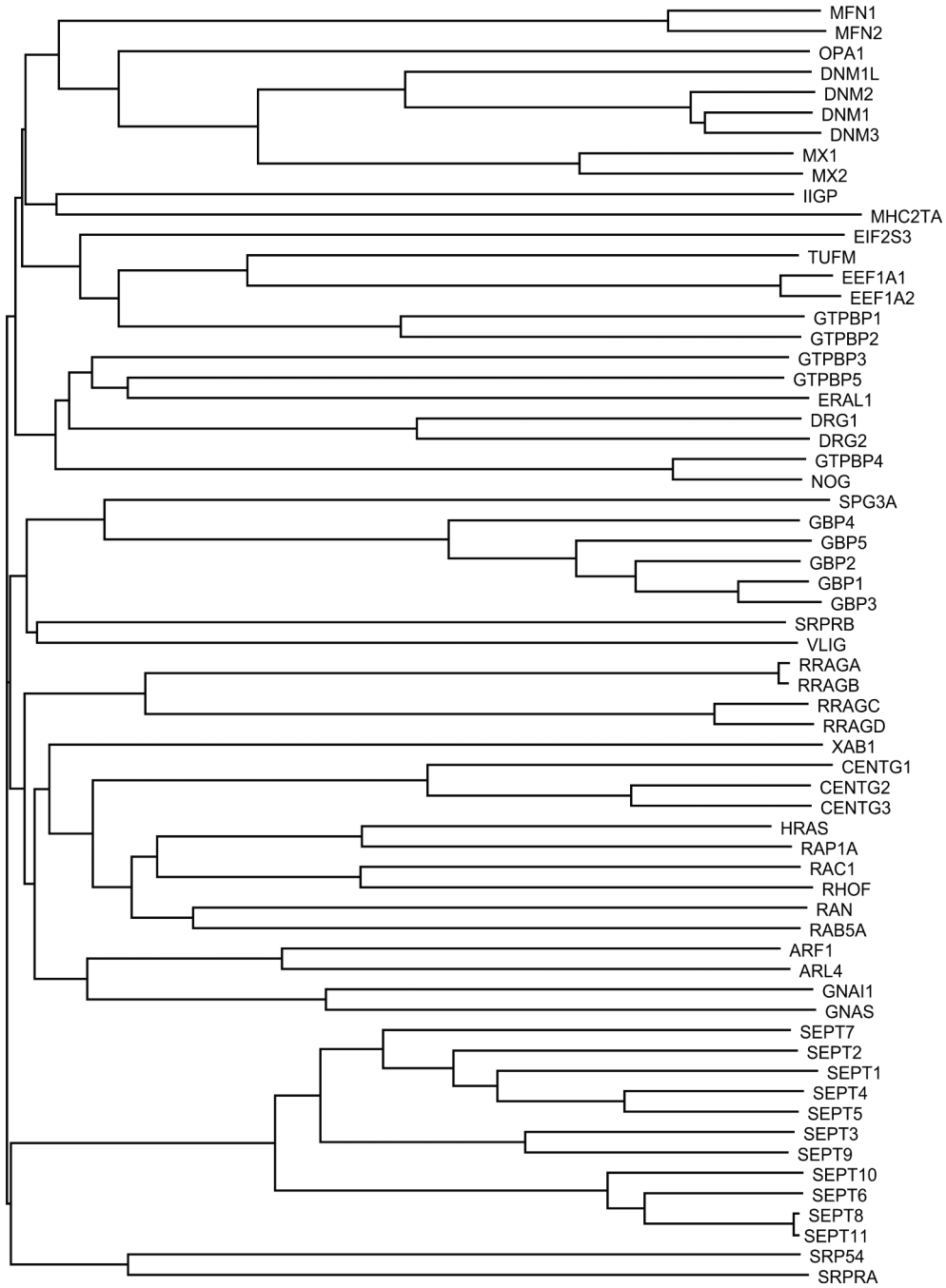


Fig. 14.

Dendrogram of distant G proteins (uppercase letters) with representative members of the RAS superfamily.

Table 1

Protein nomenclature. Human Genome Nomenclature Committee (HGNC) symbols for genes discussed in this review are shown (**left**) with common names and aliases (**right**).

HGNC name	Common names and aliases
AGTPBP1	ATP/GTP-binding protein 1, Nna1
AKT1	Akt, PKB
ANXA6	annexin 6
APPL1	DIP13α, adaptor protein with PH, PTB and Leucine zipper domains
APPL2	DIP13β
ARAF	A-Raf
ARFIP	arfaptin
ARHGAP21	ArhGAP10
ARHI	Noey2, Arhi
BIRC1	baculovirus IAP repeat containing 1, NAIP
BRAF	B-Raf
BRAP	BRap2, RNF52, IMP
CARD	caspase recruitment domain family protein
CDC42	cell division cycle 42-like, Cdc42
CENTG1	GGAP2
CENTG2	GGAP1
CENTG3	MRIP1
CHN1	RhoGAP2
CIAS1	cold autoinflamitory syndrome 1, NALP3
DAPK1	death-associated protein kinase, DAPK
DIAPH	diaphanous, mDia
DIRAS1	Di-Ras1, Rig
DIRAS2	Di-Ras2
DNM1-3	dynamin 1-3, Dnm1-3
DNM1L	dynamin 1-like, Dnm1L
DRG1 and 2	developmentally regulated GTP-binding protein
EEA1	early endosome antigen
EEF1A1	eukaryotic translation elongation factor 1 α1, eEF1A, eEF1α
EEF1A2	eukaryotic translation elongation factor 1 α2
EGFR	epidermal growth factor receptor, EGF-R
EIF2S3	eukaryotic translation initiation factor 2 subunit 3, Eif2 γ
EIF4EBP1	eukaryotic translation inititation factor 4E binding protein 1
ERAL1	Era G protein-like 1, Hera-B
ERAS	ERas, Eras
ERBB2	HER2, neu
ERK	mitogen activated protein kinase, MAPK, Erk1, 2
EXO8	Exo84
FRAP	mTOR, mammalian target of rapamycin
GBP1-5	guanylate-binding protein 1-5

GEM	Kir
GGA	Golgi-localized, γ-adaptin-ear-containing, Arf-binding
GMIP	GEM interacting protein, Gmip
GNA11	$G\alpha_{11}$
GNA12	$G\alpha_{12}$
GNA13	$G\alpha_{13}$
GNA14	$G\alpha_{14}$
GNA15	$G\alpha_{15}$, $G\alpha_{16}$
GNAI1	$G\alpha_{i\text{-}1}$
GNAI2	$G\alpha_{i\text{-}2}$
GNAI3	$G\alpha_{i\text{-}3}$
GNAL	$G\alpha_{l\ (olfactory)}$
GNAO	$G\alpha_{o}$
GNAQ	$G\alpha_{q}$
GNAS	$G\alpha_{s}$
GNAT1	transducin 1
GNAT2	transducin 2
GNAT3	transducin 3, gustducin
GNAZ	$G\alpha_{z}$
GNL1	guanine nucleotide binding protein-like 1, HSR1
GRLF1	p190A RhoGAP
GTBP1-5	GTP binding protein
HRAS	H-Ras, c-Ha-ras
IFNG	IFN-γ
IIGP5	interferon-inducible GTPase 5
KIF9	kinesin family member 9
KRAS2B	K-Ras, c-Ki-ras
M6PRBP1	TIP47
MEK	mitogen activated protein kinase kinase, Mek1, 2
MEN1	multiple endocrine neoplasia 1, menin
MFN1	mitofusin 1, Mfn1
MFN2	mitofusin 2, Mfn2
MHC2TA	major histocompatibility complex class II transactivator, CIITA
MLLT4	mixed-lineage leukemia translocated to 4, AF6
MLPH	melanophilin
MX1	Myxovirus resistance 1
MX2	Myxovirus resistance 2
NALP	NACHT, leucine rich repeat and PYD contianing
NF1	neurofibromin 1
NFKB	nuclear factor of κ gene enhancer in B cells, NF-κB
NFKBI	nuclear factor of κ gene enhancer in B cells inhibitor, IκB
NGB	neuroglobin, Nog1

NKIRAS1	NF-κB inhibitor interacting Ras 1, κB-ras1
NKIRAS2	NF-κB inhibitor interacting Ras 2, κB-ras2
NORE1	Rassf5, RapL
NRAS	N-Ras
OPA1	optic atrophy 1, Opa1
PAK1-6	Pak, p21-accociated kinase
PARD3	par-3, partitioning defective 3 homolog
PARD6	Par-6, partitioning defective 6 homolog
PDPK1	3-phosphoinositide dependent protein kinase, PDK1
PIK3C2A	phosphoinositide-3-kinase class 2 α
PIK3C2B	phosphoinositide-3-kinase class 2 β
PIK3C2G	phosphoinositide-3-kinase class 2 γ
PIK3CA	phosphoinositide-3-kinase p110α
PIK3CB	phosphoinositide-3-kinase p110β
PIK3CD	phosphoinositide-3-kinase p110δ
PIK3CG	phosphoinositide-3-kinase p110γ
PKN1-3	protein kinase N, PRK, DBK
PLCB	PLCβ
PLCE1	PLCε
RAB10	Rab10
RAB11A	Rab11A, Rab11
RAB11B	RAB11B
RAB11FIP1	arfophilin 1, RCP
RAB12	Rab12
RAB13	Rab13
RAB14	Rab14
RAB15	Rab15
RAB17	Rab17
RAB18	Rab18
RAB19	Rab19
RAB1A	Rab1A, Rab1
RAB1B	Rab1B
RAB2	Rab2
RAB20	Rab20
RAB21	Rab21
RAB22A	Rab22A, Rab22
RAB23	Rab23
RAB24	Rab24
RAB25	Rab25
RAB26	Rab26
RAB27A	Rab27A, Rab27, Ram
RAB27B	Rab27B
RAB28	Rab28
RAB29	Rab29

RAB2B	Rab2b
RAB30	Rab30
RAB31	Rab31, Rab22B
RAB32	Rab32
RAB33A	Rab33A, RabS10
RAB33B	Rab33B
RAB34	Rab34
RAB35	Rab35
RAB36	Rab36
RAB37	Rab37
RAB38	Rab38
RAB39	Rab39
RAB39B	Rab39B
RAB3A	Rab3A
RAB3B	Rab3B
RAB3C	Rab3C
RAB3D	Rab3D, Rab16
RAB40A	Rab40A, Rar2
RAB40C	Rab40C, RasL8C, RarL
RAB40C	Rab40C, RarL
RAB41	Rab41
RAB42	Rab42
RAB43	Rab43, Rab41, Rab11B
RAB44	Rab44, RASD3, RASL13
RAB4A	Rab4A, Rab4
RAB4B	Rab4B
RAB5A	Rab5A, Rab5
RAB5B	Rab5B
RAB5C	Rab5C, RabL
RAB6A	Rab6A, Rab6
RAB6B	Rab6B
RAB6C	Rab6C
RAB7	Rab7
RAB7B	Rab7B
RAB7L1	Rab7L1, Rab7L
RAB8A	Rab8A, Mel
RAB8B	Rab8B
RAB9A	Rab9A, Rab9
RAB9B	Rab9B, Rab9L
RABEP1	rabaptin-5, neurocrescin
RABEP1, 2	rabaptin 1, 2
RABL2A	RabL2A
RABL2B	RabL2B
RABL3	RabL3

RABL4	RabL4, RayL
RABL5	RabL5
RAC1	Ras-related C3 botulinum toxin substrate 1, Rac1, TC25
RAC2	Rac2
RAC3	Rac3
RAC4	Rac4
RAF1	c-Raf, Raf1
RALA	RalA
RALB	RalB
RALBP1	RalBP1, RLIP
RALGDS	ral guanine nucleotide dissociation stimulator, RalGDS, RalGEF
RAN	Ran
RAP1A	Rap1-A
RAP1B	Rap1-B
RAP2A	Rap2-A
RAP2B	Rap2-B
RAP2C	Rap2-C
RASD1	DexRas
RASD2	Rhes
RASEF	RasEF, Rab45
RASIP1	Ras interacting protein 1, RAIN
RASL10A	RasL10A
RASL10B	RasL10B
RASL11A	RasL11A
RASL11B	RasL11B
RASL12	RasL12, RIS
RASSF1	Rassf1
RASSF2	Rassf2
RASSF3	Rassf3
RASSF4	Rassf4
RASSF6	Rassf6
REM1	Rem1, rem, ges
REM2	Rem2
RERG	Rerg, rerg
RGL1	ral guanine nucleotide dissociation stimulator-like 1, Rgl
RGL2	ral guanine nucleotide dissociation stimulator-like 1, Rgl2
RGL3	Rgl3
RHEB	Rheb1
RHEBL1	Rheb2
RHOA	RhoA
RHOB	RhoB
RHOBTB1	RhoBTB1
RHOBTB2	RhoBTB2, DBC2
RHOC	RhoC

RHOD	RhoD
RHOF	Rif
RHOG	RhoG
RHOH	RhoH
RHOJ	RhoJ, Tcl
RHOQ	RhoQ, Tc10
RHOT1	Miro1
RHOT2	Miro2
RHOU	RhoU, wrch-1
RHOV	RhoV, wrch-2, chp
RILP	Rab7-interacting lysosomal protein
RIN1	Ras and Rab interacting 1, Rin1
RIN2	Ras and Rab interacting 2, Rin2
RIN3	Ras and Rab interacting 3, Rin3
RIT1	rit
RIT2	rin
RND1	Rho6
RND2	RhoN, Rho7, ARHE
RND3	RhoE, Rho8, ARHN
ROCK1	Rock1, Rho-associated protein kinase 1
ROCK2	Rock2, Rho-associated protein kinase 2
RPH11	rabphilin 11
RPH3A	rabphilin 3A
RPS6K	ribosomal protein S6 kinase
RRAD	Rad
RRAGA	Rag A, Gtr1
RRAGB	Rag B
RRAGC	Rag C, GTR2
RRAGD	Rag-D
RRAS1	R-Ras
RRAS2	TC21
RRAS3	M-Ras
SARA1	Sar1
SARA2	Sar2
SEC10L1	Sec10
SEC5L1	Sec5
SEPT1	PNUTL3
SEPT10	Sept10
SEPT11	Sept11
SEPT2	NEDD5, DIFF6
SEPT3	Sept3
SEPT4	Sept4, PNULT2, CDCREL-2, ARTS
SEPT5	Sept5, PNUTL1, CDCREL-1
SEPT6	SEP2, Sept6

SEPT7	Sept7, CDC10
SEPT8	Sept8
SEPT9	Sept9, MSF, PNUTL4
SOS1	son of sevenless, mSOS
SPG3A	spastic paraplegia, atlastin
SRP54	Srp54
SRPRA	SRPR, SrpRa, Signal recognition peptide receptor subunit α
SRPRB	SrpRb, Signal recognition peptide receptor subunit β
STK4	serine/threonine kianse 4, MST1
TIAM1	T cell lymphoma invasion and metastsis, Tiam1
TOCA1	transducer of Cdc42-dependent actin assembly
TSC1	tuberous sclerosis 1, hamartin
TSC2	tuberous sclerosis 2, uberin
TSN	translin, TRSLN, TB-RBP
TUBB	β-tubulin
TUFM	EFTu
VLIG1	very large inducible GTPase 1
WAS	Wiskott-Aldrich syndrome, WASP
XAB1	MBDin
ZNF179	BFP