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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 G α 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 Mg²⁺ 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

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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 $(3.4 \times 10^{-4} \text{ s}^{-1}$ 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 $(4.2 \times 10^{-4} \text{ s}^{-1} \text{ for HRAS})$ (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 G α subfamily proteins, cotranslational modification of glycine by myristoylation occurs. For some G α 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 (<u>rat sarcoma</u>) 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- κ B 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 (Rasrelated 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 cysteinerich 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 PIP₃ (phosphatidylinositol 3,4,5-trisphosphate) and the subsequent plasma membrane recruitment of PIP₃-binding PH domain proteins such as the protein kinases AKT1 and PDPK1 (3-phosphoinositide–dependent protein kinase 1, also called PDK1). RASmediated 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 PLCɛ) 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 Ca²⁺-calmodulin binding site (153), which appears to be required for its neurite outgrowth function (150). Although an activated (GTPasedeficient) 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

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 I κ B), an inhibitor of the transcription factor NFKB (usually called NF- κ B) (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 Ca²⁺ 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 (*Ras homolog*) 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 DIP13 α) and APPL2 (also called DIP13 β) 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 G α 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 G α subunits relative to those of RAS [(244), and reviewed in (243)]. Most G α proteins undergo N-terminal lipid modification by myristate and/or palmitate fatty acids.

Mutant G α proteins are associated with several diseases including cancers. Activating mutations in G α_s are found in some pituitary tumors, and G α_i mutations have been reported in tumors of the adrenal cortex (245).

The functions of G α -type G proteins are inextricably linked to their association with $\beta\gamma$ 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 $\beta\gamma$ dimers [in some cases, however, the heterotrimer remains intact (246)]. Downstream effectors of G α include multiple adenylyl cyclase isoforms, several ion channels and transporters, and various other cell regulatory components [reviewed in (247)].

The G α subfamily of proteins is well conserved in evolution (Fig. 11). The main branches of the G α tree (the branches containing G_s and G_l, G_i and G_t, G₁₂ and G₁₃, and G_q and G₁₁) 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 G α 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 G α 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, SRPR α), SRPRB (also called SRPR β), 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 G α 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 IFNinducible 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 IFNinducible 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

- Human Genome Nomenclature Committee. All prediced proteins discussed in this review are supported by both genomic and cDNA sequences. (HGNC, http://www.gene.ucl.ac.uk/nomenclature) symbols are used throughout (Table 1 provides a list of some common gene names corresponding to HGNC symbols)
- 2. ClustalW was used for all sequence alignments and for the generation of dendrograms. Only GTPase domains were used in the analysis (i.e., extraneous sequences were removed).
- Dever TE, Glynias MJ, Merrick WC. GTP-binding domain: Three consensus sequence elements with distinct spacing. Proc. Natl. Acad. Sci. U.S.A 1987;84:1814–1818. [PubMed: 3104905]
- Bourne HR, Sanders DA, McCormick F. The GTPase superfamily: Conserved structure and molecular mechanism. Nature 1991;349:117–127. [PubMed: 1898771]
- Walker JE, Saraste M, Runswick MJ, Gay NJ. Distantly related sequences in the alpha- and betasubunits of ATP synthase, myosin, kinases and other ATP-requiring enzymes and a common nucleotide binding fold. EMBO J 1982;1:945–951. [PubMed: 6329717]
- White MA, Nicolette C, Minden A, Polverino A, Van Aelst L, Karin M, Wigler MH. Multiple Ras functions can contribute to mammalian cell transformation. Cell 1995;80:533–541. [PubMed: 7867061]
- 7. Joneson T, White MA, Wigler MH, Bar-Sagi D. Stimulation of membrane ruffling and MAP kinase activation by distinct effectors of RAS. Science 1996;271:810–812. [PubMed: 8628998]
- Rodriguez-Viciana P, Warne PH, Khwaja A, Marte BM, Pappin D, Das P, Waterfield MD, Ridley A, Downward J. Role of phosphoinositide 3-OH kinase in cell transformation and control of the actin cytoskeleton by Ras. Cell 1997;89:457–467. [PubMed: 9150145]
- 9. Vetter IR, Wittinghofer A. The guanine nucleotide-binding switch in three dimensions. Science 2001;294:1299–1304. [PubMed: 11701921]
- Herrmann C, Horn G, Spaargaren M, Wittinghofer A. Differential interaction of the ras family GTPbinding proteins H-Ras, Rap1A, and R-Ras with the putative effector molecules Raf kinase and Ralguanine nucleotide exchange factor. J. Biol. Chem 1996;271:6794–6800. [PubMed: 8636102]
- Milburn MV, Tong L, deVos AM, Brunger A, Yamaizumi Z, Nishimura S, Kim SH. Molecular switch for signal transduction: Structural differences between active and inactive forms of protooncogenic ras proteins. Science 1990;247:939–945. [PubMed: 2406906]
- 12. Neal SE, Eccleston JF, Hall A, Webb MR. Kinetic analysis of the hydrolysis of GTP by p21N-ras. The basal GTPase mechanism. J. Biol. Chem 1988;263:19718–19722. [PubMed: 2848838]
- 13. Van Dyke K, Robinson R, Urquilla P, Smith D, Taylor M, Trush M, Wilson M. An analysis of nucleotides and catecholamines in bovine medullary granules by anion exchange high pressure liquid chromatography and fluorescence. Evidence that most of the catecholamines in chromaffin granules are stored without associated ATP. Pharmacology 1977;15:377–391. [PubMed: 918142]

- Chardin P, Camonis JH, Gale NW, van Aelst L, Schlessinger J, Wigler MH, Bar-Sagi D. Human Sos1: A guanine nucleotide exchange factor for Ras that binds to GRB2. Science 1993;260:1338– 1343. [PubMed: 8493579]
- Quilliam LA, Rebhun JF, Castro AF. A growing family of guanine nucleotide exchange factors is responsible for activation of Ras-family GTPases. Prog. Nucleic Acid Res. Mol. Biol 2002;71:391– 444. [PubMed: 12102558]
- 16. Feig LA, Cooper GM. Inhibition of NIH 3T3 cell proliferation by a mutant ras protein with preferential affinity for GDP. Mol. Cell. Biol 1988;8:3235–3243. [PubMed: 3145408]
- Chen SY, Huff SY, Lai CC, Der CJ, Powers S. Ras-15A protein shares highly similar dominantnegative biological properties with Ras-17N and forms a stable, guanine-nucleotide resistant complex with CDC25 exchange factor. Oncogene 1994;9:2691–2698. [PubMed: 8058333]
- Rak A, Pylypenko O, Durek T, Watzke A, Kushnir S, Brunsveld L, Waldmann H, Goody RS, Alexandrov K. Structure of Rab GDP-dissociation inhibitor in complex with prenylated YPT1 GTPase. Science 2003;302:646–650. [PubMed: 14576435]
- Olofsson B. Rho guanine dissociation inhibitors: Pivotal molecules in cellular signalling. Cell. Signal 1999;11:545–554. [PubMed: 10433515]
- Wu SK, Zeng K, Wilson IA, Balch WE. Structural insights into the function of the Rab GDI superfamily. Trends Biochem. Sci 1996;21:472–476. [PubMed: 9009830]
- 21. McCormick F. Going for the GAP. Curr. Biol 1998;8:R673–R674. [PubMed: 9768349]
- 22. Boguski MS, McCormick F. Proteins regulating Ras and its relatives. Nature 1993;366:643–654. [PubMed: 8259209]
- 23. Tamanoi, F.; Sigman, DS., editors. Protein Lipidation. Vol. 21. Academic Press; San Diego, CA: 2001.
- Okada T, Masuda T, Shinkai M, Kariya K, Kataoka T. Post-translational modification of H-Ras is required for activation of, but not for association with, B-Raf. J. Biol. Chem 1996;271:4671–4678. [PubMed: 8617731]
- 25. Porfiri E, Evans T, Chardin P, Hancock JF. Prenylation of Ras proteins is required for efficient hSOS1promoted guanine nucleotide exchange. J. Biol. Chem 1994;269:22672–22677. [PubMed: 8077219]
- 26. McGeady P, Kuroda S, Shimizu K, Takai Y, Gelb MH. The farnesyl group of H-Ras facilitates the activation of a soluble upstream activator of mitogen-activated protein kinase. J. Biol. Chem 1995;270:26347–26351. [PubMed: 7592846]
- Rubio I, Wittig U, Meyer C, Heinze R, Kadereit D, Waldmann H, Downward J, Wetzker R. Farnesylation of Ras is important for the interaction with phosphoinositide 3-kinase gamma. Eur. J. Biochem 1999;266:70–82. [PubMed: 10542052]
- Williams JG, Drugan JK, Yi GS, Clark GJ, Der CJ, Campbell SL. Elucidation of binding determinants and functional consequences of Ras/Raf-cysteine-rich domain interactions. J. Biol. Chem 2000;275:22172–22179. [PubMed: 10777480]
- Gotoh T, Tian X, Feig LA. Prenylation of target GTPases contributes to signaling specificity of Rasguanine nucleotide exchange factors. J. Biol. Chem 2001;276:38029–38035. [PubMed: 11500499]
- Degtyarev MY, Spiegel AM, Jones TL. The G protein alpha s subunit incorporates [3H]palmitic acid and mutation of cysteine-3 prevents this modification. Biochemistry 1993;32:8057–8061. [PubMed: 8347607]
- Linder ME, Middleton P, Hepler JR, Taussig R, Gilman AG, Mumby SM. Lipid modifications of G proteins: Alpha subunits are palmitoylated. Proc. Natl. Acad. Sci. U.S.A 1993;90:3675–3679. [PubMed: 8475115]
- Veit M, Nurnberg B, Spicher K, Harteneck C, Ponimaskin E, Schultz G, Schmidt MF. The alphasubunits of G-proteins G12 and G13 are palmitoylated, but not amidically myristoylated. FEBS Lett 1994;339:160–164. [PubMed: 8313967]
- 33. Kirsten WH, Mayer LA. Malignant lymphomas of extrathymic origin induced in rats by murine erythroblastosis virus. J. Natl. Cancer Inst 1969;43:735–746. [PubMed: 4309615]
- 34. Harvey JJ. An unidentified virus which causes the rapid production of tumours in mice. Nature 1964;204:1104–1105. [PubMed: 14243400]
- Perucho M, Goldfarb M, Shimizu K, Lama C, Fogh J, Wigler M. Human-tumor-derived cell lines contain common and different transforming genes. Cell 1981;27:467–476. [PubMed: 6101201]

- 36. Krontiris TG, Cooper GM. Transforming activity of human tumor DNAs. Proc. Natl. Acad. Sci. U.S.A 1981;78:1181–1184. [PubMed: 6940134]
- Shih C, Padhy LC, Murray M, Weinberg RA. Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts. Nature 1981;290:261–264. [PubMed: 7207618]
- Zhang K, DeClue JE, Vass WC, Papageorge AG, McCormick F, Lowy DR. Suppression of c-ras transformation by GTPase-activating protein. Nature 1990;346:754–756. [PubMed: 2201922]
- Feig LA, Cooper GM. Relationship among guanine nucleotide exchange, GTP hydrolysis, and transforming potential of mutated ras proteins. Mol. Cell. Biol 1988;8:2472–2478. [PubMed: 3043178]
- 40. Patel G, MacDonald MJ, Khosravi-Far R, Hisaka MM, Der CJ. Alternate mechanisms of ras activation are complementary and favor and formation of ras-GTP. Oncogene 1992;7:283–288. [PubMed: 1549350]
- Mitsuuchi Y, Testa JR. Cytogenetics and molecular genetics of lung cancer. Am. J. Med. Genet 2002;115:183–188. [PubMed: 12407699]
- 42. Grady WM, Markowitz SD. Genetic and epigenetic alterations in colon cancer. Annu. Rev. Genomics Hum. Genet 2002;3:101–128. [PubMed: 12142355]
- Jaffee EM, Hruban RH, Canto M, Kern SE. Focus on pancreas cancer. Cancer Cell 2002;2:25–28. [PubMed: 12150822]
- 44. Garcia-Rostan G, Zhao H, Camp RL, Pollan M, Herrero A, Pardo J, Wu R, Carcangiu ML, Costa J, Tallini G. ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. J. Clin. Oncol 2003;21:3226–3235. [PubMed: 12947056]
- Vageli D, Kiaris H, Delakas D, Anezinis P, Cranidis A, Spandidos DA. Transcriptional activation of H-ras, K-ras and N-ras proto-oncogenes in human bladder tumors. Cancer Lett 1996;107:241–247. [PubMed: 8947520]
- 46. von Lintig FC, Dreilinger AD, Varki NM, Wallace AM, Casteel DE, Boss GR. Ras activation in human breast cancer. Breast Cancer Res. Treat 2000;62:51–62. [PubMed: 10989985]
- 47. Xu GF, O'Connell P, Viskochil D, Cawthon R, Robertson M, Culver M, Dunn D, Stevens J, Gesteland R, White R, et al. The neurofibromatosis type 1 gene encodes a protein related to GAP. Cell 1990;62:599–608. [PubMed: 2116237]
- 48. Xu GF, Lin B, Tanaka K, Dunn D, Wood D, Gesteland R, White R, Weiss R, Tamanoi F. The catalytic domain of the neurofibromatosis type 1 gene product stimulates ras GTPase and complements ira mutants of S. cerevisiae. Cell 1990;63:835–841. [PubMed: 2121369]
- 49. Martin GA, Viskochil D, Bollag G, McCabe PC, Crosier WJ, Haubruck H, Conroy L, Clark R, O'Connell P, Cawthon RM, et al. The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21. Cell 1990;63:843–849. [PubMed: 2121370]
- Ballester R, Marchuk D, Boguski M, Saulino A, Letcher R, Wigler M, Collins F. The NF1 locus encodes a protein functionally related to mammalian GAP and yeast IRA proteins. Cell 1990;63:851– 859. [PubMed: 2121371]
- Shinohara N, Ogiso Y, Tanaka M, Sazawa A, Harabayashi T, Koyanagi T. The significance of Ras guanine nucleotide exchange factor, son of sevenless protein, in renal cell carcinoma cell lines. J. Urol 1997;158:908–911. [PubMed: 9258117]
- Silvius JR. Mechanisms of Ras protein targeting in mammalian cells. J. Membr. Biol 2002;190:83– 92. [PubMed: 12474073]
- Choy E, Chiu VK, Silletti J, Feoktistov M, Morimoto T, Michaelson D, Ivanov IE, Philips MR. Endomembrane trafficking of ras: The CAAX motif targets proteins to the ER and Golgi. Cell 1999;98:69–80. [PubMed: 10412982]
- 54. Apolloni A, Prior IA, Lindsay M, Parton RG, Hancock JF. H-ras but not K-ras traffics to the plasma membrane through the exocytic pathway. Mol. Cell. Biol 2000;20:2475–2487. [PubMed: 10713171]
- 55. Roy S, Wyse B, Hancock JF. H-Ras signaling and K-Ras signaling are differentially dependent on endocytosis. Mol. Cell. Biol 2002;22:5128–5140. [PubMed: 12077341]
- Jiang X, Sorkin A. Coordinated traffic of Grb2 and Ras during epidermal growth factor receptor endocytosis visualized in living cells. Mol. Biol. Cell 2002;13:1522–1535. [PubMed: 12006650]

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- 57. Chiu VK, Bivona T, Hach A, Sajous JB, Silletti J, Wiener H, Johnson II RL, Cox AD, Philips MR. Ras signalling on the endoplasmic reticulum and the Golgi. Nat. Cell Biol 2002;4:343–350. [PubMed: 11988737]
- 58. Prior IA, Harding A, Yan J, Sluimer J, Parton RG, Hancock JF. GTP-dependent segregation of H-ras from lipid rafts is required for biological activity. Nat. Cell Biol 2001;3:368–375. [PubMed: 11283610]
- Hancock JF. Ras proteins: Different signals from different locations. Nat. Rev. Mol. Cell Biol 2003;4:373–384. [PubMed: 12728271]
- 60. Finlin BS, Gau CL, Murphy GA, Shao H, Kimel T, Seitz RS, Chiu YF, Botstein D, Brown PO, Der CJ, Tamanoi F, Andres DA, Perou CM. RERG is a novel ras-related, estrogen-regulated and growth-inhibitory gene in breast cancer. J. Biol. Chem 2001;276:42259–42267. [PubMed: 11533059]
- Ballester R, Furth ME, Rosen OM. Phorbol ester- and protein kinase C-mediated phosphorylation of the cellular Kirsten ras gene product. J. Biol. Chem 1987;262:2688–2695. [PubMed: 3546293]
- 62. Mallis RJ, Buss JE, Thomas JA. Oxidative modification of H-ras: S-thiolation and S-nitrosylation of reactive cysteines. Biochem. J 2001;355:145–153. [PubMed: 11256959]
- Baker TL, Booden MA, Buss JE. S-Nitrosocysteine increases palmitate turnover on Ha-Ras in NIH 3T3 cells. J. Biol. Chem 2000;275:22037–22047. [PubMed: 10801823]
- Williams JG, Pappu K, Campbell SL. Structural and biochemical studies of p21Ras S-nitrosylation and nitric oxide-mediated guanine nucleotide exchange. Proc. Natl. Acad. Sci. U.S.A 2003;100:6376–6381. [PubMed: 12740440]
- 65. Zou JX, Wang B, Kalo MS, Zisch AH, Pasquale EB, Ruoslahti E. An Eph receptor regulates integrin activity through R-Ras. Proc. Natl. Acad. Sci. U.S.A 1999;96:13813–13818. [PubMed: 10570155]
- 66. Zou JX, Liu Y, Pasquale EB, Ruoslahti E. Activated SRC oncogene phosphorylates R-ras and suppresses integrin activity. J. Biol. Chem 2002;277:1824–1827. [PubMed: 11682467]
- Shimizu K, Birnbaum D, Ruley MA, Fasano O, Suard Y, Edlund L, Taparowsky E, Goldfarb M, Wigler M. Structure of the Ki-ras gene of the human lung carcinoma cell line Calu-1. Nature 1983;304:497–500. [PubMed: 6308465]
- McGrath JP, Capon DJ, Smith DH, Chen EY, Seeburg PH, Goeddel DV, Levinson AD. Structure and organization of the human Kiras proto-oncogene and a related processed pseudogene. Nature 1983;304:501–506. [PubMed: 6308466]
- 69. Guil S, de La Iglesia N, Fernandez-Larrea J, Cifuentes D, Ferrer JC, Guinovart JJ, Bach-Elias M. Alternative splicing of the human protooncogene c-H-ras renders a new Ras family protein that trafficks to cytoplasm and nucleus. Cancer Res 2003;63:5178–5187. [PubMed: 14500341]
- Bar-Sagi D, Feramisco JR. Microinjection of the ras oncogene protein into PC12 cells induces morphological differentiation. Cell 1985;42:841–848. [PubMed: 2996779]
- 71. Simon MA, Bowtell DD, Dodson GS, Laverty TR, Rubin GM. Ras1 and a putative guanine nucleotide exchange factor perform crucial steps in signaling by the sevenless protein tyrosine kinase. Cell 1991;67:701–716. [PubMed: 1934068]
- 72. Han M, Sternberg PW. let-60, a gene that specifies cell fates during C. elegans vulval induction, encodes a ras protein. Cell 1990;63:921–931. [PubMed: 2257629]
- 73. Brambilla R, Gnesutta N, Minichiello L, White G, Roylance AJ, Herron CE, Ramsey M, Wolfer DP, Cestari V, Rossi-Arnaud C, Grant SG, Chapman PF, Lipp HP, Sturani E, Klein R. A role for the Ras signalling pathway in synaptic transmission and long-term memory. Nature 1997;390:281–286. [PubMed: 9384379]
- 74. Chen HJ, Rojas-Soto M, Oguni A, Kennedy MB. A synaptic Ras-GTPase activating protein (p135 SynGAP) inhibited by CaM kinase II. Neuron 1998;20:895–904. [PubMed: 9620694]
- 75. Kim JH, Liao D, Lau LF, Huganir RL. SynGAP: A synaptic RasGAP that associates with the PSD-95/ SAP90 protein family. Neuron 1998;20:683–691. [PubMed: 9581761]
- 76. Komiyama NH, Watabe AM, Carlisle HJ, Porter K, Charlesworth P, Monti J, Strathdee DJ, O'Carroll CM, Martin SJ, Morris RG, O'Dell TJ, Grant SG. SynGAP regulates ERK/MAPK signaling, synaptic plasticity, and learning in the complex with postsynaptic density 95 and NMDA receptor. J. Neurosci 2002;22:9721–9732. [PubMed: 12427827]
- 77. Kim JH, Lee HK, Takamiya K, Huganir RL. The role of synaptic GTPase-activating protein in neuronal development and synaptic plasticity. J. Neurosci 2003;23:1119–1124. [PubMed: 12598599]

- 78. Dhaka A, Costa RM, Hu H, Irvin DK, Patel A, Kornblum HI, Silva AJ, O'Dell TJ, Colicelli J. The RAS effector RIN1 modulates the formation of aversive memories. J. Neurosci 2003;23:748–757. [PubMed: 12574403]
- 79. Van Aelst L, Barr M, Marcus S, Polverino A, Wigler M. Complex formation between RAS and RAF and other protein kinases. Proc. Natl. Acad. Sci. U.S.A 1993;90:6213–6217. [PubMed: 8327501]
- Vojtek AB, Hollenberg SM, Cooper JA. Mammalian Ras interacts directly with the serine/threonine kinase Raf. Cell 1993;74:205–214. [PubMed: 8334704]
- Warne PH, Viciana PR, Downward J. Direct interaction of Ras and the amino-terminal region of Raf-1 in vitro. Nature 1993;364:352–355. [PubMed: 8332195]
- Zhang XF, Settleman J, Kyriakis JM, Takeuchi-Suzuki E, Elledge SJ, Marshall MS, Bruder JT, Rapp UR, Avruch J. Normal and oncogenic p21ras proteins bind to the amino-terminal regulatory domain of c-Raf-1. Nature 1993;364:308–313. [PubMed: 8332187]
- Koide H, Satoh T, Nakafuku M, Kaziro Y. GTP-dependent association of Raf-1 with Ha-Ras: Identification of Raf as a target downstream of Ras in mammalian cells. Proc. Natl. Acad. Sci. U.S.A 1993;90:8683–8686. [PubMed: 8378348]
- Kolch W. Meaningful relationships: The regulation of the Ras/Raf/MEK/ERK pathway by protein interactions. Biochem. J 2000;351:289–305. [PubMed: 11023813]
- Morrison DK, Cutler RE. The complexity of Raf-1 regulation. Curr. Opin. Cell Biol 1997;9:174–179. [PubMed: 9069260]
- Oldham SM, Clark GJ, Gangarosa LM, Coffey RJ Jr. Der CJ. Activation of the Raf-1/MAP kinase cascade is not sufficient for Ras transformation of RIE-1 epithelial cells. Proc. Natl. Acad. Sci. U.S.A 1996;93:6924–6928. [PubMed: 8692920]
- Hamaguchi M, Meth JL, von Klitzing C, Wei W, Esposito D, Rodgers L, Walsh T, Welcsh P, King MC, Wigler MH. DBC2, a candidate for a tumor suppressor gene involved in breast cancer. Proc. Natl. Acad. Sci. U.S.A 2002;99:13647–13652. [PubMed: 12370419]
- 88. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. Nature 2002;417:949–954. [PubMed: 12068308]
- Lambert JM, Lambert QT, Reuther GW, Malliri A, Siderovski DP, Sondek J, Collard JG, Der CJ. Tiam1 mediates Ras activation of Rac by a PI(3)K-independent mechanism. Nat. Cell Biol 2002;4:621–625. [PubMed: 12134164]
- 90. Malliri A, van der Kammen RA, Clark K, van der Valk M, Michiels F, Collard JG. Mice deficient in the Rac activator Tiam1 are resistant to Ras-induced skin tumours. Nature 2002;417:867–871. [PubMed: 12075356]
- Rodriguez-Viciana P, Warne PH, Dhand R, Vanhaesebroeck B, Gout I, Fry MJ, Waterfield MD, Downward J. Phosphatidylinositol-3-OH kinase as a direct target of Ras. Nature 1994;370:527–532. [PubMed: 8052307]
- Rodriguez-Viciana P, Warne PH, Vanhaesebroeck B, Waterfield MD, Downward J. Activation of phosphoinositide 3-kinase by interaction with Ras and by point mutation. EMBO J 1996;15:2442– 2451. [PubMed: 8665852]
- 93. Spaargaren M, Bischoff JR. Identification of the guanine nucleotide dissociation stimulator for Ral as a putative effector molecule of R-ras, H-ras, K-ras, and Rap. Proc. Natl. Acad. Sci. U.S.A 1994;91:12609–12613. [PubMed: 7809086]
- 94. Kikuchi A, Demo SD, Ye ZH, Chen YW, Williams LT. ralGDS family members interact with the effector loop of ras p21. Mol. Cell. Biol 1994;14:7483–7491. [PubMed: 7935463]
- Hofer F, Fields S, Schneider C, Martin GS. Activated Ras interacts with the Ral guanine nucleotide dissociation stimulator. Proc. Natl. Acad. Sci. U.S.A 1994;91:11089–11093. [PubMed: 7972015]
- 96. Peterson SN, Trabalzini L, Brtva TR, Fischer T, Altschuler DL, Martelli P, Lapetina EG, Der CJ, White GC. Identification of a novel RalGDS-related protein as a candidate effector for Ras and Rap1. J. Biol. Chem 1996;271:29903–29908. [PubMed: 8939933]

- 97. Ehrhardt GR, Korherr C, Wieler JS, Knaus M, Schrader JW. A novel potential effector of M-Ras and p21 Ras negatively regulates p21 Ras-mediated gene induction and cell growth. Oncogene 2001;20:188–197. [PubMed: 11313946]
- 98. Urano T, Emkey R, Feig LA. Ral-GTPases mediate a distinct downstream signaling pathway from Ras that facilitates cellular transformation. EMBO J 1996;15:810–816. [PubMed: 8631302]
- 99. Ward Y, Wang W, Woodhouse E, Linnoila I, Liotta L, Kelly K. Signal pathways which promote invasion and metastasis: Critical and distinct contributions of extracellular signal-regulated kinase and Ral-specific guanine exchange factor pathways. Mol. Cell. Biol 2001;21:5958–5969. [PubMed: 11486034]
- 100. Hamad NM, Elconin JH, Karnoub AE, Bai W, Rich JN, Abraham RT, Der CJ, Counter CM. Distinct requirements for Ras oncogenesis in human versus mouse cells. Genes Dev 2002;16:2045–2057. [PubMed: 12183360]
- Wang Y, Waldron RT, Dhaka A, Patel A, Riley MM, Rozengurt E, Colicelli J. The RAS effector RIN1 directly competes with RAF and is regulated by 14-3-3 proteins. Mol. Cell. Biol 2002;22:916– 926. [PubMed: 11784866]
- 102. Han L, Wong D, Dhaka A, Afar D, White M, Xie W, Herschman H, Witte O, Colicelli J. Protein binding and signaling properties of RIN1 suggest a unique effector function. Proc. Natl. Acad. Sci. U.S.A 1997;94:4954–4959. [PubMed: 9144171]
- 103. Tall GG, Barbieri MA, Stahl PD, Horazdovsky BF. Ras-activated endocytosis is mediated by the Rab5 guanine nucleotide exchange activity of RIN1. Dev. Cell 2001;1:73–82. [PubMed: 11703925]
- 104. Afar DE, Han L, McLaughlin J, Wong S, Dhaka A, Parmar K, Rosenberg N, Witte ON, Colicelli J. Regulation of the oncogenic activity of BCR-ABL by a tightly bound substrate protein RIN1. Immunity 1997;6:773–782. [PubMed: 9208849]
- 105. Hu, H.; Colicelli, J. unpublished
- 106. Khokhlatchev A, Rabizadeh S, Xavier R, Nedwidek M, Chen T, Zhang XF, Seed B, Avruch J. Identification of a novel Ras-regulated proapoptotic pathway. Curr. Biol 2002;12:253–265. [PubMed: 11864565]
- 107. Kelley GG, Reks SE, Ondrako JM, Smrcka AV, Phospholipase C. (epsilon): A novel Ras effector. EMBO J 2001;20:743–754. [PubMed: 11179219]
- 108. Boettner B, Govek EE, Cross J, Van Aelst L. The junctional multidomain protein AF-6 is a binding partner of the Rap1A GTPase and associates with the actin cytoskeletal regulator profilin. Proc. Natl. Acad. Sci. U.S.A 2000;97:9064–9069. [PubMed: 10922060]
- 109. Mitin NY, Ramocki MB, Zullo AJ, Der CJ, Konieczny SF, Taparowsky EJ. Identification and characterization of rain, a novel Ras-interacting protein with a unique subcellular localization. J. Biol. Chem 2004;279:22353–22361. [PubMed: 15031288]
- Rodriguez-Viciana P, Sabatier C, McCormick F. Signaling specificity by Ras family GTPases is determined by the full spectrum of effectors they regulate. Mol. Cell. Biol 2004;24:4943–4954. [PubMed: 15143186]
- 111. Matheny SA, Chen C, Kortum RL, Razidlo GL, Lewis RE, White MA. Ras regulates assembly of mitogenic signalling complexes through the effector protein IMP. Nature 2004;427:256–260. [PubMed: 14724641]
- 112. Kwong L, Wozniak MA, Collins AS, Wilson SD, Keely PJ. R-Ras promotes focal adhesion formation through focal adhesion kinase and p130(Cas) by a novel mechanism that differs from integrins. Mol. Cell. Biol 2003;23:933–949. [PubMed: 12529399]
- 113. Furuhjelm J, Peranen J. The C-terminal end of R-Ras contains a focal adhesion targeting signal. J. Cell Sci 2003;116:3729–3738. [PubMed: 12890755]
- 114. Chan AM, Miki T, Meyers KA, Aaronson SA. A human oncogene of the RAS superfamily unmasked by expression cDNA cloning. Proc. Natl. Acad. Sci. U.S.A 1994;91:7558–7562. [PubMed: 8052619]
- 115. Graham SM, Cox AD, Drivas G, Rush MG, D'Eustachio P, Der CJ. Aberrant function of the Rasrelated protein TC21/R-Ras2 triggers malignant transformation. Mol. Cell. Biol 1994;14:4108– 4115. [PubMed: 8196649]

- 116. Ehrhardt GR, Leslie KB, Lee F, Wieler JS, Schrader JW. M-Ras, a widely expressed 29-kD homologue of p21 Ras: Expression of a constitutively active mutant results in factor-independent growth of an interleukin-3-dependent cell line. Blood 1999;94:2433–2444. [PubMed: 10498616]
- 117. Cox AD, Brtva TR, Lowe DG, Der CJ. R-Ras induces malignant, but not morphologic, transformation of NIH3T3 cells. Oncogene 1994;9:3281–3288. [PubMed: 7936652]
- 118. Huang Y, Saez R, Chao L, Santos E, Aaronson SA, Chan AM. A novel insertional mutation in the TC21 gene activates its transforming activity in a human leiomyosarcoma cell line. Oncogene 1995;11:1255–1260. [PubMed: 7478545]
- Clark GJ, Kinch MS, Gilmer TM, Burridge K, Der CJ. Overexpression of the Ras-related TC21/R-Ras2 protein may contribute to the development of human breast cancers. Oncogene 1996;12:169– 176. [PubMed: 8552388]
- Barker KT, Crompton MR. Ras-related TC21 is activated by mutation in a breast cancer cell line, but infrequently in breast carcinomas in vivo. Br. J. Cancer 1998;78:296–300. [PubMed: 9703274]
- 121. Marte BM, Rodriguez-Viciana P, Wennstrom S, Warne PH, Downward J. R-Ras can activate the phosphoinositide 3-kinase but not the MAP kinase arm of the Ras effector pathways. Curr. Biol 1997;7:63–70. [PubMed: 8999998]
- 122. Rosario M, Paterson HF, Marshall CJ. Activation of the Ral and phosphatidylinositol 3' kinase signaling pathways by the ras-related protein TC21. Mol. Cell. Biol 2001;21:3750–3762. [PubMed: 11340168]
- 123. Gao X, Satoh T, Liao Y, Song C, Hu CD, Kariya Ki K, Kataoka T. Identification and characterization of RA-GEF-2, a Rap guanine nucleotide exchange factor that serves as a downstream target of M-Ras. J. Biol. Chem 2001;276:42219–42225. [PubMed: 11524421]
- 124. Spaargaren M, Martin GA, McCormick F, Fernandez-Sarabia MJ, Bischoff JR. The Ras-related protein R-ras interacts directly with Raf-1 in a GTP-dependent manner. Biochem. J 1994;300:303– 307. [PubMed: 8002932]
- 125. Rosario M, Paterson HF, Marshall CJ. Activation of the Raf/MAP kinase cascade by the Ras-related protein TC21 is required for the TC21-mediated transformation of NIH 3T3 cells. EMBO J 1999;18:1270–1279. [PubMed: 10064593]
- 126. Reedquist KA, Ross E, Koop EA, Wolthuis RM, Zwartkruis FJ, van Kooyk Y, Salmon M, Buckley CD, Bos JL. The small GTPase, Rap1, mediates CD31-induced integrin adhesion. J. Cell Biol 2000;148:1151–1158. [PubMed: 10725328]
- 127. McLeod SJ, Shum AJ, Lee RL, Takei F, Gold MR. The Rap GTPases regulate integrin-mediated adhesion, cell spreading, actin polymerization, and Pyk2 tyrosine phosphorylation in B lymphocytes. J. Biol. Chem. 2003
- 128. Kitayama H, Sugimoto Y, Matsuzaki T, Ikawa Y, Noda M. A ras-related gene with transformation suppressor activity. Cell 1989;56:77–84. [PubMed: 2642744]
- 129. Vossler MR, Yao H, York RD, Pan MG, Rim CS, Stork PJ. cAMP activates MAP kinase and Elk-1 through a B-Raf- and Rap1-dependent pathway. Cell 1997;89:73–82. [PubMed: 9094716]
- 130. Enserink JM, Christensen AE, de Rooij J, van Triest M, Schwede F, Genieser HG, Doskeland SO, Blank JL, Bos JL. A novel Epac-specific cAMP analogue demonstrates independent regulation of Rap1 and ERK. Nat. Cell Biol 2002;4:901–906. [PubMed: 12402047]
- 131. Dupuy AJ, Morgan K, von Lintig FC, Shen H, Acar H, Hasz DE, Jenkins NA, Copeland NG, Boss GR, Largaespada DA. Activation of the Rap1 guanine nucleotide exchange gene, CalDAG-GEF I, in BXH-2 murine myeloid leukemia. J. Biol. Chem 2001;276:11804–11811. [PubMed: 11278453]
- 132. Ishida D, Kometani K, Yang H, Kakugawa K, Masuda K, Iwai K, Suzuki M, Itohara S, Nakahata T, Hiai H, Kawamoto H, Hattori M, Minato N. Myeloproliferative stem cell disorders by deregulated Rap1 activation in SPA-1-deficient mice. Cancer Cell 2003;4:55–65. [PubMed: 12892713]
- 133. Yajnik V, Paulding C, Sordella R, McClatchey AI, Saito M, Wahrer DC, Reynolds P, Bell DW, Lake R, van den Heuvel S, Settleman J, Haber DA. DOCK4, a GTPase activator, is disrupted during tumorigenesis. Cell 2003;112:673–684. [PubMed: 12628187]
- 134. Mirey G, Balakireva M, L'Hoste S, Rosse C, Voegeling S, Camonis J. A Ral guanine exchange factor-Ral pathway is conserved in Drosophila melanogaster and sheds new light on the connectivity of the Ral, Ras, and Rap pathways. Mol. Cell. Biol 2003;23:1112–1124. [PubMed: 12529414]

- 135. Song C, Satoh T, Edamatsu H, Wu D, Tadano M, Gao X, Kataoka T. Differential roles of Ras and Rap1 in growth factor-dependent activation of phospholipase C epsilon. Oncogene 2002;21:8105– 8113. [PubMed: 12444546]
- 136. Katagiri K, Maeda A, Shimonaka M, Kinashi T. RAPL, a Rap1-binding molecule that mediates Rap1-induced adhesion through spatial regulation of LFA-1. Nat. Immunol 2003;4:741–748. [PubMed: 12845325]
- 137. Feig LA. Ral-GTPases: Approaching their 15 minutes of fame. Trends Cell Biol 2003;13:419–425. [PubMed: 12888294]
- 138. Lu Z, Hornia A, Joseph T, Sukezane T, Frankel P, Zhong M, Bychenok S, Xu L, Feig LA, Foster DA. Phospholipase D and RalA cooperate with the epidermal growth factor receptor to transform 3Y1 rat fibroblasts. Mol. Cell. Biol 2000;20:462–467. [PubMed: 10611224]
- Chien Y, White MA. RAL GTPases are linchpin modulators of human tumour-cell proliferation and survival. EMBO Rep 2003;4:800–806. [PubMed: 12856001]
- 140. Shipitsin M, Feig LA. RalA but not RalB enhances polarized delivery of membrane proteins to the basolateral surface of epithelial cells. Mol. Cell. Biol 2004;24:5746–5756. [PubMed: 15199131]
- 141. Park SH, Weinberg RA. A putative effector of Ral has homology to Rho/Rac GTPase activating proteins. Oncogene 1995;11:2349–2355. [PubMed: 8570186]
- 142. Jullien-Flores V, Dorseuil O, Romero F, Letourneur F, Saragosti S, Berger R, Tavitian A, Gacon G, Camonis JH. Bridging Ral GTPase to Rho pathways. RLIP76, a Ral effector with CDC42/Rac GTPase-activating protein activity. J. Biol. Chem 1995;270:22473–22477. [PubMed: 7673236]
- 143. Cantor SB, Urano T, Feig LA. Identification and characterization of Ral-binding protein 1, a potential downstream target of Ral GTPases. Mol. Cell. Biol 1995;15:4578–4584. [PubMed: 7623849]
- 144. Jullien-Flores V, Mahe Y, Mirey G, Leprince C, Meunier-Bisceuil B, Sorkin A, Camonis JH. RLIP76, an effector of the GTPase Ral, interacts with the AP2 complex: Involvement of the Ral pathway in receptor endocytosis. J. Cell Sci 2000;113:2837–2844. [PubMed: 10910768]
- 145. Nakashima S, Morinaka K, Koyama S, Ikeda M, Kishida M, Okawa K, Iwamatsu A, Kishida S, Kikuchi A. Small G protein Ral and its downstream molecules regulate endocytosis of EGF and insulin receptors. EMBO J 1999;18:3629–3642. [PubMed: 10393179]
- 146. Rosse C, L'Hoste S, Offner N, Picard A, Camonis J. RLIP, an effector of the Ral GTPases, is a platform for Cdk1 to phosphorylate epsin during the switch off of endocytosis in mitosis. J. Biol. Chem 2003;278:30597–30604. [PubMed: 12775724]
- 147. Moskalenko S, Henry DO, Rosse C, Mirey G, Camonis JH, White MA. The exocyst is a Ral effector complex. Nat. Cell Biol 2002;4:66–72. [PubMed: 11740492]
- 148. Moskalenko S, Tong C, Rosse C, Mirey G, Formstecher E, Daviet L, Camonis J, White MA. Ral GTPases regulate exocyst assembly through dual subunit interactions. J. Biol. Chem 2003;278:51743–51748. [PubMed: 14525976]
- 149. Sugihara K, Asano S, Tanaka K, Iwamatsu A, Okawa K, Ohta Y. The exocyst complex binds the small GTPase RalA to mediate filopodia formation. Nat. Cell Biol 2002;4:73–78. [PubMed: 11744922]
- 150. Hoshino M, Nakamura S. Small GTPase Rin induces neurite outgrowth through Rac/Cdc42 and calmodulin in PC12 cells. J. Cell Biol 2003;163:1067–1076. [PubMed: 14662747]
- 151. Hynds DL, Spencer ML, Andres DA, Snow DM. Rit promotes MEK-independent neurite branching in human neuroblastoma cells. J. Cell Sci 2003;116:1925–1935. [PubMed: 12668729]
- 152. Spencer ML, Shao H, Andres DA. Induction of neurite extension and survival in pheochromocytoma cells by the Rit GTPase. J. Biol. Chem 2002;277:20160–20168. [PubMed: 11914372]
- 153. Lee CH, Della NG, Chew CE, Zack DJ. Rin, a neuron-specific and calmodulin-binding small Gprotein, and Rit define a novel subfamily of ras proteins. J. Neurosci 1996;16:6784–6794. [PubMed: 8824319]
- 154. Rusyn EV, Reynolds ER, Shao H, Grana TM, Chan TO, Andres DA, Cox AD. Rit, a non-lipidmodified Ras-related protein, transforms NIH3T3 cells without activating the ERK, JNK, p38 MAPK or PI3K/Akt pathways. Oncogene 2000;19:4685–4694. [PubMed: 11032018]
- 155. Sakabe K, Teramoto H, Zohar M, Behbahani B, Miyazaki H, Chikumi H, Gutkind JS. Potent transforming activity of the small GTP-binding protein Rit in NIH 3T3 cells: Evidence for a role of a p38gamma-dependent signaling pathway. FEBS Lett 2002;511:15–20. [PubMed: 11821041]

- 156. Shao H, Kadono-Okuda K, Finlin BS, Andres DA. Biochemical characterization of the Ras-related GTPases Rit and Rin. Arch. Biochem. Biophys 1999;371:207–219. [PubMed: 10545207]
- 157. Takahashi K, Mitsui K, Yamanaka S. Role of ERas in promoting tumour-like properties in mouse embryonic stem cells. Nature 2003;423:541–545. [PubMed: 12774123]
- 158. Kontani K, Tada M, Ogawa T, Okai T, Saito K, Araki Y, Katada T. Di-Ras, a distinct subgroup of ras family GTPases with unique biochemical properties. J. Biol. Chem 2002;277:41070–41078. [PubMed: 12194967]
- 159. Ellis CA, Vos MD, Howell H, Vallecorsa T, Fults DW, Clark GJ. Rig is a novel Ras-related protein and potential neural tumor suppressor. Proc. Natl. Acad. Sci. U.S.A 2002;99:9876–9881. [PubMed: 12107278]
- 160. Yu Y, Xu F, Peng H, Fang X, Zhao S, Li Y, Cuevas B, Kuo WL, Gray JW, Siciliano M, Mills GB, Bast RC Jr. NOEY2 (ARHI), an imprinted putative tumor suppressor gene in ovarian and breast carcinomas. Proc. Natl. Acad. Sci. U.S.A 1999;96:214–219. [PubMed: 9874798]
- 161. Wang L, Hoque A, Luo RZ, Yuan J, Lu Z, Nishimoto A, Liu J, Sahin AA, Lippman SM, Bast RC Jr. Yu Y. Loss of the expression of the tumor suppressor gene ARHI is associated with progression of breast cancer. Clin. Cancer Res 2003;9:3660–3666. [PubMed: 14506155]
- 162. Kemppainen RJ, Behrend EN. Dexamethasone rapidly induces a novel ras superfamily memberrelated gene in AtT-20 cells. J. Biol. Chem 1998;273:3129–3131. [PubMed: 9452419]
- 163. Chan SL, Monks LK, Gao H, Deaville P, Morgan NG. Identification of the monomeric G-protein, Rhes, as an efaroxan-regulated protein in the pancreatic beta-cell. Br. J. Pharmacol 2002;136:31– 36. [PubMed: 11976265]
- 164. Graham TE, Key TA, Kilpatrick K, Dorin RI. Dexras1/AGS-1, a steroid hormone-induced guanosine triphosphate-binding protein, inhibits 3',5'-cyclic adenosine monophosphate-stimulated secretion in AtT-20 corticotroph cells. Endocrinology 2001;142:2631–2640. [PubMed: 11356714]
- 165. Vaidyanathan G, Cismowski MJ, Wang G, Vincent TS, Brown KD, Lanier SM. The Ras-related protein AGS1/RASD1 suppresses cell growth. Oncogene 2004;23:5858–5863. [PubMed: 15184869]
- 166. Vargiu P, De Abajo R, Garcia-Ranea JA, Valencia A, Santisteban P, Crespo P, Bernal J. The small GTP-binding protein, Rhes, regulates signal transduction from G protein-coupled receptors. Oncogene 2004;23:559–568. [PubMed: 14724584]
- 167. Fenwick C, Na SY, Voll RE, Zhong H, Im SY, Lee JW, Ghosh S. A subclass of Ras proteins that regulate the degradation of IkappaB. Science 2000;287:869–873. [PubMed: 10657303]
- 168. Chen Y, Wu J, Ghosh G. KappaB-Ras binds to the unique insert within the ankyrin repeat domain of IkappaBbeta and regulates cytoplasmic retention of IkappaBbeta × NF-kappaB complexes. J. Biol. Chem 2003;278:23101–23106. [PubMed: 12672800]
- 169. Finlin BS, Andres DA. Rem is a new member of the Rad- and Gem/Kir Ras-related GTP-binding protein family repressed by lipopolysaccharide stimulation. J. Biol. Chem 1997;272:21982–21988. [PubMed: 9268335]
- 170. Finlin BS, Shao H, Kadono-Okuda K, Guo N, Andres DA. Rem2, a new member of the Rem/Rad/ Gem/Kir family of Ras-related GTPases. Biochem. J 2000;347:223–231. [PubMed: 10727423]
- 171. Reynet C, Kahn CR. Rad: A member of the Ras family overexpressed in muscle of type II diabetic humans. Science 1993;262:1441–1444. [PubMed: 8248782]
- 172. Maguire J, Santoro T, Jensen P, Siebenlist U, Yewdell J, Kelly K. Gem: An induced, immediate early protein belonging to the Ras family. Science 1994;265:241–244. [PubMed: 7912851]
- 173. Finlin BS, Crump SM, Satin J, Andres DA. Regulation of voltage-gated calcium channel activity by the Rem and Rad GTPases. Proc. Natl. Acad. Sci. U.S.A 2003;100:14469–14474. [PubMed: 14623965]
- 174. Beguin P, Nagashima K, Gonoi T, Shibasaki T, Takahashi K, Kashima Y, Ozaki N, Geering K, Iwanaga T, Seino S. Regulation of Ca2+ channel expression at the cell surface by the small Gprotein kir/Gem. Nature 2001;411:701–706. [PubMed: 11395774]
- 175. Piddini E, Schmid JA, de Martin R, Dotti CG. The Ras-like GTPase Gem is involved in cell shape remodelling and interacts with the novel kinesin-like protein KIF9. EMBO J 2001;20:4076–4087. [PubMed: 11483511]

- 176. Chardin P. GTPase regulation: Getting aRnd Rock and Rho inhibition. Curr. Biol 2003;13:R702– R704. [PubMed: 13678607]
- 177. Aresta S, de Tand-Heim MF, Beranger F, de Gunzburg J. A novel Rho GTPase-activating-protein interacts with Gem, a member of the Ras superfamily of GTPases. Biochem. J 2002;367:57–65. [PubMed: 12093360]
- 178. Louro R, Nakaya HI, Paquola AC, Martins EA, da Silva AM, Verjovski-Almeida S, Reis EM. RASL11A, member of a novel small monomeric GTPase gene family, is down-regulated in prostate tumors. Biochem. Biophys. Res. Commun 2004;316:618–627. [PubMed: 15033445]
- 179. Patel PH, Thapar N, Guo L, Martinez M, Maris J, Gau CL, Lengyel JA, Tamanoi F. Drosophila Rheb GTPase is required for cell cycle progression and cell growth. J. Cell Sci 2003;116:3601– 3610. [PubMed: 12893813]
- 180. Clark GJ, Kinch MS, Rogers-Graham K, Sebti SM, Hamilton AD, Der CJ. The Ras-related protein Rheb is farnesylated and antagonizes Ras signaling and transformation. J. Biol. Chem 1997;272:10608–10615. [PubMed: 9099708]
- 181. Im E, von Lintig FC, Chen J, Zhuang S, Qui W, Chowdhury S, Worley PF, Boss GR, Pilz RB. Rheb is in a high activation state and inhibits B-Raf kinase in mammalian cells. Oncogene 2002;21:6356– 6365. [PubMed: 12214276]
- 182. Castro AF, Rebhun JF, Clark GJ, Quilliam LA. Rheb binds tuberous sclerosis complex 2 (TSC2) and promotes S6 kinase activation in a rapamycin- and farnesylation-dependent manner. J. Biol. Chem 2003;278:32493–32496. [PubMed: 12842888]
- 183. Inoki K, Li Y, Xu T, Guan KL. Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. Genes Dev 2003;17:1829–1834. [PubMed: 12869586]
- 184. Garami A, Zwartkruis FJ, Nobukuni T, Joaquin M, Roccio M, Stocker H, Kozma SC, Hafen E, Bos JL, Thomas G. Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. Mol. Cell 2003;11:1457–1466. [PubMed: 12820960]
- 185. Tee AR, Manning BD, Roux PP, Cantley LC, Blenis J. Tuberous sclerosis complex gene products, Tuberin and Hamartin, control mTOR signaling by acting as a GTPase-activating protein complex toward Rheb. Curr. Biol 2003;13:1259–1268. [PubMed: 12906785]
- 186. Zhang Y, Gao X, Saucedo LJ, Ru B, Edgar BA, Pan D. Rheb is a direct target of the tuberous sclerosis tumour suppressor proteins. Nat. Cell Biol 2003;5:578–581. [PubMed: 12771962]
- 187. Burridge K, Wennerberg K. Rho and rac take center stage. Cell 2004;116:167–179. [PubMed: 14744429]
- 188. Wennerberg K, Der CJ. Rho-family GTPases: It's not only Rac and Rho (and I like it). J. Cell Sci 2004;117:1301–1312. [PubMed: 15020670]
- 189. Sahai E, Marshall CJ. RHO-GTPases and cancer. Nat. Rev. Cancer 2002;2:133–142. [PubMed: 12635176]
- 190. Jordan P, Brazao R, Boavida MG, Gespach C, Chastre E. Cloning of a novel human Rac1b splice variant with increased expression in colorectal tumors. Oncogene 1999;18:6835–6839. [PubMed: 10597294]
- 191. Kimura K, Ito M, Amano M, Chihara K, Fukata Y, Nakafuku M, Yamamori B, Feng J, Nakano T, Okawa K, Iwamatsu A, Kaibuchi K. Regulation of myosin phosphatase by Rho and Rho-associated kinase (Rho-kinase). Science 1996;273:245–248. [PubMed: 8662509]
- 192. Watanabe N, Kato T, Fujita A, Ishizaki T, Narumiya S. Cooperation between mDia1 and ROCK in Rho-induced actin reorganization. Nat. Cell Biol 1999;1:136–143. [PubMed: 10559899]
- 193. Amano M, Mukai H, Ono Y, Chihara K, Matsui T, Hamajima Y, Okawa K, Iwamatsu A, Kaibuchi K. Identification of a putative target for Rho as the serine-threonine kinase protein kinase N. Science 1996;271:648–650. [PubMed: 8571127]
- 194. Watanabe G, Saito Y, Madaule P, Ishizaki T, Fujisawa K, Morii N, Mukai H, Ono Y, Kakizuka A, Narumiya S. Protein kinase N (PKN) and PKN-related protein rhophilin as targets of small GTPase Rho. Science 1996;271:645–648. [PubMed: 8571126]
- 195. Wing MR, Snyder JT, Sondek J, Harden TK. Direct activation of phospholipase C-epsilon by Rho. J. Biol. Chem 2003;278:41253–41258. [PubMed: 12900402]

- 196. Peck JW, Oberst M, Bouker KB, Bowden E, Burbelo PD. The RhoA-binding protein, rhophilin-2, regulates actin cytoskeleton organization. J. Biol. Chem 2002;277:43924–43932. [PubMed: 12221077]
- 197. Reid T, Furuyashiki T, Ishizaki T, Watanabe G, Watanabe N, Fujisawa K, Morii N, Madaule P, Narumiya S. Rhotekin, a new putative target for Rho bearing homology to a serine/threonine kinase, PKN, and rhophilin in the rho-binding domain. J. Biol. Chem 1996;271:13556–13560. [PubMed: 8662891]
- 198. Didsbury J, Weber RF, Bokoch GM, Evans T, Snyderman R. rac, a novel ras-related family of proteins that are botulinum toxin substrates. J. Biol. Chem 1989;264:16378–16382. [PubMed: 2674130]
- 199. Bagrodia S, Taylor SJ, Creasy CL, Chernoff J, Cerione RA. Identification of a mouse p21Cdc42/ Rac activated kinase. J. Biol. Chem 1995;270:22731–22737. [PubMed: 7559398]
- 200. Snyder JT, Singer AU, Wing MR, Harden TK, Sondek J. The pleckstrin homology domain of phospholipase C-beta2 as an effector site for Rac. J. Biol. Chem 2003;278:21099–21104. [PubMed: 12657629]
- 201. Aspenstrom P, Lindberg U, Hall A. Two GTPases, Cdc42 and Rac, bind directly to a protein implicated in the immunodeficiency disorder Wiskott-Aldrich syndrome. Curr. Biol 1996;6:70–75. [PubMed: 8805223]
- 202. Symons M, Derry JM, Karlak B, Jiang S, Lemahieu V, McCormick F, Francke U, Abo A. Wiskott-Aldrich syndrome protein, a novel effector for the GTPase CDC42Hs, is implicated in actin polymerization. Cell 1996;84:723–734. [PubMed: 8625410]
- 203. Kolluri R, Tolias KF, Carpenter CL, Rosen FS, Kirchhausen T. Direct interaction of the Wiskott-Aldrich syndrome protein with the GTPase Cdc42. Proc. Natl. Acad. Sci. U.S.A 1996;93:5615– 5618. [PubMed: 8643625]
- 204. Ho HY, Rohatgi R, Lebensohn AM, Le M, Li J, Gygi SP, Kirschner MW. Toca-1 mediates Cdc42dependent actin nucleation by activating the N-WASP-WIP complex. Cell 2004;118:203–216. [PubMed: 15260990]
- 205. Garrard SM, Capaldo CT, Gao L, Rosen MK, Macara IG, Tomchick DR. Structure of Cdc42 in a complex with the GTPase-binding domain of the cell polarity protein, Par6. EMBO J 2003;22:1125– 1133. [PubMed: 12606577]
- 206. Wennerberg K, Forget MA, Ellerbroek SM, Arthur WT, Burridge K, Settleman J, Der CJ, Hansen SH. Rnd proteins function as RhoA antagonists by activating p190 RhoGAP. Curr. Biol 2003;13:1106–1115. [PubMed: 12842009]
- 207. Riento K, Guasch RM, Garg R, Jin B, Ridley AJ. RhoE binds to ROCK I and inhibits downstream signaling. Mol. Cell. Biol 2003;23:4219–4229. [PubMed: 12773565]
- 208. Heo WD, Meyer T. Switch-of-function mutants based on morphology classification of Ras superfamily small GTPases. Cell 2003;113:315–328. [PubMed: 12732140]
- 209. Fransson A, Ruusala A, Aspenstrom P. Atypical Rho GTPases have roles in mitochondrial homeostasis and apoptosis. J. Biol. Chem 2003;278:6495–6502. [PubMed: 12482879]
- Aspenstrom P, Fransson A, Saras J. Rho GTPases have diverse effects on the organization of the actin filament system. Biochem. J 2004;377:327–337. [PubMed: 14521508]
- 211. Touchot N, Chardin P, Tavitian A. Four additional members of the ras gene superfamily isolated by an oligonucleotide strategy: Molecular cloning of YPT-related cDNAs from a rat brain library. Proc. Natl. Acad. Sci. U.S.A 1987;84:8210–8214. [PubMed: 3317403]
- 212. Nimmo ER, Sanders PG, Padua RA, Hughes D, Williamson R, Johnson KJ. The MEL gene: A new member of the RAB/YPT class of RAS-related genes. Oncogene 1991;6:1347–1351. [PubMed: 1886711]
- 213. Segev N. Ypt/rab gtpases: Regulators of protein trafficking. Sci. STKE 2001;2001:re11. [PubMed: 11579231]
- 214. Stenmark H, Olkkonen VM. The Rab GTPase family. Genome Biol 2001;2:REVIEWS3007. [PubMed: 11387043]
- 215. Pereira-Leal JB, Seabra MC. Evolution of the Rab family of small GTP-binding proteins. J. Mol. Biol 2001;313:889–901. [PubMed: 11697911]

- 216. Stahl B, Chou JH, Li C, Sudhof TC, Jahn R. Rab3 reversibly recruits rabphilin to synaptic vesicles by a mechanism analogous to raf recruitment by ras. EMBO J 1996;15:1799–1809. [PubMed: 8617225]
- 217. Christoforidis S, McBride HM, Burgoyne RD, Zerial M. The Rab5 effector EEA1 is a core component of endosome docking. Nature 1999;397:621–625. [PubMed: 10050856]
- 218. Stenmark H, Vitale G, Ullrich O, Zerial M. Rabaptin-5 is a direct effector of the small GTPase Rab5 in endocytic membrane fusion. Cell 1995;83:423–432. [PubMed: 8521472]
- 219. Miaczynska M, Christoforidis S, Giner A, Shevchenko A, Uttenweiler-Joseph S, Habermann B, Wilm M, Parton RG, Zerial M. APPL proteins link Rab5 to nuclear signal transduction via an endosomal compartment. Cell 2004;116:445–456. [PubMed: 15016378]
- 220. Jordens I, Fernandez-Borja M, Marsman M, Dusseljee S, Janssen L, Calafat J, Janssen H, Wubbolts R, Neefjes J. The Rab7 effector protein RILP controls lysosomal transport by inducing the recruitment of dynein-dynactin motors. Curr. Biol 2001;11:1680–1685. [PubMed: 11696325]
- 221. Cantalupo G, Alifano P, Roberti V, Bruni CB, Bucci C. Rab-interacting lysosomal protein (RILP): The Rab7 effector required for transport to lysosomes. EMBO J 2001;20:683–693. [PubMed: 11179213]
- 222. Carroll KS, Hanna J, Simon I, Krise J, Barbero P, Pfeffer SR. Role of Rab9 GTPase in facilitating receptor recruitment by TIP47. Science 2001;292:1373–1376. [PubMed: 11359012]
- 223. Mammoto A, Ohtsuka T, Hotta I, Sasaki T, Takai Y. Rab11BP/Rabphilin-11, a downstream target of rab11 small G protein implicated in vesicle recycling. J. Biol. Chem 1999;274:25517–25524. [PubMed: 10464283]
- 224. Desnos C, Schonn JS, Huet S, Tran VS, El-Amraoui A, Raposo G, Fanget I, Chapuis C, Menasche G, de Saint Basile G, Petit C, Cribier S, Henry JP, Darchen F. Rab27A and its effector MyRIP link secretory granules to F-actin and control their motion towards release sites. J. Cell Biol 2003;163:559–570. [PubMed: 14610058]
- 225. Weis K. Regulating access to the genome: Nucleocytoplasmic transport throughout the cell cycle. Cell 2003;112:441–451. [PubMed: 12600309]
- 226. Carazo-Salas RE, Gruss OJ, Mattaj IW, Karsenti E. Ran-GTP co-ordinates regulation of microtubule nucleation and dynamics during mitotic-spindle assembly. Nat. Cell Biol 2001;3:228–234. [PubMed: 11231571]
- 227. Wilde A, Lizarraga SB, Zhang L, Wiese C, Gliksman NR, Walczak CE, Zheng Y. Ran stimulates spindle assembly by altering microtubule dynamics and the balance of motor activities. Nat. Cell Biol 2001;3:221–227. [PubMed: 11231570]
- 228. Kahn RA, Gilman AG. Purification of a protein cofactor required for ADP-ribosylation of the stimulatory regulatory component of adenylate cyclase by cholera toxin. J. Biol. Chem 1984;259:6228–6234. [PubMed: 6327671]
- Sewell JL, Kahn RA. Sequences of the bovine and yeast ADP-ribosylation factor and comparison to other GTP-binding proteins. Proc. Natl. Acad. Sci. U.S.A 1988;85:4620–4624. [PubMed: 3133654]
- 230. Price SR, Nightingale M, Tsai SC, Williamson KC, Adamik R, Chen HC, Moss J, Vaughan M. Guanine nucleotide-binding proteins that enhance choleragen ADP-ribosyltransferase activity: Nucleotide and deduced amino acid sequence of an ADP-ribosylation factor cDNA. Proc. Natl. Acad. Sci. U.S.A 1988;85:5488–5491. [PubMed: 3135549]
- 231. Randazzo PA, Nie Z, Miura K, Hsu VW. Molecular aspects of the cellular activities of ADPribosylation factors. Sci. STKE 2000;2000:re1. [PubMed: 11752622]
- 232. Kanoh H, Williger BT, Exton JH. Arfaptin 1, a putative cytosolic target protein of ADP-ribosylation factor, is recruited to Golgi membranes. J. Biol. Chem 1997;272:5421–5429. [PubMed: 9038142]
- 233. Shin OH, Ross AH, Mihai I, Exton JH. Identification of arfophilin, a target protein for GTP-bound class II ADP-ribosylation factors. J. Biol. Chem 1999;274:36609–36615. [PubMed: 10593962]
- 234. Zhao L, Helms JB, Brunner J, Wieland FT. GTP-dependent binding of ADP-ribosylation factor to coatomer in close proximity to the binding site for dilysine retrieval motifs and p23. J. Biol. Chem 1999;274:14198–14203. [PubMed: 10318838]
- 235. Bigay J, Gounon P, Robineau S, Antonny B. Lipid packing sensed by ArfGAP1 couples COPI coat disassembly to membrane bilayer curvature. Nature 2003;426:563–566. [PubMed: 14654841]

- 236. Prigent M, Dubois T, Raposo G, Derrien V, Tenza D, Rosse C, Camonis J, Chavrier P. ARF6 controls post-endocytic recycling through its downstream exocyst complex effector. J. Cell Biol 2003;163:1111–1121. [PubMed: 14662749]
- 237. Honda A, Nogami M, Yokozeki T, Yamazaki M, Nakamura H, Watanabe H, Kawamoto K, Nakayama K, Morris AJ, Frohman MA, Kanaho Y. Phosphatidylinositol 4-phosphate 5-kinase alpha is a downstream effector of the small G protein ARF6 in membrane ruffle formation. Cell 1999;99:521–532. [PubMed: 10589680]
- 238. Jones DH, Morris JB, Morgan CP, Kondo H, Irvine RF, Cockcroft S. Type I phosphatidylinositol 4-phosphate 5-kinase directly interacts with ADP-ribosylation factor 1 and is responsible for phosphatidylinositol 4,5-bisphosphate synthesis in the golgi compartment. J. Biol. Chem 2000;275:13962–13966. [PubMed: 10747863]
- 239. Dell'Angelica EC, Puertollano R, Mullins C, Aguilar RC, Vargas JD, Hartnell LM, Bonifacino JS. GGAs: A family of ADP ribosylation factor-binding proteins related to adaptors and associated with the Golgi complex. J. Cell Biol 2000;149:81–94. [PubMed: 10747089]
- 240. Boman AL, Zhang C, Zhu X, Kahn RA. A family of ADP-ribosylation factor effectors that can alter membrane transport through the trans-Golgi. Mol. Biol. Cell 2000;11:1241–1255. [PubMed: 10749927]
- 241. Puertollano R, Randazzo PA, Presley JF, Hartnell LM, Bonifacino JS. The GGAs promote ARFdependent recruitment of clathrin to the TGN. Cell 2001;105:93–102. [PubMed: 11301005]
- 242. Haucke V. Vesicle budding: A coat for the COPs. Trends Cell Biol 2003;13:59–60. [PubMed: 12559754]
- 243. Conklin BR, Bourne HR. Structural elements of G alpha subunits that interact with G beta gamma, receptors, and effectors. Cell 1993;73:631–641. [PubMed: 8388779]
- 244. Markby DW, Onrust R, Bourne HR. Separate GTP binding and GTPase activating domains of a G alpha subunit. Science 1993;262:1895–1901. [PubMed: 8266082]
- 245. Lyons J, Landis CA, Harsh G, Vallar L, Grunewald K, Feichtinger H, Duh QY, Clark OH, Kawasaki E, Bourne HR, et al. Two G protein oncogenes in human endocrine tumors. Science 1990;249:655–659. [PubMed: 2116665]
- 246. Bunemann M, Frank M, Lohse MJ. From The Cover: Gi protein activation in intact cells involves subunit rearrangement rather than dissociation. Proc. Natl. Acad. Sci. U.S.A 2003;100:16077– 16082. [PubMed: 14673086]
- 247. Neves SR, Ram PT, Iyengar R. G protein pathways. Science 2002;296:1636–1639. [PubMed: 12040175]
- 248. Faty M, Fink M, Barral Y. Septins: A ring to part mother and daughter. Curr. Genet 2002;41:123– 131. [PubMed: 12111093]
- 249. Zhang J, Kong C, Xie H, McPherson PS, Grinstein S, Trimble WS. Phosphatidylinositol polyphosphate binding to the mammalian septin H5 is modulated by GTP. Curr. Biol 1999;9:1458– 1467. [PubMed: 10607590]
- Danino D, Hinshaw JE. Dynamin family of mechanoenzymes. Curr. Opin. Cell Biol 2001;13:454– 460. [PubMed: 11454452]
- 251. Andersen GR, Nissen P, Nyborg J. Elongation factors in protein biosynthesis. Trends Biochem. Sci 2003;28:434–441. [PubMed: 12932732]
- 252. Pestova TV, Hellen CU. Functions of eukaryotic factors in initiation of translation. Cold Spring Harb. Symp. Quant. Biol 2001;66:389–396. [PubMed: 12762041]
- 253. Nagai K, Oubridge C, Kuglstatter A, Menichelli E, Isel C, Jovine L. Structure, function and evolution of the signal recognition particle. EMBO J 2003;22:3479–3485. [PubMed: 12853463]
- 254. Xia C, Ma W, Stafford LJ, Liu C, Gong L, Martin JF, Liu M. GGAPs, a new family of bifunctional GTP-binding and GTPase-activating proteins. Mol. Cell. Biol 2003;23:2476–2488. [PubMed: 12640130]
- 255. Nitta M, Saijo M, Kodo N, Matsuda T, Nakatsu Y, Tamai H, Tanaka K. A novel cytoplasmic GTPase XAB1 interacts with DNA repair protein XPA. Nucleic Acids Res 2000;28:4212–4218. [PubMed: 11058119]

- 256. Sekiguchi T, Hirose E, Nakashima N, Ii M, Nishimoto T. Novel G proteins, Rag C and Rag D, interact with GTP-binding proteins, Rag A and Rag B. J. Biol. Chem 2001;276:7246–7257. [PubMed: 11073942]
- 257. Boehm U, Guethlein L, Klamp T, Ozbek K, Schaub A, Futterer A, Pfeffer K, Howard JC. Two families of GTPases dominate the complex cellular response to IFN-gamma. J. Immunol 1998;161:6715–6723. [PubMed: 9862701]
- 258. MacMicking JD, Taylor GA, McKinney JD. Immune control of tuberculosis by IFN-gammainducible LRG-47. Science 2003;302:654–659. [PubMed: 14576437]
- 259. Prakash B, Renault L, Praefcke GJ, Herrmann C, Wittinghofer A. Triphosphate structure of guanylate-binding protein 1 and implications for nucleotide binding and GTPase mechanism. EMBO J 2000;19:4555–4564. [PubMed: 10970849]
- 260. Zhao X, Alvarado D, Rainier S, Lemons R, Hedera P, Weber CH, Tukel T, Apak M, Heiman-Patterson T, Ming L, Bui M, Fink JK. Mutations in a newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. Nat. Genet 2001;29:326–331. [PubMed: 11685207]
- 261. Klamp T, Boehm U, Schenk D, Pfeffer K, Howard JC. A giant GTPase, very large inducible GTPase-1, is inducible by IFNs. J. Immunol 2003;171:1255–1265. [PubMed: 12874213]
- 262. Kudo H, Senju S, Mitsuya H, Nishimura Y. Mouse and human GTPBP2, newly identified members of the GP-1 family of GTPase. Biochem. Biophys. Res. Commun 2000;272:456–465. [PubMed: 10833435]
- 263. Senju S, Nishimura Y. Identification of human and mouse GP-1, a putative member of a novel G-protein family. Biochem. Biophys. Res. Commun 1997;231:360–364. [PubMed: 9070279]
- 264. Jensen BC, Wang Q, Kifer CT, Parsons M. The NOG1 GTP-binding protein is required for biogenesis of the 60 S ribosomal subunit. J. Biol. Chem 2003;278:32204–32211. [PubMed: 12788953]
- 265. Britton RA, Chen SM, Wallis D, Koeuth T, Powell BS, Shaffer LG, Largaespada D, Jenkins NA, Copeland NG, Court DL, Lupski JR. Isolation and preliminary characterization of the human and mouse homologues of the bacterial cell cycle gene era. Genomics 2000;67:78–82. [PubMed: 10945472]
- 266. Akiyama T, Gohda J, Shibata S, Nomura Y, Azuma S, Ohmori Y, Sugano S, Arai H, Yamamoto T, Inoue J. Mammalian homologue of E. coli Ras-like GTPase (ERA) is a possible apoptosis regulator with RNA binding activity. Genes Cells 2001;6:987–1001. [PubMed: 11733036]
- 267. Li B, Trueb B. DRG represents a family of two closely related GTP-binding proteins. Biochim. Biophys. Acta 2000;1491:196–204. [PubMed: 10760581]
- 268. Kumar S, Tomooka Y, Noda M. Identification of a set of genes with developmentally down-regulated expression in the mouse brain. Biochem. Biophys. Res. Commun 1992;185:1155–1161. [PubMed: 1378265]
- 269. Ishikawa K, Azuma S, Ikawa S, Morishita Y, Gohda J, Akiyama T, Semba K, Inoue J. Cloning and characterization of Xenopus laevis drg2, a member of the developmentally regulated GTP-binding protein subfamily. Gene 2003;322:105–112. [PubMed: 14644502]
- 270. Harton JA, Cressman DE, Chin KC, Der CJ, Ting JP. GTP binding by class II transactivator: Role in nuclear import. Science 1999;285:1402–1405. [PubMed: 10464099]
- 271. Raval A, Weissman JD, Howcroft TK, Singer DS. The GTP-binding domain of class II transactivator regulates its nuclear export. J. Immunol 2003;170:922–930. [PubMed: 12517958]
- 272. Koonin EV, Aravind L. The NACHT family a new group of predicted NTPases implicated in apoptosis and MHC transcription activation. Trends Biochem. Sci 2000;25:223–224. [PubMed: 10782090]
- 273. Nogales E, Downing KH, Amos LA, Lowe J. Tubulin and FtsZ form a distinct family of GTPases. Nat. Struct. Biol 1998;5:451–458. [PubMed: 9628483]
- 274. Vernet C, Ribouchon MT, Chimini G, Pontarotti P. Structure and evolution of a member of a new subfamily of GTP-binding proteins mapping to the human MHC class I region. Mamm. Genome 1994;5:100–105. [PubMed: 8180467]
- 275. Burbelo PD, Miyamoto S, Utani A, Brill S, Yamada KM, Hall A, Yamada Y. p190-B, a new member of the Rho GAP family, and Rho are induced to cluster after integrin cross-linking. J. Biol. Chem 1995;270:30919–30926. [PubMed: 8537347]

- 276. Deiss LP, Feinstein E, Berissi H, Cohen O, Kimchi A. Identification of a novel serine/threonine kinase and a novel 15-kD protein as potential mediators of the gamma interferon-induced cell death. Genes Dev 1995;9:15–30. [PubMed: 7828849]
- 277. Inbal B, Bialik S, Sabanay I, Shani G, Kimchi A. DAP kinase and DRP-1 mediate membrane blebbing and the formation of autophagic vesicles during programmed cell death. J. Cell Biol 2002;157:455–468. [PubMed: 11980920]
- 278. Harris A, Morgan JI, Pecot M, Soumare A, Osborne A, Soares HD. Regenerating motor neurons express Nna1, a novel ATP/GTP-binding protein related to zinc carboxypeptidases. Mol. Cell. Neurosci 2000;16:578–596. [PubMed: 11083920]
- 279. Chennathukuzhi VM, Kurihara Y, Bray JD, Yang J, Hecht NB. Altering the GTP binding site of the DNA/RNA-binding protein, Translin/TB-RBP, decreases RNA binding and may create a dominant negative phenotype. Nucleic Acids Res 2001;29:4433–4440. [PubMed: 11691931]
- 280. Bandorowicz-Pikula J, Kirilenko A, van Deursen R, Golczak M, Kuhnel M, Lancelin JM, Pikula S, Buchet R. A putative consensus sequence for the nucleotide-binding site of annexin A6. Biochemistry 2003;42:9137–9146. [PubMed: 12885247]
- 281. Yaguchi H, Ohkura N, Tsukada T, Yamaguchi K. Menin, the multiple endocrine neoplasia type 1 gene product, exhibits GTP-hydrolyzing activity in the presence of the tumor metastasis suppressor nm23. J. Biol. Chem 2002;277:38197–38204. [PubMed: 12145286]
- 282. I thank R. Lovering and other members of the HUGO Nomenclature Committee (H. Wain, E. Bruford, M. Lush, V. Khodiyar, C. Talbot, M. Wright, and S. Povey) for extensive assistance in determining gene symbols; A. Bernards for help in identifying some GTPase sequences; and C. Der, F. Taminoi, A. van der Bliek, and J. Lengyel for insightful comments and criticisms.



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.

		N terminus											\rightarrow		
	UDAC	MURVEI	G1	TRAL TITOL TONIL	EVDEVDD	J2	KOWATDOFFECT	G3	TACOPEVO	AMD	DOVMDECE	CRI CURATNNI	VOPEDTU		
	NRAS	MTEYKLVV	VGAGGVGP	KSALTIOLIONH-	-FVDEIDP	TIEDSYR	-KOVVIDGETCL	LDILD	TAGOEEYS.	AMR	DQIMRIGE DOYMRTGE	GFLCVFAINNI	SKSFADIN		
	KRAS2B	MTEYKLVV	VGAGGVGP	KSALTIQLIQNH-	-FVDEYDP	TIEDSYR	-KQVVIDGETCL	LDILD	TA <mark>G</mark> QEEYS.	AMR	DQYMRTGE	GFLCVFAINNT	TKSFEDIH		
	ERAS	ME^LPEYKAVV	VGASG <mark>VG</mark> I	KSALTIQLNHQC-	- FVEDHDP	F IQDSYW	-KELTLDSGDCI	LNVL <mark>D</mark>	TA <mark>G</mark> QAIHR.	ALR	DQCLAVCD	GVLGVFALDDF	PSSLIQLQ		
	RALA	MV LALHKVIM	VGSGGVGP	KSALTLQFMYDE-	- FVEDYEP	KADSYR	- KKVVLDGEEVQ	IDILD	TAGQEDYA	AIR	DNYFRSGE	GFLCVFSITEM	IESFAATA		
	RRAS1	MS^SETHKLVV	VGGGGVGI	KSALTIQFIQSY-	-FVEDIEF	TIEDSYT	-KICSVDGIPAR	LDILD	TAGQEEFG.	AMR	EQYMRAGH	GFLLVFAINDR	QSFNEVG		
	RRAS2	MA^QEKYR <mark>LVV</mark>	VGGGG <mark>VG</mark> F	KSALTIQFIQSY-	- FVTDYDP	IEDSYT	-KQCVIDDRAAR	LDILD	TA <mark>G</mark> QEEFG.	AMR	EQYMRTGE	GFLLVFSVTDR	GSFEEIY		
	MRAS	MA^LPTYKLVV	VGDGGVGF	KSALTIQFFQKI-	- FVPDYDP	TIEDSYL	-KHTEIDNQWAI		TA <mark>G</mark> QEEFS.	AMR	EQYMRTGD	GFLIVYSVTDK	CASFEHVD		
	RIT1 RTT2	MD SREYKLVM		KSAMTMQFISHR-	- FPEDHDP	TEDAYK	- IRIRIDDEPAN	PDIPD	TAGQAEFT.	AMR	DQYMRAGE	GFIICYSITDR	RSFHEVR		
	RAPIA	MREYKLVV	LGSGGVG	KSALTVOFVOGI-	-FVEKYDP	TIEDAIR	-KOVEVDCOOCM	LEILD	TAGTEOFT.	AMR	DLYMKNGC	GFALVYSITAC	STFNDLO		
	RAP1B	MREYK <mark>LVV</mark>	LGSGG <mark>VG</mark> F	KSALTVQFVQGI-	-FVEKYDP	TIEDSYR	- KQVEVDAQQCM	LEIL <mark>D</mark>	TA <mark>G</mark> TEQFT.	AMR	DLYMKNGQ	GFALVYSITAÇ	STFNDLQ		
	RAP2A	MREYKVVV	LGSGGVGH	KSALTVQFVTGT-	-FIEKYDP	IEDFYR	-KEIEVDSSPSV	LEILD	TAGTEQFA	SMR	DLYIKNGQ	GFILVYSLVNQ	QSFQDIK		
	RAP2C RAP2B	MREYKVVV	LGSGGVGP	KSALTVQFVTGT-	-FIEKYDP	TEDFYR	-KEIEVDSSPSV	PEIPD	TAGTEOFA	SMR	DLYIKNGQ DLYIKNGO	GFILVYSLVNQ	QSFQDIK		
	DIRAS1	MP^SNDYRVVV	FGAGGVG	KSSLVLRFVKGT-	-FRDTYIP	TIEDTYR	-QVISCDKSVCT	LQITD	TTGSHQFP.	AMQR	LSISKGH	AFILVFSVTSK	QSLEELG		
	DIRAS2	MP [^] SNDYRVAV	F <mark>G</mark> AGG <mark>VG</mark> I	KS <mark>SLVLRFVKGT-</mark>	-FRESYIP	P VEDTYF	-QVISCDKSICT	LQIT <mark>D</mark>	TTGSHQFP	AMQR	LSISKGH	AFILVYSITSR	RQSLEELK		
	ARHI	MG [^] IRDYRVVV	VGTAGVGH	KSTLLHKWASGN-	-FRHEYLP	IENTYC IENTYC	-QLLGCSHGVLS	LHITD	SKSGDGNR	ALQR	HVIARGH	AFVLVYSVTKK	CETLEELK		
	RASD1 RASD2	MM^KNSYRMVI	LGSSRVG	KSSIVSRFLNG	RFEDAIIP	TEDFHR	-KVYNIRGDMYO		TSGNHPFP.	AMR	RLSILIGD	VEILVESLDNR	ESFDEVK		
	RASL10B	MVSTYRVAV	LGARGVG	KSAIVRQFLYNEF	-SEVCVPT	TARRLYI	- PAVVMNGHVHD	LQILD	FPPISAFP	VNTLQE-WA	ADTCCRGLRSVH	AYILVYDICCF	DSFEYVK		
	RASL10A	M <mark>G</mark> GSLR <mark>V</mark> AV	LGAPG <mark>V</mark> GI	KT <mark>AIIRQFLFGDY</mark>	-PERHRPT	DGPRLYF	-PAVLLDGAVYD	LSIR <mark>D</mark>	GDVAGPGS	SPGGPEEWI	PDAKDWSLQDTE	AFVLVYDICSF	PDSFDYVK		
	NKIRAS1	MGKGCKVVV	CGLLSVG	KTAILEQLLYGNH	TIGMEDCE	MEDVYN	IASVETDRGVKEQ	LHLYD	TRGLQEGV	ELP	KHYFSFAD	GFVLVYSVNNI	LESFQRVE		
	RERG	MAKSAEVKLAI	FGRAGVGI	KSALVVRFLTKR-	-FIWEYDP	LESTYF	-HOATIDDEVVS	MEILD	TAGOEDTI	0	REGHMRWGE	GFVLVYDITDR	RGSFEEVL		
	RASL11B	MR [^] RRLVK <mark>I</mark> AV	VGASGVGI	KTALVVRFLTKR-	-FIGDYER	NAGNLYI	-RQVQIEGETLA	LQVQD	TPGIQVHE	NSLSCSEQ-	LNRCIRWAD	AVVIVFSITDY	KSYELIS		
	RASL11A	MS [^] PKDIK <mark>L</mark> AV	'LGAGR <mark>V</mark> GI	KSG^IVRFLTKR-	-FIGDYEP	NTGKLYS	-RLVYVEGDQLS	LQIQ <mark>D</mark>	TP <mark>G</mark> GVQIQ	DSLPQVVDS	SLSKCVQWAE	GFLLVYSITDY	DSYLSIR		
	RASL12	MS^PLEVNLAI	LGRRGAGE	KSALTVKFLTKR-	-FISEYDP	NLEDTYS	-SEETVDHQPVH		TADLDTPR	N	CERYLNWAH	AFLVVYSVDSR	QSFDSSS		
	RRAD	MT SVYKVL	LGAPGVGP	KSALARIFGGVED	GPEAE	AAGHTYE	-RILMVDGESAI	LMVYD	IWENKGE-	GRWLP	GHCMAMGD	AYVIVYSVTDK	GSFEKAS		
	REM1	MT [^] EALYR <mark>VVL</mark>	LGDPGVGF	KTSLASLFAGKQ-	-ERDLHEQ	LGEDVYE	-RTLTVDGEDTT	LVVVD	TWEAEKLD	KSWSQ	ESCLQGGS	AYVIVYSIADR	GSFESAS		
	REM2	MH^DGIFK <mark>VML</mark>	VGESGVGF	KSTLAGTFGGLQ-	GDSAHEPE	NPEDTYE	-RRIMVDKEEVT	LVVY <mark>D</mark>	IWEQGD-A	GGWLR	DHCLQTGD	AFLIVFSVTDR	RRSFSKVP		
	RHEB	MPQSKSRKIAI	LGYRSVG	KSSLTIQFVEGQ-	- FVDSYDP	I ENTFI	-KLITVNGQEYH	LQLVD	TAGQDEYS	IFP	QTYSIDIN	GYILVYSVTSI	KSFEVIK		
	Continued	MPLVKIKKVVI	LGIRCVGI	TSTWUGLARGE-	-FSEGIDP	L VENIIS	-KIVILGKDEFH		INGQUEIS	TPb	ISFIIGVN	GIVLVISVISL	USLAATE	C +	orminue
	oomozmaoa			G4						G5					ormanab
HRAS	QYREQIKRV	KDS	-DD-V	PMVLV <mark>GNK</mark> C	DLAA	RTVES	SRQAQDLAR	SYG-	IPYI	ETSAKT	R-QGVEDA	FYTLVREI	RQH [^] E	SGPG <mark>C</mark> M	ISCKCVLS
NRAS	LYREOIKRVE	XDS	-DD-V	PMVLVGNKC	DLPT	RTVD	TKOAHELAK	SYG-	IPFI	ETSAKT	R-OGVEDA	FYTLVRET	ROY^D	gtog <mark>c</mark> m	IGLPCVVM
KRAS2B	HYREOTKRVP	XDS	-ED-V	PMVLVGNKC	DLPS	RTVD		SYG-	TPFT	ETSAKT	R-OGVDDA	FYTLVRET	RKH^K	KKKKKS	KTKCVTM
FDAG		D	- 4070	DIVINCNKC		ACDAL		GMC-		FTCART	P_OCVEEN	PCLIVUET			UCCOSVA
DATA	QIWAIWG	 750		DELLVONKC		DOVCO				ETOART.	R-QGVEEA	REDIMDET			DEDCOTI
RALA	DFREQILRVI		-EN-V	PFLLVGINKS		ROVS	VEEAKINKAE	QWIN-		EISARI.		FDLMREI	RAK N	SLARRI	RERCCIL
RALB	EFREQILRVE	(AE	-EDKI	PLLVVGNKS	DLEER-	RQVP	VEEARSKAE	EWG-	vQ	ETSAKT.	R-ANVDKV	FFDLMREI	RTK S	KNKKSF	KERCCLL
RRASI	KLF"TQILRVF	KDR	- DD - F	PVVLVGNKA	DLESQ-	RQVPI	RSEASAFGA	SHH-	VAYF	EASAKL.	R-LNVDEA	FEQLVRAV	RKYA	PRKKGG	GCPCVLL
RRAS2	KFQRQILRVI	KDR	-DE-F	PMILI <mark>GNK</mark> A	DLDHQ-	RQVT	QEEGQQLAR	QLK-	VTYM	EASAKI	R-MNVDQA	FHELVRVI	RKF ^R	KEKDKK	GCHCVIF
MRAS	RFHQLILRVH	KDR	-ES-F	PMILVA <mark>NK</mark> V	DLMHL-	RKITI	REQGKEMAT	KHN -	IPYI	ETSAKD	PPLNVDKA	FHDLVRVI	RQQ^D	RATGTH	.KLQ <mark>C</mark> VIL
RIT1	EFKQLIYRVF	RRT	-DD-T	PVVLV <mark>GNK</mark> S	DLKQL-	RQVTI	KEEGLALAR	EFS-	CPFF	ETSA <mark>AY</mark>	R-YYIDDV	FHALVREI	RRK ^ R	L <mark>K</mark> SPFR	KKKDSVT
RIT2	KFKELIFOVE	RHT	-YE-I	PLVLV <mark>GNK</mark> I	DLEOF-	ROVS	reeglslao	EYN-	CGFF	ETSAAL	R-FCIDDA	FHGLVREI	RKK [^] K	L <mark>K</mark> GSLK	KKRENMT
RAP1A	DLREOILRVE	XDT	-ED-V	PMILV <mark>GNK</mark> C	DLEDE-	RVVGI	KEOGONLAR	OWCN	N-CAFL	ESSAKS	K-INVNEI	FYDLVROI	NRK [^] V	EKKKPK	KKSCLLL
RAP1R	DLREOTLRVE	ייי	-DD-V	PMTLVGNKC	DLEDE-	RVVGI	KEOGONI AR	OWNIN	J-CAFL	ESCARC	K - TNVNET	EVDL.VROT	NRK^V	PGKARK	KSSCOLL.
DAD2A		ZDV	-FK-W	DVTIVCNKV		DEVIC	CECCONTAE	EMC-		ETCAVC					CGACNITO
RAPZA	PMRDQIIRVI	XR1		PVILVGINKV		REVO	SSEGRALAE	EWG-	CPFM	EISARS.	K-IMVDEL	PAEIVROM			CSACINIQ
RAPZC	PMRDQIVRVP	KR I	- EK - V	PLILVGNKV	DLEPE-	REVM	SSEGRALAQ	EWG-	CPFM	ETSAKS.	K-SMVDEL	FAEIVRQM	INYS P.	EKQDQC	CITICVVQ
RAP2B	PMRDQIIRVI	KRY	- ER - V.	PMILVGNKV	DLEGE-	REVS	YGEGKALAE	EWS-	CPFM	ETSAKN.	K-ASVDEL	FAEIVRQM	INYA PI	NGDEGC	CSACVIL
DIRAS1	PIYKLIVQIH	KG-S	-VEDI	PVMLV <mark>GNK</mark> C	DETQ	REVD'	FREAQAVAQ	EWK-	CAFM	ETSAKM	N-YNVKEL	FQELLTLE	TRR^Q.	KRTDRV	KGKCTLM
DIRAS2	PIYEQICEI	KG-D	-VESI	PIMLV <mark>GNK</mark> C	DESPS-	REVQS	SSEAEALAR	TWK-	CAFM	ETSAKLI	N-HNVKEL	FQELLNLE	KRR^Q	KRKEKL	1 <mark>KGKC</mark> VIM
ARHI	AFYELICKI	KGNN	-LHKF	PIVLV <mark>GNK</mark> S	DDTH	REVA	LNDGATCAM	EWN-	CAFM	EISAKT	D-VNVQEL	FHMLLNYK	KKP^P	NTTE <mark>K</mark> L	'TD <mark>KC</mark> IIW
RASD1	RLRQQILDTH	KSCLKNKTK	ENVDV	PLVIC <mark>GNK</mark> G	DRDFY-	REVD	QREIEQLVG	DDPQ	ORCAYF	EISAKK	NSS-LDQM	FRALFAMA	KLP^A	gsqa <mark>k</mark> d	KERCVIS
RASD2	RLOKOILEVE	KSCLKNKTK	EAAEL	PMVIC <mark>GNK</mark> N	DHGELC	ROVP	TTEAELLVS	GDE -	-NCAYF	evsakk	NTN-VDEM	FYVLFSMA	KLP [^] R	EGOARE	RDKCTIO
RASL10B	TTROOTLETE	RVTG	-TSET	PTTTVGNKR	DLORG-	RVTP	WNVSHLVR	KTW-	- KCGYV	ECSAKY	NWH - TT.T.T.	ESELLKSV	GCA^R	FOGALR	RNRCATM
PAGE 10A				DTLANCINK		DECDI		DCW-	-PCCVL	FCGARV		PRELLOCA	TADAD		DADCCIM
NETDICA	TINGUTABII	CFAG	DUUDU			DOVE		a T							CNONODN
NKIRASI	LLKKEIDKFR	<	DKKEV		DLSEQ-	ROVDA	AE VAQQWAK	51	EKVRLW.		RKT-LIEP	FILLASKL	JSQP L	PGRKNK	GNSNSEN
NKIRAS2	LLKKEIDKSP	<u> </u>	DKKEV.	TIVVLGNKC	DLŐEŐ-	RRVDI	PDVAQHWAK	SF	EKVKLW.	EVSVAD	RRS-LLEP	FVYLASKM	TTQP P.	LSRKNK	GSGSLDG
RERG	PLKNILDEIN	KKP	KNV'	TLILV <mark>GNK</mark> A	DLDHS-	RQVS	FEEGEKLAT	ELA-	CAFY	ECSACT	GEGNITEI	FYELCREV	vrrr^v	KQAINK	MLTKISS
RASL11B	QLHQHVQQLH	HLG	TRL	pvvvva <mark>nk</mark> a	DLLHI -	KQVDI	PQLGLQLAS	MLG-	CSFY	EV <mark>SV</mark> SEI	NYNDVYSA	FHVLCKEV	SHK [^] K	QALSA <mark>K</mark>	VRTVTSV
RASL11A	PLYQHIRKVH	HPD	SKA	PVIIV <mark>GNK</mark> G	DLLHA-	RQVQ	FQDGIQLAN	ELGS	SLFL	EISTSE	NYEDVCDV	FQHLCKEV	/SKMHQ	alsp <mark>k</mark> v	KAPSALG
RASL12	SYLELLALHA	AKET	-QRSI	PALLLGNKL	DMAOY-	RQVTI	KAEGVALAG	RFG-	CLFF	EVSACL	DFEHVOHV	FHEAVREA	RRE [^] K	APTLTL	L <mark>K</mark> GF <mark>K</mark> IF
GEM	ELRIOLRRAF	ROT	EDT	PIILVGNKS	DLVRC-	REVST	VSEGRACAV	VFD-	CKFT	ETSAAV	OHN-VKEL	FEGIVROV	RLR [^] F	KLKSKS	CHDLSVI
RRAD	ELRVOLRRAD	~- ?OT	1	PTTLVGNKS		REVS	VDEGRACAV	VFD-	CKFT	ETSAAL	HHN-VOAT	FEGVUROT	RLR^F	RAKSKS	CHDLSVI
DEM1	FI.PTOT DDm		ייעם	DTTLACAN		DEVO	FEGRACAN			ETCATT		FEGINIDOT	DT.P^T	KADCKO	CHNI AVT
DEMO				F T T T VONKA	DIARC-	DEVO	EEGRACAV	vг D- тт О	OWITT	ETORILI				KARSKS	
REM2	EILLKLKAGH	KPH	HDL	FATTAGURS	DLARS-	REVS	LEEGKHLAG	тцS-	CKHI	EISAAL.	NUM TREL	EGAVKQI	KLK F	RUKSKS	CHULSVL
RHEB	VIHGKLLDM	/GK	VQI	PIMLVGNKK	DLHME-	RVIS	YEEGKALAE	SWN-	AAFL	ESSAKE	NQ'I'-AVDV	FRRIILEA	LEKM D	JAASQG	KSSCSVM
RHEBL1	SLYQKLHEGH	HGK	TRV	PVVLVGNKA	DLSPE-	REVQ	AVEGKKLAE	SWG-	ATFM	ESSARE	NQL-TQGI	FTKVI-QE	IAR^V	ENSYGQ	ERRCHLM

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.

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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.

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	N terminus			\rightarrow
	G1	G2	G3	
RAC1	MQAIKCVVVGDGAVGKTCLLIS	-YTTNAFPGEYIPTVFDNY	SANVMVDGKPVNLGLWDTAGQEDYDRLRPLSYP	QTDVFLICFSLVSPASFEN
RAC2	MQAIKC <mark>VVVGD</mark> GAV <mark>GKT</mark> CLLIS	-YTTNAFPGEYIPTVFDNY	SANVMVDSKPVNLGLWDTAGQEDYDRLRPLSYP	QTDVFLICFSLVSPASYEN
RAC3	MQAIKC <mark>VVVGD</mark> GAV <mark>GKT</mark> CLLIS	-YTTNAFPGEYIPTVFDNY	SANVMVDGKPVNLGLWDTAGQEDYDRLRPLSYP	QTDVFLICFSLVSPASFEN
RAC4	MQAIKG <mark>VVVGD</mark> GAV <mark>GKT</mark> CLLIS	-YTTNAFPGEDIPTAFDNY	SANVMVDGKLVNLGLWNTA <mark>G</mark> QEDYDRLRPLSYP	QADVFLICFSLVSPASFEN
RHOG	MQSIKC <mark>VVVGD</mark> GAV <mark>GKT</mark> CLLIC	-YTTNAFPKEYIPTVFDNY	SAQSAVDGRTVNLNLW <mark>DT</mark> A <mark>G</mark> QEEYDRLRTLSYP	QTNVFVICFSIASPPSYEN
RHOJ	MN^DEKKMLKCVVVGDGAVGKTCLLMS	-YANDAFPEEYVPTVFDHY	AVTVTVGGKQHLLGLY <mark>DT</mark> A <mark>G</mark> QEDYNQLRPLSYP	NTDVFLICFSVVNPASYHN
RHOQ	MP^PGALMLKCVVVGDGAVGKTCLLMS	-YANDAFPEEYVPTVFDHY	AVSVTVGGKQYLLGLY <mark>DTAG</mark> QEDYDRLRPLSYP	MTDVFLICFSVVNPASFQN
CDC42	MQTIKC <mark>VVVGD</mark> GAVGKTCLLIS	-YTTNKFPSEYVPTVFDNY	AVTVMIGGEPYTLGLFDTAGQEDYDRLRPLSYP	QTDVFLVCFSVVSPSSFEN
RHOU	MP^AEGRGVKCVLVGDGAVGKTSLVVS	-YTTNGYPTEYIPTAFDNF	SAVVSVDGRPVRLQLCDTAGQDEFDKLRPLCYT	NTDIFLLCFSVVSPSSFQN
RHOV	MP^PPELGIKCVLVGDGAVGKSSLIVS	-YTCNGYPARYRPTALDTF	SVQVLVDGAPVRIELWDTAGQEDFDRLRSLCYP	DTDVFLACFSVVQPSSFQN
RHOH	MLSSIKCVLVGDSAVGKTSLLVR	-FTSETFPEAYKPTVYENT	GVDVFMDGIQISLGLWDTAGNDAFRSIRPLSYQ	QADVVLMCYSVANHNSFLM
RHOA	MAAIRK <mark>KLVIVGD</mark> GAC <mark>GKT</mark> CLIVFS	KDQFPEVYVPTVFENY	VADIEVDGKQVELALW <mark>DT</mark> A <mark>G</mark> QEDYDRLRPLSYP	DTDVILMCFSIDSPDSLEN
RHOC	MAAIRKKLVIVGDGACGKTCLLIVFS	KDQFPEVYVPTVFENY	IADIEVDGKQVELALW <mark>DT</mark> A <mark>G</mark> QEDYDRLRPLSYP	DTDVILMCFSIDSPDSLEN
RHOB	MAAIRKKLVVVGDGACGKTCLLIVFS	KDEFPEVYVPTVFENY	VADIEVDGKQVELALW <mark>DT</mark> A <mark>G</mark> QEDYDRLRPLSYP	DTDVILMCFSVDSPDSLEN
RHOD	MT_PGVRSVKVVLVGDGGCGKTSLLMVFA	DGAFPESYTPTVFERY	MVNLQVKGKPVHLHIWDTAGQDDYDRLRPLFYP	DASVLLLCFDVTSPNSFDN
RHOF	MT^PGRKELKIVIVGDGGCGKTSLLMVYS	QGSFPEHYAPSVFEKY	TASVTVGSKEVTLNLY <mark>DT</mark> A <mark>G</mark> QEDYDRL <mark>R</mark> PLS Y Q	NTHLVLICYDVMNPTSYDN
RND3	MK^NQNVKCKIVVVGDSQCGKTALLHVFA	KDCFPENYVPTVFENY	TASFEIDTQRIELSLW <mark>DT</mark> S <mark>G</mark> SPYYDNVRPLSYP	DSDAVLICFDISRPETLDS
RND2	MEGQSGRCKIVVVGDAECGKTALLQVFA	KDAYPGSYVPTVFENY	TASFEIDKRRIELNMWDTS <mark>G</mark> SSYYDNVRPLAYP	DSDAVLICFDISRPETLDS
RND1	MK^PVVARCKLVLVGDVQCGKTAMLQVLA	KDCYPETYVPTVFENY	TACLETEEQRVELSLWDTSGSPYYDNVRPLCYS	DSDAVLLCFDISRPETVDS
RHOBTB1	MD^PNVETIKCVVVGDNAVGKTRLICARACNT	fltqyqllathv pt vwaidqyrvcq	EVLERSRDVVDEVSVSLRLW <mark>DTFG</mark> DHHKDRRFAYG	RSDVVVLCFSIANPNSLNF
RHOBTB2	MDPNVETIKCVVVGDNAVGKTRLICARACNA	rltqyqlLathv pt vwaidqyrvcq	EVLERSRDVVDDVSVSLRLW DT F G DHHKD R RFA M G	RSDVVVLCFSIANPNSLH
RHOT1	MKKDVR <mark>ILLVG</mark> EPRV <mark>GKT</mark> SLIMSLVS	EEFPEEVPPRAEEIT	IPADVTPERVPTHIVDYSEAEQSDEQLHQEIS	QANVICIVYAVNNKHSIDF
RHOT2	MRRDVRILLLGEAQVGKTSLILSLVG	EEFPEEVPPRAEEIT	IPADVTPEKVPTHIVDYSEAEQTDEELREEIH	KANVVCVVYDVSEEATIEF
	Continued	PWO de servit	ar.	C terminus
D 3.01	Continued	RHO insert		C terminus
RAC1	Continued VRAKWYPEVRHHCPNTPIILVCTKLDLRDI UDAYMPERVRHHCPNTPIILVCTKLDLRDI	RHO insert	G5 POGLAMAKE IGAVKULECSAL TORG - LKTVEDEA IRA	C terminus
RAC1 RAC2	Continued VRAKWYPEVRHHCPNTPIILVGTKLDLRDI VRAKWFPEVRHHCPSTPIILVGTKLDLRDI URAYGNPEVRHUCP	RHO insert DKDTIEKLKEKK-LTPITY DKDTIEKLKEKK-LAPITY	G5 POGLAMAKEIGAVKVLECSALTORG-LKTVFDEAIRA POGLALAKEIDSVKVLECSALTORG-LKTVFDEAIRA POGLALAKEIDSVKVLECSALTORG-LKTVFDEAIRA	C terminus VLC-PPVKKRKRKCLLL VLCPQPTRQQKRACSLL
RAC1 RAC2 RAC3 BAC4	Continued VRAKWYPEVRHHCPNTPIILVGTKLDLRD VRAKWYPEVRHHCPSTPIILVGTKLDLRD VRAKWYPEVRHHCPHTPILLVGTKLDLRD VLAWYDEVRHCPNTPIILVGTKLDLRD	RHO insert DKDTIEKLKEKK-LTPITY DKDTIEKLKEKK-LAPITY DKDTIEKLRDKK-LAPITY	G5 PQGLAMAKEIGAVKYLECSALTQRG-LKTVFDEAIRA PQGLALAKEIDSVKYLECSALTQRG-LKTVFDEAIRA PQGLAMAREIGSVKVLECSALTQRG-LKTVFDEAIRA PQGLAMAREGAVKVLECSALTQRG-LKTVFDEAIRA	C terminus VLC-PPVKKRKRKCLLL VLCPQPTRQQKRACSLL VLCPPPVKRPGKKCTVF
RAC1 RAC2 RAC3 RAC4 BHOC	Gontinued 64 VRAKWYPEVRHCPNTPIILVGTKLDIRD VRAKWPEVRHCPSTPIILVGTKLDIRD VRAKWPEVRHCPNTPIILVGTKLDIRD VLAKWYEVGHCPNTPIILVGTKLDIRD VLAKWYEVGHCPNTPIILVGTKLDIRD VLAKWYEVGHCPNTPIILVGTKLDIRD	RHO insert DKDTIEKLKEKK-LAPITY OKDTIEKLKEKK-LAPITY OKDTIERLKDKK-LAPITY DKDRIQKLKEKK-LTPITY	05 POGLAMAKE IGAVK VECCALTORG - LKTVEDE IRA POGLALAKE IDSVK LECCALTORG - LKTVEDE IRA POGLAMARE IGSVK LECCALTORG - LKTVEDE IRA POGLAMAKEMGAVK LECLALTERG - LKTVEDE IRA POGLAMAKEMGAVK LECLALTERG - LKTVEDE IRA	C terminus VLC-PPVKKRKKCLLL VLCPOPVKRCKACSLL VLCPOPVKRCKCTVF VLCPPPVKRKKCLQL VLN-PTBVCRCSIL
RAC1 RAC2 RAC3 RAC4 RHOG PHOJ	Continued G4 VRAKWYPBVRHCPNTPIILVGTKLDLRD VRAKWPBVRHCPSTPIILVGTKLDLRD VRAKWYPBVRHCPSTPIILVGTKLDLRD VRAKWPBVRHCPNTPILLVGTKLDLRD VLAKWYPBVRHCPNTPILLVGTKLDLRD VRAKWPBVCHCPNTPILVGTKLDLRD VRAKWPBVCHCPNTPILVGTKLDLRD VRAKWPBVCHCPNTPILVGTKLDLRD VRAKWPBVCHCPNTPILVGTKLDLRD VRAKWPBVCHCPNTPILVGTKLDLRD	RHO insert KKDTIEKLKEKK-LTPITY KKDTIEKLKEKK-LAPITY KKDIEKLKEKK-LAPITY KKDRIQKLKEK-LTPITY PDTLRRLKEQG-QAPITY DWTLAPLIVWE EWDITY	95 PQGLAMAKE IGAVKYLECSAL TQRG - LKTVIDEA IRA PQGLALAKE IDSVKYLECSAL TQRG - LKTVIDEA IRA PQGLAMAREIGSVKYLECSAL TQRG - LKTVIDEA IRA OQGALAKEGAVKYLECLA ITRRG - LKTVIDEA IRA OQGALAKO IHAVENLECSAL OQDG - VKEVIDEA IRA PQGVLAKE IGOOVERGEAT TOGG - LKAVDEF ILT	C terminus VLC-PPVKKRKKKLLL VLCPPPVK PCKKRKLLU VLCPPPVK PCKKCLQL VLCPPPVKKRKKLQL VLN-PTPIKKGKS ILL TUP*ZPSEGUSTGGI
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ PHOO	Gontinued 64 VRAKWYPEVRHCPNTPIILVORKDIRD VRAKWPEVRHCPSTPIILVORKDIRD VRAKWYPEVRHCPNTPIILVORKDIRD VRAKWYEVOHCPNTPIILVORKDIRD VRAKWYEVOHCPNTPIILVORKDIRD VCREWYELVORCHCPNTPIILVORKDIRD VRAKWYEVOHCPNTPIILVORKDIRD VCREWYELVORCHCPNTPIILVORKDIRD VRAKWYEVOHCPNTPIILVORKDIRD VCREWYELVORCHCPNTPIILVORKDIRD VRAKWYEVOHCPNTPIILVORKDIRD VCREWYELVORTOND VRAKWYEVOHCPNTPIILVORKDIRD VCREWYELVORTOND VRAKWYEVOHCPNTPIILVORKDIRD VCREWYELVORTOND	RHO insert CKDTIEKLKEKK-LTPITY CKDTIEKLKEKK-LAPITY CKDRICKLEKK-LAPITY CKDRICKLEKK-LIPITY POTLIERLENGG-QAPITP POTLIERLENGG-QAPIT	05 POGLAMAKE IGAVKVECGALTORG-LKTVEDE IRA POGLALAKE IDSVK LECGALTORG-LKTVEDE IRA POGLAMARE IGSVK LECGALTORG-LKTVEDE IRA POGLAMARE IGSVK LECGALTORG-LKTVEDE IRA OGQALAKOLAKALGAQCKLECGALTORG-LKAVEDE ILTA EEGVKLAKALGAQCKLECGALTORG-LKAVEDE ILTA	C terminus VLC-PPVKKRKRCLLL VLCPOPTROCKRASLL VLCPPPVKRKRKCLQL VLCPPPVKRKRKCLQL UL-PPTKRGSSILL IFH^KRSEGNCCLIT
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ RHOQ CDC42	Continued <u>94</u> VRAKWYPEVRHHCPNTPIILVGTKLDLED VRAKWYPEVRHHCPSTPIILVGTKLDLED VRAKWYPEVRHHCPTHPILVGTKLDLED VLAKWYPEVRHCPNTPILVGTKLDLED VRIKWPEVCHHCPDYPILLVGTKLDLED VRIKWPEVCHHCPNTPILLVGTKLDLED VKEEWYPELKEYAPNUPFLLIGGTLDLED VKEEWYPELWEYAPNUPFLLIGGTLDLED	RHO insert DKDTIEKLKEKK-LTPITY DKDTIEKLKEKK-LAPITY DKDIREKLRUKK-LAPITY DKDIRLKEKGG-QAPITY PKTLARLUMK-EKPLTY PKTLARLNMK-EKPICY DESTIEKLAWK-OKPIT	95 POGLAMAKE IGAVK VEGSALTORG-LKTVEDE IRA POGLALAKE IDSVK LECSALTORG-LKTVEDE IRA POGLAMARENGAVK LECSALTORG-LKTVEDE IRA OGGAMAKEMGAVK LECSALTORG-LKTVEDE IRA OGGALAKO IHAVE LECSALOODG-VKEVFAE VEA ENGVKLAKE IGAC VECSALTORG-LKTVEDE ILT EOGKLAKE IGAC VECSALTORG-LKTVEDE ILT	C terminus VLC-PPVKKKRK LLL VLCPQPTROCKAS SLL VLCPPPVK PSKKTVF VLCPPPVKKRKK CLQL VLN-PTPIKSGS LLL IFH^KRSEGHSCSII LLT^RIGSRINCLIT
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ RHOQ CDC42 PHOU	Gontinued 64 VRAKWYPEVRHHCPNTPIILVGTKLDIRD VRAKWPEVRHHCPTPIILVGTKLDIRD VRAKWYPEVRHHCPTPIILVGTKLDIRD VRAKWYPEVRHCPTPIILVGTKLDIRD VRAKWYPEVRHCPTPIILVGTKLDIRD VRAKWYPEVRHCPTPIILVGTKLDIRD VRAKWYPEVRHCPTPIILVGTKLDIRD VRAKWYPEVRHCPTPIILVGTKLDIRD VRAKWYPEVRHCPTPIILVGTKLDIRD VRAKWPETRENDER VRAKWYPEVRHCPTPIILVGTKLDIRD VRAKWPETRENDER VREBWYPELKDCMPWPFLLIGTCTIDED VRAKWPETRENDER VREBWYPELFTHCPXREPLIJVGTCIDED VRAKWPETRENDER VREBWYPELFTHCPSTEPLIJVGTCIDED VRAKWPETRENDER	RHO insert KDTIEKLKEKK-LTPITY KKDTIEKLKEKK-LAPITY KKDRIQKLKEKK-LTPITY KKDRIQKLKEKK-LTPITY POTIRKLKGQ-QAPITP PKTLARLUNK-EKPLTY PKTLARLUNK-EKPLTY VEVLTENKAKK-QKPIT	G5 PQGLAMAKE IGAVKVECGALTORG-LKTVEDE I RA PQGLALAKE IDSVK LECGALTORG-LKTVEDE I RA PQGLANARE IGSVK LECGALTORG-LKTVEDE I RA PQGLAMAREMGAVK LEGLALTORG-LKTVEDE I RA OQGQALAKOLAVA LEGLALTORG-LKTVEDE I TA EHGVKLAKI GAQCV LECGALTORG-LKAVEDE I TA ETARKLARDLKAVK VYCGALTORG-LKAVEDE I TA ETARKLARDLKAVK VYCGALTORG-LKNVEDE I TA	C terminus VLC-PPVKKKKKCLLL VLCPPVKRPCKRCLL VLCPPVKRPCKKKCLL VLCPPVKRFKKCLL VLCPPVKRKKCLL ILT*RISEGISCII IIT*KISEGISCII IIT*RISEGISCII ALE-PPSTOFKRCCF J1012SCWKVCFP
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ RHOJ CDC42 RHOU RHOU	Continued <u>64</u> VRAKWYPEVRHHCPNTPIILVGrKLDLED VRAKWYPEVRHHCPSTPIILVGrKLDLED VRAKWYPEVRHHCPHTPIILVGrKLDLED VLAKWYPEVCHHCPNTPIILVGrKLDLED VRKKWPEVCHHCPDYPILLVGRKLDLEA VCEBWYPELKSYAPNVPFLLIGTOINED VKEBWYPEILKSYAPNVPFLLIGTOINED VKEBWYPEILCHCPTPFLLVGROEDLER VSEKWYPEIRCHCPXAPIILVGROEDLER VSEKWYPEIRCHCPXAPIILVGROEDLER	RHO insert CKDTIEKLKEKK-LTPITY CKDTIEKLKEKK-LAPITY CKDICKLKEKK-LAPITY CKDRICKLKEKK-LTPITY PDTIRKLKEGG-QAPITY PKTLARLIVMK-EKPLTY PKTLARLNMK-EKPICY PKTLELDKCK-EKPVP UNVL/LCHOCGREECEVP0	95 POGLAMAKEIGAVKVEGSALTORG-LKTVEDE IRA POGLALAKEIDSVKVEGSALTORG-LKTVEDE IRA POGLALAKEIDSVKVEGSALTORG-LKTVEDE IRA POGLAMARRIGSVKIEGLAITORG-LKTVEDE, IRA OGGAMARENGAVKIEGLAITORG-LKTVEDE, IRA SOGOALAKOIHAVRIEGSALTORG-LKTVEDE, ILA BEGYKLAKEIGACYVEGSALTORG-LKTVEDE, ILA ERAKLOAEBIKASYIEGSALTORG-LKTVEDE, ILA EAAKLOAEBIKASYIEGSALTORG-LKTVEDE, ILA EAAKLOAEBIKASYIEGSALTORG-LKTVEDE, ILA	C terminus
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ RHOQ CDC42 RHOU RHOV RHOH	Continued 64 VRAKWYPEVRHHCPNTPIILVGTKLDIRD VRAKWPEVRHHCPTPIILVGTKLDIRD VRAKWPEVRHHCPTPIILVGTKLDIRD VRAKWPEVCHHCPNTPIILVGTKLDIRD VRAKWPEVCHHCPTPIILVGTKLDIRD VRAKWPEVCHHCPNTPIILVGTKLDIRD VRAKWPEVCHHCPTPIILVGTKLDIRD VRAKWPEVCHCPVPILLVGTKLDIRD VRAKWPEVFLKKCHCPVPILLVGTKLDIRD VRAKWPEVFLKCHCPVPILLVGTKLDIRD VRESWPELKCCMPNTPFLLVGTCDIRD VRESWPELTCCMPNTPFLLVGTCDIRD VRESWPERKENTPITHCP	RHO insert CKDTIEKLKEKK-LTPITY CKDTIEKLKEKK-LAPITY CKDTIEKLKEKK-LAPITY CKDTIEKLAKKG-QAPIT	G5 PQGLAMAKE IGAVK VECSALTORG-LKTVEDE I RA PQGLALAKE IDSVK VECSALTORG-LKTVEDE I RA PQGLANARE IGSVK VECSALTORG-LKTVEDE I RA PQGLAMAREMGAVK VESCLALTORG-LKTVEDE I RA PQGALAKE INAVE VECSALTORG-LKTVEDE I ITA ENGVKLAKI GAQCV BECSALTORG-LKTVEDE I ITA ETABKLARD I KASK I BECSALTORG-LKNVEDE I ITA PQAGIALAE I TACCI VECSALTORG-LKNVEDE I ITA EXALCAE BITABCI VECSALTORG-LKNVEDE I ITA PQAGIALAE I RACSI BECSALTORG VECSALTORGALTORA I VA	C terminus
RAC1 RAC2 RAC3 RAC4 RHOJ RHOJ CDC42 RHOU RHOV RHOV RHOH RHOA	Continued <u>64</u> VRAKWYPEVRHHCPNTPIILVGRKLDIRD VRAKWPEVRHHCPBTPIILVGRKLDIRD VRAKWPEVRHHCPPTPILLVGRKLDIRD VRAKWPEVQHHCPDVPILLVGRKLDIRD VRAKWPEVCHHCPDVPILLVGRKLDIRD VKEWVPELKSYAPNVPFLLIGGIDIRD VKEWVPEIRHCPVPFLLVGGIDIRD VKEWVPEIRHCPXAPIILVGGSDIRE JTKKNLPERTHPPCDVPLVVGGDIRD LKNKRUFERDVPULVVGGDIRD LKNKRUFERDVPULVVGGDIRD	RHO insert CRDTIEKLKEKK-LTPITY CRDTIEKLKEKK-LAPIT	65 POGLAMAKE IGAVK VLECSALTORG - LKTVEDE IRA POGLALAKE IDSVK ULECSALTORG - LKTVEDE IRA POGLAMARE IGSVK ULECSALTORG - LKTVEDE IRA OGLAMAREMGAVK LECLALTORG - LKTVEDE IRA SOGLAMAREMGAVK ULECLALTORG - LKTVEDE ILA EGYKLAKA IGACO LECSALTORG - LKTVEDE ALLA EGYKLAKE IGACO VECSALTORG - LKTVEDE ALLA PAGOLAKEN IGACO VECSALTORG - LKTVEDE ALLA EARLICAEE IKASY I ECSALTORG - LKTVEDE ALLA EARLICAEE IKASY I ECSALTORG - LKTVEDE ALLA MERKIKLAOVTARCO LECSALSING - VQOVECS VET MERKIKADOVRAKCI LECSALSING - VQOVECS VET	C terminus VLC-PPVKKKKKCLLL VLCPPVKKPKKCLL VLCPPVKKPKKCLQ VLCPPVKKPKKCLQ VLCPPVKKPKCLQ VLCPPVKKPKCLT LLT*LGSRINCIT LLT*LSSRVKKYCPV ALE-PPEIQKKCTPV ALE-PSINCVKKFPC VLCPKKKFFC VLC-SNCKKFFC VLC-SNCKKFFC
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ RHOQ CDC42 RHOU RHOV RHOH RHOA RHOA	Continued 94 VRAKWYPEVRHHCPNTPIILVGTKLDIRD VRAKWYPEVRHHCPTPIILVGTKLDIRD VRAKWYPEVOHHCPNTPIILVGTKLDIRD VRAKWYPEVOHHCPNTPIILVGTKLDIRD VRAKWYPEVOHHCPNTPIILVGTKLDIRD VRAKWYPEVOHHCPNTPIILVGTKLDIRD VRAKWYPEVOHHCPNTPIILVGTKLDIRD VRAKWYPEVOHHCPNTPIILVGTKLDIRD VRAKWYPENCHCPNTPIILVGTKLDIRD VRAKWYPENCHCPNTPILLVGTKLDIRD VRAKWYPENCHCPNTPILLVGTKLDIRD VRAKWYPENCHCPNTPILLVGTKLDIRD VRAKWYPENCHCP	RHO insert CKDTIEKLKEKK-LTPITY SKDTIEKLKEKK-LAPITY SKDRIQKLKEKK-LAPITY SKDRIQKLKEKK-LTPITY POTLRELKENG-QAPITY PSTIEKLAKNK-GKPLTY PSTIEKLAKNK-GKPITY SVKVLIELDCKG-EKFVPA COHTRELAKMKGEPVK	95 PQGLAMAKE IGAVKUECSALTORG-LKTVEDE IRA PQGLALAKE IDSVKUECSALTORG-LKTVEDE IRA PQGLANAREIGSVKUECSALTORG-LKTVEDE IRA PQGLAMAREMGAVKUECLALTORG-LKTVEDE IRA PQGLAMAREMGAVKUECLALTORG-LKTVEDE IRA ENGVKLAKIGAQCUECSALTORG-LKAVEDE ILT ETAEKLARDLKAVKVECSALTORG-LKAVEDE ILT ETAEKLARDLKAVKVECSALTORG-LKKVEDE ILT ETAEKLARDLKAVKVECSALTORG-LKKVEDE ILT BARKLCAEBIKASCIECSALTORG-LKKVEDE ILT BARKLCAEBIKASCIECSALTORG-LKKVEDE ILT BEGREMANNIGAFOMECSAKTENG-VERVEMMTRA	C terminus
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ RHOQ CDC42 RHOU RHOV RHOV RHOH RHOA RHOC RHOB	Continued 64 VRAKWYPEVRHHCPNTPIILVCGKLDLED VRAKWPEVRHHCPNTPIILVCGKLDLED VRAKWPEVRHHCPNTPILLVCGKLDLED VLAKWYPEVRHHCPNTPILLVCGKLDLED VRAKWPEVRHHCPNTPILLVCGKLDLED VRAKWPEVRHCPNTPILLVCGKLDLED VRAKWPEVRHCPNTPILLVCGKLDLED VKBKWPELKDCMPNVPILLVGGKLDLED VKEKWVPELKDCAPNVPFLLGGCDLED VKEKWVPETRHCPSAPIILVCGQDLED VSEKWVPETRHCPSAPIILVCGQDLED LKNKKIGEIRSNLPCPVLVVGQDLED LPEKWFPEVKHFCPNVPIILVCMKKDIEN IPEKWFPEVKHFCPNVPIILVCMKKDIEN LPEKWFPEVKHFCPNVPIILVCMKKDIEN	RHO insert DKDTIEKLKEKK-LTPITY OKDTIEKLKEKK-LAPITY OKDERQKLKEKK-LPPITY OKDERQKLKEKK-LTPITY PKTLARLI/MK-EKPITY PKTLARLI/MK-EKPITY OFSTIEKLAKMK\QEPVTQ UMPHTASCVNA DHTRRELAKMKQEPVRS DHTRRELAKMKQEPVRS DHTRRELAKMKQEPVRS DHTRRELAKMKQEPVR	65 POGLAMAKE IGAVK VECCATTORG - LKTVEDE IRA POGLALARE IDSVK UECCATTORG - LKTVEDE IRA POGLAMARE IGSVK UECCATTORG - LKTVEDE IRA POGLAMARE IGSVK UECCATTORG - LKTVEDE IRA QEGOALAKOITAVKILGCIATTORG - LKTVEDE IRA QEGOALAKOITAVKILGCIATTORG - LKTVEDE ILA EGOKULAKEIGACI VECCATTORG - LKTVEDE ILA FARKLARDIGAKVK VECSATTORG - LKTVEDE ILA RAAKLOAEEIKAASI IE CSATTOKI- LKEVEDE ILA RAAKLOAEEIKAASI IE CSATTOKI- LKEVEDE ILA BEGREMANEIGACI DE CSATTOKI- LKEVEDE ILA BEGREMANEIGACI DE CSATTOKI- LKEVEDE ILA BEGREMANEIGACI DE CSATTOKI- LKEVEDE ILA DEGRAMANEIGACI DE CSATTOKI- LKEVEDE ILA DEGREMANEIGACI DE CSATTOKI- LKEVEDE ILA	C terminus VLC-PPVKKKKKCLLL VLCPOPTOCIASSLL VLCPPVKKKKKCLLL VLCPPVKKKKKCLLL VLCPPVKKKKKKCLLL VLN-PTPIKGSSISILL IIT*ISSEINCKCLT IIT*ISSEINCKCLT SLC-SSISKKKKCFFC VLC-SSISKKKKFFC VLC-SSISKKKCT VLC-SSISKKKCLT VLC-SSISKKCLT VLC-SSISKKCLT
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ CDC42 RHOU RHOV RHOH RHOC RHOB RHOD	Continued 94 VRAKMYPEVRHHCPSTPIILVGTKLDIRD VRAKMYPEVRHHCPSTPIILVGTKLDIRD VRAKMYPEVRHHCPHTPILLVGTKLDIRD VRAKMYPEVCHHCPSTPILLVGTKLDIRD VRAKMYPEVCHHCPNTPILLVGTKKLDIRD VRAKMYPEVCHCPSTPILLVGTKKLDIRD VKKENVPELKDCHPVPVFLLVGTKKDIRD VRAKMYPEVGHCPSTPILLVGTKKDIRD VKKENVPEIRTHEVSTPFLLVGTCDIRD VKKENVPEIRTHEVSTPFLLVGTCDIRD VKKENVPERTHEV	RHO insert CKDTIEKLKEKK-LTPITY SKDTIEKLKEKK-LAPITY SKDRIGKLKEKK-LAPITY SKDRIGKLKEKK-LTPITY POTLRELKENG-QAPITY PSTIEKLAKNK-EKPICV PSTIEKLAKNK-CKPITA DEHTRELAKMKOEPVK	95 POGLAMAKE IGAVK UE CSALTORG - LKTVE DE IRA POGLALAKE IDSVK UE CSALTORG - LKTVE DE IRA POGLAMARE IGSVK UE CSALTORG - LKTVE DE IRA POGLAMAREMGAVK UE CLALTORG - LKTVE DE IRA COGOALAKO ILAVEL SCALTORG - LKTVE DE IRA ENGVKLAKA IGAOCI UE CSALTORG - LKTVE DE ILA ETAEKLARD LKAVK VECSALTORG - LKAVE DE ILA ETAEKLARD LKAVK VECSALTORG - LKAVE DE ILA ETAEKLARD LKASI IE CSALTORG - LKTVE DE ILA ETAEKLARD LKASI IE CSALTORG - LKTVE DE ILA BERGKLARD KASI IE CSALTORG - LKTVE DE ILA EGROMANE IGAFON ECSALTORG - LKTVE DE ILA EERGENANE IGAFON ECSALTORG - VERVE EM TRA DOGRAMAVE IGAFON ECSALTORG - VERVE EM TRA DOGRAMAVE IGATON ECSALTEGO - VERVE EM TRA DOGRAMAVE IGANDO ECSALTORG - VERVE EM TRA	C terminus VLC-PPVKERKE LLL VLC-PPVKERKE LLL VLC-PPVKERKE LLL VLC-PPVKERKE LLL VLC-PPVKERKE LLL VLC-PPVKERKE LLL VLC-PPVKERKE LLL VLC-PVKERKE LLL VLC-PVKERKE LLL VLC-VERKE LLL VLC-VERKE LLL VLC-VERKE LLL VLC-VERKERKE LLL
RAC1 RAC2 RAC3 RAC4 RHOG RHOJ RHOQ CDC42 RHOU RHOV RHOV RHOH RHOA RHOC RHOB RHOD RHOF	Continued 64 VRAKWYPEVRHHCPNTPIILVOGKLDIED VRAKWPEVRHHCPHTPILLVOGKLDIED VRAKWPEVOHHCPNTPILLVOGKLDIED VLAKWYPEVOHHCPNTPILLVOGKKLDIED VRHKNEP-VENCHCPNTPILLVOGKKLDIED VKESWYPELKDCMPNTPILLVOGKKLDIED VKESWYPELKDCMPNTPILLVOGKKLDIED VKESWYPELKDCMPNTPILLVOGKCDIED VKESWYPELKDCMPNTPILLVOGKCDIED VKESWYPEKKEYAPNTPILLVOGKCDIEND VSKKWYPERCHCPTPVLVVAGCDADEND LYKKKVPEVKFECPNTPILVOKKDIEND IPEKWTPEVKHFCPNTPILVOKKDIEND IPEKWFPEVKHFCPNTPILVICKKDIEND IPEKWFPEVKHFCPNTPILVOKKDIEND IPEKWTPEVKHFCPNTPILVOKKDIEND IPEKWTPEVKHFCPNTPILVOKKDIEND IPEKWTPEVFUHFCKGENTLIVOKKDIEND IPEKWTPEVTHFCKSETIENVLIGCKTDEKK	RHO insert DKDTIEKLKEKK-LTPITY OKDTIEKLKEKK-LAPITY OKDIEKLKEKK-LAPITY OKDERQKLKEKK-LTPITY DPKTLARLANKKG-QAPITY DPKTLARLANK-CKPITY DPKTLARLANK-CKPITY DPKTLELKEKK-CKPIT	65 POGLAMAKE IGAVK VECCATTORG - LKTVEDE IRA POGLALARE IDSVK NECCATTORG - LKTVEDE IRA POGLAMARE IGSVK NECCATTORG - LKTVEDE IRA POGLAMARE IGSVK NECCATTORG - LKTVEDE IRA QOGALAKGI INVENECTATORG - LKTVEDE ILA EKGVKLAKAIGAQCI LECSATTORG - LKTVEDE ILA EKGVKLAKAIGAQCI LECSATTORG - LKTVEDE ILA EKGVKLAKEIGACCI VECSATTORG - LKTVEDE ILA PAGGALAKEIGACI DE CATTORG - LKTVEDE ILA EARLICAEEIKAASTI ECSATTORG - LKTVEDE ILA EARLICAEEIKAASTI ECSATTORG - LKTVEDE ILA EGGNANARI GACOTE DE SATTORG - LKTVEDE ILA EARLICAEEIKAASTI ECSATTORG - LKTVEDE ILA BEGRANARI GACOTE DE SATTORG - VQCVED A IVA MEGKKLAQUVARKOTE CSATTEGO - VQCVED A IVA HEGGNANARI SAFOTE CSATTEGO - VREVEMITRA EGGNANARI SAFOTE CSATTEGO - VREVEMITRA HEGGNARSVGAVATECSALIDON - VHAVO FAAEV	C terminus VLC-PPVKKKKKCLLL VLCPOPTOCKASLL VLCPPVKKKKKCLLL VLCPPVKKKKKCLCL VLCPPVKKKKKCSSI IFI-KKSSGSSI IFI-KKSSGSSI IFI-KKSSGSSI IFI-KKSSKKKKFFFFV VLCPKKSSI IFI-SSGKKKFFFFV VLCPKKSSI IFI-SSGKKKSSCLL IFI-SSGKKKSSCLL IFI-SSGKKSSGKSSGKSS IFI-SSGKKSSGKSSGKSSGKSSGKSSGKSSGKSSGKSSGKSS
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RAC1 RAC2 RAC3 RAC4 RHOJ RHOJ RHOJ RHOJ RHOJ RHOV RHOV RHOA RHOC RHOD RHOD RHOP RHOP RHOJ RHOF RHOJ RHOFB1 RHOFB1 RHOFB1 RHOT1	Continued GA WARKWYPEVRHHCPNTPIILVGRKLDIED VRAKWYPEVRHHCPBTPILLVGRKLDIED VLAKWYPEVRHHCPNTPIILVGRKLDIED VLAKWYPEVRHHCPNTPIILVGRKLDIED VREWYPEVRHCPDVPILLVGRKLDIED VREWYPELKDCMPHVPIVLIGRIDIED VREWYPEVRHCPNTPILLVGRKLDIED VREWYPEVRHCPNTPILVGRIDIED VREWYPEVRHCPNTPILVGRIDIED VREWYPEVRHCPNTPILVGRGDIE 1PEKWTPEVRHCPNTPILVGRGDIE 1PEKWTPEVRHCPNTPILVGRKDIEN 1PEKWTPEVRHCPNTPILVGRKDIEN 1PEKWTPEVRHCPNTPILVGRKDIEN 1PEKWTPEVRHCPNTPILVGRKDIEN 1PEKWTPEVRHCPNTPILVGRKDIEN 1FRWFIENTHCPSTPVILVGRKTLEK VLKWGEIGEFCPNTKMLLJGCKTLEK VLKWGEIGEFCPNTKMLLJGCKTLEK VLKWGFUEFCPNTPVILVGGLDIEN VKTMWYPENRHCFCRTPVILVGGLDIEN VKTMWYPENRHCFCRTPVILVGGLDIEN VKTMWYPENRHCFCRTPVILVGGLDIEN VKTMWYPENRHCFCRTPVILVGGLDIEN VTSRUTPUNGGTGGRPUEJULVGKRSDUE	RHO insert DKDTIEKLKEKK-LTPITY SKDTIEKLKEKK-LAPITY SKDTIEKLKEKK-LPFITY SKDIEKLKKK-LPFITY PKTLARLI/MK-EKPITY PKTLARLI/MK-EKPITY PKTLARLI/MK-EKPITY SKURLSKAK-QKPIT DKTLELKKKQEPVK DHTRRELAKMKQEPVK DHTRRELAKMKQEPVK DHTRRELAKMKQEPVK	05 POGLAMAKE I GAVK VLECS ALTORG - LKTVEDE I FRA POGLALAKE I DSVKILECS ALTORG - LKTVEDE I FRA POGLAMARE I GSVKLECS ALTORG - LKTVEDE I FRA POGLAMARE I GSVKLECS ALTORG - LKTVEDE I FRA QUGOALAKO I HAVRI LECS AL QQDG - VKEV AE VRA EVENTAKI GAQCI LECS ALTORG - LKTVEDE I FLA EQGVKLAKA I GAQCI LECS ALTORG - LKTVEDE I FLA POGLAMARE I GACT LECS ALTORG - LKTVEDE I LLA EGGVKLAKA I GAQCI LECS ALTORG - LKTVEDE I LLA EGGVKLAKA I GAQCI LECS ALTORG - LKTVEDE I LLA EGGVKLAKA I GAQCI LECS ALTORG - LKTVEDE I LLA BAAKLCAEE I KAAST I E CS ALTORG - LKTVEDE I LLA EGGVALAKO VLECS ALSING - VQCVECVENTE EGGDVANNE I GACTI DECS ALTORG - LKTVEDE I LLA MEGKLAQUERAKO VLECS ALSING - VQCVECVENT HEGGERMARE I GACTI LECS ALTORG - VREVENTE TRA HEGGERMARE I GATTI CS ALLORG - VREVENTE TRA EGGTALAKO SVECS SASSERS VREDI HVV TLA EGGCALTAKOLGAET I LECS ALTORG - I KDV DNN I FRA EKGEVAKELG I – VETSVEDORG - I KDV DNN I FRA EKGEVAKELG I – VETSVEDORG - I KDV DNN I FRA TI LE TINQVTE I ETCVECS KNLKN - I SEL YY DORA	C terminus VLC-PPVKKKKKCLLI VLCPOPVKKKKKCLLI VLCPOPVKKKKKCLLI VLCPPVKKKKKCLI VLCPPVKKKKKCLI VLCPPVKKKKKCLI VLCPVKKKKKKKCLI VLCPVKKKKKKCLI VLCPVKKKKKKKKLI VLCPVKKKKKKKKKKKKKKKKKKKKKKKKKKKKKKKKKKK

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.





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.

	N terminus					\rightarrow
		G1	_	G2		
RAN	MA^EPQVQFKLVL	VGDGGTGKT	TFVKRHLTGEFEKK	-YVATLG	/EVHPLVFHTNR	GPIK FNV
RABL2A	MA^DADDNVKIIC	LGDSA <mark>V</mark> GKS	KLMERFLMDGFQPQ	-QLS T YAI	LTLYKHTATVDGKT	ILVDF
RABL2B	MA~DADDNVKIIC	LGDSAVGK	KLMERFLMDGFQPQ	-QLS T YAI	LTLYKHTATVDGRT	ILVDF
RABL3	MASLDRVKVLV		SLVHLLCQNQVLGN	- PSWTVDC	SVDVRVHDYKEGTPEEKT-	CYIEL
RABLS RABIA	MG^FVDVLFKLLL		CLUBEADDTVTES		VERTERENERVISING	TGCEFED
RAB1B	MNPEYDYLFKLLL	IGDSGVGKS	CLLLRFADDTYTES	-YISTIG	DFKIRTIELDGK	TIKLOI
RAB35	MSRDYDHLFKLLI	IGDSGVGKS	SLLLRFADNTFSGS	-YITTIG	DFKIRTVEINGE	KVKLÕI
RAB13	MAKAYDHLF <mark>KLLL</mark>	IGDSG <mark>V</mark> GKT	CLIIRFAEDNFNNT	-YIS <mark>T</mark> IGI	DFKIRTVDIEGK	KIKLQV
RAB8A	MAKTYDYLF <mark>KLLL</mark>	IGDSG <mark>V</mark> GKT	CVLFRFSEDAFNST	-FIS <mark>T</mark> IGI	IDFKIRTIELDGK	RIKLQI
RAB8B	MAKTYDYLFKLLL	IGDSG <mark>V</mark> GKT	CLLFRFSEDAFNTT	-FIS <mark>T</mark> IGI	IDFKIRTIELDGK	KIKLQI
RAB10	MA TYDLLFKLLL	IGDSGVGK	CVLFRFSDDAFNTT	-FISTIGI	IDFKIKTVELQGK	KIKLQI
RAB12	ML PADFKLQVII	IGSRGVGKI	SLMERFTDDTFCEA	-CKSTVG	DFKIKTVELRGK	KIRLQI
RABSC	MR^NFDYMFKLLL	IGNSSVGKI	SFLFRYADDSFTSA	-FVSIVGI	DFKVKTVFKNEK	BIKTOI
RAB3B	MA^NFDYMFKLLI	IGNSSVGKT	SFLFRYADDTFTPA	-FVSTVG	DFKVKTVYRHEK	RVKLOI
RAB3D	MA^NFDYMFKLLL	IGNSSVGKT	SFLFRYADDSFTPA	-FVSTVGI	DFKVKTVYRHDK	RIKLÕI
RAB40A	MS^AYDFLLKFLL	VGDRD <mark>V</mark> GKS	EILESLQDGAAESP	-YSHLGGI	IDYKTTTILLDGQR	VKLKL
RAB40B	MS^AYDFLLKFLL	VGDSD <mark>VGK</mark> O	EILASLQDGAAESP	-YGHPAGI	IDYKTTTILLDGRR	VKLQL
RAB40C	MG^SYDYLLKFLL	VGDSDVGKO	GEILESLQDGAAESP	-YAYSNG]	IDYKTTTILLDGRR	VKLEL
RAB15	MAKQYDVLFRLLL		CLLCRFTDNEFHSS	-HISTIG	DFRMKTIEVDGIK	VRIQI
RAD44 RAB27A	MG^DVDVLTKFLA	LGDSRVGK	SPLHLLHQNSFAIG	- EIAIVG	DFRVKILLVDNKC	
RAB27B	MT^DYDYLIKITA	LGDSGVGK	TFLYRYTDNKFNPK	-FITTVG	DFREKRVVYNAOGPNGSSG	KAFKVHLOL
RASEF	ME [^] SSOKAYKIVL	AGDAAVGK	SFLMRLCKNEFREN	-ISATLG	/DFOMKTLIVDGER	TVLÕL
RAB26	ML	VGDSG <mark>V</mark> GKT	CLLVRFKDGAFLAGT	-FIS <mark>T</mark> VG]	DFRNKVLDVDGV	KVKLQM
RAB37	MD^NDHVLHKTIL	VGDSG <mark>V</mark> GKT	SLLVQFDQGKFIPGS	-FSA <mark>T</mark> VGI	IGFTNKVVTVDGV	RVKLQI
RAB2	MAYAYLFKYII	IGDTG <mark>V</mark> GKS	CLLLQFTDKRFQPV	-HDLTIG	/EFGARMITID-GK	QIKLQI
RAB2B	MTYAYLFKYII MO^TTYAYLFKYII	IGDTGVGKS	CLLLQF'I'DKRF'QPV	-HDLTIG	EFGARMVNID-GK	QIKLQI
RAB4A	MS TYDFLFKFLV	IGNAGIGKE	CLLHQFIEKKFKDD	SNHTIG	EFGSKIINVG-GK	YVKLQI
RADID RABIA	MA^NVSVIEKVII		CLUHOFTERKEMAD		/EFGSRVVNVG-GR	KIKIOI
RAB11A	MG [^] EYDYLFKVVL	IGDSGVGK	NLLSRFTRNEFNLE	-SKSTIG	/EFATRSIOVD-GK	TIKAOI
RAB11B	MG [^] EYDYLFKVVL	IGDSGVGKS	NLLSRFTRNEFNLE	-SKSTIG	/EFATRSIQVD-GK	TIKAQI
RAB25	M <mark>G</mark> ^DYNFVF <mark>KVVL</mark>	IGESG <mark>V</mark> GKT	NLLSRFTRNEFSHD	-SRT <mark>T</mark> IG	/EFSTRTVMLG-TA	AVKAQI
RAB39	METIWIYQFR <mark>LIV</mark>	IGDST <mark>V</mark> GKS	CLLHRFTQGRFPGLRSPA	-CDP T VG	/DFFSRLLEIEPGK	RIKLQL
RAB39B	MEAIWLYQFRLIV	IGDSTVGKS	CLIRRFTEGRFAQV	-SDPTVG	/DFFSRLVEIEPGK	RIKLQI
2014/5 DAD42	ML PADFKLQVII				DFKIKIVELRGKK	IKLQI
RAB12	MH^NEDYLEKTTL	IGDSNVGK	CVVOHEKSGVYTET		DETVRSLDID-GK	KAKWOA
RAB43	MA^OYDFLFKLVL	VGDASVGKT	CVVORFKTGAFSER	-OGSTIG	DFTMKTLEIO-GK	RVKLOI
RAB30	MS [^] DYDFLF <mark>KIVL</mark>	IGNAGVGKT	CLVRRFTQGLFPPG	-QGATIG	DFMIKTVEIN-GE	KVKLÕI
RAB33A	MA^VQIRIF <mark>KIIV</mark>	IGDSN <mark>V</mark> GKT	CLTFRFCGGTFPDK	-TEA <mark>T</mark> IG\	/DFREKTVEIE-GE	KIKVQV
RAB33B	MA^ARSRIFKIIV	IGDSNVGK	CLTYRFCAGRFPDR	-TEATIG	/DFRERAVEID-GE	RIKIQL
RAB18	MDEDVLTTLKILI	IGESGVGKS	SLLLRFTDDTFDPE	-LAATIG	DFKVKTISVDGNK	AKLAI
RABI/ DAB5A	MA SUPRVFKLVL	LGESAVGK	SLALRIVENDFES		AFFIRVVDVGAIS	UKEET
RAB5C	MA^NKICOFKLVL	LGESAVGK	SLVLRFVKGOFHEY	-OESTIG	AFLTOTVCLDDTT	VKFET
RAB5B	MT [^] SKICOFKLVL	LGESAVGKS	SLVLRFVKGOFHEY	-ÕESTIGA	AFLTOSVCLDDTT	VKFEI
RAB22A	MALRELKVCL	LGDTG <mark>V</mark> GKS	SIVWRFVEDSFDPN	- ÎNP <mark>T</mark> IGA	ASFMTKTVQYQNEL	HKFLI
RAB31	MMAIRELKVCL	LGDTG <mark>V</mark> GKS	SIVCRFVQDHFDHN	-ISP <mark>T</mark> I G A	ASFMTKTVPCGNEL	HKFLI
RAB21	MA~GRAYSFKVVL	LGEGCVGK	SLVLRYCENKFNDK	-HITTLQA	ASFLTKKLNIGGKR	VNLAI
RAB20	MRKPDSKIVL.	LGDMNVGKI	SLLQRYMERRFPD	-TVSTVGC	JAFYLKQWRS	YNISI
RAB24 RAB6A	MSCORVDVRVVM.	LGEOSVGKI	SLVERIVEDRFLVGP		DFLSKTMYLEDRT	
RAB6C	MS^NPLRKFKLVF	LGEOSVAK	SLITRFRYDSFDNT	-YOAIIGI	IDFLSKTMYLEDGT	IGLRL
RAB6B	MS [^] NPLRKF <mark>KLV</mark> F	LGEQSVGKT	SLITRFMYDSFDNT	-YQATIGI	DFLSKTMYLEDRT	VRLQL
RAB41	MS [^] QSLCKS <mark>KLL</mark> F	LGEQS <mark>V</mark> GKT	SIISRFMYNSFGCA	-CQA <mark>T</mark> VGI	IDFLSKTMYLEDQI	VQLQL
RAB34	MN^VGFKISKIIV	VGDLS <mark>V</mark> GKT	CLINRFCKDTFDKN	-YKA <mark>T</mark> IG	/DFEMERFEVLGIP	FSLQL
RAB36	MV VGLKLSKVVV	VGDLYVGK	SLIHRFCKNVFDRD	-YKATIG	DFEIERFEIAGIP	YSLQI
RAB/LL RAB/CL	MC^SPDULFKVLV	VGDAAVGK	SLVQKISQDSFSKH	- IKSIVG		ETAKTŐT
RAB32	MA^TREHLFKVLV	IGELGVGK	SIIKRYVHOLFSOH	-YRATTC	/DFALKVLNWDSR	TLVRLOL
RAB38	MQ^HKEHLYKLLV	IGDLGVGKT	SIIKRYVHQNFSSH	-YRATIG	/DFALKVLHWDPE	TVVRLOL
RAB23	ML^DMEVAIKMVV	VGNGA <mark>V</mark> GKS	SMIQRYCKGIFTKD	-YKK <mark>T</mark> IG	/DFLERQIQVND	EDVRLÑL
RAB28	MS^SQDRQLKIVV	LGDGTSGKT	SLTTCFAQETFGKQ	-YKQ <mark>T</mark> IGI	DFFLRRITLPGN	LNVTLQI
RABL4	MVKLAAKCI	LADPAVGK	ALAQIFRSDGAHFQKS	-YTLTTGN	MDLVVKTVPVPDTG	DSVELFI
KAB/ DAB7D	MISRKKVLLKVII.		SLMNQYVNKKFSNQ		ADLPLIKEAMADD	KLVTMQI
RAB9R	MSGKSLITKALL	LGDGGVGK	SLMNRYVTNKEDSO		ZEFLNRDLEVDG	BEALIUI
RAB9A	MAGKSSLFKVIL	LGDGGVGKS	SLMNRYVTNKFDTQ	-LFHTIG	/EFLNKDLEVDG	HFVTMQI

	Continued	\rightarrow
DAM		T
RAN RABL2A	WDTAGQEKFGGLRDGYYIQAQCAIIMFDVTS-RVTYKNVPNWHRDLVRVCENIPIVLCGNKV WDTAGOERFOSMHASYYHKAHACIMVEDIOR-KVTYRNLSTWYTELREFRPEIPCIVVANKI	
RABL2B	WDTAGQERFQSMHASYYHKAHACIMVFDVQR-KVTYRNLSTWYTELREFRPEIPCIVVANKI	DD
RABL3	WDVGCSVGSASSVKSTRAVFYNSVNGIIFVHDLTN-KKSSQNLRRWSLEALNRDLVPTG^QIPLLVIGTKL	DQ
RABL5 RAB1A	WDCGGDAKFESCWPALMKDAHGVVIVFNADI-PSHRKEMEMWYSCFVQQPSLQDTQCMLIAHHKP WDTAGOERFRTITSSYYRGAHGIIVVYDVTD-OESFNNVKOWLOFIDRYASENVNKLLVGNKC	DL
RAB1B	WDTAGQERFRTITSSYYRGAHGIIVVYDVTD-QESYANVKQWLQEIDRYASENVNKLLVG <mark>NK</mark> S	DL
RAB35	WDTAGQERFRTITSTYYRGTHGVIVVYDVTS-AESFVNVKRWLHEIN-QNCDDVCRILVGNKN	DD
RABI3 RAB8A	WDTAGQERFRTITTAYYRGAMGIILVYDITD-EKSFENIQNWMKSIKENASAGVERLLLGNKC WDTAGOERFRTITTAYYRGAMGIMLVYDITN-EKSFDNIRNWIRNIEEHASADVEKMILGNKC	
RAB8B	WDTAGOERFRTITTAYYRGAMGIMLVYDITN-EKSFDNIKNWIRNIEEHASSDVERMILGNKC	DM
RAB10	WDTAGQERFHTITTSYYRGAMGIMLVYDITN-GKSFENISKWLRNIDEHANEDVERMLLGNKC	DM
RABIZ RABIZ	WDTAGQERFNSITSAYYRSAKGIILVYDITK-KETFDDLPKWMKMIDKYASEDAELLLVGNKL WDTAGOERYRTTTTAYYRGAMGFILMYDTTN-EESFNAVODWSTOIKTYSWDNAOULLVGNKC	DC MC
RAB3C	WDTAGQERYRTITTAYYRGAMGFILMYDITN-EESFNAVQDWSTQIKTYSWDNAQVILVGNKC	DM
RAB3B	WDTAGQERYRTITTAYYRGAMGFILMYDITN-EESFNAVQDWATQIKTYSWDNAQVILVG <mark>NK</mark> C	DM.
RAB3D RAB15	WDTAGQERYRTITTAYYRGAMGFLLMYDIAN-QESFAAVQDWATQIKTYSWDNAQVILVG <mark>NK</mark> C WDTAGOEDYOTITKOVYRDAOGIELWYDISS-ERSYOHIMKWYSDVDEVGD-ATSLOGCGEGA	SP
RAB44	WDTAGQERYHSMTRQLLRKADGVVLMYDITS-QESFAHVRYWLDCLQDAGSDGVVILLLG <mark>NK</mark> M	iDC
RAB27A	WDTAGQERFRSLTTAFFRDAMGFLLLFDLTN-EQSFLNVRNWISQLQMHAYCENPDIVLCGNKS	DL
RAB27B RASEF	WDTAGQMRFRSLTTAFFRDAMGFLLMFDLTS-QQSFLNVRNWMSQLQANAYCENPDIVLIGNKA WDTAGOERFRSTAKSYFRKADGVLLLVDVTC-EKSFLNIREWVDMIEDAAH-ETVPIMLVGNKA	. ДЦ
RAB26	WDTAGQERFRSVTHAYYRDAHALLLLYDVTN-KASFDNIQAWLTEIHEYAQHDVALMLLGNKV	DS
RAB37	WDTAGQERFRSVTHAYYRDAQALLLLYDITN-KSSFDNIRAWLTEIHEYAQRDVVIMLLG <mark>NK</mark> A	DM
RAB2 RAB2B	WDTAGQESFRSITRSYYRGAAGALLVYDITR-RDTFNHLTTWLEDARQHSN-SNMVIMLIGNKS WDTAGOESFRSITRSYYRGAAGALLVYDITR-RETFNHLTSWLEDAROHSS-SNMVIMLIGNKS	
RAB4A	WDTAGQERFRSVTRSYYRGAAGALLVYDITS-RETYNALTNWLTDARMLAS-QNIVIILCGNKK	DL
RAB4B	WDTAGQERFRSVTRSYYRGAAGALLVYDITS-RETYNSLAAWLTDARTLAS-PNIVVILCGNKK	DL
RAB14 RAB11A	WDTAGQERFRAVTRSYYRGAAGALMVYDITR-RSTYNHLSSWLTDARNLTN-PNTVIILIGNKA WDTAGOERYRATTSAYYRGAVGALLVYDIAK-HLTYENVERWLKELRDHAD-SNIVIMLVGNKS	
RAB11B	WDTAGQERYRRITSAYYRGAVGALLVYDIAK-HLTYENVERWLKELRDHAD-SNIVIMLVGNKS	DL
RAB25	WDTAGLERYRAITSAYYRGAVGALLVFDLTK-HQTYAVVERWLKELYDHAE-ATIVVMLVGNKS	DL
RAB39 RAB39B	WDTAGQERFRSITRSYYRNSVGGFLVFDITN-RRSFEHVKDWLEEAKMYVQPFRIVFLLVGHKC WDTAGOERFRSITRAVVRNSVGGLLFDITN-RRSFEHVKDWLEETKVHVOPYOIVFULVGHKC	
201475	WDTAGQERFNSITSAYYRSAKGIILVYDITK-KETFDDLPKWMKMIDKYASEDAELLLVG <mark>NK</mark> L	DC
RAB42	WDTAGHERFRCITRSFYRNVVGVLLVFDVTN-RRSFEHIQDWHQEVMATQGPDKVIFLLVGHKS	DL
RAB19 RAB43	WDTAGQERFRTITQSYYRSAHAAIIAYDLTR-RSTFESIPHWIHEIEKYGA-ANVVIMLIGNKC WDTAGOERFRTITOSYYRSANGAILAYDITK-RSSFLSVPHWIEDVRKYAG-SNIVOLLIGNKS	
RAB30	WDTAGQERFRSITQSYYRSANALILTYDITC-EESFRCLPEWLREIEQYAS-NKVITVLVGNKI	DL
RAB33A	WDTAGQERFRKSMVEHYYRNVHAVVFVYDVTK-MTSFTNLKMWIQECNGHAVPPLVPKVLVGNKC	DL
RAB33B RAB40A	WDTAGQERFRKSMVQHYYRNVHAVVFVIDMIN-MASFHSLPSWIEECKQHLLANDIPRILVGNKC WDTSGOGRFCTIFRSYSRGAOGVILVYDIAN-RWSFEGMDRWIKKIEEHAPGVPKILVGNRL	HI.
RAB40B	WDTSGQGRFCTIFRSYSRGAQGVILVYDIAN-RWSFDGIDRWIKEIDEHAPGVPKILVGNRL	HL
RAB40C	WDTSGQGRFCTIFRSYSRGAQGILLVYDITN-RWSFDGIDRWIKEIDEHAPGVPRILVGNRL	HL
RABI8 RAB17	WDTAGQERFRTLTPSYYRGAQGVILVYDVTR-RDTFVKLDNWLNELETYCTRNDIVNMLVGNKI WDTAGOEKYHSVCHLYFRGANAALLVYDTTR-KDSFLKAOOWLKDLEEELHPGEVLVMLVGNKT	ם- דמי.
RAB5A	WDTAGQERYHSLAPMYYRGAQAAIVVYDITN-EESFARAKNWVKELQRQASP-NIVIALSGNKA	DL
RAB5C	WDTAGQERYHSLAPMYYRGAQAAIVVYDITN-TDTFARAKNWVKELQRQASP-NIVIALAGNKA	DL
RAB22A	WDTAGOERFRSLAPMYYRGAQAAIVVIDIIN-QEIFARARIWVRELQRQASP-SIVIALAGNRA WDTAGOERFRALAPMYYRGSAAAIIVYDIIK-EETFSTLKNWVKELROHGPP-NIVVAIAGNRC	
RAB31	WD <mark>TAGQ̃E</mark> RFHSLAPMYYRGSAAAVIVY <mark>D</mark> ITK-QDSFYTLKKWVKELKẼHGPE-NIVMAIAG <mark>NK</mark> C	DL.
RAB21	WDTAGQERFHALGPIYYRDSNGAILVYDITD-EDSFQKVKNWVKELRKMLGN-EICLCIVGNKI	DL
RAB20 RAB24	WDTAGSERYEAMSRIYYRGAKAAIVCYDLTD-SSSFERAKFWVKELRTLEEGCOIYLCGTKS	
RAB6A	WDTAGQERFRSLIPSYIRDSAAAVVVYDITN-VNSFQQTTKWIDDVRTER-GSDVĨIMLVG <mark>NK</mark> T	'DL
RAB6C	WDTAGQERLRSLIPRYIRDSAAAVVVYDITN-VNSFQQTTKWIDDVRTER-GSDVIITLVGNRT	
RAB41	WDTAGOERFHSLIPSIIRDSIIAVVVIDIIN-LNSFQUISAWIDDVRIER-GSDVIIMLVGNKI WDTAGOERFHSLIPSIIRDSIIAVVVVDIIN-INSFKETDKWVEHVRAER-GDDVVIMLLGNKI	DL
RAB34	WDTAGQERFKCIASTYYRGAQAIIIVFNLND-VASLEHTKQWLADALKENDPSSVLLFLVG <mark>SK</mark> K	DL
RAB36	WDTAGQEKFKCIASAYYRGAQVIITAFDLTD-VQTLEHTRQWLEDALRENEAGSCFIFLVGTKK	
RAB29	WDIAGQERFTSMTRLYYRDASACVIMFDVTN-ATTFSNSQRWKQDLDSKLTLPSGEPVPCLLLANKS	
RAB32	WDIAGQERFGNMTRVYYKEAVGAFVVFDISR-SSTFEAVLKWKSDLDSKVHLPNGSPIPAVLLANKC	DQ
RAB38 RAB23	WDIAGQERFGNMTRVYYREAMGAFIVFDVTR-PATFEAVAKWKNDLDSKLSLPNGKPVSVVLLANKC	DQ
RAB28	WDIGGQTIGGKMLDKYIYGAQGVLLVYDITN-YOSFENLEDWYTVVKKVSEESE-TOPLVALVGNKI	DL
RABL4	FDSAGKELFSEMLDKLWESPÑVLCLVYDVTN-EESFNNCSKWLEKARSQAPGISLPGVLVG <mark>NK</mark> T	DL
RAB7 RAB7R	WDTAGQERFQSLGVAFYRGADCCVLVFDVTA-PNTFKTLDSWRDEFLIQASPRDPENFPFVVLGNKI	DL
RAB9B	WDTAGQERFKSLRTPFYRGADCCLLTFSVDD-RQSFENLGNWQKEFIYYADVKDPEHFPFVVLGNKV	DK
RAB9A	WDTAGQERFRSLRTPFYRGSDCCLLTFSVDD-SQSFQNLSNWKKEFIYYADVKEPESFPFVILG <mark>NK</mark> I	DI

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PAN	$\frac{G5}{G5}$
RABL2A	INVTOKARSIFARKTS-LPLYFVSAADGTNVVKLFNDAIRLAVSYKONSODFM^SSIETPSEEVASPHS
RABL2B	${\tt INVT} \widetilde{{\tt Q}} {\tt KSFNFAKKFS-LPLYFV} \widetilde{{\tt SA}} {\tt ADGTNVVKLFNDAIRLAVSYK} \widetilde{{\tt Q}} {\tt NS} \widetilde{{\tt Q}} {\tt DFM}^{-} {\tt SSIETPSEEAASPHS}$
RABL3	IHETKRHE^AEDFNPEEINLDCTNPRYLAAGSSNAVKLSRFPKVIEKRYFLREGNQIPG^DRKRFGAGTLKSLHYD
RABL5	GDDKGSLSLSPPLNK-LKLVH-SNLEDDPEEIKMEFIKYLKSIINSMSESRDREEMSIMT
RABIB	TTKKVVDITTAKEFADSLG-IPFLETSAKNATIVEOAFMIMAAEIKKRMGPGAASG^DSTPVKPAGGGCC
RAB35	PERKVVETEDAYKFAGQMG-IQLF <mark>ETSAK</mark> ENVNVEEMFNCITELVLRAKKDNLAKQ [^] KLTKNSKRKKRCC
RAB13	EAKRKVQKEQADKLAREHG-IRFF <mark>ETSAK</mark> SSMNVDEAFSSLARDILLKSGGRRSGN^LKTCDKKNTNKCSLG
RAB8A DAB8B	NDKRQVSKERGEKLALDYG-IKFMETSAKAN IN VENAFF'ILARDIKAKMDKKLEGN PDQCKRSSFFRCVLL
RAB10	NDKRQ VSREGECIAREHG - IRFFETSAKANINIEKAFITIARDIIRKUMAN SEGGVTGWISKCC
RAB12	ETDREITRQQGEKFAQQITGMRFC <mark>EASAK</mark> DNFNVDEIFLKLVDDILKKMPLDILRN [^] PELPPP <mark>R</mark> PHVRCC
RAB3A	EDERVVSSERGRQLADHLG-FEFF <mark>EASAK</mark> DNINVKQTFERLVDVICEKMSESLDTA^LSDQQVPPHQD <mark>C</mark> AC
RAB3C	EDERVISTERGQHLGEQLG-FEFFETSAKDNINVKQTFERLVDIICDKMSESLETD'LKETPPPQPNQAC
RAB3D	EDERVVFIENGQLIMEGUIG-FEFFEASAKENINVKOVFELIVDVICEKMNESIEPS^VGDAPAPOPSSOSO
RAB15	GKARRGPDGKANASRKLCL-PQPWMKTSGTHQKASRRSLLGIRLMRSRNGRWEESK^QVPAPTSTIKSHSRV
RAB44	EEERQVSVEAGQQLAQELG-VYFG <mark>ECSA</mark> ALGHNILEPVVNLAR
RAB27A	EDQRVVKEEEAIALAEKYG-IPYFETSAANGTNISQAIEMLLDLIMKRMERCVDKS DQLSEEKEKGAGGC
RASEF	PDQREVNBCQRELANTG-IFFEISARIGQNVERAVEILDDIMRKWEQCVERI RDTAATE^KCVPGHFGEKLANTYGALFCETSAKDGSNIVEAVLHLAREVKKRTDKDSRS^TNSKKSPOMKNCCNG
RAB26	AHERVVKREDGEKLAKEYG-LPFM <mark>ETSAK</mark> TGLNVDLAFTAIAKELKQRSMKAPSEP [^] DYV <mark>KR</mark> EG <mark>R</mark> GAS <mark>CC</mark> RP
RAB37	SSERVIRSEDGETLAREYG-VPFLETSAKTGMNVELAFLAIAKELKYRAGHQADEP^DYVESQKKRSSCCSFM
RAB2	ESRREVKKEEGEAFAREHG-LIFMETSAKTASNVEEAFINTAKEIYEKIQEGVFDI "GNQGGQQAGGGCC
RAB2B	DADREVIFLEASRFACENE-IMFLETSALIGENVEEAFVOCARKIINKIESGELDP^PRACCAPADOECG
RAB4B	dperevtfleasrfaqene-lmfl <mark>etsal</mark> tgenveeaflkcartilnkidsgeldp^p <mark>r</mark> saqavapqp <mark>cgc</mark>
RAB14	EAQRDVTYEEAKQFAEENG-LLFL <mark>EASAK</mark> TGENVEDAFLEAAKKIYQNIQDGSLDL^LTSEPQPQREGCGC
RABIIA DABIID	RHLRAVPTDEARAFAEKNG-LSFIETSALDSTNVEARAFQTLLTEIYRIVSQKQMSD PPTTENKPKVQCCQNI
RAB11D RAB25	SOARE VPTEEARMFAENNG - LIFLETSALDSTNVELAFETING ITAKUSKORONS ^WFOISDGSLFTAPSGS
RAB39	AŠQRQVTREEAEKLSADCG-MMYIETSAKDATNVEESSTILTRDIFDLIKKĞEICI^PSEEAVKPRKECSC
RAB39B	DTQRQVTRHEAEKLAAAYG-MKYI <mark>ETSA</mark> RDAINVEKAFTDLTRDIYELVKRGEITI^SSEEVVKSE <mark>RRCLC</mark>
201475 BAB42	ETDREITRQQEKFAQQITGMRFCEASAKDNFNVDEIFLKLVDDILKKMPLDILRN"PELPPPRPHVRCC
RAB12 RAB19	WEKRHVJAGEAEDIABABIG-MATVETSAKESKNIEEVFVLMAKELIARNSLHLYGE^LMAOGPSEKTHOTO
RAB43	SELREVSLAEAQSLAEHYDILCAI <mark>ETSAK</mark> DSSNVEEAFLRVATELIMRHGGPLFSE [^] LNS <mark>K</mark> DIGEGWG <mark>C</mark> GC
RAB30	AERREVSQQRAEEFSEAQD-MYYLETSAKESDNVEKLFLDLACRLISEARQNTLVN^PGEGKSISYLTCCNFN
RAB33A DAB33B	REQIQVPSNLALKFADAHN-MLLFETSAKDPKESQNVESIFMCLACRLKAQKSLLY EFPQEANSKTSOPC
RAB40A	AFKROVPREOAOAYAERLG-VTFFEVSPLCNFNIIESFTELARIVLIRHRMMLGR^OSPFNCTENSCKIS
RAB40B	AFKRQVPTEQAQAYAERLG-VTFFEVSPLCNFNITESFTELARIVLLRHGMDRLWR^QSPPKNCTRNSCKIS
RAB40C	AFKRQVPTEQARAYAEKNC-MTFFEVSPLCNFNVIESFTELSRIVLMRHGMEKIWR ² QSPPQNCSRSNCKIS
RABI8 RAB17	KENRE VDRNEGLKFARKHS-MLFIEASAKITCDGVQCAFEELVEKIIQTPGLWESEN EGQGGAACGGUSVL SOF PFVTFOGKFEFADSOK - LIFNFTSAKINHOVSFVENTVAOFLIOPSDFFGOAL ^AIMGDADAKOGAH
RAB5A	ANKRAVDFOEAOSYADDNS-LLFMETSAKTSMNVNEIFMAIAKKLPKNEPONPGAN^LTEPTOPTRNOCCSN
RAB5C	askravefqeaqayaddns-llfm <mark>etsak</mark> tamnvneifmaiakklpknepqnatga^lqennPas <mark>r</mark> sq <mark>cc</mark> sn
RAB5B	ANKRWVEYEEAQAYADDNS-LLFMETSAKTAMNVNDLFLAIAKKLPKSEPQNLGGA^LHEQSQQNKSQCCSN
RABZZA RAB31	IDVREVMERDARDIADSIH-AIFVEISANAININEEIEISRRIPSIDANLPSGE LARVESSEARSCC SDIREVPILKDAKEVAESIC-AIVVETSAKNAININEELEOGISROIPULDHENGNN ^VEVETMOASERCC
RAB21	EKERHVSIQEAESYAESVG-AKHYHTSAKQNKGIEELFLDLCKRMIETAQVDERAK^DEPQAQTSGGGCCSSG
RAB20	TEEGALAGQEKEEDEQD-VPAAE-QMCF <mark>ETSAK</mark> TGYNVDLLFETLFDLVVPMILQQRAER^SHKPPKNTRSGCCA
RAB24	LEEDQERRVDFHDVQDYADNIK-AQLFETSSKTGQSVDELFQKVAEDVSVAAFQVMTE''LGQKPMPYFYSCCHH
RAB6C	ADKRQ - VSILEGE - RKAKGIN - WFIEISAAGIN KQUFRKVAAALPGMESIQDES KAKGEVSEGGSQ¥
RAB6B	ADKRQITIEEGEQRAKELS-VMFIETSAKTGYNVKQLFRRVASALPGMENVQEKSK^KPQEPPASEGGCSC
RAB41	DNKRQVTAEQGEEKSRNLN-VMFI ETSAK TGYNVKKLFRRVASALLSTRTSPPPKEÊELESFE <u>ESG</u> NR <mark>SYC</mark>
RAB34 PAB36	STPAQYALMEKDALQVAQEMK-AEYWAVSSLTGENVREFFFRVAALTFEANVLAELEK'LYLTASKKKPTCCP
RAB7L1	SPWAVSRD-OIDRFSKENGFTGWTETSVKENKNINEARRVLIEKMMRNSTEDIMSL'NLOTK-SSSWGC
RAB29	SPWAVSRDQ̃IDRFSKENGFTGWT <mark>ETS</mark> VKENKNINEAMRVLVEKMMNNSREDIMSS^NLQ̃TKPSPGWTCC
RAB32	NKDSSQSP-SQVDQFCKEHGFAGWF <mark>ETSAK</mark> DNINIEEAARFLVEKILVNHQSFPNEE [^] QETL <mark>R</mark> AENKSQCC
RAB38	GKDVLMNNGLKMDQFCKEHGFVGWF <mark>ETSAKENINIDEASRCLVKHILANECDLMESI</mark> LTSTKVASCSCAKS
RAB28	EHMRTIKPEKHLRFCOENG-FSSHFVSAKTGDSVFLCFOKVAAEILGIKLNKAEIE^NOHTTSTOSTICSVO
RABL4	AGRRAVDSAEARAWALGQG-LECF <mark>ETSVK</mark> EMENFEAPFHCLAKQFHQLYREKVEVFRALA
RAB7	ENRQVATKRAQAWCYSKNNIPYF <mark>ETSAK</mark> EAINVEQAFQTIARNALKQETEVELYN [^] KNDRAKASAESCSC
RAB7B	ADKKVPQEVAQGWCKEK-DIPYFEVSAKNDINVVQAFEMLASKALSKYQSILENHLTESIKLSPDQSK FDROVTTE-FAOTWOMENGDVDVLETSKAKNDINVVQAFEMLAVDOVLAVEFALEVEMA DINGCOVACOS
RAB9A	SERQVSTEEAQAWCRDNGDYPYF <mark>ETSAK</mark> DATNVAAAFEEAVRRVLATEDRSDHLI [^] NLH <mark>RK</mark> PKPSSS <mark>CC</mark>

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.

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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).

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

	N terminus		\rightarrow
		Gl	G2
GNAL	MGC [^] KTTEDQGVDEKERREANKKIEKQLQKERLAYKATH	LLLLGAGESGKSTIVKOMRILHVN^	RCRVLTSGIFE
GNAS	MGC [^] SKTEDORNEEKAOREANKKIEKOLOKDKOVYRATH	RLLLLGAGESGKSTIVKÕMRILHVN [*]	`RCRVL <mark>T</mark> SGIFE
GNAI1	MGCTLSAEDKAÄVERSKMIDRNLREDGEKAAREVI	LLLLGAGESGKSTIVKÕMKIIHEA [^]	`RTRVK <mark>T</mark> TGIVE
GNAI3	MGCTLSAEDKAAVERSKMIDRNLREDGEKAAKEV	ULLLGAGESGKSTIVKOMKTTHED^	`RTRVK <mark>T</mark> TGTVE
GNAT2		ULLLGAGESGKSTIVKOMKITHED^	`RTRVKTTGIVE
GNA01		T.L.L.GAGESGKSTIVKOMKITHED^	`RTRVKTTGIVE
GNAU1		TITICAGES GROTIVKOMKITHOD^	DCDVKTTCTTF
CNATT		TITICACEC CKETIVKOMKIIHOD^	CONVETCIE
GNAIZ			KSKVKIIGIIE MCDV///
GNAIS			HSKVKIIGIIE
GNAZ			RSRDMIIGIVE
GNALL	MT SMMACCLSDEVKESKRINAEIEKQLRRDKRDARREL	LLLLGTGESGKSTFIKQMRIIHGA	RVRVPTTGIIE
GNAQ	MT SIMACOLSEEAKEARRINDEIERQLRRDKRDARRELF	LLLLGTGESGKSTFIKQMRIIHGS	RAKADILGITE
GNA14		(LLLLGTGESGKSTFIKQMRIIHGS	RVRVPTTGIIE
GNA15	MA RCCPWCLTEDEKAAARVDQEINRILLEQKKQDRGELF	CLLLLGPGESGKSTFIKQMRIIHGA	RSRMPTTGINE
GNA12	MA [^] RRAGSGARDAEREARRRSRDIDALLARERRAVRRLVI	(<mark>ILLLG</mark> AGES <mark>GKS</mark> TFLKQMRIIHGR^	`LARKA <mark>T</mark> KGIVE
GNA13	MA ^C FPGCLLTSGEAEQQRKSKEIDKCLSREKTYVKRLV	<pre>(ILLLGAGESGKSTFLKQMRIIHGQ^</pre>	`LARRP <mark>T</mark> KGIHE
	Continued		_
	Concinaed		
CINTA T			mtat
GNAL		A DINTINGLESSIULFESIWNNEWLE	
GNAS	TRFQVDKVNFHMFDVGGQRDERRKWIQCFNDVTAIIYVA	A DNQTNRLQEALNLFKSIWNNRWLR	CTISV DDDGT
GNAIL	'I'HF'I'F'KDLHF'KMFDVGGQRSERKKWIHCFEGVAAIIF'CVA	A DEEMNRMHESMKLFDSICNNKWF'I	.DTSI
GNAI3	THFTFKDLYFKMFDVGGQRSERKKWIHCFEGVTAIIFCVA	A DEEMNRMHESMKLFDSICNNKWF1	ETSI
GNAI2	THFTFKDLHFKMFDVGGQRSERKKWIHCFEGVTAIIFCVA	A^DEEMNRMHESMKLFDSICNNKWF1	DTSI
GNA01	THFTFKNLHFRLFDVGGQRSERKKWIHCFEDVTAIIFCVA	A^DETTNRMHESLMLFDSICNNKFFI	IDTSI
GNAT1	TQFSFKDLNFRMFDVGGQRSERKKWIHCFEGVTCIIFIAA	A^DDEVNRMHESLHLFNSICNHRYFA	ATTSI
GNAT2	TKFSVKDLNFRMFDVGGQRSERKKWIHCFEGVTCIIFCA	A^DDEVNRMHESLHLFNSICNHKFFA	ATSI
GNAT3	TQFSFKDLHFRMFDVGGQRSERKKWIHCFEGVTCIIFCAA	A^DEEVNRMHESLHLFNSICNHKYFS	STTSI
GNAZ	NKFTFKELTFKMVDVGGQRSERKKWIHCFEGVTAIIFCVH	E^DNQTSRMAESLRLFDSICNNNWFI	INTSL
GNA11	YPFDLENIIFRMVDVGGQRSERRKWIHCFENVTSIMFLVA	A [^] SDNEN <mark>R</mark> MEESKALFRTIITYPWFQ	2NSSV
GNAQ	YPFDLQSVIFRMVDVGGQRSERRKWIHCFENVTSIMFLVA	A [^] SDNENRMEESKALFRTIITYPWFQ	NSSV
GNA14	YPFDLENIIFRMVDVGGQRSERRKWIHCFESVTSIIFLVA	A [^] CDNENRMEESKALFKTIITYPWFI	JNSSV
GNA15	YCFSVOKTNLRIVDVGGOKSERKKWIHCFENVIALIYLAS	S [^] NNOENRMKESLALFGTILELPWFK	KSTSV
GNA12	HDFVIKKIPFKMVDVGGORSOROKWFOCFDGITSILFMV8	S^DRRTNRLVESMNIFETIVNNKLFF	NVSI
GNA13	YDFEIKNVPFKMVDVGGORSERKRWFECFDSVTSILFLVS	S [^] DRLTNRLTESLNIFETIVNNRVFS	SNVSI
	Continued	C term	ninus
		\	
CIVIA T			
GNAL	ILFLINKQDMLAEKVLA YFPEYANYTVPED HYCYPHFT		2YELL XURTI
GNAS	ILFLNKQDLLAEKVLA YFPEFARYTTPED HYCYPHFT		2YELL
GNAIL	ILFLNKKDLFEEKIKK CYQEYAGSNTYEE KEIYTHFT	C <mark>A</mark> TDTKNVQFVFDAVTDVIIKNNLKI	OCGLF'
GNAI3	ILFLNKKDLFEEKIKR CYPEYTGSNTYEE KEIYTHFT	C <mark>A</mark> TDTKNVQFVFDAVTDVIIKNNLKE	≤CGLY
GNAI2	ILFLNKKDLFEEKITH^CFPEYTGANKYDE^KEIYTHFT	C <mark>A</mark> TDTKNVQFVFDAVTDVIIKNNLKI	0CGLF
GNA01	ILFLNKKDLFGEKIKK^CFPEYTGPNTYED^KEIYCHMT(C <mark>A</mark> TDTNNIQVVFDAVTDIIIANNLRO	GCGLY
GNAT1	VLFLNKKDVFFEKIKK^CFPDYDGPNTYED^KEIYSHMT	C <mark>A</mark> TDTQNVKFVFDAVTDIIIKENLKI) <mark>C</mark> GLF
GNAT2	VLFLNKKDLFEEKIKK^CFPEYDGNNSYDD^KEIYSHMT	CATDTQNVKFVFDAVTDIIIKENLKI	O <mark>C</mark> GLF
GNAT3	VLFLNKKDIFQEKVTK ^C FPEYTGPNTFED ^{KEIYSHMT}	CATDTQNVKFVFDAVTDIIIKENLKI	D C GLF
GNAZ	ILFLNKKDLLAEKIRR [^] CFPEYKGQNTYEE [^] KEIYSHF <mark>T</mark>	CATDTSNIQFVFDAVTDVIIQNNLKY	/IG <mark>LC</mark>
GNA11	ILFLNKKDLLEDKILY^YFPEFDGPQREPQ^KIIYSHFT	CATDTENIRFVFAAVKDTILQLNLKE	EYNLV
GNAO	ILFLNKKDLLEEKIMY [*] YFPEYDGPQRDAQ [*] KINYSHFT	CATDTENIRFVFAAVKDTILÕLNLKE	EYNLV
GNA14	ILFLNKKDLLEEKIMY^YFPEYTGPKODVR^KVIYSHFT	ATDTDNIRFVFAAVKDTILÕLNLR	EFNLV
GNA15	ILFLNKTDILEEKIPT^YFPSFOGPKODAE^RRLFSHYTC	ATDTONIRKVFKDVRDSVLARYLDF	EINLL
GNA12	ILFLNKMDLLVEKVKT^HFPDFRGDPHOLE^KPLFHHFT	AIDTENVREVEHAVKDTTLOENLKI	OIMLO
GNA13	ILFINKTDIJEEKVOI VELEFEGDPHCLP KOLVHUFT	TNTENTRLVERDVKDTTLHDNIK	
OWNTO	The start a property of the pr		~

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.

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

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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), G α (orange), ARF (yellow), and RAB (blue).

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	G1 b	ox	G	box	G4	box
MFN1	VLSRRHMKVAFFGRTS	GKSSVINAMLWDKVLPSG	PKAKCALLRDDLVLV	SPGTDVTTELDSWIDKFC	KVNERLSKPNIFILNN	RWDASASEPEYMEDVRRO
MFN2	VLARRHMKVAFFGRTSN	IGKSTVINAMLWDKVLPSG	PNSKCPLLKDDLVLMD	SPGIDVTTELDSWIDKFC	KVSERLSRPNIFILNN	RWDASASEPEYMEEVRRÕ
DNM2	SCHLDLPOIAVVGGOS/	GKSSVLENFVGRDFLPRG	NLRVYSPHVLNLTLID	LPGITKVPVGDOPPDIEY	AKEVDPOGLRTIGVIT	KLDLMDEGTDARDVLENŘ
DNM3	SCLLELPÕIAVVGGÕSI	GKSSVLENFVGRDFLPRG	NLRVYSPHVLNLTLID	LPGITKVPVGDÕPPDIEY	AKEVDPÕGLRTIGVIT	KLDLMDEGTDARDVLENK
DNM1	NADLDLPÕIAVVGGÕSA	GKSSVLENFVGRDFLPRG	NLRVYSPHVLNLTLVD	LPGMTKVPVGDÕPPDIEF	AKEVDPÕGORTIGVIT	KLDLMDEGTDARDVLENK
DNM1L	ADIIOLPÕIVVVGTÖSS	GKSSVLESLVGRDLLPRG	HLKIFSPNVVNLTLVD	LPGMTKVPVGDÕPKDIEL	SREVDPDGRRTLAVIT	KLDLMDAGTDAMDVLMGR
MX1	EQDLÃLPÃIAVIGDOSS	GKSSVLEALSGVAL-PRG	TLEISSRDVPDLTLID	LPGITRVAVGNÕPADIGY	AQEVDPEGDRTIGILT	KPDLVDKGTEDKVVDVVR
MX2	EQDLALPAIAVIGDOSS	GKSSVLEALSGVAL-PRG	SLEITSPEVPDLTIID	LPGITRVAVDNQPRDIGL	AHEVDPEGDRTIGILT	KPDLMDRGTEKSVMNVVR
GBP1	AITQPMVVVAIVGLYR	GKSYLMNKLAGKKKGFSL	CVPHPKKPGHILVLLD	TEGLGDVEKGDNQNDSWI	EDSADFVSFFPDFVWT	LRD FSLDLEADGQPLTPD
GBP3	AITQPVVVVAIVGLYR	GKSYLMNKLAGKNKGFSL	CVPHPKKPEHTLVLLD	TEGLGDVKKGDNQNDSWI	EDSADFVSFFPDFVWT	LRD FSLDLEADGQPLTPD
GBP2	AITQPVVVVAIVGLYRT	GKSYLMNKLAGKKNGFSL	CVPHPKKPEHTLVLLD	TEGLGDIEKGDNENDSWI	DDSADFVSFFPAFVWT	LRD FTLELEVDGEPITAD
GBP5	AITQPVVVVAIVGLYRT	GKSYLMNKLAGKNKGFSV	CVPHPNWPNHTLVLLD	TEG LGDVEKADNKNDIQI	EDPADSASFFPDLVWT	LRD FCLGLEIDGQLVTPD
GBP4	KISQPVVVVAIV <mark>GLYR</mark>	GKSYLMNRLAGKRNGFPL	CVPHLSKPNHTLVLLD	TEG LGDVEKSNPKNDSWI	EDSSEFASFFPDFIWT	VRD FTLELKLDGNPITED
XAB1	GGPRHPVCLLVLGMAG	SGKT TFVQRLTGHLHAQGT	KFIEKAQNMSKYVLI	TPG QIEVFTWSASGTIIT	CSILYKTKLPFIVVMN	KTD IIDHSFAVEWMQDFE
CENTG1	SRSIPELRLGVL <mark>GDARS</mark>	SGKSSLIHRFLTGSYQVLE	KEMLVDGQTHLVLIR	EAG APDAKFSGWADAVIF	LRGEGRGGLALALVG	DR ISASSPRVVGDARAR
CENTG2	SRSVPELKVGIV <mark>GNLAS</mark>	SGKSALVHRYLTGTYVQEE	KEIVVDGQSYLLLIRD	EGG PPEAQFAMWVDAVIF	ANYRNTSEIPLVLVG	DA ISSANPRVIDDARAR
CENTG3	SRSVPELKVGIVGNLS	GKS ALVHRYLTGTYVQEE	KEIVVDGQSYLLLIRD	EGGPPELQFAAWVDAVVF	CSFRNASEVPMVLVGT	DA ISAANPRVIDDSRAR
HRAS	MTEYKLVVVGAGG	GKSALTIQLIQNHFVDEY	KQVVIDGETCLLDILD	TAGQEEYSAMRDQYMRTG	KRVKDSDDVPMVLVGN	KCDLAARTVESRQAQDLA
RAPIA	MREYKLVVLGSGG	GKSALTVQFVQGIFVEKY	KQVEVDCQQCMLEILD	TAGTEQFTAMRDLYMKNG	LRVKDTEDVPMILVG <mark>N</mark>	KCDLEDERVVGKEQGQNL
RAC1	MQAIKCVVVGDGA	GKTCLLISYTTNAFPGEY	ANVMVDGKPVNLGLWD	TAGQEDYDRLRPLSYPQT	EVRHHCPNTPIILVGT	KLDLRDDKDTIEKLKEKK
RHOF	GPGRKELKIVIVGDGGC	GKTSLLMVYSQGSFPEHY	ASVTVGSKEVTLNLYD	TAGQEDYDRLRPLSYQNT	EVTHFCRGIPMVLIGC	KTD LRKDKEQLRKLRAAQ
RAN	GEPQVQFKLVLVGDGG	GKTTFVKRHLTGEFEKKY	LVFHTNRGPIKFNVWD	TAGQEKFGGLRDGYYIQA	DLVRVCENIPIVLCGN	KVD1KDRKVKAKS1VFHR
RAB5A	GNKICQFKLVLLGESA	GKSSLVLRFVKGQFHEFQ	QTVCLDDTTVKFEIWD	TAGQERYHSLAPMYYRGA	LQRQASPNIVIALSGN	KADLANKRAVDFQEAQSY
ARF1	LFGKKEMRILMVGLDAA	GKTTILYKLKLGEIVIII	NVETVEYKNISFTVWD	VGGQDKIRPLWRHYFQNT	LAEDELRDAVLLVFAN	KODLPNAMNAAETTDKLG
ARL4	LPSFQSFHIVILGLDCA	GKTTVLYRLQFNEFVNTV	KVILGNSKIVIFHFWD	VGGQEKLRPLWKSYTRCT	TRISENQGVPVLIVAN	KODLENSLSLSEIEKLLA
GNALL	EKAAREVKLLLLGAGEE	GKSTIVKOMKIIHEAGYS	VETHFTFKDLHFKMFD	VGGORSERKKWIHCFEGV	CNNKWFTDTSIILFLN	KKDLFEEKIKKSPLTICY
GNAS	OVIRATHRLLLLGAGES	GKSIIVKOMRILHVNGGF	FEIKFOVDKVNFHMFD	VGGORDERRKWIQCFNDV	WINNRWERTISVIEFEN.	KODLLAEKVLAGKSKIED
RRAGA	PNTAMKKKVLLMGKSGS	GKISMRSIIFANYIARDI	HSHVRFLGNLVLNLWD	CGGODTFMENYFTSORDN	AILONSPDAKIFCLVH.	KMDLVQEDQRDLIFKERE
RRAGB	CADCCKDDIIIMCLDDC	GKISMRSIIFAN IIARDI	KDDICNCCEWEOIWD	EDCOMDEEDDTEDVENIE	KAVKUNDDMNEEVELU	CI CDDUKIETODDIU
RRAGC	GADSSKPRILLMGLRR	GRESIQKVVF HAMSPNEI	DEDUCNCCEVNEOTWD	FPGQMDFFDP1FD1EM1F	DAVEUNEDINFEVEIL	CI CDDUKIETORDIU
CEDT4				TPOULDFFDFIFDIEMIF	EMEAT HODUNITUDIT	
CEDT5	VKKGFDFTLMVAGESGI		VDIEEKGVKLKLTIV	TREECDAVNNTECWKFVA	EMEAL DEVINITUDI TA	CLUDGETDVL VEDTD
GRDT1	VKKGFDFTLMVAGESGI	CKSTLINGI.FLTNI.VEDP	VEIEECGVKVKLTLVD	TPGFGDAVINNTECWICFTT	FIRADHERVNITDVTC	KAD ALMOOFTOALKOKIR
SEDT2	VKKGEFETI.MVVGESCI	CKSTLINSLFLTDLVDFP	VETEERGVKVRDITUV	TPCVCDAINCRDCEKTII	FMKATHNKUNTUDUTA	KADTI.TI.KEPEPI.KKPTI.
SEPT7	VKRGFEFTIMVVGESCI	CKSTLINSLFLTDLYSPE	VIIKEGGVOLLITIV	TPGFGDAVDNSNCWOPVI	FMKRI.HEKVNITPI.TA	KADTI TPEECOOFKKOIM
SEPT3	MKTGFDFNIMVVGOSGI	GKSTLVNTLFKSOVSRKA	HVIEEGGVKMKLTVI	TPGFGDOINNENCWEPIE	FMKHLSKVVNTTPVTA	KADTMTLEEKŠĚFKOŘVR
SEPT9	MKOGFEFNIMVVGOSGI	GKSTLINTLEKSKISRKS	HDIEEKGVRMKLTVI	TPGFGDHINNENCWOPIM	FMKRLSKVVNTVPVTA	KADTITIEERVHFKORTT
SEPT6	VSOGFCFNILCVGETGI	GKSTLMDTLFNTKFEGEP	YDLOESNVRLKLTIVS	TVGFGDOINKEDSYKPIV	TMKKLDSKVNIIPIIA	KADAISKSELTKFKĨKIT
SEPT8	VTOGESENILCVGETGI	GKSTLMNTLFNTTFETEE	YDLÕESNVOLKLTIVD	AVGFGDOINKDERPIVDY	TMKKLDSKVNIIPIIA	KADTISKSELHKFKIKIM
SEPT11	TSÕGFCFNILCVGETG1	GKSTLMDTLFNTKFESDP	YELÕESNVÄLKLTIVD	TVGFGDÕINKDDSYKPIV	TMKKLDSKVNIIPIIA	KADTIAKNELHKFKSKIM
SEPT10	IQÕGFCFNILCVGETG1	GKSTLIDTLFNTNFEDYE	YELÕESNVOLKLTIVN	TVGFGDÕINKEESYOPIV	TMKNLDSKVNIIPVIA	KADTVSKTELOKFKIKLM
DRG1	VÄKTGDARIGFVGFPS	/GKSTLLSNLAGVYSEVAA	VPGVIRYKGAKIQLLD	LPG I I EĜAKDGKGRĜROV	VVEGNRVYIPCIYVLN	KIDQISIEELÕIIYKVPH
DRG2	VMKSGDARVALIGFPS	/GKSTFLSLMTSTASEAAS	IPGVIEYKGANIQLLD	LPGIIEGAAQGKGRGRQV	VIVGNRVYMPCLYVYN	KIDQISMEEVDRLARKPN
GTPBP4	TIDPNTRTLLLCGYPN	IGKSSFINKVTRADVDVQP	FVGHMDYKYLRWQVVD	TPGILDHPLEDRNTIEMQ	NIRPLFINKPLIVVAN	KCD VKRIAELSEDDQKIF
EEF1A1	GKEKTHINIVVI <mark>GHVD</mark> S	GKS TTTGHLIYKCGGIDK	SLWKFETSKYYVTIID	APGHRDFIKNMITGTSQA	LLAYTLGVKQLIVGVN	KMDSTEPPYSQKRYEEIV
EEF1A2	GKEKTHINIVVI <mark>GHVD</mark> S	GKS TTTGHLIYKCGGIDK	SLWKFETTKYYITIID	APGHRDFIKNMITGTSQA	LLAYTLGVKQLIVGVN	KMD STEPAYSEKRYDEIV
TUFM	VRDKPHVNVGTI <mark>GHVD</mark> F	IGKT TLTAAITKILAEGGG	AHVEYSTAARHYAHTD	CPGHADYVKNMITGTAPL	LLARQIGVEHVVVYV	KADAVQDSEMVELVELEI
SPG3A	VRDKEVVAVSVAGAFRI	(GKSFLMDFMLRYM	YNQESVD	WVGDYNEPLTGFSWRGGS	RETTGIQIWSEIFLIN	KPD GKKVAVLLMDTQGTF
GTPBP1	DNDFLEVRVAVVGNVD	GKSTLLGVLTHGELDNGR	HKHEIESGRTSSVGND	ILGFDSEGNVVNKPDSHG	LGLALALNVPVFVVVT	KIDMCPANILQETLKLLQ
GTPBP2	NQQFLDLRVAVLGNVDS	GKSTLLGVLTQGELDNGR	HLHEIQSGRTSSISF	ILGFNSKEEVVNYSDSRT	LGLALALKVPFFIVVS.	KIDLCAKTTVERTVRQLE
OPA1	NTQDHLPRVVVVGDQS4	GKTSVLEMIAQARIFPRG	SLNVKGPGLQRMVLVD	LPG VINTVTSGMAPDTKE	VSQMDPHGRRTIFVL	KVDLAEKNVASPSRIQQI
GTPBP3	QRLRSGAHVVVTGPPNA	GKSSLVNLLSRKPVSIVS	LETPVDLAGFPVLLSD	TAGLKEGVGPVEQEGVRR	AQSPSDSSQRLLLVLN	KSDLLSPEGPGPGPDLPP
GTPBP5	LELKTVAHAGMVGFPNA	GKSSLLRAISNARPAVAS	VGIVHYEGHLQIAVAD	TPGIIRGAHQNRGLGSAF	MIEKGLSARPHAIVAN	TELPEAQANLSQLRDHL
ELF2S3	I SKOATINIGTIGHVAF	GKSTVVKAISGVHTVRFK	CIRSCGSSTPDEFPTD	TPGIKGNFKLVRHVSFVD	AAIEIMKLKHILILQN	KIDEWAATAAROOGUDU
VLLG EDAI1	LGDKRLFVLS1LGLQS	GKSTVLNALFGLQFTVSA	A CUITER COULT	TEGLKAPEHSNKSKDRDN	ATATDOTMDGRRRLEQ	KUDEMAAIAAEQEQCLDV
EKALL TTCD	CTECTDI EUCUT	CKOLLSNULLGKKVFPVS		L DC A C C DC C DA D V V V OV	A VETICOCYVEVEN	VUCLAUASVLLELTAAL
TIGN	CDDCCODAUTIVCI CESCA			L DOURCI DI ORI FDEVOC	Demoi KNTDERI TACN	KODTAMAKEAKI TOOOLE
CDD54	DTKCKONVINEVCLOC	CKTTTCCKLAVVODVCW	CAEKEKNENEELIIIO	TCODUKOFDCI.FFFMI OV	DONGLINIFORDIACI	KT D CHY KCCCYT CYNY Y T
SEPEA	ORRORPVINTECCUNICI	CKSTNI.AKISEWII.ENCE	GGRTMVOLFEKGVGKD	ACTAMENTAFARNOGED	HSMAOTPRI.TDGTVL	KEDTIDDKVGAAISAVAAI
MHC2TA	REPETRVIAVIGRAG	CKSYWAGAVSRAWACGRI.	DEVESVECHCLINEPGD	AVGLODILESLGPOPLVA	LILTARPRGRLVOSLS	KADALFELSGESMEDADA

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.





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**).

HONG	
HGNC name Com	non names and anases
AGTPBPI	ATP/GTP-binding protein 1, Nna1
AKTI	Akt, PKB
ANXA6	annexin 6
APPL1	DIP13 α , 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 α 1, eEF1A, eEF1 α
EEF1A2	eukaryotic translation elongation factor 1 $\alpha 2$
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, y-adaptin-ear-containing, Arf-binding
GMIP	GEM interacting protein, Gmip
GNA11	Ga_{11}
GNA12	$G\alpha_{12}$
GNA13	Ga ₁₃
GNA14	$G\alpha_{14}$
GNA15	Ga_{15}, Ga_{16}
GNAI1	Ga _{i-1}
GNAI2	Ga _{i-2}
GNAI3	Ga _{i-3}
GNAL	$G\alpha_{l (olfactory)}$
GNAO	Gα _o
GNAQ	Gα _q
GNAS	Gas
GNAT1	transducin 1
GNAT2	transducin 2
GNAT3	transducin 3, gustducin
GNAZ	Gα _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, $I\kappa B$
NGB	neuroglobin, Nog1

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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 p110a
PIK3CB	phosphoinositide-3-kinase p110β
PIK3CD	phosphoinositide-3-kinase p1108
PIK3CG	phosphoinositide-3-kinase p110γ
PKN1-3	protein kinase N, PRK, DBK
PLCB	ΡLCβ
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

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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

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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