The Ras superfamily at a glance

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The Ras superfamily of small guanosine triphosphatases (GTPases) comprise over 150 human members (Table S1 in supplementary material), with evolutionarily conserved orthologs found in Drosophila, C. elegans, S. cerevisiae, S. pombe, Dictyostelium and plants (Colicelli, 2004). The Ras oncogene proteins are the founding members of this family, which is divided into five major branches on the basis of sequence (Fig. S1 in supplementary material) and functional similarities: Ras, Rho, Rab, Ran and Arf. Small GTPases share a common biochemical mechanism and act as binary molecular switches (Vetter and Wittinghofer, 2001). Although similar to the heterotrimeric G protein α subunits in biochemistry and function, Ras family proteins function as monomeric G proteins. Variations in structure (Biou and Cherfils, 2004), post-translational modifications that dictate specific subcellular locations and the proteins that serve as their regulators and effectors allow these small GTPases to function as sophisticated modulators of a remarkably complex and diverse range of cellular processes. Here, we present the basic structural features of Ras proteins, with respect to specific Ras sequences, to highlight the general properties of this family of proteins and discuss features that distinguishes the various branches of the superfamily from Ras.

Ras superfamily structure

Ras superfamily GTPases function as GDP/GTP-regulated molecular switches (Vetter and Wittinghofer, 2001). They share a set of conserved G box GDP/GTP-binding motif elements beginning at the N-terminus: G1,
GXXXGKS/T; G2, T; G3, DXXQ0/H/T; G4, T/NKXD; and G5, C/SAX/L/T (Bourne et al., 1991) (Fig. S1 in supplementary material). Together, these elements make up an ~20 kDa G domain (Ras residues 5-166) that has a conserved structure and biochemistry shared by all Ras superfamily proteins, as well as Gα and other GTPases.

**Ras superfamily GTPase biochemistry and regulation**

Small GTPases exhibit high-affinity binding for GDP and GTP, and possess low intrinsic GTP hydrolysis and GDP/GTP exchange activities. GDP/GTP cycling is controlled by two main classes of regulatory protein. Guanine-nucleotide-exchange factors (GEFs) promote formation of the active, GTP-bound form (Schmidt and Hall, 2002), whereas GTPase-activating proteins (GAPs) accelerate the intrinsic GTPase activity to promote formation of the inactive GDP-bound form (Bernards and Settleman, 2004). GTPases within a branch use shared and distinct GAPs and GEFs. GTPases in different branches exhibit structurally distinct but mechanistically similar GAPs and GEFs. The two nucleotide-bound states have similar conformations but these have pronounced differences corresponding to the switch I (Ras residues 30-38) and switch II (59-67) regions: the GTP-bound form (Bernards and Hall, 2000; Repasky et al., 2004). The two switches undergo significant conformational changes during GDP/GTP cycling. Although the GTP-bound form is the active form for all Ras superfamily GTPases, the cycling between the GDP-bound and GTP-bound states, in which distinct functions are associated with each nucleotide-bound form, is also critical for the activities of Rab, Arf and Ran GTPases. The core effector domain (Ras residues 32-40) includes the switch I domain and is critical for direct association with effectors (Herrmann, 2003).

**Lipid modification and membrane targeting**

A second important biochemical feature of a majority of Ras superfamily proteins is their post-translational modification by lipids. The majority of Ras and Rho family proteins terminate with a C-terminal CAAX (C=Cys, A=aliphatic, X=any amino acid) tetrapeptide sequence (Cox and Der, 2002). This motif, when coupled together with residues immediately upstream (e.g. cysteine residues modified by the fatty acid palmitate), comprises the membrane-targeting sequences that dictate interactions with distinct membrane compartments and subcellular locations. The CAAX motif is the recognition sequence for farnesyltransferase and geranylgeranyltransferase I, which catalyze the covalent addition of a farnesyl or geranylgeranyl isoprenoid, respectively, to the cysteine residue of the tetrapeptide motif. Rab family proteins terminate in a distinct set of cysteine-containing C-terminal motifs (CC, CXC, CCX, CXX, or CXXX) that are similarly modified by geranylgeranyltransferase II, which also attaches geranylgeranyl groups. Some members of the Arf family are modified at their N-termini by a myristate fatty acid. These modifications are essential for facilitating membrane association and subcellular localization critical for biological activities. Rho and Rab GTPases are regulated by a third class of proteins, guanine nucleotide dissociation inhibitors (GDIs), which mask the prenyl modification and promote cytosolic sequestration of these GTPases (Seabra and Wasseimer, 2004). Some Ras superfamily members do not appear to be modified by lipids, but still associate with membranes (e.g. Rit, RhoBTB, Miro and Sar1). Others (e.g. Ran and Rerg) are not lipid modified and are not bound to membranes.

**Subgrouping of the Ras superfamily**

The Ras superfamily has traditionally been divided into five different major branches. The classification of some less-studied proteins into these major subfamilies is arbitrary, and sequence comparisons of the G domains suggest that they may define distinct subfamilies.

In the absence of any functional data, a definitive classification of these GTPases is not yet possible. Here, we group the proteins that, on the basis of structure, function or both, clearly belong to a specific subfamily. In cases where neither structural nor functional data support putting a protein in one of the major subfamilies, we leave the protein as ‘Unclassified’ even though some of these proteins have previously been labeled as belonging to a certain subfamily. In the human genome, there are also a large number of Ras superfamily pseudogenes. We have chosen not to include gene sequences from databases where no evidence of transcription has been found. Furthermore, in addition to the proteins listed here, there are many genes that have regions predicted to encode sequences similar to parts of a small GTPase domain, but we have chosen only to include proteins that contain complete Ras-like GTPase domains.

**The Ras family**

The Ras sarcoma (Ras) oncoproteins are the founding members of the Ras family (36 members) and have been the subject of intense research scrutiny, in large part because of their critical roles in human oncogenesis (Repasky et al., 2004). Ras proteins serve as signaling nodes activated in response to diverse extracellular stimuli. Activated Ras interacts with multiple, catalytically distinct downstream effectors, which regulate cytoplasmic signaling networks that control gene expression and regulation of cell proliferation, differentiation, and survival.

The best characterized Ras signaling pathway is activation of Ras by the epidermal growth factor receptor tyrosine kinase through the RasGEF Sos (Repasky et al., 2004). Activated Ras binds to and promotes the translocation of the Raf serine/threonine kinase to the plasma membrane, where additional phosphorylation events promote full Raf kinase activation. Raf phosphorylates and activates the MEK1/2 dual specificity protein kinase, which phosphorylates and activates the ERK1/2 mitogen-activated protein (MAP) kinase. Activated ERK translocates to the nucleus, where it
phosphorylates Ets-family transcription factors, which in turn activate Ets-responsive promoters.

Other Ras family proteins, including Rap, R-Ras, Rap1 and Rheb proteins, also regulate signaling networks. Finally, although biochemically similar to Ras, several Ras family proteins appear to act as tumor suppressors, rather than as oncogenes (e.g. Rerg, Noey2 and D-Ras), in cancer development (Colicelli, 2004).

The Rho family
Like Ras, Ras homologous (Rho) proteins also serve as key regulators of extracellular-stimulus-mediated signaling networks that regulate actin organization, cell cycle progression and gene expression (Etienne-Manneville and Hall, 2002). Twenty members have been identified, RhoA, Rac1 and Cdc42 being the best studied. Rho GTPases are key regulators of actin reorganization. RhoA promotes actin stress fiber formation and focal adhesion assembly; Rac1 promotes lamellipodium formation and membrane ruffling; and Cdc42 promotes actin microspikes and filopodium formation. Consequently, Rho GTPases have been implicated in the regulation of cell polarity, cell movement, cell shape, and cell-cell and cell-matrix interactions, as well as in regulation of endocytosis and exocytosis (Ridley, 2001). Reflecting their involvement in such a diversity of cellular processes, RhoA, Rac1 and Cdc42 proteins are each regulated by a surprising diversity of GEFs and GAPs (Schmidt and Hall, 2002; Moon and Zheng, 2003) and utilize a similarly diverse set of downstream effectors (Bishop and Hall, 2000). Actin reorganization functions have also been observed for other Rho family GTPases, in particular Rnd proteins, which antagonize RhoA.

Although the Miro proteins were first described as Rho proteins, these atypical GTPases instead appear to form their own subgroup of the Ras superfamily (Wennerberg and Der, 2004). In addition to their N-terminal GTPase domain, they contain EF-hand domains and one C-terminal GTPase-like domain. They lack the insert domain that is characteristic of Rho GTPases (Fig. S1 in supplementary material). The Miro proteins do not regulate the cytoskeleton; instead they are localized to mitochondria and regulate the integrity of these cellular compartments.

The Rab family
First described as Ras-like proteins in grain (Rab), Rab proteins comprise the largest branch of the superfamily, with 61 members (Pereira-Leal and Seabra, 2001). Rab GTPases are regulators of intracellular vesicular transport and the trafficking of proteins between different organelles of the endocytic and secretory pathways (Zerial and McBride, 2001). Rab proteins facilitate vesicle formation and budding from the donor compartment, transport to the acceptor compartment, and vesicle fusion and release of the vesicle content into the acceptor compartment.

Rab proteins localize to specific intracellular compartments consistent with their function in distinct vesicular transport processes (Zerial and McBride, 2001). This localization is dependent on prenylation, and specificity is dictated by divergent C-terminal sequences. For example, Rab1 is located in the intermediate compartment of the cis-Golgi network and is involved in ER-to-Golgi transport. By contrast, Rab5 is located in early endosomes and regulates clathrin-coated-vesicle-mediated transport from the plasma membrane to early endosomes. Similar distinct intracellular locations and roles in vesicular transport have been established for other Rab members.

The Ran family
The Ras-like nuclear (Ran) protein is the most abundant small GTPase in the cell and is best known for its function in nucleocytoplasmic transport of both RNA and proteins (Weis, 2003). Although related to the Rab proteins in sequence, it has features that distinguish it. Unlike other small GTPases, Ran function is dependent on a spatial gradient of the GTP-bound form of Ran. There is a single human Ran protein that is regulated by a Ran-specific nuclear GEF and cytoplasmic GAP activities. This results in a high concentration of Ran-GTP in the nucleus, which facilitates the directionality of nuclear import and export. Nuclear Ran-GTP interacts with importin to promote cargo release, and with exportin-complexed cargo, to facilitate nuclear import and export of cargo, respectively. By a similar mechanism, Ran GDP/GTP cycling also regulates mitotic spindle assembly, DNA replication and nuclear envelope assembly (Li et al., 2003).

The Arf family
Like the Rab proteins, the ADP-ribosylation factor (Arf) family proteins are involved in regulation of vesicular transport, Arf1 being the best characterized (Memon, 2004). Arf GDP/GTP cycling is regulated by distinct GEFs and GAPs (Nie et al., 2003). Arf-GTP, the active form, interacts with effectors including vesicle coat proteins. Conformational differences between the two nucleotide-bound forms include not only the switch I and II regions, but also changes in the N-terminal region that allow the myristate group to interact with membranes in their GTP-bound state (Pasqualato et al., 2002).

Arf1 regulates the formation of vesicle coats at different steps in the exocytic and endocytic pathways (Nie et al., 2003; Memon, 2004). GTP- and donor-membrane-bound Arf associates with and activates coat proteins. The Arf–coat-protein complex then facilitates cargo sorting and vesicle formation and release. GAP-mediated formation of Arf-GDP is required for dissociation of the Arf–coat-protein complex and subsequent vesicle fusion with acceptor membranes. In contrast to Rab proteins, which function at single steps in membrane trafficking, Arf proteins can act at multiple steps. For example, Arf1 controls the formation of coat protein I (COPI)-coated vesicles involved in retrograde transport between the Golgi and ER, of clathrin/adapter protein 1 (AP1)-complex-associated vesicles at the trans-Golgi network (TGN) and on immature secretory vesicles, and of AP3-containing endosomes. Arf6 is functionally distinct from Arf1 and can regulate actin organization as well as endocytosis. Regulation and function of Sar1 is
similar to that of Arf1, controlling the assembly of the COPI-coated vesicles at the ER. Arf1 also functions in membrane trafficking. Other family members exhibit different or poorly characterized cellular functions.

The complex modes of regulation of Ras superfamily small GTPases facilitate their key involvement in an amazingly diverse spectrum of biochemical and biological processes. The extent of this superfamily, when combined with Gα subunits and up to 50 other human GTPases (Colicelli, 2004), reveals the versatile role of GTPase switches in the control of cellular processes.

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### Table: Alignment of the GTPase domain of the Ras superfamily members

| Gene | Core effector domain/G2 |
|------|-------------------------|
| Arf1 | 18 MRILVMGLDAAGKTTILYKLKG--EEIVTIP----II--GFNVET 55 |
| Arf3 | 18 MRILVMGLDAAGKTTILYKLKG--EEIVTIP----II--GFNVET 55 |
| Arf4 | 18 MRILVMGLDAAGKTTILYKLKG--EEIVTIP----II--GFNVET 55 |
| Arf5 | 18 MRILVMGLDAAGKTTILYKLKG--EEIVTIP----II--GFNVET 55 |
| Arf6 | 18 MRILVMGLDAAGKTTILYKLKG--EQSTIP----IV--GFNVET 55 |
| Ard1 | 405 IRVVTIQLGDAGKTTILFKLKQD--EMQPIP----II--GFNVET 442 |
| Ar11 | 18 MRILILGLDAAGKTTILYQLQVQ--EEIVTIP----II--GFNVET 55 |
| Arl5 | 17 HKKVIVGLDAGKTTILYQFSMN--EEIVHSP----II--GSMVPE 54 |
| Arl8 | 16 HKKVIVGLDAGKTTILYQFSMN--EEIVHSP----II--GSMVPE 53 |
| Arl12 | 17 LRLLMGLDAAGKTTILKFPNGE--DIDSIP----LL--GFNKRI 54 |
| Arl13 | 18 VRLILLGLDAAGKTTLLKLAQE--DIHITP----Q----GFNKS 55 |
| Arl16 | 19 VHLCLGLDAGKTTINLKLPSNA--QSSQPLS----II--GFSIEM 58 |
| Arl14 | 21 FHIIVGLDAAGKTTVLRLQFPN--EFVNTVP----KK--GFNTEK 58 |
| Arl17 | 14 LHIVMLGLDAAGKTTVLRLKFPN--EFVNTVP----II--GFNTEK 51 |
| Arf4L | 22 LHVVVGLDAGKTTLLYLKFKP--EFVQSP----KK--GFNTEK 59 |
| Arl11 | 13 AOVMGLDAGKTTLLYKLQKH--QLVETLP----IV--GFNVPE 50 |
| FLJ22595 | 14 AQLVLGLDAGKTTLLYKLRA--KDITIP----II--GFNVEM 51 |
| ArfrP1 | 18 YCILILGLDAAGKTTFLQGKRNKMYLGLSLKTT--IV--GLNIGT 63 |
| Arl12L1 | 22 YVLMLGLDAGKTTAKGIOQY----PEDVAP----IV--GFSKIN 59 |
| Arl9 | 19 KQILMLGLDAAGKTTSLVhLSNRA--QDSVAP----Q----GFHACD 57 |
| Arl10A | 78 REVVLGLDAGKTTFLVLSKGP--PLECHIP----W----GFNSVRE 116 |
| Sarla | 26 GKLVLGLDAGKTTLLHLMKDL----RLQGVHP----L--HPTSEE 63 |
| SarlB | 26 GKLVLGLDAGKTTLLHLMKDL----RLQGVHP----L--HPTSEE 63 |
| Arl10B | 21 MEILVLQGYSKTTYTVNIAQG--QNNEDMIP--Q----GFNMRRK 59 |
| Arl10C | 21 MEILVLQGYSKTTYTVNIAQG--QNNEDMIP--Q----GFNMRRK 59 |
| LOC339231 | 24 GMCLLGLATGVKTLVRLQEVSSRDGKDLGEFPEKTRP--IV--GTELTD 71 |
| RhoA | 6 KKLIVVGLDAGKTTCLLIVFSKQQ--FFEVPVP----TF--ENVYAD 45 |
| RhoC | 6 KKLIVVGLDAGKTTCLLIVFSQDQ--FFEVPVP----TF--ENVYAD 45 |
| RhoB | 6 KKLIVVGLDAGKTTCLLIVFSKQDQ--FFEVPVP----TF--ENVYAD 45 |
| Rnd2 | 8 CKIVVGLDAGKTTCLLIVSFKQD----FPYQYP----TF--ENYTA 47 |
| Rnd3 | 24 CKIVVGLDAGKTTCLLIVSFKQD----FPYQYP----TF--ENYTA 47 |
| Rnd1 | 14 CLLVVGLDAGKTTCLLIVSFKQD----FPYQYP----TF--ENYTA 47 |
| RhoD | 18 VKVVLGLDAGKTTSLMVFADGAP--FPESYP----TF--ERYMVE 57 |
| Rif | 20 KLVIVVGLDAGKTTSLMVSQGQG--FPEHYAP----SVF--EKTASA 59 |
| Rac1 | 4 IKCVVGLDAGKTTCLLISSTNTA--FPGEYIP----TFV--DNYSAN 43 |
| Rac2 | 4 IKCVVGLDAGKTTCLLISSTNTA--FPGEYIP----TFV--DNYSAN 43 |
| Rac3 | 4 IKCVVGLDAGKTTCLLISSTNTA--FPGEYIP----TFV--DNYSAN 43 |
| RhoG | 4 IKCVVGLDAGKTTCLLISSTNTA--FPGEYIP----TFV--DNYSAN 43 |
| TC10 | 18 KKVVGLDAGKTTCLLMSYANDA--FPEEPYP----TFV--DHYAVS 57 |
| TCL | 22 KKVVGLDAGKTTCLLMSYANDA--FPEEPYP----TFV--DHYAVT 61 |
| Cdc42 | 4 2 KKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TFV--DNYSAN 43 |
| Wrch-2 | 32 IKCLVGLDAGKTTSLIVSTSCTNG--YPARYRP----CAL--DTFSVQ 71 |
| Wrch-1 | 50 IKCLVGLDAGKTTSLIVSTSCTNG--YPARYRP----CAL--DTFSVQ 71 |
| RhoH | 5 2 KKVVLGLDAGKTTSLMVFADGAP--FPESYP----TFV--DHYAVS 57 |
| RhoB1 | 15 IKCVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| RhoB2 | 15 IKCVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| H-Ras | 4 YKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| K-Ras2B | 2 YKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| N-Ras | 4 YKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| R-Ras | 30 HKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| TC21 | 15 YKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| M-Ras | 14 YKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| Rit1 | 22 YKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| Rit2 | 21 YKLIVVGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| Rap1A | 4 YKLVLGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| Rap1B | 4 YKLVLGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| Rap2A | 4 YKLVLGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| Rap2C | 4 YKLVLGLDAGKTTCLLISSTNTA--FPGEYIP----TF--DNYSAN 43 |
| Protein  | Length | Sequence | Description |
|----------|--------|----------|-------------|
| Rab23    | 12     | IVMVVGNAVGKSSLMQRCKG -------------- -IFTKD--YKGI GF DFLERQ | 50 |
| RabL4    | 8      | AAACILAPAVGKTALAQIFRSDG-------- -AHF QKSS YLTG MD LVLVKT | 47 |
| Rab9A    | 10     | FKVILLGDGGVGSMLMNRYVTSN-------- -KFDTQS--LPF H GVE FLN K | 47 |
| Rab9B    | 10     | FKVILLGDGGVGSMLMNRYVTSN-------- -KFDSQS--APH H GVE FLN R | 47 |
| Rab7A    | 8      | KPVILGDSGVGSLMNQYVNK-------- -KFSNQ--YA KIGAD FLK | 48 |
| Rab7B    | 8      | KLVIGVAIGVGTSLPHQVYHKL-------- -TFYEE--YQT G LGA SI L K | 48 |
| Rab32    | 38     | FKVILGAVGKTSLMVIFRSDG--------- -AHFQ---LFSQH--YRAIGVD FALK | 49 |
| Rab38    | 10     | YKVILGADLGKSTKIRR YVHKL-------- -NFSSH--YRAIGVD FALK | 49 |
| Rab7L1   | 7      | FKVILGAVGKTSLMVIFRSDG--------- -AHFQ---LFSQH--YRAIGVD FALK | 47 |
| Rab5A    | 21     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab5C    | 21     | FKLVLGDSGVGSSLMVRF VKG------ -QPEH--QESTGAAFLT Q | 60 |
| Rab5B    | 21     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab22A   | 5      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab22B   | 5      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab24    | 5      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab21    | 5      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab17    | 29     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab6A    | 14     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab6C    | 14     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab6B    | 14     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab28    | 13     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab22B   | 8      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab15    | 9      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab34    | 53     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Rab36    | 53     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Ran      | 11     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| RabL2A   | 22     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| RabL2B   | 22     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Miro1    | 5      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Miro2    | 5      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| ArfRP2   | 33     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| SRPRB    | 65     | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| LOC401884| 1      | FKLVLGDSGVGSSLMRVFQK------ -QPEH--QESTGAAFLT Q | 60 |
| Protein   | Sequence     | Length |
|-----------|--------------|--------|
| Arf1      | VEYKN--------ISFTV 65 |
| Arf3      | VEYKN--------ISFTV 65 |
| Arf4      | VEYKN--------ICFTV 65 |
| Arf5      | VEYKN--------ICFTV 65 |
| Arf6      | VTYKN--------VKFNV 65 |
| Ardr1     | VEYKN--------LKFTI 452 |
| Ar1l1     | VTYKN--------LKFQV 65 |
| Ar1l5     | IVINN--------TRFLM 64 |
| Ar1l8     | IVVKN--------THFLM 63 |
| Ar1l2     | LEHRG--------FKLNI 64 |
| Ar1l3     | VQSQG--------FKLNV 65 |
| Ar1l6     | FKSSS--------LSFTV 68 |
| Ar1l4     | IKVTLGNSKT---VTFHF 73 |
| Ar1l7     | IKLSNGTAKG---VTFHF 73 |
| Arf4L     | IRVPLGGSRG---ITFQV 74 |
| Ar1l11    | LKAPG---H---VSLTL 61 |
| FLJ22595  | IELER---N---LSLTV 62 |
| ArfRP1    | VDVGK--------ARLMF 73 |
| Ar1l2l1   | LRQGK--------FEVTI 69 |
| Ar1l9     | INTED--------SOMEF 67 |
| Ar1l10A   | LPTKD--------FEVDL 126 |
| Sar1a     | LTIAG--------MTFTT 73 |
| Sar1b     | LTIAG--------MTFTT 73 |
| Ar1l10B   | ITKGN--------VTIKL 69 |
| Ar1l10C   | VTKGN--------VTIKI 69 |
| LOC339231 | IVAQR--------KITT 80 |
| RhoA      | IEVDGKQ------VELAL 57 |
| RhoC      | IEVDGKQ------VELAL 57 |
| RhoB      | IEVDGKQ------VELAL 57 |
| Rnd2      | FEIDKRR------IELNM 59 |
| Rnd3      | FEIDTQR------IELSL 75 |
| Rnd1      | LETEEQR------VELSL 65 |
| RhoD      | LQVKGKP------VHLHI 69 |
| Rif       | VTVGSKE------VSLNL 71 |
| Rac1      | VMVDGKP------VNLGL 55 |
| Rac2      | VMVDKGP------VNLGL 55 |
| Rac3      | VMVDGKP------VNLGL 55 |
| RhoG      | SAVDGRT------VNLNL 55 |
| TC10      | VTVGGKQ------YLLGL 69 |
| TCL       | VTVGGKQ------YLLGL 69 |
| Cdc42     | VMIGGEP------YTLGL 55 |
| Wrch-2    | VLVGDAP------VEREL 83 |
| Wrch-1    | VSVDGRP------VRQLQ 101 |
| RhoH      | VFMDGQ------ISLGL 56 |
| RhoBTB1   | CQVELERSRDVDEVVS--VSLRL 82 |
| RhoBTB2   | CQVELERSRDVDDVS--VSLRL 82 |
| H-Ras     | VVID-GETCL---LDI 55 |
| K-Ras2B   | VVID-GETCL---LDI 55 |
| N-Ras     | VVID-GETCL---LDI 55 |
| N-Ras     | CSVD-GIPAR---LDI 81 |
| TC21      | CVID-DRAAR---LDI 66 |
| M-Ras     | TEID-NQWAI---LDV 65 |
| Rit1      | IRID-DEPAN---LDI 73 |
| Rit2      | VRID-NEPAY---LDI 72 |
| Rap1A     | VEVDFQOQCM------LEI 55 |
| Rap1B     | VEVDFAQCM------LEI 55 |
| Rap2A     | IEVD-SSPSV------LEI 55 |
| Rap2C     | IEVD-SSPSV------LEI 55 |
| Protein     | Sequence                      | Length | Number |
|-------------|-------------------------------|--------|--------|
| Rap2B       | IEVD-SSPSV                     |        |        |
| RasA        | VVLD-GEEVQ                     |        |        |
| RasB        | VVLD-GEEVQ                     |        |        |
| E-Ras       | LTLD-SGDCI                     |        |        |
| Gem         | LMVD-GESAT                     |        |        |
| Rad         | IVVD-GEEAS                     |        |        |
| Rem1        | LTVD-GEDTT                     |        |        |
| Rem2        | IMVD-KEEVT                     |        |        |
| Rerg        | ATID-DEVVS                     |        |        |
| Ris         | ETVD-HQPVH                     |        |        |
| RasL11A     | VYVE-GDQLS                     |        |        |
| RasL11B     | VQIE-GETLA                     |        |        |
| FLJ22655    | LCLE-RKQLN                    |        |        |
| Di-Ras1     | ISCD-KSVCT                     |        |        |
| Di-Ras2     | ISCD-KSIC                      |        |        |
| Noey2       | LGCS-HGVLs                     |        |        |
| RasD1       | YSIR-GEVYQ                     |        |        |
| RasD2       | YNIR-GDMYQ                     |        |        |
| RRP22       | VLLD-GAVYD                     |        |        |
| RasL10B     | VVMN-GHVHD                     |        |        |
| Rho         | ITVN-GQEYH                     |        |        |
| Rhee        | ITDN-GQFY                     |        |        |
| NKIRas1     | VETDRGVEQ                     |        |        |
| NKIRas2     | IETDRGVEQ                     |        |        |
| Rab40A      | ILLD-QQRVK                     |        |        |
| Rab40B      | ILLD-GRRVK                     |        |        |
| Rab40C      | ILLD-GRRVR                     |        |        |
| Rab1A       | IELD-GKTIK                    |        |        |
| Rab1B       | IELD-GKTIK                    |        |        |
| Rab35       | VEIN-GEKVK                     |        |        |
| Rab3A       | VYRN-DKRIK                    |        |        |
| Rab3C       | VENK-EKRIK                    |        |        |
| Rab30       | VENK-EKRIK                    |        |        |
| Rab3B       | VENK-EKRIK                    |        |        |
| Rab3D       | VENK-EKRIK                    |        |        |
| Rab8A       | IELD-GKRIK                     |        |        |
| Rab8B       | IELD-GKRIK                     |        |        |
| Rab10       | VEIN-GKIK                     |        |        |
| Rab13       | VDIE-GKIK                     |        |        |
| Rab12       | VELR-GKIR                     |        |        |
| Rab18       | ISVD-GNRAK                    |        |        |
| Rab19       | LDID-GKVKNSSSASIIITFASIQIHQTOKMSPQIQWTKSSHYLWEPLIWTLLPVLQLMQV | 117 |
| Rab41       | LEIQ-GKRYK                     |        |        |
| Rab30       | VEIN-GKVK                     |        |        |
| Rab33A      | VEIE-GKIK                     |        |        |
| Rab33B      | VEID-GERIK                    |        |        |
| Rab2A       | ITTD-GKQIK                    |        |        |
| Rab2B       | VNDG-GKQIK                    |        |        |
| Rab4A       | INVG-GKVK                     |        |        |
| Rab4B       | VINV-GKTVK                    |        |        |
| Rab14       | IEVS-GQIK                     |        |        |
| Rab11A      | IQVD-GKTIK                    |        |        |
| Rab11B      | IQVD-GKTIK                    |        |        |
| Rab25       | VNLG-TAAVK                    |        |        |
| Rab39A      | LEIEPGKRIK                    |        |        |
| Rab39B      | VEIEPGKRIK                    |        |        |
| RasEF       | LIVDGE                        |        |        |
| Ras27A      | VVYRASPDPDATGRQQ              |        |        |
| Rab27B      | VYNAQGPNGSSGKAF               |        |        |
Rab23   IQVNDE--D---------------------------------------------------VRLML  62
RabL4   VPVPDTGDS-------------------------------------------------VELFI  61
Rab9A   DLEV-DGHF-------------------------------------------------VTMQI  60
Rab9B   DLEV-GRF-------------------------------------------------VTQLI  60
Rab7A   EVMVD-DRL-------------------------------------------------VTMQI  61
Rab7B   IIIILG-DTT-------------------------------------------------LKLQI  61
Rab32   VLNWDSDRL-------------------------------------------------VRLQL  79
Rab38   VLNWDPETV-------------------------------------------------VRLQL  63
Rab7L1  VLQWSDYEI-------------------------------------------------VRLQL  61
Rab5A   TVCLDDTT-------------------------------------------------VKFEI  73
Rab5C   TVCLDDTT-------------------------------------------------VKFEI  73
Rab5B   SVCLDDTT-------------------------------------------------VKFEI  73
Rab22A  TVQYQNEL-------------------------------------------------HKFLI  58
Rab22B  TVPCGNEL-------------------------------------------------HKFLI  59
Rab24   VNSVGDR-----------------------------------------------VTLGI  61
Rab21   KLNIGGKR-------------------------------------------------VNLAI  72
Rab17   VVVDVGATS-------------------------------------------------LKLIE  80
Rab6A   TMYLELDRT-------------------------------------------------IRLQL  66
Rab6C   TMYLEDGT-------------------------------------------------IGLRL  66
Rab6B   TMYLEDRT-------------------------------------------------VRLQL  66
Rab28   RITLPGNLN-------------------------------------------------VTLQI  66
Rab15   IEVVGIKVR-------------------------------------------------IQLI  61
Rab34   FEVLGIPFS-------------------------------------------------LQL  105
Rab36   FEIAGIPYS-------------------------------------------------LQLI  176
Ran     VFHTN-RGP-------------------------------------------------IKFNV  63
RabL2A  ATVDGKT-------------------------------------------------ILVDF  74
RabL2B  ATVDGTR-------------------------------------------------ILVDF  74
Miro1   VPT-------------------------------------------------------HI  55
Miro2   VPT-------------------------------------------------------HI  55
Rab20   WRSSYN-----------------------------------------------------IISI  53
RabL3   YKEGTPEEK-----------------------------------------------CYIEL  64
ArfRP2  VPQFN-----------------------------------------------------AILNV  80
RabL5   VTSNKNKGT-----------------------------------------------CEFEL  61
SRPRB  VNNRNGNS---------------------------------------------------LTL  115
LOC401884 AARGAGRGRG-----------------------------------------------RGR  52
Rab27B

Rab27A

RasEF

Rab37

Rab26

Rab42

Rab39B

Rab39A

Rab25

Rab11B

Rab14

Rab4B

Rab2B

Rab2A

Rab33B

Rab30

Rab41

Rab19

Rab18

Rab12

Rab13

Rab10

Rab8B

Rab3D

Rab3B

Rab3C

Rab3A

Rab35

Rab1B

Rab1A

rab40B

Rab40A

Rab40C

Rab1A

Rab1B

Rab35

Rab3A

Rab3C

Rab3B

Rab3D

Rab8A

Rab8B

Rab10

Rab13

Rab12

Rab18

Rab19

Rab41

Rab30

Rab33A

Rab33B

Rab2A

Rab2B

Rab4A

Rab4B

Rab14

Rab11A

Rab11B

Rab25

Rab39A

Rab39B

Rab42

Rab26

Rab27A

Rab27B

E-Ras

Gem

Rad

Rem1

Rem2

Rerg

Rem2

Rerg

Rem1

Rem2

E-Ras

Rad

Rem1

Rem2
Rab23  --------------------------DIPTVLVQNKIDLD-----DSCIKN----- 133
RabL4  GI------------------------SLPGVLVGNKDTLAG----------RRAVDS----- 134
Rab9A  VKEP-------------------ESFPFVILGNKIDISE-------RQVSTED------ 136
Rab9B  VKDP-------------------EHFPFVILGNKVDKED--------RQVTTED------- 136
Rab7A  PRDP-------------------ENFPFVILGNKIDKED--------RQVATK------- 137
Rab7B  PME---------------------QSYPNVLLGNKIDLAD-------RKVPOE-------- 137
Rab32  LPNG-------------------SPIAVLLANKCDQNK---------DSSQSP-------- 155
Rab38  LPNG-------------------KPVSVLLANKCDQG----------DVLMNNG------ 140
Rab7L1  LPNG-------------------EPVPCLLANKCDLSP--------WAVSRD-------- 137
Rab5A  -QAS-------------------PNIVIALSGNKADLAN-------KRAVDFQ------- 146
Rab5C  -QAS-------------------PNIALAGNKADLAN-------KRAVEFQ------- 146
Rab5B  -QAS-------------------PSIALAGNKADLAN-------KRMVEYE------- 146
Rab22A  -HGP-------------------PNIVAIAGNKCDLD-------VREVMER-------- 131
Rab22B  -HGP-------------------ENIVNAIAGNKCDLD-------IREVPLK------- 132
Rab24  -LEE-------------------G-CQIYLCGKSDLED---------RRRRVFDH------ 137
Rab21  -MLG-------------------NEICLCIVGNKIDLEK-------ERHVSIQ------- 145
Rab17  -LHP-------------------GEVLMVLGNKTLSQ---------EREVTFO------- 154
Rab6A  -ERG-------------------SDVIIMLVGNKTLAD-------KRVQSIE-------- 139
Rab6C  -ERG-------------------SDVITHLVGNKTLAD-------KRVQSVE-------- 139
Rab6B  -ERG-------------------SDVIMLVGNKTLAD-------KRVITIE-------- 139
Rab28  -ESE-------------------TQPLVAVLVGNKIDLEH-------MRTIKPE------- 142
Rab15  ATS-------------------LPCGCEGASP--------GKARRGPD------ 132
Rab34  PSSV-------------------LLFLVGSKDLST----------PAQYALME------ 180
Rab36  AGSC-------------------FIIFLVCNKNKIDLS-------GAACEQA------ 251
Ran  N-------------------------IPIVLCGNKVIDKD--------RKVKAK-------- 134
RabL2A  PE-------------------IPCIVVANKIDIN---------VT--------- 141
RabL2B  PE-------------------IPCIVVANKIDIN---------VT--------- 141
Miro1  DKDS-------------------RPLLLVGNKSLVE--------YSSMT--------- 130
Miro2  TQGP-------------------RVPIILVGNKSLRS-------GSSMEA-------- 130
Rab20  KD---------------------CLFAIVGNKVDLTE-------EGALAGQ------- 126
RabL3  VPTGVLVTNGDYEQFADNQPLLVVGTKLOIHE--KRHEVLTTAFLAED 170
ArfRP2  LCT-------------------LPFLILAHQDHPA--------ARSVQE--------I 155
Rab5  LQD---------------------TQCMLIAHKPGSG----------DK--------- 131
SRPRB  GLKN-------------------TPSFLIACKQDIAMAKS--------AKLIQQQLEK--E 200
LOC401884  LTMG-------------------MGQKEAPHCGEVVRGG--------FGTVVRGG------G 131
Rab27B  -QARELADKY-G-------------IP
Rab27A  -EAIALAEKY-G-------------IP
Rab26   -DGEKLAKEY-G-------------LP
Rab39B  -EAEKLAAAY-G-------------MK
Rab39A  -EAEKLSADC-G-------------MK
Rab25   -EARMFAENN-G-------------LL
Rab14   -EAKQFAEEN-G-------------LL
Rab4B   -EASRFAQEN-E-------------LM
Rab4A   -EASRFAQEN-E-------------LM
Rab2B   -EGEAFAREH-G-------------LI
Rab33A  -LALKFADAHNM-------------L-
Rab30   -RAEEFSEAQDM-------------Y-
Rab41   -EAQSLAEHYDI-------------LC
Rab19   -DACTLAEKYGL-------------LA
Rab18   -EGLKFARKH-S-------------ML
Rab12   -QGEKFAQQITG-------------MR
Rab13   -QADKLAREH-G-------------IR
Rab8B   -RGEKLAIDY-G-------------IK
Rab8A   -RGEKLALDY-G-------------IK
Rab3D   -DGRRLADDL-G-------------FE
Rab3B   -KGQLLAEQL-G-------------FD
Rab3A   -RGRQLADHL-G-------------FE
Rab35   -DAYKFAGQM-G-------------IQ
Rab1B   -TAKEFADSL-G-------------IP
Rab1A   -TAKEFADSL-G-------------IP
Rab40C  -QARAYAEKNC--------------MT
rab40B  -QAQAYAERLG--------------VT
Rab40A  -QAQAYAERLG--------------VT
NKIRas2 -VAQHWAKSEK--------------VK
NKIRas1 -VAQQWAKSEK--------------VR
RhebL1  -EGKKLAESWG--------------AT
Rheb    -EGKALAESWN--------------AA
RasL10B -VSHLVRKT-WK--------------CG
RRP22   -LAALVRRG-WR--------------CG
RasD2   -AELLVSGD-EN--------------CA
Noey2   -DGATCAMEWN--------------CA
Di-Ras2 -EAEALARTWK--------------CA
Di-Ras1 -EAQAVAQEWK--------------CA
FLJ22655-EGQKLALENR--------------CQ
RasL11A -DGIQLANELG--------------SL
Ris     -EGVALAGRPG--------------LW
Rerg    -EGEKLATELA--------------CA
Rem2    -EGRHLAGTLS--------------CK
Gem     -EGRACAVVFD--------------CK
E-Ras   -AAAALAHSWG--------------AH
RalA    -EAKNRAEQWN--------------VN
Rap2B   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
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Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
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Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
Rap2A   -EGKALAEYW-E-------------LM
| Protein | Sequence | Length |
|---------|----------|--------|
| Rab23   | -EEAEALAKRLK-------------LR | 172    |
| RabL4   | -EEAEALAKRLK-------------LR | 173    |
| Rab9A   | -EEAEALAKRLK-------------LR | 176    |
| Rab9B   | -EEAEALAKRLK-------------LR | 173    |
| Rab7L   | -EEAEALAKRLK-------------LR | 176    |
| Rab5A   | -EEAEALAKRLK-------------LR | 177    |
| Rab5C   | -EEAEALAKRLK-------------LR | 177    |
| Rab5B   | -EEAEALAKRLK-------------LR | 177    |
| Rab22A  | -EEAEALAKRLK-------------LR | 179    |
| Rab22B  | -EEAEALAKRLK-------------LR | 184    |
| Rab24   | -EEAEALAKRLK-------------LR | 184    |
| Rab21   | -EEAEALAKRLK-------------LR | 185    |
| Rab17   | -EEAEALAKRLK-------------LR | 185    |
| Rab6A   | -EEAEALAKRLK-------------LR | 186    |
| Rab6C   | -EEAEALAKRLK-------------LR | 186    |
| Rab6B   | -EEAEALAKRLK-------------LR | 186    |
| Rab28   | -EEAEALAKRLK-------------LR | 187    |
| Rab15   | -EEAEALAKRLK-------------LR | 187    |
| Rab34   | -EEAEALAKRLK-------------LR | 187    |
| Rab36   | -EEAEALAKRLK-------------LR | 187    |
| Ran     | -EEAEALAKRLK-------------LR | 187    |
| RabL2A  | -EEAEALAKRLK-------------LR | 188    |
| RabL2B  | -EEAEALAKRLK-------------LR | 188    |
| Rab20   | -EEAEALAKRLK-------------LR | 188    |
| RabL3   | -EEAEALAKRLK-------------LR | 188    |
| ArfRP2  | -EEAEALAKRLK-------------LR | 188    |
| SRPRB   | -EEAEALAKRLK-------------LR | 188    |
| LOC401884 | -EEAEALAKRLK-------------LR | 188    |
**Supplemental Table.** The Ras superfamily, subfamilies, accession numbers and additional information

| Protein         | Synonyms           | Accession no | Characterized | Comments               |
|-----------------|--------------------|--------------|---------------|------------------------|
| Ras family (36) |                    |              |               |                        |
| H-Ras, isoform 1|                    | NP_005334    | yes           |                        |
| H-Ras, isoform 2| H-RasIDX           | NP_789765    | yes           |                        |
| H-RasIDX        |                    |              |               |                        |
| N-Ras           |                    | NP_002515    | yes           |                        |
| K-Ras2B         |                    | NP_004976    | yes           |                        |
| K-Ras2A         |                    | NP_203524    | yes           |                        |
| R-Ras           |                    | NP_006261    | yes           |                        |
| TC21            | R-Ras2             | NP_036382    | yes           |                        |
| M-Ras           | R-Ras3             | NP_036351    | yes           |                        |
| Rap1A           | Krev-1/Smgp21      | NP_002875    | yes           |                        |
| Rap1B           |                    | NP_056461    | yes           |                        |
| Rap2A           |                    | NP_066361    | yes           |                        |
| Rap2B           |                    | NP_002877    | yes           |                        |
| Rap2C           |                    | NP_067006    | yes           |                        |
| Rit1            | Roc1/RibB         | NP_008843    | yes           |                        |
| Rit2            | Rin/Roc2/RibA     | NP_002921    | yes           |                        |
| Rem1            | Gcs                | NP_054731    | yes           |                        |
| Rem2            |                    | AAH35663     | yes           |                        |
| Rad             | R-Rad/Rem3        | NP_004156    | yes           |                        |
| Gem             | Kir                | NP_859053    | yes           |                        |
| Rheb1           | Rheb2              | NP_005605    | yes           |                        |
| Rheb2           | RhebL1             | NP_653194    | yes           |                        |
| Noey2           | ARHI/RhoI         | NP_004666    | yes           |                        |
| Di-Ras1         | Rig/GBTS1         | NP_660156    | yes           |                        |
| Di-Ras2         |                    | NP_060064    | yes           |                        |
| E-Ras           | H-Ras2/H-RasP     | NP_853510    | yes           |                        |
| Rerg            |                    | NP_116307    | yes           |                        |
| RalA, isoform 1 |                    | NP_005393    | yes           |                        |
| RalA, isoform 2 |                   | AAA36542     | yes           |                        |
| RalB            |                    | NP_002872    | yes           |                        |
| RKIRas1         | κB-Ras1            | NP_065078    | yes           |                        |
| RKIRas2         | κB-Ras2            | NP_060065    | yes           |                        |
| RasD1           | DexRas/Ags1       | NP_057168    | yes           |                        |
| RasD2           | Rhes/Tem2         | NP_055125    | yes           |                        |
| RRP22           | RasL10A           | NP_006468    | no            |                        |
| RasL10B         |                    | NP_201572    | no            |                        |
| RasL11A         |                    | NP_996563    | no            |                        |
| RasL11B         |                    | NP_076429    | no            |                        |
| Ris/RasL12      |                    | NP_057647    | no            |                        |
| FLJ22655        |                    | NP_079006    | no            | Lacks G1 box.          |
| Rho family (20) |                    |              |               |                        |
| RhoA            | ARHA/Rho H12      | NP_001655    | yes           |                        |
| RhoB            | ARHB/Rho H6       | NP_004031    | yes           |                        |
| RhoC            | ARHC/Rho H9       | NP_786886    | yes           |                        |
| RhoD            | ARHD/RhoHP1       | NP_055393    | yes           |                        |
| Rnd3            | RhoE/ARHE/Rho8    | NP_005159    | yes           |                        |
| Rnd1            | ARHS/Rho6         | NP_055285    | yes           |                        |
| Rnd2            | ARHN/RhoN/Rho7    | NP_005431    | yes           |                        |
| Rif             | ARHF/RhoF         | NP_061907    | yes           |                        |
| RhoG            | ARHG              | NP_001656    | yes           |                        |
| RhoH            | TTF/ARHH          | NP_004301    | yes           |                        |
| Rac1            | TC25              | NP_008839    | yes           |                        |
| Rac1, isoform b |                    | NP_061485    | yes           |                        |
| Rac2            |                    | NP_002863    | yes           |                        |
| Rac3            |                    | NP_005043    | yes           |                        |
| Protein      | Synonyms                        | Accession no | Characterized | Comments          |
|--------------|---------------------------------|--------------|---------------|-------------------|
| Cdc42, placental | G25K/Cdc42Hs                    | NP_001782    | yes           |                   |
| Cdc42, brain  |                                 | NP_426359    | yes           |                   |
| TCI0         | RhoQ/ARHQ/RasL7A                 | NP_036381    | yes           |                   |
| TCL          | TC10/RhoT/RhoJ/ARHJ/RasL7B      | NP_065714    | yes           |                   |
| Wrch-1       | RhoU/ARHU/Cdc42L1               | NP_067028    | yes           |                   |
| Wrch-2       | Chp/RhoV/ARHV                   | NP_598378    | yes           |                   |
| RhoBTB1      |                                 | NP_055651    | yes           | Multi-domain protein |
| RhoBTB2      | DBC2                            | NP_055993    | yes           | Multi-domain protein |
| **Arf family (27)** |                                |              |               |                   |
| Arf1         |                                 | NP_001649    | yes           |                   |
| Arf3         |                                 | NP_001650    | yes           |                   |
| Arf4         |                                 | NP_001651    | yes           |                   |
| Arf5         |                                 | NP_001653    | yes           |                   |
| Arf6         |                                 | NP_001654    | yes           |                   |
| Sar1a        | SARA1/Masra2                    | NP_064535    | yes           |                   |
| Sar1b        | SARA2/Sar1a homolog 2/CMRD     | NP_057187    | yes           |                   |
| Arl1         |                                 | NP_001168    | yes           |                   |
| Arl2         |                                 | NP_001658    | yes           |                   |
| Arl3         |                                 | NP_004302    | yes           |                   |
| Arl4         |                                 | NP_007625    | yes           |                   |
| Arl5, isoform 1 |                                | NP_036229    | yes           |                   |
| Arl6         | BBS3                            | NP_816931    | yes           |                   |
| Arl7         | LAK                             | NP_005728    | yes           |                   |
| Arl8         |                                 | NP_848930    | no            |                   |
| Arl9         |                                 | AAS07576     | no            |                   |
| Arl10A       |                                 | NP_775935    | no            |                   |
| Arl10B       | Gie2                            | NP_620150    | yes           |                   |
| Arl10C       | Gie1                            | NP_060654    | yes           |                   |
| Arl11        | ArlTS1                          | NP_612459    | no            |                   |
| Arxl1, isoform α | ArfD1/Trim23/RNF46            | NP_001647    | yes           | Multi-domain protein |
| Arxl1, isoform β |                                | NP_150230    | yes           |                   |
| Arxl1, isoform γ |                                | NP_150231    | yes           |                   |
| Arf4L        |                                 | NP_001652    | yes           |                   |
| ArfRP1       |                                 | NP_003215    | yes           |                   |
| ArfRP2       |                                 | NP_061960    | no            |                   |
| Arl2L1, isoform 1 |                             | NP_878899    | no            | Multi-domain protein |
| FLJ22595     |                                 | NP_079323    | no            |                   |
| LOC339231    |                                 | XP_290777    | no            |                   |
| **Rab family (61)** |                                |              |               |                   |
| Rab1A        |                                 | NP_004152    | yes           |                   |
| Rab1B        |                                 | NP_112243    | yes           |                   |
| Rab2A        |                                 | NP_002856    | yes           |                   |
| Rab2B        |                                 | NP_116235    | no            |                   |
| Rab3A        |                                 | NP_002857    | yes           |                   |
| Rab3B        |                                 | NP_002858    | yes           |                   |
| Rab3C        |                                 | NP_612462    | yes           |                   |
| Rab3D        | GOV/D2-2/Rab16/Rad3D            | NP_004274    | yes           |                   |
| Rab4A        |                                 | NP_004569    | yes           |                   |
| Rab4B        |                                 | NP_057238    | yes           |                   |
| Rab5A        |                                 | NP_004153    | yes           |                   |
| Rab5B        |                                 | NP_002859    | yes           |                   |
| Rab5C, isoform a | RabL/Rab5CL                   | NP_958842    | yes           |                   |
| Rab5C, isoform b |                                | NP_004574    | yes           |                   |
| Rab6A, isoform a |                               | NP_002860    | yes           |                   |
| Rab6A, isoform b |                                | NP_942599    | yes           |                   |
| Protein  | Synonyms | Accession no | Characterized | Other Comments |
|-----------|-----------|--------------|---------------|----------------|
| Rab6B     |           | NP_057661    | yes           |                |
| Rab6C     | WTH3      | NP_115520    | yes           |                |
| Rab7A     |           | NP_004628    | yes           |                |
| Rab7B     |           | NP_796377    | yes           |                |
| Rab8A     | MEL       | NP_005361    | yes           |                |
| Rab8B     |           | NP_057614    | yes           |                |
| Rab9A     |           | NP_004242    | yes           |                |
| Rab9B     | Rab9L     | NP_057454    | no            |                |
| Rab10     |           | NP_057215    | yes           |                |
| Rab11A    | YL8       | NP_004654    | yes           |                |
| Rab11B    | H-YPT3    | NP_004209    | yes           |                |
| Rab12     |           | XP_113967    | yes           |                |
| Rab13     |           | NP_002861    | yes           |                |
| Rab14     | FBP       | NP_057406    | yes           |                |
| Rab15     |           | NP_941959    | yes           | Lacks G4 box   |
| Rab17     |           | NP_071894    | yes           |                |
| Rab18     |           | NP_067075    | yes           |                |
| Rab19     | Rab19B    | XP_379935    | no            |                |
| Rab21     |           | NP_055814    | yes           |                |
| Rab22A    |           | NP_065724    | yes           |                |
| Rab22B    | Rab31     | NP_006859    | no            |                |
| Rab23     | HSPC137   | NP_057361    | yes           |                |
| Rab24     |           | AAH21263     | yes           |                |
| Rab25     | CATX-8    | AAH33322     | yes           |                |
| Rab26     |           | NP_055168    | yes           |                |
| Rab27A    | Ram       | NP_899059    | yes           |                |
| Rab27B    |           | NP_004154    | yes           |                |
| Rab28     |           | NP_004240    | yes           |                |
| Rab30     |           | NP_055303    | yes           |                |
| Rab32     |           | NP_006825    | yes           |                |
| Rab33A    | RabS10    | NP_004785    | yes           |                |
| Rab33B    |           | NP_112586    | yes           |                |
| Rab34     | Rab/Rab39 | NP_114140    | yes           |                |
| Rab35     | Ray/H-ray/Rab1C | NP_006852 | yes |                |
| Rab36     |           | NP_004905    | yes           |                |
| Rab37     |           | NP_783865    | yes           |                |
| Rab38     | NY-MEL-1  | NP_071732    | yes           |                |
| Rab39A    |           | NP_059986    | yes           |                |
| Rab39B    |           | NP_741995    | no            |                |
| Rab40A    | Rab2A/Rar-2 | NP_543155   | no            |                |
| Rab40B    | Rab/SEC4L | NP_006813    | no            |                |
| Rab40C    | Rab3/RarL/RasL8C | NP_066991 | yes |                |
| Rab41     | Rab43     | NP_940892    | no            |                |
| Rab42     |           | AK026009 (mRNA) | no |                |
| Rab7L1    | Rab29(rat) | NP_003920   | yes           |                |
| RabL4     | RayL      | NP_006851    | no            |                |
| RasEF     | Rab45     | NP_689786    | no            | Multi-domain protein |

**Ran family (1)**

Ran  
NP_006316  yes

**Unclassified (9)**

Miro-1  
NP_060777  yes  Multi-domain protein

Miro-2  
NP_620124  yes  Multi-domain protein

SRPRB  
NP_067026  no

LOC401884  
XP_377476  no  No G4 box. G1 & G3 poorly conserved

Rab20  
NP_060287  yes

RabL2A  
NP_009013  no
| Protein                | Synonyms               | Accession no  | Characterized | Comments       |
|------------------------|------------------------|---------------|---------------|----------------|
| RabL2B, isoform 2      |                        | NP_009012     | no            |                |
| RabL2B, isoform 1      |                        | NP_001003789  |               |                |
| RabL3                  |                        | NP_776186     | no            |                |
| RabL5                  |                        | NP_073614     | no            | Lacks G4 box   |