Consensus nomenclature for the human ArfGAP domain-containing proteins

Richard Kahn, Emory University
Elspeth Bruford, European Bioinformatics Institute
Hiroki Inoue, National Cancer Institute
John M. Logsdon, Jr., University of Iowa
Zhongzhen Nie, Medical College of Georgia
Richard T. Premont, Duke University
Paul A. Randazzo, National Cancer Institute
Masanobu Satake, Tohoku University
Anne B. Theibert, University of Alabama
Maria L. Zapp, University of Massachusetts

Only first 10 authors above; see publication for full author list.

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Richard A. Kahn,1 Elspeth Bruford,2 Hiroki Inoue,3 John M. Logsdon Jr.,4 Zhongzhen Nie,5 Richard T. Premont,6 Paul A. Randazzo,3 Masanobu Satake,7 Anne B. Theibert,8 Maria L. Zapp,9 and Dan Cassel10

1Department of Biochemistry, Emory University School of Medicine, Atlanta, GA 30322
2HUGO Gene Nomenclature Committee, European Bioinformatics Institute, EMBL-EBI, Wellcome Trust Genome Campus, Cambridge, UK
3Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, MD 20892
4Department of Biology, Roy J. Carver Center for Comparative Genomics, University of Iowa, Iowa City, IA 52242
5Department of Pathology, Medical College of Georgia, Augusta, GA 30912
6Department of Biology, The Rockefeller University, New York, NY 10021
7Department of Molecular Immunology, Institute of Development, Aging, and Cancer, Tohoku University, Sendai 980-8575, Japan
8Departments of Neurobiology and Cell Biology, University of Alabama at Birmingham, Birmingham, AL 35294
9Program in Molecular Medicine and Center for AIDS Research, University of Massachusetts Medical School, Worcester, MA 01605
10Department of Biology, Technion-Israel Institute of Technology, Haifa 32000, Israel

At the FASEB summer research conference on “Arf Family GTPases”, held in Il Ciocco, Italy in June, 2007, it became evident to researchers that our understanding of the family of Arf GTPase activating proteins (ArfGAPs) has grown exponentially in recent years. A common nomenclature for these genes and proteins will facilitate discovery of biological functions and possible connections to pathogenesis. Nearly 100 researchers were contacted to generate a consensus nomenclature for human ArfGAPs. This article describes the resulting consensus nomenclature and provides a brief description of each of the 10 subfamilies of 31 human genes encoding proteins containing the ArfGAP domain.

Structure, mechanism, and specificity
ArfGAP domains are ~130 amino acids in length and were originally defined as the minimal fragment possessing ArfGAP activity (Cukierman et al., 1995). They contain a characteristic Cα-type zinc finger motif and a conserved arginine that is required for activity, within a particular spacing (CX2CX19CX2CX2R). The zinc finger has an architectual rather than catalytic role (Fig. 1 B) (Goldberg, 1999). The invariant arginine was proposed to serve in a catalytic “arginine finger” mechanism, similar to that found in GAPs for other GTPases, including Ras and Rho (Scheffzek et al., 1998), and is highly exposed to solvent in the crystal structure (Fig. 1 B). However, the potential for other binding partners (e.g., coatamer; Goldberg 1999) or other domains within some ArfGAPs (e.g., PH domains) serving supportive or regulatory roles in GAP-stimulated hydrolysis has also been demonstrated. For example, the ArfGAP activity of ASAP1 is dependent on the PH domain and is sensitive to PI(4,5)P₂, and that of GITS is stimulated by PIP₃.

ArfGAPs display various degrees of specificity for individual members of the Arf family both in vitro and in live cells. However, these data are not easy to interpret due to uncertainties.
gests that the “canonical” ArfGAPs, those containing the ArfGAP domain, may not represent the entire repertoire of proteins capable of stimulating GTP hydrolysis by Arf proteins.

**Consensus nomenclature of the ArfGAP family of human genes and encoded proteins**

Like most gene families today, gene/protein discovery and the accompanying nomenclature of ArfGAPs has come from a number of different laboratories and techniques and over a span of more than a decade. We have developed a consensus nomenclature for the human ArfGAPs that is based upon the phylogeny of the ArfGAP domains and the domain organization of the proteins, and updated or clarified the acronyms in use to more accurately describe the current understanding of each protein. Table I lists the consensus nomenclature for the human genes, previously published gene symbols and names, database identifiers, chromosome locations, and accession numbers. These gene names should also be used for the encoded proteins, with appropriate
### Table I. Consensus names for human ArfGAPs, with additional information

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indications when more than one splice variant is known to exist. The 31 predicted human ArfGAPs have been classified into 10 subfamilies, based on sequence similarities of their ArfGAP domains, and supported by the conservation of the domain architecture within each subfamily (see Fig. 1A). The acquisition of additional domains throughout eukaryotic evolution has contributed to the acquisition of new functions by different ArfGAPs. A brief summary of each subfamily is presented below.

**ArfGAP1 subfamily**
This founder of the ArfGAP family is also the smallest member, at ~45 kD. ArfGAP1 shuttles between cytosol and the Golgi, where it is involved in regulating the COPI mechanism of membrane traffic. The region of ArfGAP1 C-terminal to the ArfGAP domain is predicted to be largely unstructured. This region contains two stretches, termed ALPS motifs, that have the propensity in vitro to fold into amphipathic α-helices upon interaction with membranes that are highly curved or contain loosely packed lipids (Bigay et al., 2005; Mesmin et al., 2007), and are required for Golgi targeting of the protein in vivo (Levi et al., 2008). The ALPS motifs are predicted to orient the protein on the membrane and to contribute substantially to regulation of its activity in cells. ArfGAP activity is also regulated by the COPI coat complex (Goldberg, 1999). While most studies have focused on the role of ArfGAP1 in the COPI system, ArfGAP1 also interacts with components of clathrin coated carriers (including clathrin, AP-1, and AP-2), although the functional consequences of these interactions remains to be established.

**ArfGAP2 subfamily**
ArfGAPs 1–3 are predicted to have arisen from a common ancestor (e.g., a single gene is present in *G. lamblia*) with an early split into distinctive ArfGAP1 and ArfGAP2 subfamilies and later duplications leading to the ArfGAP2/ArfGAP3 divergence. Human ArfGAP2 and 3 are closely related proteins (58% identity) with little similarity to ArfGAP1 outside the catalytic domain. ArfGAP1 and ArfGAP2/3 display functional interplay, as indicated by synthetic lethality observed between these ArfGAPs in HeLa cells (Frigero et al., 2007), and in *S. cerevisiae* (Gcs1 and Glo3; Poon et al., 1999). ArfGAP2/3 lack ALPS motifs but are found on Golgi membranes as a result of strong interactions with the COPI coat (Watson et al., 2004; Frigerio et al., 2007). Like ArfGAP1, the GAP activities of ArfGAP2/3 are stimulated by coatomer (unpublished data). How each of these ArfGAPs contributes to the COPI mechanism remains unclear.

**ADAP subfamily**
ADAP1 (ArfGAP with dual PH domains; previously centaurin α1, p42/IP3, or PIP, BP) was identified as a high affinity Pt(3,4,5)P3 and Ins(1,3,4,5)P4 binding protein. ADAP1 is proposed to function as an Arf6 GAP that regulates the actin cytoskeleton, membrane traffic, and neuronal differentiation (Thacker et al., 2004; Venkateswarlu et al., 2004). ADAP1 localizes to dendrites, spines, and synapses of developing and adult neurons and can impact traffic of regulated secretory vesicles in neuronal cells. Studies of ADAP2 have not been reported.

**SMAP subfamily**
SMAPs have been implicated as regulators of endocytosis and oncogenesis (Tanabe et al., 2006). Human SMAPs are ~50 kD and lack other defined domains, thus the acronym small ArfGAP protein. The two human SMAP proteins share 47% identity overall, which rises to 83% identity in the ArfGAP domain. SMAPs bind to clathrin heavy chain via the clathrin binding motif (LLGLD) as well as the clathrin assembly protein, CALM (Natsume et al., 2006). SMAP1 is cytosolic but is recruited to membranes where it regulates constitutive endocytosis. SMAP2 is more stably bound to endosomes and is involved in the retrograde transport of TGN46 from early endosomes to the TGN (Natsume et al., 2006).

**AGFG subfamily**
AGFG1 has been reported to be an essential HIV Rev cofactor, based on experiments that suggest that the ArfGAP domain mediates the release of Rev-directed HIV-1 RNAs from the perinuclear region (Sanchez-Velar et al., 2004). The Rev–AGFG1 interaction is indirect and possibly bridged by the nuclear export receptor CRM1. The AGFG subfamily arose very early in eukaryotes, with a predicted progenitor in *G. lamblia* and representatives in molds, plants, fish, and mammals. AGFG1 contains 10 phenylalanine-glycine (FG) repeats, reminiscent of those found in nucleoporins. Thus, the AGFGs are ArfGAPs with FG repeats. Much less information is available on AGFG2.

**GIT subfamily**
GIT genes arose in animals and were duplicated in vertebrates. GIT2 expression is nearly ubiquitous, whereas GIT1 appears absent from many major cell types (muscle, hepatocytes, neurons, adipocytes) but is especially prominent in endothelial cells (Schmalzigaug et al., 2007). Unlike other ArfGAPs, GITs tightly associate with a specific partner, the PIX/Cool proteins, to form oligomeric complexes (Premont et al., 2004). PIX/Cool proteins are GEFs for Rac1 and Cdc42 GTPases. GIT/PIX complexes function as scaffolds for a variety of signaling enzymes (including G protein receptor kinases, p21 activated kinases, focal adhesion kinases, MEK/Erk, and phospholipase Cγ) and are recruited to distinct cellular locations via specific partners (e.g., focal adhesions via paxillin or integrinα4, synapses via piccolo or liprin-α, and plasma membranes via scribble) (Hoefen and Berk, 2006). GIT/PIX complexes function as sites of signal integration from multiple GTPase inputs, a feature shared by the ARAPs (see below).

**ASAP subfamily**
The ASAPs are associated with plasma membrane specializations (e.g., focal adhesions and invadopodia), and regulate aspects of endocytic traffic and actin remodeling (Nie and Randazzo, 2006; Inoue and Randazzo, 2007; Randazzo et al., 2007). ASAPs are found exclusively in animals, and have been duplicated in vertebrates, with three genes in humans that share multiple domains (see Fig. 1A) but differ in their C termini. ASAP1 has tandem repeats of [D/ELPPKP] and an SH3 domain, ASAP2 has an SH3 domain but no E/DLPPKP repeats, and ASAP3 has neither of these motifs. These differences at the C termini have
led to confusion in nomenclature, but phylogenetic analysis of the ArfGAP domains supports the conclusion that these three ASAPs form a distinct group.

ASAP1 was identified as a Src-binding protein but also binds CrkL, focal adhesion kinase, CD2AP, and CIN85 (Inoue and Randazzo, 2007). ASAP2 binds pyk2, a focal adhesion kinase, whereas ASAP3 associates with focal adhesions and regulates stress fibres (Ha et al., 2008).

**AGAP subfamily**

AGAPs are present in animals only and there are 11 human genes predicted to encode AGAP-type proteins, arising from amplifications in regions of human chromosome 10q, with a number of pseudogenes predicted in this same region. AGAPs possess a GTP-binding domain, reported to directly bind and activate Akt and other Ras effectors (Ye and Snyder, 2004). AGAP2 has multiple splice variants with one possessing an SH3 binding motif N-terminal to the GTP-binding protein-like domain. AGAP1 and AGAP2 have been the most extensively characterized members of this group. They function in the endocytic system; AGAP1 working with AP-3 and AGAP2 with AP-1 (Nie and Randazzo, 2006).

**ACAP subfamily**

ACAPs regulate Arf6-dependent actin remodeling and endocytosis and receptor tyrosine kinase-dependent cell movement (Inoue and Randazzo, 2007). ACAP1 functions as part of an Arf6-regulated clathrin coat (Li et al., 2007). ACAPs are found in *Dictyostelium* and metazoans, with vertebrate duplications resulting in three human genes. ACAP is an acronym for ArfGAP with coiled coil, ankyrin repeat, and PH domains, though the coiled coil domain was later identified as a BAR domain.

**ARAP subfamily**

The presence of ArfGAP, RhoGAP, ankyrin repeats, and Ras association domains in ARAPs intimates that they are important coordinators of two or more GTPase signaling pathways. Although the domain structures of the three ARAPs are similar, the proteins are distinct in functions and cellular locations with individual ARAPs showing different Arf, Rho, and Ras binding specificities. Pathways affected by different family members include signaling through EGF receptor, focal adhesion dynamics, and lamellipodia formation (Inoue and Randazzo, 2007; Randazzo et al., 2007). ARAPs are specific to chordates, with three human genes.

**Summary**

ArfGAPs play critical roles in secretory and endocytic membrane traffic as well as actin remodeling. Other ArfGAPs serve as scaffolds for cell signaling, allowing them to mediate cross-talk between members of different GTPase families. Future studies aimed at dissecting ArfGAP functions and at identifying sources of specificity and regulation in their actions are certain to provide important insights into the role of ArfGAPs in cell physiology and in human pathologies. These outcomes should be facilitated by rapid adoption of the consensus nomenclature described herein.

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**References**


Liu, Y.W., C.F. Huang, K.B. Huang, and F.J. Lee. 2005. Role for Gcs1p in are facilitated by rapid adoption of the consensus nomenclature described herein.

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**NOMENCLATURE FOR THE HUMAN ARFGAP PROTEINS**

Kahn et al.


