

**Table S1.** RGS proteins and their domain compositions.

<b>Proteins</b>	<b>Domains<sup>a</sup></b>
XP_921002.3, NP_080722.1, NP_694811.1, NP_056626.2, NP_001182677.1, NP_033089.2, NP_001171266.1, NP_080694.1, NP_001074212.1, NP_033088.2, NP_075019.1, NP_067349.2, XP_894544.3, NP_064305.2, NP_035397.2, NP_001155294.1, NP_033087.2, NP_001030608.1, NP_080656.2, NP_064342.1	<b>PF00615.14</b>
NP_062370.2, NP_036068.2, NP_061357.3, NP_001106182.1, NP_036011.3, NP_001033107.1	<b>PF00615.14</b> , PF00069.20
NP_796052.2, NP_570933.1	<b>PF00615.14</b> , PF00069.20, PF00169.24
NP_599018.3	<b>PF00615.14</b> , PF00595.19, PF03153.8
NP_001185932.1, NP_036010.2, NP_001074538.1, NP_001159406.1, NP_035398.2	<b>PF00615.4</b> , PF00610.16, PF00631.17
NP_056627.1	<b>PF00615.14</b> , PF00610.16, PF00631.17, PF06718.6
NP_058038.2	<b>PF00615.14</b> , PF02188.12, PF02196.10
NP_775578.2	<b>PF00615.14</b> , PF02188.12, PF02196.10, PF00595.19, PF00640.18, PF11470.3
NP_001156984.1	<b>PF00615.14</b> , PF02196.10, PF02188.12, PF11470.3
NP_001230152.1	<b>PF00615.14</b> , PF15171.1
NP_056547.3, NP_033863.2, NP_001153070.1	<b>PF00615.14</b> , PF00778.12, PF08833.5
NP_766514.2, NP_001014973.2	<b>PF00615.14</b> , PF00787.19, PF08628.7, PF02194.10
NP_997096.2	<b>PF00615.14</b> , PF00787.19, PF08628.7, PF02194.10, PF12761.2
NP_835177.2, NP_001152957.1, NP_001152958.1	<b>PF00615.14</b> , PF00169.24, PF13716.1, PF00018.23, PF00435.16, PF00621.15
NP_001123624.1, NP_032514.1, NP_001123625.1	<b>PF09128.6</b> , PF00621.15, PF15405.1
NP_001003912.1	<b>PF09128.6</b> , PF00621.15, PF00595.19
NP_001123623.1, NP_001123622.1	<b>PF09128.6</b> , PF00621.15
NP_081420.2	<b>PF09128.6</b> , PF00621.15, PF00595.19, PF03938.9

<sup>a</sup>Domains were identified using an E-value threshold of 1.0 and without allowing overlaps. RGS domain (PF00615) and RGS-like domain (PF09128) are indicated in bold.

**Table S2.** Clusters identified in the primary MOCASSIN-prot network for the RGS proteins.

<b>Cluster<sup>a</sup></b>	<b>Node</b>	<b>NCBI Accession</b>	<b>Protein Name<sup>b</sup></b>
C1 (159.0567)	P44	NP_001155294.1	Regulator of G-protein signaling 17 isoform 1
	P53	NP_064342.1	Regulator of G-protein signaling 17 isoform 2
C2 (146.7074)	P33	NP_067349.2	Regulator of G-protein signaling 20 isoform 2
	P19	NP_001171266.1	Regulator of G-protein signaling 20 isoform 1
	P6	NP_080722.1	Regulator of G-protein signaling 19
C3 (134.7646)	P38	NP_032514.1	Rho guanine nucleotide exchange factor 1 isoform d
	P37	NP_001123622.1	Rho guanine nucleotide exchange factor 1 isoform a
	P35	NP_001123623.1	Rho guanine nucleotide exchange factor 1 isoform b
	P20	NP_001123625.1	Rho guanine nucleotide exchange factor 1 isoform c
	P2	NP_001123624.1	Rho guanine nucleotide exchange factor 1 isoform c
C4 (119.9047)	P3	NP_796052.2	Beta-adrenergic receptor kinase 2 isoform 1
	P40	NP_570933.1	Beta-adrenergic receptor kinase 1
	P47	NP_001030608.1	Beta-adrenergic receptor kinase 2 isoform 2
C5 (71.9517)	P26	NP_001185932.1	Regulator of G-protein signaling 7 isoform 2
	P54	NP_036010.2	Regulator of G-protein signaling 7 isoform 1
	P4	NP_056627.1	Regulator of G-protein signaling 6
C6 (71.1609)	P31	NP_001106182.1	G protein-coupled receptor kinase 6 isoform c
	P55	NP_036068.2	G protein-coupled receptor kinase 6 isoform b
	P22	NP_001033107.1	G protein-coupled receptor kinase 6 isoform a
	P36	XP_894544.3	PREDICTED: regulator of G-protein signaling 21
	P5	XP_921002.3	PREDICTED: regulator of G-protein signaling 21
	P24	NP_001074212.1	G protein-coupled receptor kinase 4 isoform 2
	P51	NP_080656.2	Regulator of G-protein signaling 8
	P41	NP_035397.2	Regulator of G-protein signaling 16
	P10	NP_062370.2	G protein-coupled receptor kinase 4 isoform 1
	P46	NP_033087.2	Regulator of G-protein signaling 2
	P28	NP_033088.2	Regulator of G-protein signaling 4
	P8	NP_056626.2	Regulator of G-protein signaling 1
	P14	NP_033089.2	Regulator of G-protein signaling 5
	P32	NP_075019.1	Regulator of G-protein signaling 18
	P21	NP_080694.1	Regulator of G-protein signaling 10
	P52	NP_061357.3	G protein-coupled receptor kinase 5
	P7	NP_694811.1	Regulator of G-protein signaling 13
	P18	NP_001003912.1	Rho guanine nucleotide exchange factor 11
	P17	NP_036011.3	Rhodopsin kinase precursor
	P16	NP_001014973.2	Sorting nexin-13
	P27	NP_081420.2	Rho guanine nucleotide exchange factor 12
	P39	NP_064305.2	A-kinase anchor protein 10, mit. Precursor
	P9	NP_001182677.1	Regulator of G-protein signaling 22
P1	NP_058038.2	Regulator of G-protein signaling 14	
P49	NP_766514.2	Sorting nexin-14	
P50	NP_599018.3	Regulator of G-protein signaling 3 isoform 2	
P29	NP_001156984.1	Regulator of G-protein signaling 12 isoform B	
P42	NP_997096.2	Sorting nexin-25	
P30	NP_001230152.1	Regulator of G-protein signaling protein-like	
P12	NP_775578.2	Regulator of G-protein signaling 12 isoform A	

**Table S2. (continued)**

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C7 (68.8465)	P48	NP_035398.2	Regulator of G-protein signaling 9 isoform 1
	P34	NP_001159406.1	Regulator of G-protein signaling 9 isoform 2
	P15	NP_001074538.1	Regulator of G-protein signaling 11
C8 (55.5742)	P11	NP_835177.2	Guanine nucleotide exchange factor DBS isoform 1
	P43	NP_001152958.1	Guanine nucleotide exchange factor DBS isoform 2
	P25	NP_001152957.1	Guanine nucleotide exchange factor DBS isoform 3
C9 (36.2278)	P23	NP_001153070.1	Axin-1 isoform 1
	P45	NP_033863.2	Axin-1 isoform 2
	P13	NP_056547.3	Axin-2

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<sup>a</sup>Proteins in each cluster are listed in descending order according to their optimal objective value (see Figure S3). Average optimal objective value for each cluster is shown in parentheses.

<sup>b</sup>Protein names are based on NCBI annotation.

**Table S3.** Comparison of the clustering results for 55 RGS family proteins among MOCASSIN-prot, TRIBE-MCL, and phylogenetic method.<sup>a</sup>

MOCASSIN-prot (primary)	MOCASSIN-prot (secondary)	TRIBE-MCL (I=5.0)	Phylogenetic clustering
1: NP_001155294.1, NP_064342.1	1: NP_001106182.1, NP_036068.2, NP_001033107.1	1: NP_599018.3, NP_001123625.1, NP_061357.3, NP_001106182.1, NP_035398.2, NP_035397.2, NP_835177.2, NP_033863.2, NP_081420.2, NP_001123622.1, NP_080722.1, NP_075019.1, NP_036011.3, NP_080694.1, NP_001014973.2, NP_001152957.1, NP_001152958.1	1: NP_001153070.1, NP_033863.2, NP_056547.3
2: NP_067349.2, NP_001171266.1, NP_080722.1	2: NP_032514.1, NP_001123622.1, NP_001123623.1, NP_001123525.1, NP_001123624.1	2: NP_033089.2	2: NP_033089.2
3: NP_032514.1, NP_001123622.1, NP_001123623.1, NP_001123525.1, NP_001123624.1	3: NP_062370.2, NP_036011.3, NP_061357.3	3: NP_035397.2, NP_080656.2	3: NP_035397.2, NP_080656.2
4: NP_796052.2, NP_570933.1, NP_001030608.1	4: NP_835177.2, NP_001152958.1, NP_001152957.1	4: NP_033088.2	4: NP_033088.2
5: NP_001185932.1, NP_036010.2, NP_056627.1	5: NP_001153070.1, NP_033863.2, NP_056547.3	5: NP_599018.3	5: NP_599018.3
6: NP_001106182.1, NP_036068.2, NP_001033107.1, XP_894544.3, XP_921002.3, NP_001074212.1, NP_080656.2, NP_035397.2, NP_062370.2, NP_033087.2, NP_033088.2, NP_056626.2, NP_033089.2, NP_075019.1, NP_080694.1, NP_061357.3, NP_694811.1, NP_001003912.1, NP_036011.3, NP_001014973.2, NP_081420.2, NP_064305.2, NP_001182677.1, NP_058038.2, NP_766514.2, NP_599018.3, NP_001156984.1, NP_997096.2, NP_001230152.1, NP_775578.2	6: NP_001185932.1, NP_036010.2, NP_056627.1	6: NP_036068.2, NP_001185932.1, NP_796052.2, NP_033087.2, NP_001171266.1, NP_001033107.1, NP_056627.1, NP_064305.2, NP_001182677.1, NP_064342.1	6: XP_921002.3, XP_894544.3
7: NP_035398.2, NP_001159406.1, NP_001074538.1	7: NP_796052.2, NP_570933.1, NP_001030608.1	7: NP_997096.2, NP_001155294.1	7: NP_694811.1
8: NP_835177.2, NP_001152958.1, NP_001152957.1	8: NP_035398.2, NP_001159406.1, NP_001074538.1	8: NP_570933.1, NP_001230152.1, NP_033088.2	8: NP_056626.2
9: NP_001153070.1, NP_033863.2, NP_056547.3	9: NP_001003912.1, NP_001014973.2, NP_081420.2, NP_064305.2, NP_058038.2, NP_766514.2, NP_599018.3, NP_001156984.1, NP_997096.2, NP_775578.2	9: NP_056547.3, NP_080656.2, NP_001030608.1, NP_0325514.1, NP_001159406.1, NP_775578.2, NP_001003912.1	9: NP_056626.2
	10: NP_033089.2, NP_001230152.1	10: NP_001156984.1, NP_001074538.1, NP_001074212.1, NP_062370.2, NP_766514.2, NP_067349.2	9: NP_0750019.1
	[Singletons] NP_001155294.1 NP_064342.1 NP_067349.2 NP_080722.1 NP_001171266.1 XP_894544.3 XP_921002.3 NP_001074212.1 NP_080656.2 NP_035397.2 NP_033087.2 NP_033088.2 NP_056626.2 NP_075019.1 NP_080694.1 NP_694811.1 NP_001182677.1	11: NP_033089.2, NP_997096.2, NP_001155294.1	10: NP_001155294.1, NP_064342.1, NP_080722.1, NP_067349.2, NP_001171266.1
		12: NP_570933.1, NP_001230152.1, NP_033088.2	11: NP_035398.2, NP_001159406.1, NP_001074538.1
		13: NP_001003912.1, NP_081420.2, NP_064305.2, NP_058038.2, NP_766514.2, NP_599018.3, NP_001156984.1, NP_997096.2, NP_775578.2	12: NP_080694.1, NP_058038.2, NP_001156984.1, NP_775578.2
		14: NP_001156984.1, NP_001074538.1, NP_001074212.1, NP_062370.2, NP_766514.2, NP_067349.2	13: NP_766514.2
		15: NP_001156984.1, NP_001074538.1, NP_001074212.1, NP_062370.2, NP_766514.2, NP_067349.2	14: NP_001230152.1
		16: NP_058038.2, NP_001123623.1, XP_921002.3, NP_036010.2, NP_001123624.1, XP_894544.3	15: NP_081420.2
		17: NP_058038.2, NP_001123623.1, XP_921002.3, NP_036010.2, NP_001123624.1, XP_894544.3	16: NP_796052.2, NP_570933.1
		18: NP_694811.1, NP_056626.2, NP_001153070.1	17: NP_036011.3, NP_061357.3, NP_001074212.1, NP_062370.2, NP_001033107.1, NP_001106182.1, NP_026068.2
			18: NP_835177.2, NP_001152958.1, NP_001152957.1
			19: NP_064305.2
			20: NP_001182677.1
			21: NP_001014973.2
			22: NP_033087.2, NP_001185932.1, NP_056627.1, NP_036010.2
			23: NP_001003912.1, NP_001123624.1, NP_001123623.1, NP_032514.1, NP_001123622.1, NP_001123625.1
			24: NP_001030608.1
			25: NP_997096.2

<sup>a</sup>Clusters that are identical between the ones found in the primary MOCASSIN-prot network and those found in other methods are shown in yellow background.