TABLE S2: Class-Distinctive Sites Summary

Site[1]	η amino acid	∂ amino acid (subclass)	Distinctive Class[2]	Position within Class[3]	Comments
1	D/E	A ($G\alpha_{12}$) G ($G\alpha_{13}$)[7]	G(12)	#1	
2	D/E	A ($G\alpha_{q}$) V ($G\alpha_{11}$)[7,8]	G(q)	#1	
3	K/R	A ($G\alpha_{13}$)[5,8]	G(12)	#2	
4	K/R	D ($G\alpha_{q}$) A ($G\alpha_{11}$,$G\alpha_{14}$)[7]	G(q)	#2	Less aqueous environment during GPCR-driven activation
5	K/R	A ($G\alpha_{12}$) [5,8]	G(12)	#3	Less aqueous environment during GPCR-driven activation
6	L	V (mouse $G\alpha_{q}$, $G\alpha_{14}$)[6,8]	G(q)	#3	
7	K/R	E ($G\alpha_{i}$,$G\alpha_{o}$,$G\alpha_{t}$)[4]	G(io)	#1	Potential contact to GPCR
8	K/R	G ($G\alpha_{i}$,$G\alpha_{o}$) A ($G\alpha_{t}$)[7]	G(io)	#2	Potential contact to GPCR
9	K/R	A ($G\alpha_{i}$,$G\alpha_{o}$,$G\alpha_{t}$)[4]	G(io)	#3	Potential contact to GPCR
10	K/R	A ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#1	Key for GPCR selectivity in G(q) subunits
11	A	T ($G\alpha_{q}$,$G\alpha_{11}$,$G\alpha_{14}$)[4]	G(q)	#4	
12	G	D/E ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#4	
13	F/Y	S (rat $G\alpha_{olf}$)[6,8]	G(s)	#2	
14	D/E	A ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#5	
15	F/Y	K ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#3	
16	F/Y	K/R ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#4	
17	I/L	M ($G\alpha_{q}$,$G\alpha_{11}$,$G\alpha_{14}$)[4] V (rat $G\alpha_{11}$)[6]	G(q)	#5	
18	M	R ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#6	
19	N	R ($G\alpha_{i}$,$G\alpha_{o}$,$G\alpha_{t1}$) C ($G\alpha_{t2}$)[7]	G(io)	#4	
20	C	A ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#7	
21	S	C ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#5	
22	I/L	V ($G\alpha_{11}$)[5,8]	G(q)	#6	
23	K/R	V ($G\alpha_{s}$) S ($G\alpha_{olf}$)[7]	G(s)	#6	
24	S/T	N (mouse, bovine $G\alpha_{t2}$)[6,8]	G(io)	#5	
25	R	L ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#8	
26	V	K/R ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#9	Tethers Switch I to insert in α-helical domain
27	S/T	K ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#10	Mutation diminishes P115RhoGEF binding
28	K/R	H ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#7	
29	M	L ($G\alpha_{o}$)[5,8]	G(io)	#6	
30	S	D ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#8	
31	E	Q ($G\alpha_{12}$)[5,8]	G(12)	#11	
32	K/R	Q ($G\alpha_{12}$)[5,8]	G(12)	#12	Contact to p115RhoGEF
33	I	F ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#13	Contact to p115RhoGEF
34	D/E	N ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#9	Mutant slightly reduces adenylyl cylase binding
35	V	I ($G\alpha_{12}$)[5,8]	G(12)	#14	
36	I/L	M ($G\alpha_{q}$,$G\alpha_{11}$)[5,8]	G(q)	#7	

37	A	S ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#15	
38	D	N ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#10	
39	D	S ($G\alpha_{q}$,$G\alpha_{11}$) C ($G\alpha_{14}$)[7]	G(q)	#8	
40	I	T (orangutan $G\alpha_{i1}$)[6,8]	G(io)	#7	
41	N	T ($G\alpha_{q}$,$G\alpha_{11}$,$G\alpha_{14}$)[4]	G(q)	#9	Contact to GRK2
42	K/R	P ($G\alpha_{q}$,$G\alpha_{11}$,$G\alpha_{14}$)[4]	G(q)	#10	P➔K mutation eliminates GRK2 binding
43	F	L ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#11	Important for adenylyl cyclase binding
44	I	V ($G\alpha_{t}$)[5,8]	G(io)	#8	
45	L	F ($G\alpha_{i}$,$G\alpha_{o}$,$G\alpha_{t}$)[4]	G(io)	#9	
46	P	L ($G\alpha_{13}$)[5,8]	G(12)	#16	
47	G	R ($G\alpha_{s}$) N ($G\alpha_{olf}$)[7]	G(s)	#12	
48	A	V ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#17	
49	F/Y	H (rodent $G\alpha_{o2}$)[6,8]	G(io)	#10	
50	K/R	H ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#13	Important for adenylyl cyclase binding
51	F	V ($G\alpha_{o2}$)[6] M ($G\alpha_{o1}$,$G\alpha_{t}$)[7,8]	G(io)	#11	
52	C	T ($G\alpha_{12}$,$G\alpha_{13}$)[4]	G(12)	#18	
53	D	N ($G\alpha_{13}$)[5,8]	G(12)	#19	
54	D/E	K ($G\alpha_{i}$) N ($G\alpha_{o}$) Q ($G\alpha_{t}$)[7]	G(io)	#12	Mobility changes during GPCR-driven activation, decreased rate of receptor-catalyzed exchange
55	K/R	Q ($G\alpha_{i}$,$G\alpha_{o}$)[5,8]	G(io)	#13	Mutation increased basal rate of exchange, decreased rate of receptor-catalyzed exchange
56	V	C ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#14	
57	K/R	T ($G\alpha_{i}$,$G\alpha_{o}$,$G\alpha_{t}$)[4]	G(io)	#14	Mutation decreased rate of receptor-catalyzed exchange
58	I/L	Q ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#15	
59	N	H ($G\alpha_{s}$,$G\alpha_{olf}$)[4]	G(s)	#16	

[1] Corresponds to the order of sites in Figure 2.

[2]G(io), G(q), G(s), and G(12) sites denoted by 'I', 'Q', 'S', and '2', respectively, in Figure 2.

[3] Corresponds to the site number given in Figures 3-6 and the order of sites in Figure 7.

[4] Single ∂ amino acid in <u>all</u> subclasses within distinctive class

[5] Single ∂ amino acid in some but not all subclasses within distinctive class

[6] Single ∂ amino acid in just a few sequences (but not an entire subclass) within distinctive class

[7] ∂ amino acid varies with subclass within distinctive class

[8] η amino acids found in distinctive class