Table 2: Mutational effects of global trace residues

TM	Residue (Bovine rhodopsin)		Mutated to	GPCR Family	Effect
1	N55	3	N57A N51D	α1B adrenergic(1) , Oxytocin Receptor(2) Tachykinin NK-2 receptor (3)	CA Inactive/Expression ↑ sensitivity agonist.
	T62	2	T62C T62A	Rhodopsin (4) Rhodopsin (5) NK2 receptor (6)	ME (conf. changes) Kinase Coupling Fluorescent aa to measure receptor topology.
2	L72	1	L72A	Rhodopsin (7)	Dec. G_t Activity
	N73	3	N73A N86I R395A	Rhodopsin (7) Drosophila opsin (8) Glycoprotein Hormone receptor (9)	Dec. G_t Activity Folding/Expression Expression/ligand binding
	I75	0	I75C	*Rhodopsin (10)* *Rhodopsin (11)*	NA NA
	L76	8	T398M H223R H178R/K/E/A H178R L80A	Leutinizing Hormone(12), Parathyroid Hormone (13-15) Glucagon Receptor(16) VIP-1 Receptor(17) GNRH Receptor (18) LH receptor (19)	CA, Agonist-antagonist switching, G-protein binding uncoupled cAMP abolished Precocious puberty
	N78	2 1	N58A D63N S50A	Platelet Activating Factor(20) PAF (21) A1 adenosine receptor (22)	CA Ligand binding/G-protein activation No effect
	L79	0		No Mutational Data Found	
	F85	3	 C462S	Gastrin Receptor (23) Neurokinin-1 receptor (24) Thyrotropin receptor (25)	Ligand Binding Ligand Binding Ligand Binding
	M86	6 1	F77S H150A L107F	Angiotensin 2 (26) Tachykinin NK3 receptor (27) Endothelin type A receptor (28) Endothelin type A receptor (29) Endothelin type B receptor (30) SSTR1 receptor (31) Rhodopsin (32)	CA/Ligand Binding Ligand binding Ligand binding Ligand binding Ligand Binding Ligand Binding No effect
	V87	5 2	 H81QDRAG L78F S74I C86S	Rhodopsin (33) Rhodopsin (34) Prostaglandin F2 α receptor (35) Angiotensin 2 receptor (26) ACTH receptor Glucocorticoid deficiency syndrome (36) α 1B adrenergic (37) C5A receptor (38)	ADRP Expression/ADRP Ligand Binding CA/Ligand Binding Dose response affected No Effect No effect

	F91	2	P90A V92M	C5A receptor (38) Melanocyte Stimulating hormone receptor (39)	Ligand Binding Ligand Binding
3	C110	15	 C124A D117A D117A C179A C110A C178 C106A C80S C105S C90S/A C117A C105S C116A	Melanocortin-1(40) *rhodopsin,(41)* *AcH receptor (42)* P2Y1 receptor (43) Melanocortin Receptor (44) α MSH receptor (45) Thyrotropin RH receptor (46) IL-8 Type A receptor (47) CCR-5 receptor (48) Angiotensin II (49) β2 adrenergic receptor (50) A1 adenosine receptor (51) TBXA2 receptor (52) PAF receptor (53) AT-2 receptor (54) Tachykinin NK1 receptor (55) Growth hormone receptor (56)	CA, ME ME Expression Ligand binding, Ligand binding, Ligand binding, Ligand binding, Ligand binding, Ligand binding, Ligand Binding Expression Ligand Binding Ligand Binding/ Expression Inactivation/ Ligand Binding Ligand Binding Expression/Ligand binding
	T118	7 2	H132A F98A K118S S109A K142/multiple E124Q Y129A S109A G135A	P2Y1 receptor (57) PAF receptor (58) B1 Bradykinin receptor (59) Rat Angiotensin receptor (60) Endothelin-B receptor (61) Growth Hormone receptor (62) Delta opioid receptor (63) Angiotensin receptor (64) CCK-B Gastrin receptor (65)	Ligand Binding Ligand Binding Ligand Binding Ligand Binding Ligand Binding Ligand Binding Ligand Binding No effect No effect
	G120	11	N111G N111S N113A N100A G120D N150A C106A A115V	β 2 Adrenergic Receptor (66) α 1B Adrenergic Receptor (67) Angiotensin 1(AT1) receptor (68) A1 receptor (69) Bradykinin B2 (70) Platelet Activating Factor (PAF) receptor (20) AT1 receptor (71) Rhodopsin (72) Opioid receptor (73) Dopamine D1 receptor (74) Tachykinin NK1 receptor (75)	CA CA/Ligand Binding Ligand Binding,CA CA/ Agonist-antagonist Switching CA/Inactive Ligand Binding Ligand Binding Ligand Binding Ligand Binding
	G121	5 4	S107G S159A C114S T101A G121L	Dopamine D1 receptor (74) Serotonin Receptor (76) Dopamine D3 receptor (77) PAF receptor (20)	Ligand Binding Ligand Binding Ligand Binding Ligand Binding Receptor activity

			S120G C129A F112A M117L	Rhodopsin (78) EP2 prostaglandin receptor (79) α 1B adrenergic receptor (80) CCR5 receptor (81) Neurokinin 2 receptor (82)	No Effect alone but ↑ activity with L304Y No effect No effect No effect
	L128	1	L128H	Opsin (83)	CA
	L131	1 1	L131A L122A	Acetylcholine Receptors (84) CCR5 receptor (81)	CA/ ligand binding No effect
	A132	3 2	 T123A S140A T112A	Dopamine Receptor (85) Acetylcholine Receptors (84) CCR5 receptor (81) α 1B adrenergic receptor (80) Platelet Activating Factor (PAF) receptor (20)	CA/Ligand binding CA/Ligand binding Ligand Binding No effect No effect
	E134	19	E134Q E134S/I/Q D142/all D130N D142T/A D115A/N D122N D122A	Rhodopsin (86) Rhodopsin (87) α 1B adrenergic receptor (1) β 2 adrenergic receptor(88) Chemokine C-X-C receptor(89) β adrenergic receptor (90) Acetylcholine Receptor (91) α 2A adrenergic receptor (92) AT-2 receptor (93) Rhodopsin (94) Rhodopsin (95) M1 muscarinic receptor (96) Oxytocin receptor (2) Rhodopsin (97) Rhodopsin (98) α 1B adrenergic receptor (99) Histamine H2 receptor (100) M1 muscarinic receptor (101) n-formyl peptide receptor (102)	CA CA/ G-prot coupling CA CA/ME/ Ag-An switching CA ↓ Gprotein affinity, LB ME & G-prot. coupling Ag-An switching G-protein coupling CA CA, ↑ agonist binding, ↓sequestration, IP production Expression/ No Ca^{2+} increase
	R135	12	 R139N R137H	Oxytocin receptor (2) Oxytocin receptor (103) Rhodopsin (87) *GNRH receptor (104)* Muscarinic receptor (105) *Rhodopsin (106)* AT-2 receptor (93) *Rhodopsin (107)* M1 muscarinic receptor (108) Rhodopsin (98)	CA CA/ mech importance G-prot coupling/ ↓ IP production ME G-protein coupling ME ↓ IP production ME ME & G-prot. coupling

			R183A R116A R123G R464H	Vasopressin Receptor (109) Serotonin Receptor (110) Histamine H2 receptor (100) N-formyl peptide receptor (111) Gonadotropin receptor (112)	 ↑ antagonist bind Folding G-protein binding ↓ cAMP prod.
	Y136	6 1	Y127A Y135A Y139F Y127H Y136A Y132A	Angiotensin-2 receptor (93) CXCR4 receptor (113) CCR2 receptor (114) AT1 receptor (115) IL-8 receptor (in combo with other neighboring mutants) (116) GNRH receptor (117) CXCR-4 receptor (118) (DRY → NAA motif mutant)	G-protein coupling Expression Kinase coupling IP production/ G_q coupling $G_i\alpha$ coupling Internalization/Expression Not reqd. for co-receptor function
	V138	3	V138H S134A	β 2 adrenergic receptor (119) Rhodopsin (120) α2A adrenergic receptor (121) (in association with L134S)	G-protein coupling G-protein specificity
4	A153	2	E179A E156N	Bradykinin receptor (122) GNRH receptor (104) (combo mutant)	Ligand Binding ↑ internalization
	W161	10 2	W192F W173A W200A W161A W153A W155A W173A W163A W161L	M3 muscarinic receptor (123) β 2 adrenergic receptor (124) Neuropeptide Y1 receptor (125) Delta opiod receptor (63) Formyl peptide receptor (126) Serotonin receptor (127) Histamine H1 receptor (128) AT1 receptor (64) Neurokinin-1 receptor (129) δ opioid receptor (63) Neuropeptide Y receptor (125) Rhodopsin (130)	Ligand binding Ligand binding Ligand binding Ligand binding Ligand binding/ expression/ Ligand Binding Ligand Binding Ligand Binding Ligand Binding Ligand Binding Ligand Binding No effect No effect
5	V204	7 3	V185A A204V K200A K198A H198A M213K A213K G196W/I S219A S212A	α 1B adrenergic receptor (37) α 1B adrenergic receptor (131) Histamine H1 receptor (128) Tachykinin NK2 receptor (132) NK-2 receptor (132) Growth Hormone receptor (56) Orphanin/Opioid receptor (133) AT-1A receptor (134) CCK-B receptor (65) Gastrin releasing peptide receptor (135)	Ligand binding CA/ Ligand binding Ligand Binding Ligand Binding Ligand Binding Ligand Binding Ligand Binding No effect No effect No ligand binding effect

	P215	3	P214A	C5A receptor (38) Dopamine D2 receptor (136) M3 muscarinic receptor (123)	Ligand Binding Ligand Binding Expression
	C222	2	C600S	Rhodopsin ADRP (33) Thyrotropin receptor (137)	CA
	Y223	3	Y216A Y601H Y215F	Neurokinin-1 receptor(138) Thyrotropin receptor (139) Angiotensin-2 receptor (140)	Ligand binding/ME G-protein coupling G-protein coupling
6	V254	10	V285A T410P T410P T343/K/P/A	Muscarinic (141) PTH receptor (142) PTH receptor (143) Secretin receptor (15) Glucagon receptor (16) VIP receptor (144) M1/M3 acetylcholine muscarinic receptor (145) M2 muscarinic receptor(146) M2 muscarinic receptor (147) M2 muscarinic receptor (141)	CA/G-protein coupling CA CA CA/Ag-An switching CA CA G-protein specificity/coupling G-protein specificity G-protein coupling G-protein coupling
	M257	3	I245T F270A	Opsins (148) AT-2 Type 1A receptor (26) Gastrin releasing peptide receptor (135)	CA CA/Ligand Binding Receptor Activity/ Ligand binding
	W265	9 2	W265/Y/F/A W327A W336A W455C W503F W265F W279S/R W346A W279A W253A W278A	Rhodopsin (130) Serotonin B receptor (149) Serotonin receptor (127) M5 muscarinic receptor (150) M3 muscarinic receptor (123) Rhodopsin (151) Gonadotropin releasing Hormone receptor (152) Gastrin receptor (65) Thyrotropin releasing hormone receptor (153) AT1 receptor (64) Gastrin releasing peptide receptor (135)	Ligand binding Ligand binding Ligand Binding ↓Receptor activity Ligand Binding/ receptor function Blue shift Ligand Binding/ IP production. ↑Ligand Binding CA/ Ligand binding No effect No effect
	P267	6	P258L P562L P267R P505F/E P267L P267N	α factor pheromone receptor (154) α factor pheromone receptor (155) *hcG receptor (156)* Rhodopsin (157) M3 muscarinic(123) Rhodopsin (158) Rhodopsin (130)	CA CA ME Folding/expression Ligand binding/ Folding/expression Expression G-protein coupling
7	N302	8 2	N322A N303A/S N396A/F N376D	β 2 adrenergic receptor (159) *Tachikinin NK2 receptor (3)* Serotonin receptor (160) Serotonin receptor (161)	Folding/expression / ligand binding. ME Ligand Binding

			D338A D289A N293A D318E/L N332D N303A/D/S N391D	 Prostaglandin EP3 receptor (162) PAF receptor (163) CCR5 receptor (81) Gonadotropin Releasing Hormone Receptor (164) μ Opioid receptor (165) Tachykinin NK-2 receptor (3) CholecystokininB receptor (166)	Expression/ Signaling Receptor activation G-protein coupling Expression Expression Ligand Binding No effect No effect
	P303	11	 P505F/E P598F P323S P591L P299A I380A P598F	β 2 adrenergic receptor (159) M3 muscarinic (123) Lutropin receptor (167) Rhodopsin (72) β adrenergic receptor (168) lutropin receptor (169) M3 muscarinic (123) Muscarinic Ach receptor (170) AT-2 Type 1 receptor (171) Endothelin B receptor (172) Lutropin receptor (167)	Folding/expression / ligand binding. Ligand binding/ Folding/expression Folding/expression Folding/expression Folding/expression Folding/expression Ligand binding/ Folding/expression Folding/expression Ligand Binding/ receptor activity ↑ receptor activity Expression
	I305	5	C417S F301L F301A L385A	M1 muscarinic receptor (173) Angiotensin 2(60) Type 1B angiotensin 2 receptor (174) AT2 Type 1 receptor (171) Endothelin B receptor (172)	Ligand binding/G-protein coupling Ligand binding Ligand binding ↓ Receptor activity
	Y306	10 4	Y348A Y302F/A Y306C Y302A Y326A Y293A Y302F Y371A Y322A Y348L Y297A Y386A Y324A	α 1B adrenergic receptor (175) *β 2 adrenergic receptor (159)* *lutropin receptor (169)* Angiotensin 2(176) Rhodopsin (177) Angiotensin 2(178) PAF (179) β 2 adrenergic receptor (180) PAF receptor (163) Lipoxin A4 receptor (181) Thrombin receptor (182) Gonadotropin releasing Hormone (183) α 1B adrenergic receptor (184) CCR5 receptor (81) CCK type A receptor (185) Gastrin releasing peptide receptor (186)	Ligand binding/ G-protein coupling/ ME/ expression ME ME ME/G-protein coupling G-protein coupling G-protein coupling G-protein coupling No receptor internalization. Expression/sequestrtion G-protein coupling CA Receptor Function G-protein coupling/ ↓ IP production No effect on ligand No effect No effect No effect
	I307	2 1	 Y372A	D3 dopamine receptor(187)	Ligand binding Receptor function

			C306A	Thrombin receptor (182) NK1 receptor (55)	No effect
	N310	2		Rhodopsin (177) Rhodopsin (188)	G-protein coupling G-protein coupling

Index:

Black Font: Mutations that had observable functional effect

Red Font: Mutations that had no recorded effect or were neutral

Grey Background: Structural studies (Not considered a mutation)

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