Table S1. Frequent intramolecular communication paths in the wild type trajectory.

#[a]	Path[b]	Rnk[c]	Frq[d]	Len[e]	Crr[f]	Scr[g]
1	M582-Y612*-M408*-S616-**D405*-N377***-S402	15	44.55	5	5	1.00
2	M582-Y612*-**N615*-N619*-D405*-N377***-S402	18	41.37	5	5	1.00
3	M582-Y612*-**N615*-N619*-D405*-N377*-P620**	19	39.05	5	5	1.00
4	Y612*-M408*-S616-**D405*-N377***-S402-L381	33	34.29	5	5	1.00
5	M582-Y612*-M408*-S616-**D405*-N377*-P620**	34	33.88	5	5	1.00
6	Y612*-**N615*-N619*-D405*-N377***-S402-L381	35	33.10	5	5	1.00
7	I585-Y612*-M408*-S616-**D405*-N377***-S402	41	32.39	5	5	1.00
8	M582-Y612*-M408*-S616-**D405*-N377***-S402-L381	42	32.19	6	6	1.00
9	S586-M582-Y612*-M408*-S616-**D405*-N377***	52	31.27	5	5	1.00
10	M582-Y612*-**N615*-N619*-D405*-N377***-S402-L381	54	31.04	6	6	1.00
11	Y612*-**N615*-N619*-D405*-N377***-S402-V380	58	30.48	5	5	1.00

[a]Path number. [b]Communication paths occurring in ≥ 30% of the trajectory frames and characterized by a length ≥ 5. The asterisk marks the amino acids that behave as hubs in more than 30% of the trajectory frames; bold and underlined labels refer, respectively, to highly conserved and spontaneously occurring mutation sites. [c]Rank number within the entire set of saved paths, i.e., those characterized by frequency ≥ 10% and length ≥ 3. [d]Path frequencies (%), i.e., number of frames holding the path divided by the trajectory frames (i.e., 10000). [e]Path length: number of amino acids, excluding the extremes, which participate in the path. [f]Number of amino acids in the paths characterized by correlated motions with at least one of the two extremes. [g]Correlation score, i.e. ratio between number of correlated amino acids (row #6) and path length (row #5).

Table S2. Frequent intramolecular communication paths in the D564$^{(6.30)}$G trajectory.

#[a]	Path[b]	Rnk[c]	Frq[d]	Len[e]	Crr[f]	Scr[g]
1	F515-Y612*-M408*-S616-D405*-N377-P620	9	75.13	5	5	1.00
2	F515-Y612*-M408*-S616-D405*-N619*-L457*	10	69.66	5	5	1.00
3	Y612*-M408*-S616-D405*-N377-P620-V380	12	66.06	5	5	1.00
4	F515-Y612*-M408*-S616-D405*-N377-P620-V380	13	59.97	6	6	1.00
5	L608-F515-Y612*-M408*-S616-D405*-N619*	22	48.13	5	5	1.00
6	T446-M408*-S616-D405*-N377-P620-V380	23	47.84	5	5	1.00
7	L608-F515-Y612*-M408*-S616-D405*-N377	24	47.55	5	5	1.00
8	L608-F515-Y612*-M408*-S616-D405*-N377-P620	25	47.20	6	6	1.00
9	L608-F515-Y612*-M408*-S616-D405*-N619*-L457*	28	43.72	6	6	1.00
10	L608-F515-Y612*-M408*-S616-D405*-S453	29	43.28	5	5	1.00
11	P584-L608-F515-Y612*-M408*-S616-D405*	31	41.56	5	4	0.80
12	P584-L608-F515-Y612*-M408*-S616-D405*-N377	32	41.07	6	5	0.83
13	P584-L608-F515-Y612*-M408*-S616-D405*-N377-P620	34	40.75	7	6	0.86
14	Y612*-M408*-S616-D405*-L401*-T456-N400*	35	38.89	5	5	1.00
15	F515-Y612*-M408*-S616-D405*-L401*-T456	36	38.46	5	5	1.00
16	L608-F515-Y612*-M408*-S616-D405*-N377-P620-V380	37	38.21	7	7	1.00
17	Y612*-M408*-S616-D405*-L401*-T456-N400*-W491	38	38.07	6	6	1.00
18	P584-L608-F515-Y612*-M408*-S616-D405*-N619*	39	37.89	6	5	0.83
19	Y612*-M408*-S616-D405*-N619*-L457*-Y623	40	37.80	5	4	0.80
20	P584-L608-F515-Y612*-M408*-S616-D405*-S453	43	37.31	6	5	0.83
21	Y612*-M408*-S616-D405*-N619*-N615-D578*-F539	44	37.26	6	6	1.00
22	M582-F539-D578*-N615-N619*-D405*-N377	46	36.21	5	5	1.00
23	M582-F539-D578*-N615-N619*-D405*-N377-P620	49	35.60	6	6	1.00
24	Y612*-M408*-S616-D405*-N619*-N615-T577	50	35.16	5	5	1.00
25	F515-Y612*-M408*-S616-D405*-L401*-T456-N400*	51	35.11	6	6	1.00
26	Y612*-M408*-S616-D405*-N619*-L457*-Y623-Y546*	55	34.39	6	5	0.83
27	F515-Y612*-M408*-S616-D405*-L401*-T456-N400*-W491	56	34.37	7	7	1.00
28	P584-L608-F515-Y612*-M408*-S616-D405*-N619*-L457*	59	33.90	7	6	0.86
29	Y612*-M408*-S616-D405*-L401*-T456-N400*-L452*	60	33.84	6	6	1.00
30	F515-Y612*-M408*-S616-D405*-N619*-N615-D578*-F539	61	33.57	7	4	0.57
31	F515-Y612*-M408*-S616-D405*-N619*-L457*-Y623	62	33.51	6	3	0.50
32	F588-L608-F515-Y612*-M408*-S616-D405*	65	33.18	5	5	1.00
33	F588-L608-F515-Y612*-M408*-S616-D405*-N619*	66	33.17	6	6	1.00
34	P584-L608-F515-Y612*-M408*-S616-D405*-N377-P620-V380	67	32.97	8	7	0.88
35	A589-L532-S586-M582-F539-D578*-L574	68	32.84	5	5	1.00
36	F588-L608-F515-Y612*-M408*-S616-D405*-N377	69	32.81	6	6	1.00
37	F588-L608-F515-Y612*-M408*-S616-D405*-N377-P620	71	32.59	7	7	1.00
38	Y612*-M408*-S616-D405*-N619*-L457*-Y623-Y546*-M571	72	32.54	7	6	0.86
39	I585-Y612*-M408*-S616-D405*-N377-P620	73	32.46	5	5	1.00
40	F515-Y612*-M408*-S616-D405*-L401*-L457*	74	32.33	5	5	1.00
41	Y612*-M408*-S616-D405*-L401*-T456-N400*-L452*-A404	76	32.21	7	7	1.00
42	F515-Y612*-M408*-S616-D405*-N377-F406	79	31.59	5	5	1.00
43	F515-Y612*-M408*-S616-D405*-N377-S402	83	30.87	5	5	1.00
44	F515-Y612*-M408*-S616-D405*-L401*-T456-N400*-L452*	84	30.66	7	7	1.00
45	F588-L608-F515-Y612*-M408*-S616-D405*-N619*-L457*	86	30.38	7	7	1.00
46	F515-Y612*-M408*-S616-D405*-N619*-L457*-Y623-Y546*	87	30.33	7	2	0.29
47	Y612*-M408*-S616-D405*-N619*-L457*-Y623-Y546*-T461	88	30.28	7	7	1.00

See the legend to Table S1.

Table S3. Frequent intramolecular communication paths in the D578$^{(6.44)}$H trajectory.

#[a]	Path[b]	Rnk[c]	Frq[d]	Len[e]	Crr[f]	Scr[g]
1	Y612*-M408-S616-**D405*-N377-P620-V380**	9	56.46	5.00	5	1.00
2	I531-E451-N535*-H578*-**N615*-N619*-D405***	13	51.54	5.00	5	1.00
3	I531-E451-N535*-H578*-**N615*-N619*-D405*-N377**	16	49.39	6.00	5	0.83
4	T446-M408-S616-**D405*-N377-P620-V380**	18	46.85	5.00	5	1.00
5	Y527*-I531-E451-N535*-H578*-**N615*-N619***	20	46.16	5.00	4	0.80
6	P501-Y527*-I531-E451-N535*-H578*-F539*	21	46.09	5.00	4	0.80
7	P501-Y527*-I531-E451-N535*-H578*-**N615*-N619***	22	45.91	6.00	3	0.50
8	I531-E451-N535*-H578*-**N615*-N619*-L401***	23	45.25	5.00	5	1.00
9	P516-Y527*-I531-E451-N535*-H578*-F539*	25	43.16	5.00	4	0.80
10	P516-Y527*-I531-E451-N535*-H578*-**N615*-N619***	26	42.7	6.00	3	0.50
11	I531-E451-N535*-H578*-**N615*-N619***-L457*	27	42.54	5.00	3	0.60
12	I531-E451-N535*-H578*-**N615*-N619*-D405*-N377-P620**	29	40.24	7.00	6	0.86
13	I531-E451-N535*-Y612*-M408-S616-**D405***	31	39.49	5.00	4	0.80
14	Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405***	32	39.46	6.00	6	1.00
15	P501-Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405***	34	38.99	7.00	5	0.71
16	I531-E451-N535*-H578*-**N615*-N619*-D405*-N377-P620-V380**	36	38.54	8.00	7	0.88
17	Y508-P501-Y527*-I531-E451-N535*-H578*-F539*	37	38.21	6.00	5	0.83
18	Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405*-N377**	38	37.94	7.00	6	0.86
19	I531-E451-N535*-Y612*-M408-S616-**D405*-N377**	39	37.91	6.00	4	0.67
20	Y508-P501-Y527*-I531-E451-N535*-H578*-**N615*-N619***	40	37.61	7.00	4	0.57
21	P501-Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405*-N377**	41	37.48	8.00	5	0.62
22	I531-E451-N535*-H578*-**N615*-N619*-D405***-S453	42	37.47	6.00	4	0.67
23	Y527*-I531-E451-N535*-H578*-**N615*-N619*-L401***	47	36.39	6.00	6	1.00
24	P501-Y527*-I531-E451-N535*-H578*-**N615*-N619*-L401***	48	35.77	7.00	5	0.71
25	L500-Y527*-I531-E451-N535*-H578*-F539*	56	34.17	5.00	4	0.80
26	P516-Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405***	57	34.06	7.00	5	0.71
27	L500-Y527*-I531-E451-N535*-H578*-**N615*-N619***	58	34	6.00	2	0.33
28	Y527*-I531-E451-N535*-H578*-**N615*-N619***-L457*	59	33.94	6.00	4	0.67
29	P501-Y527*-I531-E451-N535*-H578*-**N615*-N619***-L457*	60	33.78	7.00	4	0.57
30	P516-Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405*-N377**	62	32.67	8.00	5	0.62
31	P516-Y527*-I531-E451-N535*-H578*-**N615*-N619*-L401***	63	32.6	7.00	5	0.71
32	Y612*-M408-S616-**D405*-N377-P620-V380**-I625	66	32.49	6.00	6	1.00
33	Y508-P501-Y527*-I531-E451-N535*-V454	68	32.27	5.00	5	1.00
34	S506-Y527*-I531-E451-N535*-H578*-F539*	70	32.12	5.00	4	0.80
35	S506-Y527*-I531-E451-N535*-H578*-**N615*-N619***	71	32.02	6.00	3	0.50
36	Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405*-N377-P620**	74	31.61	8.00	7	0.88
37	P516-Y527*-I531-E451-N535*-H578*-**N615*-N619***-L457*	75	31.43	7.00	4	0.57
38	P501-Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405*-N377-P620**	76	31.26	9.00	6	0.67
39	Y612*-H578*-**N615*-N619*-L401***-T456-N400*	78	31.08	5.00	5	1.00
40	T446-M408-S616-**D405*-N377-P620-V380**-I625	79	31.07	6.00	6	1.00
41	I531-E451-N535*-Y612*-M408-S616-**D405*-N377-P620**	80	30.8	7.00	5	0.71
42	M582-F539*-H578*-**N615*-N619*-D405*-N377**	81	30.68	5.00	5	1.00
43	I531-E451-N535*-Y612*-M408-S616-**D405***-S453	82	30.58	6.00	5	0.83
44	Y527*-I531-E451-N535*-Y612*-M408-S616-**D405***	85	30.41	6.00	5	0.83
45	Y612*-H578*-**N615*-N619*-L401***-T456-N400*-M487	86	30.24	6.00	5	0.83
46	P501-Y527*-I531-E451-N535*-Y612*-M408-S616-**D405***	88	30.13	7.00	5	0.71
47	Y527*-I531-E451-N535*-H578*-**N615*-N619*-D405*-N377-P620-V380**	89	30.12	9.00	8	0.89

See the legend to Table S1.

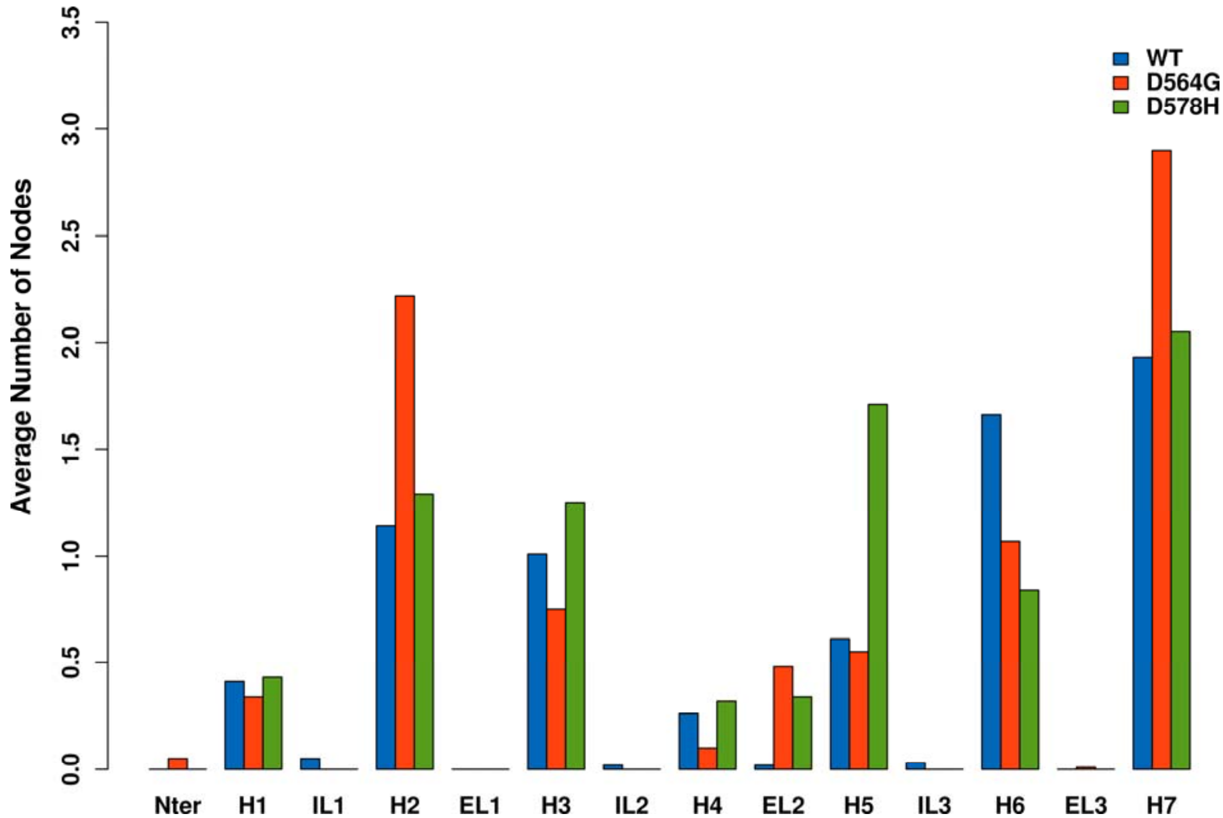


Figure S1. Helix contribution to the communication paths. The average number of residues contributed by each receptor portion to the shortest communication paths is plotted. It has been obtained by dividing the total number of amino acids contributed by each receptor portion by the total number of paths with frequency ≥ 10 and length ≥ 3. The wild type, D564$^{(6.30)}$G and D578$^{(6.44)}$H forms are indicated, respectively, by blue, red, and green histograms.

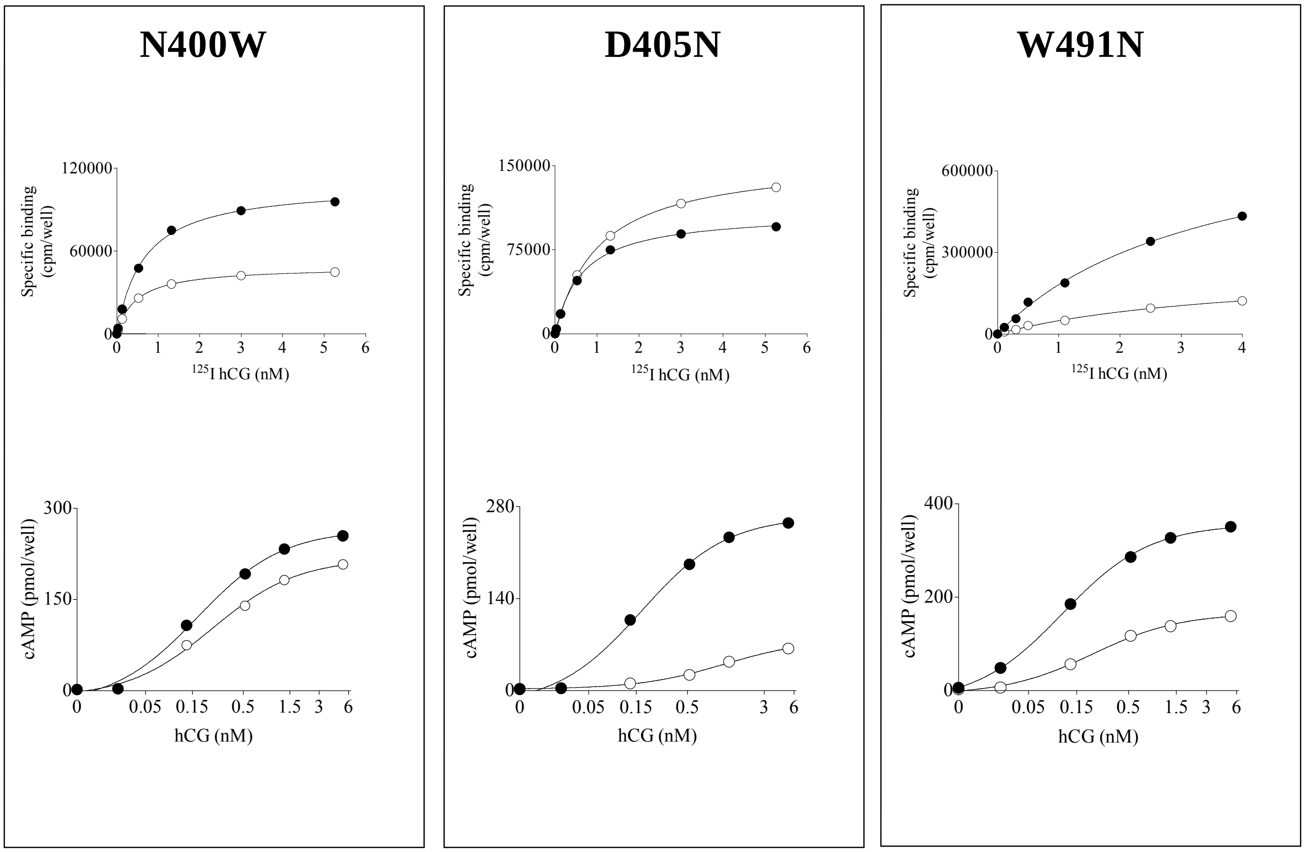


Figure S2. Representative saturation binding curves and hCG-mediated cAMP responses for wild type LHR (closed circles) and different single mutants (open circles): N400$^{(2.45)}$W and D405$^{(2.50)}$N, and W491$^{(4.50)}$N.

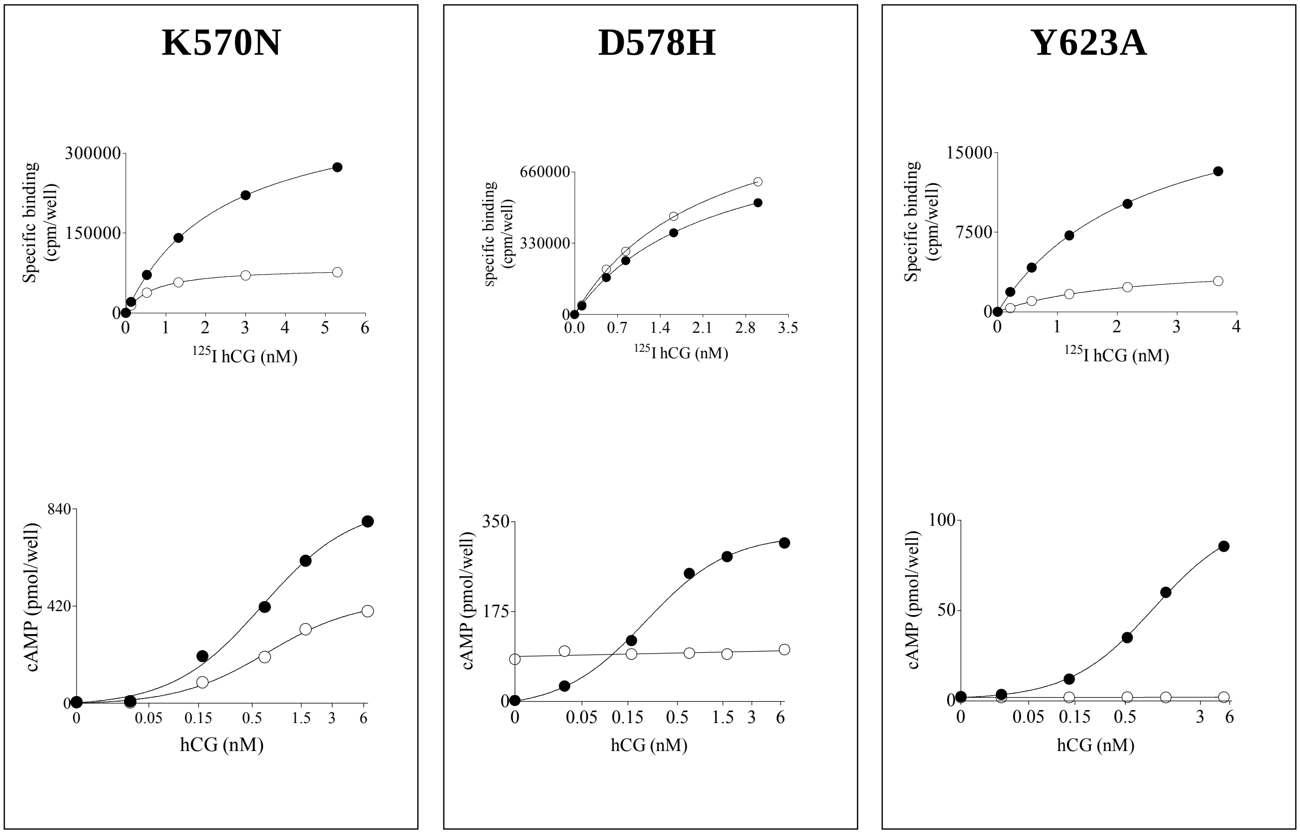


Figure S3. Representative saturation binding curves and hCG-mediated cAMP responses for wild type LHR (closed circles) and different single mutants (open circles): K570$^{(6.36)}$N and D578$^{(6.44)}$H and Y623$^{(7.53)}$A.

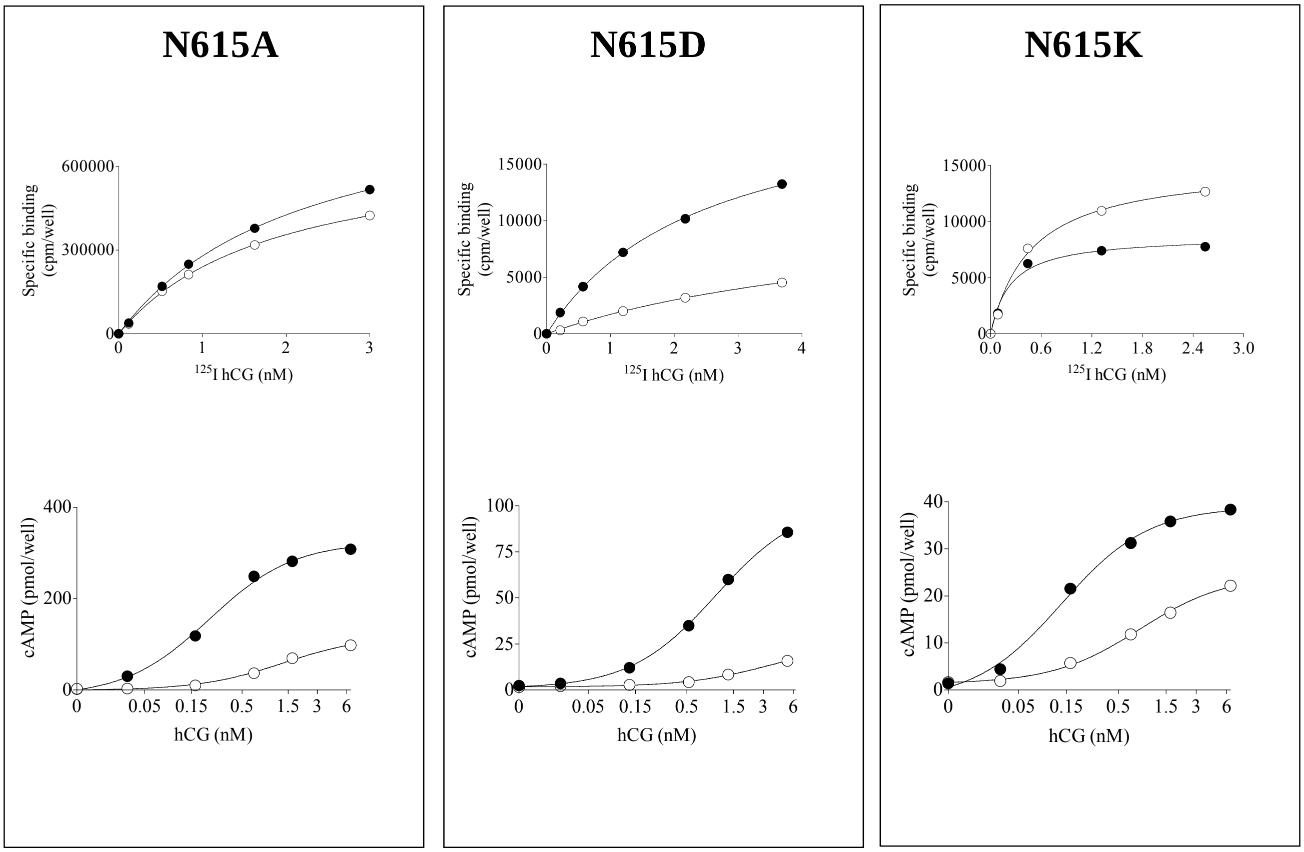


Figure S4. Representative saturation binding curves and hCG-mediated cAMP responses for wild type LHR (closed circles) and different single mutants (open circles) of N615$^{(7.45)}$.

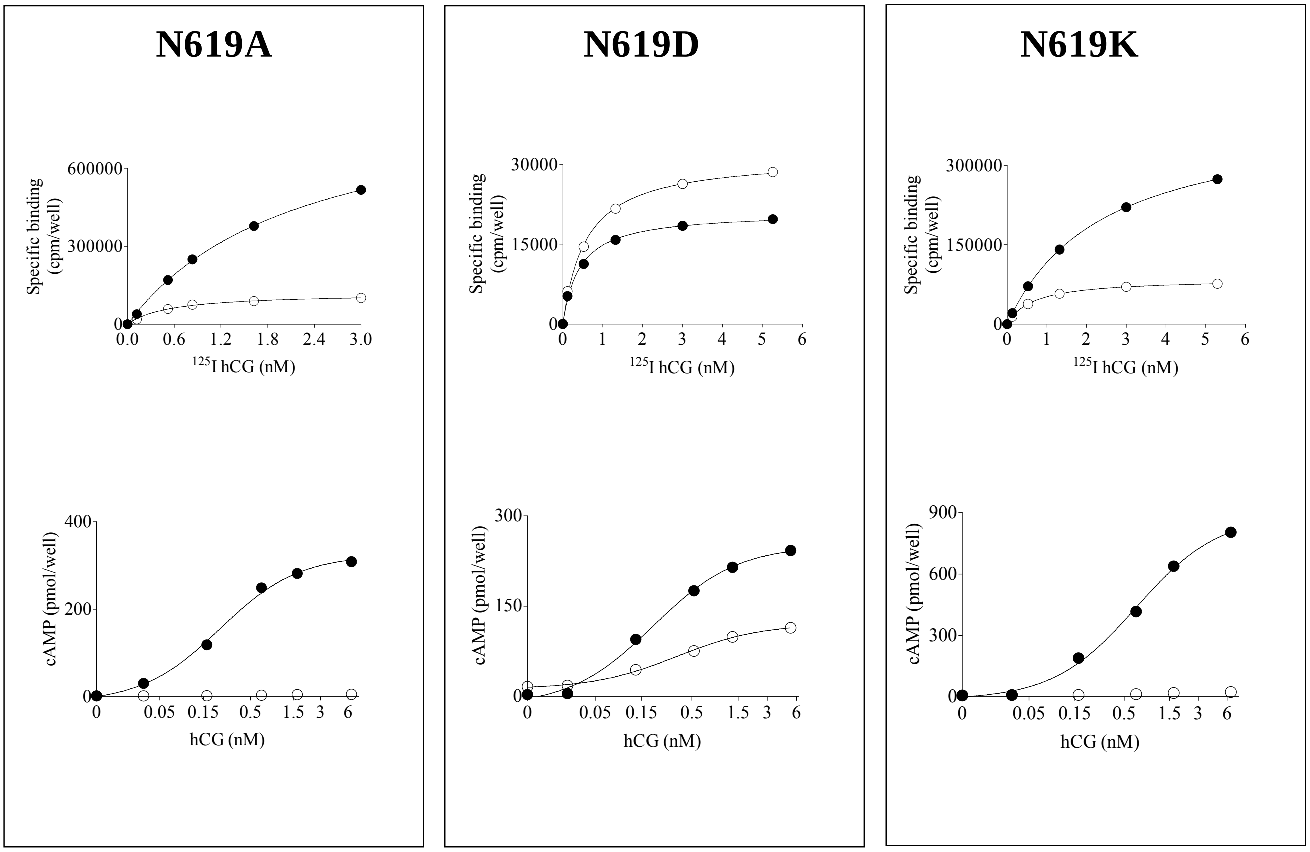


Figure S5 . Representative saturation binding curves and hCG-mediated cAMP responses for wild type LHR (closed circles) and different single mutants (open circles) of N619$^{(7.49)}$.

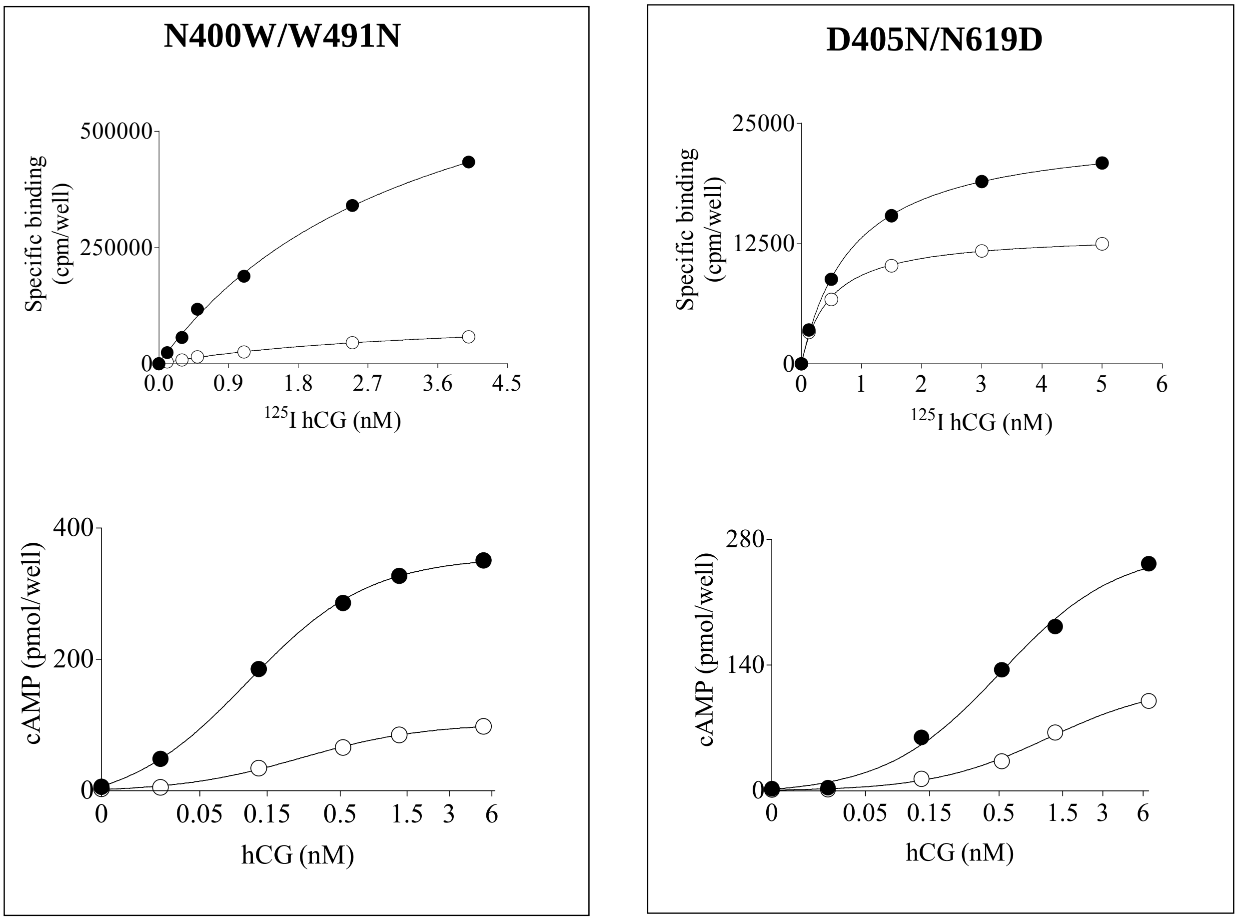
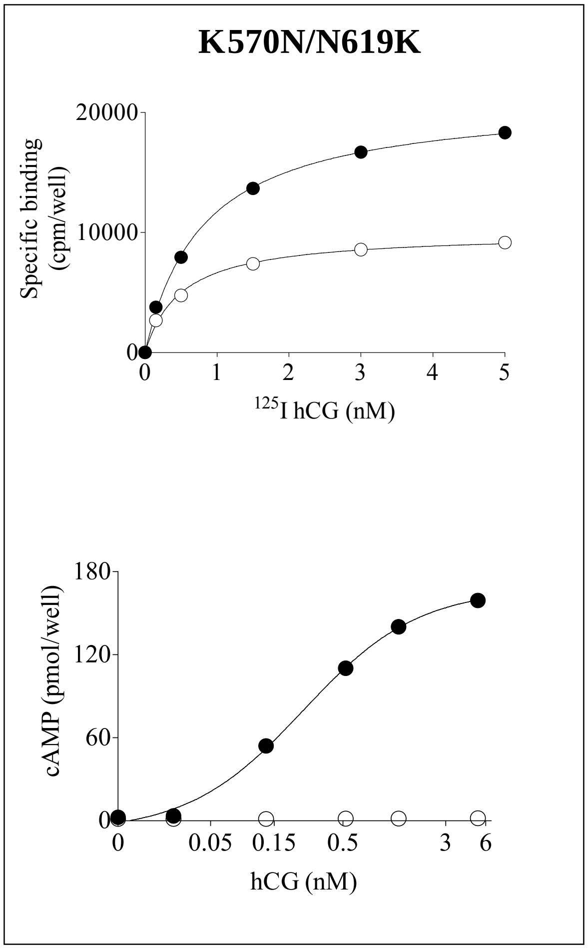


Figure S6. Representative saturation binding curves and hCG-mediated cAMP responses for wild type LHR (closed circles) and two double mutants (open circles): $N400^{(2.45)}W$ paired with $W491^{(4.50)}N$ and $D405^{(2.50)}N$ paired with $N619^{(7.49)}D$.



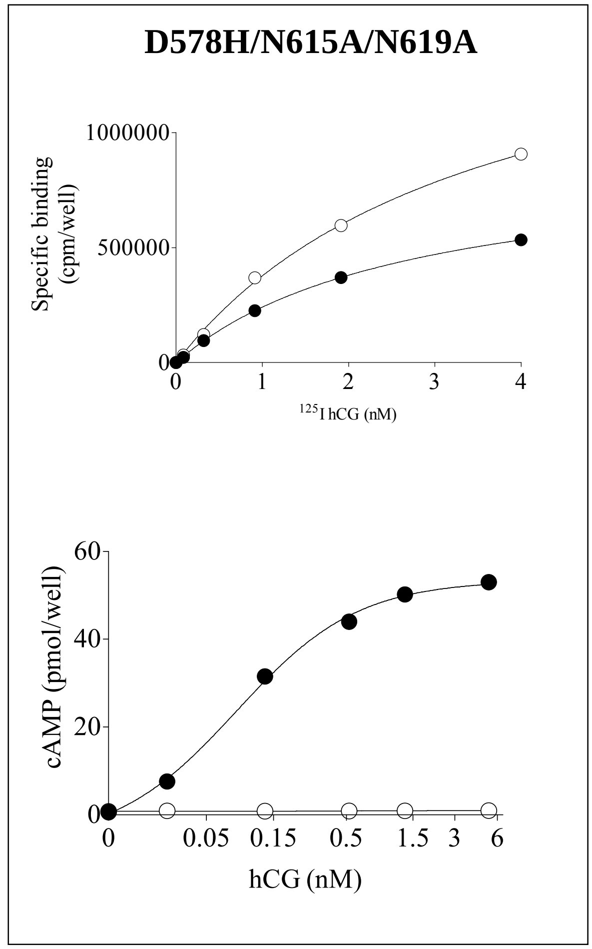


Figure S7. Representative saturation binding curves and hCG-mediated cAMP responses for wild type LHR (closed circles) and double and triple mutants (open circles): K570$^{(6.36)}$N paired with N619$^{(7.49)}$K, and D578$^{(6.44)}$H paired with N615$^{(7.45)}$A and N619$^{(7.49)}$A.