Supplements

Mutations in G protein-coupled receptors: Mechanisms, pathophysiology and potential therapeutic approaches

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Table S1 X-chromosomal GPCRs containing obvious loss-of-function (LoF) mutations
The gnomAD database (v2.1.1 https://gnomad.broadinstitute.org) was screened for stop and frameshifting mutations in X-chromosomal GPCR genes occurring in hemizygous (male) or homozygous (female) stage. Such individuals would be considered as deficient for the specific GPCR. The literature and the International Mouse Phenotyping Consortium (IMPC) website (http://www.mousephenotype.org/) were screened for the respective GPCR-deficient mouse line and their phenotypes. Light-gray rows contain GPCRs causing inherited human diseases. *LoF variants found in the C terminus, which may not interfere with function.

Symbol	# of stop/fs variants (# individuals homo/hemizygous)	human phenotype/disease	mouse phenotype	Reference for mouse phenotype
ADGRG2	1 (0/1) rs756053665*	congenital bilateral aplasia of the vas deferens	infertility	(Davies et al., 2004)
ADGRG4	44 (1/76) rs764463001* rs1310086936* rs146635325*	unknown	not determined yet	
AGTR2	8 (0/77) rs371470323*	unknown	altered drinking response, increased blood pressure	(Hein et al., 1995; Ichiki et al., 1995)
AVPR2	2 (0/3) rs37286283* Trp336Ter*	nephrogenic diabetes insipidus	nephrogenic diabetes insipidus	(Yun et al., 2000)
BRS3	1 (0/1)	unknown	metabolic defects and obesity	(Ohki-Hamazaki et al., 1997)
CXCR3	3 (0/56)	unknown	increased susceptibility to experimental autoimmune encephalomyelitis	(Liu et al., 2006)
CYSLTR1	6 (0/9) rs1310506059*	unknown	altered immune system	(Maekawa et al., 2002; Oyoshi et al., 2012)
GPR34	2 (0/2)	unknown	altered immune system	(Liebscher et al., 2011; Preissler et al., 2015)
GPR50	1 (0/1) rs756979771*	unknown	decreased percent body fat/body weight, increased food intake	(Ivanova et al., 2008)
GPR82	4 (0/4) rs1252758363*	unknown	reduced food intake and body weight	(Engel et al., 2011)
GPR101	1 (0/1)	acrogigantism	increased heart weight and serum calcium	IMPC
GPR119	8 (0/8) rs771380953*	unknown	abnormal skin morphology, decreased body weight and insulin levels	(Lan et al., 2009), IMPC
GPR143	3 (0/4)	ocular albinism type I, congenital nystagmus	hypopigmentation of the ocular fundus	(Incerti et al., 2000)
GPR173	0 (0/0)	unknown	decreased body mass, length, and bone density, abnormal coat coloration	IMPC
GPR174	2 (0/2)	unknown	abnormal T cell physiology, altered sexual dimorphism in B-cell physiology	(Barnes et al., 2015; Zhao et al., 2020)

GRPR	5 (0/5) rs1464753617* rs1418228152* rs760783114*	unknown	hyperactive, abnormal scratching behavior	(Sun and Chen, 2007; Wada et al., 1997)
HTR2C	5 (0/7) rs781872799*	unknown	decreased food intake, weight, body length, increased insulin levels	(Kawahara et al., 2008)
LPAR4	3 (0/3) rs768426033*	unknown	abnormal embryonic blood and lymphatic vessel formation	(Sumida et al., 2010)
OPN1LW	0 (0/0)	blue cone monochromacy	gene is missing	
OPN1MW	0 (0/0)	deuteranomaly, cone dystrophy	abnormal vision	(Smallwood et al., 2003)
P2RY10	2 (0/2)	unknown	unknown	
P2RY4	6 (0/1055) rs1189582496* rs41310667*	unknown	abnormal digestive secretion	(Robaye et al., 2003)
P2RY8	0 (0/0)	unknown	gene is missing	

Table S2 GPCR genes containing homozygous LoF variants in humans

The gnomAD database (v2.1.1 https://gnomad.broadinstitute.org) was screened for stop and frameshifting mutations (LoF) in all autosomal GPCR genes occurring in a homozygous stage. In total, 74 GPCR genes were identified where such individuals can be considered as deficient for the specific GPCR. The dbSNP database number is given when available. +genes tolerant for LoF (Karczewski et al., 2020). *LoF variants found in the C terminus, which may not interfere with function. #Some homozygous LoF GPCR gene variants were also identified in a study screening genomes of Pakistani adults for LoF variants (Saleheen et al., 2017).

GPCR gene	# different homozygous inactivating mutation (# individuals)	dbSNP
ADGRA1	3 (12)	rs1049378588, rs532393541, rs145811832
ADGRA2+	1 (1)	rs1442366259*
ADGRC1	2 (6)	rs749296817, rs149062226
ADGRC3+	1 (1)	rs753268601*
ADGRD2+	2 (5)	rs542304419, rs141098727
ADGRE2#+	5 (73)	rs548759776, rs534018804, rs375427337, rs143325445, rs1183101283
ADGRF2+	3 (8)	rs76859817, rs768564109, rs147106931
ADGRF3+	1 (4)	rs139522210
ADGRF4#	1 (1)	rs574873610
ADGRG7#+	1 (1)	rs535088251
ADGRL4#+	1 (1)	rs781215346
ADRA1A	1 (1)	rs778085459
ADRA2B	1 (1)	rs368204339
ADRB3+	1 (1)	rs769733135
BDKRB1+	1 (4)	rs145322761
C5AR2#	1 (1)	rs767175827
CCR5#	5 (1073)	rs777330502, rs1800560, rs938517991, rs775750898, rs146972949
CRHR2+	2 (2)	rs8192492*, rs1414971420
CXCR1+	1 (1)	rs532614335
DRD4+	6 (73)	rs146562378, rs1327643360, rs1347977789, rs751359558, rs1290906588, rs34662058
DRD5#	2 (9)	rs570059380, rs145497708
GPR1+	3 (4)	rs776449349, rs150274953, rs560796868
GPR15	1 (2)	rs771269696
GPR32	2 (8)	rs772552393, rs560406571
ϕGPR33	2 (55)	rs58865778, rs17097921
GPR35	1 (1)	rs758180346
GPR39#	2 (2)	rs371700670, rs773140509*
GPR42	1 (1)	rs770802036
GPR84#	1 (1)	rs777783623
GPR87+	1 (1)	p.Val201GlyfsTer51
GPR89B#+	2 (5)	rs143821798, rs782044418
GPR135	1 (167)	rs143521018*
GPR142#+	3 (552)	rs59375334, rs569465136, rs777583208
GPR151#	4 (30)	rs756942272, rs558001563, rs140449635, rs114285050
GPR152	1 (1)	rs745593287*
GPRC5A+	1 (3)	rs527915306
GPRC5D+	1 (1)	rs576323196*
GPRC6A+	4 (5375)	rs550458778, rs371464745, rs144698290, rs6907580
HCAR3	1 (1)	rs762492119
HTR1F#	1 (1)	Lys134Ter

HTR2B	1 (2)	rs79874540
LTB4R2#	1 (4)	rs374257326
MAS1L	1 (2)	rs559479676
MLNR	1 (1)	rs563947699
MRGPRF	1 (2)	rs756457218
MRGPRG#	4 (4)	rs749436617, rs1160877464, rs997734102, Trp184Ter
MRGPRX1	2 (2)	rs200974967, rs140371088*
MRGPRX3	2 (524)	rs188327405*, rs78408237*
MRGPRX4	1 (1)	rs528957025
NMUR2+	1 (1)	rs145273801
NPSR1+	2 (4474)	rs77892941, rs7809642*
NTSR2+	1 (1)	rs757448862
OPN4+	1 (1)	rs571378526
OPRD1	1 (1)	rs775451738
OPRM1+	2 (89)	rs17174638, rs760566402
OXER1	1 (1)	rs764276620
OXGR1	1 (62)	rs565524916
PRLHR	1 (1)	rs765894801
PTGDR	2 (16)	rs41407349, rs41533946
PTGDR2+	1 (1)	rs1485268895
PTGIR	1 (1)	rs771355379*
PTH2R+	1 (39)	rs61742329
QRFPR+	2 (2)	rs1387943774, rs768925368
RRH+	1 (1)	rs771791931
RXFP1#+	2 (4)	rs756658609, rs756658609
RXFP3	1 (1)	rs763917541
SCTR+	1 (1)	rs200497817
TAAR1	1 (1)	rs1178830423
TAAR2#	3 (550)	rs8192646, rs530446092, rs147900465
TAAR8#	1 (2)	rs200640516
TAAR9	4 (31)	rs377459700, rs752622374, rs769937555, rs749840523
UTS2R	1 (1)	rs750153792
XCR1#+	1 (1)	rs772431611*

Table S3 Mutation rate in GPCR genes

The sequence data of 125,748 exomes and 15,708 whole genomes (gnomAD dataset v2.1.1, March 2020) (https://gnomad.broadinstitute.org) were taken to analyze the individual GPCRs listed in Tables 1, S1, S2 (except for ϕGPR33). SNP: only quality-filtered non-synonymous mutations (missense, stop, frameshifting, splice site) were considered. The observed vs expected rates (o/e scores) were extracted for each GPCR gene using the gnomAD tool *Constraint* (for methodical details of the o/e score see (Lek et al., 2016)) and separated into synonymous, missense and obvious LoF mutations (stop, frameshifting, splice site): 1 is the expected value; ** $p<0.01$

	SNP	codons	SNP/100 codons	o/e score synonymous	o/e score missense	o/e score pLoF
All, N=145 mean (median)	359 (272)	580 (395)	64.0 (64.9)	1.03 (1.02)	0.92 (0.93)	0.68 (0.69)
unknown phenotype N=90, mean (median)	329 (277)	509 (387)	66.5 (69.4)	1.02 (1.01)	0.95 (0.97)	0.78 (0.79)
Disease N=55, mean (median)	409 (262)	695 (404)	59.8 (61.4)	1.06 (1.03)	**0.87 (0.89)****	**0.54 (0.49)****

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