# Mutagenetix Phenotypic Mutation 'donald'

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<th>Allele</th>
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<td>Mutation Type</td>
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<tr>
<td>Coordinate</td>
<td>10,741,508 bp (GRCm38)</td>
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<tr>
<td>Gene</td>
<td>Grm1</td>
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<td>Gene Name</td>
<td>glutamate receptor, metabotropic 1</td>
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<tr>
<td>Synonym(s)</td>
<td>Grm1, Gprc1a, mGluR1, nmf373, rcw, 4930455H15Rik</td>
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<td>Accession Number</td>
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<td>No</td>
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<tr>
<td>Amino Acid Change</td>
<td>Tyrosine changed to Stop codon</td>
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<td>Institutional Source</td>
<td>Beutler Lab</td>
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<td>APN: IGL01371:Grm1, IGL02078:Grm1, IGL02156:Grm1, IGL02476:Grm1, IGL02498:Grm1, IGL02621:Grm1, IGL03192:Grm1, IGL03342:Grm1 UTSW: IGL02796:Grm1, R0294:Grm1, R0525:Grm1, R0554:Grm1, R1184:Grm1, R1319:Grm1, R1403:Grm1, R1403:Grm1, R1403:Grm1, R1403:Grm1, R1403:Grm1, R1467:Grm1, R1494:Grm1, R1589:Grm1, R1615:Grm1, R1720:Grm1, R1738:Grm1, R1763:Grm1, R1774:Grm1, R2041:Grm1, R2092:Grm1, R2198:Grm1, R2297:Grm1, R2333:Grm1, R2333:Grm1, R2333:Grm1, R2914:Grm1, R3105:Grm1, R3106:Grm1, R3705:Grm1, R3931:Grm1, R4810:Grm1, R4892:Grm1, R4938:Grm1, R4947:Grm1, R4966:Grm1, R5152:Grm1, R5283:Grm1, R5317:Grm1, R5374:Grm1, R5428:Grm1, R5604:Grm1, R5894:Grm1, R5896:Grm1, R5899:Grm1, R6032:Grm1, R6032:Grm1, R6139:Grm1, R6144:Grm1, R6208:Grm1, X0002:Grm1</td>
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<td>Science Writers</td>
<td>Anne Murray</td>
</tr>
<tr>
<td>Authors</td>
<td>Carlos Reyna Jamie Russell Jeff SoRelle</td>
</tr>
<tr>
<td>Illustrators</td>
<td>Peter Jurek</td>
</tr>
<tr>
<td>Last Updated</td>
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<td>12/03/2014 7:24 AM by Carlos Reyna</td>
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Phenotypic Description

The *donald* phenotype was identified among *N*-ethyl-*N*-nitrosourea (ENU)-mutagenized G3 mice of the pedigree R1615, some of which exhibited ataxia (*Figure 1*), kyphosis, and premature death.

Nature of Mutation

Whole exome HiSeq sequencing of the G1 grandsire identified 62 mutations. Among these, only one affected a gene (*Grm1*) with known neurological functions. The mutation in *Grm1* was presumed to be causative because the *donald* neurological phenotype mimics other mutant alleles of *Grm1* (see MGI for a list of *Grm1* alleles). The *Grm1* mutation in *donald* is a C to A transversion at base pair 10,741,508 (v38) on chromosome 10, or base pair 340,870 in the GenBank genomic region NC_000076 encoding *Grm1*. The mutation corresponds to residue 1,931 in the NM_016976 mRNA sequence in exon 6 of 9 total exons and residue 1,931 in the NM_001114333 mRNA sequence in exon 6 of 10 total exons.

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340853
CTGAATATCGATGATTA
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Genomic numbering corresponds to NC_000076. The mutated nucleotide is indicated in red. The mutation results in substitution of tyrosine 510 (Y510) for a premature stop codon (Y510*) in all isoforms of the metabotropic glutamate receptor 1 (mGluR1) protein.

Protein Prediction
mGluR1a is a G protein-coupled receptor (GPCR). Class 3 GPCRs include class B GABA (GABA_B) receptors, taste and pheromone receptors, and calcium-sensing receptor (CaR). Class 3 GPCRs have an N-terminal signal peptide (amino acids 1-20 in mGluR1), large extracellular ligand-binding domains (LBDs), a cysteine-rich domain (CRD), seven transmembrane domains, and a variable-length intracellular C-terminal tail (Figure 2). The N-terminal LBD region of mGluR1 (amino acids 21-510) is essential for the recognition of glutamate as well as receptor agonists and competitive antagonists (1,2). The structure of the LBD of rat mGluR1 (m1-LBR) in both an active (open/closed) and resting (open/open) form have been solved (Figure 3; PDB: 1ISS; 3). Both the active and resting m1-LBR structures were a homodimer connected via a disulfide bond between Cys140 from each monomer. The role of mGluR dimerization is unknown, but is proposed to modulate the proper folding of the mGluRs, permitting the proper function of the receptor. The LBD forms two lobes [LB1 (N-terminal) and LB2 (C-terminal)] connected by three short loops and separated by a cavity where glutamate binds (3-5). The relative positions of LB1 and LB2 define the open and closed states of the receptor. Glutamate binding results in closing of the N-terminal lobes around the ligand. The conformational change between the open and closed forms is a rotation about an axis that passes across the three connecting loops (3;6). Within the dimer, the two LB1 domains rotate by about 70° (3). In the open/closed active state, two molecules of glutamate bind each monomer through an interaction only with the LB1 interface. In the closed state, glutamate interacts with both LB1 and LB2; full mGluR1 activation requires glutamate binding to both subunits (7). Several residues are known to be involved in the interaction with glutamate, including Ser165 and Thr188. Arg178 is also proposed to facilitate an interaction with an acidic group of mGluR agonists (8).

The mGluR1 LBD is separated from the transmembrane region by a cysteine (Cys)-rich region (amino acids 521-570). The Cys-rich region is essential for proper folding and trafficking of mGluRs and is proposed to be a flexible spacer that allows for the displacement of the glutamate binding pocket towards the transmembrane domains (9-12). Several cysteines within the N-terminal tail and the Cys-rich region form intramolecular disulfide bonds including Cys67-Cys109, Cys289-Cys291, Cys378-Cys394, Cys432-Cys439, Cys657-Cys746.

The second intracellular (i2) loop and the membrane-proximal C-terminal region mediate the interaction with either G_s or G_q; the role of G proteins in the G_{16} family is unclear (13-17; reviewed in (18)). Mutation of Lys690 within the i2 region switches mGluR1 coupling to different members of the G_i protein family. Amino acids within the third intracellular (i3) loop are also essential for the activation of G_s or G_q.

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mGluR1d variants causes reduced agonist potency and slower agonist-stimulated second messenger responses compared with mGluR1a.

Ubiquitin ligase, binds the C-terminal tail of mGluR1a, resulting in its degradation (PKC; see the record for).

The long C-terminal tail of mGluR1a contains motifs essential for targeting of mGluR1a in Purkinje cell (PC) spines, for inositol 1,4,5-trisphosphate (IP$_3$) receptor-mediated Ca$^{2+}$ release from the smooth endoplasmic reticulum in PCs, long-term depression induction, CF synapse elimination, and delay eye blink conditioning (32). A PSD-95/discs-large/ZO-1 (PDZ) domain binding sequence (SSSTL; amino acids 1195-1199) mediates interactions with several scaffolding and cytoskeletal proteins (33). A proline-rich domain (PPSPFR; amino acids 1152-1157) interacts with Homer proteins to mediate subsequent receptor trafficking plus the usage of an in-frame stop codon, thus generating a substitution of the last 318 amino acids of mGlu1a with 20 different residues; contains a 68 aa intracellular domain.

Table 1. Characteristics of the mGluR1 isoforms

<table>
<thead>
<tr>
<th>Isoform symbol</th>
<th>Alternative designation</th>
<th>Size (amino acids)</th>
<th>Molecular description and features</th>
<th>Source</th>
<th>Expression/Localization</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>mGluR1a</td>
<td>mGluR1?</td>
<td>1199</td>
<td>Longest isoform with a 361 aa intracellular C-terminal domain</td>
<td>Human, rat, mouse</td>
<td>Cerebellum (granule cells, Purkinje cells, and basket cells), cerebral cortex, thalamus, subthalamic nucleus, olfactory bulb, amygdala, hippocampus, substantia nigra, caudate nucleus, and putamen</td>
<td>(19-23)</td>
</tr>
<tr>
<td>mGluR1b</td>
<td>mGluR1?_1</td>
<td>906</td>
<td>Insertion of an 85-bp exon 9; exon codes for an in-frame stop codon, thus generating a substitution of the last 318 amino acids of mGlu1a with 20 different residues; contains a 68 aa intracellular domain</td>
<td>Human, rat, mouse</td>
<td>Cerebellum, olfactory bulb</td>
<td>(24)</td>
</tr>
<tr>
<td>mGluR1c</td>
<td></td>
<td>897</td>
<td>Alternatively spliced exon inserted after the seventh transmembrane domain; may derive from a recombination event; differs from mGluR1b in that the 21 C-terminal amino acids of mGluR1b are replaced by 11 aa; contains a 59 aa C-terminal domain</td>
<td>Rat only?</td>
<td>Cerebellum; less expression than mGluR1a and mGluR1b</td>
<td>(25)</td>
</tr>
<tr>
<td>mGluR1d</td>
<td>mGluR1?</td>
<td>908</td>
<td>Alternative splice acceptor site in exon 10 and subsequent frameshift inserts a stop codon 22 amino acids downstream from splice site; contains a 70 aa C-terminus</td>
<td>Human, rat</td>
<td>Cerebellum (granule cells) and kidney</td>
<td>(26-28)</td>
</tr>
<tr>
<td>mGluR1f</td>
<td>mGluR1?_2</td>
<td>906</td>
<td>Insertion of the same 85-bp exon (exon 9) that generates mGlu1?, plus the usage of an alternative splice acceptor in exon 10 that is located 35 bp downstream from the 5?'-end of the exon; contains a 68 aa C-terminus</td>
<td>Rat only?</td>
<td>Cerebellum</td>
<td>(29)</td>
</tr>
<tr>
<td>mGluR1g</td>
<td></td>
<td>887</td>
<td>Skipping of the splice donor site in exon 8; in-frame stop codon 1 bp downstream of the skipped splice site; may derive from partially processed pre-mRNA; C-terminus consists of 1 aa after the residue 886</td>
<td>Human, rat</td>
<td>Cerebellar granule cells</td>
<td>(19)</td>
</tr>
<tr>
<td>mGluR1h</td>
<td></td>
<td>897</td>
<td>Predicted C-terminal splice variant of 10 additional amino acids; encoded by two previously unidentified exons (exon IXa and exon IXb)</td>
<td>Human only?</td>
<td>Melanoma cell lines and melanocytes</td>
<td>(30)</td>
</tr>
<tr>
<td>mGluR1E55</td>
<td>mGluR1?</td>
<td>321</td>
<td>Insertion between exons 3 and 4 of a 110-bp exon (designated as exon E55), which contains an in-frame stop codon; contains only the extracellular domain; may be secreted</td>
<td>Mouse only?</td>
<td>Adult cerebellum and heart; function unknown</td>
<td>(31)</td>
</tr>
</tbody>
</table>

The long C-terminal tail of mGluR1a contains motifs essential for targeting of mGluR1a in Purkinje cell (PC) spines, for inositol 1,4,5-trisphosphate (IP$_3$) receptor-mediated Ca$^{2+}$ release from the smooth endoplasmic reticulum in PCs, long-term depression induction, CF synapse elimination, and delay eye blink conditioning (32). A PSD-95/discs-large/ZO-1 (PDZ) domain binding sequence (SSSTL; amino acids 1195-1199) mediates interactions with several scaffolding and cytoskeletal proteins (33). A proline-rich domain (PPSPFR; amino acids 1152-1157) interacts with Homer proteins to mediate subsequent interactions with signaling proteins including IP$_3$ (34,35) as well as to mediate receptor trafficking (36,37). Two calmodulin binding sites have also been identified in the C-terminal tail of mGluR1a (38). Several serine/threonine residues within the CaM-binding sites are phosphorylated by protein kinase C (PKC; see the record for Untied), which suppresses the interaction between mGluR1a and CaM (39-41). Siah1A (seven in absentia homolog 1A), an E3 ubiquitin ligase, binds the C-terminal tail of mGluR1a, resulting in its degradation (42). The shorter C-terminal tail in the mGluR1b, mGluR1c, and mGluR1d variants causes reduced agonist potency and slower agonist-stimulated second messenger responses compared with mGluR1a (17,25,26-43;44).

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extracellular loops. Mouse mGluR1 is predicted to be N-linked glycosylated at Asn98, Asn223, Asn397, Asn515, and Asn747. mGluR1 N-linked glycosylation is essential for efficient agonist-stimulated phosphoinositide hydrolysis and receptor dimerization \((45)\).

The mutation in \textit{donald} results in substitution of tyrosine 510 (Y510) for a premature stop codon (Y510\*) in all mGluR1 isoforms. Y510 is within the LBD of mGluR1; Y510 is not predicted to be involved in glutamate binding.

**Expression/Localization**

mGluR1 is expressed in all CA3 lamina of the hippocampus \((46-48)\). mGluR1 is localized mainly to the postsynapse including the periphery of the postsynaptic densities \((49)\), but mGluR1 can also be presynaptic. The mGluR1 isoforms exhibit tissue-specific expression patterns including differential expression in the cerebellum, hippocampus, olfactory bulbs, and kidneys \((\text{Table 1}) (28)\).

A coat component of caveolae, caveolin-1, binds mGluR1 \((50)\). Association between caveolin-1 and mGluR1 regulates the rate of constitutive receptor internalization and subsequent level of mGluR1 expression at the cell surface as well as mGluR1-associated ERK/MAPK activation and calcium signaling \((50;51)\).

**Background**

![Figure 4. GPCR activation cycle.](image)

\textbf{Figure 4. GPCR activation cycle.} In its inactive state, the GDP-bound \(G\) subunit and the \(G\) complex are associated. Upon agonist binding, the GPCR undergoes conformational change and exchanges GDP for GTP in the \(G\) subunit. GTP-\(G\) and \(G\) dissociate and modulate effectors. Hydrolysis of GTP to GDP by RGS leads to inactivation of the G-protein.
Glutamate-stimulated signaling through mGluR7 and mGluR1a. Upon presynaptic depolarization, Ca$^{2+}$ enters the presynapse through voltage-gated Ca$^{2+}$ channels (VGCCs) and induces glutamate release and CaM activation. Upon G-protein activation, PKC is recruited to mGluR7 through binding to PICK1. Activation of mGluR7 results in inhibition of adenylate cyclase activity (i.e., the formation of cAMP and ATP), the attenuation of N-type VGCCs, the activation of K$^{+}$ channels, and the subsequent decrease in neurotransmitter (glutamate and GABA) release. See the record for shaky for more details on the signaling pathways activated downstream of mGluR7. Upon stimulation by glutamate, mGluR1s in the post-synaptic membrane couple to multiple signaling pathways through different G proteins. Several second messenger systems are activated upon mGluR1 activation including PKB, PLC?, PI3K/AKT/mTOR, IP3/DAG, NF?B and CaM. The C-terminus of mGluR1 interacts with Homer proteins, which facilitate the association of mGluR1 with IP3 receptors in the endoplasmic reticulum. Activation of these signaling pathways result in cell survival (PKC/PLD), proliferation (PKC/ERK1/2), learning, memory, and long-term potentiation (CaM), synaptic remodeling and plasticity (cAMP, PI3K/AKT/mTOR). See the text for more details on the signaling pathways activated downstream of mGluR1a.

Glutamate is the major excitatory amino acid in the mammalian brain, mediating an estimated 50% of all synaptic transmission in the central nervous system [reviewed in (52)]. Glutamate is synthesized, stored, released from the presynaptic terminal, and acts through both ligand-gated ion channels (ionotropic glutamate receptors; see the record for swagger) and G-protein coupled receptors (mGluRs) on postsynaptic neurons [reviewed in (53)]. Activation of these receptors accounts for basal excitatory synaptic transmission and synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) that are thought to underlie learning and memory. Glutamatergic synaptic transmission is implicated in nearly all aspects of normal brain function, including learning, memory, movement, cognition, and development. However, at elevated concentrations that excessively stimulate the same receptors, glutamate acts as a neurotoxin capable of causing extensive neuronal damage and death in the development and progression of several neurological disorders. Thus, the brain maintains very low intrasynaptic concentrations of glutamate by the action of glutamate transporters present in the plasma membrane of both glial cells and neurons.

The mGluRs transduce signals through increased ion flux and second messenger signaling pathways. The mGluRs are subdivided into three groups, designated group I, II, and III, according to agonist selectivity, coupling to different effector systems, and sequence homology. Group I includes mGluR1 and mGluR5; group II includes mGluR2 and mGluR3; and group III consists of mGluR4, mGluR6, mGluR7, and mGluR8. Group I mGluRs function in inositol phospholipid metabolism leading to increased levels of intracellular calcium, the activation of ryanodine-sensitive calcium stores (54,55), and alteration in the activity of voltage-gated channels (56-58). Both group II and III are negatively coupled to adenylate cyclase activity, leading to reduced production of cyclic AMP (cAMP) and often resulting in reduced transmitter release (59).
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As a GPCR, mGluR1 couples with a heterotrimeric G protein to mediate its downstream effects. G proteins, which consist of an α subunit that binds and hydrolyzes GTP (Gα), and β and γ subunits that are constitutively associated in a complex [reviewed in (70); Figure 4]. In the absence of a stimulus, the GDP-bound subunit and the βγ complex are associated. Upon activation by ligand binding, the GPCR recruits its cognate heterotrimeric G protein, and undergoes a conformational change enabling it to act as guanine nucleotide exchange factor (GEF) for the G protein subunit. GEFs promote the exchange of GDP for GTP, resulting in dissociation of the GTP-bound subunit from the activated receptor and the βγ complex. Both the GTP-bound subunit and the βγ complex mediate signaling by modulating the activities of other proteins, such as adenyl cyclases, phospholipases, and ion channels. G protein signaling is terminated upon GTP hydrolysis. The GDP-bound G subunit reassociates with the βγ complex and is ready for another activation cycle.

mGluR1 promotes phospholipase C (PLC; see the record for queen) inositol-1,4,5-trisphosphate (IP3)/Ca2+ activation through the coupling to Gq/11 proteins upon ligand binding (Figure 5). Upon mGluR1 activation, PLC-mediated phosphatidylinositol-4,5-bisphosphate (PIP2) hydrolysis produces IP3 and diacylglycerol (DAG) (16;25;71). DAG is responsible for activating PKC and possibly the TRP calcium influx channels, while IP3 modulates calcium responses within the cell by binding to receptors on intracellular membranes to allow the mobilization of intracellular calcium (55). mGluR1-mediated changes in calcium levels can regulate neurotransmission, gene transcription, and apoptosis. mGluR1-stimulated release of intracellular calcium can also promote the activation of CaM, which acts as a second messenger to transduce calcium-related signals. Binding of calcium to CaM results in the activation of calcium/CaM-dependent kinases (CaMK) and the subsequent signaling regulates learning and memory as well as long-term potentiation (72). mGluR1-associated signaling also results in the PLC- and Ca2+/CaM-mediated phosphorylation of focal adhesion kinase (FAK) (73). FAK phosphorylation may mediate glutamate-associated effects on cytoskeleton dynamics. mGluR1-associated signaling results in induction of ERK1/2 phosphorylation independent of Ca2+ and phosphatidylinositol 3-kinase activity (74;75). In the spinal cord, mGluR1-mediated activation of ERK1/2 results in nociceptive sensitization, a feature of chronic pain (76;76). During inflammation in the spinal cord, mGluR1 is involved in functional plasticity through the activation of ERKs (76).

Homer1 binding to mGluR1 recruits Shank, a scaffold protein that facilitates an interaction between mGluR1 and NMDARs, subsequently leading to calcium influx (53). Homer1 also couples mGluR1 to PI3K to initiate signaling that will promote cell survival, metabolism, proliferation, and cancer progression (77). The PI3K-Akt-mTOR signaling pathway is activated in mGluR1-dependent long-term depression in the CA1 area of the hippocampus (78). mGluR1-mediated activation of Akt1/2 is both neuroprotective and pro-proliferative in some neuronal cell types (77;79;80); activation of mGluR1 can also be a pro-apoptotic signal in some neural substrates (81). As a pro-survival factor, Akt1 phosphorylates BAD (Bcl2-associated death protein), leading to dissociation of BAD from the Bcl-2/Bcl-XL complex (82). Akt1-mediated phosphorylation of proteins within the mTORC1 complex leads to increased mRNA translation that stimulates cell growth.

In CA3 pyramidal cells, mGluR1-induced excitatory postsynaptic currents is G protein-independent, requiring the activation of tyrosine kinases of the Src family (83). Src tyrosine kinases activate downstream messengers including ERK1/2 (83). G protein-independent signaling regulates long-term potentiation (83).

mGluR1a receptor activation can also mediate cyclic AMP (cAMP) accumulation (16;84;85); the mGluR1b, mGluR1c, and mGlu1d splice variants did not promote cAMP accumulation (17;26;86).

mGluRs have roles in epilepsy, neurotoxicity, and neurodegenerative diseases including Huntington’s Disease and Alzheimer’s disease (87;88). Mutations in GRM1 have been linked to autosomal recessive spinocerebellar ataxia (OMIM: #614831) (89;90). Patients with spinocerebellar ataxia exhibit developmental delay, stance and gait ataxia, dysarthria, dysmetria and tremors, and intellectual deficit.

mGluR1 has additional functions outside of the central nervous system. In the kidney, mGluR1 regulates podocyte foot process morphology and signaling in the podocyte. Grm1ERV/ERV mice, harboring a spontaneous splicing mutation within intron 4, exhibit albuminuria, podocyte foot process effacement, and reduced levels of proteins that regulate the maintenance of podocyte cell structure including nephrin, podocin, and ZO-1 (28). mGluR1 expression is also required for melanoma development and growth (91). Conditional expression of mGluR1 in melanocytes resulted in the formation of pigmented lesions on the ears and tails 29 weeks after transgene activation (91).

Putative Mechanism

Grm1-deficient (Grm1−/−) and Grm1 mutant mice have normal anatomy of the hippocampus, excitatory synaptic transmission from parallel fibers to Purkinje cells and from climbing fibers to Purkinje cells, and short-term potentiation in the CA1 region of the hippocampus (92;93). However, the Grm1 mutant mice exhibit ataxia by postnatal day (P) 14, action tremors, loss or ability to right themselves, spatial learning deficits, impaired long-term depression, and reduced long-term potentiation (22;67;92-96). Similar to Grm1 mutant mice, donald mice exhibit ataxia, indicating loss of function in mGluR1 donald.

References

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