<https://www.ncbi.nlm.nih.gov/pubmed/21912186>

Subjects with the G allele of rs2247215 (GRIK2) were more likely to have CFS (p = 0.0005), and CFS subjects showed decreased GRIK2 expression (10-fold; p = 0.015). Subjects with the T allele of rs356653 (NPAS2) were more likely to have CFS (p = 0.0007), and NPAS2expression was increased (10-fold; p = 0.027) in those with CFS.

Associated polymorphisms in GRIK2 (rs2247218 and rs2247215) and NPAS2 (rs356653) are located in the first and second introns of their respective genes. Since these SNPs are in introns, their impact on gene function and ultimately the associated phenotype is not immediately clear. These markers may be in linkage disequilibrium with other causative markers or they may play a direct role in gene expression by affecting transcription factor binding, alternative splicing or microRNA production. Of the 2 GRIK2 SNPs, rs2247215 showed in silico evidence for alteration of consensus binding sites for 2 overlapping transcription factors, GATA1 and EVI1. The G allele of rs2247215 creates a consensus binding site for GATA1, suggesting that GRIK2, like other GATA1-repressed genes, may be repressed through the participation of polycomb repressive complex 2 [[53](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701888/#B53)]. This potential role of rs2247215 is consistent with the association of its G allele with CFS and decreased expression of GRIK2 in CFS subjects. In silico analysis also identified a binding site for RFX1 transcription factor at rs356653 (NPAS2). The T allele of rs356653 is likely to disrupt RFX1 binding. RFX1 may be a transcriptional repressor of NPAS2[[54](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701888/#B54)], and if so the T allele would lead to increased NPAS2 expression by disrupting RFX1 binding. This interpretation is consistent with our findings that the T allele is associated with CFS and increased expression of NPAS2 in CFS. However, experimental validation is required to support the role of rs2247215 and rs356653 variants in gene expression.

For example, in GRIK2, the C allele of rs2247218 and the G allele of rs2247215 were more common in CFS cases (50.0%) than in controls (24.0%; 0.00007 < p < 0.0005); both SNPs are in linkage disequilibrium.

Among these polymorphisms, SNPs associated with suicidal ideation in patients being actively treated for depression (rs2518224) [[36](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701888/#B36)] reside in the same intron of GRIK2 that harbors the polymorphisms associated with CFS in this study (rs2247218 and rs2247215).

| **Chromo-some** | **SNP ID** | **Gene/expressed sequence tag Genome Build 36.3EST** | **Genotype** | **Frequency, n** | | **p value** | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | controls | CFS subjects | genotype | allele |
|  | rs2247215 | GRIK2 | AA | 17 (44.7) | 4 (10.3) | 0.0006 | 0.0003 |
|  |  |  | AG | 18 (50.0) | 24 (61.5) |  |  |
|  |  |  | GG | 2 (5.3) | 11 (28.2) |  |  |

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4836736/>

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Genetic Variables Selected** | | | | | | |
| **Rank Order** | **SNP** | **Information Gain**1 | **Gene Symbol** | **Chromosome**2 | **Chromosome Position**2 | **p-value**3 |
| **1** | **rs2247215** | 0.228 | GRIK2 | 6 | 101966354 | 0.08482 |

As observed, six of the nine variables were genetic, including rs2247215 (GRIK2), rs4887348 (NTRK3), rs11583978 (DLGAP3), rs7858819 (SLC1A1), rs27072 (SLC6A3) and rs548294 (GRIA1). Three non-genetic variables from the neuropsychological dataset were included in the model. These variables were related to the following domains: visuospatial ability (WISC\_Block, Wechsler Intelligence Scale for Children IV Block design), non-verbal memory (RCFT\_immediate, Rey Complex Figure Test Immediate Recall) and working memory (WISC\_Digit, Wechsler Intelligence Scale for Children IV Digit Span). Finally, none of the variables from the neuroimaging datasets (MRI and DTI) exceeded the information gain threshold and so none were included in the model.

Nine variables were used for the creation of the OCD severity predictor, including six genetic polymorphisms and three variables from the neuropsychological data. The developed model classified child and adolescent patients with OCD by disease severity with an accuracy of 0.90 in the testing set and 0.70 in the validation sample. Above its clinical applicability, the combination of particular neuropsychological, neuroimaging, and genetic characteristics could enhance our understanding of the neurobiological basis of the disorder.

<https://www.ncbi.nlm.nih.gov/gene/2898>

glutamate ionotropic receptor kainate type subunit 2

Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain and are activated in a variety of normal neurophysiologic processes. This gene product belongs to the kainate family of glutamate receptors, which are composed of four subunits and function as ligand-activated ion channels. The subunit encoded by this gene is subject to RNA editing at multiple sites within the first and second transmembrane domains, which is thought to alter the structure and function of the receptor complex. Alternatively spliced transcript variants encoding different isoforms have also been described for this gene. Mutations in this gene have been associated with autosomal recessive cognitive disability. [provided by RefSeq, Jul 2008]

<http://www.uniprot.org/uniprot/Q13002>

Ionotropic glutamate receptor. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system. Binding of the excitatory neurotransmitter L-glutamate induces a conformation change, leading to the opening of the cation channel, and thereby converts the chemical signal to an electrical impulse. The receptor then desensitizes rapidly and enters a transient inactive state, characterized by the presence of bound agonist (PubMed:[28180184](http://www.uniprot.org/citations/28180184)). May be involved in the transmission of light information from the retina to the hypothalamus. Modulates cell surface expression of NETO2 (By similarity).By similarity1 Publication

* [extracellularly glutamate-gated ion channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0005234) Source: UniProtKB
* [kainate selective glutamate receptor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015277) Source: UniProtKB
* [ligand-gated ion channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015276) Source: Reactome
* [PDZ domain binding](https://www.ebi.ac.uk/QuickGO/term/GO:0030165) Source: Ensembl
* [protein homodimerization activity](https://www.ebi.ac.uk/QuickGO/term/GO:0042803) Source: Ensembl
* [ubiquitin conjugating enzyme binding](https://www.ebi.ac.uk/QuickGO/term/GO:0031624) Source: Ensembl
* [ubiquitin protein ligase binding](https://www.ebi.ac.uk/QuickGO/term/GO:0031625) Source: Ensembl

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q13002)

#### GO - Biological processi

* [behavioral fear response](https://www.ebi.ac.uk/QuickGO/term/GO:0001662) Source: Ensembl
* [cellular calcium ion homeostasis](https://www.ebi.ac.uk/QuickGO/term/GO:0006874) Source: Ensembl
* [chemical synaptic transmission](https://www.ebi.ac.uk/QuickGO/term/GO:0007268) Source: ProtInc
* [glutamate receptor signaling pathway](https://www.ebi.ac.uk/QuickGO/term/GO:0007215) Source: ProtInc
* [inhibitory postsynaptic potential](https://www.ebi.ac.uk/QuickGO/term/GO:0060080) Source: Ensembl
* [intracellular protein transport](https://www.ebi.ac.uk/QuickGO/term/GO:0006886) Source: Ensembl
* [modulation of chemical synaptic transmission](https://www.ebi.ac.uk/QuickGO/term/GO:0050804) Source: UniProtKB
* [negative regulation of neuron apoptotic process](https://www.ebi.ac.uk/QuickGO/term/GO:0043524) Source: Ensembl
* [negative regulation of synaptic transmission, glutamatergic](https://www.ebi.ac.uk/QuickGO/term/GO:0051967) Source: Ensembl
* [neuronal action potential](https://www.ebi.ac.uk/QuickGO/term/GO:0019228) Source: Ensembl
* [neuron apoptotic process](https://www.ebi.ac.uk/QuickGO/term/GO:0051402) Source: Ensembl
* [positive regulation of neuron apoptotic process](https://www.ebi.ac.uk/QuickGO/term/GO:0043525) Source: Ensembl
* [positive regulation of synaptic transmission](https://www.ebi.ac.uk/QuickGO/term/GO:0050806) Source: UniProtKB
* [receptor clustering](https://www.ebi.ac.uk/QuickGO/term/GO:0043113) Source: Ensembl
* [regulation of JNK cascade](https://www.ebi.ac.uk/QuickGO/term/GO:0046328) Source: Ensembl
* [regulation of long-term neuronal synaptic plasticity](https://www.ebi.ac.uk/QuickGO/term/GO:0048169) Source: Ensembl
* [regulation of short-term neuronal synaptic plasticity](https://www.ebi.ac.uk/QuickGO/term/GO:0048172) Source: UniProtKB
* [synaptic transmission, glutamatergic](https://www.ebi.ac.uk/QuickGO/term/GO:0035249) Source: Ensembl
* [Cell membrane](http://www.uniprot.org/locations/SL-0039); [Multi-pass membrane protein](http://www.uniprot.org/locations/SL-9909)
* [postsynaptic cell membrane](http://www.uniprot.org/locations/SL-0219); [Multi-pass membrane protein](http://www.uniprot.org/locations/SL-9909)

###### **Plasma Membrane**

* + [integral component of plasma membrane](https://www.ebi.ac.uk/QuickGO/term/GO:0005887) Source: ProtInc
  + [kainate selective glutamate receptor complex](https://www.ebi.ac.uk/QuickGO/term/GO:0032983) Source: Ensembl
  + [plasma membrane](https://www.ebi.ac.uk/QuickGO/term/GO:0005886) Source: Reactome
  + [postsynaptic membrane](https://www.ebi.ac.uk/QuickGO/term/GO:0045211) Source: UniProtKB-SubCell
  + [presynaptic membrane](https://www.ebi.ac.uk/QuickGO/term/GO:0042734) Source: Ensembl

###### **Other locations**

* + [cell junction](https://www.ebi.ac.uk/QuickGO/term/GO:0030054) Source: UniProtKB-KW
  + [dendrite cytoplasm](https://www.ebi.ac.uk/QuickGO/term/GO:0032839) Source: Ensembl
  + [perikaryon](https://www.ebi.ac.uk/QuickGO/term/GO:0043204) Source: Ensembl
  + [postsynaptic density](https://www.ebi.ac.uk/QuickGO/term/GO:0014069) Source: Ensembl
  + [terminal bouton](https://www.ebi.ac.uk/QuickGO/term/GO:0043195) Source: Ensembl

###### [**Mental retardation, autosomal recessive 6 (MRT6)**](http://www.uniprot.org/diseases/DI-01245)**1 Publication**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionA disorder characterized by significantly below average general intellectual functioning associated with impairments in adaptive behavior and manifested during the developmental period. In contrast to syndromic or specific mental retardation which also present with associated physical, neurological and/or psychiatric manifestations, intellectual deficiency is the only primary symptom of non-syndromic mental retardation. MRT6 patients display mild to severe mental retardation and psychomotor development delay in early childhood. Patients do not have neurologic problems, congenital malformations, or facial dysmorphism. Body height, weight, and head circumference are normal.

|  |  |
| --- | --- |
| DrugBanki | [DB01351](https://www.drugbank.ca/drugs/DB01351) Amobarbital [DB01352](https://www.drugbank.ca/drugs/DB01352) Aprobarbital [DB01483](https://www.drugbank.ca/drugs/DB01483) Barbital [DB01496](https://www.drugbank.ca/drugs/DB01496) Barbituric acid derivative [DB00237](https://www.drugbank.ca/drugs/DB00237) Butabarbital [DB00241](https://www.drugbank.ca/drugs/DB00241) Butalbital [DB01353](https://www.drugbank.ca/drugs/DB01353) Butethal [DB02852](https://www.drugbank.ca/drugs/DB02852) Domoic Acid [DB01354](https://www.drugbank.ca/drugs/DB01354) Heptabarbital [DB01355](https://www.drugbank.ca/drugs/DB01355) Hexobarbital [DB00142](https://www.drugbank.ca/drugs/DB00142) L-Glutamic Acid [DB00463](https://www.drugbank.ca/drugs/DB00463) Metharbital [DB00849](https://www.drugbank.ca/drugs/DB00849) Methylphenobarbital [DB00312](https://www.drugbank.ca/drugs/DB00312) Pentobarbital [DB01174](https://www.drugbank.ca/drugs/DB01174) Phenobarbital [DB00794](https://www.drugbank.ca/drugs/DB00794) Primidone [DB02999](https://www.drugbank.ca/drugs/DB02999) Quisqualate [DB00418](https://www.drugbank.ca/drugs/DB00418) Secobarbital [DB00306](https://www.drugbank.ca/drugs/DB00306) Talbutal [DB00599](https://www.drugbank.ca/drugs/DB00599) Thiopental |

This gene encodes a subunit of a kainate glutamate receptor. Glutamate receptors mediate the majority of excitatory neurotransmission in the brain. This receptor may have a role in synaptic plasticity and may be important for learning and memory. It also may be involved in the transmission of light information from the retina to the hypothalamus. The structure and function of the encoded protein is changed by [RNA editing](https://en.wikipedia.org/wiki/RNA_editing). Alternatively spliced transcript variants encoding distinct isoforms have been described for this gene.