GABRA1 gene

gamma-aminobutyric acid type A receptor subunit alpha1

Normal Function

The *GABRA1* gene provides instructions for making one piece, the alpha-1 (α1) subunit, of the $GABA_A$ receptor protein. $GABA_A$ receptors are made up of different combinations of five protein subunits, each produced from a different gene. (Nineteen different genes provide instructions for $GABA_A$ receptor subunits.) These subunits form a hole (pore) in the cell membrane through which negatively charged chlorine atoms (chloride ions) can flow.

A chemical that transmits signals in the brain (a neurotransmitter) called gamma-amino butyric acid (GABA) attaches to $GABA_A$ receptors. Once GABA attaches, the pore formed by the subunits opens, and chloride ions flow across the cell membrane. After infancy, chloride ions flow into the cell through the open pore, which creates an environment in the cell that blocks (inhibits) signaling between neurons. The primary role of GABA in children and adults is to prevent the brain from being overloaded with too many signals. In contrast, in newborns and infants, chloride ions flow out of the cell when the pore is opened, creating an environment that allows signaling between neurons.

Health Conditions Related to Genetic Changes

Juvenile myoclonic epilepsy

A mutation in the *GABRA1* gene has been identified in at least one family with juvenile myoclonic epilepsy. This condition typically begins in childhood or adolescence and causes recurrent myoclonic seizures, which are characterized by rapid, uncontrolled muscle jerks. Affected individuals can also have other types of seizures called generalized tonic-clonic seizures (or grand mal seizures) and absence seizures. The mutation associated with this condition changes a single protein building block (amino acid) in the α1 subunit. The amino acid alanine at protein position 322 is replaced by the amino acid asparagine. This gene mutation is written as Ala322Asp or A322D.

This *GABRA1* gene mutation leads to the formation of an abnormal α1 subunit that reduces $GABA_A$ receptor function. $GABA_A$ receptors containing the abnormal subunit are broken down before they reach the cell membrane. Studies show that the altered receptors can also interfere with normal receptors inside the cell, leading to the

additional loss of normal receptors. Because of the reduction of $GABA_A$ receptor function, signaling between neurons is not regulated, which can lead to overstimulation of neurons. Researchers believe that the overstimulation of certain neurons in the brain triggers the abnormal brain activity associated with seizures.

Childhood absence epilepsy

MedlinePlus Genetics provides information about Childhood absence epilepsy

Other Names for This Gene

- ECA4
- EJM
- EJM5
- GABA(A) receptor subunit alpha-1
- GABA(A) receptor, alpha 1
- gamma-aminobutyric acid (GABA) A receptor, alpha 1
- gamma-aminobutyric acid receptor subunit alpha-1
- gamma-aminobutyric acid receptor subunit alpha-1 precursor
- GBRA1_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of GABRA1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2554[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28GABRA1%5BTIAB%5D%29+OR+%28%28EJM%5BTIAB%5D%29+OR+%28ECA4%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+2160+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-1; GABRA1 (https://omim.org/entry/137160)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2554)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=GABRA1[gene])

References

- Ben-Ari Y, Khalilov I, Kahle KT, Cherubini E. The GABA excitatory/inhibitoryshift in brain maturation and neurological disorders. Neuroscientist. 2012Oct;18(5):467-86. doi: 10.1177/1073858412438697. Epub 2012 Apr 30. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22547529)
- Bradley CA, Taghibiglou C, Collingridge GL, Wang YT. Mechanisms involved inthe reduction of GABAA receptor alpha1-subunit expression caused by the epilepsymutation A322D in the trafficking-competent receptor. J Biol Chem. 2008 Aug8;283(32):22043-50. doi: 10.1074/jbc.M801708200. Epub 2008 Jun 5. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18534981)
- Cossette P, Liu L, Brisebois K, Dong H, Lortie A, Vanasse M, Saint-Hilaire JM, Carmant L, Verner A, Lu WY, Wang YT, Rouleau GA. Mutation of GABRA1 in anautosomal dominant form of juvenile myoclonic epilepsy. Nat Genet. 2002Jun;31(2):184-9. doi: 10.1038/ng885. Epub 2002 May 6. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11992121)
- Ding L, Feng HJ, Macdonald RL, Botzolakis EJ, Hu N, Gallagher MJ. GABA(A) receptor alpha1 subunit mutation A322D associated with autosomal dominantjuvenile myoclonic epilepsy reduces the expression and alters the composition ofwild type GABA(A) receptors. J Biol Chem. 2010 Aug 20;285(34):26390-405. doi:10.1074/jbc.M110.142299. Epub 2010 Jun 15. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20551311) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924069/)
- Gallagher MJ, Ding L, Maheshwari A, Macdonald RL. The GABAA receptor alpha1subunit epilepsy mutation A322D inhibits transmembrane helix formation and causesproteasomal degradation. Proc Natl Acad Sci U S A. 2007 Aug 7;104(32):12999-3004.doi: 10.1073/pnas.0700163104. Epub 2007 Aug 1. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17670950) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1941799/)
- Kang JQ, Shen W, Macdonald RL. Two molecular pathways (NMD and ERAD) contribute to a genetic epilepsy associated with the GABA(A) receptor GABRA1 PTCmutation, 975delC, S326fs328X. J Neurosci. 2009 Mar 4;29(9):2833-44. doi:10.1523/JNEUROSCI.4512-08.2009. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19261879) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2687144/)
- Krampfl K, Maljevic S, Cossette P, Ziegler E, Rouleau GA, Lerche H, Bufler J. Molecular analysis of the A322D mutation in the GABA receptor alpha-subunitcausing juvenile myoclonic epilepsy. Eur J Neurosci. 2005 Jul;22(1):10-20. doi:10.1111/j.1460-9568.2005.04168.x. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16029191)

Genomic Location

The *GABRA1* gene is found on chromosome 5 (https://medlineplus.gov/genetics/chromosome/5/).

Last updated June 1, 2012