APP Gene

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amyloid beta precursor protein

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1. Normal Function

The *APP* gene provides instructions for making a protein called amyloid precursor protein. This protein is found in many tissues and organs, including the brain and spinal cord (central nervous system). Little is known about the function of amyloid precursor protein. Researchers speculate that it may bind to other proteins on the surface of cells or help cells attach to one another. Studies suggest that in the brain, it helps direct the movement (migration) of nerve cells (neurons) during early development.

Amyloid precursor protein is cut by enzymes to create smaller fragments (peptides), some of which are released outside the cell. Two of these fragments are called soluble amyloid precursor protein (sAPP) and amyloid beta (β) peptide. Recent evidence suggests that sAPP has growth-promoting properties and may play a role in the formation of nerve cells (neurons) in the brain both before and after birth. The sAPP peptide may also control the function of certain other proteins by turning off (inhibiting) their activity. Amyloid β peptide is likely involved in the ability of neurons to change and adapt over time (plasticity). Other functions of sAPP and amyloid β peptide are under investigation.

2. Health Conditions Related to Genetic Changes

2.1. Alzheimer disease

More than 50 different mutations in the *APP* gene can cause early-onset Alzheimer disease, which begins before age 65. These mutations are responsible for less than 10 percent of all early-onset cases of the disorder.

The most common *APP* mutation changes one of the protein building blocks (amino acids) in the amyloid precursor protein. This mutation replaces the amino acid valine with the amino acid isoleucine at protein position 717 (written as Val717Ile or V717I). Mutations in the *APP* gene can lead to an increased amount of the amyloid β peptide or to the production of a slightly longer and stickier form of the peptide. When these protein fragments are released from the cell, they can accumulate in the brain and form clumps called amyloid plaques. These plaques are characteristic of Alzheimer disease. A buildup of toxic amyloid β peptide and amyloid plaques may lead to the death of neurons and the progressive signs and symptoms of this disorder.

2.2. Hereditary cerebral amyloid angiopathy

At least six mutations in the *APP* gene have been found to cause hereditary cerebral amyloid angiopathy, a condition characterized by stroke and a decline in intellectual function (dementia), which begins in mid-adulthood. These mutations change single amino acids in the amyloid precursor protein. All of the *APP* gene mutations that cause hereditary cerebral amyloid angiopathy lead to changes near the beginning of the protein sequence. Each of these mutations causes a different type of the condition. The Dutch type, the most common of all the types, is caused by the replacement of the amino acid glutamic acid with the amino acid glutamine at position 22 in the protein sequence (written as Glu22Gln or E22Q). The Italian type and Arctic type are also caused by changes to glutamic acid at position 22. In the Italian type, glutamic acid is replaced with the amino acid lysine (written as Glu22Lys or E22K) and in the Arctic type, glutamic acid is replaced with the amino acid glycine (written as Glu22Gly or E22G). The Flemish type is caused by replacement of the amino acid alanine with glycine at position 21 (written as Ala21Gly or A21G). In the Iowa type, the amino acid aspartic acid is switched with the amino acid asparagine at position 23 (written as Asp23Asn or D23N). The Piedmont type of hereditary cerebral amyloid angiopathy is caused by the replacement of the amino acid leucine at position 34 with the amino acid valine (written as Leu34Val or L34V).

The result of all of these mutations is the production of an amyloid β peptide that is more prone to cluster together (aggregate) than the normal peptide. The aggregated protein forms amyloid deposits known as plaques that accumulate in the blood vessels of the brain. The amyloid plaques replace the muscle fibers and elastic fibers that give blood vessels flexibility, causing the blood vessels to become weak and prone to breakage. In the brain, such a break causes bleeding (hemorrhagic stroke), which can lead to brain damage and dementia. Amyloid plaques in specific parts of the brain can interfere with brain function, leading to seizures, movement problems, and other neurological features in some people with hereditary cerebral amyloid angiopathy.

3. Other Names for This Gene

- A4_HUMAN
- AAA
- ABETA
- ABPP
- AD1
- amyloid beta (A4) precursor protein
- amyloid beta-peptide
- amyloid beta-protein precursor
- amyloid precursor protein
- APPI
- cerebral vascular amyloid peptide
- CVAP
- PN-II
- PN2
- protease nexin 2
- protease nexin-II

References

1. Bornebroek M, De Jonghe C, Haan J, Kumar-Singh S, Younkin S, Roos R, VanBroeckhoven C. Hereditary cerebral he morrhage with amyloidosis Dutch type(AbetaPP 693): decreased plasma amyloid-beta 42 concentration. Neurobiol Dis. 2003 Dec;14(3):619-23.
2. Caillé I, Allinquant B, Dupont E, Bouillot C, Langer A, Müller U, ProchiantzA. Soluble form of amyloid precursor protein r egulates proliferation ofprogenitors in the adult subventricular zone. Development. 2004May;131(9):2173-81.
3. Conti L, Cattaneo E. Controlling neural stem cell division within the adultsubventricular zone: an APPealing job. Trends Neurosci. 2005 Feb;28(2):57-9.Review.
4. Cordy JM, Hooper NM, Turner AJ. The involvement of lipid rafts in Alzheimer's disease. Mol Membr Biol. 2006 Jan-Feb; 23(1):111-22. Review.
5. Edwards-Lee T, Ringman JM, Chung J, Werner J, Morgan A, St George Hyslop P,Thompson P, Dutton R, Mlikotic A, Ro gaeva E, Hardy J. An African American family with early-onset Alzheimer disease and an APP (T714I) mutation. Neurol ogy. 2005Jan 25;64(2):377-9.
6. Fernandez-Madrid I, Levy E, Marder K, Frangione B. Codon 618 variant ofAlzheimer amyloid gene associated with inh erited cerebral hemorrhage. Ann Neurol.1991 Nov;30(5):730-3.
7. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progressand problems on the road to therapeutic s. Science. 2002 Jul 19;297(5580):353-6.Review. Erratum in: Science 2002 Sep 27;297(5590):2209.
8. Harman D. Alzheimer's disease pathogenesis: role of aging. Ann N Y Acad Sci.2006 May;1067:454-60. Review.
9. Kerr ML, Small DH. Cytoplasmic domain of the beta-amyloid protein precursor ofAlzheimer's disease: function, regulati on of proteolysis, and implications fordrug development. J Neurosci Res. 2005 Apr 15;80(2):151-9. Review.
10. Levy E, Prelli F, Frangione B. Studies on the first described Alzheimer'sdisease amyloid beta mutant, the Dutch variant. J Alzheimers Dis. 2006;9(3Suppl):329-39. Review.
11. Maat-Schieman M, Roos R, van Duinen S. Hereditary cerebral hemorrhage withamyloidosis-Dutch type. Neuropatholo gy. 2005 Dec;25(4):288-97. Review.
12. Majersik JJ, Skalabrin EJ. Single-gene stroke disorders. Semin Neurol. 2006Feb;26(1):33-48. Review.

13. Obici L, Demarchi A, de Rosa G, Bellotti V, Marciano S, Donadei S, ArbustiniE, Palladini G, Diegoli M, Genovese E, Ferrari G, Coverlizza S, Merlini G. Anovel AbetaPP mutation exclusively associated with cerebral amyloid angiopathy.Ann Neurol. 2005 Oct;58(4):639-44.
14. Papassotiropoulos A, Fountoulakis M, Dunckley T, Stephan DA, Reiman EM.Genetics, transcriptomics, and proteomics of Alzheimer's disease. J ClinPsychiatry. 2006 Apr;67(4):652-70. Review.
15. Rocchi A, Pellegrini S, Siciliano G, Murri L. Causative and susceptibilitygenes for Alzheimer's disease: a review. Brain Res Bull. 2003 Jun 30;61(1):1-24. Review.
16. Salameh MA, Robinson JL, Navaneetham D, Sinha D, Madden BJ, Walsh PN, Radisky ES. The amyloid precursor protein/protease nexin 2 Kunitz inhibitor domain is ahighly specific substrate of mesotrypsin. J Biol Chem. 2010 Jan15;285(3):1939-49. doi: 10.1074/jbc.M109.057216.
17. Wolfe MS, Guénette SY. APP at a glance. J Cell Sci. 2007 Sep 15;120(Pt18):3157-61. Review.
18. Zhang H, Ma Q, Zhang YW, Xu H. Proteolytic processing of Alzheimer's β-amyloidprecursor protein. J Neurochem. 2012 Jan;120 Suppl 1:9-21. doi:10.1111/j.1471-4159.2011.07519.x.
