ABCC6 Gene

Subjects: Genetics & Heredity
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ATP binding cassette subfamily C member 6

Keywords: genes

1. Normal Function

The *ABCC6* gene provides instructions for making a protein called multidrug resistance-associated protein 6 (MRP6, also known as the ABCC6 protein). This protein is found primarily in the liver and kidneys, with small amounts in other tissues such as the skin, stomach, blood vessels, and eyes. The MRP6 protein belongs to a group of proteins that transport molecules across cell membranes; however, little is known about the substances transported by MRP6.

Some studies suggest that MRP6 stimulates the release of a molecule called adenosine triphosphate (ATP) from cells through an unknown mechanism. This ATP is quickly broken down into other molecules called adenosine monophosphate (AMP) and pyrophosphate. Pyrophosphate helps control deposition of calcium (calcification) and other minerals (mineralization) in the body.

Other studies suggest that MRP6 transports a substance that is involved in the breakdown of ATP. This unidentified substance is thought to help prevent mineralization of tissues.

2. Health Conditions Related to Genetic Changes

2.1 Generalized arterial calcification of infancy

At least 13 mutations in the *ABCC6* gene have been identified in individuals with generalized arterial calcification of infancy (GACI), a life-threatening disorder characterized by abnormal calcification in the blood vessels that carry blood from the heart to the rest of the body (the arteries). Most of these mutations have also been identified in people with pseudoxanthoma elasticum (PXE), described below. These mutations lead to an absent or nonfunctional MRP6 protein. It is unclear how a lack of properly functioning MRP6 protein leads to GACI. This shortage may impair the release of ATP from cells. As a result, little pyrophosphate is produced and calcium accumulates in the blood vessels and other tissues affected by GACI. Alternatively, a lack of functioning MRP6 may impair the transport of a substance that would normally prevent mineralization, leading to the abnormal accumulation of calcium characteristic of GACI. It is not known why the same mutations can cause GACI in some individuals and PXE in others.

2.2 Pseudoxanthoma elasticum

More than 200 *ABCC6* gene mutations that cause pseudoxanthoma elasticum (PXE) have been identified. PXE is a condition characterized by abnormal accumulation of calcium and other minerals in elastic fibers, a component of connective tissues that provide strength and flexibility to structures throughout the body. The *ABCC6* gene mutations involved in this condition lead to an absence of MRP6 protein or an altered protein that does not function properly. The most common mutation in the United States, found in about 28 percent of people with PXE, deletes part of the *ABCC6* gene. (This mutation is written as Ex23_29del.)

It is unclear how loss of MRP6 function leads to PXE. As in GACI (described above), this loss may impair the release of ATP or the transport of a substance that normally prevents mineralization. Without MRP6 function, calcium and other minerals accumulate in elastic fibers of the skin, eyes, blood vessels and other tissues affected by PXE.

3. Other Names for This Gene

- ABC34

- anthracycline resistance-associated protein
- ARA
- ATP-binding cassette, sub-family C (CFTR/MRP), member 6
- EST349056
- MLP1
- MOAT-E
- MRP6
- MRP6_HUMAN
- multidrug resistance-associated protein 6
- multispecific organic anion transporter-E

References

1. Bercovitch L, Terry P. Pseudoxanthoma elasticum 2004. J Am Acad Dermatol. 2004Jul;51(1 Suppl):S13-4. Review.
2. Bergen AA, Plomp AS, Schuurman EJ, Terry S, Breuning M, Dauwerse H, Swart J,Kool M, van Soest S, Baas F, ten Brink JB, de Jong PT. Mutations in ABCC6 causepseudoxanthoma elasticum. Nat Genet. 2000 Jun;25(2):228-31.
3. Chassaing N, Martin L, Calvas P, Le Bert M, Hovnanian A. Pseudoxanthomaelasticum: a clinical, pathophysiological and genetic update including 11 novelABCC6 mutations. J Med Genet. 2005 Dec;42(12):881-92.
4. Dabisch-Ruthe M, Kuzaj P, Götting C, Knabbe C, Hendig D. Pyrophosphates as amajor inhibitor of matrix calcification in Pseudoxanthoma elasticum. J DermatolSci. 2014 Aug;75(2):109-20. doi: 10.1016/j.jdermsci.2014.04.015.
5. Ferreira C, Ziegler S, Gahl WA. Generalized Arterial Calcification of Infancy.2014 Nov 13. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, StephensK, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK253403/
6. Hendig D, Schulz V, Arndt M, Szliska C, Kleesiek K, Götting C. Role of serumfetuin-A, a major inhibitor of systemic calcification, in pseudoxanthomaelasticum. Clin Chem. 2006 Feb;52(2):227-34.
7. Hu X, Plomp A, Wijnholds J, Ten Brink J, van Soest S, van den Born LI, Leys A,Peek R, de Jong PT, Bergen AA. ABCC6/MRP6 mutations: further insight into themolecular pathology of pseudoxanthoma elasticum. Eur J Hum Genet. 2003Mar;11(3):215-24.
8. Hu X, Plomp AS, van Soest S, Wijnholds J, de Jong PT, Bergen AA.Pseudoxanthoma elasticum: a clinical, histopathological, and molecular update.Surv Ophthalmol. 2003 Jul-Aug;48(4):424-38. Review.
9. Iliás A, Urbán Z, Seidl TL, Le Saux O, Sinkó E, Boyd CD, Sarkadi B, Váradi A. Loss of ATP-dependent transport activity in pseudoxanthoma elasticum-associatedmutants of human ABCC6 (MRP6). J Biol Chem. 2002 May 10;277(19):16860-7.
10. Jansen RS, Duijst S, Mahakena S, Sommer D, Szeri F, Váradi A, Plomp A, Bergen AA, Oude Elferink RP, Borst P, van de Wetering K. ABCC6-mediated ATP secretion bythe liver is the main source of the mineralization inhibitor inorganicpyrophosphate in the systemic circulation-brief report. Arterioscler Thromb Vasc Biol. 2014 Sep;34(9):1985-9. doi: 10.1161/ATVBAHA.114.304017.
11. Jansen RS, Küçükosmanoglu A, de Haas M, Sapthu S, Otero JA, Hegman IE, Bergen AA, Gorgels TG, Borst P, van de Wetering K. ABCC6 prevents ectopic mineralizationseen in pseudoxanthoma elasticum by inducing cellular nucleotide release. ProcNatl Acad Sci U S A. 2013 Dec 10;110(50):20206-11. doi: 10.1073/pnas.1319582110.
12. Le Saux O, Beck K, Sachsinger C, Silvestri C, Treiber C, Göring HH, JohnsonEW, De Paepe A, Pope FM, Pasquali-Ronchetti I, Bercovitch L, Marais AS, ViljoenDL, Terry SF, Boyd CD. A spectrum of ABCC6 mutations is responsible forpseudoxanthoma elasticum. Am J Hum Genet. 2001 Oct;69(4):749-64.Aug;71(2):448.
13. Li Q, Brodsky JL, Conlin LK, Pawel B, Glatz AC, Gafni RI, Schurgers L, UittoJ, Hakonarson H, Deardorff MA, Levine MA. Mutations in the ABCC6 gene as a cause of generalized arterial calcification of infancy: genotypic overlap withpseudoxanthoma elasticum. J Invest Dermatol. 2014 Mar;134(3):658-665. doi:10.1038/jid.2013.370.
14. Markello TC, Pak LK, St Hilaire C, Dorward H, Ziegler SG, Chen MY, Chaganti K,Nussbaum RL, Boehm M, Gahl WA. Vascular pathology of medial arterialcalcifications in NT5E deficiency: implications for the role of adenosine inpseudoxanthoma elasticum. Mol Genet Metab. 2011 May;103(1):44-50. doi:10.1016/j.ymgme.2011.01.018.
15. Matsuzaki Y, Nakano A, Jiang QJ, Pulkkinen L, Uitto J. Tissue-specificexpression of the ABCC6 gene. J Invest Dermatol. 2005 Nov;125(5):900-5.
16. Miksch S, Lumsden A, Guenther UP, Foernzler D, Christen-Zäch S, Daugherty C,Ramesar RK, Lebwohl M, Hohl D, Neldner KH, Lindpaintner K, Richards RI, Struk B. Molecular genetics of pseudoxanthoma elasticum: type and

frequency of mutationsin ABCC6. Hum Mutat. 2005 Sep;26(3):235-48.

17. Nitschke Y, Baujat G, Botschen U, Wittkampf T, du Moulin M, Stella J, LeMerrer M, Guest G, Lambot K, Tazarourte-Pinturier MF, Chassaing N, Roche O,Feenstra I, Loechner K, Deshpande C, Garber SJ, Chikarmane R, Steinmann B,Shahinyan T, Martorell L, Davies J, Smith WE, Kahler SG, McCulloch M, Wraige E,Loidi L, Höhne W, Martin L, Hadj-Rabia S, Terkeltaub R, Rutsch F. Generalizedarterial calcification of infancy and pseudoxanthoma elasticum can be caused bymutations in either ENPP1 or ABCC6. Am J Hum Genet. 2012 Jan 13;90(1):25-39. doi:10.1016/j.ajhg.2011.11.020.
18. Terry SF, Uitto J. Pseudoxanthoma Elasticum. 2001 Jun 5 [updated 2020 Jun 4]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington,Seattle; 1993-2020. Available from http://www.ncbi.nlm.nih.gov/books/NBK1113/
