

ENPP1 gene

ectonucleotide pyrophosphatase/phosphodiesterase 1

Normal Function

The *ENPP1* gene provides instructions for making a protein called ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1). The ENPP1 protein helps break down a molecule called adenosine triphosphate (ATP), specifically when it is found outside the cell (extracellular). Extracellular ATP is quickly broken down into other molecules called adenosine monophosphate (AMP) and pyrophosphate. Pyrophosphate is important in preventing the accumulation of abnormal deposits of calcium (calcification) and other minerals (mineralization) in the body.

The ENPP1 protein also plays a role in controlling cell signaling in response to the hormone insulin, through interaction between a part of the ENPP1 protein called the SMB2 domain and the insulin receptor. The insulin receptor is a protein that attaches (binds) to insulin and initiates cell signaling.

Insulin plays many roles in the body, including regulating blood sugar levels by controlling how much sugar (in the form of glucose) is passed from the bloodstream into cells to be used as energy. Cell signaling in response to insulin is also important for the maintenance of the outer layer of skin (the epidermis). It helps control the transport of the pigment melanin from the cells in which it is produced (melanocytes) to epidermal cells called keratinocytes, and it is also involved in the development of keratinocytes.

Health Conditions Related to Genetic Changes

Cole disease

At least three *ENPP1* gene mutations have been identified in people with Cole disease. People with this disorder have areas of unusually light-colored skin (hypopigmentation), typically on the arms and legs, and spots of thickened skin on the palms of the hands and the soles of the feet (punctate palmoplantar keratoderma).

The *ENPP1* gene mutations that cause Cole disease change the structure of the SMB2 domain, which alters its interaction with the insulin receptor and affects cell signaling. The resulting impairment of ENPP1's role in melanin transport and keratinocyte development leads to hypopigmentation and keratoderma. The mutations may also impair the protein's ability to control calcification, which likely accounts for the abnormal

calcium deposits that occur in some people with this disorder. For reasons that are unclear, the changes in insulin signaling resulting from these *ENPP1* gene mutations do not seem to affect blood glucose control.

Generalized arterial calcification of infancy

More than 40 mutations in the *ENPP1* gene have been identified in individuals with generalized arterial calcification of infancy (GACI), a life-threatening disorder characterized by calcification in the blood vessels that carry blood from the heart to the rest of the body (the arteries). The mutations that cause GACI are thought to impair the *ENPP1* protein's role in extracellular ATP breakdown and the production of pyrophosphate. Reduced availability of pyrophosphate likely interferes with the control of calcification in the body and leads to the signs and symptoms of GACI.

Hereditary hypophosphatemic rickets

MedlinePlus Genetics provides information about Hereditary hypophosphatemic rickets

Other disorders

A normal variation (polymorphism) in the *ENPP1* gene has been associated with an increased risk of type 2 diabetes (the most common form of diabetes). Type 2 diabetes is caused by resistance to the hormone insulin, which results in impaired control of blood glucose. The polymorphism associated with type 2 diabetes leads to the production of a protein with the protein building block (amino acid) glutamine in protein position 121, written as Q121, rather than the amino acid lysine in this position (K121). The Q121 variant of the *ENPP1* protein inhibits the function of the insulin receptor more strongly than the K121 version, increasing insulin resistance and the risk of type 2 diabetes.

Other Names for This Gene

- alkaline phosphodiesterase 1
- E-NPP 1
- ectonucleotide pyrophosphatase/phosphodiesterase family member 1
- Ly-41 antigen
- M6S1
- membrane component chromosome 6 surface marker 1
- membrane component, chromosome 6, surface marker 1
- NPP1
- NPPS
- PC-1
- PCA1
- PDNP1
- phosphodiesterase I/nucleotide pyrophosphatase 1

- plasma-cell membrane glycoprotein 1
- plasma-cell membrane glycoprotein PC-1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ENPP1 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5167\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5167[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28ENPP1%5BTIAB%5D%29+OR+%28ectonucleotide+pyrophosphatase/phosphodiesterase+1%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+1080+days%22%5Bdp%5D%29>)

Catalog of Genes and Diseases from OMIM

- ECTONUCLEOTIDE PYROPHOSPHATASE/PHOSPHODIESTERASE 1; ENPP1 (<https://omim.org/entry/173335>)
- HYPOPHOSPHATEMIC RICKETS, AUTOSOMAL RECESSIVE, 2; ARHR2 (<https://omim.org/entry/613312>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/5167>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=ENPP1\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=ENPP1[gene]))

References

- Bacci S, De Cosmo S, Prudente S, Trischitta V. ENPP1 gene, insulin resistance and related clinical outcomes. *Curr Opin Clin Nutr Metab Care*. 2007 Jul;10(4):403-9. doi: 10.1097/MCO.0b013e3281e386c9. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/17563456>)
- Eytan O, Morice-Picard F, Sarig O, Ezzedine K, Isakov O, Li Q, Ishida-Yamamoto A, Shomron N, Goldsmith T, Fuchs-Telem D, Adir N, Uitto J, Orlow SJ, Taieb A, Sprecher E. Cole Disease Results from Mutations in ENPP1. *Am J Hum Genet*. 2013 Oct 3;93(4):752-7. doi: 10.1016/j.ajhg.2013.08.007. Epub 2013 Sep 26. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24075184>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3791268/>)
- Galletti S, Nitschke Y, Malavolti AM, Aquilano G, Faldella G, Corvaglia L, Rutsch F.

Generalized Arterial Calcification of Infancy: Fatal Clinical Course Associated with a Novel Mutation in ENPP1. JIMD Rep. 2011;1:23-7. doi:10.1007/8904_2011_11. Epub 2011 Jun 25. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23430823>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3509810/>)

- Kalal IG, Seetha D, Panda A, Nitschke Y, Rutsch F. Molecular diagnosis of generalized arterial calcification of infancy (GACI). J Cardiovasc Dis Res. 2012 Apr; 3(2):150-4. doi: 10.4103/0975-3583.95373. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22629037>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3354462/>)
- Lorenz-Depiereux B, Schnabel D, Tiosano D, Hausler G, Strom TM. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. Am J Hum Genet. 2010 Feb 12; 86(2):267-72. doi: 10.1016/j.ajhg.2010.01.006. Epub 2010 Feb 4. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/20137773>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2820166/>)
- Nitschke Y, Baujat G, Botschen U, Wittkamp 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, Hohne W, Martin L, Hadj-Rabia S, Terkeltaub R, Rutsch F. Generalized arterial calcification of infancy and pseudoxanthoma elasticum can be caused by mutations in either ENPP1 or ABCC6. Am J Hum Genet. 2012 Jan 13; 90(1):25-39. doi:10.1016/j.ajhg.2011.11.020. Epub 2011 Dec 29. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22209248>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257960/>)
- Ruf N, Uhlenberg B, Terkeltaub R, Nurnberg P, Rutsch F. The mutational spectrum of ENPP1 as arising after the analysis of 23 unrelated patients with generalized arterial calcification of infancy (GACI). Hum Mutat. 2005 Jan; 25(1):98. doi: 10.1002/humu.9297. Erratum In: Hum Mutat. 2005 Nov; 26(5):495-6. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15605415>)

Genomic Location

The *ENPP1* gene is found on chromosome 6 (<https://medlineplus.gov/genetics/chromosome/6/>).

Last updated January 1, 2015