ENPP1 Gene

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Ectonucleotide pyrophosphatase/phosphodiesterase 1: The ENPP1 gene provides instructions for making a protein called ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1).

Keywords: genes

1. Normal Function

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.

2. Health Conditions Related to Genetic Changes

2.1 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 sugar control.

2.2 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.

2.3 Hereditary hypophosphatemic rickets

2.4 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 sugar. 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.

3. 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

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