Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section

Review

SPINK1 (Serine Peptidase Inhibitor, Kazal Type 1)

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Published in Atlas Database: December 2014
Online updated version : http://AtlasGeneticsOncology.org/Genes/SPINK1ID42375ch5q32.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/62508/12-2014-SPINK1ID42375ch5q32.pdf
DOI: 10.4267/2042/62503

Abstract

Review on SPINK1, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords: SPINK1

Identity

Other names: PSTI, TATI, SPIK

HGNC (Hugo): SPINK1

Location: 5q32

Location (base pair): location 147,204,131-147,211,349 reverse (minus) strand (Human genome assembly GRCh37.p12, Ensembl release 73 - September 2013).

Local order: Several other SPINK genes have been mapped in the same chromosomal region. From centromere to telomere (Ensembl genome browser 73): DPYSL3 (reverse strand) - JAKMIP-2 (reverse) - SPINK1 (reverse) - SCGB3A2 (forward) - C5orf46 (reverse) - SPINK5 (forward) - SPINK14 (forward) - SPINK6 (forward) - SPINK13 (forward) - SPINK7 (forward).

DNA/RNA

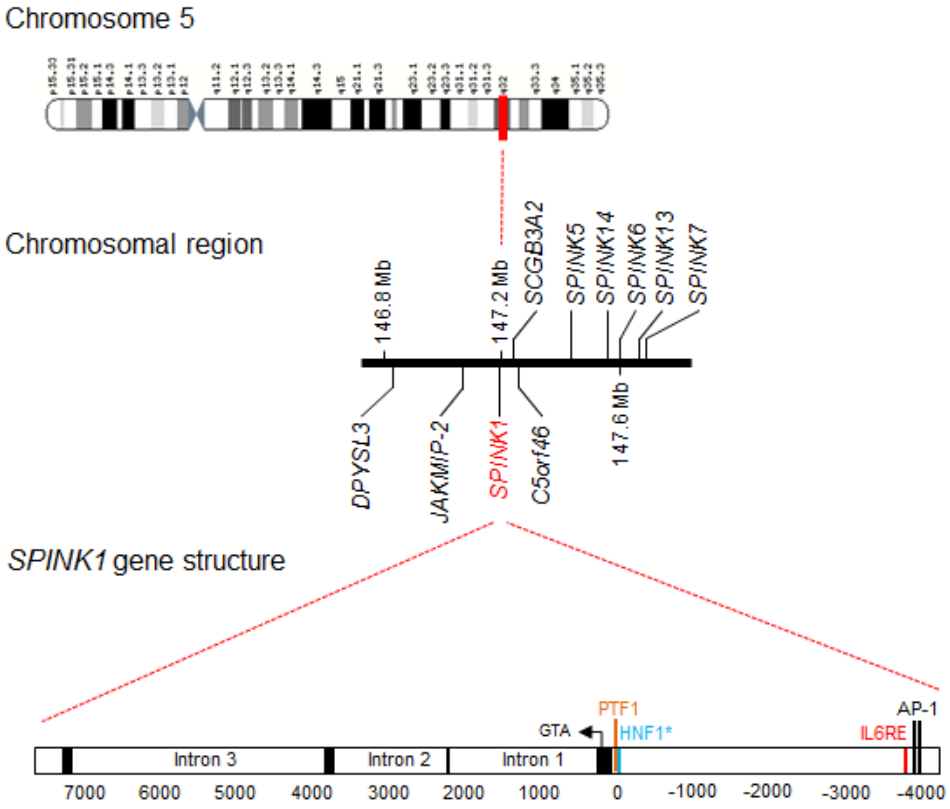
Some other SPINK family members are similar in size, are encoded for by 4 exons and contain a single Kazal type serine protease inhibitor domain.

Description

Maps to chromosomal region 5q32: 147,204,131-147,211,349 on reverse (minus) strand (7,219 bp). Gene consists of 4 exons (Horii et al., 1987). Region between 3.8 and 4.0 kb upstream from the translation initiation codon contains an interleukin-6 responsive element (IL6RE) and two potential AP-1 binding sites (Ohmachi et al., 1993; Yasuda et al., 1993). CAATCAATAAC sequence (-149 to -139) is a potential pancreas-specific regulatory element (Yasuda et al., 1998).
This region in the SPINK1 promoter has been subsequently identified as a binding site for hepatic nuclear factor (HNF1) (Boulling et al., 2011). A putative binding site for pancreas-specific transcription factor 1 (PTF1) has also been identified within the SPINK1 promoter (Boulling et al., 2011).

Transcription

SPINK1 mRNA (NCBI Reference Sequence: NM_003122.3) has 454 bp (Yamamoto et al., 1985). Expression, at least in some cell lines, is regulated by IL-6 (Yasuda et al., 1993). Three differentially spliced mRNA forms have been described (Ensembl, release 73). Two of these have been classified as protein encoding.



Chromosomal location and gene structure of SPINK1 gene (extracted from Ensembl database release 73). Some putative regulatory elements are also shown (Ohmachi et al., 1993; Yasuda et al., 1993; Yasuda et al., 1998; Boulling et al., 2011). After the translation-initiating codon (ATG) exons of the major transcript are shown in black. One splicing variant also contains parts outside of these exons. *, CAATCAATAAC, potential pancreas-specific regulatory element; IL6RE, interleukin-6 responsive element; AP-1, activator protein-1 element; HNF1, hepatic nuclear factor; PTF1, pancreas-specific transcription factor 1.

Protein

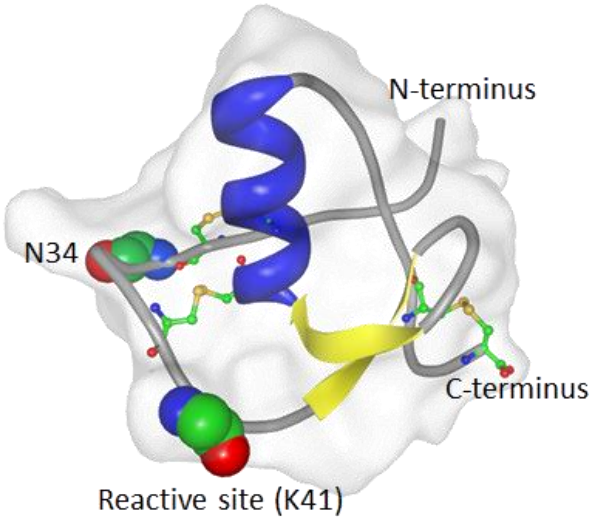
In the literature, SPINK1 is widely referred to as TATI (tumor-associated trypsin inhibitor) and PSTI (pancreatic secretory trypsin inhibitor).

Description

SPINK1(NCBI Reference Sequence: NP_003113.2 ; UniProtKB/Swiss-Prot: ISK1_HUMAN, P00995; PDB: 1cgj; 1cgi; 1hpt) is a 6242 Da secreted protein, containing 79 amino acids. Mature SPINK1 contains 56 amino acids and three disulfide bonds. It has a Kazal-type serine protease inhibitor domain and belongs to the SPINK (serine peptidase inhibitor, Kazal-type) family. SPINK1 has been reported to inhibit several proteases, including human trypsin-1 and -2 (cationic and anionic trypsins), acrosin and granzyme A (Pubols et al., 1974; Huhtala et al., 1984; Turpeinen et al., 1988; Tsuzuki et al., 2003).

Expression

SPINK1 was first characterized in bovine pancreas (Kazal et al. 1948) and pancreatic juice (Greene 1966), and later from human pancreatic juice (Fritz et al 1967). SPINK1 is mainly expressed in the pancreas, but to a lesser extent also in several other tissues, e.g., in the gastrointestinal tract, including the liver, duodenum, small intestine, gall bladder, colon, appendix, stomach, and in the genitourinary tract, e.g., prostate and urothelium (Paju and Stenman, 2006; Itkonen and Stenman, 2014). Expression has been found also in kidney, lung, breast, brain, spleen and ovary. SPINK1 is often strongly expressed in ETS-rearrangement-negative prostate cancers (Tomlins et al., 2008). A putative bipartite pancreas-specific transcription factor 1 (PTF1)-binding sequence has been identified (Boulling et al., 2011) in the SPINK1 gene. Outside the pancreas, SPINK1 has been considered an inflammatory pleiotropic cytokine, which is regulated by immune and inflammatory responses. In some cell lines, the expression is regulated by IL-6 (Yasuda et al., 1993). In cultured prostate cancer cells, SPINK1 expression has been shown to be regulated by androgens (Paju et al., 2007). In mouse, the synthesis of Spink3 (mouse orthologue of SPINK1) is dependent upon testicular androgens in the sex accessory tissues, but not in the pancreas (Mills et al., 1987).



Ribbon diagram of recombinant SPINK1 variant (RSCB Protein Data Bank code 1HPT (Hecht et al., 1991)). Protein Workshop program (Moreland et al., 2005) with the surfaces feature (Xu and Zhang, 2009) was used for visualization. Cysteines, forming three disulfide bonds, are shown as balls and sticks. The atoms of asparagine-34 (N34) residue, mutation in which is associated with chronic pancreatitis, and reactive site lysine (K41) are shown as balls without side-chains. Alpha-helix is shown in blue and beta-sheets in yellow.

Very high serum and urine concentrations occur in patients with pancreatitis (Ogawa, 1988). Serum levels of SPINK1 may also be elevated in several cancers, including prostate cancer, ovarian cancer and benign cysts, renal-cell carcinoma, bladder carcinoma, and colorectal cancer (Paju and Stenman, 2006; Itkonen and Stenman, 2014). Severe inflammation, tissue destruction and major trauma leads to an acute phase reaction causing increased circulating SPINK1 concentrations.

Localisation

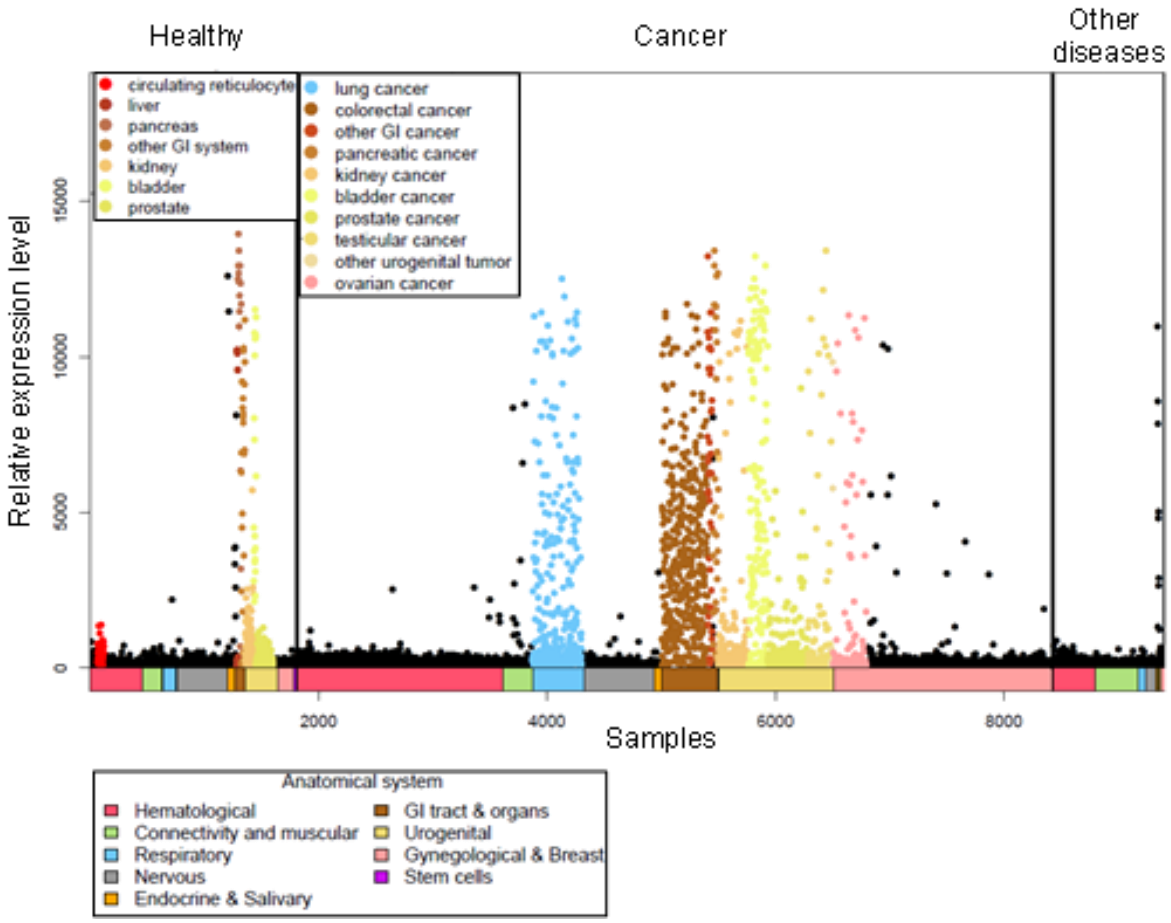
SPINK1 is highly expressed in the pancreas (Kazal et al., 1948). It has been localized to the zymogen granules of pancreatic acinar cells, where it protects the pancreas from premature activation of trypsinogens. SPINK1 is secreted into the pancreatic fluid along with digestive enzymes. Many cancers secrete SPINK1 causing elevated serum concentrations (Paju and Stenman, 2006; Itkonen and Stenman, 2014).

Function

SPINK1 is a protease inhibitor and has been reported to inhibit human trypsin-1 and -2 (cationic and anionic trypsins), but not trypsin-3 (mesotrypsin)(Sahin-Tóth, 2005). SPINK1 also inhibits granzyme A (Tsuzuki et al., 2003), plasmin, urokinase, tissue plasminogen activator (Turpeinen et al., 1988) and acrosin (Huhtala et al., 1984). SPINK1 has been reported to exert growth stimulation of cultured cells (Niinobu et al., 1990) and to activate the EGF-receptor (Ozaki 2009; Ateeq et al., 2011). However, growth stimulation by mechanisms other than via EGF receptor cannot be ruled out. It has been suggested that SPINK1 mediates tumor growth, differentiation, and angiogenesis via stimulation of the EGF-receptor or by suppression of serine-protease- or caspase-dependent apoptosis (Ateeq et al., 2011; Gouyer et al., 2008). There is evidence that SPINK1 plays a role in tissue differentiation (Ohmuraya et al., 2005) and repair (Marchbank et al., 1996), reproduction (Huhtala, 1984) and regulation of apoptosis (Lu et al., 2011). Over-expression of SPINK1 in cancer could block cancer cell apoptosis resulting in suppression of the immune response and escape of cancer cells from immune surveillance (Lamontagne et al., 2010).

Homology

SPINK1 contains a Kazal-type serine protease inhibitor domain, found in many other proteins and especially in members of SPINK family. Apart from this domain, SPINKs do not share high sequence similarity. Apart from SPINK5, SPINKs are of similar size and most genes contain the same number of exons. Some of the family members lack functional annotatation. A functional SPINK1 orthologue, Spink3 (NP_033284.1), has been found in mouse. The rat has two orthologues, Spink1 (NP_690919.1) and Spink3 (NP_036806.1) (HomoloGene, Release 67). Orhologues have been found also in common chimpanzee (XP_001160275.1), rhesus macaque (XP_001102888.1), grey wolf (XP_850557.1) and cattle (NP_001020519.1). Sequence similarity between SPINK1 and EGF has been reported (Hunt et al., 1974).



Relative mRNA expression levels of SPINK1 in different tissues. The data is from the IST4 database containing gene expression data in ~10 000 samples (http://ist.medisapiens.com/) (Kilpinen et al., 2008).

Mutations

NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP/) reports 631 SPINK1 SNPs (Homo sapiens, December 29., 2014).

At least 15 missense mutations have been described in the mature polypeptide and three in the signal peptide (Chen and Férec, 2009). Association of mutations with familial pancreatitis and other diseases has been described (see below).

Implicated in

Liver cancer

Up-regulation of SPINK1 in tissue has been shown to distinguish hepatocellular carcinoma (HCC) from benign liver disease and normal liver (Marshall A 2013). Elevated serum concentrations of SPINK1 are associated with adverse prognosis of hepatocellular cancer (Lyytinen et al., 2013). Serum SPINK1 is also a useful marker for distinguishing between patients with or without liver metastasis of colorectal and breast cancer (Taccone W 1991; Gaber A 2010).

Disease

HCC is the fifth most frequently diagnosed cancer and the second most common cause of cancer death worldwide in men (Jemal et al., 2011).

In females the rate is about half of that of men. Half of the cases occur in China and liver cancer is less common in Western countries.

HCC is the most common type of liver cancer. It may be caused by viral infections, like hepatitis B and C, or cirrhosis.

Most tumors in the liver are not primary liver cancers, but metastases of other cancers.

Prognosis

Plasma SPINK1 concentration is elevated in HCC patients and it correlates with tumor size (Ohmachi et al., 1993).

Overexpression of SPINK1 mRNA is a stage-independent prognostic factor and a predictor of early tumor recurrence in HCC (Lee et al., 2007) and in cholangiocarcinoma (Tonouchi et al., 2006). Serum SPINK1 has been shown to predict adverse prognosis in HCC (Lyytinen I 2013).

Prostate cancer

SPINK1 is often overexpressed in ETS-rearrangement-negative prostate cancers (Tomlins et al., 2008).

Disease

Prostate cancer is a considerable health care problem with 342 000 new cases and about 71 000 deaths annually in the EU countries, it is the most frequently diagnosed cancer in men and the third most common cause of cancer death (data from GLOBOCAN 2008).

Prostate cancer can be diagnosed by screening at an early stage, when most patients can be cured by radical prostatectomy or radiotherapy.

However, about one third of the tumors relapse. Most of these cases can be treated by androgen ablation, but within 3 - 5 years the tumor usually becomes castration-resistant.

Prognosis

High SPINK1 expression has been associated with adverse prognosis in prostate cancer in some (Tomlins et al., 2008; Paju et al., 2007), but not all studies (Leinonen et al., 2013; Grupp et al., 2013; Lippolis et al., 2013).

The differences may be related to the type of treatment, e.g., surgery or androgen ablation (Leinonen et al., 2013).

Breast cancer

Disease

Breast cancer is the most common cancer among women worldwide, accounting for 23% of all cases (Jemal et al., 2011). Although the prognosis has improved due to early diagnosis and therapies, breast cancer remains a major cause of death among women (14% of the cancer deaths). Most neoplasms of the breast originate from the ductal epithelium, while a minority originates from the lobular epithelium. A family history of breast cancer is associated with a 2-3-fold higher risk of the disease.

Prognosis

SPINK1 expression is associated with poor prognosis in estrogen receptor-positive breast cancer (Soon et al., 2011).

Colorectal cancer

Elevated serum SPINK1 has been observed in some patients with colorectal cancer. (Solakidi et al., 2004; Pasanen et al., 1995)

Disease

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females (Jemal et al., 2011). It originates from colon or rectum, but, based on genetic studies, these are the same tumor. When locally confined, colorectal cancer is often curable by surgery.

Prognosis

High expression of SPINK1 has been associated with adverse prognosis and liver metastases (Gaber et al., 2010; Gaber at al., 2009)

Bladder cancer

Urinary SPINK1 is a useful marker for high-grade bladder cancer (Kelloniemi et al., 2003; Shariat et al., 2005; Gkialas et al., 2008, Patschan et al., 2012).

Disease

Bladder cancer is more common in males than in females and there is great geographic variation in incidence (Jemal et al., 2011). The highest incidence rates are found in Europe, North America and Northern Africa. Smoking, occupational exposures and chronic infection with Schistosoma hematobium are major risk factors. Most bladder cancers originate from the epithelial lining of the urinary bladder. Transitional cell carcinoma is the most common type of bladder cancer.

Prognosis

Serum SPINK1 has been shown to be an independent prognostic factor for bladder cancer (Kelloniemi et al., 2003) and for prediction of the response to chemotherapy (Pectasides et al., 1996). SPINK1 expression is stronger in noninvasive than in invasive tumors and decreases with advancing tumor stage (Hotakainen et al., 2006; Patschan et al., 2012).

Ovarian cancer

The association of SPINK1 (TATI) and cancer was first observed in a patients with ovarian cancer (Stenman et al. 1982)

Disease

Ovarian cancer is the leading cause of death from gynecologic cancer. Most cases are diagnosed at advanced stages and, thus have relatively poor prognosis. The vast majority of ovarian cancers are epithelial. Cancer of the fallopian tubes is similar to ovarian cancer.

Prognosis

Increased SPINK1 expression is associated with adverse outcome in epithelial ovarian cancer (Huhtala et al., 1983; Paju et al., 2004). Elevated serum SPINK1 is an independent prognostic factor (Venesmaa et al., 1994; Venesmaa et al., 1998; Paju et al., 2004).

Gastric cancer

SPINK1 is detected in the normal gastric mucosa.

Disease

Gastric cancers account for 8% of all cancer cases and 10% of the deaths (Jamal et al., 2011). Over 70% of new cases and deaths occur in developing countries and rates are higher in males than in females.

Helicobacter pylori infection is the main risk factor, but smoking also increases the risk of gastric cancer.

Prognosis

The prognosis of gastric cancer is generally poor and metastases develop frequently. High tissue expression of SPINK1 is a sign of favorable outcome and loss of SPINK1 immunoreactivity in tumor tissue is associated with adverse prognosis (Wiksten et al., 2008). Serum SPINK1 is elevated in 50% of patients with gastric cancer (Solakidi et al., 2004).

Renal cell carcinoma

Disease

Renal cancer comprises five distinct histological types. Within each type, there is considerable variation in clinical course and survival. Presently, many tumors are detected at an early stage by sonography performed for various reasons.

Prognosis

Prognosis of metastatatic and advanced disease is poor, but surgical treatment of localized disease is often curative. There are no specific serum markers for RCC. Elevated serum SPINK1 has been shown to be an independent prognostic factor in renal cell carcinoma (Meria et al., 1995; Paju et al., 2001).

Pancreatitis, hereditary (Online Mendelian Inheritance in Man (OMIM): 167800)

SPINK1 polymorphisms are found more frequently in patients with hereditary and idiopatic chronic pancreatitis (23%) than in healthy controls (0.4%) (Witt et al., 2000; Chen and Férec, 2009). Several mutations of SPINK1 cause loss-of-function by splicing, frameshift, deletion or initiation codon mutation. Some missense mutations have been suggested to affect polypeptide folding, leading to intracellular retention and degradation of the mutated polypeptide (Boulling et al., 2012). These mutations are suggested to cause pancreatitis because of SPINK1 deficiency. The most common mutation worldwide is a 101A>G transition within exon 3 resulting in the substitution of Asp by Ser at codon 34 (N34S) (Witt et al., 2000). The frequency of the N34S mutation in pancreatitis patients is 9-29 % as compared to 0.5-2.5 % in the general population. In functional studies no differences in SPINK1 expression, trypsin inhibitory activity or binding to trypsin have been found between wild-type and N34S-SPINK1. The mutations D50E, Y54H and R67C result in marked reduction or complete loss of SPINK1 secretion, and are classified as disease-causing mutations although trypsin inhibitory activity of the mutated proteins was retained (Király et al., 2007). The P55S mutation of SPINK1 is found in healthy controls as well as in pancreatitis patients with an incidence of 0.5-1.3 % and 0.9-7 %, respectively (Witt et al., 2000; Pfutzer et al., 2000). The role of this mutation in pancreatitis remains unclear.

Disease

Elevated serum and urine concentrations are caused by pancreatitis, i.e., inflammation of pancreas. Some hereditary mutations of the SPINK1 gene, increase the risk of pancreatitis. These cases are characterized by recurrent episodes of pancreatitis starting at young age. These episodes often lead to tissue damage and loss of pancreatic function, including insulin production. This also increases the risk of pancreatic cancer.

Prognosis

The life expectancy of the pancreatitis patients is close to normal. However, patients have an increased risk of developing pancreatic cancer (Weiss, 2014).

Tropical calcific pancreatitis

SPINK1 mutations, especially the N34S mutation has been reported to associate with tropical calcific pancreatitis (Bhatia et al., 2002).

Disease

Tropical calcific pancreatitis (OMIM: 608189) is a special type of chronic pancreatitis that occurs only in tropical countries.

Prognosis

Patients usually present at young age with recurrent abdominal pain and nutritional deficiencies. The disease often leads to beta-cell deficiency and diabetes requiring insulin before the age of 30. Prognosis is dismal and many patients succumb to complications caused by malnutrition.

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This article should be referenced as such:

Koistinen H, Itkonen O, Stenman UH. SPINK1 (Serine Peptidase Inhibitor, Kazal Type 1). Atlas Genet Cytogenet Oncol Haematol. 2016; 20(1):36-44.