



## ***SPINK1* N34S Variant**

Autodigestion or inflammation of organic tissues may be caused by increased proteolytic activity or decreased proteolytic inhibition. Chronic pancreatitis (CP) is a continuing or relapsing inflammatory disease. In the hereditary form, mutations in the cationic trypsinogen gene (*PRSSI*) have been demonstrated in patients and are assumed to result in increased trypsin activity. Most CP patients do not have mutations in *PRSSI*, but several studies have shown a greater-than-expected presence of variants in other genes.

The most actively-studied gene for CP has been the serine protease inhibitor Kazal type 1 (*SPINK1*; PST1) which contains 4 exons spread over 7.5 kb on chromosome 5. *SPINK1* is a pancreatic secretory trypsin inhibitor of 79 amino acids from which a 23 amino acid signal peptide is removed to form a mature, processed peptide which has a reactive site that serves as a specific target for trypsin. Since ~20% of the capacity of total potential trypsin activity in the pancreas can be inactivated by the available *SPINK1* gene products, *SPINK1* is thought to play a major role as a first line defense in protecting the pancreas from premature trypsin activation.

A variety of genetic variants in *SPINK1* have been described, which are thought to interfere with inhibitory function thus allowing enhanced activation of trypsinogen to trypsin. The missense N34S variant which alters an asparagine to a serine residue altering rotation of the amino acid side chain and orientation of the binding loop/peptide penetration into the trypsin specificity pocket is the most widely studied. Several other *SPINK1* variants have also been reported, including variants in the 5' and 3' untranslated regions as well as the promoter region.

*SPINK1* variants by themselves have not been rigorously shown to initiate pancreatic disease by a known autosomally transmitted mechanism and are thought to most likely modulate pancreatic disease in conjunction with other genetic and environmental factors. Indeed, in the unlikely event *SPINK1* variant act in a monogenic fashion, penetrance would be very low – on the order of 1-2%. As previously noted, N34S heterozygote and homozygote genotypes are enriched in the CP population, and their presence may provide a clue that genetic factors are contributing to CP in certain individuals. The N34S variant has also been associated with fibrocalcific and tropical calcific pancreatitis in Asia.

The test employs PCR amplification of genomic DNA isolated from patient white blood cells for the region of the *SPINK1* gene containing this coding sequence followed by restriction endonuclease digestion and gel electrophoresis to identify normal, heterozygous and homozygous individuals at each locus. A customized report is generated which takes into account family history (if provided) and the inheritance pattern of this disorder

**Turnaround Time:** 7-21 business days.

**Specimen Requirements:** See Oncology/Genetics Specimen Handling Protocol or Molecular Diagnostics Genetics Requisition Form.

**Informed Consent:** It is the responsibility of the referring health care professional to obtain proper informed consent from the patient for genetic testing. Test results are released only to the primary referring physician and/or genetic counselor. The laboratory report contains information that may be useful for genetic counseling of the patient and/or family members, although adjunct use of an experienced genetic counselor or medical geneticist may be beneficial for this genetic disorder.