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REVIEW ARTICLE

PRSS-1 Gene Mutations in Etiopathogenesis of Pancreatic Cancer

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ABSTRACT:

The genetic which alters the PRSS-1 (protease serine-1) gene results in chronic pancreatitis, which further causes pancreatic cancer. The equilibrium of the protease and anti-protease is altered by the RI22H (A sub-mutation of PRSS-1) which promote the onset of pancreatic cancer. Gene conversion is the major phenomenon which create the nucleotide changes that affect the axon part of thePRSS-1 gene. Genetic factors, Alcoholism, smoking, lack of the anti-oxidants were some of the factors, which causes the PRSS-1 gene mutations.

KEYWORDS: Mutation, Gene conversion, PRSS -1 gene, Pancreatic cancer.

INTRODUCTION:

The Pancreas is an accessory organ of the digestive system that synthesize the digestive proenzyme Trypsinogen.(1) The Trypsinogen occurs in three highly similar isoforms, the encoding of the iso-enzymes by the separate genes include, PRSS 1 (Protease, serine 1) PRSS 2, PRSS 3. These are termed as cationic trypsinogen (PRSS 1), Anti-trypsinogen (PRSS 2) and meso-trypsinogen (PRSS 3).(2,3) Based on the relative isoelectric points and the electrophoretic mobility. Most probably the cationic trypsinogen represents two-thirds of the total trypsinogen in the pancreatic juice.(4) For the process of the digestion to happen, the trypsinogen must be converted to the trypsin. The conversion of the trypsinogen to the Trypsin occurs in the duodenum by the enzymes protease and the enterokinase.(5,6)

The genetic variations or stable heritable genetic changes that occurs spontaneously altering the PRSS 1 Gene/ cationic Trypsinogen will results in the chronic pancreatitis, in turn leads to the Pancreatic cancer.

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The mutations within the trypsinogen sequence were located mainly in these three clusters.(7,8,9)

1. In the trypsinogen activated peptide
2. N –Terminal portion of the trypsin
3. Congest peptide segment

Most of the pancreatitis associated mutations were discovered at the N –Terminal portions of the trypsin. The discovery of the pancreatitis associated (PRSS 1gene mutations) shows that trypsinogen plays a central role in the pancreatitis pathogenesis.(10,11)

R122H Mutations – increases Trypsin stability:

David whitcomb proposed that Arginine 122 – Valine 123 bond present in the trypsin structure will play an essential role in the destruction of the prematurely activated Trypsin in the pancreas, these R122H gene mutations causes the chronic Pancreatitis.(12,13,14) R122H mutations may increase the trypsin activity and cause the changes in the equilibrium of the protease and the anti-protease activity and also paved the way for the onset of the pancreatitis. R122H mutations may increase the stability of the trypsin, since Arginine 122 is essential for the autolysis of the trypsin, therefore the mutations of the Arginine122 amino acid may increase the Trypsin stability.(15,16)

N29I and N29T, Role in the Auto Activation:
Biochemical characterization of the N29I mutations concluded that N29I, mutations have no effect on the trypsin or trypsinogen stability.[17,18] Whereas on the other hand, N29T gene mutations exhibit the phenotype similar to RI22H, so they resulted in the increase trypsin stability and enhances the auto activation. The common pathogenic mechanism of the pancreatitis associated PRSS1 mutations is due to the enhanced auto activation of N29T. The most common mutations of PRSS1 gene are mainly R122H and N29I mutations.[19,20,21,22]

Gene conversion:
Gene conversion is the phenomenon in which the conversion/replacement/substitution of the genetic material from one gene to another gene. In most of the cases, the gene of donor is duplicated pseudogene, which resulted in the mutations leading to the pathogenic genotype.[23] The gene conversion may even create a nucleotide changes that affect the exon part of the PRSS1 gene.[24] As the result of the nucleotide changes, there exist a N29I, N54S mutations at amino acid level. Finally, the results conclude in this way that the gene conversion in turn causes the nucleotide changes and the mutations is the possible mechanism for the development of the chronic pancreatitis associated PRSS 1 mutations.[25]

Other genes conversions that may cause PRSS 1mutations:
D19A N54S
G83E A121T
D22G P36R
K92N V123M
K23R V39A
DI00H C139F
N29I+ LI04P
The biochemical properties of these genes along with their mutations may even resulted in chronic pancreatitis. [26]

TRYPSINOGEN ACTIVATION PEPTIDE MUTATIONS:
Considerations about the trypsinogen activation peptide are important, because they do not alter the trypsin structure and the physiological role of the trypsin. Pancreatitis associated mutations usually alter the properties of the pro- enzyme trypsinogen and not the active enzyme trypsin. The auto activation of the cationic trypsinogen is an important pathological mechanism in the pancreatitis.[27]

PRSS 1 MUTATIONS AND HEREDITARY PANCREATITIS:
Hereditary pancreatitis may be resulted in the families due to these cationic trypsinogen mutations. Usually 50% of the affected families shows the PRSS 1 gene mutations. These mutations may be either as the results of NS9I/R122H mutations. In addition to the genetic factors, Alcoholism, smoking, lack of the anti-oxidants were some of the factors.[28]

ROLE OF SPINK-1 MUTATIONS AND N34S MUTATIONS IN PANCREATIC CANCER:
SPINK 1 gene mutations plays an important role in modifying the expression of PRSS1 mutations. These gene modifications on the PRSS1 gene plays a vital role in Hereditary pancreatitis.[29,30] N34S mutations in the SPINK 1 gene plays a significant role in pancreatitis. There are also some other factors including the genetic as well as environmental factors.[31]

A study by Schubert M *et.al* conducted a cohort study in patients with idiopathic chronic pancreatitis and said that mutation in the CTFR, SPINK-1 and PRSS-1 doesn't seem to increase the risk of idiopathic pancreatic adenocarcinoma.[32]

F U Weiss *et.al* said that for onset of pancreatitis SPINK1 mutation may represent as a general modifier and it is yet undetermined that SPINK1 mutations may cause the idiopathic pancreatitis.

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