The most important candidate genes for pancreatic stone formation

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Stone formation is an important feature of chronic pancreatitis, especially tropical calcific pancreatitis (TCP), where the stones are large in size, highly irregular in shape and cause enormous tissue destruction. The exact mechanism of stone formation is not well-understood. It is very important to understand the initial event so that stone formation can be controlled before it causes obstruction and damage to the pancreatic tissue.

One such study was recently reported in the November 28 issue of the *World Journal of Gastroenterology* because of its significance in pancreatic diseases.

In an attempt to understand the initiating event in stone formation in chronic pancreatitis, Dr. Chandak and his group initiated this study. Protein plug formation is an important primary event in the final stone formation and hence some proteins must be increased in their concentration in the pancreatic juice.

Lithostathine (encoded by reg1 gene) has been isolated as a major protein component from stones of alcoholic chronic pancreatitis patients, and has been found to be 2 to 3 times less abundant in the pancreatic juice of chronic pancreatitis patients than in controls. Although the exact function of reg1 protein is not clear, it has been proposed to regulate the process of stone formation.

The team proposed that mutations in the promoter region of reg1 could

lead to altered levels of the protein, or that the gene variants could predispose the reg1 protein to increased cleavage by trypsin and form fibrils that may precipitate and obstruct the duct by forming protein plugs and calculi. The interaction between pancreatic inflammation and stone formation in chronic pancreatitis is also not well understood; this study also investigated the interaction between the reg1 gene and the established susceptibility genes for TCP, such as pancreatic secretory trypsin inhibitor and cathepsin B (encoded by SPINK1 and CTSB respectively).

On testing the hypothesis in a large cohort of ethnically matched TCP patients and normal individuals, Dr. Chandak and his group discovered that mutations in reg1, including those in the regulatory region either independently or in the presence of known mutations in SPINK1 and/or CTSB, might not be a cause of stone formation in TCP patients. This opens up scope for further research on alternative mechanisms, such as calcium signaling and regulation in stone formation in chronic pancreatitis.

The observations made by this study thus contribute significantly by ruling out the role of one of the most important candidate genes for pancreatic stone formation.

Source: World Journal of Gastroenterology