A Rare Mutation in Cystic Fibrosis Transmembrane Conductance Regulator Gene in a Recurrent Pancreatitis Patient Without Respiratory Symptoms

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A rare mutation in cystic fibrosis transmembrane conductance regulator gene in a recurrent pancreatitis patient without respiratory symptoms.

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Key words: cystic fibrosis, CFTR gene, D924N, recurrent pancreatitis, Japanese

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To the editors:

We report here a patient with severe recurrent pancreatitis due to the mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. A 14-year-old Japanese girl experienced recurrent pancreatitis nine times since 6 years of age. However, she did not have any respiratory symptoms such as cough, sputum, and wheeze. Endoscopic retrograde cholangiopancreatography (ERCP) showed dilatation, irregularity, and construction of her pancreatic duct, with worsening these findings from the onset of the disease (fig. 1). With our intervention to leave a stent within the duct for drainage of pancreatic exocrine, serum amylase levels went down to almost normal (100 – 150 IU/L), and she became able to eat 25 g/day fat diet without manifesting any severe symptoms of pancreatitis.

She had no obvious risk factors for pancreatitis, such as obesity, alcohol consumption and drug abuse. Also her cationic trypsinogen gene (PRSS 1) was normal. Recently, the association of some mutations in the CFTR gene with pancreatitis has been reported\textsuperscript{1,2}. Thus, we examined her CFTR gene with an informed consent. Cellular DNA was prepared from her blood by using Genomic DNA Purification Kit (Gentra, Minneapolis, Mn). Two mutations, D924N (exon 15) and 5T (intron 8), were identified in her CFTR gene. The D924N mutation locates at the transmembrane domain and may affect the charge of the CFTR protein. Although the mutation is listed in the CF mutation database (www.genet.sickkids.on.ca/ cftr/), the clinical manifestations due to this mutation have not been reported\textsuperscript{1}. Variable 5T allele in the intron 8 in cases with idiopathic chronic pancreatitis were reported previously \textsuperscript{3}. Compared with the common 7T / 9T variants, the 5T allele results in inefficient splicing of the exon 9, which in turn reduces CFTR expression\textsuperscript{4}. 
To analyze whether the two mutations in the patient were on the same chromosome or a different chromosome, *i.e.* compound heterozygote, we analyzed CFTR genes of her family members. Although her mother and brother (12-year-old) have no past history of pancreatitis, her father had acute pancreatitis once in young age. As shown in Table 1, the D924N mutation was found in her father, and the 5T allele was found in her mother. Thus, it is likely that her recurrent pancreatitis is due to compound heterozygote mutations in the CFTR gene, because cystic fibrosis is autosomal recessive disease.

CFTR has a role of HCO$_3^-$ secretion into pancreatic juice and low concentration of HCO$_3^-$ may induce pancreatitis due to hyper viscosity and acidic pH$^{5,6}$. The level of HCO$_3^-$ of her pancreatic juice was 56.6 mEq/l, much lower than normal (~140$^7$). On the other hand, her sweat chloride value was 23.2 mEq/l, lower than 60 mEq/l, excluding one of the diagnostic criteria for cystic fibrosis. Now, the exchange of stent in pancreas duct is needed for the patient every 3 months, because it is filled with protein plaque earlier than other chronic pancreatitis patients.

The typical type of cystic fibrosis is very rare in Asian population$^8$. On the other hand, we often have experienced idiopathic pancreatitis patients, even in pediatric population without any risk factors for pancreatitis$^9,10$. The patient reported here is the first to demonstrate the rare mutation D924N in the Asian population. These findings warrant analyzing the CFTR gene in the patient with idiopathic recurrent pancreatitis only, because combinations of some unique mutations in the CFTR gene, including D924N, may cause the disease.

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Table 1  Mutations found among the patient and her family members

<table>
<thead>
<tr>
<th></th>
<th>age</th>
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<tr>
<td></td>
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<td>Exon 15</td>
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<tr>
<td>patient</td>
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<td>D924N / wt</td>
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</tr>
<tr>
<td>brother</td>
<td>12</td>
<td>no</td>
<td>D924N / wt</td>
</tr>
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</table>

D: Asp, N: Asn  wt: wild type

FIGURE LEGEND

Figure 1: Progress of pancreatic duct dilatation on the endoscopic retrograde cholangiopancreatography (ERCP). (A) September, 2001 (6-year-old). (B) December, 2004 (9-year-old).
Figure 1

(A)  

(B)