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

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Running title: A phenotype of CFTR gene mutation ‘D924N’ in Japanese girl.

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[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. Variable 5T allele in the intron 8 in cases with idiopathic chronic pancreatitis were reported previously [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[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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REFERENCES

1. Cohn JA, Friedman KJ, Noone PG et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 1998; **339:** 653-658.
2. Choudari CP, Imperiale TF, Sherman S et al. Risk of pancreatitis with mutation of the cystic fibrosis gene. Am J Gastroenterol 2004; **99**: 1358-1363.
3. Aoyagi H, Okada T, Hasatani K, et al. Impact of cystic fibrosis transmembrane conductance regulator gene mutation on the occurrence of chronic pancreatitis in Japanese patients. *J Int Med Res.* 2009; 37: 378-384.
4. Chu CS, Trapnell BC, Curristin S et al. Genetic basis of variable exon 9 skipping in cystic fibrosis transmembrane conductance regulator mRNA. Nat Genet 1993; **3:** 151-15
5. Choi JY, Muallem D, Kiselyov K et al. Aberrant CFTR-dependent HCO^-_3 transport in mutations associated with cystic fibrosis. Nature 2001 410: 94-97.
6. Kopelman H, Corey M, Gaskin K et al. Impaired chloride secretion, as well as bicarbonate secretion, underlies the fluid secretory defect in the cystic fibrosis pancreas. Gastroenterology 1988; **95**: 349-355.
7. Choi JY, Lee MG, Ko S, Muallem S. Cl^- dependent $HCO3^-$ transport by cystic fibrosis transemembrane conductance regulator. JOP 2001; **2** (4 Suppl): 243-246
8. Wright SW, Morton NE. Genetic studies on cystic fibrosis in Hawaii. Am J Hum Genet 1968; **20**: 157-169.
9. Nijis E, Callahan MJ, Taylor GA. Disorders of the pediatric pancreas: imaging features. Pediatr Radiol 2005; **35**: 358-373.

10. Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systemic review. Gastrointest Endosc 2006; **63**: 1037-1045.

Table 1 Mutations found among the patient and her family members

	age	pacreatitis	CFTR gene	
			Exon 15	Intron 8
patient	14	recurrent, 9-times	D924N / wt	5T / 7T
father	42	acute, once	D924N / wt	7T / 7T
mother	40	no	wt / wt	5T / 7T
brother	12	no	D924N / wt	7T / 7T

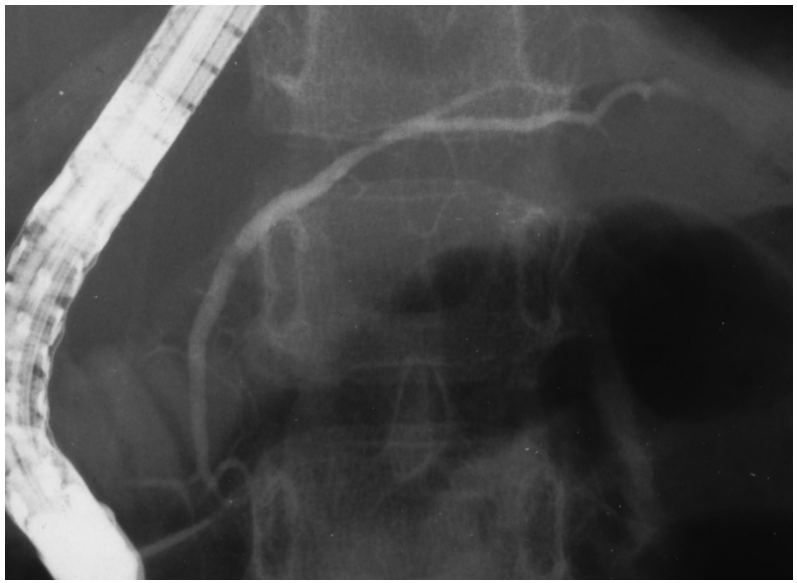
D: Asp, N: Asn wt: wild type

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)