Motion – Genetic testing is useful in the diagnosis of nonhereditary pancreatic conditions: Arguments against the motion

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JA Cohn. Motion – Genetic testing is useful in the diagnosis of nonhereditary pancreatic conditions: Arguments against the motion. *Can J Gastroenterol* 2003;17(1):53-55.

Mutations of two genes, the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) and the pancreatic secretory trypsin inhibitor gene (*PSTI*), are associated with an increase in the risk of idiopathic chronic pancreatitis. Persons who have mutations of both *CFTR* alleles (one severely and one mildly affected) are especially susceptible to this disease. Because these compound heterozygotes have sufficient residual *CFTR* function, they do not develop cystic fibrosis lung disease. One *PSTI* mutation, N34S, independently increases the risk of pancreatitis. Thus, the risk of pancreatitis is greatest among individuals who are *CFTR* compound heterozygotes and who also have the *PSTI* mutation. Nonetheless, most people with *CFTR* and *PSTI* mutations do not develop pancreatitis. This fact indicates that environmental influences and gene-gene interactions also affect pancreatitis risk. Although *CFTR* and *PSTI* genetic testing can identify persons at an increased risk of pancreatitis, there are several reasons why the routine screening of individuals with nonhereditary pancreatitis is not recommended at this time: most disease-associated mutations are not detected by readily available techniques, genetic counselling guidelines do not exist, most patients with mutations do not develop pancreatitis and the results of testing do not affect the clinical management of pancreatitis.

Key Words: *Cystic fibrosis; Cystic fibrosis transmembrane conductance regulator; DNA mutational analysis; Genetic predisposition to disease; Kazal pancreatic; Pancreatitis; Polymorphism (genetics); Trypsin inhibitor*

During the past few years, several groups have shown that the risk of nonhereditary pancreatitis is increased in those individuals who have mutations of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) and of a trypsin inhibitor gene (*PSTI*, also known as the serine protease inhibitor, Kazal type 1 gene) (1-12). The present article reviews the evidence linking pancreatitis with mutations of these two genes, and discusses the rationale and limitations of *CFTR* and *PSTI* genetic testing in the diagnosis of nonhereditary pancreatitis.

Idiopathic chronic pancreatitis (ICP) is the leading cause of chronic pancreatitis in children and nonalcoholic adults. Because most cases are sporadic, genetic factors were not ini-

L'analyse génétique est utile pour le diagnostic de maladies pancréatiques non héréditaires : Arguments contre cette proposition

RÉSUMÉ : La présence de mutations dans deux gènes, le gène régulateur de la perméabilité transmembranaire de la fibrose kystique (*CFTR*, cystic fibrosis transmembrane conductance) et le gène inhibiteur de la trypsine pancréatique (*PSTI*, pancreatic secretory trypsin inhibitory), est associée à un risque accru de pancréatite chronique idiopathique. Les personnes dont les deux allèles du *CFTR* portent des mutations (une grave et l'autre bénigne) sont particulièrement vulnérables à l'égard de cette maladie. Comme il reste une fonction *CFTR* résiduelle suffisante chez ces hétérozygotes, la fibrose kystique pulmonaire ne se manifeste pas. La mutation N34S du *PSTI* augmente de manière indépendante le risque de pancréatite. Par conséquent, celui-ci est plus élevé chez les personnes qui sont hétérozygotes à l'égard du *CFTR* et dont le *PSTI* porte également une mutation. Toutefois, la plupart des personnes ayant des mutations dans le *CFTR* et le *PSTI* ne font pas de pancréatite, ce qui indique que l'environnement et les interactions entre gènes influent également sur le risque de cette maladie. Bien que l'analyse génétique du *CFTR* et du *PSTI* permette de repérer les personnes particulièrement à risque de pancréatite, le dépistage systématique des personnes souffrant de pancréatite non héréditaire n'est pas recommandé à l'heure actuelle pour les raisons suivantes : les techniques courantes ne permettent pas de détecter la plupart des mutations associées à la maladie; il n'y a aucune ligne directrice pour le counselling génétique; la plupart des patients présentant des mutations ne font pas de pancréatite; et les résultats n'influent pas sur la prise en charge clinique de la pancréatite.

tially implicated in its pathogenesis. Nonetheless, three facts suggest that *CFTR* mutations might predispose to ICP: the earliest pathological finding in ICP often consists of plugging of the smaller pancreatic ducts which is reminiscent of the early findings in cystic fibrosis. ICP can cause sweat test abnormalities and pancreatitis is a rare complication of cystic fibrosis (with a lifetime incidence of 1%) (2). These considerations led two groups to test ICP patients for *CFTR* mutations (1,2,12). A total of 86 subjects with ICP were studied, and 20% had common cystic fibrosis-causing *CFTR* mutations. This is approximately five times the expected prevalence of cystic fibrosis carriers.

This article was originally presented at a symposium entitled, "Controversies in Gastroenterology", sponsored by Axcam Pharma, Toronto, Ontario, April 8 to 10, 2002

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On average, cystic fibrosis carrier status increases the risk of ICP by five-fold. This is important, because 3% to 4% of white people in the United States are carriers (2,13). Because fewer than 1% of these carriers develop ICP, a key question is whether all carriers are at similar risk for ICP. To address this question, Noone et al (12) recently tested a series of ICP patients with common *CFTR* mutations to determine whether the other copy of the gene was also abnormal. In most cases, the authors found an atypical or uncommon mutation involving the other copy of the gene. The subjects with ICP each had one *CFTR* mutation with virtually no function (eg, causing over 98% loss of function) together with a milder mutation of the other copy of their gene (eg, causing an 80% loss of function). These compound heterozygous genotypes are associated with a 90% reduction of *CFTR* function, which explains why these individuals do not develop cystic fibrosis lung disease. The amount of residual *CFTR* function – roughly 10% of normal – is sufficient to protect these patients from lung injury. ICP risk is increased about 50-fold in individuals with these compound heterozygous genotypes.

The large increase in ICP risk strongly implicates defective *CFTR* function in the pathogenesis of ICP. At least 95% of *CFTR* compound heterozygotes, however, do not develop ICP. Thus, unlike cystic fibrosis lung disease, ICP exhibits non Mendelian (or complex) inheritance (Table 1). Virtually all

individuals with two cystic fibrosis-causing mutations develop cystic fibrosis (13). In contrast, *CFTR* compound heterozygosity increases the risk of ICP, but does not always cause the disease. One implication of this finding is that environmental influences and gene-gene interactions might be important in determining which individuals are susceptible to develop ICP.

One mutation of the *PSTI* gene (N34S) has also been associated with many forms of pancreatitis (8,14). The N34S *PSTI* mutation occurs in roughly 1% of the general population, and it increases the risk of pancreatitis by 20-fold (12,14). Because pancreatitis does not develop in 99% of individuals who harbour N34S, the inheritance pattern is also non Mendelian.

Additional studies have shown that the N34S *PSTI* mutation is not associated with autosomal dominant hereditary pancreatitis (15). On the other hand, one recent report indicates that N34S is associated with ICP in individuals who have *CFTR* mutations. For *CFTR* compound heterozygotes who also have N34S, the risk of ICP was increased by 900-fold (12). The additive impact of *CFTR* and *PSTI* mutations on pancreatitis risk is consistent with the fact that these genes are expressed at different sites in the exocrine pancreas: *CFTR* occurs mainly in the apical membrane of duct cells (16,17), while *PSTI* occurs mainly in the zymogen granules of acinar cells (4). These data imply that *PSTI* genetic testing might help to identify *CFTR* compound heterozygotes who are at especially high risk for ICP. Even when *PSTI* and *CFTR* mutations are both present in a single individual, however, the risk of developing ICP is still less than 50%.

From a practical standpoint, *CFTR* and *PSTI* genetic testing may be useful in selected individuals with unexplained pancreatitis. It can help patients to understand their disease, and it can allow earlier recognition of extra-pancreatic *CFTR*-related problems that may be associated with ICP (eg, male infertility). In addition, it can identify cystic fibrosis carriers who may benefit from genetic counselling, and it can identify rare patients with cystic fibrosis in whom pancreatitis is the initial clinical problem. In most patients with *CFTR* mutations, the amount of residual *CFTR* protein function can be predicted from the genotype and this correlates with the clinical diagnosis (Table 2).

However, there are important limitations to *CFTR* and *PSTI* genetic testing for the diagnosis of pancreatitis. First, most patients with *CFTR*-related ICP have uncommon or atypical mutations that cannot be detected using genetic testing methods that are currently available for clinical use. This means that caution is required when a clinical testing lab

TABLE 1
Cystic fibrosis versus idiopathic chronic pancreatitis

Distinguishing feature	Classic CF	Classic ICP
Typical <i>CFTR</i> genotype	CFsev/CFsev	CFsev/CFm-v
Residual <i>CFTR</i> function	<5%	5%-25%
Penetrance	>95%	<10%
Inheritance	Mendelian	Complex
Effect of genotype	Causes disease	Increases disease risk
Gene-environment and gene-gene interactions	Minor role	Major role

CF Cystic fibrosis; *CFm-v* Mutations causing mild or variable loss of function; *CFsev* Mutations causing virtually complete loss of function; *CFTR* Cystic fibrosis transmembrane conductance regulator gene; *ICP* Idiopathic chronic pancreatitis

TABLE 2
Cystic fibrosis transmembrane conductance regulator gene (*CFTR*) genotypes correlate with clinical diagnoses

	PI-CF	PS-CF	CBADV, ICP	CF carrier
<i>CFTR</i> mutations	Severe + severe	Severe + milder	Severe + mild-variable	Severe + wild type
Residual <i>CFTR</i> function (%)	0-2	2-5	5-20	50
Pancreatic insufficiency	Typical	Rare	Unknown	Unexpected
Abnormal sweat test	Typical	Typical	Variable	Unexpected
CF lung disease	Typical	Typical	Rare	Unexpected
CBAVD	Typical	Typical	<30%	Unexpected
Pancreatitis	Absent	10%	<30%	Unexpected

CBADV Congenital bilateral absence of the vas deferens; *CF* Cystic fibrosis; *ICP* Idiopathic chronic pancreatitis; *PI* Pancreatic insufficiency; *PS* Pancreatic sufficiency

reports a nondiagnostic mutational analysis. Second, genetic counselling guidelines do not exist for individuals who have either normal or abnormal results. Third, most patients with mutations of the *CFTR* and/or *PSTI* genes do not develop ICP. Genetic testing is thus unable to definitively predict who will develop ICP, even though it can identify persons who are at increased risk. Finally, the results of *CFTR* and *PSTI* testing do not affect clinical management of pancreatitis at this time. For these reasons, it seems premature to recommend *CFTR* and *PSTI* genetic testing as routine procedures during the diagnostic evaluation of nonhereditary pancreatitis.

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