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SPINK1 variants in young-onset pancreatic cancer

To the Editor: We read with great interest the article in *Journal of Gastroenterology* by Masamune et al.[1] reporting differential roles of the serine protease inhibitor Kazal type 1 (*SPINK1*) gene alterations in patients with alcoholic and nonalcoholic chronic pancreatitis. Although not emphasized in their study, perhaps the most tantalizing finding is the observation that patients with the N34S variant had a higher prevalence of pancreatic cancer than *SPINK1* wild-type patients (3/11 N34S patients vs. 0/85 wild-type patients, $P = 0.001$, Fisher's exact test). Our own data shed further light on the role of *SPINK1* alterations in pancreatic cancer.

We analyzed nine pancreatic cancer cell lines (PancTu-I, CAPAN1, PaCa44, AsPc1, MiaPaCa2, CAPAN2, BxPc3, Panc1, and Colo357) for sequence variations of *SPINK1* exon 3 and found two cell lines harboring the N34S alteration, Paca44, and PancTu-I (Fig. 1). Mutational analysis was performed by direct sequencing of two independent polymerase chain reaction (PCR) products in both directions (forward, 5′-TGAGTTTCAGAA GGGCCATAG-3′, reverse, 5′-CTTTTCTCGGGGTGAGA TTC-3′). The cell line PaCa44 was established from a 42-year-old woman with pancreatic ductal adenocarcinoma.[2] Review of the resected specimen showed morphological signs of chronic pancreatitis. We were unable to obtain detailed information about the origin of the cell line PancTu-I.[3] These two cell lines may be used to study functional properties of the N34S protein.

Although *SPINK1* alterations are clearly associated with chronic pancreatitis, their contribution to pancreatic diseases is controversial. The N34S variant has been proposed to act as a disease modifier rather than to be disease causing.[4] Even though the N34S variant has not been shown to be associated with sporadic pancreatic cancer,[5] it may be associated with pancreatic cancer arising from long-lasting chronic pancreatitis. This is supported by the finding that N34S chronic pancreatitis patients tend to have more severe disease with earlier onset than wild-type patients.[1,4] Interestingly, four of five pancreatic cancers described by Masamune et al.[1] and us were young-onset (i.e., diagnosed before the patient reached the age of 45).

On the basis of these observations, we propose that the effect of the N34S on pancreatic cancer may be mediated by its ability to predispose to long-lasting and severe chronic pancreatitis, similarly to *PRSS1*.[6] Even though large prospective studies are required to confirm this hypothesis, patients with *SPINK1*-associated pancreatitis would likely benefit from early screening for asymptomatic pancreatic cancer.[7]

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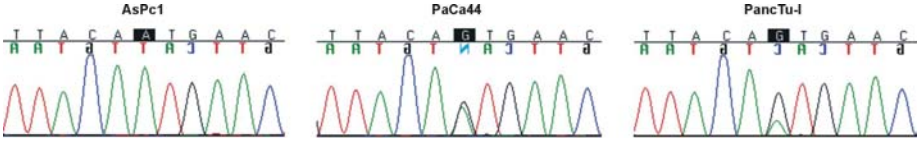

Fig. 1. Chromatograms depicting wild-type and N34S sequence variants in pancreatic cancer cell lines