effects, an omission that could have resulted in overestimation of the importance of gender-specific differences (Ann Intern Med 2010;152:697–703). Individuals born within the same time frame (birth cohort) often share similar risk characteristics, and these risk characteristics can have important effects on apparent differences in measured outcomes (such as colorectal neoplasia). Second, and perhaps more important, the role of observed data of this sort in directly influencing policy is uncertain. Screening policy must take into account not only colorectal cancer (CRC) risk (or its surrogate, adenoma prevalence), but also other clinical factors that affect the benefit of screening, such as life expectancy. Economic factors such as cost and resource utilization must also be considered. Weighing these various factors is best performed through careful mathematical modeling. In fact, prior modeling work on this very topic has suggested that gender- and race-tailored screening policy is unlikely to be efficient (Gastrointest Endosc 2009;70:96–108). Rather than leading to policy changes directly, data such as those presented by Ferlitsch et al are best used to inform existing models that can then be used to shape policy.

In summary, Ferlitsch et al provide an important contribution to the growing literature on patient-level differences in adenoma prevalence and CRC risk. These data could be useful to policymakers as they seek more robust data on gender-specific differences to inform existing models of CRC screening. However, we must be cautious in moving directly from observed data to policy without carefully considering how these observations interplay with other important clinical and economic factors.

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NOVEL GENETIC MUTATIONS SPECIFIC FOR INTRADUCTAL PAPILLARY NEOPLASM OF THE PANCREAS

***Wu J, Matthaei H, Maitra A, et al.* Recurrent *GNAS* mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med 2011;3:92ra66.**

Recent technological advances and the widespread use of abdominal imaging have resulted in a marked increase in the number of patients with pancreatic cysts (Am J Roentgenol 2008;191:802–807). Clinical, pathologic, and molecular studies have shown that intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are potential precursor lesions of invasive pancreatic ductal adenocarcinomas (PDAs), whereas serous cyst adenomas (SCAs) and other cysts, including retention cysts or congenital cysts, have minimal malignant potential (Nat Rev Gastroenterol Hepatol 2011;8:141–150). Indeed, molecular alterations that characterize PDAs, such as mutations in *KRAS* or *TP53*, are also detected in IPMNs and MCNs, supporting their nature as precancerous lesions (Nat Rev Gastroenterol Hepatol 2011;8:141–150). It is well recognized that PDAs derived from IPMNs are less aggressive and show a far better prognosis than PDAs that develop without any cystic precursors (Gastroenterology 2010;139:708–713). Thus, distinguishing pancreatic cysts with malignant potential from those without, or determining whether PDAs are derived from cystic precursors or not, is of great clinical importance. However, no specific marker is clinically available to predict the malignant tendency of pancreatic cysts. Therefore, to establish new diagnostic modalities and improve the understanding of the molecular pathogenesis of pancreatic cysts, especially those with malignant potential, it is critical to identify the genetic characteristics of pancreatic cystic neoplasms.

In their study published in *Science Translational Medicine*, Wu et al identified a novel pancreatic oncogene mutation in *GNAS*, a well-known oncogene in other tumor types that is common and specific for IPMN. Based on previous studies of various solid tumors, including PDAs, the authors selected 169 presumptive cancer genes for screening. After purifying DNA from cystic fluids obtained from 19 patients with IPMN, exonic sequences of the 169 genes were captured, and their sequence was determined by massively parallel sequencing. Two genes stood out: *KRAS* (14 of the 19 IPMNs) and *GNAS* (6 of the 19 IPMNs). All *KRAS* mutations occurred at codon 12, as previously reported for PDAs, and all *GNAS* mutations occurred at codon 201. This was the first demonstration of *GNAS* mutations in patients with pancreatic neoplasms, including IPMNs.

The authors next analyzed the frequency of *KRAS* codon 12 and *GNAS* codon 201 mutations in a larger set of 132 IPMN specimens, including 84 cystic fluid and 48 surgically resected samples using the PCR/ligation method, which has a high sensitivity for detecting mutant sequences. Mutations in *KRAS* and *GNAS* were detected in 81% and 66%, respectively. Approximately half (51%) of the IPMNs harbored both *KRAS* and *GNAS* mutations, whereas 96.2% of IPMNs had mutations in $\geq$1 of the 2 genes. The authors then evaluated whether *KRAS* or *GNAS* mutations were present in SCAs and MCNs, which are cystic neoplasms that are sometimes clinically indistinguishable from IPMNs. Importantly, no *GNAS* mutations were identified in either SCAs (n = 44) or MCNs (n = 21), whereas *KRAS* mutations were found in 33% of MCNs. These findings suggested that *GNAS* codon 201 mutations are highly specific to IPMNs.

Although there was no significant correlation between the prevalence of *GNAS* mutations and clinical parameters, such as age, gender, and history of smoking, the frequency of the *GNAS* codon 201 mutation was significantly higher in high-grade IPMNs. From this observation, the authors suspected that IPMNs harboring these

mutations could progress to an invasive carcinoma. To address this issue, the authors purified DNA from microdissected invasive PDAs accompanied by IPMNs and assessed *GNAS* mutations. In 7 of 8 patients, identical *GNAS* mutations were identified in both the IPMN and the concurrent invasive PDA. In contrast, no *GNAS* mutation was detected in 95 invasive PDAs that were not associated with IPMNs, reproducing the previous results of whole-exome sequencing data reported by Jones et al (Science 2008;321:1801–1806). These findings provide genetic evidence that defines PDA derived from IPMN as a pathologic condition distinct from conventional PDA.

Comment. Accumulating evidence has confirmed that IPMN, one of the most common cystic neoplasms of the pancreas, has the potential for malignant transformation. However, despite the establishment of evidence-based treatment guidelines (Pancreatology 2006;6:17–32) and remarkable advances in diagnostic imaging technologies, some patients with harmless cysts are still aggressively treated by surgical resection because of incorrect clinical diagnosis. Therefore, the establishment of a diagnostic system for pancreatic cysts based on molecular pathology has been eagerly awaited. In the present study, Wu et al identified the *GNAS* mutation as a highly specific genetic marker for IPMNs.

The first cases of IPMN were described in Japan in the early 1980s (Prog Dig Endoscopy 1982;20:348–351). Since then, several studies have identified a variety of molecular alterations in IPMNs (Nat Rev Gastroenterol Hepatol 2011;8:141–150; Gastroenterology 2010; 139:708–713). Confirming the characteristics of IPMNs as precancerous lesions, IPMNs share molecular alterations with PDAs, such as mutations in *KRAS* and *TP53*, loss of *CDKN2A*, and inactivation of *STK11*. In contrast, *SMAD4 (DPC4)*, which is lost in about half of PDAs, is retained in most IPMNs. Moreover, a recent report has shown that IPMNs harbor recurrent cytogenic alterations on chromosomes 5q, 6q, and 11q; these alterations are distinct from those found in PDAs (Ann Surg 2009;249: 440–447). In addition to these findings, Wu et al newly identified *GNAS* mutations in IPMNs using next-generation sequencing technology by employing a massively parallel deep sequencer. Importantly, *GNAS* mutations occurred with the second highest frequency after *KRAS* mutations in patients with IPMNs (66% vs 81%, respectively). Furthermore, they occurred exclusively in IPMNs, suggesting that the mutations may play a role in IPMN development.

GNAS mutations have been reported in several neoplasms, particularly those of the endocrine glands, including the pituitary, adrenal, and thyroid glands (Nat Clin Pract Endocrinol Metab 2006;12:681–693). Interestingly, the mutated codon in *GNAS* identified in IPMN in the present study was identical to that found in endocrine neoplasms. Common mutations in *GNAS* (R201C, R201H) are thought to inhibit guanosine triphosphate hydrolysis, which results in constitutive activation of Gsα and its effector, adenylate cyclase, leading to constitutive synthesis of cyclic adenosine monophosphate (Nature 1989;340:692–696). Thus, endocrine tumors with activating *GNAS* mutations are often characterized by hormonal hypersecretion, as observed in growth hormone-secreting pituitary adenoma. Given the crucial role of G-protein–coupled receptors in the secretion of pancreatic enzymes, bicarbonates, and mucus (Gastroenterology 1998;114: 382–397), activating *GNAS* mutations in IPMN may contribute to the pathogenesis of IPMN, especially to the characteristic mucus production and cyst formation by its hypersecretory effect. Therefore, *GNAS* mutations seem to contribute to the development of IPMN by modifying G-protein–coupled receptor signaling. However, the mechanism by which *GNAS* functions as an oncogene remains unclear.

The specific *GNAS* mutations observed in the present study suggest the possibility of a clinical application for this molecular diagnosis. Indeed, most IPMNs (96.2%) had *GNAS* and/or *KRAS* mutations, whereas SCAs had neither mutation, revealing that the detection of *GNAS/KRAS* mutations provides extremely high sensitivity and specificity for distinguishing between IPMNs and SCAs. In addition, >60% of IPMNs had *GNAS* mutations, whereas none of the MCNs did, suggesting that detection of a *GNAS* mutation can also distinguish IPMNs from MCNs. It is also notable that these authors established a method that has a high capacity to detect *GNAS* and *KRAS* mutations from no more than 250 μL of cystic fluid. Along with the development and dissemination of the endoscopic ultrasonography-guided fine needle aspiration technique, there have been many attempts to develop cystic fluid biomarkers that support cytological diagnosis. For example, protein markers, such as CEA (Gastroenterology 2004;126:1330–1336) and amylase (Gastroenterology 2006;130:1007–1009), or genetic/epigenetic markers, such as *KRAS* mutations (Gastrointest Endosc 2009;69:1095–1102), DNA methylation (Mod Pathol 2008;21:1499–1507), and microRNA expression (Cancer Biol Ther 2009;8:340–346), have been proposed as cystic fluid biomarkers. However, even by using these markers, preoperative cystic fluid evaluation still remains suboptimal, partly because of a lack of disease-specific markers. The finding of a *GNAS* mutation specific to IPMN will mark the start of a new phase in the diagnosis of pancreatic cystic neoplasms based on molecular pathology. In addition, assessment of *GNAS* mutations appears useful for the differentiation of de novo PDAs and PDAs derived from IPMN. It would also be interesting to see if a paired analysis of *KRAS* and *GNAS* mutations in IPMN could predict its prognosis. Further investigations are required to clarify whether *GNAS* with or without *KRAS* mutations contribute to the progression from IPMNs to PDAs. If *GNAS* mutations do, the molecular mechanisms would be of great interest to us to understand the pathogenesis of PDAs and explore the novel therapeutic targets for IPMNs to prevent unnecessary operative procedures.

Very recently, the finding of recurrent *GNAS* mutations in IPMNs was confirmed by whole-exome sequencing-based studies. Using whole-exome sequencing, Furukawa et al determined 17 genetic mutations, including those in *GNAS* and *KRAS*, in DNA extracted from tissue samples of IPMN. This was followed by the identification of *GNAS* mutations in 48 of 118 IPMNs (40.7%) and in none of the 32 conventional PDAs (Sci Rep 2011;1:161). Wu et al determined the exomic sequences of DNA from surgically resected SCAs, IPMNs, MCNs, and solid pseudopapillary neoplasms and found substantial genetic alterations in each neoplasm, including specific *GNAS* mutations in IPMNs (Proc Natl Acad Sci U S A 2011;108:1188–1193).

In summary, this is the first report, to our knowledge, that describes a novel mutation in a pancreatic oncogene *GNAS*. This finding provides a new insight into the molecular pathogenesis of IPMNs and PDAs derived from IPMNs. Furthermore, the work marks an important first step towards molecular-based diagnosis, prognostic prediction, and target therapy for pancreatic cystic neoplasms.

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