Activating *GNAS* and *KRAS* mutations in gastric foveolar metaplasia, gastric heterotopia, and adenocarcinoma of the duodenum

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Background: Heterotopic gastric-type epithelium, including gastric foveolar metaplasia (GFM) and gastric heterotopia (GH), is a common finding in duodenal biopsy specimens; however, there is still controversy regarding their histogenetic backgrounds.

Methods: We analysed a total of 177 duodenal lesions, including 66 GFM lesions, 81 GH lesions, and 30 adenocarcinomas, for the presence of *GNAS*, *KRAS*, and *BRAF* mutations.

Results: Activating *GNAS* mutations were identified in 27 GFM lesions (41%) and 23 GH lesions (28%). The *KRAS* mutations were found in 17 GFM lesions (26%) and 2 GH lesions (2%). A *BRAF* mutation was found in only one GFM lesion (2%). These mutations were absent in all 32 normal duodenal mucosa specimens that were examined, suggesting a somatic nature. Among the GFM lesions, *GNAS* mutations were more common in lesions without active inflammation. Analyses of adenocarcinomas identified *GNAS* and *KRAS* mutations in 5 (17%) and 11 lesions (37%), respectively. Immunohistochemically, all the *GNAS*-mutated adenocarcinomas diffusely expressed MUC5AC, indicating gastric epithelial differentiation.

Conclusions: A significant proportion of GFM and GH harbours *GNAS* and/or *KRAS* mutations. The common presence of these mutations in duodenal adenoma and adenocarcinoma with a gastric epithelial phenotype implies that GFM and GH might be precursors of these tumours.

The presence of gastric foveolar epithelium is a common finding in duodenal biopsy specimens. Depending on the absence or presence of oxyntic glands, these lesions are classified into gastric foveolar metaplasia (GFM) or gastric heterotopia (GH; Yantiss and Antonioli, 2009). GFM is generally regarded as a reactive process, as it is often associated with inflammatory conditions, including duodenal ulcer and chronic inflammatory diseases (Shousha *et al*, 1983; Wyatt *et al*, 1990; Khulusi *et al*, 1996). Previous studies characterised duodenal ulcer-associated epithelial phenotypes and suggested that GFM represents a reparative lineage histogenetically related to Brunner's glands (Hanby *et al*, 1993; Kushima *et al*, 1999a). On the other hand, GH consists of parietal and chief cells

in addition to gastric foveolar epithelium and is morphologically indistinguishable from oxyntic gland mucosa of the stomach. Because of the fully organised structure of this lesion, many authors consider it to be congenital in nature (Lessells and Martin, 1982; Shousha *et al*, 1983; Wyatt *et al*, 1990).

Recent studies have demonstrated that several lesions that had been regarded as being metaplastic or hyperplastic in nature are actually associated with frequent genetic alterations. For example, colorectal hyperplastic polyps were thought to be metaplastic lesions, as they exhibit preserved overall crypt organisation and no epithelial dysplasia (Williams *et al*, 1980); however, later studies have shown that a significant proportion of colorectal hyperplastic

polyps have an activating *BRAF* or *KRAS* mutation, and these lesions are now recognised as potential precursors of colorectal cancer (Iino *et al*, 1999; Hawkins and Ward, 2001; Chan *et al*, 2003; Yamada *et al*, 2012; Bettington *et al*, 2013). Pancreatic intraepithelial neoplasia 1A (PanIN1A) has also been previously regarded as a mucinous metaplasia; however, it is now thought to be the earliest stage precursor of invasive pancreatic adenocarcinoma (Hruban *et al*, 2001). Furthermore, the demonstration of somatic mutations, mostly *KRAS* mutations, in virtually all PanIN1A lesions strongly suggests the requirement of these genetic alterations in their development (Kanda *et al*, 2012).

Interestingly, previous reports described the association of GFM and GH with duodenal adenoma and adenocarcinoma and suggested that some duodenal tumours, particularly those with a gastric epithelial phenotype, might arise from GFM or GH (Kushima *et al*, 1999b; Kushima *et al*, 2002; Ushiku *et al*, 2014). In the present study, we analysed a series of GFM and GH lesions for the presence of *GNAS*, *KRAS*, and *BRAF* mutations based on the postulation that a subset of these lesions might harbour genetic alterations, similar to colorectal hyperplastic polyps and PanIN1A. We selected these genes for analysis based on the frequent presence of these mutations in benign/low-grade tumours of the digestive tract, which exhibit gastric-type mucin expression (Chan *et al*, 2003; Furukawa *et al*, 2011; Wu *et al*, 2011; Kanda *et al*, 2012; Matsubara *et al*, 2013; Nishikawa *et al*, 2013).

MATERIALS AND METHODS

Tissue samples. This study was approved by the Ethics Committee of the National Cancer Center, Tokyo, Japan. All the tissue samples were obtained at the National Cancer Center Hospital, Tokyo, Japan, between 1998 and 2013. All the specimens were routinely fixed in 10% formalin, embedded in paraffin, and subjected to hematoxylin-eosin (HE) staining. The present study analysed a total of 177 duodenal lesions of 165 patients, including 66 GFM lesions, 81 GH lesions, and 30 nonampullary duodenal adenocarcinomas, as well as 32 specimens of normal duodenal mucosa (Figure 1). All specimens of GFM, GH, and normal duodenal mucosa were obtained by biopsy and cases with a history of duodenal tumours were excluded. Two endoscopists reassessed the endoscopic images to confirm the duodenal origins of these specimens. For the case of GFM and GH, biopsy specimens containing at least two pits lined by gastric-type epithelium were selected to ensure the reproducible PCR amplification. Adenocarcinoma samples were obtained by endoscopic mucosal resection (2 cases), or surgical resection (28 cases).

Histological analysis. Sections of GFM and GH were subjected to alcian blue/periodic-acid Schiff (AB/PAS) double staining to confirm the presence of gastric foveolar epithelium with AB-negative/PAS-positive apical mucin. Subclassification into GFM and GH were made depending on the absence or presence of the oxyntic glands, respectively. The presence of active inflammation (characterised by intraepithelial neutrophils) and foveolar hyperplasia (defined by papillary growth associated with broad stroma) was assessed.

Immunohistochemistry was performed for the adenocarcinomas and representative GFM and GH lesions. Deparaffinized 4-μm thick sections from each paraffin block were exposed to 0.3% hydrogen peroxide for 15 min to block endogenous peroxidase activity. Antigen retrieval was performed by autoclaving in a 10 mM
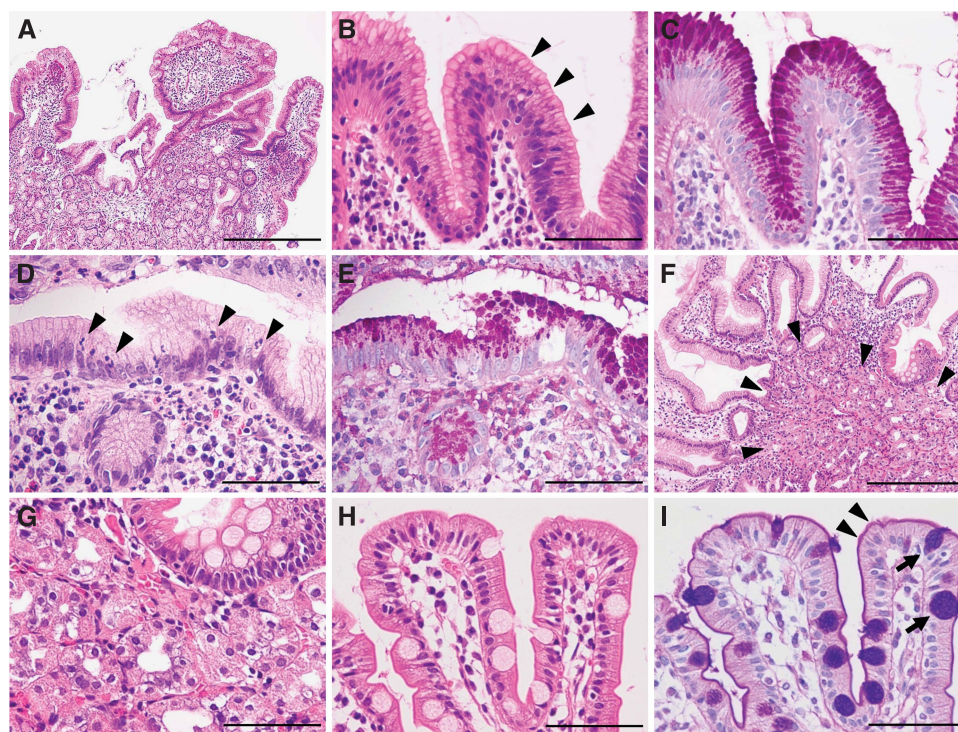
Figure 1. Histology of gastric foveolar metaplasia, gastric heterotopia, and normal duodenal mucosa. (**A–C**) Gastric foveolar metaplasia. Gastric foveolar-type epithelium exhibiting remarkable hyperplasia (**A**). Note the surface papillary projections lined by gastric foveolar-type epithelium. The lining epithelium shows an apical mucin cap (arrowheads; **B**), which is positive for periodic-acid Schiff (PAS) staining (**C**). (**D, E**) Gastric foveolar metaplasia with active inflammation. Note the intraepithelial neutrophils (arrowheads; **D**). Epithelium showing PAS-positive apical mucin (**E**). (**F, G**) Gastric heterotopia. Oxyntic glands (arrowheads) are present beneath the gastric foveolar-type epithelium showing foveolar hyperplasia (**F**). Closely packed oxyntic glands consisting of parietal and chief cells (**G**). (**H, I**) Normal duodenal mucosa. Villi lined by intestinal epithelium with a brush border. Goblet cells are intermingled with the absorptive cells (**H**). The brush border is positive for PAS staining (purple, arrowheads), whereas the goblet cells are positive for Alcian blue (blue, arrows; **I**). Scale bars indicate 400 μm in (**A** and **F**) and 100 μm in (**B–E** and **G–I**).

citrate buffer (pH 6.0) for 10 min. Anti-MUC2 (Ccp58; 1:200 dilution; Novocastra, Newcastle upon Tyne, England), anti-MUC5AC (CLH2; 1:200 dilution; Novocastra), anti-MUC6 (CLH5; 1:100, Novocastra), and anti-CDX2 (CDX2-88; 1:100; Bio Genex, San Ramon, CA, USA) were used as the primary antibodies. For staining, we used an automated stainer (Dako, Glostrup, Denmark) according to the vendor's protocol. Chem-Mate EnVision (Dako) methods were used for detection. The staining results were scored as: 0, <10% positive cells; 1+, 11%–50% positive cells; 2+, >50% positive cells.

Mutational analysis. Ten-micrometre sections of paraffin-embedded specimens were deparaffinized, stained briefly with hematoxylin, then subjected to DNA extraction. The lesions were microdissected using sterilised toothpicks under a microscope. The dissected samples were incubated in 50 μl of DNA extraction buffer (50 m$_M$ Tris-HCl, pH 8.0, 1 m$_M$ ethylenediaminetetraacetic acid, 0.5% (v/v) Tween 20, 200 μg/ml proteinase K) at 50 °C overnight. Next, the samples were heated at 100 °C for 10 min to inactivate proteinase K and then directly subjected to a PCR assay using pairs of primers encompassing exon 8 and 9 of *GNAS*, exon 2, 3, and 4 of *KRAS*, and exon 15 of *BRAF* (Table 1). The PCR products were electrophoresed on a 2% (w/v) agarose gel and were recovered using the QIAquick Gel Extraction Kit (Qiagen, Hilden, Germany). The isolated PCR products were sequenced using an Applied Biosystems 3130 Genetic Analyzer (Applied Biosystems Inc.,

Foster, CA, USA). All mutations were confirmed by reanalysis of the respective specimens, including DNA extraction.

Three GH samples that had *GNAS* mutations were further subjected to an analysis using a laser microdissection system (MMI CellCut system; Molecular Machines and Industries, Glattbrugg, Switzerland). The foveolar epithelium and oxyntic glands were separately dissected and analysed for the presence of *GNAS* mutations as described above.

Statistical analysis. Fisher's exact test was used to analyse each 2 × 2 table. *P*-values <0.05 were considered to indicate statistical significance.

RESULTS

The average ages of the patients with GFM, GH, and adenocarcinoma were 60 (range, 42–81 years), 57 (range, 25–84 years), and 64 years (range, 32–85 years), respectively. The presence of PAS-positive apical mucin was confirmed in all the GFM and GH lesions (Figure 1C and E). Evidence of active inflammation was observed in 14 GFM lesions (21%) and 1 GH lesion (1%) (Figure 1D and E). Twenty-one GFM lesions (32%) and eight GH lesions (10%) exhibited foveolar hyperplasia (Figure 1A and F).

Sequencing analyses identified activating *GNAS* mutations in 27 GFM lesions (41%), 23 GH lesions (28%), and 5 adenocarcinomas (17%; Table 2, Figure 2A). Activating *KRAS* mutations were found

Table 1. Primer sequences

Gene	Region	Forward 5'-3'	Reverse 5'-3'
GNAS	Exon 8	GGCTTTGGTGAGATCCATTGAC	TGGCTTACTGGAAGTTGACTTTG
	Exon 9	GACATTCACCCCAGTCCCTCTGG	GAACAGCCAAGCCCACAGCA
KRAS	Exon 2	ACATGTTCTAATATAGTCACATTTTCA	TTAGCTGTATCGTCAAGGCA
	Exon 3	AGGATTCCTACAGGAAGCAAG	AAAGAAAGCCCTCCCCAGT
	Exon 4	CTCTGAAGATGTACCTATGGTCCT	TTTCAGTGTTACTTACCTGTCTTGTC
BRAF	Exon 15	TGCTTGCTCTGATAGGAAAATG	CTGATGGGACCCACTCCAT

Table 2. GNAS and KRAS mutations in duodenal lesions

		GNAS				KRAS				BRAF			
	N	Total mutated	n	Nucleotide	Amino acid	Total mutated	n	Nucleotide	Amino acid	Total mutated	n	Nucleotide	Amino acid
Normal	32	0				0				0			
Gastric foveolar metaplasia	66	27 (41%)	12	c.601C>T	p.R201C	17 (26%)	1	c.34G>C	p.G12R	1 (2%)	1	c.1801A>G	p.K601E
			2	c.601C>A	p.R201S		3	c.35G>A	p.G12D				
			13	c.602G>A	p.R201H		6	c.35G>T	p.G12V				
							1	c.35G>C	p.G12A				
							1	c.38G>A	p.G13D				
							2	c.183A>C	p.Q61H				
							1	c.183A>T	p.Q61H				
							2	c.437C>T	p.A146V				
Gastric heterotopia	81	23 (28%)	11	c.601C>T	p.R201C	2 (2%)	1	c.35G>T	p.G12V	0			
			1	c.601C>A	p.R201S		1	c.35G>C	p.G12A				
			11	c.602G>A	p.R201H								
Adenocarcinoma	30	5 (17%)	1	c.601C>T	p.R201C	11 (37%)	1	c.34G>C	p.G12R	0			
			3	c.602G>A	p.R201H		7	c.35G>A	p.G12D				
			1	c.680A>G	p.Q227R		1	c.35G>T	p.G12V				
							2	c.38G>A	p.G13D				

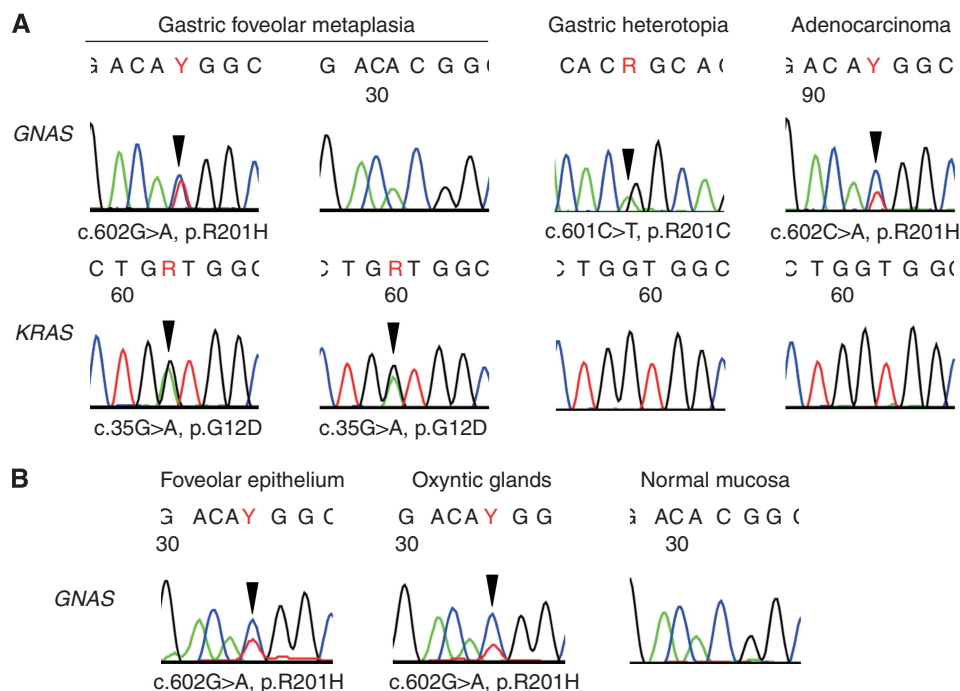*N*, Total number of lesions; *n*, number of lesions with mutations.

Figure 2. *GNAS* and *KRAS* mutations in gastric foveolar metaplasia and gastric heterotopia. (**A**) Representative *GNAS* and *KRAS* mutations identified in gastric foveolar metaplasia, gastric heterotopia, and adenocarcinoma of the duodenum. (**B**) *GNAS* mutations in each epithelial component of gastric heterotopia. An identical missense mutation is present in both the foveolar epithelium and oxyntic glands. Missense mutations are indicated by arrowheads. *GNAS* was sequenced using reverse primers.

Table 3. Combined occurrence of *GNAS* and *KRAS* mutations in each duodenal lesion					
	Total number	*GNAS*(+)/*KRAS*(+)	*GNAS*(+)/*KRAS*(−)	*GNAS*(−)/*KRAS*(+)	*GNAS*(−)/*KRAS*(−)
Gastric foveolar metaplasia	66	8 (12%)	19 (29%)*	9 (14%)	30 (45%)
Gastric heterotopia	81	2 (2%)	21 (26%)	0	58 (72%)
Adenocarcinoma	30	1 (3%)	4 (13%)	10 (33%)	15 (50%)
*One lesion had concurrent *GNAS* and *BRAF* mutations.					

in 17 GFM lesions (26%), 2 GH lesions (2%), and 11 adenocarcinomas (37%). An activating *BRAF* mutation was found only in one GFM lesion (2%). None of the normal duodenal mucosa specimens showed any genetic alterations. Taken together, 36 GFM lesions (55%), 23 GH lesions (28%), and 15 adenocarcinomas (50%) harboured at least one of these genetic alterations (Table 3). Multiple independent lesions of GFM or GH were analysed in 10 patients. Among them, the mutational statuses of the lesions were discordant in six patients, confirming the multifocality of these lesions (Table 4).

We further performed a microdissection-based analysis of the GH lesions to test for the presence of genetic alterations in two epithelial components: the foveolar epithelium and the oxyntic glands. A tissue sample sufficient for the analysis was available for three GH lesions with *GNAS* mutations. In all three lesions that were examined, identical *GNAS* mutations were detected in both the foveolar epithelium and the oxyntic glands (one lesion with c.601C > T and two lesions with c.602G > A; Figure 2B).

An examination of the correlations between the clinicopathological features and the mutational statuses showed that in the case of GFM lesions, both *GNAS* and *KRAS* mutations were significantly more common in lesions showing foveolar hyperplasia (Table 5). In the GH lesions as well, the presence of *GNAS* mutations was significantly associated with foveolar hyperplasia. Conversely, an inverse association was observed between the presence of *GNAS* mutations and the presence of active inflammation in the GFM lesions.

The adenocarcinomas were immunohistochemically examined for gastric and intestinal epithelial markers and the results were further analysed for correlations with the *GNAS* and *KRAS* mutation statuses (Table 6, Supplementary Figure 1 and 2, Supplementary Table 1). These results showed that the presence of *GNAS* mutations was significantly associated with the expression of MUC5AC (gastric foveolar mucin) and inversely correlated with the expression of CDX2 (intestinal transcription factor). No significant correlation with the expression of MUC6 (pyloric and Brunner's gland mucin) or MUC2 (major intestinal goblet cell mucin) was observed. *KRAS* mutations were not associated with the expression of any of the markers.

DISCUSSION

Gastric foveolar metaplasia in the duodenum is generally regarded as a reactive process caused by inflammatory conditions (Shousha *et al*, 1983; Wyatt *et al*, 1990; Hanby *et al*, 1993; Khulusi *et al*, 1996; Kushima *et al*, 1999a). However, we identified recurrent *GNAS* and/or *KRAS* mutations in a significant proportion of GFM lesions, implying a potential role of these genetic alterations in the development of these lesions. All the mutations, including a rare *BRAF* K601E mutation, are known to be activating mutations and have been previously reported in various types of tumours (Chan *et al*, 2003; Ikenoue *et al*, 2003; Furukawa *et al*, 2011; Wu *et al*, 2011; Yamada *et al*, 2012; Matsubara *et al*, 2013;

Nishikawa *et al*, 2013). Furthermore, both *GNAS* and *KRAS* mutations were more prevalent among GFM lesions associated with foveolar hyperplasia, suggesting that these genetic alterations induce the proliferation of metaplastic epithelium. Conversely, genetic alterations were rare among GFM lesions histologically associated with active inflammation. This observation indicates that these mutations do not have a major role in the development of inflammation-related GFM and is supportive of a reactive nature of these lesions. Overall, we interpreted these findings to suggest that GFM consists of a heterogeneous group of lesion that are related to at least two different conditions: genetic alterations and inflammation.

Gastric heterotopia is generally thought to be congenital in nature (Lessells and Martin, 1982; Shousha *et al*, 1983; Wyatt *et al*, 1990). However, unexpectedly, the present study identified *GNAS* and/or *KRAS* mutations in 28% of the GH lesions. Nevertheless, it seems unlikely that these genetic alterations initiate the transdifferentiation of intestinal epithelium into well-organised oxyntic glands. Of note, these mutations were more frequently found in GH with foveolar hyperplasia. Therefore, these mutations might have occurred in the preexisting GH and led to foveolar hyperplasia. Thus, we think that the identification of *GNAS* and *KRAS* mutations does not necessarily exclude a congenital origin of GH. On the other hand, a microdissection-based analysis identified common *GNAS* mutations in both foveolar epithelium and oxyntic glands in three GH lesions. This suggests that *GNAS* mutations occurred in stem cells that can differentiate into both of the two epithelial components, but do not cause detectable morphological changes in oxyntic glands.

It should be noted that the prevalence of genetic alterations, particularly those in GFM, can differ considerably depending on the patient background. Considering the inverse association between the presence of genetic alterations and active inflammation in GFM, *GNAS* and *KRAS* mutations are expected to be less common among patients with peptic disorders. Also, our study analysed relatively large GFM and GH lesions to facilitate reproducible genetic analyses. It is conceivable that minute GFM lesions, which are more commonly encountered in daily diagnostic situations, might have a different mutational prevalence.

GNAS and *KRAS* mutations were identified in 17 and 37% of the duodenal adenocarcinomas. Consistent with our results, a previous study reported the occurrence of *KRAS* mutations in 32% of duodenal adenocarcinomas (Fu *et al*, 2012). To our knowledge, there have been no previous studies of *GNAS* mutations in duodenal adenocarcinoma. Interestingly, all the *GNAS*-mutated adenocarcinomas diffusely expressed MUC5AC, a gastric foveolar mucin, and showed focal or no expression of CDX2, an intestinal transcription factor. On the other hand, no association was found between the expression of any of these markers and *KRAS* mutations. These findings indicate that *GNAS* mutations are more common in duodenal adenocarcinomas with a gastric epithelial phenotype, whereas *KRAS* mutation is not specifically related to either gastric or intestinal epithelial differentiation. Remarkably, previous reports have described the occurrence of GFM and GH in association with duodenal adenocarcinoma and have suggested that adenocarcinomas with a gastric epithelial phenotype might arise from GFM and GH (Kushima *et al*, 2002; Ushiku *et al*, 2014). Ushiku *et al* (2014) further reported that GFM and GH are often

Table 4. *GNAS* and *KRAS* mutation statuses in multifocal lesions

			Mutation	
Patients	Lesion	Histology	*GNAS*	*KRAS*
11	(1)	Gastric foveolar metaplasia	—	—
	(2)	Gastric heterotopia	—	—
20	(1)	Gastric foveolar metaplasia	c.601C>T	—
	(2)	Gastric foveolar metaplasia	c.602G>A	—
	(3)	Gastric foveolar metaplasia	c.601C>T	—
30	(1)	Gastric foveolar metaplasia	—	—
	(2)	Gastric foveolar metaplasia	—	—
	(3)	Gastric foveolar metaplasia	—	—
48	(1)	Gastric foveolar metaplasia	—	c.35G>C
	(2)	Gastric foveolar metaplasia	c.601C>T	c.34G>C
53	(1)	Gastric foveolar metaplasia	—	c.183A>C
	(2)	Gastric foveolar metaplasia	c.602G>A	c.183A>C
74	(1)	Gastric heterotopia	c.601C>T	—
	(2)	Gastric heterotopia	c.602G>A	—
84	(1)	Gastric heterotopia	—	—
	(2)	Gastric heterotopia	—	—
93	(1)	Gastric heterotopia	—	—
	(2)	Gastric heterotopia	—	—
105	(1)	Gastric heterotopia	—	—
	(2)	Gastric heterotopia	c.601C>T	—
115	(1)	Gastric heterotopia	c.601C>T	—
	(2)	Gastric heterotopia	c.602G>A	—

Table 5. Correlations among the presence of *GNAS* and *KRAS* mutations and the clinicopathological features

	Gastric foveolar metaplasia (*N* = 66)					Gastric heterotopia (*N* = 81)				
	Total number	*GNAS* mutation	*P*-value	*KRAS* mutation	*P*-value	Total number	*GNAS* mutation	*P*-value	*KRAS* mutation	*P*-value
Age										
<65	31	10 (32%)	0.22	9 (29%)	0.59	43	10 (23%)	0.33	2 (5%)	NA
⩾65	35	17 (49%)		8 (23%)		38	13 (34%)		0	
Site										
Bulbs	42	14 (33%)	0.12	10 (23%)	0.56	70	17 (24%)	0.067	2 (3%)	NA
Others	24	13 (54%)		7 (30%)		11	6 (55%)		0	
Active inflammation										
Present	14	1 (7%)	0.0047	2 (14%)	0.72	1	1 (100%)	0.28	0	NA
Absent	52	26 (50%)		15 (29%)		80	22 (28%)		2 (3%)	
Foveolar hyperplasia										
Present	21	16 (76%)	1.1×10^{-4}	9 (43%)	0.039	8	7 (88%)	4.6×10^{-4}	2 (25%)	NA
Absent	45	11 (24%)		8 (18%)		73	16 (22%)		0	
P-values were assessed by Fisher's exact test. *N*, number of cases; NA, not assessed.										

Table 6. Expression of gastric and intestinal epithelial markers and genetic alterations in adenocarcinoma

	Gastric epithelial markers						Intestinal epithelial markers					
	MUC5AC			MUC6			MUC2			CDX2		
	2+	1+	0	2+	1+	0	2+	1+	0	2+	1+	0
GNAS												
Mutated	5	0	0	2	2	1	0	1	4	0	2	3
Wild type	8	4	13	2	6	17	2	5	18	14	7	4
P-value	0.009			0.13			1.0			0.045		
KRAS												
Mutated	5	1	5	2	2	7	0	2	9	3	4	4
Wild type	8	3	8	2	6	11	2	4	13	11	5	3
P-value	1.0			0.69			0.52			0.14		

The results of immunohistochemistry were scored as: +2, >50% positive cells; +1, 10%–50% positive cells; 0, <10% positive cells. *P*-values were assessed by Fisher's exact test (2+ vs 1+ or 0).

associated with adenocarcinomas with a gastric epithelial phenotype, but not with those with an intestinal epithelial phenotype.

In addition, several lines of evidence also imply a potential histogenetic link between GFM and GH and a particular subtype of duodenal adenoma. Pyloric gland adenoma, which is characterised by a gastric epithelial phenotype, can also be associated with GH (Kushima *et al*, 1999b). Furthermore, our previous study demonstrated the common presence of *GNAS* mutations in duodenal pyloric gland adenomas (Matsubara *et al*, 2013). On the other hand, *GNAS* mutations were absent in intestinal-type adenoma, which is a more common type of adenoma characterised by an intestinal epithelial phenotype (Matsubara *et al*, 2013). Considering the shared presence of *GNAS* mutations and the common phenotypic features, GFM and GH with genetic alterations might be potential precursors of pyloric gland adenoma and gastric-type adenocarcinoma. However, the rarity of duodenal tumours with a gastric epithelial phenotype, in contrast to the relatively common presence of GFM and GH, suggests that tumorigenesis from GFM and GH is an infrequent event.

The present study demonstrated the presence of recurrent *GNAS* and *KRAS* mutations in GFM and GH lesions in the duodenum. In contrast to the general understanding, a subset of GFM and GH lesions, particularly those unassociated with active inflammation, harbour genetic alterations. Importantly, pyloric gland adenoma and adenocarcinoma of the duodenum frequently have common genetic alterations, suggesting that GFM and GH are potential precursors of these duodenal neoplasms.

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