

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sugimoto S, Yamada H, Takahashi M, Morohoshi Y, Yamaguchi N, Tsunoda Y, Hayashi H, Sugimura H, Komatsu H.	Early-onset diffuse gastric cancer associated with a de novo large genomic deletion of CDH1 gene.	Gastric Cancer			2013
Kahyo T, Tao H, Shinmura K, Kamo T, Igarashi H, Maruyama K, Tajima M, Ogawa H, Tanahashi M, Niwa H, Funai K, Kohno T, Suda T & Sugimura H.	Identification and association study with lung cancer for novel insertion polymorphisms of human endogenous retrovirus.	Carcinogenesis.	34	2531-2538	2013
Matsuura S, Shinmura K, Iwaizumi M, Yamada H, Funai K, Kobayashi J, Tanahashi M, Niwa H, Ogawa H, Takahashi T, Inui N, Suda T, CHida K, Watanabe Y & Sugimura H.	CD74-ROS1 fusion transcripts in resected non-small cell lung carcinoma.	Oncology Reports	30	1675-1680	2013
Matsuura S, Kahyo T, Shinmura K, Iwaizumi M, Yamada H, Funai K, Kobayashi J, Tanahashi M, Niwa H, Ogawa H, Takahashi T, Inui N, Suda T, CHida K, Watanabe Y & Sugimura H.	SGOL1 variant B induces abnormal mitosis and resistance to taxane in non-small cell lung cancers.	Sci Rep.			2013
Shinmura K, Kato H, Matsuura S, Inoue Y, Igarashi H, Nagura K, Nakamura S, Maruyama K, Tajima M, Funai K, Ogawa H, Tanahashi M, Niwa H & Sugimura H.	A novel somatic FGFR3 mutation in primary lung cancer.	Oncol Rep.	31	1219-1224	2014
Natsume H, Shinmura K, Tao H, Igarashi H, Suzuki M, Nagura K, Goto M, Yamada H, Maeda M, Konno H, Nakamura S & Sugimura H.	The CRKL gene encoding an adaptor protein is amplified, overexpressed, and a possible therapeutic target in gastric cancer.	J Transl Med.	10		2012
Sugimura H.	How can research fields be integrated with PET imaging?	Gastric Cancer			2012
Suzuki S, Toyoshima M, Nihashi F, Tsukui H, Baba S, Sugimura H & Suda T.	An autopsy case of malignant pleural mesothelioma associated with nephrotic syndrome.	Intern Med	53	243-246	2014

Suzuki S, Tanioka F, Minato H, Ayhan A, Kasami M & Sugimura H.	Breakages at YWHAЕ, FAM22A, and FAM22B loci in uterine angiosarcoma: a case report with immunohistochemical and genetic analysis.	Pathol Res Pract.	210	130-134	2014
Suzuki S, Kurabe N, Minato H, Ohkubo A, Ohnishi I, Tanioka F & Sugimura H.	A rare Japanese case with a NUT midline carcinoma in the nasal cavity: A case report with immunohistochemical and genetic analyses.	Pathol Res Pract,	210	383-388	2014
Shinmura K, Goto M, Tao H, Kato H, Suzuki R, Nakamura S, Matsuda T, Yin G, Morita M, Kono S & Sugimura H.	Impaired 8-Hydroxyguanine Repair Activity of MUTYH Variant p.Arg109Trp Found in a Japanese Patient with Early-Onset Colorectal Cancer.	Oxid Med Cell Longev			2014
Harada M, Kotake Y, Ohhata T, Kitagawa K, Niida H, Matsuura S, Funai K, Sugimura H, Suda T & Kitagawa M.	YB-1 promotes transcription of cyclin D1 in human non-small-cell lung cancers.	Genes Cells			2014
Takayama T, Takaoka N, Nagata M, Johnin K, Okada Y, Tanaka S, Kawamura M, Inokuchi T, Ohse M, Kuhara T, Tanioka F, Yamada H, Sugimura H & Ozono S.	Ethnic differences in GRHPR mutations in patients with primary hyperoxaluria type 2.	Clin Genet.			2013
Sugimura H & Osawa S.	Internal frontier: the pathophysiology of the small intestine.	World J Gastroenterol,	19	161-164	2013
Sugimura H.	An obsession with subtyping gastric cancer.	Gastric Cancer	16	451-453	2013
Shimizu K, Funai K, Sugimura H, Sekihara K, Kawase A & Shiiya N.	D2-40-positive lymphatic vessel invasion is not a poor prognostic factor in stage I lung adenocarcinoma.	Pathol Int	63	201-205	2013
Kurabe N, Hayasaka T, Ogawa M, Masaki N, Ide Y, Waki M, Nakamura T, Kurachi K, Kahyo T, Shinmura K, Midorikawa Y, Sugiyama Y, Setou M & Sugimura H.	Accumulated phosphatidylcholine (16:0/16:1) in human colorectal cancer; possible involvement of LPCAT4.	Cancer Sci,	104	1295-1302	2013

Kurabe N, Hayasaka T, Igarashi H, Mori H, Sekihara K, Tao H, Yamada H, Kahyo T, Onishi I, Tsukui H, Kawase A, Matsuura S, Inoue Y, Shinmura K, Funai K, Setou M & Sugimura H.	Visualization of phosphatidylcholine (16:0/16:0) in type II alveolar epithelial cells in the human lung using imaging mass spectrometry.	Pathol Int	63	195-200	2013
Kahyo T, Sugimura H.	Establishment and characterization of a mutagenized cell line exhibiting the 'cell-in-cell' phenotype at a high frequency.	Genes Cells	18	1042-1052	2013
Shinmura K, Kiyose S, Nagura K, Igarashi H, Inoue Y, Nakamura S, Maeda M, Baba M, Konno H & Sugimura H.	TNK2 gene amplification is a novel predictor of a poor prognosis in patients with gastric cancer.	J Surg Oncol	109	189-197	2014
Shinmura K, Goto M, Tao H, Matsuura S, Matsuda T & Sugimura H.	Impaired suppressive activities of human MUTYH variant proteins against oxidative mutagenesis.	World J Gastroenterol	18	6935-6942	2012
Makita R, Yamashita M, Fujie M, Yamaoka M, Kiyofuji K, Yamada M, Yamashita J, Tsunekawa K, Asai K, Suyama T, Toda M, Tanaka Y, Sugimura H, Magata Y, Ohnishi K & Nakamura S.	Research on phospho sugar analogues to develop novel multiple type molecular targeted antitumor drugs against various types of tumor cells.	Phosphorus, Sulfur and Silicon	188	213-223	2013
Suzuki T, Shibata T, Takaya K, Shiraishi K, Kohno T, Kunitoh H, Tsuta K, Furuta K, Goto K, Hosoda F, Sakamoto H, Motohashi H, Yamamoto M	Regulatory nexus of synthesis and degradation deciphers cellular Nrf2 expression levels.	Mol Cell Biol.	33(12)	2402-2412	2013
Mizukami T, Shiraishi K, Shimada Y, Ogiwara H, Tsuta K, Ichikawa H, Sakamoto H, Kato M, Shibata T, Nakano T, Kohno T.	Molecular mechanisms underlying oncogenic RET fusion in lung adenocarcinoma.	J Thoracic Oncol.	9(5)	622-630	2014
Saeki N, Sakamoto H, Yoshida T.	Mucin 1 gene (MUC1) and gastric-cancer susceptibility.	Int J Mol Sci	15	7958-7973	2014
Arai E, Sakamoto H, Ichikawa H, Totsuka H, Chiku S, Gotoh M, Mori T, Nakatani T, Ohnami S, Nakagawa T, Fujimoto H, Wang L, Aburatani H, Yoshida T, Kanai Y.	Multilayer-omics analysis of renal cell carcinoma, including the whole exome, methylome and transcriptome.	Int J Cancer		in press	2014
Nakaoku T, Tsuta K, Ichikawa	Druggable oncogene fusions	Clinical Cancer		in press	2014

H, Shiraishi K, Sakamoto H, Enari M, Furuta K, Shimada	in invasive mucinous lung adenocarcinoma.	Res.			
Kohno T et al	RET fusion gene: translation to personalized lung cancer therapy.	Cancer Sci	104	1396-1400	2013
Oike T, Kohno T et al	A synthetic lethality-based strategy to treat cancers harboring a genetic deficiency in the chromatin remodeling factor BRG1.	Cancer Res	73	5508-5518	2013

#### IV. 研究成果の刊行物・別冊

## Early-onset diffuse gastric cancer associated with a de novo large genomic deletion of *CDH1* gene

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**Abstract** A 41-year-old man with no familial history of gastric cancer was diagnosed as with intramucosal early gastric cancer. Two months after the first endoscopic submucosal dissection for signet-ring cell carcinoma (SRCC), the appearance of previously unrecognized multiple erosions of SRCC was noticed. Pathological examination after a total gastrectomy and Roux-en-Y reconstruction with D2 lymph node dissection were performed. Postoperative pathological examination revealed 90 and more lesions, which tempted the attending pathologist to refer to genetic tests for the predisposition though the patient had no familial history of gastric cancer. There were no mutations in all the exons of *CDH1* with conventional DNA sequencing, but multiplex ligation-dependent probe amplification, and reverse transcription-polymerase chain reaction analyses disclosed a large genomic deletion (c.1566-?\_1711+?del), leading to the mRNA with loss of the exon 11. Among family members, his son was found to be a carrier of this change, while his parents were negative

for the familial *CDH1* mutation, implying that this change is a de novo event in the proband. The present report is the first description of a de novo large genomic deletion of *CDH1* gene associated with early-onset diffuse gastric cancer. When the clinician finds a relatively-young patient who has multiple SRCCs, *CDH1* germline mutation should be considered, even for patients with no familial history.

**Keywords** Endoscopic submucosal dissection · Signet-ring cell carcinoma · Stomach neoplasms · *CDH1* · Mutation

### Introduction

Endoscopic submucosal dissection (ESD) is the preferred treatment method for locally dissecting early gastric cancer (EGC) with a negligible risk of lymph node metastasis [1]. Currently nearly 100 % curability has been achieved for EGC with radical surgery, thus ESD is also expected to be performed at a comparable success rate. Metachronous recurrence of EGC after ESD is an important problem, but recurrence can be detected with adequate follow-up endogastroduodenoscopy (EGD), and most patients can receive early endoscopic treatment again [2]. In Japan, the previous consensus has recommended curative ESD that are indicated only for small intramucosal differentiated-type EGC [1]. Recently, the criteria have been expanded to other pathological types such as the undifferentiated-type under regulated conditions [3–5].

In Japan, gastric cancer is a major cause of cancer death, and *Helicobacter pylori* infection is considered to be a major cause of gastric cancer [6]. Although epidemiological studies have shown that there are patients who have a significant familial history of gastric cancer, the

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pathogenesis of familial gastric cancer (FGC) has not been clearly explained. *CDH1* germline mutations are associated with the development of autosomal cancer syndrome, namely hereditary diffuse gastric cancer (HDGC); about 25–30 % of families fulfilling the clinical criteria for HDGC established by the International Gastric Cancer Linkage Consortium (IGCLC) have constitutional alterations of the *CDH1* gene [7]. The *CDH1* gene maps to chromosome 16q22.1 and consists of 16 exons that encode E-cadherin, which is a major component of adherens junctions. Carrying the abnormal *CDH1* gene confers more than an 80 % lifetime risk of developing gastric cancer.

In 2012, the first conclusive case of a de novo *CDH1* germline mutation (c.1792 C>T (R598X)) in a woman whose daughter was diagnosed with early-onset diffuse gastric cancer was reported [8]. On the other hand, *CDH1* germline mutations can also be identified in sporadic early-onset gastric cancer in less than 4 % of patients who are 35 years of age at the time of diagnosis, presenting as de novo mutations [9]. Although the incidence of gastric cancer is relatively high in Japan, the detection rate of *CDH1* germline mutations in Japanese patients with FGC is low compared to that in European patients [10].

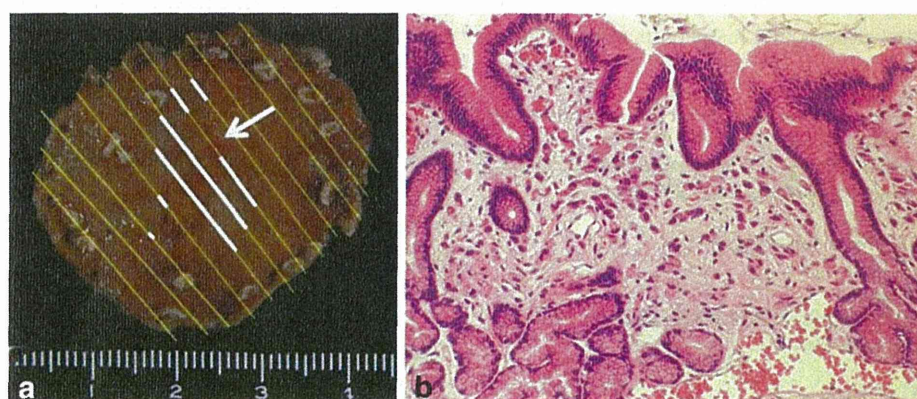
We report the first case of early-onset diffuse gastric cancer associated with a de novo large genomic deletion of *CDH1* gene, and the pathological feature including gross appearance of the surgical specimen of the stomach was pathognomonic.

### Case report

An asymptomatic 41-year-old man was admitted to our hospital with EGC revealed by cancer screening EGD.

There were no abnormalities in the physical examination or laboratory data, and no medical history of malignant tumors. He smoked 20–60 cigarettes a day for 22 years. An enzyme immunoassay to qualitatively detect serum IgG antibodies to *Helicobacter pylori* was negative. A protruding lesion, 5-mm in size, with erosion was observed on the greater curvature of the antrum and no other lesions were observed endoscopically. Biopsy from the erosion indicated signet-ring cell carcinoma (SRCC). ESD was performed on the lesion in accordance with clinical trial (JCOG1009/1010) [5], resulting in en bloc resection. Precise pathological examination of 3- to 4-mm slices from the entire specimen revealed a lesion, 13 × 13 mm in size, which was a SRCC limited in the mucosal layer (Fig. 1a, b). Lymphovascular involvement was not observed and horizontal/vertical margins were negative. According to the above-mentioned pathological analysis, the definitive diagnosis was f Stage IA SRCC (L, Gre, 0-IIb, pT1a, cN0, cH0, cP0, cM0) and resection was thought to be curative [1].

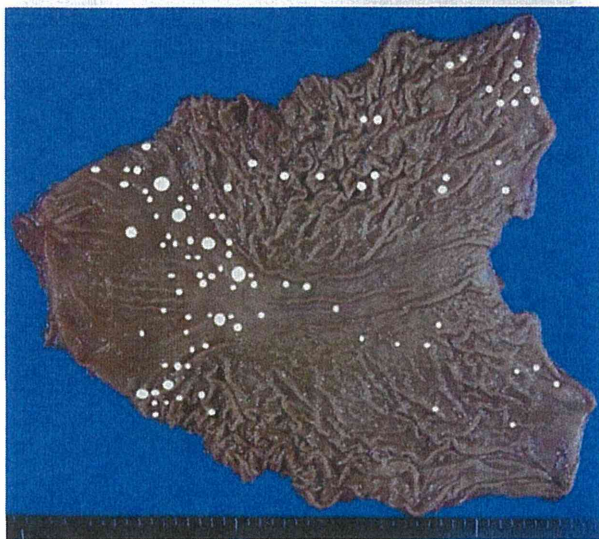
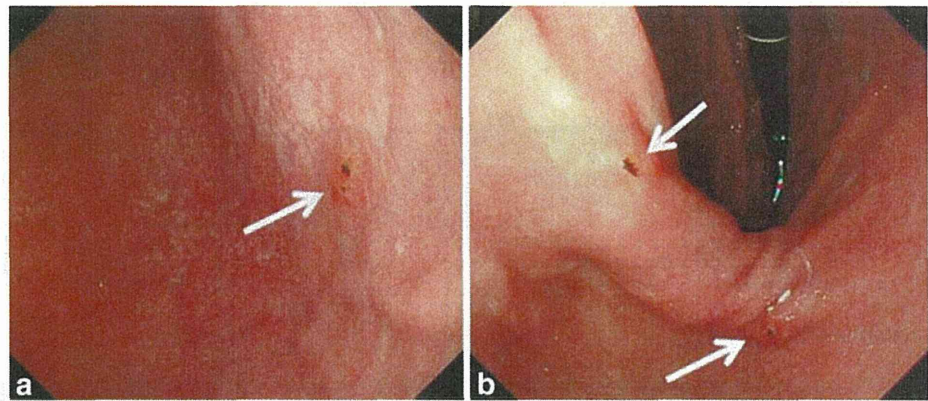
Follow-up EGD performed 2 months later revealed no local recurrences at the ESD site, but three new erosions appeared on the gastric angle and antrum (Fig. 2a, b). Biopsies from these erosions again indicated multiple lesions of SRCC. Apparently they were likely to be intramucosal, but there was a high incidence of metachronous multiple lesions. We considered the possibility of HDGC that we could not control multiple SRCCs by repeated ESD or distal gastrectomy similar to a previous report [11]. After the explanation about the risk for recurrence or metachronous lesions in any part of the stomach, next month, a total gastrectomy and Roux-en-Y reconstruction with D2 lymph node dissection were carried out as the patient wished. Postoperative pathological examination revealed that 90 and more lesions, each less than 5-mm in



**Fig. 1** **a** Lesion resected with ESD. Resected specimen was 40 × 38 mm. The lesion was step-sectioned at 3- to 4-mm intervals, and then examined pathologically. Although SRCCs at the biopsy site disappeared (as an arrow indicates), the entire specimen revealed a lesion 13 × 13 mm in size (as white lines indicate). The resection

was curative and the horizontal margin was 6.5 mm. **b** The specimen showed localized neoplastic cells with signet-ring features limited to the mucosal layer. Signet-ring cells are easily detected on Haematoxylin and eosin (H&E) sections

**Fig. 2** EGD view 2 months after ESD. EGC is visible as the arrows indicate. **a** The posterior wall of the lower gastric body, near the gastric angle. **b** The lesser curvature of the gastric angle and the distal antrum



**Fig. 3** Surgical specimen. Postoperative pathological examination revealed 90 and more lesions. White circles indicate infiltrating SRCCs

size, showing type 0-IIb SRCCs in the mucosal layer, and they were distributed in the whole stomach (Fig. 3). The lesions may be missed by a cursory look. The reason for the discrepancy between preoperative endoscopic findings and final pathological diagnosis would be the difficulty in locating endoscopically SRCC foci in the superficial lamina propria, just beneath normal-looking surface epithelium or gastric pits. The tumor cells had a low proliferative index and reduced expression of E-cadherin with immunohistochemistry (Fig. 4c). We suspected the involvement of a genetic abnormality of *CDH1*, although he had no familial history of gastric cancer and did not meet clinical criteria for HDGC defined by the IGCLC [7].

After informed consent was obtained, DNA was extracted from the peripheral blood of the patient. First, a polymerase chain reaction (PCR)-direct sequencing analysis was performed for all the exons of *CDH1*, but no

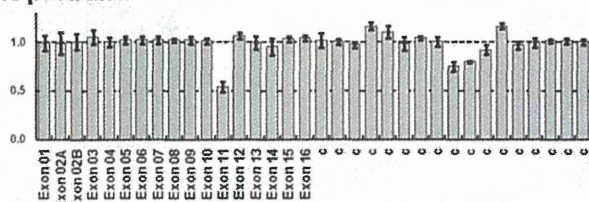
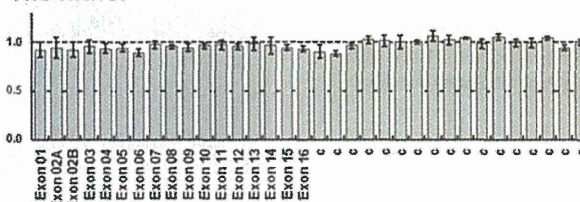
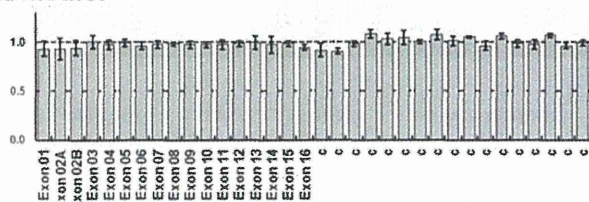
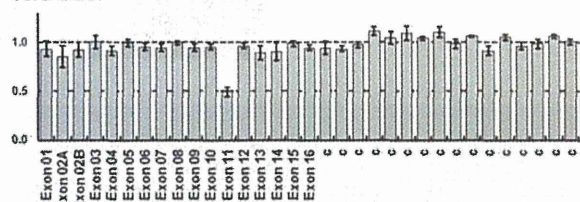
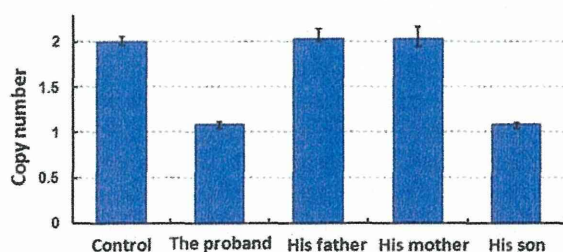
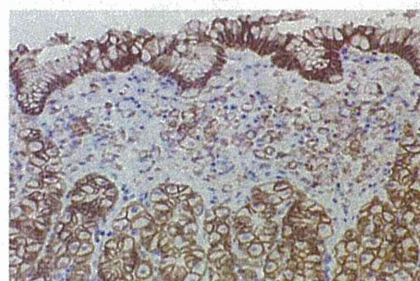
mutations were identified. Next, a multiplex ligation dependent probe amplification (MLPA) analysis was performed as previously described [12] (Fig. 4a). This revealed that the exon 11 of the *CDH1* transcript was heterozygously deleted in this case; thus, a heterozygous c.1566-?\_1711+?del germline mutation existed in the proband. For validation, *CDH1* copy numbers in exons 11 were measured using TaqMan copy number assays according to the manufacturer's instructions, and the copy number was 1 (the normal copy number is 2) (Fig. 4b).

A program of genetic counseling and DNA testing was provided to other members of his family (Fig. 5). We could not contact his brother. Predictive genetics testing was performed on his parents and his son. Among family members, his 15-year-old son was a carrier of the mutation, and his 71-year-old father and 65-year-old mother were negative for the familial *CDH1* mutation. These results lead to the conclusion that a large genomic deletion of *CDH1* gene identified in this proband and in his son probably occurred de novo in the proband. The proband's 13-year-old daughter has not yet been tested.

## Discussion

E-cadherin is a calcium-dependent cell membrane protein involved in cell-cell adhesion and confers cell polarity [13]. *CDH1* mutations are associated with a risk of early-onset diffuse gastric cancer, in addition to increased risk of lobular breast cancer and signet-ring colon cancer [7]. There was a report of six patients from one large kindred who underwent total gastrectomy for *CDH1* mutation without any evidence of gastric cancer from detailed preoperative imaging studies, including high magnification endoscopy with methylene blue chromoendoscopy and multiple random biopsies. Each patient was found to have multiple sites of invasive diffuse SRCC without lymph node metastases [14]. The guideline recommends advising *CDH1* mutation positive patients with normal gastric



**a MLPA****The proband****His father****His mother****His son****b TaqMan Copy Number Assay****c E-cadherin with immunohistochemistry**

**Fig. 4** **a, b** Germline copy number change in the *CDH1* gene of a patient. Since there were no point mutation of *CDH1*, the DNAs were tested for large genomic deletions in the *CDH1* gene using the SALSA P083-B1 *CDH1* multiplex ligation-dependent probe amplification (MLPA) kit (MRC-Holland, Amsterdam, The Netherlands). The reactions were performed according to the manufacturer's instruction. The results are presented as the ratios to the normal copy numbers (two in this case). Seventeen columns in the *right side* of the

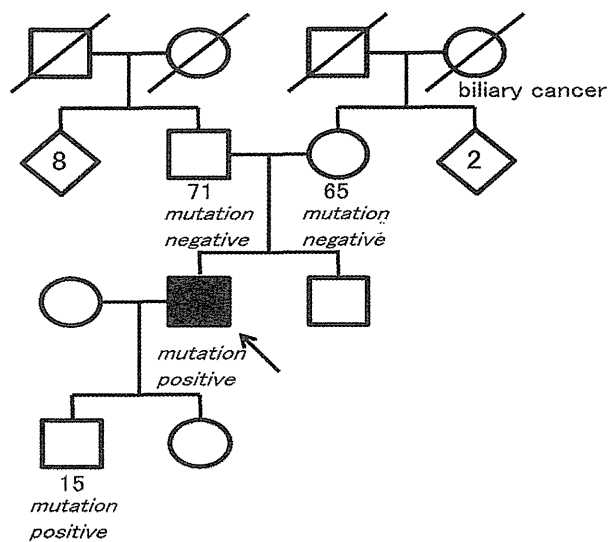
graph are control DNAs. Probe ratios below 0.7 and above 1.3 were regarded as indicative of a decrease and increase, respectively, in the gene dosage. As shown in the figure, unambiguous decreases in exon 11 were noticed in the proband and his son. **c** E-cadherin with immunohistochemistry. E-cadherin expression was suppressed in signet-ring cells, while normal glands were uniformly and intensely positive

biopsies to undergo prophylactic gastrectomy once the genetic testing results are known and once individuals are older than 20 years. Rare cases of clinically significant diffuse gastric cancer have been reported in affected families before the age of 18, but the overall risk of diffuse gastric cancer before the age of 20 is low [15]. In the present case, the proband's children should receive surveillance EGD in the future.

To date, over 100 kindreds with *CDH1* germline mutations have been identified, and few cases of a concluded de novo *CDH1* germline mutation have been reported [8]. However, we think there are many unidentified patients who were not tested or in whom mutations could not be identified with conventional DNA sequencing. Importantly, 4% of these mutation positive families exhibited large germline deletions of *CDH1* that were not

detectable with conventional DNA sequencing [16]. Analyses of large genomic deletions with MLPA are recommended in cases where simple DNA sequencing is unrevealing [16, 17]. We propose that screening for germline large rearrangements of *CDH1* should be included in *CDH1* genetic testing for FGC in young patients with diffuse gastric cancer [12].

The present report is the first description of a de novo large genomic deletion of the *CDH1* gene associated with the production of a truncated CDH1 protein. The c.1566-?\_1711+?del germline mutation observed in this case has not been reported previously either as a somatic or a germline mutation, so we think this is novel and further characterization of its RNA would be interesting. Importantly, it was verified that this mutation passes the gene on to the proband's offspring without change.



**Fig. 5** Pedigree of family with germline *CDH1* alteration. Squares indicate males; circles indicate females. Solid symbols indicate the gastric cancer patient. Symbols with a slash indicate deceased individuals. An arrow points to the proband. The numbers below the symbols indicate age at the time family members were analyzed

The ESD technique has rapidly permeated worldwide for treating EGC, but obviously it is not suitable for multiple occurrences such as in *CDH1* mutation positive patients. As this instructive case shows, unusual morphologic feature may suggest prepared endoscopists should suspect genetic predisposition. In such a case, genetic counseling should also be provided. A prudent follow-up is necessary not only for the proband but also for the proband's family. When a clinician finds the relatively-young patient who has multiple SRCCs, unusual conditions such as *CDH1* germline mutation should be considered, even if patients have no familial histories of gastric cancer.

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**Conflict of interest** None.

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## References

1. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer*. 2011;14:113–23.

2. Nakajima T, Oda I, Gotoda T, Hamanaka H, Eguchi T, Yokoi C, et al. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? *Gastric Cancer*. 2006;9:93–8.
3. Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer*. 2009;12:148–52.
4. Okada K, Fujisaki J, Yoshida T, Ishikawa H, Suganuma T, Kasuga A, et al. Long-term outcomes of endoscopic submucosal dissection for undifferentiated-type early gastric cancer. *Endoscopy*. 2012;44:122–7.
5. Takizawa K, Takashima A, Kimura A, Mizusawa J, Hasuike N, Ono H, et al. A Phase II clinical trial of endoscopic submucosal dissection for early gastric cancer of undifferentiated type: Japan clinical oncology group study JCOG1009/1010. *Jpn J Clin Oncol*. 2013;43:87–91.
6. Suzuki H, Iwasaki E, Hibi T. Helicobacter pylori and gastric cancer. *Gastric Cancer*. 2009;12:79–87.
7. Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, et al. International gastric cancer linkage consortium. *J Med Genet*. 2010;47:436–44.
8. Shah MA, Salo-Mullen E, Stadler Z, Ruggeri JM, Mirander M, Pristiyazhnyuk Y, et al. De novo *CDH1* mutation in a family presenting with early-onset diffuse gastric cancer. *Clin Genet*. 2012;82:283–7.
9. Corso G, Pedrazzani C, Pinheiro H, Fernandes E, Marrelli D, Rinnovati A, et al. E-cadherin genetic screening and clinicopathologic characteristics of early onset gastric cancer. *Eur J Cancer*. 2011;47:631–9.
10. Shinmura K, Kohno T, Takahashi M, Sasaki A, Ochiai A, Guilford P, et al. Familial gastric cancer: clinicopathological characteristics, RER phenotype and germline p53 and E-cadherin mutations. *Carcinogenesis*. 1999;20:1127–31.
11. Tokunaga M, Ohyama S, Kuraoka K, Hiki N, Fukunaga T, Tsuchida T, et al. Twenty-two metachronous multiple signet-ring cell carcinomas treated with repeated gastrectomies and repeated endoscopic mucosal resections: report of a case. *Surg Today*. 2009;39:430–3.
12. Yamada H, Shinmura K, Ito H, Kasami M, Sasaki N, Shima H, et al. Germline alterations in the *CDH1* gene in familial gastric cancer in the Japanese population. *Cancer Sci*. 2011;102:1782–8.
13. Humar B, Guilford P. Hereditary diffuse gastric cancer: a manifestation of lost cell polarity. *Cancer Sci*. 2009;100:1151–7.
14. Norton JA, Ham CM, Van Dam J, Jeffrey RB, Longacre TA, Huntsman DG, et al. *CDH1* truncating mutations in the E-cadherin gene: an indication for total gastrectomy to treat hereditary diffuse gastric cancer. *Ann Surg*. 2007;245:873–9.
15. Blair V, Martin I, Shaw D, Winship I, Kerr D, Arnold J, et al. Hereditary diffuse gastric cancer: diagnosis and management. *Clin Gastroenterol Hepatol*. 2006;4:262–75.
16. Oliveira C, Senz J, Kaurah P, Pinheiro H, Sanges R, Haegert A, et al. Germline *CDH1* deletions in hereditary diffuse gastric cancer families. *Hum Mol Genet*. 2009;18:1545–55.
17. Kim S, Chung JW, Jeong TD, Park YS, Lee JH, Ahn JY, et al. Searching for E-cadherin gene mutations in early onset diffuse gastric cancer and hereditary diffuse gastric cancer in Korean patients. *Fam Cancer* 2012 (Epub ahead of print).