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Commentary Open Access

Sexy Small Copy Numbers in Hereditary Gastric Carcinogenesis

Hidetaka Yamada[1], **Hiromi Sakamoto**[2] **and Haruhiko Sugimura**[1*]

[1]*Hamamatsu University School of Medicine, Shizuoka, Japan*

[2]*National Cancer Center Research Institutes, Tokyo, Japan*

[*]**Corresponding author:** Haruhiko Sugimura, Hamamatsu University School of Medicine, Shizuoka, Japan, Tel: +81-53-435-2220; Fax: +81-53-435-2225; E-mail: hsugimur@hama-med.ac.jp

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Commentary

Occurrence of gastric cancer in a family has been known for many years, and since the discovery of germline mutations of CDH1 in Maori families [1], the entity of hereditary diffuse gastric cancer (HDGC) (OMIM #137215) has been almost established. The guidelines of diagnosis and management have been regularly updated [2-5]. In many countries including Japan, where gastric cancer is endemic, the search and surveillance of the family has been continued. Reviewing the publications for the past two decades, the progress is not rapid, but considerably steady. New mutations are coming out from many countries every few months. The cases do not always fulfill the criteria of age and family histories; some occurred in the older patients [6], and the others occur in the patients without any family history [7-9]. The reports on the related diseases, lobular carcinoma of the breast [10], prostate cancer [11], colorectal cancer [12], and cleft lips [13,14] are also among the literatures.

I would like to draw the readers' attention to four reports recently published in the journals related to gastroenterology. They are on the germline alterations of CDH1 copy numbers in diffuse hereditary gastric cancer. With an introduction of Multiplex ligation-dependent probe amplification (MLPA) [15] method to CDH1 germline test, Oliveira et al. [16] identified exon-size CDH1 deletions in 6 probands. The sizes of the deletions encompassed 5'UTR-exon1 (1 family), exon1 to exon2 (3 families), exon14 to exon16 (1 family), and exon16 (1 family) of the CDH1. Next, we reported a case of exon3 deletion in Japanese family [17]. Japan has been notorious for being endemic with gastric cancer and a pursuit for HDGC was difficult because the application of the consensus guidelines to recommend genetic test pick up too many cases. The pessimism has been rampant on the prevalence of CDH1 germline changes in Japanese familial gastric cancer for the last 15 years especially in the community of clinicians [18]. The improved detection methods, easier sequencing (no more single-strand conformation polymorphism) covering whole exons and MLPA, re-motivated the attending clinicians such as endocsopists, surgeons, and attending pathologists to refer to genetic test labs when they fell any peculiarities in cases. The case referred to us 2 years after the first publication of a Japanese copy number deletion case was prominent. The multiple signet ring cell carcinoma occurred in a 30's without any family history of gastric cancer. Since the attending pathologists noticed that the features of the case resembled to the ones of HDGC [19], they asked us on testing for them. The sequencing of the whole exons of CDH1 and MLPA analysis was performed. The exon 11 of CDH1 was deleted in the germline of this proband and in his son. De novo occurrence of this deletion was confirmed by showing absence of it in his parents. Importantly his son succeeded it from his father [20] and surveillance program was considered. Just after this report, another very impressive case was reported from National Cancer Center Hospital, Tokyo appeared [21]. They applied array-comparable genomic hybridization (CGH) technology (Agilent Technologies, Santa Clara, CA) to the cases (the proband and his mother, a 56 years old post operative recurrence case) and discovered 275 kb deletion encompassing exon 7 to 16 of CDH1, a largest deletion in HDGC so far demonstrated (Table 1).

Authors	Ethnic origin	Cancer type	Copy number changes Ordered by the exons of CDH1
Oliveria et al. (16)	Southern European	HDGC	Deletion of 5'-UTR-exon 1
Oliveria et al. (16)	Northern European	HDGC	Deletion of exon 1-2
Oliveria et al. (16)	Canadian	HDGC	Deletion of exon 1-2
Oliveria et al. (16)	Eastern European	HDGC	Deletion of exon 1-2
Yamada H et al. (17)	Japanese	HDGC	Deletion exon 3
Benusiglio et al. (10)	French	LBC	Deletion exon 3
Yamada M et al. (21)	Japanese	HDGC	Deletion of exon 7-16
Sugimoto et al. (20)	Japanese	Early-onset DGC	Deletion of exon 11
Benusiglio et al. (10)	French	HDGC	Deletion of exon 11
Oliveria et al. (16)	Central European	HDGC	Deletion of exon 14-16
Oliveria et al. (16)	Central European	HDGC	Deletion of exon 16

Table 1: Summary of the cases with germline copy number change in CDH1 gene; HDGC: hereditary diffuse gastric cancer; DGC: diffuse gastric cancer; LBC: lobular breast carcinoma

The lesson we experienced is obvious. Our methods are still insufficient to recover all the deleterious genetic alterations from the subjects who daily visit the clinic; limitation of the access, lack of sharing the knowledge, and insufficient resource in genetics including history takers and counselors are hurdles in practical settings, even in Japan, where complete national health insurance coverage is famous. Insufficiency in our methods will be continued in front of us as to

identification of the genes besides CDH1, which are responsible for familial gastric cancer, more than 50% of them.

Usages of next generation sequencing (NGS) would be an obvious option for the institutes where the instruments and fund are available. In the recent American Association Cancer Research Annual Meeting in San Diego, two posters presented the first results of exome analyses. Identification of novel susceptibility genes in familial gastric cancer using next generation sequencing and identity-by-descent mapping; Genetic basis of hereditary gastric cancer: Beyond the CDH1 locus). Both and another Japanese group adopted whole exome analysis approaches, and we are now watching their validation and replication processes. Whole exome sequence (WES) will provide other gene mutations. Actually CTNNA1 mutation was identified using exome analysis [22] in a hereditary gastric cancer family. CTNNA1, a candidate gene associated with CDH1 in signal transduction, was not changed in another cohort of hereditary gastric cancer family [23]. This may cool-down our hyper-expectation on NGS (exactly WES) to identify new responsible genes. The genes found by WES may be sporadic or anecdotal ones.

Like the history of searches for CDH1 changes in Japan, the copy number changes in other gene loci would be possible culprit for familial occurrence of gastric cancer. Understanding the human genome variations [24] showed us there are numerous copy number variations in human genome. The copy numbers variations, from amylases to glutathione-S-transferases, are related to from our evolutionally fixed eating styles to inter-individual differences in xenobiotics adaptations, but the true significance of the most of them awaits further investigation. Inferring these genetic changes to the association of any disease require robust replication and control study. Actually some of the single nucleotide variations are found in our "control" DNAs (Table 2), thus the analyses of the "robust" controls are necessary. On the other hand some deletions (1-30 kb, small exonic CNVs) have been revealed to be responsible autism disorder [25]. Gastric cancer like autism spectrum disorders is relatively common, and occurs in modestly earlier stage of human life. It is obviously a very environmental disease according to the immigrant studies and the trends of the incidence observed in the past decades. Several platforms to survey the genome-wide alterations of copy numbers including NGS became available in genetic test labs for clinical use to detect large, moderately large, and exonic size deletions in the genome. When these platforms become more popular and economically feasible, the more numbers of endoscopists in practice are encouraged to refer any strange cases, such as early-onset, multiplicity, signet ring cell type, and of course, familial aggregation.

Nucleotide change	Amino acid change	Minor Allele Count	MAF	dbSNP ID	1000 Genomes*	
					Minor Allele Count	MAF
c.546A>C	p.Lys182Asn	1	0.003	rs201141645	1	0
c.2494G>A	p.Val832Met	2	0.005	rs35572355 ("pathogenic allele")	2	0.001
Duplication of exon 11	unknown	2	0.005	NA	NA	NA

Table 2: Single nucleotide variations of CDH1 gene found in 189 healthy aged Japanese controls (Yamada H et al. unpublished results) MAF: Minor allele frequency; NA: not available *http://www.1000genomes.org/announcements/may-2011-data-release-2011-05-12

At this moment, a greater question how this initiating genetic change brings about a full-blown gastric cancer remains to be investigated. Genetic and epigenetic changes at CDH1 locus are known, but the precise profile of the consequence in this particular disease, not like in common gastric cancer [26], awaits further investigation. The mouse model [27] and omics analysis including tumor microenvironment [28] may provide the clue.

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