Synergistic triad epistasis of epigenetic H3K27me modifier genes, *EZH2*, *KDM6A*, and *KDM6B*, in gastric cancer susceptibility

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Received: 23 July 2018 / Accepted: 20 October 2018 / Published online: 29 October 2018
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Abstract

Background For an epigenetic regulation of human genome, three enzymes write or erase methylation of lysine-27 residue on histone H3 (H3K27me). This methylation is catalyzed by *EZH2* (KMT6A) methyltransferase and reversed by *KDM6A* (UTX) or *KDM6B* (JMJD3) demethylase. Genetic cancer risk association has been reported on *EZH2*, but not on *KDM6A* or *KDM6B* yet.

Methods A total of 23 tag single-nucleotide polymorphisms (SNPs) of the three genes were genotyped in 2349 Korean participants, and their gastric cancer risk associations and epistases were statistically examined by comparing the SNP genotypes of 1100 gastric cancer patients and 1249 healthy controls.

Results All three genes are individually associated with gastric cancer susceptibility, as evident with the genotypes of *KDM6A* SNP rs5952279 ($P=0.00010$) and rs144974719 ($P=0.00024$), *KDM6B* rs78633955 ($P=0.0019$) and rs11657063 ($P=0.0036$), and *EZH2* rs67648693 ($P=0.0028$) and rs1061037 ($P=0.023$). Furthermore, when odds ratio of interaction (OR_{int}) is calculated for all intergenic SNP pairs, synergistic epistasis is evident among the three genes. Specifically, the interaction is synergistic between *EZH2* rs58579167 and *KDM6A* rs5952279 ($OR_{int}=3.2$, $P=0.00066$), between *KDM6A* rs2230018 and *KDM6B* rs78633955 ($OR_{int}=1.9$, $P=0.044$), and between *KDM6B* rs78633955 and *EZH2* rs73158295 ($OR_{int}=1.7$, $P=0.00030$). These inter-SNP interactions together constitute a synergistic triad epistasis of ring-type topology.

Conclusions All three H3K27me modifier genes are individually associated with gastric cancer susceptibility with synergistic triad interaction. Not only two enzymes with the same function (*KDM6A* and *KDM6B*), but also those with opposite functions (*EZH2* versus *KDM6A* or *KDM6B*) synergistically affect H3K27me consequences such as gastric cancer susceptibility.

Keywords Cancer susceptibility association · Epigenetic code · Gene–gene interaction · Histone methylation · Single-nucleotide polymorphism

Introduction

Epigenetic regulations play critical roles in diverse functions of genome including those related with cancer. Among human epigenetic codes, histone methylation regulates specific gene expression patterns and is manifested by interplay between methyltransferases and demethylases acting on the same histone residue. For example, trimethylation

of lysine-27 residue on histone H3 (H3K27me₃) is strongly associated with gene silencing and tightly regulated by three enzymes, *EZH2*, *KDM6A* and *KDM6B* [1].

EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit), a.k.a. KMT6A (lysine methyltransferase 6A), is a methyltransferase subunit of polycomb repressor complex 2 (PRC2). *KDM6A* (lysine demethylase 6A), a.k.a. UTX (ubiquitously transcribed X-chromosome tetratricopeptide repeat protein), and *KDM6B* (lysine demethylase 6B), a.k.a. JMJD3 (Jumonji domain containing protein 3), are demethylases.

All three enzymes have both tumor-promoting and -suppressing functions depending on cancer types [2–7], but genetic association of cancer risk has been reported only on *EZH2*, not *KDM6A* or *KDM6B* yet. A recent article surveyed 12 case–control studies where *EZH2* single-nucleotide

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polymorphisms (SNPs) have been associated with susceptibilities to diverse cancer types including lung and breast cancers, digestive system cancers (gastric, liver, colorectal, esophageal, and oral cancers), and urogenital system cancers (prostate, urothelial, and bladder cancers) [8].

Gastric cancer, a.k.a. stomach cancer, is the fourth most common cause of cancer-related death in the world, and recently the most commonly diagnosed cancer in Korea [9]. *EZH2* SNPs have been associated with susceptibility to gastric cancer [10] and primary tumor invasion depth and lymph node metastasis in gastric cancer [11]. In this study, not only is *EZH2* reexamined, but also *KDM6A* and *KDM6B* are examined for gastric cancer risk association of their SNPs to investigate gene–gene interaction, a.k.a. epistasis, among the three functionally related genes.

Materials and methods

Subject genotyping

Gastric cancer patients and healthy controls were recruited at Hanyang University Guri Hospital, Chungnam National University Hospital, and Pusan National University Hospital, which participate in the National Biobank of Korea. Tag SNPs were selected for genotyping using Haploview 4.2 [12], based on their statistical power estimated using the PS Power and Sample Size Calculations [13]. Genomic DNA extracted from peripheral blood samples were genotyped using the Sequenom's MassARRAY platform.

Statistical analyses

Control sample genotypes were analyzed for Hardy–Weinberg equilibria. Odds ratio (OR), 95% confidence interval (CI) and *P* value were calculated for each SNP association, and OR of interaction (OR_{int}) was calculated for each intergenic SNP pair, using PLINK software [14]. The interaction is regarded synergistic if OR_{int} > 1, and antagonistic if OR_{int} < 1 [15].

Results

Cancer susceptibility association tests

A total of 23 tag SNPs were genotyped in 2349 Korean participants including 1100 gastric cancer patients and 1249 healthy controls, whose demographic characteristics are summarized in Table 1. Excluding four SNPs with control sample genotypes out of Hardy–Weinberg equilibria ($P < 0.05/23 = 0.0022$, a Bonferroni correction threshold for 23-SNP testing), 19 SNPs including four in *KDM6A*, six

Table 1 Characteristics of the study participants

Characteristics	Controls	Gastric cancers	<i>P</i> value
<i>n</i>	1249	1100	
Male	703 (56.3%)	763 (69.4%)	6.6×10^{-11} (χ^2 test)
Female	546 (43.7%)	337 (30.6%)	
Mean age $\pm$ SD, year	54.7 $\pm$ 11.6	60.8 $\pm$ 12.1	1.5×10^{-34} (<i>t</i> test)
Tumor type			
Diffuse type	–	408 (37.1%)	
Intestinal type	–	582 (52.9%)	
Unclassified	–	110 (10.0%)	

SD standard deviation

in *KDM6B*, and nine in *EZH2* were tested for association with gastric cancer susceptibility using multivariate logistic regression with adjustment for age and gender (Table 2) because age distribution and gender ratio were different between the cases and controls (Table 1).

Female and male subjects were analyzed together according to additive genetic models for *EZH2* and *KDM6B* SNPs located on human chromosomes 7 and 17, respectively. However, for SNPs of *KDM6A*, which is located on X chromosome but escapes from female X-inactivation [16], female and male subjects were separately analyzed according to additive and allelic genetic models, respectively.

Among all documented SNPs located in the three gene loci, each spanning from 2 kb upstream of transcription start site to 2 kb downstream of polyadenylation site, only those having a sufficient statistical power (> 0.8) were tagged with $r^2 \geq 0.8$. The power was estimated for expected OR of 1.4 using the Han Chinese and Japanese data of the 1000 Genomes Project. Their minor allele frequencies (MAFs) were ≥ 0.057 for *EZH2* and *KDM6B* SNPs (1100 cases versus 1249 controls), and ≥ 0.18 for *KDM6A* SNPs (337 female cases versus 546 female controls).

SNPs associated with cancer susceptibility

Gastric cancer risk is significantly associated with three SNPs (Table 2). *KDM6A* rs5952279 ($P = 1.0 \times 10^{-4}$), *KDM6A* rs144974719 ($P = 2.4 \times 10^{-4}$), and *KDM6B* rs78633955 ($P = 1.9 \times 10^{-3}$) pass a Bonferroni correction threshold, $\alpha = 0.05/19 = 2.6 \times 10^{-3}$. Three additional SNPs, *EZH2* rs67648693 ($P = 0.0028$), *KDM6B* rs11657063 ($P = 0.0036$), and *EZH2* rs1061037 ($P = 0.023$) show marginal association. Thus, two *KDM6A*, two *KDM6B*, and two *EZH2* SNPs are significantly or marginally associated with gastric cancer susceptibility in additive genetic models, supporting individual associations of the three genes with gastric cancer risk.

Table 2 SNPs tested for association with gastric cancer risk

SNP $M>m^a$	Controls MAF/MM/Mm/mm ^a	Gastric cancers MAF/MM/Mm/mm ^a	Gastric cancer risk		DGC risk P^b	IGC risk P^b
			OR (95% CI) ^b	P^b		
<i>KDM6A (UTX)</i> on Xp11.3 in female subgroups ^c						
rs5952279 $G>A$	0.36/197/227/58	0.26/185/78/40	0.64 (0.52–0.80)	1.0×10^{-4}	2.6×10^{-6}	0.075
rs144974719 $C>A$	0.046/426/43/0	0.096/256/61/0	2.23 (1.45–3.42)	2.4×10^{-4}	1.1×10^{-4}	0.032
rs2230018 $C>A$	0.35/161/205/39	0.38/88/124/29	1.13 (0.88–1.47)	0.34	0.74	0.55
rs147585648 $C>T$	0.051/471/51/1	0.049/278/30/0	1.03 (0.64–1.67)	0.89	0.049	0.083
<i>KDM6B (JMJD3)</i> on 17p13.1 in all samples						
rs78633955 $C>T$	0.12/914/235/21	0.16/689/232/32	1.33 (1.11–1.60)	1.9×10^{-3}	0.75	0.31
rs11657063 $C>T$	0.070/1021/139/12	0.049/981/91/7	0.69 (0.53–0.88)	0.0036	0.019	0.017
rs2270517 $C>T$	0.13/841/256/23	0.12/818/220/18	0.85 (0.71–1.02)	0.082	0.036	0.24
rs3744248 $C>T$	0.37/426/528/149	0.40/404/468/195	1.12 (0.99–1.27)	0.084	0.014	0.52
rs7406493 $C>T$	0.24/690/459/60	0.23/632/381/59	0.94 (0.82–1.09)	0.43	0.066	0.70
rs62059713 $C>T$	0.23/732/418/75	0.23/649/384/56	0.96 (0.84–1.11)	0.61	0.11	0.70
<i>EZH2 (KMT6A)</i> on 7q36.1 in all samples						
rs67648693 $T>C$	0.38/459/512/174	0.32/379/347/86	0.81 (0.70–0.93)	0.0028	0.069	2.5×10^{-3}
rs1061037 $T>G$	0.15/833/270/35	0.12/768/213/17	0.81 (0.68–0.97)	0.023	0.0061	0.39
rs77247209 $T>C$	0.093/763/151/10	0.11/818/195/17	1.19 (0.96–1.48)	0.11	0.12	0.060
rs3757441 $T>C$	0.28/549/433/78	0.26/399/277/49	0.90 (0.77–1.06)	0.20	0.26	0.38
rs58579167 $C>T$	0.11/937/224/24	0.11/858/211/14	0.94 (0.78–1.14)	0.54	0.57	0.61
rs73158295 $T>C$	0.14/866/257/29	0.15/717/132/71	1.04 (0.88–1.23)	0.62	1.9×10^{-8}	0.32
rs111851041 $C>A$	0.0073/1231/9/0	0.0065/1069/7/0	0.83 (0.30–2.33)	0.73	1.0	0.95
rs2302427 $C>G$	0.090/917/167/15	0.083/878/151/10	0.98 (0.79–1.22)	0.84	0.95	0.78
rs12670401 $T>C$	0.46/330/630/235	0.47/286/527/220	1.00 (0.88–1.13)	0.95	0.45	0.81
<i>KDM6A (UTX)</i> on Xp11.3 in male subgroups ^c						
rs5952279 $G>A$	0.31/347/156 ^d	0.27/484/177 ^d	0.73 (0.56–0.96)	0.024	2.1×10^{-4}	0.47
rs144974719 $C>A$	0.00/589/0	0.00/569/0	–	–	–	–
rs2230018 $C>A$	0.32/272/127	0.31/296/130	0.82 (0.59–1.13)	0.23	0.13	0.47
rs147585648 $C>T$	0.00/544/0	0.00/651/0	–	–	–	–

SNPs are listed for each gene in ascending order of P values for gastric cancer risk association

CI confidence interval, DGC diffuse-type gastric cancer, IGC intestinal-type gastric cancer, MAF minor allele frequency, OR odds ratio, SNP single-nucleotide polymorphism

^aMajor allele (M)> minor allele (m)

^bAdditive genetic models used in logistic regression analysis with adjustment for age and gender

^cSeparate analysis of female and male subjects

^dMAF/ M/m of male subjects

KDM6A rs5952279 showing the lowest P value in the additive model analyses has minor-allele protective association in a dominant ($P=2.0 \times 10^{-8}$, OR 0.42) rather than recessive ($P=0.72$) genetic model. Two-copy carriage of the risk-associated major allele has 2.9-fold higher risk than one-copy carriage. Additionally, this SNP shows association with diffuse-type ($P=2.6 \times 10^{-6}$, OR 0.47) rather than intestinal-type ($P=0.075$) gastric cancer risk.

The lowest- P *KDM6B* SNP rs78633955 fits to a dominant model ($P=0.0051$, OR 1.35) better than a recessive model ($P=0.032$). This SNP is not associated with diffuse ($P=0.75$) or intestinal ($P=0.31$) type risk. The lowest- P *EZH2* SNP rs67648693 favors a recessive ($P=0.0070$, OR

0.67) over a dominant model ($P=0.021$, OR 0.80). Intestinal-type risk is most significantly associated with this SNP rs67648693 ($P=2.5 \times 10^{-3}$, OR 0.76), while diffuse-type risk is most significantly associated with *EZH2* rs73158295 ($P=1.9 \times 10^{-8}$).

Synergistic triad epistasis

Interactions between two SNPs in separate genes were calculated to discover gene–gene interactions that contribute to cancer susceptibility. We tested 114 SNP pairs including 36 *EZH2*–*KDM6A* pairs (9×4), 24 *KDM6A*–*KDM6B* pairs (4×6), and 54 *KDM6B*–*EZH2* pairs (6×9). Interactions of

a *KDM6A* SNP (on X chromosome) with others were tested only with females.

OR values were recalculated for risk-associated versus nonrisk-associated alleles rather than for minor versus major alleles according to additive genetic models, and used in calculation of $OR_{int} = (OR \text{ for SNP pair}) \div (OR \text{ for one SNP} \times OR \text{ for the other SNP})$. Now, new $OR \geq 1$ for every SNP, but OR_{int} for each SNP pair can be higher or lower than 1, respectively, indicating synergistic or antagonistic interaction, if not equal to 1 for null interaction [15].

Six SNP pairs show significant or marginal interaction after Bonferroni correction with $\alpha = 0.05/114 = 4.4 \times 10^{-4}$ (Table 3). A significant interaction between *EZH2* rs73158295 and *KDM6B* rs78633955 is synergistic ($OR_{int} = 1.7$, $P = 3.0 \times 10^{-4}$) in gastric cancer risk. Four SNP pairs between *EZH2* and *KDM6A* have marginal synergistic interaction ($0.00066 \leq P \leq 0.046$), with the lowest P value for synergistic interaction of *EZH2* rs58579167 and *KDM6A* rs5952279 ($OR_{int} = 3.2$). Additionally, a marginal *KDM6A*–*KDM6B* interaction is also synergistic as revealed between their respective SNPs, rs2230018 and rs78633955 ($OR_{int} = 1.9$, $P = 0.044$). All these inter-SNP interactions among the three genes together form a synergistic triad epistasis network of ring-type topology (Fig. 1).

Discussion

We report here that the three H3K27me modifier genes, *EZH2*, *KDM6A*, and *KDM6B*, are individually associated with gastric cancer risk and synergistically interact with each other in conferring the risk. Therefore, super-synergism can be expected for carriage of all three risk-associated alleles that form a triad interaction network of

Fig. 1 Synergistic triad epistasis of *EZH2*, *KDM6A*, and *KDM6B*. The three pairwise interactions are all synergistic in gastric cancer risk and together form a ring-type network. Between *EZH2* and *KDM6A*, only one exemplary SNP pair is shown among the four epistasis pairs listed in Table 3

ring-type topology where all links are synergistic (Fig. 1). Inclusion of this synergistic effect in weighted genetic risk score would improve risk prediction.

No cancer risk has been previously associated with *KDM6A* or *KDM6B* SNPs, but several cancer types with *EZH2* SNPs [8]. Among them, gastric cancer risk association of *EZH2* was reported from a Chinese study with Han people (311 cases and 425 controls), but their cancer-associated SNPs [10] are different from ours. The Chinese study reported association of a linkage disequilibrium block of rs12670401 and rs6464926 and another block of rs2072407, rs734005, and rs734004, but rs12670401 ($P = 0.95$) of the former block is not associated in this study with Koreans (Table 2). This discrepancy could be due to differences in ethnicity, gender ratio, or age distribution between the two study populations, among other differences.

Six SNPs in the three genes are associated with cancer risk, and thereby additional SNPs highly correlated with them would have the same association. *KDM6B* rs11657063 (genotyped) is perfectly correlated ($r^2 = 1.0$) with rs3744252 and rs3840058 (ungenotyped) in the Han Chinese and Japanese populations of the 1000 Genomes Project. Both rs11657063 and rs3744252 overlap with promoter histone marks (H3K4me3 and H3K9ac), enhancer histone marks (H3K4me1 and H3K27ac), and DNase hypersensitivity regions according to the HaploReg v4.1 [17], possibly affecting *KDM6B* transcription.

At least one SNP in each gene is significantly associated with susceptibility to gastric cancer, diffuse type, or intestinal type (Table 2). The *EZH2*–*KDM6B* interaction is significant, but *EZH2*–*KDM6A* and *KDM6B*–*KDM6A* interactions are merely marginal (Table 3). It warrants replication studies with other populations to verify cancer risk association of the H3K27me modifier genes and their synergistic triad interaction.

Table 3 Intergenic SNP interactions in gastric cancer risk

SNP 1	SNP 2	OR_{int}	P
<i>EZH2</i> – <i>KDM6B</i> interaction			
<i>EZH2</i> rs73158295 ^a	<i>KDM6B</i> rs78633955 ^a	1.7	0.00030
<i>EZH2</i> – <i>KDM6A</i> interaction			
<i>EZH2</i> rs58579167	<i>KDM6A</i> rs5952279 ^a	3.2	0.00066
<i>EZH2</i> rs58579167	<i>KDM6A</i> rs144974719 ^a	3.9	0.022
<i>EZH2</i> rs1061037 ^a	<i>KDM6A</i> rs144974719 ^a	2.4	0.043
<i>EZH2</i> rs73158295	<i>KDM6A</i> rs144974719 ^a	2.8	0.046
<i>KDM6A</i> – <i>KDM6B</i> interaction			
<i>KDM6A</i> rs2230018	<i>KDM6B</i> rs78633955 ^a	1.9	0.044

SNP pairs are listed for each gene pair in ascending order of P values on the rightmost column

OR_{int} odds ratio of interaction, SNP single-nucleotide polymorphism

^aSNPs individually associated with gastric cancer risk ($P \leq 0.05$ in Table 2)

Acknowledgements We thank Drs. Kwangwoo Kim, Suk-Jo Kang, Ji-Joon Song, and J. Eugene Lee for helpful discussion.

Funding This work was supported by a grant from the National Research Foundation of Korea (2015052849). The National Biobank of Korea is supported by the Korean Ministry of Health and Welfare.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Ethical approval This study was approved by the institutional review boards of the three sample-recruiting hospitals and KAIST. Informed consent was obtained from all participants.

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