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ORIGINAL PAPER

Genetic variants A1826H and D2937Y in GAG-β domain of versican influence susceptibility to intestinal-type gastric cancer

Hyoungseok Ju · Byungho Lim · Minjin Kim · Seung-Moo Noh · Dong Soo Han · Hang-Jong Yu · Bo Youl Choi · Yong Sung Kim · Woo Ho Kim · Chunhwa Ihm · Changwon Kang

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Abstract
Purpose Versican regulates adhesion, migration, proliferation, and survival of cells, and plays an important role in cancer development. A case–control association study was performed to test genetic association of versican polymorphisms with susceptibility to gastric cancer.
Methods In this study, 1,101 unrelated Korean subjects including 612 gastric cancer patients and 489 healthy controls were genotyped for all 21 exonic polymorphisms in the versican gene (*VCAN*) encoding amino acid changes in versican. Cancer susceptibility associations with the polymorphisms were assessed using multivariate logistic regression analysis with adjustment for age and gender and with control for multiple testing.
Results Two amino acid changes in GAG-β domain of versican encoded by two almost fully correlated ($r^2 = 0.97$) nonsynonymous single-nucleotide polymorphisms in *VCAN* were associated with gastric cancer. The association was evident in intestinal-type but not in diffuse-type gastric cancer. The minor-allele homozygote of rs188703 (G > A, R1826H) or rs160277 (G > T, D2937Y) was significantly associated with a twofold decreased susceptibility to intestinal-type gastric cancer when compared with the other genotypes (adjusted odds ratio = 0.52 or 0.51, $P = 0.0098$ or 0.0087, respectively).
Conclusions The intestinal-type gastric cancer susceptibility is associated with two amino acid changes of versican in the GAG-β domain, which is critical for enhancement of cell proliferation and activation of EGFR signal pathway by versican, and changes from the major to minor alleles may impair the function to decrease susceptibility to cancer.

H. Ju · B. Lim · M. Kim · C. Kang (✉)
Department of Biological Sciences, Korea Advanced Institute of Science and Technology, 335 Gwahangno, Yuseong-gu, Daejeon 305-701, Korea
e-mail: ckang@kaist.ac.kr

S.-M. Noh
Department of General Surgery, Chungnam National University College of Medicine, Daejeon 301-721, Korea

D. S. Han
Department of Medicine, Hanyang University Guri Hospital, Guri 471-701, Korea

H.-J. Yu
Korea Gastric Cancer Center, Seoul Paik Hospital, Seoul 100-032, Korea

B. Y. Choi
Department of Preventive Medicine, Hanyang University College of Medicine, Seoul 133-792, Korea

Y. S. Kim
Genome Research Center, Korea Research Institute of Bioscience and Biotechnology, Daejeon 305-806, Korea

W. H. Kim
Department of Pathology, Seoul National University College of Medicine, Seoul 110-744, Korea

C. Ihm
Department of Laboratory Medicine, Eulji University College of Medicine, Daejeon 302-120, Korea

Keywords CSPG2 · Genetic association · Intestinal-type gastric cancer · SNP · Versican

Abbreviations

CI	Confidence interval
GAG	Glycosaminoglycan
LD	Linkage disequilibrium
OR	Odds ratio
SNP	Single-nucleotide polymorphism

Introduction

Extracellular matrix is a highly-ordered structure, providing tissues with biological and biomechanical properties and regulating cell phenotypes and functions (Theocharis 2008). Versican (VCAN or CSPG2) is one of main components of the extracellular matrix, and is detected throughout the body (Theocharis 2008), and provides cells with a highly malleable pericellular-matrix environment, supporting cell shape changes required for cell migration and proliferation (Evanko et al. 1999; Wight 2002).

The *VCAN* gene is located at human chromosome 5q14.3 spanning 109.4 kb and contains 15 exons. In human, four isoforms of versican (V0, V1, V2, and V3) are generated by alternative splicing of mRNA (Dours-Zimmermann and Zimmermann 1994) and each isoform appears to have distinct biological functions. According to previous over-expression experiments, the V1 isoform and globular domains of versican enhance cell proliferation, migration, tumor growth, angiogenesis, and invasion as well as reduce cell adhesion and apoptosis (Cattaruzza et al. 2004; Wu et al. 2005; Yang et al. 1999; Yee et al. 2007; Zhang et al. 1998; Zheng et al. 2004). In contrast, the V2 (Sheng et al. 2005) and V3 (Lemire et al. 2002; Serrano and Massague 2000) isoforms inhibit cell proliferation and migration.

These observations suggest that versican regulates adhesion, migration, proliferation, and survival of cells, and plays an important role in cancer development (Theocharis 2008; Wight 2002; Wight and Merrilees 2004). Indeed, elevated levels of versican have been detected in various cancer types, such as melanoma (Touab et al. 2002), brain tumors (Paulus et al. 1996), prostate cancer (Sakko et al. 2001), breast cancer (Brown et al. 1999; Ricciardelli et al. 2002; Theocharis 2008), and gastric cancer (Boussioutas et al. 2003; Hippo et al. 2002; Kim et al. 2007), and associated with cancer progression and poor prognosis (Theocharis 2008).

In this study, the first evidence for genetic association of versican with susceptibility to gastric cancer is presented. Two closely-correlated single-residue polymorphisms at the GAG-β domain of versican, encoding changes of amino acid arginine to histidine (rs188703 or R1826H) and aspartic acid to tyrosine (rs160277 or D2937Y), were associated with decreased susceptibility to gastric cancer.

Materials and methods

Study subjects

This study included 1,101 unrelated Korean subjects (Table 1). They were recruited in the years 2000 through 2004, with written informed consent at Seoul National University Hospital, Hanyang University Guri Hospital, and Inje University Seoul Paik Hospital in the Seoul metropolitan area and at Chungnam National University Hospital and Eulji University Hospital in Daejeon city, with approval by the institutional review board of Hanyang University Medical Center.

The 612 patients with gastric cancer were aged 58.2 ± 12.8 years (mean ± standard deviation) ranging from 22 to 86 years, and the percentage of male individuals was 66.3%. Initially, 914 healthy participants were

Table 1 Characteristics of study subjects

Characteristic	Controls	All patients	Intestinal-type	Diffuse-type
n	489	612	255	357
Age (years), mean ± SD	52.5 ± 9.1	58.2 ± 12.8	62.3 ± 10.0	55.3 ± 13.8
Gender: male	324 (66.3%)	409 (66.8%)	184 (72.2%)	225 (63.0%)
Gender: female	165 (33.7%)	203 (33.2%)	71 (27.8%)	132 (37.0%)
Stage IA	–	67	46	21
Stage IB	–	83	47	36
Stage II	–	114	49	65
Stage IIIA	–	147	59	88
Stage IIIB	–	93	24	69
Stage IV	–	108	30	78
Tumor depth: early	–	85	57	28
Tumor depth: advanced	–	527	198	329

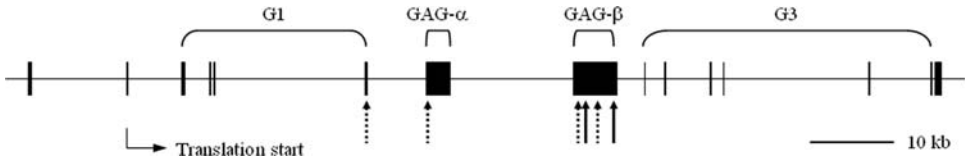

Fig. 1 Structure of *VCAN* gene with gastric cancer-associated SNP markers. The translation start codon and four domains of versican, G1, GAG-α, GAG-β, and G3, are shown and 15 exons are marked by *solid boxes*. The position of tested SNP is indicated by an *arrow*, in the order of rs2652098, rs2287926, rs309559, rs188703, rs160278, and rs160277 from the *left side*. *Solid arrows* indicate significantly associated SNPs and *dotted arrows* indicate non-associated SNPs

recruited during the study period, but only 489 subjects were included as age- and gender-matched controls and were 52.5 ± 9.1 years old (ranging from 28 to 81 years), and the percentage of male individuals was 66.8%. All the control subjects were confirmed free of gastric cancer by health examinations including an endoscopy or an upper gastrointestinal track radiography.

The tumor stages at diagnosis were diverse; stage IA ($n = 67$), IB ($n = 83$), II ($n = 114$), IIIA ($n = 147$), IIIB ($n = 93$), and IV ($n = 108$) according to the AJCC Cancer Staging Manual, and 85 of them were early and 527 were advanced gastric carcinoma by tumor depth. The gastric cancers were classified into intestinal- ($n = 255$) or diffuse-type ($n = 357$) according to the Lauren's classification by a pathologist in each hospital, and the mixed-type or ambiguous cases were not included in the study.

Genotyping

Genomic DNA was extracted from blood samples of healthy controls using the Puregene™ DNA purification kit (Gentra, Minneapolis, MN, USA) or from frozen normal gastric tissues (free of tumor cells) of patients using DNeasy® tissue kit (Qiagen, GmbH, Germany), and quantified using the double-stranded DNA-specific fluorescent dye, PicoGreen® (Molecular Probes, Eugene, OR, USA). The final concentration of each DNA sample was adjusted to 2.5–10 ng/μl for individual genotyping assays.

A DNA pool was prepared by mixing equal amounts of individual DNA from 391 controls and 342 cases, and subjected to genotyping for validation of 21 polymorphisms. The subjects were then individually genotyped for the six validated single-nucleotide polymorphisms (SNPs). Polymorphisms of *VCAN* were genotyped using the MassARRAY™ system (Sequenom, San Diego, CA, USA) according to the manufacturer's instructions and the overall call rate for the six SNPs was 99.2%.

Statistical analyses

Linkage disequilibrium was calculated using Haploview 4.1 and haplotypes were constructed using PHASE 2.1 (Barrett et al. 2005; Stephens and Donnelly 2003; Stephens et al. 2001). Allele and haplotype associations with gastric cancer susceptibility and Hardy–Weinberg equilibrium were assessed by Chi-square tests. Genotype and diplotype associations were assessed by logistic regression analyses with adjustment for age and gender using the SPSS 11.5 program.

Multiple testing-associated errors were minimized by setting the significance level of association to be $\alpha = 0.012 = 1 - (1 - 0.05)^{1/4.1}$, as the effective degree of freedom was estimated to be 4.1 for the six tested SNPs using the EDF software (Menashe et al. 2008). The 98.8% confidence interval of odds ratio was computed based on the significance level. Thus, the association was considered to be significant when P value was lower than 0.012, but marginal when P value ranged between 0.012 and 0.050.

Results

Functional variants of *VCAN* associated with gastric cancer

To test genetic association of versican with susceptibility to gastric cancer, all *VCAN* exonic polymorphisms encoding amino-acid changes were retrieved from the dbSNP database of NCBI (genome build 36.3) regardless of their validation status. Throughout the 15 exons of *VCAN*, there were 19 nonsynonymous SNPs and two frameshift polymorphisms only in the exons 6, 7, 8, and 11 (Table 2). All 21 polymorphisms were subjected to validation using a genomic DNA pool made of 391 control and 342 case samples of this study, and only 6 nonsynonymous SNPs were common in the sense that their minor allele frequencies were higher than 5% (Table 2; Fig. 1).

An initial study subset of only 430 gastric cancer patients and 406 controls were individually genotyped for the six polymorphic SNPs. Genotype distributions in control subjects did not deviate from Hardy–Weinberg equilibrium with respect to any of the six SNPs. Susceptibility to gastric cancer was marginally associated with two nonsynonymous SNPs, rs188703 (R1826H, OR = 0.79, $P = 0.019$) and rs160277 (D2937Y, OR = 0.80, $P = 0.027$), but not with the other four nonsynonymous SNPs (Table 2).

Table 2 Gastric cancer susceptibility associations of *VCAN* polymorphisms encoding amino acid changes

SNP	Location	Allele[a]	Function[b]	MAF[c]	Minor allele association	
					OR (95% CI)	*P*
rs36065652	Exon 6	*C* > *T*	L255F	<0.05	–	–
rs2652098	Exon 6	*C* > *T*	S300L	0.13	1.03 (0.77–1.38)	0.83
rs12651836	Exon 6	*G* > *T*	G333V	<0.05	–	–
rs2287926	Exon 7	*G* > *A*	G428D	0.20	0.89 (0.70–1.14)	0.37
rs11745614	Exon 7	*C* > *G*	S817C	<0.05	–	–
rs309559	Exon 8	*A* > *G*	K1516R	0.46	0.85 (0.70–1.03)	0.096
rs35443373	Exon 8	*G* > *A*	S1577N	<0.05	–	–
rs3813671	Exon 8	*A* > *G*	T1670A	<0.05	–	–
rs34469464	Exon 8	– > *C*	Frameshift	<0.05	–	–
rs188703	Exon 8	*G* > *A*	R1826H	0.42	0.79 (0.65–0.96)	0.019
rs35949614	Exon 8	*G* > *T*	E1857D	<0.05	–	–
rs34050047	Exon 8	*C* > *A*	A1859E	<0.05	–	–
rs1061380	Exon 8	*A* > *C*	I2216L	<0.05	–	–
rs34421683	Exon 8	*A* > –	Frameshift	<0.05	–	–
rs160278	Exon 8	*T* > *A*	F2301Y	0.46	0.84 (0.69–1.02)	0.083
rs3734094	Exon 8	*G* > *C*	V2315L	<0.05	–	–
rs59948995	Exon 8	*G* > *A*	V2685I	<0.05	–	–
rs160277	Exon 8	*G* > *T*	D2937Y	0.42	0.80 (0.66–0.98)	0.027
rs16900532	Exon 8	*C* > *A*	N3011K	<0.05	–	–
rs13184139	Exon 11	*A* > *T*	D3165V	<0.05	–	–
rs13166485	Exon 11	*T* > *A*	D3165E	<0.05	–	–

Crude χ^2 test for association of the minor allele versus the major allele

[a] Major > minor allele

[b] Amino acid positions referring to NP_004376 (NCBI Genome Build 36.3)

[c] Minor allele frequency (MAF) in controls

For the two marginally associated SNPs, 265 additional subjects were genotyped, so that the entire 1,101 subjects of the study had become individually genotyped for the two SNPs. The marginal associations of the two SNPs with gastric cancer susceptibility were still maintained with the full set of genotype data in logistic regression analysis with adjustment for age and gender (Table 3). The minor allele in each SNP decreased the risk of gastric cancer by ~20% compared with the major allele.

Gastric cancer subtype-specific association of *VCAN*

Gastric cancer can be classified into two distinct histological subtypes, intestinal- and diffuse-types. Subtype stratification of the patient samples revealed that the two nonsynonymous SNPs were associated with the intestinal-type gastric cancer rather than the diffuse-type. The associations were significant ($P \leq 0.012$) rather than marginal ($0.012 < P \leq 0.050$) with the susceptibility to intestinal-type gastric cancer in a recessive genetic model (Table 3). Decreased susceptibility to intestinal-type gastric cancer was significantly associated with minor-allele homozygote (*A/A* genotype in rs188703 and *T/T* in rs160277) in comparison with the other genotypes combined (adjusted OR = 0.52 and 0.51, $P = 0.0098$ and 0.0087, respectively). In contrast, genetic associations with susceptibility to diffuse-type gastric cancer were not significant or marginal ($P = 0.22$ and 0.21, respectively). Accordingly, rs188703 and rs160277 were associated with susceptibility to intestinal-type but not diffuse-type gastric cancer.

In order to see whether the cancer susceptibility association was compounded by cancer progression association, the patients with intestinal-type gastric cancer were divided into two subgroups according to cancer stages. The first subgroup ($n = 142$) included stages IA, IB, and II and the second subgroup ($n = 113$) included stages IIIA, IIIB, and IV (Table 1). When the two subgroups were compared with each other, however, no association was found with rs188703 or rs160277 in a recessive genetic model ($P = 0.46$ and 0.47, respectively). Next, the intestinal-type patients were divided according to tumor depth (Table 1). When the early tumor group ($n = 57$) was compared with the advanced tumor group ($n = 198$), no association was found either with rs188703 or rs160277 in a recessive

Table 3 Genotype association of *VCAN* SNPs with susceptibility to gastric cancer

Genotype	Control (n = 489)	All patients (n = 611)			Intestinal-type patients (n = 255)			Diffuse-type patients (n = 357)		
	n	n	OR (98.8% CI)	P	n	OR (98.8% CI)	P	n	OR (98.8% CI)	P
rs188703										
GG	173	246	1	–	102	1	–	144	1	–
GA	222	283	0.89 (0.63–1.26)	0.41	125	0.98 (0.61–1.58)	0.93	158	0.85 (0.58–1.26)	0.30
AA	92	82	0.65 (0.41–1.05)	0.024	28	0.51 (0.26–1.02)	0.015	54	0.73 (0.43–1.22)	0.12
GG + *GA*	395	529	1	–	227	1	–	302	1	–
AA	92	82	0.70 (0.45–1.07)	0.034	28	0.52 (0.27–0.98)	0.0098	54	0.79 (0.49–1.27)	0.22
rs160277										
GG	179	245	1	–	101	1	–	144	1	–
GT	217	283	0.96 (0.68–1.35)	0.74	125	1.07 (0.67–1.72)	0.71	158	0.91 (0.62–1.34)	0.53
TT	92	82	0.67 (0.42–1.08)	0.035	28	0.53 (0.27–1.06)	0.022	54	0.75 (0.45–1.26)	0.16
GG + *GT*	396	528	1	–	226	1	–	302	1	–
TT	92	82	0.69 (0.45–1.06)	0.31	28	0.51 (0.27–0.97)	0.0087	54	0.79 (0.49–1.27)	0.21

Logistic regression analysis with adjustment for age and gender

Significant values after multiple-testing correction ($P < 0.012$) are underlined

Table 4 Haplotype association of *VCAN* with susceptibility to gastric cancer

Group	n	Haplotype allele				*AT* versus *GG*	
		GG	*AT*	*AG*	*GT*	OR (98.8% CI)	P
Control	978	570	401	6	1	1	–
All patients	1,124	775	449	0	0	0.82 (0.66–1.03)	0.027
Intestinal-type	510	329	181	0	0	0.78 (0.59–1.04)	0.030
Diffuse-type	714	446	268	0	0	0.85 (0.66–1.10)	0.12

Crude χ^2 test for association of *AT* haplotype versus *GG* haplotype

Haplotypes are designated with alleles in sequence of rs188703 and rs160277

genetic model ($P = 0.74$ and 0.71, respectively). Accordingly, the two cancer susceptibility-associated SNPs were not associated with cancer progression.

Haplotype analysis

The two associated SNPs, rs188703 and rs160277, were almost perfectly correlated with each other ($r^2 = 0.97$) in the controls, and the correlation was perfect ($r^2 = 1.00$) in the patients. When haplotypes were constructed using the PHASE program, two haplotypes, *GG* and *AT* in the order of rs188703 and 160277, constituted 99.3 and 100% of entire haplotypes in controls and cases, respectively (Table 4). The *AT* haplotype with the minor alleles at both SNPs was marginally associated with decreased susceptibility to gastric cancer (OR = 0.82, $P = 0.027$) compared with the *GG* haplotype with the major alleles. The association was marginal only with intestinal-type gastric cancer (OR = 0.78, $P = 0.030$), not with diffuse-type cancer (OR = 0.85, $P = 0.12$).

In logistic regression analysis for diplotype association (Table 5), the *AT/AT* diplotype showed a significant, not-marginal association with twofold decreased susceptibility to intestinal-type gastric cancer in comparison with the *GG/GG* and *GG/AT* diplotypes (adjusted OR = 0.51, $P = 0.0085$), although its association with decreased susceptibility to gastric cancer was marginal (adjusted OR = 0.70, $P = 0.039$). Accordingly, the *AT* haplotype with minor allele in the two SNPs had a protective effect on susceptibility to intestinal-type gastric cancer.

Discussion

In this study, we found that two nonsynonymous SNPs, rs188703 (G > A) and rs160277 (G > T) in *VCAN*, nearly perfectly linked to each other ($r^2 = 0.97$), were associated with susceptibility to intestinal-type gastric cancer. Associations of the two SNPs were significant with susceptibility to intestinal-type gastric cancer in a recessive genetic model

Table 5 Diplotype association of *VCAN* with susceptibility to gastric cancer

Diplotype	Controls ($n = 489$)	All patients ($n = 611$)			Intestinal-type patients ($n = 255$)			Diffuse-type patients ($n = 357$)		
	n	*n*	OR (98.8% CI)	*P*	*n*	OR (98.8% CI)	*P*	*n*	OR (98.8% CI)	*P*
GG/GG	174	246	1	–	102	1	–	144	1	–
GG/AT	218	283	0.92 (0.65–1.30)	0.54	125	1.02 (0.64–1.64)	0.91	158	0.88 (0.59–1.29)	0.39
AT/AT	91	83	0.67 (0.42–1.07)	0.033	28	0.52 (0.26–1.03)	0.017	55	0.75 (0.45–1.26)	0.16
Others[a]	6	0	–	–	0			0		
GG/GG + GG/AT	392	529	1	–	227	1	–	302	1	–
AT/AT	91	83	0.70 (0.46–1.08)	0.039	28	0.51 (0.27–0.97)	0.0085	55	0.81 (0.50–1.29)	0.25

Logistic regression analyses with adjustments for age, gender

Significant values after multiple testing corrections ($P < 0.012$) are underlined

[a] Rare diplotypes, *AG/GG* ($n = 4$), *AG/AG* ($n = 1$), and *AT/GT* ($n = 1$) were found only in the control subjects

($P = 0.0098$ and 0.0087, respectively), but not with susceptibility to diffuse-type (Table 3). Diplotype association was additionally significant ($P = 0.0085$), as individuals homozygous for the minor allele in both SNPs had twofold reduced odds of having intestinal-type cancer compared with the other diplotype carriers (adjusted OR = 0.51, Table 5).

The two associated SNPs are nonsynonymous encoding for R1826H (arginine to histidine) and D2937Y (aspartate to tyrosine) and both located within exon 8, which encodes the GAG-β domain of versican (Fig. 1). Several functions related to oncogenic properties have been observed with the GAG-β domain based on the previously examined functions of different splicing isoforms of human versican. Four different isoforms of versican are generated by alternative splicing and differ from each other in the presence and absence of exons 7 and 8; V0 isoform carries both exons, V1 lacks exon 7, V2 lacks exon 8, and V3 lacks both exons (Dours-Zimmermann and Zimmermann 1994). The two exons together encode 17–23 potential glycosaminoglycan (GAG) attachment sites, as exon 7 alone encodes 5–8 GAG sites (called as GAG-α domain), and exon 8 encoding 12–15 GAG sites (GAG-β domain) (Theocharis 2008).

The V1 isoform having GAG-β domain is mainly detected in late stages of embryonic development (Landolt et al. 1995), but over-production of V1 enhances cell proliferation, cell cycle progression, and inhibits apoptosis in NIH 3T3 cells (Sheng et al. 2005) and induces tumor formation in nude mice (LaPierre et al. 2007). V1 activates proto-oncogene EGFR expression and CDK2 kinase activity, induces p27 degradation, and inhibits pro-apoptotic Bad expression (Sheng et al. 2005). Moreover, V1 induces mesenchymal–epithelial transition in NIH 3T3 fibroblasts (Sheng et al. 2006), which plays pivotal roles in the progression of cancer (Theocharis 2008). In contrast, the V2 isoform without GAG-β domain, a major component of mature brain (Schmalfeldt et al. 1998), inhibits cell proliferation and EGFR expression, and does not affect apoptosis resistance (Sheng et al. 2005).

These observations altogether suggest that GAG-β domain is involved in enhancement of cell proliferation and activation of the EGFR signal pathway. Thus, a functional impairment of GAG-β domain could decrease susceptibility to cancer. In fact, rs160277 (D2937Y) is predicted to affect the function or structure of versican by PolyPhen (*Poly*morphism *Phen*otyping at http://genetics.bwh.harvard.edu/pph/), where predictions are based on straightforward empirical rules (Ramensky et al. 2002). However, it remains to be experimentally elucidated whether a function of versican is impaired by any of the two associated SNPs themselves or other variations highly correlated with them.

All known amino-acid changing polymorphisms of human versican were genotyped and tested in this study, but other potentially functional variations were not tested. The small sample size and lack of information on *H. pylori* infection status are limits of this study, and the association reported here needs to be replicated in other populations to be confirmed.

In summary, among all the known nonsynonymous polymorphisms in *VCAN*, two SNPs in exon 8 were identified to be associated with susceptibility to intestinal-type gastric cancer. Two amino-acid changes at the GAG-β domain of versican encoded by the two associated SNPs could affect susceptibility to cancer, possibly impairing a function of versican.

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