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Research paper

Expression analysis of genes located within the common deleted region of del(20q) in patients with myelodysplastic syndromes

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ABSTRACT

Deletion of the long arm of chromosome 20 (del(20q)) is observed in 5–10% of patients with myelodysplastic syndromes (MDS). We examined the expression of 28 genes within the common deleted region (CDR) of del (20q), which we previously determined by a CGH array using clinical samples, in 48 MDS patients with (n = 28) or without (n = 20) chromosome 20 abnormalities and control subjects (n = 10). The expression level of 8 of 28 genes was significantly reduced in MDS patients with chromosome 20 abnormalities compared to that of control subjects. In addition, the expression of *BCAS4*, *ADA*, and *YWHAB* genes was significantly reduced in MDS patients without chromosome 20 abnormalities, which suggests that these three genes were commonly involved in the molecular pathogenesis of MDS. To evaluate the clinical significance, we analyzed the impact of the expression level of each gene on overall survival (OS). According to the Cox proportional hazard model, multivariate analysis indicated that reduced BCAS4 expression was associated with inferior OS, but the difference was not significant (HR, 3.77; 95% CI, 0.995-17.17; $P = 0.0509$). Functional analyses are needed to understand the biological significance of reduced expression of these genes in the pathogenesis of MDS.

1. Introduction

Deletion of the long arm of chromosome 20 (del(20q)), a common chromosome abnormality in myelodysplastic syndromes (MDS), is observed in 5–10% of patients with MDS [1,2]. Although the biological significance of del(20q) in the pathogenesis of MDS is not clear, genes within the common deleted regions (CDRs) of del(20q) are likely involved in the molecular pathogenesis of MDS. We and others have identified target genes within del(20q) by different molecular biological approaches [3–6]. The location and size of CDRs in del(20q) vary, and the causative genes remain unclear. Previously, we determined a CDR of del(20q) in MDS and AML patients by array comparative genomic hybridization analysis using genomic DNA derived from bone marrow samples of patients [5]. In MDS cases, the size of the CDR was 11.2 Mb flanked by the *MAFB* gene at the centromere and the *ADNP* gene at the telomere, containing more than 150 genes.

Target genes may be tumor suppressor genes (TSGs), which are disrupted by chromosome deletion. TSGs are inactivated by different molecular mechanisms, including allelic loss, loss of function mutations, and promoter methylation in human cancers [7]. The classical model of TSG inactivation is a hemizygous deletion with a loss-of-function mutation in the remaining allele, which is called the two-hit hypothesis. However, no recurrent mutations of genes within the CDRs of del(20q) have been reported. Haploinsufficiency is another mechanism for inactivation of TSGs in MDS. Decreased expression of candidate TSGs because of the loss of a single allele without somatic mutations in the remaining allele may be sufficient for the loss of function of some TSGs. Haploinsufficiency of several genes on chromosome 20q has been reported in myeloid neoplasms [8,9]. However, the role of the reduced expression of these genes on the molecular pathogenesis of MDS is not clear. Moreover, it is unclear whether other target genes are present within CDRs because CDRs are large and contain many genes. It is possible that multiple target genes may be present within the CDRs.

Here, we examined 28 genes located within the CDR, which are candidate TSGs and/or genes involved in cell growth, death, and differentiation, and performed expression analysis by quantitative RT-PCR to determine target genes disrupted by del(20q) in MDS.

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Table 1
Characteristics of the 48 patients.

	Del(20q) and Monosomy 20	Other Karyotypes	Total
Sex (female/male)	13/15	9/11	22/26
Median age (range)	72.5 (48–82)	66 (40–90)	70 (40–90)
MDS subtypes[1)]			
RCUD	7	0	7
RARS	3	1	4
RCMD	10	11	21
RAEB-1	3	5	8
RAEB-2	1	3	4
RAEB-T	4	0	4
IPSS			
Low	8	7	15
INT-1	6	6	12
INT-2	6	6	12
High	4	1	5
Missing	4	0	4
IPSS-R			
Very low	4	1	5
Low	5	3	8
Intermediate	5	9	14
High	4	5	9
Very high	6	2	8
Missing	4	0	4
Karyotypes[2)]			
Good risk	18	10	28
Intermediate risk	2	4	6
Poor risk	8	6	14

[1)] Patients were categorized into subgroups according to the WHO classification in 2008, except for 4 patients (RAEB-T).

[2)] The good risk category included normal, -Y, del(5q), and del(20q). The poor risk category included complex abnormalities (three or more abnormalities) and chromosome 7 abnormalities. All other chromosome abnormalities were included in the intermediate risk category.

2. Materials and methods

2.1. Patient samples

A total of 48 MDS patients with (n = 28) or without (n = 20) chromosome 20 abnormalities and control subjects (n = 10) were analyzed for the expression of 28 genes. Karyotype analysis by G-banding using bone marrow cells was carried out in all patients included into this study to determine chromosome abnormalities. Chromosome 20 abnormalities included del(20q) (n = 25) and monosomy 20 (n = 3). Median percentage of nuclei with del(20q) or monosomy 20 in analyzed cells was 75% (range, 10–100%) among these 28 patients. The clinical characteristics of the patients are summarized in Table 1. Among 28 patients with chromosome 20 abnormalities, 10 patients had other chromosome abnormalities, including chromosome 7 abnormalities (n = 5), del(5q) (n = 3) and trisomy 8 (n = 2), and 7 patients showed complex karyotypes. Among 20 patients without chromosome 20 abnormalities, 10 patients showed normal karyotypes followed by trisomy 8 (n = 5), chromosome 7 abnormalities (n = 3), and del(5q) (n = 2), and complex karyotypes were observed in 4 patients.

Bone marrow samples obtained from the patients with MDS at the time of diagnosis were used. Mononuclear cells were separated from bone marrow samples at the time of diagnosis and were stored in liquid nitrogen until analysis. As controls, 10 bone marrow samples obtained from lymphoma patients without bone marrow involvement of lymphoma cells were used. Written informed consents were obtained from the patients before analysis. Clinical data were collected from clinical records and a laboratory database. The study was conducted according to the Declaration of Helsinki, and the protocol was reviewed by an institutional ethics committee (No. 3426). Total RNA was isolated from mononuclear cells and subjected to cDNA synthesis as described as previously [10].

Table 2
List of the 28 genes analyzed.

	Gene (Accession Number)	Location	Size(bp)	Product
1	CTNNBL1 (NM_030877)	35755848–35933934	180187	Catenin beta like1
2	MAFB (NM_005461)	38747931–38751290	5460	V-MAF family protein B
3	TOP1 (NM_003286)	39090876–39186540	97765	DNA topoisomerase 1
4	EMILIN3 (NM_052846)	39422020–39428912	8993	Elastin microfibril interfacer 3
5	PTPRT (NM_133170)	40134806–41251971	1119266	Protein tyrosine phosphatase, receptor type
6	SFRS6 (NM_006275)	41519932–41525655	7824	Serine/arginine rich splicing factor 6
7	L3MBTL (NM_015478)	41576467–41603949	29583	L3MBT, drosophila homolog of 1
8	MYBL2 (NM_002466)	41729123–41778536	51514	MYB homolog like-2
9	SERINC3 (NM_198941)	42561315–42584140	24926	Serine incorporator 3
10	PKIG (NM_007066)	42593850–42681092	89343	Protein kinase inhibitor gamma
11	ADA (NM_000022)	42681577–42713790	34314	Adenosine deaminase
12	WISP2 (NM_003881)	42777299–42789866	14668	WNT1-inducible signaling pathway protein 2
13	YWHAB (NM_003404)	42947758–42970575	24918	Tyrosine 3-/Tryptophan 5- monooxygenase
14	TOMM34 (NM_006809)	43004185–43022528	20444	34 kDa-translocase of the outer membrane of mitochondria
15	STK4 (NM_006282)	43028534–43142007	115574	Serine-threonine kinases
16	DBNDD2 (NM_001048223)	43470329–43472661	4433	Dysbindin domain-containing
17	UBE2C (NM_007019)	43874662–43879003	6442	Ubiquitin–conjugating enzyme
18	ZNF335 (NM_022095)	44010699–44034240	25642	Zinc finger protein 335
19	MMP9 (NM_004994)	44070954–44078607	9754	Matrix metalloproteinase
20	TP53RK (NM_033550)	44746411–44751683	7373	TP53-regulating kinase
21	NCOA3 (NM_181659)	45564064–45719021	157058	Nuclear co-activator 3
22	SULF2 (NM_018837)	45719557–45848767	131311	Sulfatase 2
23	B4GALT5 (NM_004776)	47682890–47763828	83039	beta-GlcNAc beta-1,4-galactosyl polypeptide 5
24	SNAI1 (NM_005985)	48032934–48038827	7994	SNAIL, drosophila, homolog 1
25	UBE2V1 (NM_199203)	48131068–48165901	36934	Ubiquitin–conjugating enzyme
26	CEBPB (NM_005194)	48240783–48242619	3937	CCAAT/enhancer-binding protein beta
27	BCAS4 (NM_017843)	48844874–48927121	84348	Breast carcinoma amplified sequence 4
28	ADNP (NM_181442)	48940290–48980934	42745	Activity-dependent neuroprotector homeobox

Genes are ordered from centromeric to telomeric sides.

2.2. Quantitative RT-PCR to examine the expression of 28 genes in MDS patients

Quantitative RT-PCR was performed to examine the expression of 28 genes (Table 2) in bone marrow cells from control subjects and patients by the TaqMan probe method using an ABI 7500 real-time PCR system with a standard protocol. The *GAPDH* gene was used as an internal control. The relative expression value of each sample was calculated as a ratio to that of K562 cell lines.

2.3. Statistical analyses

To compare the expression level of each gene among the groups, a non-parametric Mann-Whitney-Wilcoxon test was used. Kaplan-Meier plots were used to estimate survival. The Cox proportional hazards model was used to analyze the impact of the expression of each gene on overall survival. For statistical analyses, JMP Pro 11.2 (SAS Institute Inc.) was used. A significant result was considered as a *P*-value < 0.05.

3. Results

3.1. Comparison of the expression levels of 28 genes in 48 MDS patients with or without chromosome 20 abnormalities and 10 control subjects

We excluded *PTPRT* and *WISP2* genes from the analyses because expression of these two genes in bone marrow cells was nearly absent in both MDS patients and controls. Among the remaining 26 genes, the expression level of eight genes (30.8%) was significantly reduced in MDS patients with chromosome 20 abnormalities compared to that of the controls (Table 3). In addition, expression of *BCAS4, ADA, and YWHAB* genes was significantly reduced in 20 MDS patients without chromosome 20 abnormalities.

Table 4
Impact of the expression level (low vs high) of each gene on overall survival.

Gene	Univariate			Multivariate		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
MYBL1	1.1	0.46–2.70	0.84			
TOP1	2.39	0.93–7.32	0.07			
MAFB	1.19	0.50–1.99	0.69			
UBE2C	2.24	0.91–6.30	0.08			
CEBPB	1.16	0.48–2.76	0.74			
SNAI1	0.9	0.35–2.13	0.81			
MMP9	3.38	1.32–10.3	**0.0101**	2.48	0.43-11.95	0.29
YWHAB	2.05	0.86–1.16	0.104			
ADA	1.06	0.45–2.62	0.89			
CTNNBL1	0.76	0.31–1.87	0.5449			
MMRN2	1.44	0.61–3.53	0.41			
SSRF6	1.5	0.62–3.98	0.37			
L3MBTL	1.39	0.58–3.54	0.46			
SERINC3	2.38	0.96–6.70	0.059			
PKIG	0.59	0.23–1.34	0.24			
UBE2V1	1.34	0.58–3.40	0.46			
BCAS4	3.63	1.50–9.33	**0.0042**	3.77	0.995–17.17	0.0509
ADNP	0.98	0.41–2.42	0.97			
TOMM34	1.31	0.55–3.22	0.54			
BGALT5	2.99	1.24–7.91	**0.0144**	1.38	0.34–7.85	0.67
DBNNBL1	1.37	0.56–3.32	0.49			
SULF2	2.92	1.21–7.75	**0.0169**	0.66	0.13–3.11	0.36
TP53RK	1.16	0.50–2.89	0.71			
ZNF335	2.43	1.02–6.16	**0.0455**	0.91	0.28–3.05	0.87
NCOA3	1.67	0.70–4.22	0.25			
STK4	1.48	0.62–3.75	0.38			

The Cox proportional hazards model was used to analyze the impact of the expression level of each gene on overall survival. Patients were divided into two categories according to each gene expression level: a low expression group (less than median value) and a high expression group (median value and higher). HR hazard ratio; CI confidence interval.

Table 3
Relative expression level of each gene in MDS patients with or without chromosome 20 abnormalities and controls.

Gene	Controls (A) (n = 10) Median	MDS cases with Chr. 20 abnormalities (B) (n = 28) Median	MDS cases without Chr. 20 abnormalities (C) (n = 20) Median	(A) vs (B) *P*-value	(A) vs (C) *P*-value
CTNNBL1	2.856531	1.759382	2.031534	0.0941	0.8088
MAFB	17398.3	6905.1	7049.37	0.1402	0.3741
TOP1	1.865173	0.543903	0.781515	0.3120	0.8776
EMILIN3	0.789127	0.436806	2.376649	0.7781	0.1083
SFRS6	2.555572	1.849037	2.174967	**0.0299**	0.3442
L3MBTL	1.282702	0.923174	1.007801	0.2263	0.4088
MYBL2	1.55345	1.037401	2.221953	0.2668	0.6129
SERINC3	1.858591	0.94378	1.224138	**0.0229**	0.5526
PKIG	10.821	6.917017	16.07929	**0.0252**	0.5235
ADA	11.33738	7.422593	6.58392	**0.0384**	**0.0263**
YWHAB	4.264231	0.656335	1.199851	**0.0076**	**0.0366**
TOMM34	0.47223	0.299407	0.464215	**0.0299**	0.9817
STK4	7.686636	1.661557	5.582995	0.0658	0.6760
DBNDD2	0.421736	0.236636	0.307051	0.0876	0.3217
UBE2C	194.8931	103.1456	206.1923	0.3281	0.5235
ZNF335	6.256139	4.598786	4.859945	0.1079	0.5824
MMP9	523.7435	111.3724	700.521	**0.0252**	0.9825
TP53RK	10.47928	3.391888	11.53044	0.0525	0.9818
NCOA3	3.220517	1.712489	1.722406	0.0818	0.0990
SULF2	16300.17	8960.838	16428.89	0.0611	0.9825
B4GALT5	4.532213	4.202698	5.916722	0.2019	0.3222
SNAI1	0.66364	0.420726	1.045745	0.2813	0.6760
UBE2V1	10.84777	1.80708	4.200864	0.3979	0.6411
CEBPB	10.14456	7.505104	14.17259	0.5844	0.1749
BCAS4	28.3705	16.54435	13.4074	**0.0449**	**0.0329**
ADNP	2.26774	1.527915	1.732114	0.1904	0.6760

The median value of the expression level of each gene in MDS patients with or without chromosome 20 abnormalities and control subjects are shown. Expression levels were compared between control subjects (A) and MDS patients with chromosome 20q abnormalities (B), and also between control subjects (A) and MDS patients without chromosome 20 abnormalities (C). A non-parametric Mann-Whitney-Wilcoxon test was used for statistical analysis, and $P < 0.05$ was considered significant. Two genes, *PTPRT* and *WISP*2, genes were excluded from the analysis because expression of these genes was nearly absent in both MDS patients and control subjects

Table 5
Impact of clinical factors on overall survival.

	Univariate			Multivariate		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (70 years or more vs. less than 70 years)	1.12	0.45–2.84	0.80			
Sex (female vs male)	1.25	0.50–3.12	0.62			
BCAS4 expression (L vs. H)[1)]	3.60	1.42–9.82	0.0068	1.10	0.27–4.52	0.89
IPSS (higher risk vs. lower risk)[2)]	6.07	2.34–16.93	0.0002	6.07	2.34–16.93	0.0118

The Cox proportional hazards model was used to analyze the impact of each factor on overall survival. HR hazard ratio; CI confidence interval.
[1)] Patients were divided into two categories according to each gene expression level: a low expression group (less than median value) (L) and a high expression group (median value and higher) (H).
[2)] Patients were divided into two risk groups according to the IPSS score: a higher risk group (high and intermediate-2 risk groups) and a lower risk group (intermediate-1 and low risk groups).

3.2. Clinical significance of reduced gene expression

To evaluate the clinical significance of the reduced expression of genes examined, we analyzed the impact of the expression level of 26 genes on overall survival (OS). For the analysis, the patients were divided into two categories according to the expression level of each gene: a high expression group (median value or higher) and a low expression group (less than the median value). The Cox proportional hazards model was used to evaluate the impact of the expression level of each gene on OS. Univariate analysis indicated a significant association between inferior OS and reduced expression in five genes, *MMP9* (hazard ratio (HR) 3.38; 95% confidence interval (CI), 1.32–10.3; $P = 0.0101$), *BCAS4* (HR, 3.63; 95%CI, 1.50–9.33; $P = 0.0042$), *BGALT5* (HR, 2.99; 95% CI, 1.24–7.91; $P = 0.0042$), *SULF2* (HR, 2.92; 95% CI, 1.21–7.75; $P = 0.0169$), and *ZNF335* (HR, 2.43; 95% CI, 1.02–6.16; $P = 0.0455$) (Table 4). Multivariate analysis indicated that reduced *BCAS4* expression was associated with lower OS, but the difference was not significant (HR, 3.77; 95% CI, 0.995–17.17; $P = 0.0509$) (Table 5). Kaplan-Meier plots indicated that estimated 1-year, 2-year, and 5-year OS rates were 82.1%, 79.1%, and 44.5% in the MDS cohort; median OS was 52 months with a 95% CI of 36–67 months (Fig. 1A). Forty-eight MDS patients were divided into two groups according to the BCAS4 expression level, a low expression group (less than the median value) and a high expression group (median or higher), and OS was compared between the two groups. Kaplan-Meier plots revealed that patients with a high BCAS4 expression (median or higher) (H-group) had higher survival compared to those with low BCAS4 expression (less than the median) (L-group) (P = 0.0022, log-rank test) (Fig. 1B). Estimated median OS times were 67 months (H-group) and 32 months (L-group); estimated OS rates in the H-group and L-group were 95.2% and 65.8% at 1 year, 89.6% and 65.8% at 2 years, 82.7% and 36.5% at 3 years, and 66.2% and 19.5% at 5 years, respectively.

4. Discussion

In the present study, expression of *PTPRT* and *WISP2* genes was nearly absent in both controls and MDS patients. Previous study showed that expression of the *PTPRT* gene is restricted in central nervous system in adult [11]. Expression of the *WISP2* gene is various among organs and tissues, and almost absent in bone marrow [12]. Results from our present study and previous studies suggest limited roles of PTPRT and WISP2 in normal hematopoiesis and/or MDS development. Comparative gene expression analyses for the remaining 26 genes within the CDR by quantitative RT-PCR demonstrated that the expression of 8 genes was significantly reduced in MDS cases with del(20q) and control subjects, which suggests that more than half of the genes are candidate genes inactivated by haploinsufficiency because of del (20q). In addition, expression of three genes (*YWHAB, BCAS4, and ADA*) was significantly reduced in not only MDS cases with chromosome 20 abnormalities but also in those without chromosome 20 abnormalities compared with that of control subjects. Decreased expression of these three genes was not specific for MDS cases with del(20q) and may be a common molecular event in MDS. The molecular mechanism of decreased expression of these three genes in MDS patients without del(20q) remains unclear. It is possible that epigenetic mechanisms including alteration of promoter methylation has a role in the decreased expression of these genes. Aberrant promotor methylation is often observed in TSGs in human cancers. In the molecular pathogenesis of MDS, alteration of epigenetic processes plays a key role, and expression of many genes, including TSGs, is reduced by aberrant methylation of the promotor region [13]. Hypomethylating agents alter the methylation of these genes and induce gene expression. The clinical efficacy of hypomethylating agents in MDS patients suggests that aberrant methylation status plays crucial roles in the molecular pathogenesis of MDS.

We analyzed the impact of the expression of 26 genes on overall

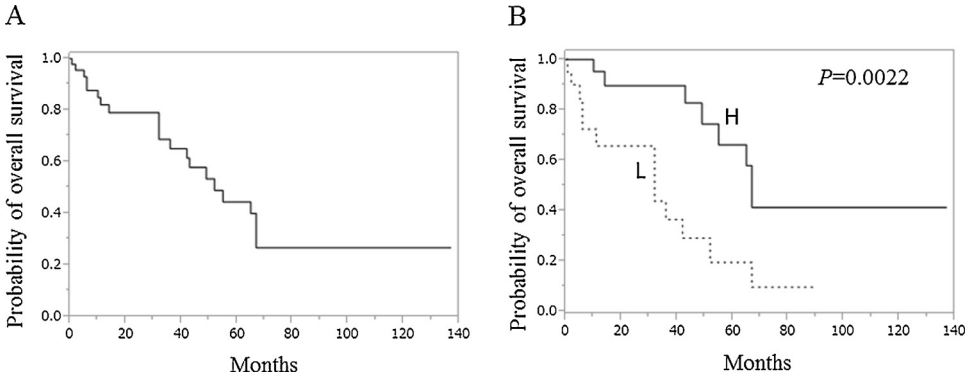

Fig. 1. Overall survival (OS) of 48 MDS patients and the impact of BCAS4 expression level on OS. (A) A Kaplan-Meier plot showed that the estimated median OS time was 52 months in the 48 MDS patients analyzed. The estimated survival rates at 1 year, 2 years, 3 years, and 5 years were 82.1%, 79.1%, 65.1%, and 44.5%, respectively. (B) The impact of BCAS4 expression on OS. Patients with high BCAS4 expression (median or higher) (H-group) had higher survival compared to those with low BCAS4 expression (less than the median) (L-group) (P = 0.0022, log-rank test). The estimated median OS times were 67 months (H-group) and 32 months (L-group). The estimated OS rates in the H-group and L-group were 95.2% and 65.8% at 1 year, 89.6% and 65.8% at 2 years, 82.7% and 36.5% at 3 years, and 66.2% and 19.5% at 5 years, respectively.

survival (OS) in 48 MDS patients, which suggests that the reduced expression of five genes (*MMP9, BCAS4, B4GALT5, SULF2*, and *ZNF335*) had a negative impact on OS. In particular, multivariable analysis in the Cox proportional hazards model showed decreased *BCAS4* expression and an inferior OS, which suggests that the expression level of BCAS4 could be a prognostic factor. To evaluate clinical significance of BCAS4 expression as a prognostic factor, more extensive analysis for BCAS4 expression in MDS patients is required. The *BCAS4* gene was cloned from breast cancer cells as an amplified sequence [14], and overexpression of the *BCAS4* gene is observed in breast cancer cells. The *BCAS4* gene encodes a 211-amino acid protein with no significant homology to known proteins. Function of this protein in hematopoiesis remains unclear. Molecular and biological analyses are required to evaluate function of BCAS4 in normal and malignant hematopoiesis

5. Conclusions

In conclusion, we analyzed the expression of 28 genes located within the CDR of del(20q), and expression of 8 genes was significantly reduced in MDS patients with chromosome 20 abnormalities compared to that of control subjects. In addition, expression of *BCAS4*, *ADA*, and *YWHAB* genes was significantly reduced in 20 MDS patients without chromosome 20 abnormalities. Five genes (*MMP9, BCAS4, B4GALT5, SULF2*, and *ZNF335*) were clinically significant. Based on these findings, functional analysis of selected genes is needed to elucidate the molecular and biological significance of reduced gene expression on the molecular pathogenesis of MDS. In addition, there may still be other candidate genes involved in MDS development within the CDR. We are carrying out expression analysis for additional set of genes within the CDR.

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Contributions. MS designed the work, analyzed the clinical and experimental data, and wrote the manuscript. MI, MO, and YW were involved in experiments, including material preparation and RT-PCR analysis. KY and NM collected the clinical data. TM and JT supervised this work and supported the manuscript preparation. All authors approved the final version of manuscript.

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