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Studies on the mechanisms of suppression in *Aspergillus nidulans*

Ⅱ. The characteristics of the suppressors for acriflavin resistant and nicotinamide auxotrophic phenotypes

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*Aspergillus nidulans*의 抑制의 遺傳子의 作用機作에 關한 硏究

Ⅱ. Acriflavin耐性과 nicotinamide要求性에 對한 抑制遺傳子의 特性

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ABSTRACT

From *Aspergillus nidulans*, six suppressor mutants, MS1-MS6, were isolated, and their characteristics were analysed. These were the suppressor mutants for acriflavin resistant and nicotinamide auxotrophic mutant phenotypes.

MS1, MS2, MS5 and MS6 had the single super-suppressors that suppressed two markers simultaneously. Three of these, MS1, MS5 and MS6, were linked to the chromosome Ⅳ, Ⅰ, Ⅱ respectiv ely, and MS2 was linked to one of the rest chromosomes, MS3 and MS6 mutants had both suppressors for acriflavin resistant marker and for nicotinamide auxotrophic marker.

In order to know the stability and efficiency of the suppressors, their reversion frequencies, that is, frequencies of losing the suppressibility, were analysed. Only MS3 and MS5 were reversed with high frequency. The four mutants didn't lose their suppressibilities, and this meant that the suppressors of these four were very stable and highly efficient.

The suppressor specificities of these mutants were tested for other mutant's phenotype marker.

One of the six suppressors, MS1, had the suppressor specificity for acriflavin resistant marker of 163 strain.

INTRODUCTION

Since the pioneer works of Bonnier (1927) on vermilion-duplication, the mechanisms of suppression were studied extensively. The elaborate studies have revealed that correction mechanisms through suppression occured during the transcription and translation steps of gene expression, and also level of final products

of the genes. The existence of several types of genetic suppression and their molecular bases were studied (Hartman & Roth, 1973).

These are nonsense suppression (Garen, 1970), missense suppression (Hill, 1975), frameshift suppression (Roth, 1974), and ribosomal suppression (Gorini, 1970).

In addition to procaryotes, the existence of the suppressors were reported in *Saccharomyces cervisiae* (Hawthorn & Mortimer, 1963, Piper*et al.* 1976, Singh *et al.* 1977, Singh *et al.* 1979, Mortimer & Hawthorn 1973, Liebman *et al.* 1976), and in Drosophila (Wosnick *et al.* 1977). The super-suppressors that could revert many different mutant phenotypes simultaneously were reported in *Saccaromyces cervisiae* first by Hawthorn *et al.*, and by others (Gilmore, 1976, Chalmers *et al.* 1971, Seal, 1972). In *Aspergillus nidulans*, Choi *et al.* (1979) studied on the super-suppressors of the various colour markers.

Many genes other than suppressors were revealed to have influence on suppression in both procaryotes and eukaryotes. These genes are the modifiers that enhance the effiency of the suppressors (allosuppressors), and lower the efficiency of the suppressors (antisuppressors).

In *Saccaromyces cervisiae*, many mendelian allosuppressors and non-mendelian extrachromosomal element as allosuppressor were reported (DougBradly *et al.* 1981, Bun-Ichiro *et al* 1979, Coppin-Raynal 1977, Liebman *et al.* 1976, Singh *et al.* 1979).

The antisuppressors that lower the efficency of the ribosomal-like suppression, and of tRNA mediated suppression were also investgatigated (Liebman *et al.* 1979, Laten *et al.* 1978, Anita *et al.* 1980).

In this paper, the isolation of suppressor mutants, the identification of the super-suppression of the suppressors, the stability and efficiency of the suppressors and the specificity of the suppressors were discussed.

MATERIALS AND METHODS

1. Strains: The haploid strains of 154, 475, 163 from FGSC were used in this study. The suppressor mutants were isolated from 154 strain by UV irradiation.

Strains 475 and 163 were used for genetic analysis of the mutants. The genotypes and the result of marker test were shown in Fig. 1. and Table Ⅱ. respectively.

2. Growth media: *Aspergillus* culture media were prepared as described by Harsanyi *et al.* (1977). To restrict colony size, sterilized 0.06 ~0.08% sodium desoxycholate was added to complete media.

In preparing for acriflavin containing plates, 0.005% (w/v) of acriflavin solution sterilized by membrane filtration (0.02μm, Millipore) was added to the sterilized complete media (Roper & Kafer, 1957).

For genetic analysis, specific supplements were added to minimal medium.

3. UV-mutagenesis: Six suppressor mutants were isolated by UV-irradiation. To determine the proper UV-irradiation time, the survival rate of conidiospores after UV-irradiation was examined (Table Ⅰ). The 5% survival rate was obtained after 10 minutes irradiation with 6~10erg/mm^2/sec UV lamp.

The conidia were harvested from the CM plates incubated for 4 days at 37°C. 0.01% Tween 80 solution was used to separate conidia from mycellium. Conidia suspension containing 10^6~10^7 conidia/m*l* on the sterilized petridish was irradiated for 10 minutes. The U.V. irradiated conidia were planted on the acriflavin containing plate, and incubated for 5 days. Acriflavin resistant colonies were isolated from the plates. Their acriflavin resistance was conformed three times.

As above-mentioned procedure, acriflavin re

154 : wdE20 biA1 / IR — wA2 / IIL — cnxE16 / IIR — sC12 / III — meth / IV — nicA2 / V — lacA1 / VI — choA1 / VII — chaA1 / VIII

163 : suA1ad20 / IL — yA2 adE20 / IR — AcrA1 / IIL — phenA2 / III — pyroA4 / IVR — lysB5 sB3 / V VI — nicB8 / VII — coA1 / VIIIL

475 : fpaB37 galD5 suA1adE20 riboA1 anA1 / IL — pabaA1 yA2 adE20 biA1 / IR — sD85 fw / VIIIR

Fig. 1. Genotypes of the strains used in this study.

Requirement; ad: adenine, paba: p-aminobenzoicacid, bi: biotin, pyro: pyridoxine, cho: cholin, ribo: riboflavin,
phen: phenylalanine,
an: thiamin-Hcl, lys: lysin
Inability to utilize; cnx: nitrite, s: sulfate Resistance; Acr: acriflavin
Chromosome number; I, II, III, IV, V, VI, VII, VIII
R: right from centromere
L: left from centromere

Table 1. The UV-survival rate of 154

time(min) / dilution rate	0(control)	4	6	8	10	12
10^{-2}				503	166	47
				526	173	48
10^{-3}	245	153	102	61	17	5
	259	161	105	55	15	7
10^{-4}	26	15	10	7	1	0
	29	18	13	11	2	0
10^{-5}	5	1	1			
	8	3	3			
10^{-6}	0					
	0					
No. of conidiospores/ml	2.6×10^{9}	1.5×10^{6}	1.0×10^{6}	5.0×10^{5}	1.6×10^{5}	5.0×10^{4}
% of survival	100	60	40	20	6	2

sistant mutants were treated with the second UV-mutageneiss to induce suppressor mutation. These UV-irradiated conidia were incubated on the plates free of nicotinamide for 4days, and then nicotinamide autotrophic conidia were isolated. These nicotinamide prototrophic conidia were tested for the sensitivity to acriflavin on the acriflavin-plates with replica-method. In this step, acriflavin sensitive, nicotinamide prototrophic colonies were isolated.

4. Marker test: As prerequisite experiment, marker test was done before main experiment. Auxotrophic markers were tested on the minimal media plate with supplements except the nutrient for the tested marker. The distinct markers from the results of the marker test were used for this study. The results of the marker test were shown in Table Ⅱ.

5. Genetic analysis: Segregation rates of ascospores were used in genetic analysis of the mutants. Ascospores were obtained from perithecium formed from 3 week-old heterokaryon in the sealed petridish. Heterokaryon was induced by the method of Pricard (1968). Ascospores selected as recombinant types from karyogamy between two parents were analysed.

RESULTS AND DISCUSSION

1. Isolation of mutants: The UV-survival rate was shown in Table Ⅰ.

The fluence of UV lamp was 8erg/mm²/sec. 10 minutes was required for about 5% survival level of irradiation.

To show clearly the procedures of the mutant isolation, the mutation steps and the mutant's phenotypes in each step were described (Fig. 2). By the lst mutation, fifteen MSo mutants were isolated form 154. All MSo mutants has primary mutation phenotypes for acriflavin and nicotinamide. To obtain MS mutants, from 2nd mutation of the MSo nicotinmide prototrophic mutants were isolated firstly. Secondly, these 15000 of nic^+ mutants were tested for acriflavin sensitivity. Only twelve among these mutants were sensitive to acriflavin.

Twelve mutants were checked for the two marker three times. Finaly, six MS mutants were selected. These were the mutants whose two phenotypic markers were reverted to wild type.

Six MS mutants were named MS1, MS2, MS3, MS4, MS5 and MS6. All the strains used in this study were tested their markers, and Table Ⅱ. showed the results.

MSo from which MS1 was derived was designated MSo 1 and its acriflavin resistant marker was Acr1. The other five MSo were named as same way and their acriflavin marker, too.

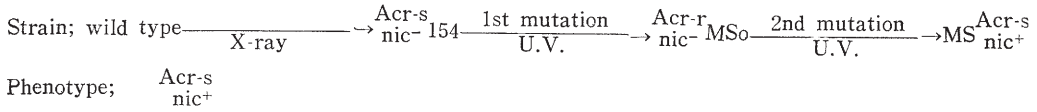

Fig. 2. Mutation steps and the mutant's phenotypes.
Acr-s: sensitive to acriflavin Acr-r: risistant to acriflavin nic^+: nicotinamide prototrophic
nic^-: nicotinamide auxotrophic U.V.: ultraviolet light

2. Linkage relationship between acriflavin resistant markers and white colour marker:

In MSo mutants, it was revealed whether their acriflavin markers were linked to white colour marker on the chromosome Ⅱ or not. The results were shown in Table Ⅲ. If 50% of the acriflavin resistant ascospores were white, the Acr marker were not linked to white colour marker, and if 100% of the acriflavin resistant ascospores were white, the markers were linked to white colour marker. In MSo 2, MSo 3, and MSo 4, their Acr2, Acr3, Acr 4 markers were not linked to white colour marker. In MSo 1, MSo 5, MSo 6 mutants, their Acr1, Acr5, and Acr6 markers were linked to white colour marker.

3. Exsistence of the suppressors and the linkage relationships between the suppressors and the suppressed: In suppressor mutant, though it had wild or peudo-wild phenotype, it still maintained primary mutation. It could be a good proof for existence of suppressor that some of the segregants between suppressor mutant and true wild type had primary mutation phenotype.

In order to show the existence of the suppressors in MS mutants, MS mutants and 475 that was true wild type for acriflavin sensitive and nicotinamide prototrophic were crossed, and their segregants were analyzed.

The result was shown in Table Ⅳ. All MS mutants had suppressors for acriflavin resistant marker and for nicotinamidea uxotrophic marker, since acriflavinresistant and nicotinamide auxotrophic segregants were resulted from all crosses betweenMS mutants and 475.

The suppressor for acriflavin resistant marker was named su-Acr, and the suppressor for nicotinamide, su-nic. The su-Acr of MS1 was su-Acr1, and su-Acr of MS2, was su-Ac r2, and so on.

Table Ⅳ. also showed the linkage relationships between the suppressors and the suppressed. When 25% of segregants had primary mutant phenotype, the suppressor was unliked

Table 2. Results of the marker test

markers / strain	ad	bi	cnx	sul	meth	nic	cho	lys	phe	Acr	pyro	ribo	paba	an
154	+	+	+	+	−	−	+	##	##	−	##	##	##	##
MS1	+	+	+	+	−	##	+	##	##	−	##	##	##	##
MS2	+	+	+	+	−	##	+	##	##	−	##	##	##	##
MS3	+	+	+	+	−	##	+	##	##	−	##	##	##	##
MS4	+	+	+	+	−	##	+	##	##	−	##	##	##	##
MS5	+	+	+	+	−	##	+	##	##	−	##	##	##	##
MS6	+	+	+	+	−	##	+	##	##	−	##	##	##	##
475	##	+	##	+	+	##	##	##	##	−	##	−	+	+
163	##	##	##	##	##	##	##	−	−	+	+	##	##	##

*##; good growth +; bad growth −; not growth

Table 3. Linkage of Acr1-Acr6 to white colour marker.

crossed strains	selected markers for recombinant type	Acr-resistant segregants		% of white, Acr-resistant segregants
		white	non-white	
MS.1×475	ribo$^+$ meth$^+$	68	3	97.0
MS.2×475	ribo$^+$ meth$^+$	51	54	48.0
MS.3×475	ribo$^+$ meth$^+$	69	65	51.5
MS.4×475	ribo$^+$ meth$^+$	72	80	47.3
MS.5×475	ribo$^+$ meth$^+$	70	5	94.1
MS.6×475	ribo$^+$ meth$^+$	82	7	92.1

Table 4. Acr-resistant segregants and nic$^-$ segregants from cross between MS mutants and 475

crossed strain	selected markers	total number	Acriflavin resistant		nicotinamide auxotroph	
			number	%	number	%
MS1×475	ribo$^+$ meth$^+$	105	46	45.5	49	48.4
MS2×475	ribo$^+$ meth$^+$	224	64	28.7	58	25.9
MS3×475	ribo$^+$ meth$^+$	104	24	23.1	6	5.77
MS4×475	ribo$^+$ meth$^+$	120	55	45.8	29	24.2
MS5×475	ribo$^+$ meth$^+$	160	10	6.3	7	4.4
MS6×475	ribo$^+$ meth$^+$	131	22	16.3	39	27.5

to the suppressed. When all of the segregants had wild phenotype, the suppressor were linked to the suppressed.

Based on this expectation, su-Acr2, su-Acr3 were were unlinked to Acr2, Acr3 respectively and su-nic2, su-nic4, su-nic6 were unlinked to nic marker respectively.

In MS6, the frequency of the acriflavin resistant segregants was relatively high, this result suggested that su-Acr6 was slightly linked to Acr6 marker, that is, the map distance between two genes was long to compare with the case of su-Acr5 and Acr5, su-nic3 and nic, su-nic5 and nic.

In the case of su-Acr5, su-nic3 and su-nic5, another linkage relationships had to be considered. It might be possible that they were linked to ribo marker on the chromosome I,

because all the ascospores analysed in Table Ⅳ. was selected by the ribo marker and had chromosome Ⅰ of 154.

Su-Acr1, su-Acr4 and su-nicl were linked to the meth marker on the chromosome Ⅳ. This was because 50% of the segregants showed the primary mutation phenotype only when the suppressor didn't exist in any segregants.

Table Ⅴ. showed that su-Acr3 and su-nic6 were linked to white colour marker on the ch romosome Ⅱ respectively. The su-Acr3 and su-nic6 that were unliked to their Acr3 and nic marker were found to be linked to white marker on the chromosome Ⅱ.

Table 5. Linkage relationship of suppessors and white colour marker.

crossed strain	selected markers	total number	Acr-r		nic⁻	
			No.	%	No.	%
MS3×475	ribo⁺meth⁺ white	53	2	3.8	*—	*—
MS6×475	ribo⁺meth⁺ white	67	*—	*—	10	14.7

*—; unexamined

Table 6. The result of crossing between MS mutants and 475 to confirm the existence of super-suppressors.

crossed strain	selected marker	total number	nic⁺	nic⁻
MS1×475	ribo⁺ meth⁻ white Acr-r	43	22	21
MS2×475	ribo⁺ meth⁺ Acr-r	50	23	27
MS6×475	ribo⁺ meth⁺ white Acr-s	48	42	6

4. Existence of the super-suppressors and their linkage relationship: The exsistence of the super-suppressors meant the identity of su-Acr and su-nic in the mutants.

In MS4, there was no super-suppressor, because su-Acr4 and su-nic4 were distinct suppressors that were located on different chromo somes.

As shown before, su-Acr1 and su-nic1 were linked to meth marker on the chromosome Ⅳ, and su-Acr6 and su-nic6 were linked to white colour on the chromosome Ⅱ. These results have implicated the strong possibility of exis tence of the super-suppressor.

In order to prove this, the MS mutants were crossed with 475 and their segregants were analyzed. The result was shown in Table Ⅵ. In the case of cross between MS1 and 475, All the segregants had Acr1 marker, and did n't have su-Acr1. 50% of the selected segregants were nic, and this meant su-Acr suppressed nic marker, too. Su-Acr1 and su-nic1 were the same suppressor, and it was super-suppressor.

In the case of cross between MS2 and 475, the selected segregants didn't have su-Acr2, and the half of selected segregants were nic⁺ This indicated that su-Acr2 was the super-suppressor, the three-fourths of the segregants were nic⁺.

In the case of cross between MS6 and 475, all the selected segregants had su-Acr6. Most of the segregants were nic⁺, this meant that su-Acr6 was the super-suppressor that could suppress nic marker simultaneously.

In MS3 and MS5 mutants, not only the existence of the super-suppressors but also the existence of the distinct su-acr and su-nic was possible (Table Ⅵ).

5. Reversion of the suppressor mutant:

To analyze the stabilities of the suppressors, the mutants were mutagenized again (the 3rd mutation), and then the loss of their suppressibility was examined.

The loss of their suppressibiilty indicated that the mutants failed to suppress the primary mutant phenotype. There were two possibilites for the mutantsto regain the primary mutant phenotypes. First, if the MS mutants lost their suppressibilities, their primarymutant phenotypes, acriflavin resistant and nicotinamide auxotrophic, would appear. Second, those mutants should show the primary mutant phenotypes when new mutation arose in

the gene or genes for acriflvuin resistant and nicotinamide auxotrophic phenotype while the suppressors still could suppress the primary mutant phenotypes (Richard, E., *et al.* 1980). But the result in Table Ⅶ. excluded the second possibility. In all six MS mutants, genes for acriflavin resistant and nicotinamide auxo trophic phenotypes had equal possiblity of being mutated. As shown in Table Ⅷ, MS1, MS2, MS4, and MS6 were reverted at relatively high frequencies.

MS1, MS2, MS4 and MS6 mutants didn't lose their suppressibilities, This seemed to be because the suppressors of these mutants were very stable and highly efficient. It could be possible that MS3 and MS5 mutants were rev erted through the mutation of their specific suppressors themselves, or the interactions be tween suppressors and other mutated antisuppressor-like genes relatedto the suppressors.

Table 7. The reversion frequency of the MS mutants.

Strain	No. of tested spore	Acr-r	nic⁻
MS1	9.3×10^4	0	0
MS2	2.8×10^4	0	0
MS3	2.3×10^5	102	1
MS4	5×10^5	0	0
MS5	3.6×10^5	57	56
MS6	4.2×10^6	0	0

Table 8. Co-reversion frequency of the suppressor mutants.

Strain	revertant			% of co-reversion
	total	Acr-r	nic⁻	
MS3	102	102	1	0.89
MS5	57	57	56	98.2

In yeast, six partially dominant antisuppressor were obtained that reduce the efficiency of two omnipotent yeast suppressors (Liebman *et al.* 1979). They were specific for ribosomal suppression, and had no effect on tRNA-like suppressor. Antisuppressors specific for the tRNA suppressors were also discussed(Thuriaux *et al.* 1975). In Yeast, the mutants which fails to excise intervening sequences from precu ssor tRNA were revealed to lose their suppressibility of the tRNA mediated suppression(Anita *et al.* 1980). The antisuppressors caused chan ges in ribosomal proteins, tRNA modification and processing, or changes in other componen ts of the protein-synthesizing machinery.

It was very important that the reversion of the suppressors conformed the existence of the super-suppressors. Co-reversion of the suppressor mutants were shown in Table Ⅷ.

From the result of Table Ⅵ, the existence of the super-suppressor in MS3 and MS5 was uncertain. If the two markers were suppressed by single super-suppressor, they were co-reve rted to primary mutation through the mutation that caused the loss of suppressibility. In MS3, it could be explained that there existed su-Acr 3 and su-nic3 independently, since their co-reversion frequencies were very low, and MS5 mutants had the super-suppressor, since the two markers were co-reverted.

6. The specificity of the suppressors to other mutation: To test the specificity of the suppres sors to other marker, the AcrAl marker of 163 was chosen. The analysis of the ascospores from the cross between MS mutants and 163 was shown in Table Ⅸ.

All the non-white segregants had AcrAl marker of one of their parents, 163. If AcrAl marker couldn't be suppressed, all the segreg ants were acriflarvin resistant. The suppressors in MS2, MS3, MS4 and MS5 mutants had no specificity to AcrAl marker, because they couldn't suppress AcrAl marker. In only MS1 mutant, the suppressor had specificity to AcrAl marker, because 50% of the segregants were acrflavin sensitive.

In *Aspergillus nidulans*, the specificity of adenine suppressors for mutations in other

genes were discussed (Jerzy *et al.* 1979). They revealed that adenine suppressors could suppress many other mutations in other loci than adenine.

And Choi *etal.* (1978) studied on the super-suppressors that could suppress four nonallelic colour and one adenine auxotrophic mutation.

The most important property of nonsense suppressors is their allele-specificity but non-specificity to locus. Robert *et al.* (1978) also studied the allele-specific suppressor mutation in *Aspergillus nidulans*.

The relationships between the suppressors and the suppressed were summarized in Fig. 3. Their locations on the chromosoms were described, and the antisuppressor activities that were induced by UV-irradiation were shown (Fig. 3(a), (b).

Table 9. Analysis of thsegregants between MS mutants and 1e3.

crossed strain	selected markers	tota number	Acriflavin resistant	Acriflavin sensitive
MS1×163	lys$^+$, non-white	254	133	121
MS2×163	lys$^+$, non-white	333	312	21
MS3×163	lys$^+$, non-white	187	178	9
MS4×163	lys$^+$, non-white	230	218	12
MS5	lys$^+$, non-white	262	243	19

Fig. 3. (a)

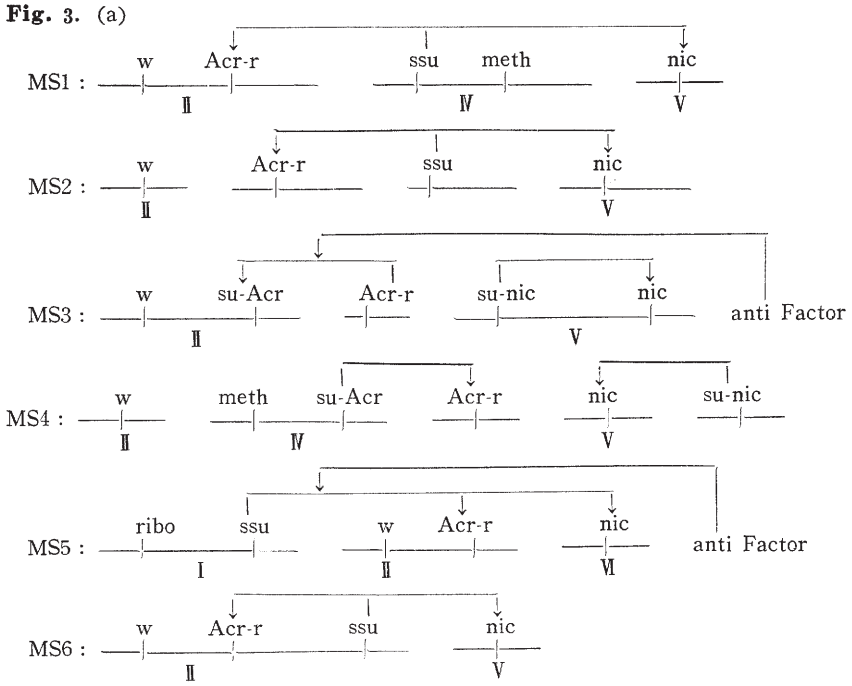

Fig. 3. (b)

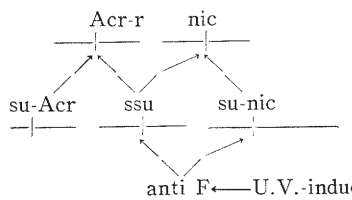

Fig. 3. The relationships between the suppressors and the suppressed.
(a) linkage relationships (b) summarized scheme

摘 要

*Aspergillvs nidulans*에서 억제 유전자를 가진 6개의 돌연변이주를 분리하여, 그 특성을 분석하였다.

이들 MS1～MS6의 변이주는 acriflavin내성과 nicotinamide요구성에 대한 억제 유전자를 갖고 있었다.

이들중 MS1, MS2, MS5, MS6의 4변이주는 두 돌연변이 표현형을 동시에 억제하는 단일억제 유전자, 즉 초억제 유전자를 가지며, MS1에서는 염색체 Ⅳ에, MS5에서는 염색체 Ⅱ에 각각 연관되어 있었다.

MS3, MS4변이주는 acriflavin내성에 대한 억제 유전자와 nicotinamide 요구성에 대한 억제 유전자를 독립적으로 다 갖고 있다.

억제유전자의 안정성과 효율을 알아보기 위해 reversion빈도, 즉 억제능의 상실빈도를 조사하였다.

MS3와 MS5변이주만이 높은 빈도를 억제능을 잃어버렸고, 나머지 4개는 억제능을 유지하였다.

이것은 I MS1, MS2, MS4, MS6의 억제 유전자는 매우 안정하며, 효율적이라는 것을 의미한다.

다른 돌연변이 표현형에 대해 각 돌연변이주의 억제 유전자 특성을 조사하였다. 그결과 163변이주의 acriflavin 내성에 대해 억제특이성을 가진것은 MS1변이주 하나였다.

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