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Research Paper

Stratification of Outbred ICR Mice Stocks by Genetic Variation

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ABSTRACT

The mouse is a commonly used animal in life science studies and is classified as outbred when genetically diverse and inbred when genetically homogeneous. We investigated whether outbred Institute of Cancer Research (ICR) mice stocks can be classified using SNP variation, and determined the specific genetic variation in the Korl: ICR strain. We also genotyped three ICR stocks at 1319 SNP loci; 307 genotypes were identified exclusively for each stock (chi-square test, df = 6, $P < 0.05$) and the number of loci with stock-specific alleles were 22 in A: ICR, 13 in B: ICR, and 7 in Korl: ICR (minor allele frequency ≥ 5%). Principle component analysis confirmed three genetically distinct stocks and Identity by Descent (IBD) and genomic best linear unbiased prediction analysis verified the genetic distance existing among the three ICR stocks. These results showed that outbred ICR mice stocks can be distinguished using SNP variation. Despite the difference in genetic variation between ICR stocks, we suggested that discrepancies in biological responses to external stimuli would be minimal due to genetic heterogeneity among stocks, rare homozygous mutants and scarcity of the regional mutations affecting genetic expression.

Key words: SNP, genetic drift, Korl: ICR stock, drug-testing, rodent.

INTRODUCTION

Laboratory mice are model species used in life sciences research and drug development. In particular, they are useful animal models for testing the potency and safety of drugs in pre-clinical trial stages. Laboratory mice are classified into two types, inbred strains and outbred stocks, according to the absence or presence of genetic variation (Chia et al., 2005). Inbred strains are bred by sib-mating for at least 20 generations and are genetically homogeneous (Staats, 1964). As such, characteristics of the genetic architecture are well-known and researchers use these genetic characteristics to manage source colonies (Lindblad-Toh et al., 2000; Waterston et al., 2002; Wade et al., 2002; Graber et al., 2006; Frazer et al., 2007; Petkov et al., 2007).

In contrast, outbred mice are bred using methods such as Poiley's system, Falconer's system, and the HAN-rotational system to specifically maintain maximum heterozygosity and preserve genetic diversity, such that each outbred mouse is genetically unique (Rapp, 1972; Nomura and Yonezawa, 1996; Festing, 1999; Honda et al., 2004; Holt et al., 2004; Windig and Kaal, 2008). Occasionally, the extent of inter-individual biological variation in responses of genetically diverse mice to experimental tests makes it challenging to achieve statistically valid results. However, this animal model is more realistic and has greater applicability for testing drugs for a genetically diverse human population (Festing, 2010). Nevertheless, information on the genetic variation in outbred laboratory mice is rare compared to that for inbred strains (Aldinget et al., 2009).

The most popular stock of outbred mice is the Institute of Cancer Research colony known as ICR used in toxicology, oncology, pharmacology and pharmaceutical products safety testing (Rice and O' Brien, 1980; Cui et al., 1993; Chia et al., 2005; O' Connor et al., 2009; Zhong et al., 2009). ICR mice derived from two males and seven females, known as

Table 1. Comparison of minor allele frequencies among three ICR stocks.

MAF (%)	#SNPs		
	A:ICR	B:ICR	Korl: ICR
0	494	745	424
<5	74	68	135
5-20	257	201	286
≥20	494	305	474
Total	1319	1319	1319

Abbreviations: MAF, minor allele frequency; SNP, single nucleotide polymorphism.

'Swiss' mice, that were crossed in 1926 and then adopted by the Institute of Cancer Research in 1947 (subsequently merged with "Fox Chase" in 1974). Commercial production of ICR by companies began in 1959 and the strain was made available to academic and commercial breeders (Lynch, 1969; Rice and O' Brien, 1980; Chia et al., 2005).

Currently, a number of worldwide breeders produce their own ICR stocks for commercial or academic purposes. Differences between ICR stocks have arisen in newly established stocks (founder effects) in different places worldwide and those that have been bred for a long time (drift effects). These differences have even been observed in identical stocks maintained by the same breeder.

The National Institute of Food and Drug Safety Evaluation (NIFDS) in Korea has an established ICR stock that has been used for the last 50 years, named "Korl: ICR" in the Guidelines for Nomenclature of Mouse and Rat Strains (Snell, 1941). We investigated the possibility of identifying different ICR stocks by using their unique genetic variation and whether genetic variation between stocks explains variation in biological responses of different ICR stocks.

MATERIALS AND METHODS

Animals

Three-week-old A: ICR and B: ICR were purchased from two different commercial animal breeding laboratory companies in Korea. Korl: ICR is the resident stock of National Institute of Food and Drug Safety Evaluation (NIFDS). All mice were bred in the same conditions: temperature 22 ± 1°C, humidity 50 ± 10% and light 12/12 h light/dark cycle and had free access to drinking water and a standard diet *ad libitum*. All aspects of the study were approved by the NIFDS Institutional Animal Care and Use Committee (IACUC) and the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC-I).

Genome-wide SNP analysis

Genomic DNA was extracted from tail clippings of 48 A: ICR, 48 B: ICR and 96 Korl: ICR. Lysis the tail at 55°C for overnight and genomic DNA precipitated with isopropanol as previously described by Laird et al. (1991). A total of 192 samples were genotyped using Mouse Medium Density (MD) Linkage Panel (Illumina®) with 1449 SNP loci.

Population stratification

Information from 1319 SNPs was analyzed, excluding those found on the sex chromosomes. Population stratification was examined using principal components analysis (PCA) using the Golden Helix SNP and Variation Suite (SVS 8, software; Bozeman, MT, USA). Phylogenetic trees were constructed using the PHYLIP program dnapars (phylogeny inference package) version 3.695 (http://evolution.genetics.washington.edu/phylip.html) based on alignment of SNPs. The PHYLIP program neighbor was used to draw a phylogenetic tree from Fst values. Identity by Descent (IBD) allele-sharing proportions, genomic best linear unbiased prediction (GBLUP) and the fixation index Fst were analyzed to estimate the genetic distance and genomic relationships between samples using Golden Helix SNP and Variation Suite (SVS 8, software; Bozeman, MT, USA).

Statistics

Comparative analysis of allele frequencies in ICR stocks was performed using chi-square test.

RESULTS

Genetic diversity in 1319 SNP loci of ICR stocks

Mouse MD Linkage Panel array showed that the number of SNPs with more than 95% call rate was 1407. Excluding 88 SNPs found on sex chromosomes, 1319 SNPs were used in the analysis. The number of SNPs in which the minor allele frequency (MAF) was 0 was 494 in A: ICR, 745 in B: ICR, and 424 in Korl: ICR (Table 1). In addition, the number of SNPs in which MAF was > 20% was 494 in A: ICR, 305 in B:

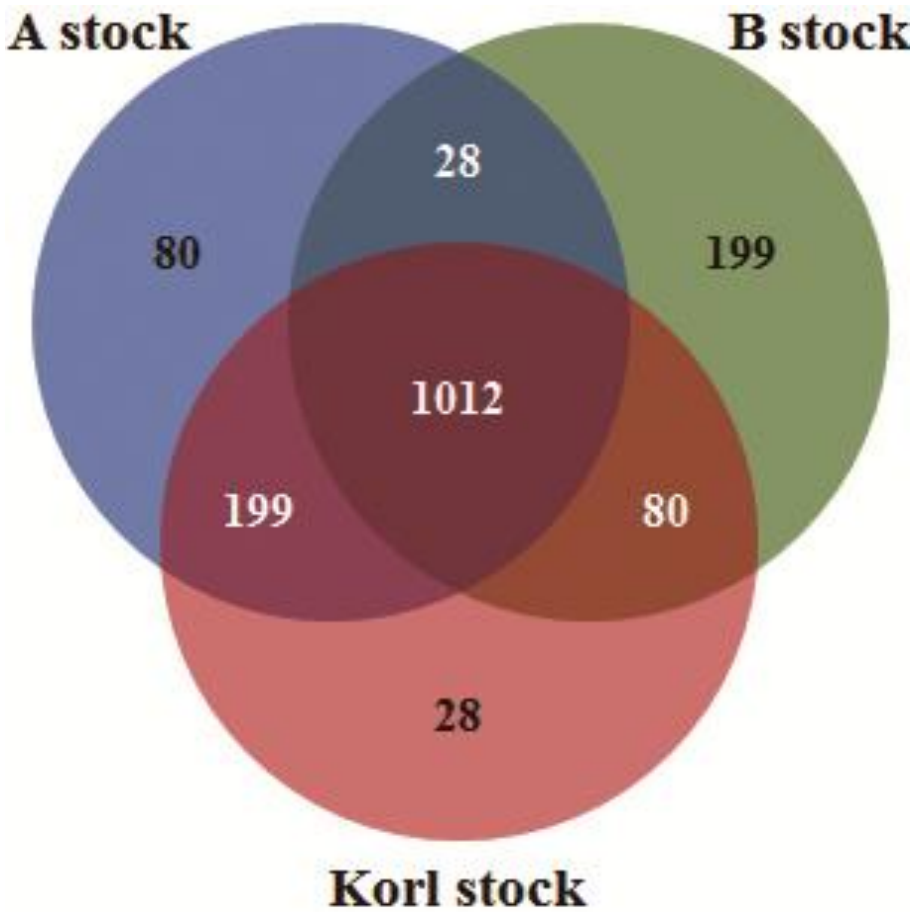

Figure 1. Venn diagrams illustrating the overlap of SNP genotypes for three different ICR stocks.

ICR and 474 in Korl: ICR (Table 1).

The number of exclusive loci in each stock was 80 in A: ICR, 199 in B: ICR, and 28 in Korl: ICR (data not shown). There were also 1012 loci without stock-specific alleles (Figure 1). We classified 307 SNPs with unique genotypes in each stock into four types (non-synonymous, synonymous, non-coding, and intergenic). We also grouped them into ≥ 5% MAF and < 5% MAF, according to their frequency in the intergenic region among unique SNPs: 48 in A: ICR, 108 in B: ICR and 17 in Korl: ICR. The number of SNPs within genes was 32 in A: ICR, 91 in B: ICR and 11 in Korl: ICR. Of these, the number of SNPs located in coding regions was 4 in A: ICR (including 2 non-synonymous and 2 synonymous), 13 in B: ICR (including 6 non-synonymous and 7 synonymous) and 0 in Korl: ICR. The remaining SNPs were found in non-coding regions (Table 2). There was a total of 42 SNP loci with unique alleles (MAF ≥ 5%): 22 A: ICR stock-specific, 13 B: ICR stock-specific and 7 Korl: ICR stock-specific (Table 3).

Genetic population stratification

Principal component analysis (PCA) was performed using 1319. Figure 2 shows the results of principal components 1 (PC1) versus 2 (PC2) plotted. Definitive clusters of A: ICR, B: ICR, and Korl: ICR were clearly visible, indicating that ICR stocks from different breeders had unique genetic variation. In addition, to visualize the genetic relationships between the three ICR stocks in more detail, the IBD and GBLUP distances were presented as heat maps (Figure 3). From these distance matrices, one can infer the nature of the identified stock differences and the genetic relationships between them. The distance between ICR stocks are shown in green that is closer, in red that is farther. This indicated that B stock has small genetic diversity as compared with A stock and Korl stock and there is large genetic diversity between A stock and B stock. In addition, Korl stock is genetically distinct from A and B stock.

DISCUSSION

Studies reported that genetic components of offspring from different outbred ICR stocks are not identical (Yamada et al., 1979; Hayakawa et al., 1980; Rice and O'Brien, 1980; Waltz, 2010). For example, it was previously reported that the Es-1 gene showed differences in gene frequencies (Hayakawa et al., 1980). This might be a result of genetic drift, which

Table 2. Summary statistics to distinguish SNPs in each ICR stock.

#distinguishing SNPs	SNP type				Total
	Non-synonymous	Synonymous	Non-coding	Intergenic	
A:ICR	2	2	28	48	80
(MAF ≥ 5%)	(1)	(1)	(9)	(12)	(23)
(MAF < 5%)	(1)	(1)	(19)	(36)	(57)
B:ICR	6	7	78	108	199
(MAF ≥ 5%)	(1)	(2)	(6)	(4)	(13)
(MAF < 5%)	(5)	(5)	(72)	(104)	(186)
Korl: ICR	0	0	11	17	28
(MAF ≥ 5%)			(2)	(5)	(7)
(MAF < 5%)			(9)	(12)	(21)

Abbreviations: MAF: Minor allele frequency; **SNP:** Single nucleotide polymorphism; **# distinguishing SNPs:** Number of distinguishing SNPs in each ICR stock; Non-synonymous: non-synonymous SNPs (changes in the amino acid sequence of a protein) within the coding regions; **Synonymous:** Synonymous SNPs (do not affect the protein sequence) within the coding regions; **Non-coding:** SNPs within non-coding regions of genes; Intergenic: SNPs in the regions between genes; **MAF ≥ 5%:** SNPs with minor allele frequency of 5% or greater in each ICR stock (other stocks are MAF < 5%); **MAF < 5%:** SNPs with minor allele frequency of less than 5% in each ICR stock (other stocks are MAF ≥ 5%).

occurs spontaneously over time in small populations, or due to environmental influences, such as food or different breeding methods. Commercial companies that breed ICR stocks overcome these issues by periodically establishing a new colony. Although, this can contribute to ensuring the homogeneity of offspring from the same brand stock, it has limited power to resolve the differences between different stocks. Therefore, animal breeders used in a particular study are labeled to enable appropriate comparison of results from different studies. Despite this, scientific evidence of the validity of comparison of different studies is lacking.

Recently, the development of genomics technology enabled the analysis of genome-wide genetic variation. To analyze genetic components of outbred mice, we analyzed the genetic variation between three ICR stocks from 1449 SNPs identified using multiplex genotyping. Population stratification between outbred ICR stocks using SNP information was identified, confirming the suitability of this method for distinguishing between ICR stocks, which was previously not reported. A: ICR and B: ICR stocks purchased from different commercial breeders and the offspring of Korl: ICR stock bred by NIFDS were completely distinguished on the basis of SNP variation (Figure 2). This confirmed that it is possible to apply this method to distinguish the commercial breeding stock that offspring are derived from and whether there are further sub-divisions with the stocks. In particular, it is notable that Korl: ICR, which has been bred through rotation-breeding for over 50 years has completely different genetic variation from offspring of other stocks, identifying it as a new stock with unique alleles and significantly different allele frequencies.

These results are similar to previous studies showing that outbred ICR have relatively consistent genetic diversity within a stock that can persist in isolation for a long time. We were unable to speculate in this study on the length of time required or the method necessary for the differentiation of ICR stocks.

Unfortunately, genetic variation of outbred mice in each stock did not explain differences in biological responses and physiological function by external stimuli, thus, we could not determine whether experimental results would differ depending on the ICR stocks used. However, it is ideal that researchers would consider genetic information of the stock or breeder of outbred mice that were used when interpreting their own results or comparing with results of other studies.

Throughout this study, we suggested that it is preferable to consider the genetic variation of various outbred stocks produced and supplied by various breeders when interpreting biological responses by experimental material. In addition, it would be useful for resource management to apply the characteristics of genetic components to the identification of stocks in breeding organizations. Considering that ICR stocks are produced by many breeders worldwide and are used without loss of the essential characteristics and genetic variation of ICR, the difference in genetic variation between stocks found in this study is of use for distinguishing breeders.

In all likelihood, not all of the 1319 SNP loci used in this study are necessary to distinguish an outbred ICR stock. Additional studies may help to reduce the number of loci expressing genetic mutations to distinguish stocks through simple and accurate population stratification. We could not find a specific locus or stock-specific genetic characteristic that distinguished each stock in this study and which analyzed genotyping rather than sequencing information.

Additionally, as this information was obtained from the offspring of currently existing stock, it is unrealistic to expect the same results from the offspring of future generations due to the possibility of spontaneous mutations,

Table 3. List of SNPs as unique alleles in specific stocks.

SNP ID	Chr.	Position (bp)	Type	Gene	Allele	MAF (%)		
						A:ICR	B:ICR	Korl: ICR
A: ICR stock-specific								
rs13476636	2	91,539,303	Non-synonymous	Zfp408	G/A	36.5		
rs8260975	7	33,835,314	Synonymous	Kcnc1	T/G	14.6		
rs13479830	8	72,013,995	Non-coding	Large	T/C	25.5		
rs13479863	8	82,188,194	Non-coding	Rnf150	G/T	44.8		
rs13480014	8	118,001,545	Non-coding	Cdh13	C/T	14.6		
rs13480103	9	23,359,729	Non-coding	Bmper	T/C	21.9		
rs3707097	13	33,614,779	Non-coding	Slc22a23	T/C	27.1		
rs3725637	18	34,867,922	Non-coding	Pkd2l2	G/T	18.8		
rs3699816	18	39,756,682	Non-coding	Arhgap26	C/T	20.8		
rs13483368	18	54,949,689	Non-coding	Redrum	C/A	13.5		
CEL-1_105423103	1	105,423,103	Intergenic		T/C	42.7		
rs3685919	1	109,634,975	Intergenic		T/C	27.7		
rs3722345	2	80,509,747	Intergenic		G/A	32.3		
rs13478388	5	89,674,255	Intergenic		C/T	29.2		
rs13478719	6	38,474,383	Intergenic		C/T	31.3		
rs4226520	7	18,758,740	Intergenic		T/C	20.8		
rs3666398	9	56,790,950	Intergenic		T/C	20.8		
rs6190748	10	55,832,573	Intergenic		T/C	25.0		
rs6190775	11	6,306,994	Intergenic		C/T	20.8		
rs13481983	13	100,181,409	Intergenic		C/T	22.9		
CEL-17_39772541	17	39,772,541	Intergenic		A/G	12.5		
rs13483319	18	41,351,739	Intergenic		C/T	33.3		
B: ICR stock-specific								
rs13476454	2	41,244,144	Non-synonymous	Lrp1b	G/A		39.6	
rs3713616	1	74,900,046	Synonymous	Usp37	A/G		18.8	
rs13481556	12	75,962,840	Synonymous	Slc39a9	C/T		18.8	
rs6322485	1	63,649,681	Non-coding	Zdbf2	A/T		11.5	
rs13476439	2	38,071,109	Non-coding	Dennd1a	T/C		21.9	
rs3723643	2	122,067,606	Non-coding	Duox1	T/A		57.3	
rs3712541	4	59,103,430	Non-coding	Snx30	A/G		62.5	
gnf07.013.809	7	10,926,083	Non-coding	Klc3	T/C		11.5	
rs6372901	8	63,043,201	Non-coding	Tll1	T/C		28.1	
rs6335414	3	53,103,565	Intergenic		C/T		35.4	
CEL-4_40541402	4	40,541,402	Intergenic		G/A		28.1	
rs13478780	6	59,609,561	Intergenic		C/G		16.7	
rs6361142	7	9,296,425	Intergenic		T/C		10.4	
Korl: ICR stock-specific								
rs13477404	3	130,952,894	Non-coding	Col25a1	G/A			22.1
rs13481061	11	62,605,165	Non-coding	Cdrt4	G/T			21.4
rs6389420	6	127,676,012	Intergenic		C/T			7.8
rs3023251	11	20,848,871	Intergenic		C/T			11.5
rs13480910	11	22,709,634	Intergenic		T/G			11.5
rs3655558	12	70,010,856	Intergenic		G/A			17.7
CEL-15_36490596	15	36,490,596	Intergenic		G/A			8.9

Abbreviations: MAF: minor allele frequency; **SNP ID:** single nucleotide polymorphism GeneBank accession number; **Chr:** chromosome; **bp:** basepairs. MAF was more than 5%.

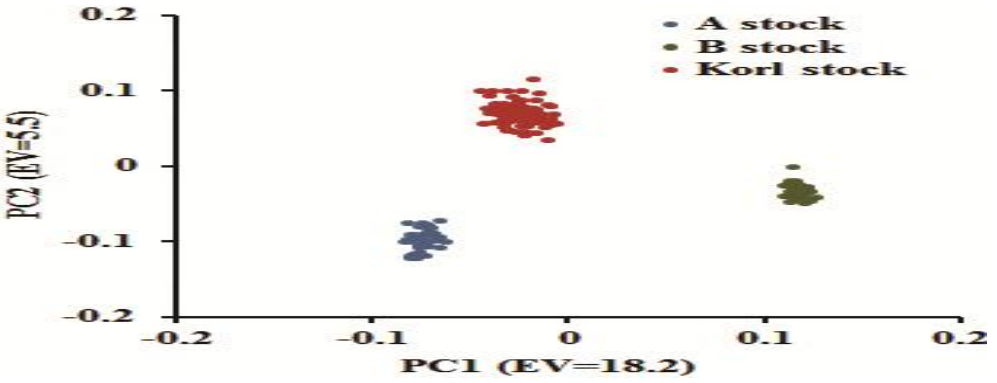

Figure 2. Principal component analysis (PCA): PC1 and PC2 indicated the first and second principal components (PC) of each population, respectively. Relatedness between 48 A: ICR, 48 B: ICR, and 96 Korl: ICR mice was analyzed using genotype information from 1319 SNPs.

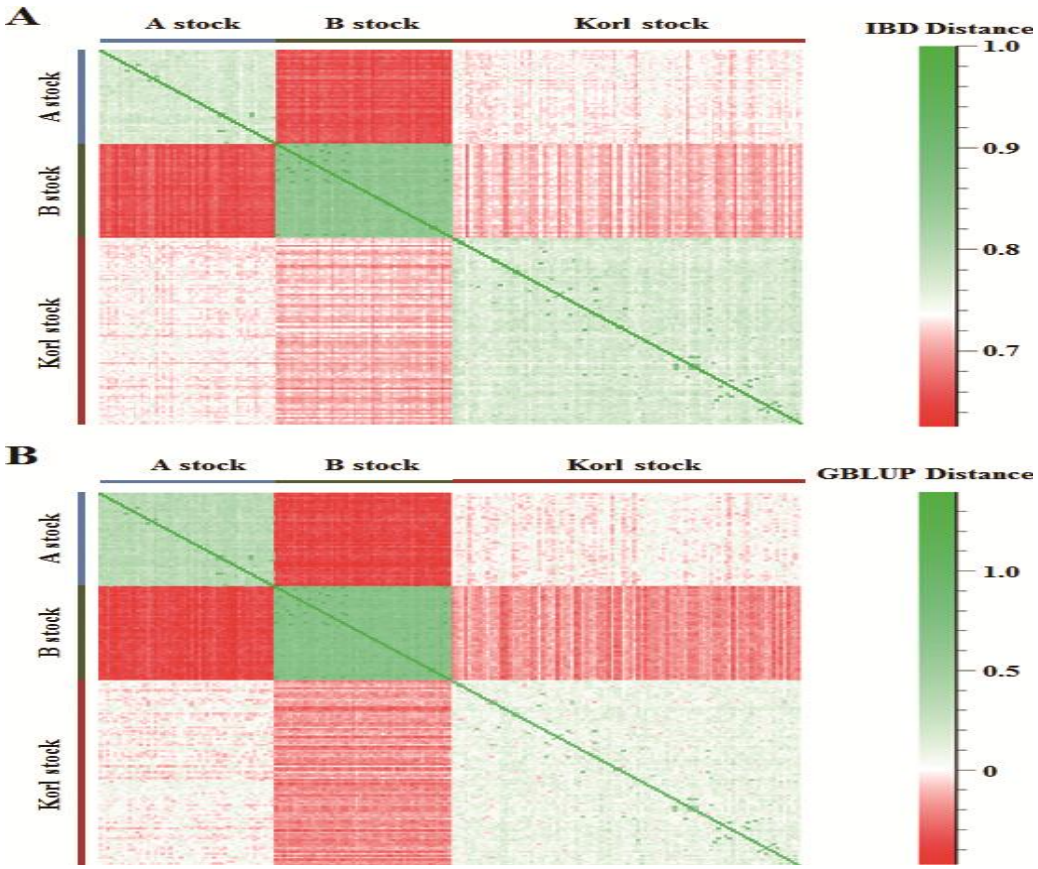

Figure 3. Heat maps of the IBD distance (A) and the GBLUP genomic relationship matrix (B) for 192 mouse samples with 1319 SNPs.

genetic drift and environmental effects. Despite these limitations, the concept of using genome-wide genetic variation to distinguish stocks remains robust.

In conclusion, we verified that Korl: ICR is a new stock genetically distinct from other ICR stocks and suggest that distinguishing stocks based on genetic variation is an appropriate method that provides the potential to resolve conflicts over outbred rodent resources with exclusive rights, which may occur in the future.

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