WHICH C57BL/6 SUBSTRAIN WAS USED FOR THE BACKGROUND STRAIN OF YOUR MOUSE?

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The C57BL/6 is most frequently used as the background strain in biomedical studies. In Japan, several C57BL/6 derived from C57BL/6J and C57BL/6N substrains that are core substrains of C57BL/6 are commercially available from different sources. It has been reported that there are phenotypic differences between C57BL/6J and C57BL/6N substrains; however, the importance of their differences has not yet been well understood among biomedical researchers. Here, we report on the usage of C57BL/6 substrains for congenic and mutant strains in Japan. In Japan about 16% of C57BL/6 background strains were from mixed or uncertain C57BL/6 substrains. We also carried out a screening on the functional deletion of the nicotinamide nucleotide transhydrogenase (*Nnt*) gene and comprehensive SNPs genotyping among C57BL/6 substrains, that data demonstrated there were clear genetic differences between C57BL/6J and C57BL/6N substrains. Our data renewed the importance of the substrain status of C57BL/6 when using those resources to investigate gene function, and will be useful to provide accurate genetic verification of the C57BL/6 background strains.

Key words: intrastrain variation, microsatellite, PCR.

Introduction

The C57BL/6 is the most well-known inbred strain and has been widely used as a general purpose strain and the genetic background for spontaneous and genetically modified mice. C57BL/6 separated from the C57BL parent strain along with C57BL/10 in the mid-1930s, and several C57BL/6 substrains were established in the 1970s. C57BL/6J of The Jackson Laboratory (JAX) and C57BL/6N of the National Institutes of Health (NIH) are core substrains of C57BL/6, that were developed from the ancestral C57BL/6 line during the 1940s and 1950s (Philip L. Altman, 1979).

The RIKEN BioResource Center (RIKEN BRC) was established in 2001 and designated as the core facility for the mouse resources of the National BioResource Project operated by the Ministry of Education, Culture, Sports, Science and Technology of Japan, and has collected a number of spontaneous and induced mutant mice of the C57BL/6 background that were developed in Japan. In Japan several C57BL/6 substrains derived from C57BL/6J and C57BL/6N substrains are commercially available from different sources. Most of the spontaneous and induced mutant mouse strains deposited to RIKEN BRC were generated by using these substrains.

It has been reported that there are phenotypic differences between C57BL/6J and C57BL/6N substrains (Sluyter *et al*., 1999; Stiedl *et al*., 1999; Roth *et al*., 2002; Wotjak 2003). The functional deficiency of the nicotinamide nucleotide transhydrogenase (*Nnt*) gene was also reported in C57BL/6J (JAX) (Freeman *et al*., 2006; Huang *et al*., 2006). In the C57BL/6J (JAX), exons 7–11 in the *Nnt* gene was deleted, while the Nnt gene remained intact in C57BL/6JEiJ, C57BL/6NCrl and C57BL/6ByJ (Toye *et al*., 2005). Since the *Nnt* gene is important for glucose homeostasis and controls insulin secretion, the C57BL/6J (JAX) lacks these important characteristics. This should have alerted scientists to the necessity of recognizing these phenotypic differences in the C57BL/6 substrains and to choose an appropriate substrain for the specific purpose of their studies.

To choose the most appropriate C57BL/6 substrain for a specific research purpose, it

is important to understand the exact genetic background and the substrain differences. The use of SNP markers must help to distinguish genetically close strains such as substrains with potential genetic differences. However, SNP information between C57BL/6J and C57BL/6N substrains has not thoroughly investigated yet.

Here, we report which substrains of C57BL/6 were used for the genetic background of congenic and induced mutant mice in Japan. We also demonstrated SNPs between C57BL/6J and C57BL/6N substrains, and the presence of the functional deletion of the *Nnt* gene in C57BL/6J substrains. This study should sound a warning alarm about the inappropriate mixing of C57BL/6 substrains in the biomedical research.

Materials and Methods

The number of C57BL/6 used for the genetic background of congenic and induced mutant mice deposited at RIKEN BRC was counted on a substrain basis. The information on the C57BL/6 substrains for each congenic and mutant mouse was collected from the data sheet provided by the depositors/developers, publications related to the mouse strain or direct personal communication with the depositors/developers.

The mouse strains used in this study are listed in Table 1. Genomic DNA were extracted from the tail tips and kidneys of the mice, or directly purchased from The Jackson Laboratory. These samples were used for SNP genotyping and exon specific PCR for *Nnt* gene analyses as shown in Table 1.

To determine if the C57BL/6J (JAX) specific deletion of the *Nnt* gene locus existed in the C57BL/6 substrains in Japan, exon-specific primers for the *Nnt* gene were designed according to a previously report (Huang *et al*., 2006). All oligonucleotides used in this study were synthesized by Invitrogen Japan (Tokyo, Japan). PCRs were performed in a total volume of 12 µl. The reaction mixture contained 6,0 µl of 2x QIAGEN Multiplex PCR Master Mix (QIAGEN GmbH, Hilden, Germany), 1,2 µl of 2,0 µM primer mix of forward and reverse primers, 3,3 µl of RNase-free water, and 1,5 µl of template DNA (less than 1 µg DNA/50 µl). Thermal cycling conditions for the PCR were as follows: 15 min at 95 ºC, followed by 32 cycles at 94 ºC for 30 sec, 60 ºC for 90 sec, and 72 ºC for 90 sec, with a final extension at 72 ºC for 10 min. All PCR amplifications were performed on a T1 Biometra thermal cycler (Whatman Biometra GmbH, Niedersachsen, Germany). The PCR products were electrophoresed on 4 % NuSieve 3 : 1 Agarose gel (Lonza Rockland, Inc., Rockland, Maine, USA). The gel was stained

Table 1

The C57BL/6 substrains used in this study

Strain name	Purchased from	Analysis	
		SNP genotyping	Exon specifc PCR for Nnt
C57BL/6J (JAX)	Charles River Laboratories Japan, Inc. (Yokohama, Japan)	○	○
C57BL/6JJcl	CLEA Japan, Inc. (Tokyo, Japan)	○	○
C57BL/6JJmsSlc	Japan SLC, Inc. (Jamamatsu, Japan)	○	○
C57BL/6JEiJ	The Jackson Laboratory (Bar Harbor, Maine, USA)	–	○
C57BL/6NJcl	The Jackson Laboratory (Bar Harbor, Maine, USA)	○	○
C57BL/6NCrlCrlj	Charles River Laboratories Japan, Inc. (Yokohama, Japan)	○	○
C57BL/6NTac	Taconic Farms, Inc. (Hudson, New York, USA)	○	○
C57BL/6NJ	The Jackson Laboratory (Bar Harbor, Maine, USA)	–	○
C57BL/6NSea	Kyudo Co, Ltd. (Kumamoto, Japan)	–	○
C57BL/6CrSlc	Japan SLC, Inc. (Jamamatsu, Japan)	○	○
C57BL/6By	The Jackson Laboratory (Bar Harbor, Maine, USA)	–	○
C57BL/6ByJ	The Jackson Laboratory (Bar Harbor, Maine, USA)	–	○

Genomic DNA of C57BL/6JEiJ, C57BL/6NJ, C57BL/6By and C57BL/6ByJ used for this study were directly purchased from The Jackson Laboratory. Other genomic DNA were extracted from the tail tips or kidneys of the mice.

with 1,0 μg/ml ethidium bromide solution and photographed by an ultraviolet trans-illuminator and digital photograph device.

Genotyping of 1,449 SNP loci covering the genome was carried out by using the Golden Gate Assay (Illumina Inc, California, USA) (Fan *et al*., 2006) of Illumina's Mouse MD Linkage Panel. Based on information of over 13,000 SNPs from 480 strains performed by the Welcome Trust Centre for Human Genetics (http://www.well.ox.ac.uk/mouse/INBREDS), the SNP loci of the Illumina's Mouse MD Linkage Panel were standardized to maximize the genetic information across the common inbred strains, including 129S1/SvImJ, AKR/J, BALB/cJ, C3H/HeJ, C57BL/6J, CBA/J, DBA/2J, FVB/NJ, NOD/LtJ and SJL/J. Their loci were designed to include approximately three SNPs per five megabase.

Results

According to information provided by depositors/developers of the mouse strains, 659 C57BL/6 congenic, semicongenic and mutant strains were classified as follows: 62 % were crossed with the C57BL/6J substrains including C57BL/6 (JAX), C57BL/6JJcl and other C57BL/6JJmsSlc, 12 % with the C57BL/6N substrains including C57BL/6NJcl, C57BL/6NCrlCrlj and C57BL/6N, and 10 % with C57BL/6CrSlc. The other 16 % were of mixed background among C57BL/6 substrains or uncertain C57BL/6 substrains (Fig. 1).

Deletion of exons 7–11 in the *Nnt* gene was surveyed among the C57BL/6 substrains and C57BL/10SnJSlc (Fig. 2). The deletion of exons 7–11 in the *Nnt* gene was only detected in C57BL/6J substrains, except for C57BL/6JEiJ and not in any of the other strains examined. The results on the deletion of exons for C57BL/6J (JAX), C57BL/6JEiJ and C57BL/6ByJ were the same as a previous report (Toye *et al*., 2005).

SNP genotyping was carried out on seven C57BL/6 substrains and C57BL/10SnJSlc by using Illumina's Mouse MD Linkage Panels for 1,449 SNP loci. The targeted SNP loci were successfully genotyped in 1,427 (98,5 %). The remainder of the assays produced statistically unreliable values. Eleven novel SNPs were detected between the C57BL/6J and C57BL/6N substrains, as shown in Table 2. In addition, we found another SNP at the rs13477019 locus on chromosome 3 between C57BL/6J (JAX) and other C57BL/6J substrains. Therefore, there were 12 SNPs detected between the C57BL/6J (JAX) and C57BL/6N substrains, indicating that 0,8 % of the SNPs loci were genetically distinct between the C57BL/6J (JAX) and C57BL/6N substrains. All twelve SNPs were in the genome SNP or the intronic SNP, located in non-coding regions of the genome, according to the Ensembl Mouse Genome Server (www.ensembl.org/Mus_musculus/index.html) (Hubbard *et al*., 2007). The genotypes of the 1,427 SNP loci were the same among the C57BL/6N substrains (C57BL/6NJcl, C57BL/6NCrlCrlj and C57BL/6NTac) and C57BL/6CrSlc substrains.

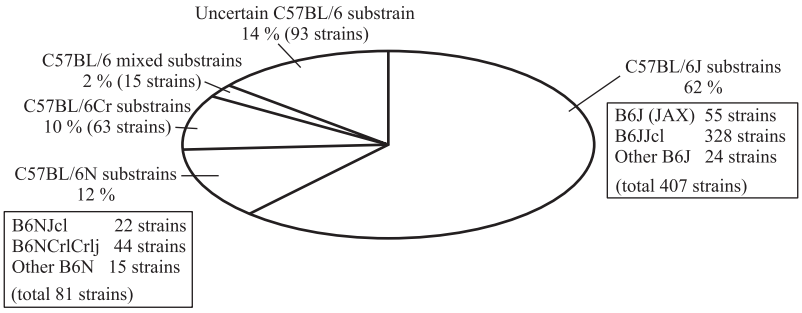

Fig. 1. Summary of a survey for the use of C57BL/6 substrains in Japan. According to information provided by developers of mouse strains deposited at RIKEN BRC, 659 C57BL/6 congenic, semicongenic, spontaneous and induced mutant strains were classified as follows: 62 % were crossed with the C57BL/6J substrains including C57BL/6 (JAX), C57BL/6JJcl and C57BL/6JJmsSlc, 12 % with the C57BL/6N substrains including C57BL/6NJcl, C57BL/6NCrlCrlj and C57BL/6NTac, and 10 % with C57BL/6CrSlc. The remaining 2 % had a mixed background with C57BL/6 substrains or 14 % with uncertain C57BL/6 substrains. B6J (JAX): C57BL/6J (JAX), B6JJcl: C57BL/6JJcl, B6NJcl: C57BL/6NJcl, B6NCrlCrlj: C57BL/6NCrlCrlj.

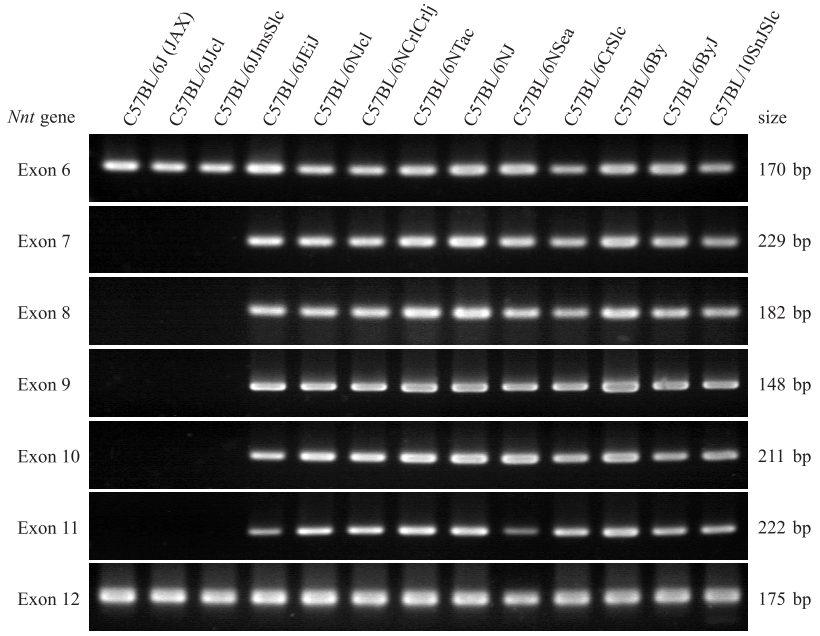

Fig. 2. Absence of exons 7–11 of the *Nnt* gene specific for C57BL/6 substrains. Genomic PCR specific for exons 6–12 of the *Nnt* gene showed the absence of PCR products from exons 7–11 in C57BL/6J (JAX), C57BL/6JJcl and C57BL/6JJmsSlc, suggesting a deletion encompassing exons 7 to 11 in parts of C57BL/6J substrains exclusively. PCR products size was from a previous report (Huang *et al*., 2006).

Discussion

A survey among congenic and induced mutant mice with the C57BL/6 background used in Japan revealed that there were mixed backgrounds among the C57BL/6 substrains (2 %) or uncertain C57BL/6 substrains (14 %) (Fig. 1). This statistical result clearly indicated that about 16 % of biomedical researchers in Japan had insufficient knowledge about the existence of different C57BL/6 substrains. All C57BL/6J substrains, except for C57BL/6JEiJ, in this study showed the deletion of the *Nnt* gene, indicating that they must exhibit impaired glucose tolerance, as was found in the C57BL/6J (JAX) (Freeman *et al*., 2006; Huang *et al*., 2006). Biomedical researchers must understand that there are phenotypic differences between C57BL/6 substrains for a related gene function, and mixed usage of substrains must be avoided for a correct interpretation of the data from functional analyses of the genes.

Our data clearly indicated the genetic differences between C57BL/6J and C57BL/6N substrains by using the SNPs (Table 2). It was striking that one of the twelve SNPs detected between C57BL/6J (JAX) and C57BL/6N substrains was an unique allele only found in the C57BL/6J (JAX). These results may also indicate that there could potentially be more SNPs not only between C57BL/6J and N, but also among the C57BL/6J substrains. Therefore, biomedical researchers must pay sufficient attention to compare the sequence data of their own C57BL/6 mice with the BLAST data created from the C57BL/6J (JAX) genome. In this study we could not find any SNPs among the C57BL/6N or C57BL/6Cr substrains. According to the breeder catalogs, these strains have their own different breeding histories, even after 20 to 30 years of separation. This result might indicate that the genome of these substrains has been maintained with high stability during extensive inbreeding. It must be clarified that further high-density SNPs analyses may reveal genetic differences among the C57BL/6N substrains in the near future.

Currently, large-scale mutagenesis programs are ongoing to mutate all protein-encoding genes in the mouse by using gene trapping and targeting in ES cells (Collins *et al*., 2007). In these projects the C57BL/6 strain is planned to be used as the genetic background for the induced mutations (http://www.sanger.ac.uk/Teams/Team87). In the future, an explosive number of C57BL/6 mice car-

Table 2

SNPs among C57BL/6 substrains and C57BL/10

Chromosome	1	2	2	3	4	4	4	4	4	4	4	4	4	4	4	6	6
Locus	mCV 23695025	rs 13476874	rs 3671849	rs 13477019	rs 3711477	rs 6271003	rs 13477866	rs 6381371	rs 3692563	rs 3675629	rs 13477952	gnf04.123 .367	rs 3663950	rs 3688566	rs 3719891	rs 13478617	CEL6_ 57082524
C57BL/6J (JAX)	A/A	G/G	C/C	T/T	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/6JJcl	A/A	G/G	C/C	A/A	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/6JJmsSlc	A/A	G/G	C/C	A/A	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/6NJcl	A/A	G/G	C/C	A/A	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/6NCrlCrlj	A/A	G/G	C/C	A/A	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/6NTac	A/A	G/G	C/C	A/A	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/6CrSlc	A/A	G/G	C/C	A/A	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/10SnJSlc	**G/G**	**A/A**	**G/G**	A/A	**G/G**	**G/G**	**C/C**	**T/T**	**A/A**	**A/A**	**C/C**	**A/A**	**G/G**	**G/G**	**C/C**	**G/G**	**A/A**

Chromosome	6	7	8	8	8	8	8	8	8	8	8	8	8	8	8	9	9
Locus	rs 13478783	rs 13479522	rs 3661760	rs 3719401	CEL-8_ 51607005	rs 13479776	rs 3725286	rs 6285803	rs 6287320	rs 3706149	rs 3669235	rs 13479956	gnf08.108 .032	gnf08.118 .027	rs 13480014	rs 13480122	rs 3655717
C57BL/6J (JAX)	A/A	A/A	G/G	C/C	C/C	G/G	C/C	A/A	A/A	G/G	A/A	G/G	T/T	T/T	C/C	T/T	T/T
C57BL/6JJcl	A/A	A/A	G/G	C/C	C/C	G/G	C/C	A/A	A/A	G/G	A/A	G/G	T/T	T/T	C/C	T/T	T/T
C57BL/6JJmsSlc	A/A	A/A	G/G	C/C	C/C	G/G	C/C	A/A	A/A	G/G	A/A	G/G	T/T	T/T	C/C	T/T	T/T
C57BL/6NJcl	G/G	G/G	G/G	C/C	C/C	G/G	C/C	A/A	A/A	G/G	A/A	G/G	T/T	T/T	C/C	C/C	T/T
C57BL/6NCrlCrlj	G/G	G/G	G/G	C/C	C/C	G/G	C/C	A/A	A/A	G/G	A/A	G/G	T/T	T/T	C/C	C/C	T/T
C57BL/6NTac	A/A	G/G	C/C	A/A	A/A	A/A	T/T	C/C	G/G	C/C	T/T	C/C	A/A	A/A	T/T	T/T	G/G
C57BL/6CrSlc	G/G	G/G	G/G	C/C	C/C	G/G	C/C	A/A	A/A	G/G	A/A	G/G	T/T	T/T	C/C	C/C	T/T
C57BL/10SnJSlc	G/G	G/G	**T/T**	**T/T**	**T/T**	**C/C**	**T/T**	**G/G**	**G/G**	**T/T**	**G/G**	**A/A**	**C/C**	**C/C**	**T/T**	C/C	**C/C**

Chromosome	10	10	10	11	11	11	11	11	11	11	11	11	11	11	11	12	13
Locus	rs 13480619	CEL-10_ 58149652	rs 13480759	rs 13480837	rs 3682937	rs 6190775	rs 6359329	rs 6164170	rs 3701734	rs 3654344	rs 13481009	rs 13481014	rs 6199956	rs 4228731	rs 3684076	rs 13481565	rs 13481706
C57BL/6J (JAX)	T/T	G/G	C/C	T/T	C/C	T/T	A/A	A/A	A/A	T/T	C/C	T/T	T/T	T/T	C/C	T/T	C/C
C57BL/6JJcl	T/T	G/G	C/C	T/T	C/C	T/T	A/A	A/A	A/A	T/T	C/C	T/T	T/T	T/T	C/C	T/T	C/C
C57BL/6JJmsSlc	T/T	G/G	C/C	T/T	C/C	T/T	A/A	A/A	A/A	T/T	C/C	T/T	T/T	T/T	C/C	T/T	C/C
C57BL/6NJcl	C/C	A/A	T/T	T/T	C/C	T/T	A/A	A/A	A/A	T/T	C/C	C/C	T/T	T/T	C/C	T/T	C/C
C57BL/6NCrlCrlj	C/C	A/A	T/T	T/T	C/C	T/T	A/A	A/A	A/A	T/T	C/C	C/C	T/T	T/T	C/C	T/T	C/C
C57BL/6NTac	C/C	A/A	T/T	T/T	C/C	T/T	A/A	A/A	A/A	T/T	C/C	C/C	T/T	T/T	C/C	T/T	C/C
C57BL/6CrSlc	C/C	A/A	T/T	T/T	C/C	T/T	A/A	A/A	A/A	T/T	C/C	C/C	T/T	T/T	C/C	T/T	C/C
C57BL/10SnJSlc	C/C	A/A	T/T	**C/C**	**T/T**	**C/C**	**G/G**	**G/G**	**G/G**	**G/G**	**G/G**	C/C	**G/G**	**C/C**	**T/T**	**G/G**	**T/T**

Chromosome	13	13	13	13	13	13	14	14	14	15	15	15	16	17	18	18
Locus	rs 3679784	rs 13481734	rs 3710348	rs 3707097	rs 3725187	rs 13481764	rs 6169105	rs 3665550	CEL-14_1 16404928	rs 13482629	rs 13482637	rs 13482642	rs 4165065	rs 13483055	rs 13483436	rs 3706601
C57BL/6J (JAX)	C/C	A/A	A/A	C/C	G/G	T/T	A/A	A/A	G/G	T/T	T/T	T/T	T/T	T/T	C/C	A/A
C57BL/6JJcl	C/C	A/A	A/A	C/C	G/G	T/T	A/A	A/A	G/G	T/T	T/T	T/T	T/T	T/T	C/C	A/A
C57BL/6JJmsSlc	C/C	A/A	A/A	C/C	G/G	T/T	A/A	A/A	G/G	T/T	T/T	T/T	T/T	T/T	C/C	A/A
C57BL/6NJcl	C/C	G/G	A/A	C/C	G/G	T/T	A/A	A/A	A/A	T/T	T/T	T/T	C/C	C/C	C/C	A/A
C57BL/6NCrlCrlj	C/C	G/G	A/A	C/C	G/G	T/T	A/A	A/A	A/A	T/T	T/T	T/T	C/C	C/C	C/C	A/A
C57BL/6NTac	C/C	G/G	A/A	C/C	G/G	T/T	A/A	A/A	A/A	T/T	T/T	T/T	C/C	C/C	C/C	A/A
C57BL/6CrSlc	C/C	G/G	A/A	C/C	G/G	T/T	A/A	A/A	A/A	T/T	T/T	T/T	C/C	C/C	C/C	A/A
C57BL/10SnJSlc	**T/T**	G/G	**C/C**	**T/T**	**A/A**	**C/C**	**G/G**	**C/C**	A/A	**C/C**	**G/G**	**A/A**	C/C	C/C	**T/T**	**G/G**

After comparing 1,427 of the successfully amplified SNP assay by using Mouse MD Linkage Panels for 1,449 SNP loci, twelve loci (rs13477019, rs13478783, rs13479522, rs13480122, rs13480619, CEL-10_58149652, rs13480759, rs13481014, rs13481734, CEL-14_11644928, rs4165065 and rs13483055) were newly detected as polymorphic between C57BL/6J (JAX) and other C57BL/6N substrains. One of the SNPs (rs13477019) was polymorphic between C57BL/6 (JAX) and other C57BL/6J substrains. In the twelve SNP loci specific to C57BL/6J (JAX), the SNP patterns of other C57BL/6 substrains were consistent with those of C57BL/10SnJSlc.

rying targeted mutations will be distributed across national boundaries. Accordingly, the selection of substrain when using C57BL/6 resources is becoming increasingly important, and biomedical researchers must seriously consider the substrain status of C57BL/6. These data will be useful to provide an exact genetic verification of C57BL/6 substrains and an accurate genetic monitoring of your C57BL/6 background strains.

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