Research in Biotechnology, 6(6): 31-41, 2015 ISSN: 2229-791X
www.researchinbiotechnology.com

Regular Article

Evaluation of genetic relationship within and between mice strains using microsatellite markers

Nishtha Purohit[1], Mahadeo kumar[2*], Anurag Kumar Srivastav[2] and Dinesh Chandra Purohit[2]

[1]Department of Microbiology and Biotechnology, Rajasthan University of Veterinary and Animal Sciences, Bikaner
[2]Animal Facility, CSIR-Indian Institute of Toxicology Research, 226001, Lucknow, India
*Corresponding author email: mahadeo@iitr.res.in

Mouse is the most commonly used animal research model in biology with hundreds of established inbred, outbred, and transgenic strains. They are mammal sharing a high degree of homology with human and other non human primates. In current study to evaluate the genetic relationship between different strains of mice 5 samples of each 14 different strain of mice were used and tested for different 14 microsatellite markers. The analysis of data revealed that the observed number of alleles varied from 2 to 6 for the strains of mice between the strains. The Effective number of alleles was reported from 2.543-10.515 in overall experimental population. Shannon's Index range from 1.218 to 2.459 show limited genetic variation. The observed homozygosity obtained ranges from 0.5143 to 8.571 at selected loci. The observed heterozygosity obtained ranges from 0.142 to 0.485. In case D1Mit16 loci showed maximum Polymorphic information content (PIC) values up to 0.4486 while minimum PIC value of 0.2923 using D1Mit356. The maximum expected average heterozygosity of inbred strain of mice was 0.2486 for D1Mit17 whereas minimum of 0.0922 using D17Mit62. It is observed that different genetic sites in these strains are showing low genetic diversity and low selection potentials and therefore, may also act as genetic markers to find out the source of origin and contamination. However, it is suggested that in future this study should be conducted by testing more number of individuals and for greater number of microsatellite markers.

Keywords: mouse; molecular characterization; genetic variation; microsatellite; Phylogenetic analysis

Mouse is the most commonly used animal research model in biology with hundreds of established inbred, outbred, and transgenic strains. They are mammal sharing a high degree of homology with human and other non human primates. The mouse (*Mus musculus musculus*) genome has been sequenced, and virtually all mouse genes have been found to have human homologues. There are more than 400 inbred strains of mice and 150 inbred strains of rats. Most laboratory mice are hybrids of different subspecies, most commonly of *Mus musculus domesticus* and *Mus musculus musculus*. The first such inbred strains were produced by Clarence Cook Little in 1909 (Little, 1916). Inbred strains of a species are individuals derived from inbreeding (sister x brother or

parent x offspring matings) which are genotypically nearly identical and have high level of homozygosity. Genetic characterization refers to the detection of variation as a result of differences in either DNA sequences or specific genes or modifying factors (Vicente et al., 2005). Thus the characterization of genetic resources refers to the process by which accessions are identified or differentiated. Molecular characterization also helps to determine the breeding behavior of species, individual reproductive success and the existence of gene flow, that is, the movement of alleles within and between populations of the same or related species and its consequences (Papa and Gepts, 2003). Previously Restriction fragment length polymorphism (RFLPs) has been the choice for many species to measure genetic diversity (Bonstein et al., 1980). But this technique is slow, cumbersome and it requires a large amount of DNA sample. So the use of SNPs (Single nucleotide polymorphism) has replaced the need of RFLP but they are less informative as less allele are present and use a large amount of DNA samples and data analysis.

So overcoming the hurdles of RFLP and SNP, the more efficient technique used is microsatellite which are the arrays of repeat sequences that display length variations, different alleles containing different number of repeat units. This markers is locus specific, highly polymorphic, co-dominant (Brown, 2001), amenable to analysis by PCR as PCR typing which is much quicker and more accurate as due the high heterozygosities and very high mutation rates of 10^{-3} and 10^{-4} (Jeffreys et al., 1988; Kelly and Mckinnon, 1991; Henderson and Peter, 1992) thus, microsatellite markers are appropriate for the study of molecular taxonomy, evolution and population genetics (Bowcock et al., 1994) and also applied for DNA typing for individual identification and for assessing the degree of genetic relatedness between individuals. The data interpretation of microsatellite assays is also straight forward and based on visual identification of the polymorphisms. Thus, we implemented microsatellite marker based DNA fingerprinting technique to detect the genetic relationship between the selected strains.

Table 1:- Sample (different strains) collection from CSIR laboratories.

Strains	*Type	Institute	No. of female	No. of male	Total sample
BALB/c	Inbred	IITR	5	5	20
		CDRI	5	5	
Swiss	Outbred	IITR	5	5	10
C57BL/6	Inbred	IITR	5	5	20
		CDRI	5	5	
SKH	Inbred	IITR	5	5	10
CD-1	Outbred	IITR	5	5	10
DBA 1/J	Inbred	CDRI	5	5	10
A/J	Inbred	CDRI	5	5	10
db/db +	Inbred	CDRI	5	5	10
db/db obese	Inbred	CDRI	5	5	10
NZB	Inbred	CDRI	5	5	10
NOD	Inbred	CDRI	5	5	10
APO/E	Inbred	CDRI	5	5	10
C3H/HES	Inbred	CDRI	5	5	10
AKR	Inbred	CDRI	5	5	10

*Charles River Locations Worldwide

MATERIALS AND METHODS

Selection of inbred strain and tail tissue sampling

Fourteen strains of mice (12 inbred and 2 outbred) were selected for the present study that belonged to the CSIR-Indian Institute of Toxicology Research, Lucknow, (IITR) and The Central Drug Research Institute (CDRI), Lucknow. All the experimental mice utilized in the present study were maintained as inbred stock. A total of 160 mice were sampled as 5 individuals per strain with equal representation of each sex were chosen randomly as shown in Table 1.

DNA Extraction and Selection of Microsatellite Markers

The tail samples were subjected to DNA extraction by using standard protocol of Sambrook and Russel (1989). In the present study, a set of 14 microsatellite markers were used. Some of these markers selected from mouse genome informatics (MGI) and were already used in different studies to determine the genetic diversity of mice as shown in Table 2. The primers were synthesized from Integrated DNA Technology (IDT).

Table 2: - Primer sequences and other information of the microsatellite markers used.

Primer	Repeat Motif	Genetic location	Sequence (5′-3′)	GC Content (%)	Fragment Range (bp)	Reference
D1Mit16	(CA)23	1	F:AGAGTTAGCTGCCTAGCTTGAGTG	50	162-197	Dietrich *et al.*(1992)
			R:TGGAAAGATCTAGGGTTGTCAAAA	37.5		
D1Mit17	(GT)14	1	F: GTGTCTGCCTTTGCACCTTT	50	170-190	Dietrich *et al.* (1992)
			R: CTGCTGTCTTTCCATCCACA	50		
D1Mit136	(GT)19	1	F:TAGCCCTACACACTGTAGAAATGC	45.8	86-108	Gill and Boyle (2005)
			R: TGAACACAAAGTAGTAAATGCGTG	37.5		
D1Mit171	(CA)12	1	F: TGCAGATTCAGTCTGCCTTG	50	148-200	Oharaseki *et al.* (2005)
			R: AGCCATGGGAACACTCTCAC	55		
D1Mit356	(GT)30	1	F: GGGAGAACCTGTCAAGACCA	55	112-152	Namiki *et al* (2003)
			R: TTTTGGAAATGAGTGTCTGGC	42.8		
D2Mit75	(CA)24	2	F: TCAGCATGTGGATGAATACACA	40.9	16-112	Kaerlsson *et al.* (2003)
			R: AACTTTTTAAAAACTACGAGCGTG	33.3		
D3Mit200	(GT)23	3	F: CAACTTCAGTTTCTCATTTGAATTG	32	99-131	Cook *et al.* (2001)
			R: GCAAATGGAAGAGGTTTCTCC	47.6		
D7Mit259	(CA)22	7	F: CCCCTCCTCCTGACCTCTT	63.1	116-152	Cattanach *et al.* (2000)
			R: GTCTCCATGGGAACCACACT	55		
D11Mit227	(CA)34	11	F: CCAGCATTTGAACCCTGATT	45	116-188	Johannesn *et al.* (2006)
			R: AAACCCATAGCCTGCATCTG	50		
D11Mit260	(CA)19	11	F: ACTTTGCCTTTATACTATATGGTGG	36	74-118	Farber *et al.* (2007)
			R: CATTTGTTTAGTTCTCAGCACCA	39.1		
D13Mit130	(GT)24	13	F: TCTGCTGAAGGCCAGGAC	61.1	139-148	Juriloff *et al.* (1996)
			R: TTGAAGTGTCATGTTGATTTTAATG	28		
D16Mit5	(GT)21	16	F: CGGGGATCATCCCTAAAAAC	50	132-161	Narita *et al.* (2002)
			R: TCCCCAATTCCTCTTGTGTC	50		
D17Mit62	-	17	F: CCACATCTTCTAATCCTGCTCA	45.4	158-176	Gregorova *et al.* (1996)
			R: CATATAGCCTGAGACATTCTGCC	47.8		
D17Mit124	(CA)15	17	F: TGTTGATGAGATCTTAAATCAGCC	37.5	149-163	Rocha *et al.* (2004)
			R:TTTAACTAGTTGTTATTGCATGTGTG	30.7		

PCR Amplification

After the extraction of DNA, the microsatellite loci were amplified though polymerase chain reaction (PCR) using primer set for selected microsatellite markers (Table 2). A total of 15µL reaction mixture was prepared for each reaction which included 10 pmol of each primer, 7.5 µL of 2X Master Mixture, 6.1 µL of nuclease free water, 0.2 µL of each forward primer and reverse primer (10 picomoles/ µL) and 1 µL genomic DNA as a template. For PCR amplification of different samples following procedure was followed. Initial denaturation at 95 °C for 10 minutes, and then for each of 40 cycles following procedure was used, denaturation at 94 °C for 0.45 seconds, annealing at primer specific temperature (*i.e.* 52°C-54°C) for 0.45 second, 72°C for 1 minute for extension process that followed by a final extension at 72 °C for 10 minutes. After PCR amplification a 12µL of the subsequent PCR product for each sample was loaded along with 50 bp standard ladder onto the 3% agarose gel after mixing it with loading dye (3B BioBlack) and allowed to run on the gel at 80 volts for 2-3 hours and the remaining PCR product (about 2 µL) were run on 8% native polyacrylamide gel electrophoresis (PAGE) for 4-6 hours at 100 volt for estimating allele size and visualized by silver staining.

Statistical Analysis

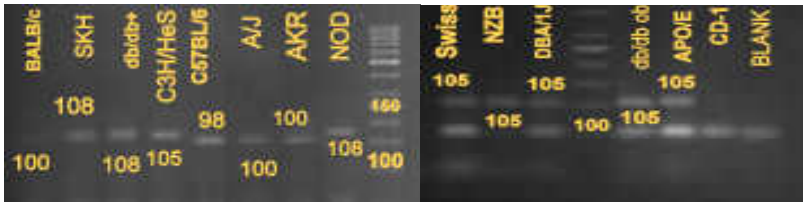
Each PCR product was genotyped and gel documentation data was analyzed to work out the standard parameters of genetic diversity among strains of mice under study. POPGEN 32 software (version 1.32) was used to evaluate the values of observed and expected heterozygosity, observed and effective number of alleles, Shannon's information index, genetic relationships and Nei's genetic distance. Dendogram was also generated by using Tree Viewer (Java version 1.7) from the data generated. Whereas, polymorphic information contents (PIC) were calculated by using online PIC calculator (University of Pannonia Georgion Faculty 2008).

RESULTS

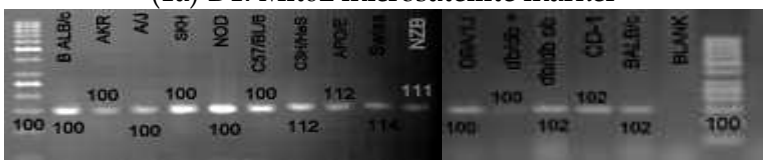
Using different microsatellite marker for 14 different strains of mice revealed different parameters for calculating the genotype of mouse. Over all, the maximum observed number of alleles were found to be 6 in marker D1Mit16 and D11Mit227 (Figure 2a & b) and minimum of 2 alleles were obtained in D1Mit356 (Figure 2c). Mean and standard deviation for observed number of alleles for all the loci were calculated as 9.57 and 2.10 respectively (Table 3). The maximum effective number of alleles was obtained in D1Mit16 as 10.51 and the minimum effective number of alleles was in D1Mit356 as 2.54 with mean of 6.206±2.309 for all loci. For richness of deviation in a population we used Shannon's Index which was calculated maximum as 2.4592 in D1Mit16 and minimum 1.218 in D1Mit356 with a mean of 1.954±0.736 in all loci. The observed homozygosity was maximum for the marker D17Mit62 as 0.8714 (Figure 1a) and minimum 0.5143 for D1Mit17 (Figure 1b) with the mean of 0.7723±0.1106. The observed hetero-zygosity were measured maximum in the marker D17Mit124 as 0.4571 (Figure 1c) and minimum 0.5286 in D17Mit62 (Figure 1d) with mean of 0.1790±0.0776 in all loci. The expected heterozygosity was obtained maximum using D1Mit16 as 0.9114 and minimum in D1Mit356 as 0.6112 and mean of 0.8210±0.0776. The maximum average heterozygosity was reported in D1Mit17 as 0.2486 and minimum in D17Mit62 as 0.0929 with mean of 0.1321±0.0519. The maximum PIC value was obtained in D1Mit16 as 0.4486 and minimum of D1Mit356 as 0.2923(Table 3&4).

We also estimated the genetic relationships among the individuals using POPGENE 32 software (version 1.32) (Table

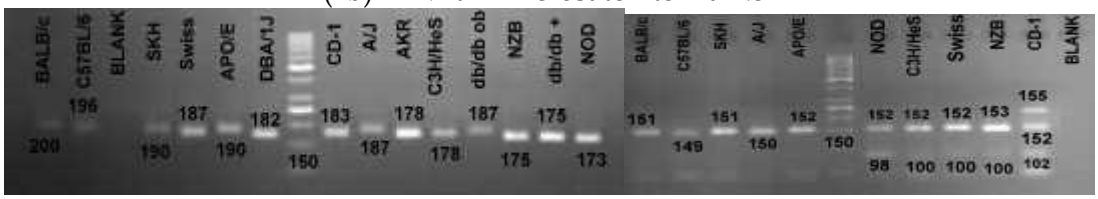
5) and constructed UPGMA dendrogram of genetic similarity using the Tree Viewer software (Java version 1.7) (Figure 3). In our study the UPGMA dendrogram, consisted of two main groups. The first main group encloses four subgroups, NOD, C57BL6, BALB/c, APO/E, Swiss and CD-1. The second main group includes the remaining strains were further sub grouped. The minimum genetic distance of 0.00 was found in BALB/c and APO/E, SKH and db/db+, A/J and NZB and C3H/HeS and AKR whereas maximum genetic distance was obtained 0.660 between AKR and NOD (Figure 3).



(1a) D17Mit62 microsatellite marker



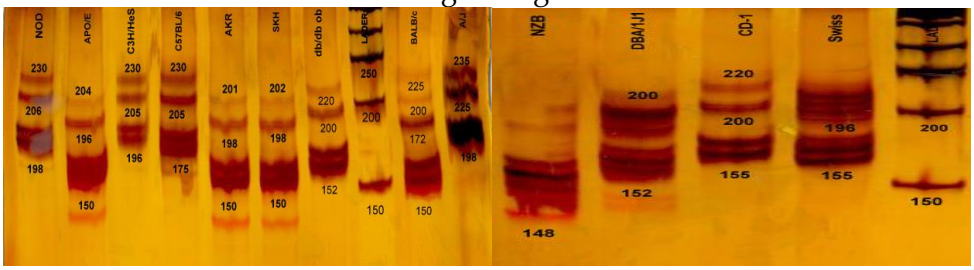
(1b) D1Mit17 microsatellite marker



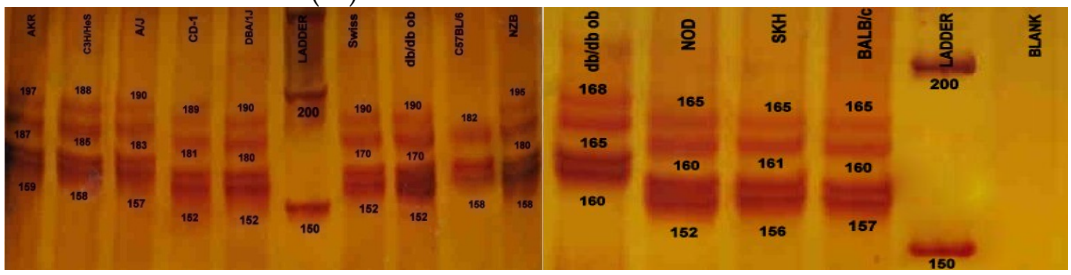
(1c) D17Mit124 microsatellite marker

(1d) D17Mit62 microsatellite marker

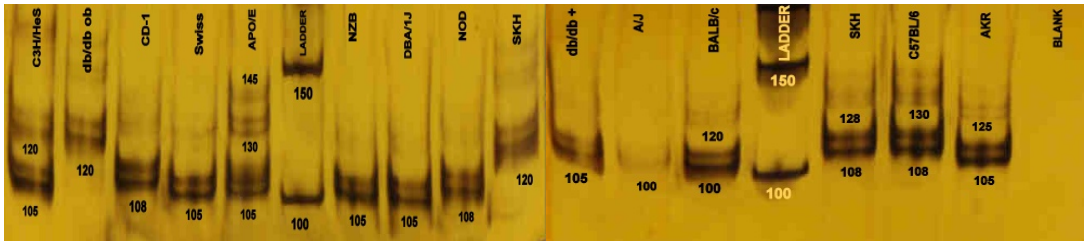
Figure 1(a, b, c & d):- Gel image of Microsatellite-PCR of mouse DNA from different strains on 3 % agarose gel.



(2a) D1Mit16microsatellite marker.



(2b) D11Mit227microsatellite marker.



(2c) D1Mit356 microsatellite marker.

Figure 2 (a, b & c):- Allelic variation of microsatellite markers in mouse strains on 8% native PAGE and visualization by silver staining

Table 3: - Diploid data for Genetic variation statistics for effective number of alleles and Shannon's index.

Locus	Sample Size	Observed Number of Alleles (Na)	Effective Number of Alleles*(Ne)	Shannon's Information Index (I)
D1Mit16	140	13	10.515	2.459
D1Mit17	140	11	8.368	2.252
D1Mit136	140	8	4.741	1.726
D1Mit171	140	10	5.552	1.9461
D1Mit356	140	6	2.543	1.218
D2Mit75	140	7	3.899	1.564
D3Mit200	140	10	6.507	2.071
D7Mit259	140	11	7.435	2.161
D11Mit227	140	13	10.092	2.411
D11Mit260	140	7	4.444	1.689
D13Mit130	120	10	7.354	2.456
D16Mit5	140	9	4.720	1.880
D17Mit62	140	9	5.423	1.898
D17Mit124	140	10	5.208	1.929
Mean	**139**	**9.571**	**6.206**	**1.954**
St. Dev		**2.101**	**2.309**	**0.736**

*Na = Observed number of alleles; *Ne = Effective number of alleles; I = Shannon's Information index*

DISCUSSION

Assay genetic variation by using microsatellite loci between the different inbred strain of mouse revealed that there were some differences in levels of allelic variation among the selected microsatellite loci, as measured by the total number of alleles, effective number of alleles, Shannon index, the observed homozygosity (*Ho*), the expected heterozygosity (*He*), the average heterozygosity, PIC value and genetic distance. The use of microsatellite marker for the genetic monitoring of different strain of mice has several advantages (Wood et al., 1996 and Otsen et al., 1995) over classical markers such as histocompatability and isoenzyme variations (Kahan et al., 1989). Thus it can be stated that all microsatellite markers are much more accurate, easy to handle, required much less time and economical sound technique, which requires only a small tissue sample (a few micro liters of blood or a tail tip) from which DNA is extracted. Finally, detect genetic divergence between sub strains or even very close-related strains are also possible. Although minisatellite mutations previously were used to determine genetic heterogeneity in a

BALB/c mouse colony (by means of DNA fingerprinting) (Benavides et al., 1998), our results imply that there is very less abundant genetic variation in populations selected samples of mice. Most of the selected microsatellite loci were polymorphic between studied strains, however there was no variation/ polymorphism observed within the strains. The mean number of alleles was found to be 9.571 for each locus. The *Ho* and *He* values were 0.7723 and 0.2277, respectively. These values are comparable to Yu's study on house mice in Taiwan (2002), which suggested that a mean of 3.17–8.50 alleles were found at six microsatellite loci, and the expected heterozygosity varied between 0.35 and 0.83. Also previous study by (Kloting et al., 2003) comparing genetic profiles of outbred with wild rats suggested that heterozygosity in Rj:SD, Crl:WIST and wild rats were 0.27+0.19, 0.41+0.19 and 0.35+0.21, respectively. Thus, inbred strain of mice possess considerable low genetic variability and is a suitable inbred stock for the development of purposes of pure bred lines in laboratory for study of genetic variation, cloning, gene mapping and mutation study.

Table 4: Overall Observed and Expected Homozygosity and Heterozygosity

Locus	Sample Size	Observed Hom	Observed Het	Expected Hom*	Expected Het*	Nei	Average Het.	PIC Value
D1Mit16	140	0.8571	0.1429	0.0886	0.9114	0.9049	0.0943	0.4486
D1Mit17	140	0.5143	0.4857	0.1132	0.8868	0.8805	0.2486	0.4225
D1Mit136	140	0.8571	0.1429	0.2052	0.7948	0.7891	0.0943	0.3794
D1Mit171	140	0.7571	0.2429	0.1742	0.8258	0.8199	0.1357	0.399
D1Mit356	140	0.8143	0.1857	0.3888	0.6112	0.6068	0.1043	0.29235
D2Mit75	140	0.8429	0.1571	0.2511	0.7489	0.7436	0.0957	0.35305
D3Mit200	140	0.8000	0.2000	0.1476	0.8524	0.8463	0.1486	0.41135
D7Mit259	140	0.7714	0.2286	0.1283	0.8717	0.8655	0.1314	0.42575
D11Mit227	140	0.7857	0.2143	0.0926	0.9074	0.9009	0.1300	0.44625
D11Mit260	140	0.7571	0.2429	0.2194	0.7806	0.7750	0.1357	0.3646
D13Mit130	140	0.7833	0.2167	0.1287	0.8713	0.8640	0.1014	0.42525
D16Mit5	140	0.8571	0.1429	0.2062	0.7938	0.7882	0.0943	0.38475
D17Mit62	140	0.8714	0.1286	0.1785	0.8215	0.8156	0.0929	0.397
D17Mit124	140	0.5429	0.4571	0.1832	0.8168	0.8109	0.2429	0.39295
Mean	**139**	**0.7723**	**0.2277**	**0.1790**	**0.8210**	**0.8151**	**0.1321**	**0.3957**
St. Dev	**-**	**0.1106**	**0.1106**	**0.0776**	**0.0776**	**0.0770**	**0.0519**	

The number of polymorphic loci is : 14; The percentage of polymorphic loci is : 100.00 %

Table 5: Measures of Genetic distance between selected inbred strain of mice

Pop ID	BALB	Swiss	C57	SKH	CD-1	NOD	APO	C3H	AKR	DBA	A/J	db/db	Dbobe	NZB
BALB	****													
Swiss	0.187	****												
C57	0.117	0.125	****											
SKH	0.150	0.239	0.278	****										
CD-1	0.098	0.250	0.166	0.248	****									
NOD	0.151	0.050	0.120	0.061	0.150	****								
APO	****	0.174	0.231	0.147	0.347	0.222	****							
C3H	0.109	0.241	0.077	0.073	0.067	0.074	0.142	****						
AKR	0.192	0.051	0.183	0.097	0.025	0.660	0.113	****	****					
DBA	0.218	0.116	0.115	0.221	0.028	0.222	0.214	0.142	0.151	****				
A/J	0.151	0.180	0.140	0.133	0.150	0.076	0.074	0.074	0.156	0.148	****			
db/db	0.074	0.068	0.117	****	0.103	0.264	0.254	0.291	0.192	0.291	0.226	****		
dbobe	0.075	0.104	0.117	0.038	0.029	0.152	0.073	0.243	0.175	0.257	0.290	0.156	****	
NZB	0.123	0.183	0.060	0.104	0.136	0.052	0.152	0.273	0.032	0.152	****	0.257	0.449	****

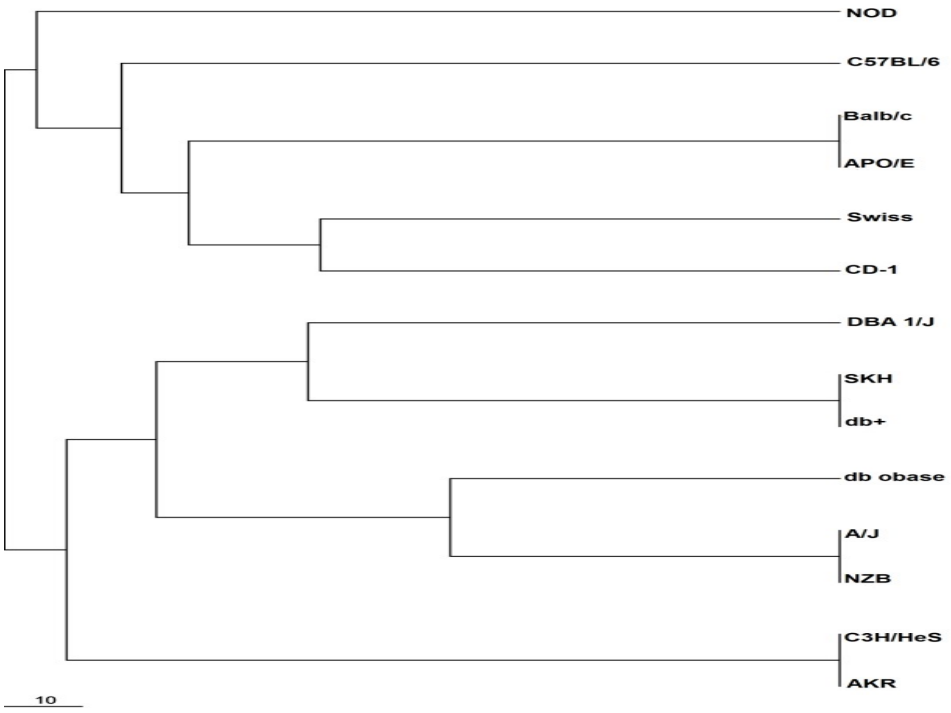


Figure3: UPGMA dendrogram of genetic similarity among the different strains of mice belonging to fourteen populations

Moreover polymorphisms were also tested in SKH and CD-1 as they are outbred stocks with microsatellites. Generally up to four alleles were found at each locus using microsatellite marker with previous genetic testing of the mouse with allozymes, and a low heterozygosity was obtained by (Cui et al., 1993) and (Rice et al., 1980). Also study conducted by Teppner et al. (2004) using 153 polymorphic microsatellite markers to check the purity of outbred CFW and ICR stock for generating congenic mice using C57BL6 as a background. They found 76 and 70 informative microsatellite markers which could be used for the generation of C57BL/6 congenic mice derived from the CFW and ICR stock, respectively. At least three polymorphic markers per chromosome were reported with the maximum genomic distance between two marker loci was 58 cM and 70 cM. Consequently, microsatellites are a more suitable marker for genetic monitoring of the outbred strains of mice with genetic heterozygosity, as more detailed genetic profiles can be described according to the greater number of alleles at each locus and sufficient loci can thus be selected for extensive distribution in the genome which are suitable for analysis and essential molecular variation of genes which can be compiled using microsatellites as a DNA marker. Hence, microsatellite markers can be also employed as a prospective method for genetic monitoring of the outbred stock because of their good reproducibility, high throughput, automation and low cost. Similar study conducted by (Frazer et al., 2007) and (Nei, 1978) by using more than eight million SNPs that have been found in the mouse genome and a variety of SNP genotyping approaches have been developed for genetic detecting of mice. Thus only good polymorphic and reproducible loci were adopted for analysis.

The genetic distance observed and compared by Nei's (1987) was estimated as reported in results with maximum distance between NOD and AKR. Similar study conducted by

Rice et al., (1980) and Nei, (1978) for the estimation of genetic distances of Swiss and wild mouse populations that ranged from 0.019 to 0.081. Therefore, the genetic distance between the populations was not much considerable, there being a high genetic identity observed between them (Table 5).

Parsimony analysis was done using tree viewer software and the results were compared to that of (Petkov et al., 2004) according to clustering analysis for constructing the parsimony tree of mouse strains as they performed by the neighbor-joining method (Saitou and Nei, 1987). We find two main groups and seven subgroups that correspond exactly to the number of populations/locations under study (figure 3). This dendrogram allows us to suggest that marker systems have enough specificity to discriminate outbred as well as inbred strains of mice.

Thus, effective comparisons of experimental results would not be easy to obtain using different inbred and outbred mouse strain together. Therefore, in nutshell it can be concluded that the PCR-based microsatellite analysis seems to have considerable advantages over biochemical and immunological methods as a tool for the genetic monitoring of inbred strains, especially in those developing countries where the classical techniques have never been established. Also the basis of our data it can be concluded that inbred strain of mice have low level of heterozygosity genetic diversity in term of numbers of alleles, Polymorphic information contents, heterozygosity and Nei genetic distance. As maximum value of PIC content was 0.4486 showing that genomic sites tested in this study were having polymorphisms up to medium extent. The present study indicated that even with the limited number of samples and marker considerable level of genetic diversity between the strains, under study, was observed.

Acknowledgement

I would like to take this opportunity to express my profound gratitude and deep regard to director IITR for the providing the facility to carry out this research work. The present research was financially supported by grant from CSIR- Empowered project (OLP-07) of Indian Institute of Toxicology Research, Lucknow.

REFRENCESS

Benavides FD, Cazalla CP, Fontanals A, Salaverri M, Goldman A, Buggiano B, Oran G and Corley E. 1998. Evidence of genetic heterogeneity in a BALB/c mouse colony as determined by DNA finger printing. Lab. Anim 32:80–85.

Bonstein D, White RL, Skolnick M and Davis RW. 1980.Constuction of a genetic linkage map in man using Restriction fragment length polymorphism. Amer. J. Human Genet 32: 314-331.

Bowcock AM, Ruiz-linares A, Ttomfogrde J, Minch E and Kidd JR. 1994. High resolution of human evolutionary trees with polymorphic microsatellites. Nature 368: 455-457.

Brown TA. 2002. Studing genomes, Genome, II, Manchester, Oxford: WikyLiad.

Cattanach BM, Peters J, Ball S and Rasberry C. 2000. Two imprinted gene mutation, 3 phenotypes .Hum Mol genet 9: 2263-2273.

Cook SA, Akeson EC, Calvano C, Johnson KR, Mandell J, Hawes NL, Bronson RT, Roderick TH and Davisson MT. 2001. Mouse paracentric inversion In(3)55Rk mutates the urate oxidase gene. Cytogenet Cell Genet 93: 77-82.

Cui S, Chesson C and Hope R. 1993. Genetic variation within and between strains of outbred Swiss mice. Lab Anim 27:116–123.

Dietrich W, Katz H, Lincoln SE, Shin H, Friedman J, Dracopoli, NC and Lander ES. 1992. A Genetic Map of the Mouse Suitable for Typing Intraspecific Crosses.

The Genetics Society of America. Genetics 131: 423-447.

Farber CR and Medrano JF. 2007. Fine mapping reveals sex bias in quantitative trait loci affecting growth, skeletal size and obesity- related traits in mouse chromosome 2 and 111. Genetics 175: 349-360.

Frazer KA, Eskin E, Kang HM, Bogue MA, Hinds DA, Beilharz EJ, Gupta RV, MontgomeryJ, Morenzoni MM, Nilsen GB, PethiyagodaCL, Stuve LL, Johnson FM, Daly MJ, WadeCM and CoxDR. 2007. A sequence-based variation map of 8.27 million SNPs in inbred mouse strains. Nature 448: 1050–1053.

Gill KJ and Boyle AE. 2005. Genetic basis for the psychostimulant effects of nicotine: a quantitative trait locus analysis in AcB /BcA recombinant congenic mice. Genes Brain Behav. 24: 401-411.

Gregorova S, Mnukova- Fajdelova M, Trachtulee Z, Capkova J, Loudova M, Hoylund M, Hamvas R, Lehrach H, Vincek V, Klein J and Forejt J. 1996. Sub-millimorgn map of the proximal part of mouse chromosome 17 including the hybrid sterility 1 gene. Mamm genome 7: 107-113.

Henderson ST and Petes TD. 1992. Instability of simple sequence DNA in *Saccharomyces cerevisie.* Molecular Cell Biolog.12: 2749-2757.

Jeffreys AJ, Royle NJ, Wilson V and Wong Z. 1988. Spontaneous mutation rates of new length alleles at tandem-repetitive hypervariable loci in human DNA. Nature322: 278-281.

Johannes F, Blizard DA, Lionikas A, Lang DH, Vandenbergh DJ, Stout JT, Strauss JA, McClearn GE and Vogler GP. 2006. QTL influencing baseline hematocrit in the C57BL/6J and DBA/2J lisneage: age-related effects. Mammalian Genome. 17: 689-699.

Juriloff DM, Harris MJ, Mah DG and Benson A. 1996. The lid gap-gate (IgGa) mutation for open eyelid at birth maps to mouse chromosome 13. Mamm Genomes 7: 403-407.

Kaerlsson J, Zhao X, Lonskaya I, Neptin M, Holmdahl R and Andersson A. 2003. Novel quantitative trait loci controlling development of experimental auto-immune encephalomyelitis and proportion of lymphocyte sub-populations. J Immuno 170: 1019-1026.

Kahan B, Auerbach R, Alter B J and Bach F H. 1982. Histocompatibility and isoenzyme differences in commercially supplied "BALB/c'" mice. Science 217: 379-381.

Kelly PB and McKinnon DA. 1991. Familal multiple polyposis of the colon: review and description of large kindred. McGill Med 30: 67-85.

Kloting I, Nitschke C, Van den Brandt J. 2003. Impact of genetic profiles on experimental studies: outbred versus wild rats. Toxicol Appl Pharmacol 189: 68–71.

Little CC. 1916 Cancer and inbred mice. Genetics 161: 1357–1361.

Namiki Y, Endoh D and Kon Y. 2003. Genetic mutation associated with meiotic metaphase specific apoptosis in MRL/MpJ mice genome feature. Mol. Reprod. Dev 64: 179-188.

Narita M, Wang Y, Kita A, Omi N, Yamada Y and Mia H. 2002. Genetic analysis of nakano cataract and its modifier genes in mice. Exp. Eye res 75: 745-751.

Nei M. 1978. Estimation of average heterozygosity and genetic distance from a small number of individuals. Genetics 89: 583–590.

Nei M. 1987. Molecular evolutionary genetics. Columbia University Press, New York.

Oharaseki T, Kameoka Y, Kura F, Persad AS, Suzuki K and Naoe S. 2005. Susceptibility loci to coronary arteritis in animal model of Kawasaki disease induced with *Candida albicans* derived

substances. Microbiol Immuno l49: 181-189.

Otsen M, Den-Bieman M, Winer ES, Jacob HJ, Szpirer J, Szpirer C, Bender K and Van Zutphen LF. 1995. Use of simple sequence length polymorphisms for genetic characterization of rat inbred strains. Mamm. Genome 6: 595–601.

Papa R and Gepts P. 2003. Asymmetry of gene flow and differential geographical structure of molecular diversity in wild and domesticated common bean (*Phaseolus vulgaris* L.) from Mesoamerica. Theor Appl Genet 106: 239–250.

Petkov PM, Ding Y, Cassell MA, Zhang W, Wagner G, Sargent EE, Asquith S, Crew V, Johnson KA, Robinson P, Scott VEs and Wiles MV, 2004. An efficient SNP system for mouse genome scanning and elucidating strain relationships. Genome Research 14: 1806–1811.

Rice MC and O'Brien SJ. 1980. Genetic variance of laboratory outbred Swiss mice. Nature 283: 157–161.

Rocha JL, Eisen EJ, Van Vleck LD and Pomp D. 2004. A large-sample QTL study in mice: II. Body composition. Mamm Genome 15: 100-113.

Saitou N and Nei M. 1987. The neighbor-joining method: A new method for reconstructing phylogenetic trees. Mol. Biol. Evol 4: 406–425.

Sambrook J and Russell DW. 1989. Molecular Cloning a laboratory manual. 3rd edition. New York: Cold Spring Harbor laboratory Press.

Teppner I, Aigner B, Schreiner E, Muller M and Windisch M. 2004. Polymorphic microsatellite markers in the outbred CFW and ICR stocks for the generation of speed congenic mice on C57BL/6 background. Laboratory Animals 38**:** 406–412**.**

Vicente MC, Guzman FA, Engels J and Rao VR. 2005. Genetic characterization and its use in decision making for the conservation of crop germplasm. The Role of Biotechnology 134: 121-128.

Wood PA, Hamm DA, Cartner SC and Lindsey JR. 1996. Simple sequence length polymorphism analysis of mice for genetic monitoring. Contemp. Topics Lab. Anim. Sci. 35: 60–62.

www.criver.com/

www.informatics.jax.org/

Yu HT and Peng YH.2002. Population differentiation and gene flow revealed by microsatellite DNA markers in the house mouse (*Mus musculus castaneus*) in Taiwan. Zool. Sci. 19: 475–483.