The Journal of Experimental Biology 208, 4445-4450
Published by The Company of Biologists 2005
doi:10.1242/jeb.01920

The absence of mitochondrial DNA diversity among common laboratory inbred mouse strains

Ji-gang Dai[1], Jia-xin Min[1,*], Ying-bin Xiao[1], Xia Lei[1], Wen-hao Shen[1] and Hong Wei[2]

[1]*Department of Thoracic Surgery, Xinqiao Hospital, The Third Military Medical University, Chongqing 400037, China* and [2]*Center of Laboratory Animal, The Third Military Medical University, Chongqing 400038, China*

*Author for correspondence (e-mail: minjiaxin8@yahoo.com.cn)

Accepted 5 October 2005

Summary

Mitochondrial DNA (mtDNA), which exhibits a maternal inheritance and a high rate of evolution, has been widely used as a genetic marker when analyzing maternal lineage and inferring phylogenetic relationships among species. In this study, mtDNA variations among four classical (BALB/c, C3H, C57BL/6J and DBA/2) and three Chinese (TA2, 615 and T739) inbred strains of laboratory mice were analyzed by PCR-RFLP (polymerase chain reaction coupled with restriction fragment length polymorphism) and PCR-SSCP (polymerase chain reaction coupled with single-stranded conformational polymorphism) techniques. PCR-RFLP analyses on 46 restriction sites revealed no variations in mtDNA D-loop (displacement loop), $tRNA^{Met+Glu+Ile}$ and ND3 (NADH dehydrogenase subunit 3) gene fragments in these strains. Furthermore, PCR-SSCP analyses demonstrated no variations in D-loop 5′ and 3′ end fragments in them. In view of enormous polymorphisms in mtDNA among mice and dramatic differences in nuclear genomes of these seven strains, our findings were surprising. However, in light of the maternal inheritance of mtDNA, the results indicate that the three Chinese strains, including TA2, T739 and 615, and the four classical strains, share a common maternal lineage.

Key words: inbred strain, mouse, mtDNA, PCR-RFLP, PCR-SSCP, polymorphism.

Introduction

Thanks to special laboratory inbreeding processes, genetic diversity among mice of a certain inbred strain is absent; in other words, different individual mice share an identical genotype, except that the Y chromosome occurs only in the males (Wei et al., 1998). Such a highly stable and pure lineage makes inbred mice one of the frequently used laboratory animals in biomedical research. Moreover, toleration of complete inbreeding has produced hundreds of inbred strains (Beck et al., 2000). Inbred mouse strains can be classified into two categories, classical and wild-derived, and the latter consists of several dozens of strains derived from wild mice that were trapped at different times and places and from different populations (Ideraabdullah et al., 2004). Some of these inbred strains were derived from *Mus* species and *Mus musculus* subspecies and also from their intersubspecific hybrids (Bonhomme and Guenet, 1996; Wada et al., 2000).

Most of the classical inbred mouse strains commonly used in biomedical research descend from the colonies of a single mouse breeder, Abbie Lathrop of Granby, MA, USA, in the early 20th century (Beck et al., 2000). These colonies were largely derived from European ‘fancy’ mice (derivatives of the *domesticus* subspecies of *Mus musculus*) and East Asian ‘fancy’ mice (derivatives of *castaneus*, *molossinus* and *musculus* subspecies). It has long been recognized that because of this unique man-made bottleneck, the genomes of these inbred strains originate from a mixed but very limited pool of founders from the various subspecies (Ferris et al., 1982; Bonhomme, 1987; Tucker et al., 1992; Ideraabdullah et al., 2004).

T739, 615 and TA2 are the main inbred mouse strains in China and are recognized on a worldwide scale. These strains differ substantially from classical strains such as BALB/c, C3H, C57BL/6J and DBA2, which were established more than 60 years ago and are also designated as ‘old inbred’ strains in terms of anatomy, behavior and protein structure (Ferris et al., 1983; Zhang et al., 1998). The TA2 strain originated from ‘Kunming’ mice outbred at Beijing Bioproduct Institute in 1962, and has been inbred since then. The T739 strain was derived from the mating of a female ‘Kunming’ mouse with a male 615 mouse, followed by sib mating [data from the Mouse Genome Database (MGD)] at the Mouse Genome Informatics Web Site of The Jackson Laboratory, Bar Harbor, MA, USA; http://www.informatics.jax.org. However, little is known about the phylogenetic relationships and recorded origin of these strains.

Mitochondrial DNA (mtDNA) is a short circular molecule that, with the exception of viruses, represents the most

economically packed form of DNA in the whole biosphere (Anderson et al., 1981). The rapid evolution and maternal inheritance of mtDNA make it a valuable marker for progeny of a given mother (Brown et al., 1979; Hecht et al., 1984; Finnila et al., 2000). In the present study, we investigated mtDNAs from four classical (BALB/c, C3H, C57BL/6J and DBA/2) and three Chinese (TA2, 615 and T739) mouse strains to determine the phylogenetic relationships among these strains. Although it has been known for many years that the four classical strains share a common maternal origin, the question of whether the Chinese strains are of the same origin has still to be answered, and is of interest for the study of laboratory animals.

Materials and methods

Animals and chemicals

The seven mouse strains, namely (TA2, 615, T739, BALB/c, C3H, C57BL/6J and DBA2, were obtained from the Center of Laboratory Animal, Third Military Medical University Chongqing, China. Animal breeding and tissue collection were performed in accordance with China's laws on animal experimentation and the Guide to the Care and Use of Laboratory Animals. Animals were housed in laminar flow hoods in an environmentally controlled animal facility and were fed on a standard rodent chow. Restriction endonucleases, including *Hae*III, *Hin*fI, *Eco*RV, *Hin*dIII, *Hpa*I, *Bam*HI, *Apa*I, *Nde*II, *Xho*I, *Xba*I, *Alu*I, *Rsa*I, *Stu*I, *Dra*I, *Ava*I and *Hae*II, were purchased from Boehringer Mannheim (Mannheim, Germany) and Promega (Madison, WI, USA). The PCR kits were also purchased from Boehringer Mannheim.

PCR amplification

The primers were synthesized by Shanghai Institute of Cell Biology (Table 1). mtDNAs of mouse liver cells were prepared by nuclei/cytoplasm partitioning (Dai et al., 2000).

PCR reactions were done in a volume of 100 μl and included 0.5 μg mtDNA as template. Amplification in the PCR consisted of an initial denaturation step at 94°C for 5 min followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 1 min, and extension at 72°C for 1 min. Following the final cycle, the mixture was incubated at 72°C for 10 min.

PCR-RFLP analysis of the D-loop, tRNA$^{Met+Glu+Il}$ and ND3 gene fragments

Two units of restriction endonucleases and 1.2 μl of 10× buffer were added to 5 μl of PCR products, and then appropriate volumes of sterilized water were added until the total volume reached 12 μl; the mixture was then incubated at 37°C overnight. After digestion, each sample was subjected to 1% gel electrophoresis with TBE buffer (Dai et al., 1999). Following electrophoresis at 3 V cm^{-1} for 1–2 h, the resultant gel was observed under ultraviolet and gel images were obtained.

PCR-SSCP analysis of D-loop 5′ and 3′ end fragments

PCR products were denatured with TE buffer (Dai et al., 1999; diluted 1:10, pH 8.0). 5 μl of each diluted solution was mixed with 5 μl of deionized formamide solution containing 20 mmol l^{-1} EDTA, followed by incubation at 95°C for 5 min. After chilling on ice for 10 min, samples were subjected to 9% polyacrylamide gel electrophoresis (acrylamide:bisacrylamide = 49:1 v/v, containing 5% glycerol in 0.5× TBE). The electrophoresis was performed at a constant voltage of 25 V for 3–5 h under a controlled gel temperature of 20°C, and visualized by silver staining.

Results

Restriction fragment length polymorphisms in the D-loop, tRNA$^{Met+Glu+Il}$ and ND3 gene fragments

MtDNA D-loop, tRNA$^{Met+Glu+Il}$ and ND3 fragments from T739, TA2, 615, BALB/C, C3H, C57BL/6J and DBA/2, were

Table 1. *Primer sequences and the lengths of the amplified fragments*

Amplified fragment	Length (bp)	Location	Primer sequence
D-loop	1100	L strand (15294–15320)	5′-ATAAACATTACTCTGGTCTTGTAAACC-3′
		H strand (98–72)	5′-ATTAATAAGGCCAGGACCAAACCT-3′
tRNA$^{Met+Glu+Ile}$	1126	L strand (3401–3419)	5′-CGGCCCATTCGCGTTATTC-3′
		H strand (4527–4508)	5′-AGGTTGAGTAGAGTGAGGGA-3′
ND3 fragment	534	L strand (9364–9385)	5′-ACGTCTCCATTTATTGATGAGG-3′
		H strand (9897–9876)	5′-GAGGTTGAAGAAGGTAGATGGC-3′
D-loop 5′ fragment	342	L strand (15371–15389)	5′-CCACCACCAGCACCCAAAG-3′
		H strand (15712–15694)	5′-CGGGTTGTTGGTTTCACGG-3′
D-loop 3′ fragment	437	L strand (15950–15968)	5′-AGGCATGAAAGGACAGCAC-3′
		H strand (91–73)	5′-ATAAGGCCAGGACCAAACC-3′

L strand, light strand of mtDNA; H strand, heavy strand of mtDNA.

PCR reactions were done in a volume of 100 μl and included 0.5 μg mtDNA as template. Amplification in the PCR consisted of an initial denaturation step at 94°C for 5 min followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 1 min, and extension at 72°C for 1 min. Following the final cycle, the mixture was incubated at 72°C for 10 min.

cleaved by 16 restriction endonucleases, including *Hae*III, *Hin*fI, *Eco*RV, *Hin*dIII, *Hpa*I, *Bam*HI, *Apa*I, *Nde*II, *Xho*I, *Xba*I, *Alu*I, *Rsa*I, *Stu*I, *Dra*I, *Ava*I and *Hae*II, respectively. No differences in restriction maps were observed, nor were there any variations in the 46 restriction sites in mtDNA D-loop, $tRNA^{Met+Glu+Ile}$ and ND3 fragments in these strains (Fig. 1, Table 2).

Single-stranded conformation polymorphisms in D-loop 5′ and 3′ end fragments

To further analyze the genetic variations in these strains, D-loop 5′ and 3′ end fragments, both of high variability, were subjected to PCR-SSCP analysis. No differences in the SSCP electrophoresis bands were observed (Fig. 2).

Discussion

The mammalian mitochondrial genome (mtDNA) is a 16–17 kb double-stranded circular DNA molecule of characteristic low-molecular mass, simple structure, high evolution rate and maternal inheritance, as well as absence of tissue specificity. On average, each somatic cell has 100–500 mitochondria, and each mitochondrion has 1–15 mtDNA molecule(s) (Satoh et al., 1991). A mature spermatozoon may have no more than 50–80 mitochondria in its middle portion, while a mammalian ovum may contain more than 100 000 mitochondria (Marchington et al., 1998). Upon fertilization, only the head of a spermatozoon penetrates the ovum and, therefore, the mitochondrial genome of an embryo is exclusively of maternal origin and is also of maternal heritance. Due to the lack of mitochondrial genomes of paternal origin, exchange of DNA segments between biparental homologous chromosomes, such as occurs with autosomes during meiosis, does not take place between mitochondrial genomes. Thus, mitochondrial mutations are the sole source of variations among individuals belonging to a common matrilineage.

Owing to reactive oxygen species (ROS)-enhanced aggression, high sensitivity to damage, and deficiency in repair

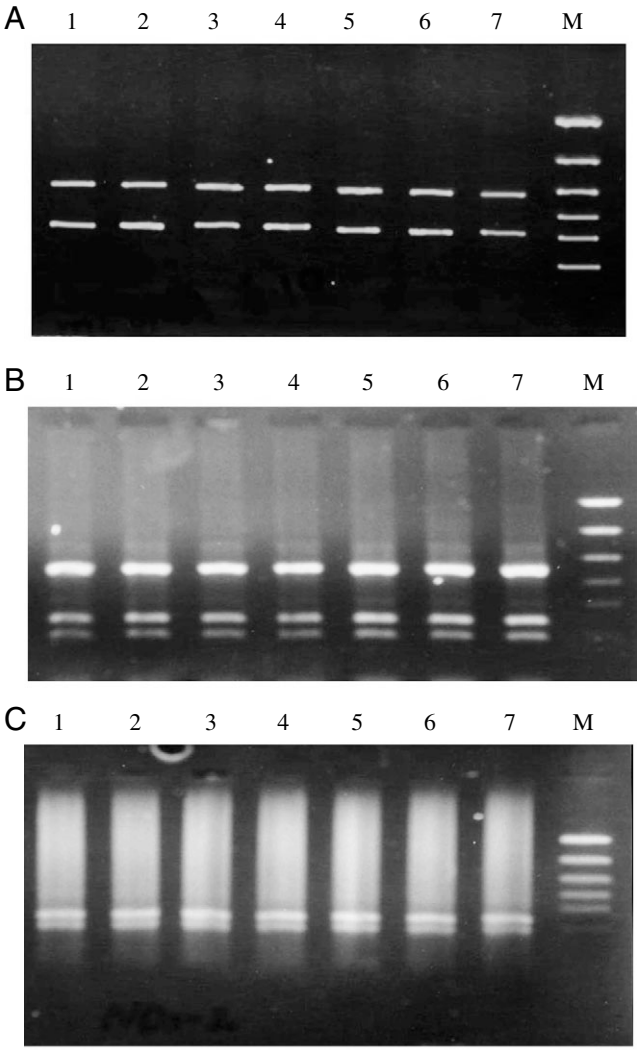

Fig. 1. Restriction patterns of amplified fragments. Restriction patterns of (A) mtDNA D-loop *Xba*I; (B) $tRNA^{Ile+GlN+Met}$ *Stu*I; (C) ND3 fragment *Alu*I. Mouse strains: lanes 1, TA2; 2, 615; 3, T739; 4, BALB/c; 5, C3H; 6, C57BL/6J; 7, DBA/2. The standard marker (M) of Huamei Company was adopted as the molecular mass standard to determinate the length of enzyme-cutting fragments.

Table 2. *Restriction patterns of mouse mt DNA D-Loop, $tRN^{Ile+GlN+Met}$ and ND3 fragments*

	D-loop (1100 bp)		$tRNA^{Ile+GlN+Met}$ (1126 bp)		ND3 (534 bp)	
Enzyme	Sites	Fragment length	Sites	Fragment length	Sites	Fragment length
*Hae*III	4	456,445,122, …	4	470,290,136, …	1	392,142
*Hin*fI	1	700,400	0	1126	4	253,84…
*Apa*I	1	655,445	1	658,469	0	534
*Alu*I	4	545,269,102, …	3	665,318,135, …	1	310,224
*Bam*HI	0	1100	2	710,252,164	0	534
*Dra*I	0	1100	1	634,493	1	451,83
*Stu*I	0	1100	2	605,297,225	1	391,143
*Nde*II	2	845,118,37	0	1126	0	534
*Rsa*I	6	720,178,125, …	4	392,259,228, …	2	353,103,78
*Xba*I	1	680, 420	0	1126	0	524

Note: There are no other restriction enzyme sites.

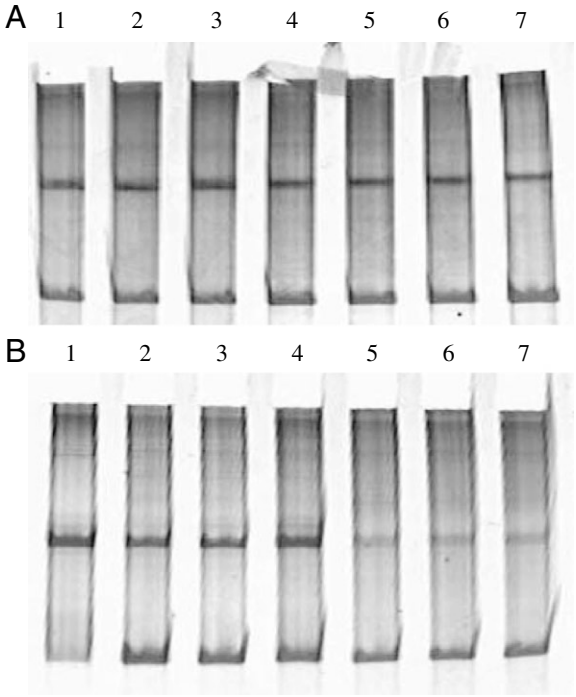

Fig. 2. SSCP analysis of D-loop fragment. (A) SSCP analysis of D-loop 5′ fragment; (B) SSCP analysis of D-loop 3′ fragment. Mouse strains: lanes 1, T739; 2, TA2; 3, 615; 4, BALB/c; 5, C3H; 6, C57BL/6J; 7, DBA/2.

of lesions, the rate of sequence evolution in mtDNA is 10–20 times higher than that in the nuclear genome and, consequently, any two mtDNAs may differ by 10–66 nucleotides (nt). The variability of different functional regions in mtDNA is as follows (from least to greatest): ribosomal RNA, transfer RNA, known proteins and displacement loop (Zeviani et al., 1998; Chinnery et al., 1999). These mutations have accumulated sequentially along radiating maternal lineages and now characterize animal populations in different geographical regions of the world.

Restriction fragment length polymorphism (RFLP) or restriction maps obtained by digesting mtDNA with restriction endonucleases can both be endowed with species stability and reflect the relationship among species. mtDNA RFLP is an efficient genetic marker with which to identify different animal species and to infer the phylogenetic relationships among species; thus, analysis of mtDNA RFLP has been extensively applied in the study of animal origination and genetic differentiation (Brdicka et al., 1994; Zhang et al., 1992; Oleinik et al., 2003). Ferris et al. (1983) analyzed mtDNA RFLPs in more than 140 wild mouse types collected from all around the world and in some ‘newly’ inbred mouse strains (including MOR, PAC and SF/Cam /J). They found many polymorphisms in fragment patterns and high levels of variations in about 200 out of the 300 restriction sites studied.

Prior to the use of PCR techniques, analysis of mtDNA polymorphism involved the isolation of mtDNA from cellular homogenates by separating nuclei and cytoplasmic organelles, subsequent mtDNA purification by preparative centrifugation in sucrose gradients, and then the search of RFLPs. With the advent of PCR techniques, the analysis has become easier: the isolation of mtDNA from total DNA is carried out by mitochondrion-specific primers rather than biophysical methods, and the amount of tissue used to extract DNA decreases from g to a few μg or even ng. In this study, the genetic variations in mtDNA among the four classical (BALB/c, C3H, C57BL/6J and DBA2) and the three Chinese (TA2, T739 and 615) strains were analyzed by PCR-RFLP technique. Our findings showed no differences in the 46 restriction sites of mtDNA D-loop, $tRNA^{Met+Glu+Ile}$ and ND3 gene fragments from these strains, which is in agreement with the RFLP results for old inbred mice (Ferris et al., 1983 and Wang et al., 1992).

A set of enzymes used in the RFLP analysis allows about 20% of the mtDNA sequence to be examined (Wallace, 1994); therefore, a number of polymorphisms may remain undetected. In recent years, different methods based on gel electrophoresis of PCR products have been developed for detecting single-base mismatches in DNA, including SSCP analysis (Thomas et al., 1994), denaturing gradient gel electrophoresis (Gross et al., 1994), and mutation detection enhancement gel matrix (Alonso et al., 1996; Finnila et al., 2000). In addition, sequencing the variable regions of mtDNA can ensure that a mutation is not missed. In this way, Prager et al. (1996) were able to detect differences between house mice that were indiscernible by other methods. A newly developed program, Mutation Quantifiercan, accurately detect mutations with frequencies as low as 3% (Song et al., 2005). In this study, to know more about the genetic variations in these inbred strains, we analysed mtDNA D-loop 5′ and 3′ end fragments (both of high variability) by the PCR-SSCP technique. PCR-SSCP analysis, first described in 1989, has been established as a reliable, simple and fast method with high sensitivity and specificity for detecting point mutations and sequence polymorphisms in short PCR-fragments up to 350 bp. In PCR-SSCP, single-base-pair differences lead to varying mobility patterns on nondenaturing polyacrylamide gels, as a result of altered secondary and tertiary structures of DNA. Compared with direct sequencing, PCR-SSCP analysis can reach a sensitivity (i.e. the ability to detect defined point mutations) of 98% (Jaksch et al., 1995). Nevertheless, we found no variations in the SSCP electrophoretic band pattern in these strains.

In view of enormous polymorphisms in mtDNA among mice and dramatic differences in nuclear genomes of these seven inbred strains, our findings were surprising (Nadeau et al., 1981; Zhang et al., 1998; Wiltshire et al., 2003; Yalcin et al., 2004). Compared with nuclear DNA, mtDNA is characterised by faster evolution and more polymorphisms. In mammals, the variation rate of mtDNA sequence is about 1% (Upholt et al., 1977; Brown et al., 1981). However, the absence of mtDNA variations contrasts sharply with the presence of large nuclear differences in these strains we studied. This finding may be explained by a close kinship and narrow genetic background (Dai et al., 1999). It was reported that all of the

'old inbred' strains (BALB/c, C3H, C57BL/6J, DBA2, C58/J, SWR/J, AU/SsJ, PL/J and AKR/Cum), unlike wide or wild-derived inbred mouse strains, had an identical mtDNA restriction endonuclease fragment pattern, suggesting a single maternal lineage (Ferris et al., 1982). The nine 'old inbred' strains are thought to stem from a minimum of five different female mice, which founded the primary strains. If these five females had been picked at random from wild strains, the probability that all of them shared a common type of mtDNA would have been extremely low (~10^{-7}; Ferris et al., 1982). However, most or all of them came from the pet mouse trade, where the 'old inbred' type of mtDNA could already have been present at a high frequency. Non-random sampling, selective advantage and interstrain contamination are three possible explanations that all the 'old inbred' strains contain a common type of mtDNA and thus appear to be of a single maternal lineage.

In the present study, we corroborate the conclusion by Ferris et al. (1982) using RFLP analysis. Moreover, we suggest that the TA2, T739 and 615 strains, although established in China, share a common maternal lineage with 'old inbred' strains. The polymorphisms in nuclear DNA among these strains are caused primarily by mating with different males. This conclusion is also consistent with the recorded origin of the inbred strains. Many of the strains are related, have come from a common outbred colony, or have a common ancestry or other form. For example, the TA2 strain originated from 'Kunming' outbred 'Swiss' strain obtained from Haffkin Medical Science Institute of India in 1946 (Wang et al., 1992); the 615 strain was derived from a 'Kun Ming' mouse mated with a C57BL/6 mouse (Li et al., 1989) and the T739 strain was derived from a cross between an albino 'Kunming' female mouse with a male mouse of 615 strain, followed by sib mating, in 1973. The 'Swiss' mice from mainly commercial sources, inbred in different laboratories, are the origin of many inbred strains. For example, SWR mouse, an 'old inbred' strain, originated from Swiss mice inbred by Lynch since 1926 (data from the Mouse Genome Database at the Mouse Genome Informatics Web Site, The Jackson Laboratory, Bar Harbor, ME, USA; http://www.informatics.jax.org). Therefore, the TA2, T739 and 615 strains, as well as the 'old' strains such as BALB/c, DBA and C57BL, originated from relatively closed and population-limited pet mouse colonies, and the chances are that these inbred strains are of a common maternal lineage.

References

Alonso, A., Martin, P., Albarran, C., Garcia, O. and Sancho, M. (1996). Rapid detection of sequence polymorphisms in the human mitochondrial DNA control region by polymerase chain reaction and single-stranded conformation analysis in mutation detection enhancement gels. *Electrophoresis* **17**, 1299-1301.

Anderson, S., Bankier, A. T., Barriel, B. G., De Brujin, M. H. L., Coulson, A. R., Drouin, J., Eperon, I. C., Nierlich, D. P., Roe, B. A., Sanger, F., et al. (1981). Sequence and organization of the human mitochondrial genome. *Nature* **290**, 457-465.

Beck, J. A., Lloyd, S., Hafezparast, M., Lennon-Pierce, M., Eppig, J. T., Festing, M. F. and Fisher, E. M. (2000). Genealogies of mouse inbred strains. *Nat. Genet.* **24**, 23-25.

Bonhomme, F. and Guenet, J. L. (1996). The laboratory mouse and its wild relatives. In *Genetic Variants and Strains of the Laboratory Mouse*, 3rd edn (ed. M. F. Lyon and A. G. Searle), pp. 1577-1596. Oxford, New York: Oxford University Press.

Bonhomme, F., Guenet, J. L., Dod, B., Moriwaki, K. and Bulfield, G. (1987). The polyphyletic origin of laboratory inbred mice and their rate of evolution. *J. Linn. Soc.* **30**, 51-58.

Brdicka, R. (1994). Modern methods of mitochondrial genome analysis. *Cas. Lek. Cesk.* **133**, 751-754.

Brown, G. G. and Simpson, M. V. (1981). Intra- and interspecific variation of the mitochondrial genome in *Rattus norvegicus* and *Rattus rattus*: restriction enzyme analysis of variant mitochondrial DNA molecules and their evolutionary relationships. *Genetics* **97**, 125-143.

Brown, W. M. and Wright, J. W. (1979). Mitochondrial DNA analyses and the origin and relative age of parthenogenetic lizards (genus *Cnemidophorus*). *Science* **203**, 1247-1249.

Chinnery, P. F., Howell, N., Andrews, R. M. and Turnbull, D. M. (1999). Mitochondrial DNA analysis: polymorphisms and pathogenicity. *J. Med. Genet.* **36**, 505-510.

Dai, J., Wei, H. and Xiao, Y. (1999). PCR-RFLP analysis on mitochondrial DNA D-Loop area of six inbred mice. *J. Med. Coll. PLA* **21**, 709-711.

Dai, J., Wei, H. and Xiao, Y. (2000). A simple and quick producing way of mitochondrial DNA. *J. Med. Coll. PLA* **15**, 391-392.

Ferris, S. D., Sage, R. D. and Wilson A C. (1982). Evidence from mtDNA sequences that common laboratory strains of inbred mice are descended from a single female. *Nature* **295**, 163-165.

Ferris, S. D., Sage, R. D., Prager, E. M., Ritte, U. and Wilson, A. C. (1983). Mitochondrial DNA evolution in mice. *Genetics* **105**, 681-721.

Finnila, S., Hassinen, I. E., Ala-Kokko, L. and Majamaa, K. (2000). Phylogenetic network of the mtDNA haplogroup U in Northern Finland based on sequence analysis of the complete coding region by conformation-sensitive gel electrophoresis. *Am. J. Hum. Genet.* **66**, 1017-1026.

Gross, A. W., Aprille, J. R. and Ernst, S. G. (1994). Identification of human mitochondrial DNA fragments corresponding to the genes for ATPase, cytochrome c oxidase, and nine tRNAs in a denaturing gradient gel electrophoresis system. *Anal. Biochem.* **222**, 507-510.

Hecht, N. B., Liem, H., Kleene, K. C., Distel, R. J. and Ho, S. M. (1984). Maternal inheritance of the mouse mitochondrial genome is not mediated by a loss or gross alteration of the paternal mitochondrial DNA or by methylation of the oocyte mitochondrial DNA. *Dev. Biol.* **102**, 452-461.

Ideraabdullah, F. Y., de la Casa-Esperon, E., Bell, T. A., Detwiler, D. A., Magnuson, T., Sapienza, C. and de Villena, F. P. (2004). Genetic and haplotype diversity among wild-derived mouse inbred strains. *Genome Res.* **14**, 1880-1887.

Jaksch, M., Gerbitz, K. D. and Kilger, C. (1995). Screening for mitochondrial DNA (mtDNA) point mutations using nonradioactive single strand conformation polymorphism (SSCP) analysis. *Clin. Biochem.* **28**, 503-509.

Li, Z. (1989). *615 Inbred Strain and its Application in the Experimental Tumor Research,* pp. 12-13. Beijin: The Republic Sanitary Publishing House.

Marchington, D. R., Macaulay, V., Hartshome G. M., Barlow, D. and Poulton, J. (1998). Evidence from human oocytes for a genetic bottleneck in an mtDNA disease. *Am. J. Hum. Genet.* **63**, 769-775.

Nadeau, J. H., Wakeland, E. K., Gotze, D. and Kline, J. (1981). The population genetics of the H-2 polymorphism in European and North African populations of the house mouse (*Mus musculus* L.). *Genet. Res.* **37**, 17-31.

Oleinik, A. G., Skurikhina, L. A. and Brykov, V. A. (2003). Genetic differentiation of three sympatric charr species from genus *Salvelinus* inferred from PCR-RFLP analysis of mitochondrial DNA. *Genetika* **39**, 1099-1105.

Prager, E. M., Tichyt, H. and Sage, R. D. (1996). Mitochondrial DNA sequence variation in the eastern house mouse, *Mus musculus*: comparison with other house mice and report of a 75-bp tandem repeat. *Genetics* **143**, 427-446.

Satoh, M. and Kuroiwa, T. (1991). Organization of multiple nucleoids and DNA molecules in mitochondria of a human cell. *Exp. Cell Res.* **196**, 137-140.

Song, X., Deng, J. H., Liu, C. J. and Bai, Y. (2005). Specific point mutations may not accumulate with aging in the mouse mitochondrial DNA control region. *Gene* **350**, 193-199.

Thomas, A. W., Morgan, R., Sweeney, M., Rees, A. and Alcolado, J. (1994). The detection of mitochondrial DNA mutations using single stranded conformation polymorphism (SSCP) analysis and heteroduplex analysis. *Hum. Genet.* **94**, 621-623.

Tucker, P. K., Lee, B. K., Lundrigan, B. L. and Eicher, E. M. (1992). Geographical origin of the Y chromosomes in 'old' inbred strains of mice. *Mamm. Genome* **3**, 254-261.

Upholt, W. B. and Dawid, I. B. (1977). Mapping of mitochondrial DNA of individual sheep and goats: rapid evolution in the D loop region. *Cell* **11**, 571-583.

Wada, A., Kakizoe-Ishida, Y., Katoh, H., Muguruma, K., Ebukuro, M., Okumoto, M. and Tsudzuki, M. (2000). Establishment and characterization of the MSKR inbred strain originated from Japanese wild mice (*Mus musculus molossinus*). *J. Vet. Med. Sci.* **62**, 427-434.

Wallace, D. C. (1994). Mitochondrial DNA variation in human evolution and disease. *Proc. Natl. Acad. Sci. USA* **91**, 8739-8746.

Wang, Q., Xin, R., Fan, W. and Wang, M. (1992). Mitochondrial DNA restriction endonuclease enzyme-cuting analyzing on Chinese inbred line mice TA1 et al. *J. Ch. Exp. Zool.* **2**, 153-156.

Wei, H. (1998). *Medical Laboratory Animal Science*, pp. 24-54. Chengdu: Sichuan Science and Technology Publishing House.

Wiltshire, T., Pletcher, M. T., Batalov, S., Barnes, S. W., Tarantino, L. M., Cooke, M. P., Wu, H., Smylie, K., Santrosyan, A., Copeland, N. G. et al. (2003). Genome-wide single-nucleotidepolymorphism analysis defines haplotype patterns in mouse. *Proc. Natl. Acad. Sci. USA* **100**, 3380-3385.

Yalcin, B., Fullerton, J., Miller, S., Keays, D. A., Brady, S., Bhomra, A., Jefferson, A., Volpi, E., Copley, R. R., Flint, J. et al. (2004). Unexpected complexity in the haplotypes of the commonly used inbred strains of laboratory mice. *Proc. Natl. Acad. Sci. USA* **26**, 9734-9739.

Zeviani, M., Tiranti, V. and Piantadosi, C. (1998). Reviews in molecular medicine: mitochondrial disorders. *Medicine* **77**, 59-72.

Zhang, X., Meng, Y. and Cai, Y. (1998). The analysis of mouse DNA restriction fragment length polymorphism. *J. Zool.* **44**, 360-364.

Zhang, Y. and Shi, L. (1992). General research progress of animal mitochonduial DNA polymorphism. *Zool. Res.* **13**, 289-293.