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Phenotypic characteristics of commonly used inbred mouse strains

(Running title: Characteristics of common inbred mice)

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Abstract

The laboratory mouse is the most commonly used mammalian model for biomedical research. An enormous number of mouse models, such as gene knockout, knockin, and overexpression transgenic mice, have been created over the years. A common practice to maintain a genetically modified mouse line is backcrossing with standard inbred mice over several generations. However, the choice of inbred mouse for backcrossing is critical to phenotypic characterization because phenotypic variabilities are often observed between mice with different genetic backgrounds. In this review, the major features of commonly used inbred mouse lines are discussed. The aim is to provide information for appropriate selection of inbred mouse lines for genetic and behavioral studies.

Keywords

Gene targeting, Genetics, Inbred, Mouse, Phenotype, Transgenic

Introduction

The laboratory mouse is the most commonly used mammalian animal model for a wide range of biomedical research fields, such as genetics, pharmacology, and learning and behavioral studies. The advantages of using mouse models include well-defined genomic information, well-established protocols for transgenic and genetic manipulation, relatively short life-cycle, relatively large litter size for use in multiple studies, and ease in maintaining a genetically pure line.

Over the past century, a vast number of genetically modified mouse models have been generated in laboratories around the world. Genetic modifications can be produced by gene knockout, gene knockin, transgenic manipulation, gene trapping, physical- or chemical-induced mutagenesis, and spontaneous mutation. After obtaining the founder mice with the desired genetic modification, the mouse line must be maintained in a defined genetic background. A common practice is to intercross the mutant mouse with a control inbred mouse for at least ten generations to obtain congenic strains [1]. Traditionally, by definition, an inbred strain is produced by 20 or more consecutive generations of brother-sister mating such that an average of at least 98.6% of the genome is homozygous in every individual mouse [2,3]. Contemporary approach, namely “speed congenesis”, which involves selection of the best breeder that carries the highest percentage of recipient genome indicated by strain-specific microsatellite DNA markers, is a faster and more efficient approach of congenic production [4]. Inbred mice are hence relatively more genetically and phenotypically stable than outbred stocks [3]. Several studies have attempted to investigate phenotypic differences among inbred strains and their F1 hybrids in a way to examine the phenotypes of mice with mixed genetic background [5-10].

In this review, the generation and substrains, major phenotypic characteristics, genotypes and tumorigenesis of some commonly used inbred mouse strains were described. The advantages

and potential problems of using inbred mice were also discussed. The aim is to provide general information for selecting appropriate mouse strains for maintaining genetically modified mice to minimize the artifacts from the genetic background when carrying out experiments using a mouse model. We attempted to cover the most representative strain from the following clusters based on genealogy and phylogenetic studies [2,11-14], including DBA and Bagg albino-derived strains (DBA, CBA, C3H, BALB/c, A), C57 group (C57BL/6J, C57BL/6N, C57BL/10), Swiss strains (SWR, SJL, FVB), and Castle's mice (129) (Figure 1). For those inbred mouse strains not covered in this review, further information can be found in the databases listed in Table 1.

DBA and Bagg albino-derived

DBA

Generation and substrains DBA, the oldest inbred mouse strain, was produced by Clarence C. Little in 1909 and was named after its coat color mutations (*diluted* (*d*), *brown* (*b*), and *nonagouti* (*a*)) [2,11,13]. Two major substrains of DBA (DBA/1 and DBA/2) mice have been derived and both substrains are used as models of sudden unexpected death in epilepsy (SUDEP) in human patients [15,16].

Phenotype and genotype DBA/1 mice spontaneously develop age-related arthritis in the hind paws at the age of 10 weeks [17] and subsequently progress into entheseal ossification, leading to marginal ankyloses at approximately six months of age [18].

DBA/2 mice have been found to have hippocampal dysfunction at the age of three months [19], as reflected by their poor performance in spatial learning tasks, such as the Morris water maze [20], radial arm maze [21], Y maze [22], and contextual fear conditioning [23]. The impaired

hippocampal function of DBA/2 mice may be associated with shortened intra/infrapyramidal mossy fiber projection in the CA3 neurons [21] and a reduced expression level of protein kinase C in the hippocampus [20,23]. In addition, DBA/2 mice may have a higher bursting in their CA3 hippocampal neurons and thus perform better than DBA/1 mice in shuttle box experiments [24].

DBA/2 mice also display social deficit and anxiety-like behavior, as indicated by elevated plus maze and dark-light exploration test [25,26]. In contrast, other studies showed that they are less anxious and more exploratory in open field test [27,28]. The difference could possibly be due to single mouse housing in the former studies and group housing in the latter studies. DBA/2J mice develop progressive glaucoma during aging, as characterized by the thinning of inner retinal layers, as well as reductions in the number of ganglion neurons and subpopulations in GABAergic and cholinergic amacrine cells, and elevated intraocular pressure [29]. DBA/2 mice have also been used as experimental models of schizophrenia because they have impaired inhibitory auditory processing of the P20-N40 auditory evoked potential (AEP), which is analogous to the insufficient inhibitory processing of P50 AEP observed in schizophrenia patients. The deficiency in P50 AEP gating may lead to overwhelming sensory input and thus contribute to the development of hallucinations [30]. Notably, DBA/2J mice develop age-related hearing loss as indicated by their failure to respond initially to high frequency sound first noticed at three weeks of age and progressing until they are unable to respond to a broad range of frequencies between two and three months of age [31], rendering the strain an extensively useful model for hearing research [32].

The early-onset and progressive hearing loss in DBA/2J mice is caused by at least two mutations, namely, the G→A transition at nucleotide 753 in exon 7 of *Cadherin 23* (*Cdh23*) (*Cdh23*$^{753G \rightarrow A}$) and *Fascin-2* (*Fscn2*) (R109H) [32-34]. Cadherin 23 is a single-pass

transmembrane protein that belongs to a family of calcium-dependent cell-cell adhesion molecules. This cadherin protein localizes at the upper end of the extracellular tip link filaments in both inner and outer hair cells of the inner ear [35], and it is thought to be one of the two structural components of tip links that is critical for mechanoelectrical transduction of cochlear hair cells [35]. Cdh23 is essential for the development of hair cell stereocilia, and the loss of Cdh23 function results in hair cell death and thus sensorineural deafness [36]. Cdh23 mutations have been found in many inbred mice that also exhibit age-related hearing loss [37]. It is known that different strains of inbred mice present with variable phenotypes in terms of the severity and time of onset of age-related hearing loss, among which DBA/2J mice demonstrate a much earlier onset and more rapid deterioration in hearing than do DBA/1J and C57BL/6J mice [37]. In addition, in contrast to the *Cdh23* mutation, which is commonly found in many inbred mouse strains, the *Fscn2* mutation is unique to DBA/2J mice [34]. *Fscn2* encodes an actin cross-linking protein that is abundantly expressed in stereocilia in the inner ear and plays a critical role in stabilizing stereocilia [34]. In particular, age-related expression of Fscn2 was observed in which rapid elevation of Fscn2 in the tip of the stereocilia was found from postnatal day 5 to postnatal day 10 and remained high in the adult stage. Furthermore, restoration of the functional *Fscn2* gene in DBA/2J mice rescues hearing [34], suggesting the association of Fscn2 with early onset and severe phenotypes. For these reasons, DBA/2J mice constitute an extremely valuable strain to study aged-related hearing loss and the histopathological and genetic basis involved. However, it may not be a suitable strain for testing for prepulse inhibition (PPI), a neurological phenomenon that relies on proper auditory function [5,37-39].

Tumorigenesis DBA mice prone to high incidences of mammary tumors as they are carriers of the retrovirus mouse mammary tumor virus (MMTV) [40-42], which integrates into the host genome and is transmitted via germline or lactation [40,43].

CBA

Generation and substrains CBA mice constitute a strain produced by Strong in 1920 [44,45]. Mice of this strain have a close relationship with DBA mice as CBA mice are derived from crossing Bagg albino females with DBA males according to known genealogical records [11,13]. Two major strains CBA/J and CBA/CaJ are commonly used for auditory [46,47] and leukemia research [48].

Phenotype and genotype Prominent spontaneous abortion [49,50] results from the intercrossing of female CBA (in particular CBA/J) mice and male DBA/2 mice (About 30% fetal resorption, compared to 8-13% in CBA ♀ × BALB/c ♂ mice, CBA ♀ × CBA ♂ mice, DBA/2 ♀ × CBA ♂ mice, and DBA/2 ♀ × DBA ♂ mice) [49-52]. Later, studies showed that the resorption of the fetus is a result of infiltration of immune cells, predominantly natural killer cells, into the ectoplacental cone [53] beginning at approximately gestational day 7 and persisting until day 10-12, when the fetal placental units are obviously resorbed [54]. In addition, it has been proposed that complement activation leading to dysregulation of angiogenesis plays an important role in the CBA × DBA/2 mouse model of pregnancy loss, as activation of complement during the process of implantation occurs in the CBA × DBA/2 mouse model but not in the CBA × BALB/c mouse model, as suppression of the self-targeting immune response can be mediated in BALB/c mice

[51]. Thus, the model of CBA × DBA/2 mice has served as the most widely used model for studying pregnancy loss since the early 1980s [55-59].

It has been suggested that CBA mice are relatively more aggressive than DBA or C57BL mice, although there is no significant difference in the levels of serotonin in various parts of the brain in these three strains [60]. CBA/J mice are susceptible to otitis media [8,46,59], and in contrast to that of DBA/2 mice, aging-associated auditory loss occurs only in late life of the CBA/J mice [61,62]. The recessive *retinal degeneration 1* (*rd1*) mutation in the *Phosphodiesterase 6B* (*Pde6b*) (*Pde6b*^{rd1}) [63] leads to the blindness of all adult CBA/J mice by nine weeks of age [56] which prevents this strain from cognitive behavioral experiments involving visual memory. On the other hand, CBA/J mice develop exocrine pancreatic insufficiency syndrome at two weeks of age [64-66] and a high incidence of renal tubulointerstitial lesions at approximately three months [67].

Tumorigenesis The incidence of spontaneous tumors in CBA mice was rare up to two years of age, although occasions of visceral tumors in the mammary gland, liver, uterine and ovary were observed in CBA females at the age around 18 months [44]. Besides, CBA mice have a low likelihood (0.1-1% incidence) of developing spontaneous acute myeloid leukemia (AML) upon exposure to radiation, but they demonstrate cytogenetic, molecular and histopathological features of disease that resemble those of human AML, making the strain favorable for modeling radiation-induced AML and studying human AML [48].

C3H

Generation and substrains C3H mice are close relatives of CBA mice because the C3H strain was also developed in 1920 by Strong, who crossed Bagg albino females with DBA males

[11,13,68] . The most commonly used substrain of C3H is the C3H/He strain derived by Heston [13,69]. Other C3H substrains are reviewed elsewhere [68].

Phenotype and genotype There are some known gene mutations in the C3H/HeJ mice in the Jackson Laboratory. The first is the spontaneous mutation in *Toll-like receptor 4* (*Tlr4*) gene at the lipopolysaccharide (LPS) response locus ($Tlr4^{Lps\text{-}d}$), which makes C3H/HeJ mice more resistant than *Tlr4* wild-type C3H/HeN mice to endotoxin-induced death [70,71]. The second is the homozygous mutation in $Pde6b^{rd1}$, the same gene mutation found in the CBA mice, that causes retinal degeneration by weaning age [8,59,63]. Therefore, both CBA and C3H mice are unfavorable choices for backcrossing strains for mutant mice with a vision phenotype. In addition, *Pecanex-like 2* (*Pcnxl2*) and *Ionotropic glutamate receptor AMPA4 (alpha 4)* (*Gria4*) are mutated as a result of an insertion of an natural murine intracisternal A-type particle (IAP) retrotransposon in the C3H/HeJ mice, but not in another C3H substrain, C3Heb/FeJ [72]. The reduced expression of *Pcnxl2* and *Gria4* leads to an increase in both the incidence and duration of spike-wave discharges, abnormal brain waves that are associated with absence epilepsy (nonconvulsive seizure) in C3H/HeJ mice [72]. Therefore, genetic background should be taken into account when epilepsy research is carried out in mice with a C3H/HeJ background. Besides, C3H substrains (C3H/HeJ, C3H/HeJBir, C3H/HeN/J, and C3H/OuJ) have spontaneous hair loss from 7 months to 12 months, and can be used as animal models for human alopecia areata [73,74].

Tumorigenesis C3H is another mouse line with high incidence of spontaneous mammary gland carcinoma development at about 8 to 9 months old [75] due to the dominant expression of MMTV that activates signaling cascades involved in oncogenesis, e.g., Wnt signaling. It is, in fact, results from a comparison of differential genes in MMTV mammary tumors and normal mammary tissues that led to the discovery of the first mammalian *Wnt* gene [76]. Therefore, C3H strain is

useful as a mouse mammary tumor model not only for testing interventions but also for identifying novel oncogenes in human breast cancers [43]. In addition, 85% of male C3H mice develop spontaneous primary hepatomas at 14 months of age [77].

BALB/c

Generation and substrains The BALB/c mouse strain, with its name deriving from **B**agg **ALB**ino (**c** refers to the albino allele), is composed of albino mice developed in 1913 by Halsey Bagg [13,78,79]. Many BALB/c substrains have been created and used in immunology research [79,80].

Phenotype and genotype BALB/c mice are among the most commonly used inbred mice in the laboratory for immunology research and they have Th2 biased responses to pathogens [81,82]. Female BALB/c mice are highly susceptible to proteoglycan-induced polyarthritis and spondylitis, with significant mononuclear cell infiltration and edema in synovial tissues of the knee joint [83]. Besides, it has been found that the number of B cell precursors in BALB/c mice is significantly decreased in aged mice (22-24 months old) compared to the level in young mice (2-4 months old) [84]. Such reduction in the precursors also linked to a significant reduction of mature marginal zone B cells ($CD21^{+}CD23^{-}$) in the spleen of aged BALB/c mice as compared to the young counterparts [85,86]. As the marginal zone B cells play a central role in the first line of immune defense against blood-borne antigens, reduction in this cell population during aging was therefore believed to reflect a decline in immune response in aged mice. However, later research showed that the number of marginal zone B cells was maintained across ages in C57BL/6 strain (which has Th1-predominant immune response) [82,87,88], indicating distinct lymphogenesis during

aging between strains. Moreover, the two strains also exhibit different responses towards infection with *Ureaplasma parvum*, a bacterium that is commonly found in the amniotic fluid of women with chorioamnionitis that is associated with preterm labor, premature rupture of amniotic membrane, fetal infection and fetal morbidity. C57BL/6 mice infected with *U. parvum* showed only mild to moderate chorioamnionitis, which may be associated with significant reduction of proinflammatory cytokines, low level of CD14 (high level of CD14 was suggested to induce damages to fetuses) and high density of macrophages in placental tissues. In contrast, *U. parvum*-infected BALB/c showed much severe responses, such as significant elevations of CD14 and proinflammatory cytokines, and a reduced density of placental macrophages. Furthermore, the production of interleukin 12 (Il-12) in BALB/c antigen-presenting cells upon induction by keyhole limpet hemocyanin (KLH) is significantly less than that in DBA/2 mouse cells, and the KLH-primed CD4 T cells in BALB/c mice produce relatively high amounts of Il-4 and less interferon gamma (Ifng) [89]. Overall, all these studies have demonstrated that cytokine syntheses and immune responses in BALB/c mice are distinctive, and these features should be considered when using BALB/c mice for immunological research.

BALB/c mice have poor visual acuity [90] and progressive sensorineural hearing loss with an onset of 10 months of age [39,91]. Besides, several studies showed that BALB/c mice display autism-like behaviors, such as low sociability, resistance to change, high levels of anxiety and aggressiveness. For example, BALB/cJ mice spent less time than C57BL/6J mice in direct contact with the stimulus mouse in the three-chambered apparatus test [92-94]. BALB/c mice carry a single nucleotide polymorphism (C1473G) in *Tryptophan hydroxylase 2* (*Tph2*) and are found to have a significant reduction in serotonin synthesis in the frontal cortex and striatum, and these features may be associated with symptoms of autism spectrum disorder [95,96]. In addition,

BALB/c mice have been used for the study of circadian rhythms because of their diminished capacity to sustain stable rhythmicity [97-99]. In response to stress, however, BALB/c mice exhibited anxious and stress-sensitive behavior, such as significant body weight loss [100] and longer times spent grooming [95,101]. Compared to other inbred strains, BALB/c mice demonstrated a moderate to high level of inter-male aggressiveness [94,102]. These autism-like behaviors may be attributed to the absence or reduced size of the corpus callosum [103-105] and an overall smaller brain [106].

BALB/c mice have also been used for cardiovascular research. For example, BALB/c mice were found to carry a resistant allele of *Ath-1* (subsequently called *tumor necrosis factor (ligand) superfamily member 4*, *Tnfsf4*), and they have higher levels of high-density lipoprotein cholesterol (HDL-C) than are observed in C57BL/6J mice, which carry a susceptibility allele, when fed an atherogenic diet [107,108]. On the other hand, a genetic study showed abnormally high levels of *α-cardiac* and *α-skeletal actin* mRNAs in the cardiac tissues of BALB/c mice due to duplication of the gene promotor and the first three exons of the *α-cardiac actin* gene, although such mutations do not affect mouse cardiac function or survival [109].

Tumorigenesis Upon aging, BALB/c mice spontaneously develop various types of tumors, such as reticular neoplasm, lung tumors, renal tumors, reticule sarcoma and leukemia [110,111]. Despite this apparent predisposition to tumorigenesis, BALB/c mice demonstrate a low incidence of mammary tumors. However, they are highly susceptible to exogenous MMTV infection [112,113]. Therefore, it is suspected that the reported high incidences of mammary tumors in BALB/c mice could be the result of MMTV infection in the mammary tissues rather than germline defects [113].

Plasmacytoma, although rarely develop in young BALB/c mice, can be induced via intraperitoneal injection of mineral oil, a natural saturated terpenoid alkane called pristine, solid plastic implant, and silicone gel [114,115]. These agents share a common feature, which serve as chronic inflammatory agents that initially stimulate the formation of granulomas, which then adhere to the peritoneal connective tissue and gradually develop into plasmacytoma [116]. BALB/c showed exceptionally high incidence of plasmacytoma, while other common strains, such as C57, C3H, CBA, DBA, and SWR, are relatively resistant to the induction [117]. In addition, around 90-95% of induced plasmacytomas carry a non-random chromosomal translocation of immunoglobulin gene loci (on either chromosome 6, 12 or 16) with *Myelocytomatosis oncogene* (*Myc*) in chromosome 15, such that the deregulated *Myc* gene drives neoplastic development of B cell, resulting in the development of plasmacytoma. The chromosomal translocation exhibited in BALB/c T(12;15) is very similar to that of Burkitt lymphoma in human, thus offering an extremely useful model to help understanding the B cell neoplastic development. For example, it has been reported that BALB/c demonstrated resistance to pristine-induced plasmacytoma when crossing with CBA mouse carrying a gene encoded for a defective Bruton agammaglobulinemia tyrosine kinase (Btk), a cytoplasmic tyrosine kinase that transduce signals from B cell receptor [118]. Research in the past two decades have shown that B cell receptor pathway plays a key role in proliferation, differentiation and survival in B-cell malignancies, as well as the potential use of Btk inhibitor in the target therapy for B-cell lymphoma [119].

A

Generation and substrains Strain A is an albino strain established by Strong in 1921 [120,121] and then passed to John J. Bittner in 1927 [122]. Substrains of A/J, A/He and A/WySn were further derived from this strain [13].

Phenotype and genotype Compared to those of C57BL/6 mice, the skeletal muscles of A/J mice have a significantly higher level of the proinflammatory cytokine *Tumor necrosis factor alpha* (*Tnf-α*) [123], which is likely the result of inflammatory macrophage infiltration upon progressive muscle fiber damage [124]. A study comparing the rotarod performance of 8 strains of inbred mice (129, A, BALB/c, C3H, B6, CBA, D2, and FVB strains) indicated that strain A ranked the lowest in terms of rotarod (both active and passive) performance [125], possibly due to the muscular dystrophic condition of these mice. On the other hand, strain A mice displayed the highest levels of spontaneous anxiety-related behavior, as shown by a very low number of transitions in the light/dark box [126]. Compared with those of the C57BL/6J mice, the shorter-lived A/J mice have higher error rates in the T-maze and shorter retention times on a balance beam, suggesting that A/J mice may not be an ideal model to study age-related behavioral performance [127].

A/J mice carry the homozygous *Cdh23*$^{753G\rightarrow A}$ mutation and thus develop age-related hearing loss [33,128]. Strain A mice also serve as mouse models for limb-girdle muscular dystrophy type 2B (LGMD2B). In humans, LGMD2B is characterized by progressive muscular dystrophy, affecting mainly the pelvic and shoulder girdles and lower limb muscles as a result of mutation in a gene called Dysferlin (*DYSF*) [129]. Dysferlin is a transmembrane protein that plays a role in sarcolemma resealing to prevent muscle fiber degeneration [130]. It is also expressed in the T-tubule system in skeletal muscle and contributes to sarcolemma repair [131,132]. Harboring

a retrotransposon insertion in intron 4 that leads to abnormal splicing of the *Dysf* gene, strain A mice exhibit muscle weakness at 4 to 5 months of age [133-135].

Tumorigenesis Strain A mice have been used to study both spontaneous and chemically-induced lung tumor. It has been reported that strain A mice develop lung tumors spontaneously by 24 months [136-139]. While studies demonstrated that strain A (strain A/J and A/HeJ from JAX) showed a high incidence of lung tumor development upon exposure to cigarette smoke compared to that of the sham air negative control [140-142], such high susceptibility to cigarette smoke-induced lung tumor development was not observed in some resistant strains (e.g., C3H and DBA strains) [141]. Although both strain A and SWR mice develop spontaneous lung tumors [138,139], it has been shown that strain A is more susceptible to cigarette smoking-induced lung tumors than are SWR mice [141], making strain A a comparatively more useful model for studying the impact of cigarette smoking on lung tumorigenesis.

C57 group

C57BL/6J

Generation and substrains C57BL/6 substrains are the most commonly used inbred mice for maintaining mutant lines. Initially, this strain was established at the Jackson Laboratory by Clarence C. Little in 1921 and was designated C57BL/6J. In the 1950s, the National Institutes of Health (NIH) derived its own mouse line from the C57BL/6J mice, and designated the line as C57BL/6N [143-147]. Several sublines, such as C57BL/6Ei, C57BL/6By, C57BL/6JOlaHsd, etc. have also been created and maintained by commercial vendors. Genetic trees and detailed breeding

histories of C57BL/6 substrains are reviewed elsewhere [143-147]. C57BL/6J genome was the first one to be sequenced [148].

Phenotype and genotype Compared with C57BL/6N, there are 34 SNPs and 2 indels in the coding region as well as 2 structural variants overlapping with the *Vmn2r65* and *Nnt* genes and the *Cyp2a22* gene in the two substrains [144,149]. Nicotinamide nucleotide transhydrogenase (Nnt) is an inner mitochondrial membrane protein that catalyzes the reversible transfer of protons between NAD^+ and $NADP^+$ [150]. A large deletion in the *Nnt* gene in C57BL/6J mice greatly impairs the functions of their mitochondria and may be associated with defective physiological processes, such as a reduction of insulin secretion and manifestation of glucose intolerance [151,152] and suboptimal capacity for gas exchange and heat production in C57BL/6J mice compared to those of the C57BL/6N mice [149].

Despite the fact that C57BL/6N mice were derived from C57BL/6J mice, these two major C57BL/6 substrains have substantial genetic, physiological, and behavioral differences. A substantial difference in the expression of gene transcripts was found in the cortex, hippocampus, cerebellum, and ventral brain region in the C57BL/6J and C57BL/6NCrl mice [153]. In addition, higher level of reactive oxygen species (ROS) are generated by the cardiac mitochondria isolated from C57BL/6J mice than those found in the C57BL/6N mice [154]. The increase in H_2O_2 production in C57BL/6J mouse mitochondria also reduces the successful rate of *in vitro* fertilization of cryopreserved sperm, which may affect colony preservation [155,156]. Differences also include visual, hearing, bone development, and alopecia [157-163]. Although both C57BL/6 substrains develop cataracts in an age-dependent manner, the age of onset was much earlier in C57BL/6J mice (start at 37 weeks) as compared to C57BL/6N mice (start at 47 weeks) [157]. C57BL/6J mice develop age-related hearing loss, which is attributed to two homozygous mutations

in *Cdh23, Cdh23*^{10497del11} and *Cdh23*$^{753G\rightarrow A}$ [159], and may account for the differences in auditory functions between C57BL/6J and C57BL/6N mice [160]. During postnatal osteogenic development, these two substrains have distinctive bone formation and morphology, with the C57BL/6J mice having higher bone-to-tissue (v/v) ratios than C57BL/6N mice shown at 9 and 11 weeks of age [162]. Furthermore, among three C57BL/6J substrains (C57BL/6J, C57BL/6J-RccHsd, and C57BL/6J-OlaHsd), trabecular bone fraction is significantly lower in C57BL/6J-OlaHsd mice, which uniquely carry *Synuclein, alpha* (*Snca*) and *Multimerin 1* (*Mmrn1*) mutations [161]. Finally, alopecia in focal, dorsal and thoracic regions are more frequently observed in C57BL/6J mice than in C57BL/6NCr [158,163].

Detailed examinations on the influence of the aging process on the behaviors of C57BL/6J mice have been performed by comparing young (2 to 3 months old) and old (8 to 12 months old) mice. Decreases in locomotor activity, sociability, and working and spatial memory were found, as were increases in anxiety-related behavior and pain sensitivity, in the mice of old age compared with the levels of these attributes found in the younger counterparts [164,165]. Other studies found that C57BL/6J mice displayed shorter latency in the hot plate test, longer time before falling in the rotarod test, longer duration in the open arms in the elevated plus maze test, shorter period of freezing during contextual fear and altered context tests, and longer distance traveled in an open field than were displayed by C57BL/6N mice [143,166].

Other distinctive phenotypes of C57BL/6J include portosystemic shunting with high level of glutamine in the brain [167] and relatively higher incidence of microphthalmia [168].

Tumorigenesis C57BL/6J mice in general have low susceptibility to tumor development, although it has been reported that the occurrence of spontaneous pituitary tumors in C57BL/6J female mice increases from 6 to 61% between 14 and 30 months [169].

C57BL/6N

Generation and substrains As mentioned C57BL/6N line was derived from the C57BL/6J mice by NIH [143-147]. The C57BL/6N mice were later sent to different commercial facilities to establish their own mouse lines, such as the C57BL/6NCrl strain (Charles River Laboratory), C57BL/6NHsd strain (Harlan Laboratories) and C57BL/6NTac strain (Taconic Biosciences) [170]. Importantly, all mutants generated in the Knockout Mouse Project (KOMP) are based on embryonic stem (ES) cell lines derived from C57BL/6N mice [171]

Phenotype and genotype C57BL/6N mice exhibit a poorer cardiac function than that exhibited by C57BL/6J mice [172], as shown by the reduced ejection fraction of left ventricle and cardiac output in the C57BL/6N mice [173], which may be associated with higher oxygen consumption by cardiac mitochondria in the C57BL/6N mice [154].

A serine to phenylalanine (S968F) mutation in the *Cytoplasmic FMRP interacting protein 2* (*Cyfip2*) was found specifically in C57BL/6N mice, that leads to an acute and sensitized response to cocaine relative to C57BL/6J mice [147].

Another genetic difference that indicates significant phenotype variations involves the *retinal degeneration 8* (*rd8*) mutation, which is a single nucleotide deletion in exon 9 in the *Crumbs family member 1* (*Crb1*) gene ($Crb1^{rd8}$), and it is specific to C57BL/6N mice but absent in C57BL/6J mice [174]. Crb1 is a transmembrane protein localized at the apical membrane of

Müller cells. The *rd8* mutation leads to the truncation of the Crb1 protein and the loss of its transmembrane domain toward the C-terminal. Thus, the Crb1 protein is not localized to the apical membrane, and its loss eventually leads to the disruption of the external limiting membrane [175]. The *rd8* mutation also leads to an increase in the total number of $Iba1^{+ve}$ subretinal microglia/macrophages and the activation of proinflammatory genes in aging C57BL/6N mice but not in C57BL/6J mice [176]. These results suggest that the contribution of the *rd8* mutation to the visual acuity of mice with a C57BL/6N background is an important concern.

Comparing the C57BL/6N and C57BL/6J mice, there was no significant baseline difference in sucrose preference test and forced swim test. However, C57BL/6N mice had significantly less exploratory locomotor activity in the open field test. Upon a chronic application of corticosterone, C57BL/6N mice consumed more food and gained body weight, had significantly decrease in center visits in the open field, reduced sucrose consumption, and increased immobility in forced swim test, implying the overall increase in anxiety-related behavior. While these behavioral changes were not observed in C57BL/6J mice. Therefore, C57BL/6N mice seem to be more sensitive to a long-term exposure to corticosterone [177].

With the C57BL/6N and C57BL/6J mice having phenotypic differences in various aspects of specific processes, it is strongly recommended that the two C57BL/6 substrains are not be used interchangeably.

Tumorigenesis It has been suggested that C57BL/6N is a tumor-resistant strain with very low incidence of spontaneous liver tumor development [178].

<u>C57BL/10</u>

Generation and substrains C57BL/10 mice share the same origin as C57BL/6. The subline 6 and 10 were separated sometime prior to 1937 [179]. There were two sublines derived in 1947 by the Jackson Laboratory (C57BL/10J) and G. D. Snell (C57BL/10Sn) [13]. The C57BL/10Sn was transferred to NIH and became C57BL/10ScN, which further led to the C57BL/10CR (Clarence Reeder of Frederick Cancer Research Center) strain [179]. Some other substrains, such as C57BL/10ScSn, C57BL/10Sx, C57BL/10WtRk, have been derived sometime later [180].

Phenotype and genotype Although C57BL/10 and C57BL/6 mice share the same origin, there are substantial phenotypic and genotypic differences between them. Behavioral studies have shown that C57BL/10ScSnOlaHsd mice are performed worse than C57BL/6JOlaHsd mice in some of the species-typical tests (e.g., burrowing, digging), cognitive tests (e.g., T-maze), and motor tests (e.g., horizontal bar) [180]. In terms of immune response, C57BL/10ScSnOlaHsd mice are more resistant against the infection of *Mycobacterium avium* than C57BL/6J mice [181]. Genetically, there are strain differences at multiple loci on chromosome 4 [182] and microsatellite polymorphisms [183].

C57BL/10 mice have been suggested as Th1-responsive [81] and are widely used in immunology research, especially on studying Tlr4 signaling. One subline, C57BL/10ScCR, was characterized as *Escherichia coli* LPS-resistant [179], which could be associated with a 74,723 bp deletion in *Tlr4* gene [71,184]. Such deletion was not found in closely related sublines C57BL/10ScSn [71,184] and C57BL/10J [185]. Therefore, C57BL/10ScCR ($Tlr4^{-/-}$) and C57BL/10J ($Tlr4^{+/+}$) mice are studied pair-wise to investigate Tlr4 signaling pathway [185,186]. Besides, it is found that the Goblet cell lectin, encoded by a gene called *Intelectin b* (*Itlnb*), was naturally deleted in C57BL/10 mice [187]. Up-regulation of *Itlnb* in response to nematode parasite *Trichinella spiralis* infection is exhibited in strains such as 129/SvEv and BALB/c. Such up-

regulation was however absent in C57BL/10 due to the natural gene deletion, although the function of Itlnb in immune response against parasite infection is not clear [187]. On the other hand, C57BL/10 mice have prominent loss of scotopic electroretinogram b-wave and thinner retinal layers with currently unknown genetic cause [188]. Whether such retinal abnormality affecting visual ability requires further investigation.

Tumorigenesis It has been observed that C57BL/10 is a strain with very low incidence of spontaneous hepatic tumors up to two years of age, although they are sensitive to hepatocarcinogens [189,190].

Swiss strains

SWR

Generation and substrains Swiss mice were imported to the US from Lausanne, Switzerland in 1926 by Clara Lynch. SWR is one of the inbred strains derived from the Swiss stocks in the Jackson Laboratories in 1947 [191].

Phenotype and genotype SWR mice, similar to other Swiss-derived strains such as FVB/N and SJL mice, naturally carry a 25 base pair deletion in exon 6 in *Disrupted in schizophrenia-1* (*Disc1*), resulting in a frameshift mutation that leads to the generation of a novel 13 amino acid peptide and with a premature stop codon in exon 7 [192-195]. *DISC1* is the first gene suggested to be associated with schizophrenia in humans [196]. Disc1 is a cytoskeletal protein highly expressed in dense postsynaptic dendritic spines, where it interacts with other synaptic proteins and is essential for synaptic plasticity [197,198]. Although not tested in SWR mice, C57BL/6J mice carried this *Disc1* mutation (derived from 129S6/SvEv mice) have deficits in working memory

without observable changes in gross brain morphology [193]. For this reason, SWR mice is expected to have some schizophrenia-like behavior. Besides, SWR mice also possess the *Pde6b*^{rd1} mutation leading to retinal degeneration [199]. Furthermore, deletions of segments of *T-cell receptor beta, variable region* (*Tcrb-V*) genes in SWR (as well as in FVB/NJ and SJL) may contribute to the resistance against arthritis induction [200].

In addition, symptoms of diabetes insipidus, including polyuria and polydipsia, are also observed in SWR/J mice [201-203]. SWR mice have been used for research on fat metabolism because they have less fat intake and are obesity-resistant on a high-fat diet [204,205]. High blood pressure and heart rate (compared with those of C3H/HeJ mice) are also observed in SWR mice, which render them relevant mouse models of hypertension in humans [206].

SWR is also highly susceptible to *Mycobacterium tuberculosis* infection in the lungs, which may be associated with a lower percentage of CD4 and CD8 T cells [207]. Hence, the SWR strain is suggested to be a good mouse model to study tuberculosis. On the other hand, T cell defects may also be associated with resistance to collagen-induced arthritis, as SWR mice produce antibodies against type II collagen [208]. The T cell deficiency and lack of the C5 component of the complement system [209] make SWR/J mice an interesting model for immunology research.

Tumorigenesis Relatively high incidences of spontaneous tumors, including lung (from 10 months onward), ovary (from one month onward) and mammary tumors (from 9 months onward), have been reported in SWR mice [201,210,211].

SJL

Generation and substrains SJL is one of the inbred strains derived from the Swiss colonies in the Jackson Laboratories in 1955 [191].

Phenotype and genotype SJL mice, similar to strain A mice, also develop myopathy and have been used as alternative mouse model for studying LGMD2B [133,212]. However, the onset of muscle degeneration is much earlier in SJL mice compared to that displayed by strain A mice [133,134]. This phenotype difference could be due to different mutations (in-frame deletion of 171 bp in the 3' splicing junction of exon 45) in the *Dysf* gene [133,213]. SJL mice also carry the mutations of *Disc1*, *Pde6b*^{rd1}, and *Tcrb-V* [133,194,200]. The exceptionally aggressive behavior of SJL mice renders them a widely used strain to study aggression in the mouse [214,215].

In addition, SJL mice have immunologic defects, such as limited immunoglobulin E (IgE) production and abolished *Il-4* mRNA expression upon injection of anti-IgD, reduced numbers of natural killer T cells upon anti-CD3 stimulation, and susceptibility to myelin-derived peptide-induced encephalomyelitis, a T-cell mediated autoimmune inflammatory disease in animal models that resembles many clinical features of multiple sclerosis in humans [216-218]. Injection of proteolipid protein (PLP) peptide induced a relapsing-remitting form of experimental autoimmune encephalitis (EAE) in the SJL/J strain but not in the BALB/c or C57BL/6 mice (in contrast, they produce a chronic form of EAE) [219]. The pattern of recurrent attack followed by periods of remission is the most common clinical form of multiple sclerosis, making SJL mice among the most widely used models of experimental autoimmune encephalitis to investigate multiple sclerosis etiology [220,221].

Tumorigenesis A high incidence (>85%) of massively enlarged lymph nodes and spleens [222], B-cell lymphomas and Hodgkin's-like multicellular reticulum-cell neoplasms [223,224] have been found in SJL/J mice beginning from 5 months of age.

FVB/N

Generation and substrains FVB/N mice compose another strain developed by the NIH in the 1970s, which was named because of its sensitivity to the Friend leukemia B-type virus [225]. These mice are commonly used for generating transgenic mice because of their intrinsic advantages, such as large pronuclei for easier microinjection, a very high survival rate of eggs that have been microinjected, high breeding performance and large litters [225,226]. Several vendors provide FVB/N strains, such as FVB/NTac (Taconic Biosciences), FVB/NHsd (Envigo), FVB/NCrl (Charles River Laboratories), and FVB/NJ (The Jackson Laboratory).

Phenotype and genotype One of the prominent features of FVB/N mice is retinal degeneration resulting from the *Pde6b*^{rd1} gene, which leads to rapid rod photoreceptor degeneration by 30 days [227,228]. Besides, FVB/N mice have a 6-kb deletion of *Beaded filament structural protein 2* (*Bfsp2*) that led to the deficiency of beaded intermediate filaments in the lens and reduction in lens optical quality [229]. Hence, due to the visual impairment of FVB/N mice, they are expected to have relatively poor performance in behavioral tests that rely on visual cues (e.g., the Morris water maze) [230]. In addition, the FVB/N strain comprises albino mice with a *Tyrosinase* (*Tyr*) mutation and unpigmented eyes, which further weaken their visual acuity [8]. Interestingly, their olfactory capacity is relatively high compared to that of the C57BL/6N mice, and their hearing ability seems to be good, as their auditory brainstem response threshold is low. The enhanced olfactory and hearing abilities could be a self-regulated mechanism to compensate for their early visual impairment [37,231]. Their inability to sense light may also cause dysregulated circadian rhythms, which may be manifested in the observed increase in running wheel activity of the FVB/N mice compared to that of the C57BL/6J mice during the light phase [230]. It has also been reported that

FVB/N mice are susceptible to neuropathologic seizures [232,233] and kainic acid-induced seizure [234,235]. FVB/N mice also carry the *Disc1* [193,194] and *Tcrb-V* mutation [200]. Since the FVB/N strain is commonly used for transgenic mouse production, these intrinsic properties should be taken into account when characterizing newly generated transgenic mice with a FVB/N background, particularly when the phenotypes to be characterized involve visual components or when physical activities, such as running wheel and rotarod, are to be assessed, especially during daytime.

Genetic background influences the susceptibility to experimental atherosclerosis induction. Taking *Apolipoprotein E* (*Apoe*)-deficient mice as an example, mutant mice with FVB/NJ background is known to be more resistant in the atherosclerosis induction as compared to those with C57BL/6J background [236]. It was later revealed that a NFκB-inhibitory protein A20 (aka Tumor necrosis factor, alpha-induced protein 3, Tnfaip3) is functionally more potent in FVB/NJ mice as compared to C57BL6/J in terms of suppressing the NFκB-IFNγ signaling-related atherosclerosis [237,238]. Recently, the genome of the FVB/NJ mice has been sequenced, and the genome data helps to elucidate how the genomic composition of FVB/NJ may contribute to atherosclerosis resistance [239]. As more genomes of inbred mice have been sequenced, these genomic data definitely facilitate the examination of genotype-phenotype relationships.

Tumorigenesis FVB/N mice have a relatively high rate of alveolar-bronchiolar tumors in the lung at the age of 24 months [240]. Spontaneous mammary hyperplasia has also been reported in female FVB/NCr mice by 13 months of age [241,242]. Spontaneous pituitary and mammary tumors were reported in aging FVB/NTac females (about 80 week-old) [243]. Besides, mucinous metaplasia in the prostate has been observed in about 50% of the male FVB/N mice [244].

Castle's mice

129

Generation and substrains 129 inbred strain was originated from crossing coat-color stocks from English fanciers and chinchilla stock from W. Castle by L. C. Dunn in 1928 [13,245]. Many 129 substrains were generated, and the complex breeding history has been reviewed elsewhere [246].

Phenotype and genotype In the early days of gene-targeting technology, targeted gene mutations were created in embryonic stem (ES) cells, of which most lines were derived from the 129 mouse substrains because of the particularly high successful rate in germline transmission [246-249]. The founder mutant mice were usually crossed with C57BL/6 mice to maintain a mixed or congenic background [7,248]. However, maintaining the mutant mice in a pure 129 genetic background is not preferred because 129 substrains have been reported to have anatomical defects, such as dysgenesis of the corpus callosum [247]. Additionally, variations in performance during zero-maze, open field, rotarod, fear conditioning tests, and behavior upon exposure to novel environment have been observed among the substrains of 129 mice [248,250-252]. This could complicate the interpretation of phenotypes of mutant mice with mixed 129 background. Following the successful establishment of highly-germline competent ES cell lines from C57BL/6 mice [253], maintaining gene-altered mice in isogenic background became feasible.

Genetically, the 129 substrains carry the same *Disc1* mutation (as those Swiss-derived strains) and thus is expected that mice of the 129 strain may exhibit some schizophrenia-like behaviors. In fact, subtle behavioral change was observed when a modified *Disc1* locus from

129SvEv mice was transferred to a mouse with a C57BL/6J background [193]. Therefore, the behavior of the mice with a 129 genetic background requires careful interpretation. Besides, a spontaneous six-amino acid deletion in the PEST domain (Δ^6PEST allele) of Chromatin licensing and DNA replication factor 1 (Cdt1) in 129 substrains (129/Ola, 129/J, and 129/Sv) has been reported. Cdt1 is a cofactor for pre-replication complex formation, and the PEST domain is essential for the interaction between Cdt1 and chromatin during mitosis. The effect of *Cdt1* mutation requires further characterization, as mice derived from 129 strains are viable [254].

Tumorigenesis It has long been reported that spontaneous testicular teratomas developed in various 129 sublines as early as 8 days old and the occurrence ranges from 3 to 30%, depending on the substrain [255-257]. Interestingly, both increased risk of the teratomas and ES derivation efficiency are associated with genetic factors on chromosome 18 in 129 substrains [258,259]. The high incidence of testicular teratomas also impairs reproductive ability and thus makes it more difficult to maintain the mouse line, although female factors have also been suggested for the low fertility of the strain [260].

Conclusion

This review summarizes important features of several commonly used inbred mouse strains. The major phenotypes of some commonly used inbred mouse lines are listed in Table 2. These strains have been used as various disease models (e.g., retinal degeneration or muscular dystrophy) or used to maintain a mutant mouse line through backcrossing. Some of the phenotypes may be acquired from the genetic background rather than from the intended genetic manipulation. It should be noted that new mutations could be introduced to the genome in every generation and

passed on to the offsprings by traditional inbreeding [261]. Besides, during the generation of genetically modified congenic mice, the targeted gene is flanked by passenger genes that are originated from the donor strain. These passenger genes, usually harboring mutations (passenger mutations), will still be retained in the congenic mice even after intensive backcrossing [262]. All of these could contribute to unexpected phenotypes and reduce the reproducibility of a particular mouse strain. It is not uncommon to observe distinctive phenotypes of mutant mice with different genetic backgrounds that may result from variations in penetrance, dominance, expressivity, and pleiotropy [55,263-268]. For example, *Fragile X mental retardation 1* (*Fmr1*)-knockout mice, a mouse model for studying intellectual disability, display behavioral phenotype variability because of different genetic backgrounds [264]. Low sociability is observed only in *Fmr1*-knockout mice ($Fmr1^{-/y}$) with a FVB/N-129/OlaHsd background, but not those with a C57BL/6J background [266]. Similarly, the percentage of prenatal lethality in *Transforming growth factor beta 1* (*Tgfb1*) homozygous knockout mutant embryos ($Tgfb1^{-/-}$) also vary in mice of different genetic backgrounds [265]. Therefore, to enhance validity and reproducibility, the selection of a control inbred strain with a well-defined genetic background is critical for generating the desired phenotypic expression of the mouse [269]. In addition, some of the inbred mouse lines have a high incidence of spontaneous tumor development. Therefore, they may not be suitable for long-term studies, such as aging research. Careful consideration should be given to selecting the strain with the most appropriate genetic background to minimize the manifestation of unexpected phenotypes. As more and more "quiet mutations" are being discovered among inbred strains and substrains [3], it is impossible to include all these information into a single paper. Therefore, it is highly recommended to study detail genetic information from the vendors before importing a particular mouse line. Attention should be paid to genetic variations at substrain level, as certain mutations

may only exist in some substrains but not the others. Apart from genotype, environment and its interaction with genotype also contribute to phenotypic alternation [270]. The procedures on animal handling and environmental control are also critical factors influencing the phenotype of the mice. However, since inter-laboratory environmental differences exist inevitably, increasing standardization of environmental conditions may result in lower external validity of experimental data [271]. Instead, systematic environmental variation, which allows experimental and control mice subjected to the same microenvironment, is suggested to improve both reproducibility and external validity [271-273]. Overall, all these approaches and measures hopefully can help to validate and support the translational utilization of animal models for the studies of human diseases.

Author contributions

WYT and KKC wrote this review article.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial, financial or non-financial relationships that could be construed as a potential conflict of interest.

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Figure 1 **Genealogy of selected inbred mouse strains in this review**

Table 1 **Databases of mouse strains information**

Table 2 **Examples of spontaneous phenotypes of some commonly used inbred mouse lines**

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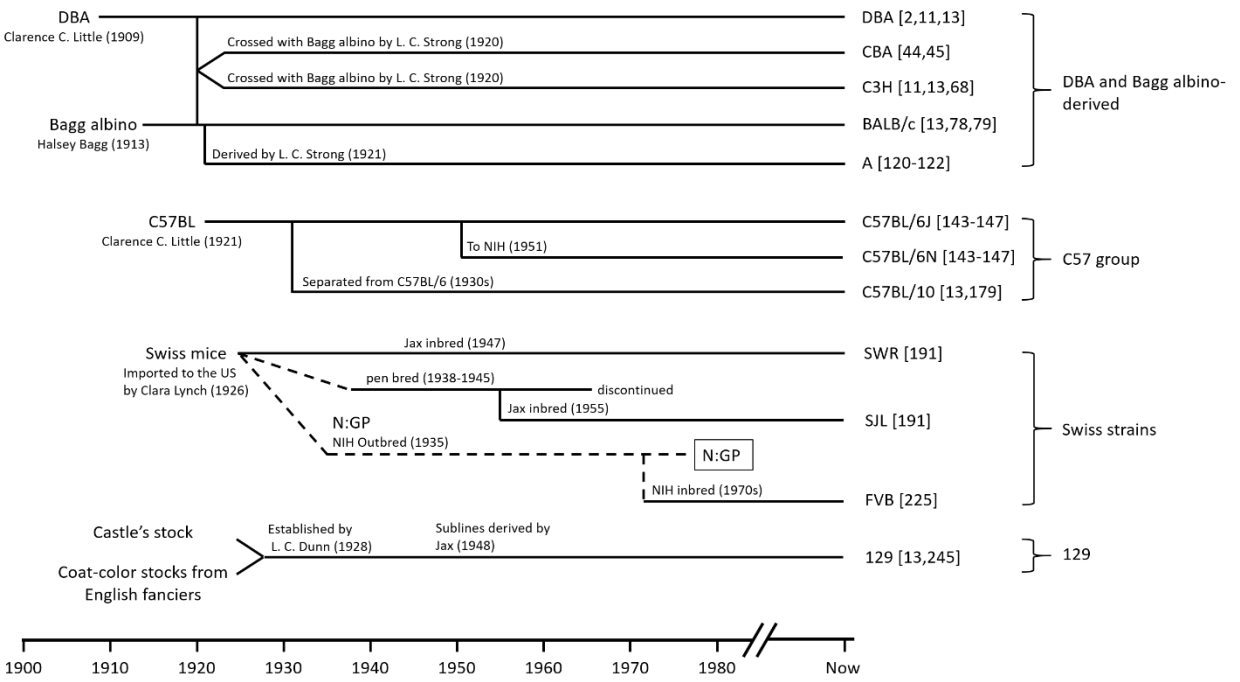
DBA
Clarence C. Little (1909)
Crossed with Bagg albino by L. C. Strong (1920)
Crossed with Bagg albino by L. C. Strong (1920)
Bagg albino
Halsey Bagg (1913)
Derived by L. C. Strong (1921)
DBA [2,11,13]
CBA [44,45]
C3H [11,13,68]
BALB/c [13,78,79]
A [120-122]
DBA and Bagg albino-derived
C57BL
Clarence C. Little (1921)
To NIH (1951)
Separated from C57BL/6 (1930s)
C57BL/6J [143-147]
C57BL/6N [143-147]
C57BL/10 [13,179]
C57 group
Swiss mice
Imported to the US
by Clara Lynch (1926)
Jax inbred (1947)
pen bred (1938-1945)
discontinued
Jax inbred (1955)
N:GP
NIH Outbred (1935)
N:GP
NIH inbred (1970s)
SWR [191]
SJL [191]
FVB [225]
Swiss strains
Castle's stock
Coat-color stocks from
English fanciers
Established by
L. C. Dunn (1928)
Sublines derived by
Jax (1948)
129 [13,245]
129
1900
1910
1920
1930
1940
1950
1960
1970
1980
Now

1