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# An Efficient SNP System for Mouse Genome Scanning and Elucidating Strain Relationships

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A set of 1638 informative SNP markers easily assayed by the Amplifluor genotyping system were tested in 102 mouse strains, including the majority of the common and wild-derived inbred strains available from The Jackson Laboratory. Selected from publicly available databases, the markers are on average ~1.5 Mb apart and, whenever possible, represent the rare allele in at least two strains. Amplifluor assays were developed for each marker and performed on two independent DNA samples from each strain. The mean number of polymorphisms between strains was  $608 \pm 136$  SD. Several tests indicate that the markers provide an effective system for performing genome scans and quantitative trait loci analyses in all but the most closely related strains. Additionally, the markers revealed several subtle differences between closely related mouse strains, including the groups of several I29, BALB, C3H, C57, and DBA strains, and a group of wild-derived inbred strains representing several *Mus musculus* subspecies. Applying a neighbor-joining method to the data, we constructed a mouse strain family tree, which in most cases confirmed existing genealogies.

[Supplemental material is available online at [www.genome.org](http://www.genome.org).]

For almost a century, mouse models have played an important role in helping us understand the genetics and pathophysiology of human diseases and other traits determined by either single genes or sets of multiple loci. Two recent and substantial advancements have substantially improved these capabilities. First, maps constructed with a high density of simple sequence length polymorphism (SSLP) markers and expressed sequence tag (EST) loci (Dietrich et al. 1996; Rowe et al. 2003) greatly facilitated the process of identifying candidate genes for genetic traits. Second, the comparison of the completely sequenced genome of strain C57BL/6J (Waterston et al. 2002) with sequences from other mouse strains (Grupe et al. 2001; Wade et al. 2002; Wiltshire et al. 2003) revealed an extremely abundant type of genetic variants, single nucleotide polymorphisms (SNPs). The greater abundance and cheaper costs of assaying SNPs promise substantial advantages over the use of SSLPs in genetic mapping. Several groups have described tens of thousands of SNPs each in up to 15 (Grupe et al. 2001), four (Wade et al. 2002), and nine (Wiltshire et al. 2003) mouse strains. In doing so, these groups have laid the foundation for SNP genotyping in the mouse. To further genetic mapping in mice, we have developed a robust set of SNP markers sufficiently polymorphic to perform quantitative trait locus (QTL) analyses between nearly any two mouse strains, including virtually all of the inbred and wild-derived inbred strains available from The Jackson Laboratory. A recent paper from our laboratory described ~240 SNP markers in 48 strains and showed that markers from only a few strains can successfully be used to type a wide variety of strains, including those that are wild-derived (Petkov et al. 2004). By consulting public databases, we selected an additional set of 2158 evenly spaced markers. After testing them in a variety of mouse strains for their utility and informa-

tion content, we settled on a panel of 1638, slightly more than one per 1.5 Mb. On average,  $608 \pm 136$  SD of the 1638 were polymorphic between any two mouse strains, providing a powerful, standardized marker system for genetic analyses with an average interstrain resolution of 4.2 Mb.

Using these 1638 markers and the neighbor-joining method (Saitou and Nei 1987), we also constructed the most comprehensive mouse family tree to date, recognizing that it may exaggerate the differences between the strains originally used to select the SNPs.

## RESULTS AND DISCUSSION

### Selecting SNP Markers and Testing Their Assays

Our two major objectives were to choose markers that would: (1) facilitate genome-wide scans in all possible crosses between the 102 strains we analyzed and (2) be successfully and reliably assayed by Amplifluor technology (Assay Architect software, <https://apps.serologicals.com/aaa/login.aspx>). From publicly available databases (Wade et al. 2002; Wiltshire et al. 2003) we selected 2158 candidate SNPs using the following four criteria: (1) they were preferably 0.8–1.2 Mb apart (at most 0.6–1.4 Mb apart in SNP-poor regions); (2) their flanking sequences mapped to a single and unequivocal position in the ENSEMBL mouse genomic sequences; (3) available information indicated polymorphism in more than two mouse strains; and (4) they were preferably located in coding regions (in the end, about 3% were cSNPs).

Using Amplifluor assays, we tested the 2158 markers on a panel of six laboratory and two wild-derived strains which had data in publicly available databases, namely 129X1/SvJ, A/J, AKR/J, BALB/cByJ, C3H/HeJ, C57BL/6J, DBA2/J, CAST/EiJ, and SPRET/EiJ. In all, 1654 of the 2158 assays (76.8%) successfully amplified their target SNPs. Of the remainder, 223 (10.3%) did not amplify the corresponding sequence from any sample, 107 (4.9%) amplified both alleles poorly, 61 (2.8%) amplified the same allele from

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all samples and were considered monomorphic, 53 (2.5%) did not distinguish heterozygotes, 41 (2%) amplified one allele well but not the other, and 18 (0.8%) amplified their target SNPs inconsistently. We made no attempts to optimize any failed assays.

After comparing 1654 of the successfully amplified SNPs to Build 30 of the mouse sequence database ([www.ensembl.org](http://www.ensembl.org)), we excluded 16 more: 14 mapped to two regions and obviously represented duplications; one was not found in Build 30, and one was mapped on a different chromosome, making its status uncertain. Our final marker set consisted of 1638 successful SNP assays, which we used to genotype 102 mouse strains (Supplemental Table 1). All assays were identified by their physical position in the mouse genome and by their refSNP ID in the dbSNP (<http://www.ncbi.nlm.nih.gov/SNP>).

The average distance between them was 1.56 Mb, or about 0.8 cM (Table 1), with a minimum resolution power of 5 Mb for most chromosomal regions. Exceptions were the middle of Chromosome 10, a large part of Chromosome X, both of which have been reported as “SNP deserts” (Wade et al. 2002; Wiltshire et al. 2003), and the distal end of Chromosome 16 (70–90 Mb), where very few of the available SNPs converted to useful assays. The SNP panel described here will be included in the Mouse Phenome Project web site (<http://aretha.jax.org/pub/cgi/phenome/mpdcgi?rtn=docs/home>). All assays are available from The Jackson Laboratory, Bar Harbor, ME.

### Information Content of the Marker Set

Previous information regarding the distribution of SNPs among inbred mouse strains was limited to a modest number of strains; about two-thirds of the reported polymorphisms were described in two or three strains (Wade et al. 2002), and about one-third were reported in up to nine strains (Wiltshire et al. 2003). To determine whether the SNPs we chose would be informative for genome-wide scans in a variety of crosses, we calculated the polymorphism information content (PIC) for all 102 strains, where  $PIC = 2pq$ ,  $p$  and  $q$  being the allelic frequencies of an SNP, and PIC can range from 0.0 to 0.5 (Botstein et al. 1980; Anderson et al.

1993). The SNPs we selected had an average PIC of 0.39, and 96.3% were either highly informative (86.7% with  $PIC > 0.25$ ) or informative (11.6% with  $0.1 < PIC < 0.25$ ; Fig. 1). Although the remaining 3.7% were only slightly informative across the whole set of 102 strains, they are highly valuable for selected strain pairs.

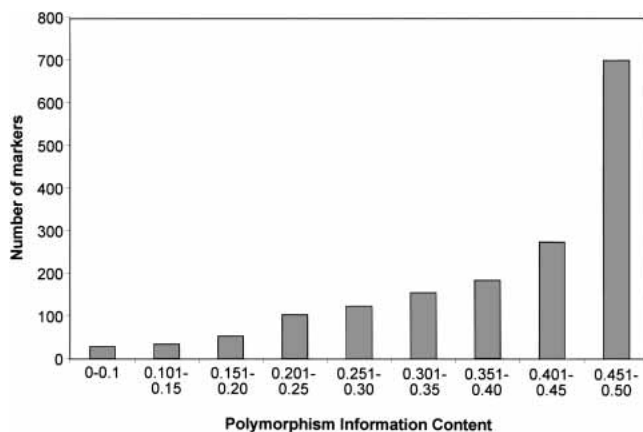
Our SNP set appears to be adequate for performing genome scans in almost all possible crosses. The number of polymorphisms between all possible pairs of strains is shown in Figure 2 and Supplemental Table 2. The average was  $608 \pm 136$  SD, with 97% having at least 300. The average number for all possible crosses between 17 commonly used laboratory strains and five wild-derived strains (the four *Mus musculus* subspecies and *Mus spretus*) was  $616 \pm 136$  SD, which corresponds to an average marker density of 4.1 Mb or 2.3 cM, with 98% having at least 300 for a marker density of 8.5 Mb or 4.67 cM (Table 2).

### Wild-Derived Strains

Because they are becoming increasingly important in QTL analyses and evolutionary studies, we tested our marker set in an extensive group of wild-derived inbred strains. Most of the common laboratory strains are predicted to have a mixed ancestry of *M. m. musculus* and *M. m. domesticus*, possibly with a small contribution from *M. m. castaneus* (Ferris et al. 1982; Bishop et al. 1985; Yonekawa et al. 1994; Beck et al. 2000). In contrast, most of the wild-derived strains are largely pure subspecies of wild mice trapped in various locations, including *M. m. domesticus* strains WSB/Eij (MD, USA), LEWES/Eij (DE, USA), CALB/RkJ (CA, USA), WMP/PasDnj (Tunisia), TIRANO/Eij (Italy), ZALENDE/Eij (Switzerland), PERA/Eij and PERC/Eij (Peru); *M. m. musculus* strains SKIVE (Denmark), CZECHI/Eij, CZECHII/Eij and PWK/PhJ (Czech Republic). *M. m. molossinus* subspecies strains MOLC/RkJ, MOLD/RkJ, MOLF/RkJ, and MSM/Ms were derived from mice trapped in Japan, *M. m. castaneus* CASA/RkJ and CAST/Eij originated in Thailand. The *musculus*, *domesticus*, and *castaneus* subspecies are thought to have diverged from a common ancestor about one million years ago (Silver 1995). *M. m. molossinus* is considered a more recent hybrid between *M. m. musculus* and *M.*

**Table 1.** Marker Distribution Along the Chromosomes

Chromosome	Chromosome length [Mb] (Ensembl)	Number of markers	Minimal distance [Mb]	Maximal distance [Mb]	Average distance [Mb]
1	196	169	0.002	5.924	1.135
2	181	99	0.001	8.492	1.806
3	161	100	0.1	6.647	1.564
4	153	102	0.039	6.477	1.478
5	150	96	0.016	4.925	1.534
6	150	91	0.007	8.326	1.617
7	135	89	0.001	5.6	1.474
8	129	84	0.021	4.877	1.477
9	125	79	0.041	6.346	1.539
10	131	57	0.243	14.221	2.237
11	123	78	0.094	7.537	1.529
12	114	77	0.003	8.157	1.447
13	116	75	0.023	6.824	1.517
14	116	86	0.037	5.303	1.308
15	104	73	0.034	6.934	1.383
16	99	58	0.019	14.432	1.649
17	94	60	0.001	7.737	1.517
18	91	72	0.076	4.439	1.193
19	61	43	0.033	4.899	1.356
X	150	50	0.001	27.082	2.802
Total	2579	1638			
Average			0.039	8.259	1.578



**Figure 1** Distribution of polymorphism information content (PIC) of the SNPs among 102 strains. The PIC was calculated as  $2pq$ , where  $p$  and  $q$  are the frequencies of the corresponding alleles.

*m. castaneus*, although the data supporting these estimates are anecdotal. There are indications that *M. m. musculus* and *M. m. domesticus* may represent different species rather than subspecies (Sage et al. 1986; Tucker et al. 1992). Among the other mouse species represented in this study, *M. hortulanus* (PANCEVO/EiJ) was separated from the common ancestor between it and *M. musculus* ~two million years ago, and *M. spretus* (SPRET/EiJ) ~three million years ago, according to the same estimate (Silver 1995). Although the wild-derived strains have been separated for one to three million years, our SNP panel successfully genotyped all of them, including the most genetically distant ones, with a marker density comparable to that used for genotyping laboratory strains: 86% of the assays worked well with SPRET/EiJ, over 90% with PANCEVO/EiJ, and over 96% with CAST/EiJ and CASA/RkJ. Our panel of robust SNP assays can provide further studies of wild mouse populations with the necessary tool for establishing the evolutionary relationships between species on firm factual basis.

### Evolutionary Origin of SNPs

The distribution of SNPs in wild-derived inbred strains suggested that many of them originated before the progenitors of these strains diverged in evolution. In 42% of our SNP set, both alleles were found in strains belonging to each of the two subspecies *M. m. musculus* and *M. m. domesticus*, suggesting that the mutations causing the polymorphisms originated before the two subspecies separated. It is unlikely that these SNPs arose after evolutionary divergence by independent mutation in each lineage, either at the population level or during the process of inbreeding, given the estimated mutation rate in mouse of  $1.8 \times 10^{-10}$  mutations per nucleotide per generation (Drake et al. 1998) and the separation time of *M. musculus* subspecies as one million years ( $\sim 3 \times 10^6$  generations).

### Persistence of Residual Heterozygosity During Inbreeding

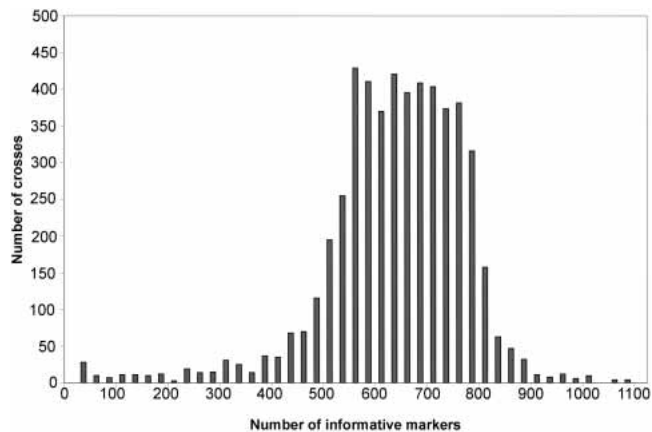
An analysis of SNPs in closely related strains suggests that residual heterozygosity has persisted during the process of inbreeding strains long after theoretical calculations suggest it should be gone. For example, C57BL/10J and C57BL/6J were separated from the original C57BL strain in the mid-1930s, after about 40 generations of inbreeding (Festing 1996). Forty-nine (3%) of the 1638 SNPs we tested were polymorphic between these two strains. Thirty-three of these 49 were also polymorphic in a variety of other laboratory and wild-derived strains, indicating that

they almost certainly represent old SNPs still segregating at the time the two strains separated. Two percent segregating loci after about 40 generations of inbreeding (the C57BL strain was developed around 1921) is considerably more than would be expected by chance. This suggests that there is selection for residual heterozygosity at some loci during the process of inbreeding.

Further evidence for the persistence of heterozygosity at selected loci during inbreeding came from a comparison of C57BL/6 substrains. The low-frequency allele of seven SNPs from our marker set was found only in C57BL/6J and strains derived from it after it separated from C57BL/10J, possibly representing the loss of this allele in C57BL/10J or new mutations fixed in C57BL/6J after its separation from the BL/10 lineage. Five of the seven SNPs were polymorphic between C57BL/6J and C57BL/6ByJ, the rare allele in all of them being found only in C57BL/6J and strains partially derived from C57BL/6J after the 1960s, including BPL/1J, BPH/2J, BPN/3J, and MOR/RkJ. C57BL/6ByJ was separated in the 1950s from C57BL/6NCr, a substrain maintained at the National Cancer Institute (NCI) since 1951. We tested a group of six more C57BL/6 strains separated at different times and found that: (1) those originating from the substrain maintained at the NCI shared the same genotype as C57BL/6ByJ, (2) two strains separated from The Jackson Laboratory stock after the 1970s shared the five alleles with C57BL/6J, and (3) C57BL/6JeiJ, separated in 1975, shared two alleles with the NCr substrain and three with the J substrain. Although it is possible that new mutations were randomly fixed, it is more likely that this allelic distribution resulted from residual heterozygosity at the time the J and NCr substrains were separated.

### Recapitulating Strain Histories

We evaluated the usefulness of our marker set for genome scanning by testing how well it could either verify or detect events known to have happened during the origin of mouse strains. For example, we know that 129S1/SvImJ was created by crossing 129/Sv with C3HeB/FeJ, backcrossing to the parental 129/Sv, and selectively breeding the offspring with the highest teratoma incidence. The C3HeB/FeJ contribution has been located on Chromosome 7 and includes the wild-type alleles of the *Tyr* and *p* loci (Simpson et al. 1997; Threadgill et al. 1997). Our SNP set confirmed that the entire 129S1/SvImJ genome has but one substantial C3HeB/FeJ segment, a single DNA block between markers at 22.3 Mb and 82.7 Mb on Chromosome 7. As a second example, we know that another strain of this group, 129X1/SvJ, was contaminated with unknown genetic material around 1987 (Simpson et al. 1997). An analysis with our SNP marker set revealed



**Figure 2** Distribution of informative markers in all possible crosses of 102 mouse strains.

**Table 2.** Distribution of Informative Markers in All Possible Crosses of 22 Mouse Strains

Strain	129S1/SvImj	A/J	AKR/J	BALB/cByJ	BTBR T <sup>+</sup> tf/J	BUB/BnJ	C3H/HeJ	C57BL/6J	CAST/EiJ	CBA/J	DBA/2J	FVB/NJ	JF1/Ms	KK/HIJ	MRL/MpJ	NOD/LtJ	NZW/LacJ	PL/J	PWK/PhJ	SJL/J	SPRET/EiJ	WSB/EiJ	
129S1/SvImj																							
A/J	785																						
AKR/J	778	469																					
BALB/cByJ	816	363	526																				
BTBR T <sup>+</sup> tf/J	534	623	622	694																			
BUB/BnJ	730	513	425	562	646																		
C3H/HeJ	818	400	519	525	706	530																	
C57BL/6J	1047	882	786	880	747	747	981																
CAST/EiJ	747	710	674	713	707	687	749	769															
CBA/J	798	455	518	533	675	522	205	902	696														
DBA/2J	744	576	569	631	660	570	479	825	702	456													
FVB/NJ	729	495	480	567	604	430	558	760	678	526	574												
JF1/Ms	774	774	775	790	778	775	808	772	286	765	744	791											
KK/HIJ	639	624	590	676	601	560	680	711	684	637	579	539	703										
MRL/MpJ	754	434	352	530	681	472	432	833	716	463	550	532	784	613									
NOD/LtJ	731	493	471	552	612	405	590	736	697	582	551	412	777	564	520								
NZW/LacJ	582	606	567	649	584	529	658	688	670	609	554	525	715	468	575	540							
PL/J	712	475	396	511	626	470	518	810	697	527	575	514	770	577	427	502	557						
PWK/PhJ	762	734	742	730	739	736	764	782	300	720	710	748	142	697	755	754	691	735					
SJL/J	660	487	472	510	592	387	525	734	648	501	547	328	738	523	467	414	477	452	699				
SPRET/EiJ	627	630	598	649	630	605	649	703	249	617	616	594	300	595	602	609	567	586	291	571			
WSB/EiJ	722	634	610	653	656	610	671	730	552	630	661	584	662	619	624	614	588	621	633	550	486		

that the strain has contributions by C57BL/6J on Chromosomes 5, 7, 14, 18, and 19, and by BALB/cJ on Chromosomes 7, 8, 10, 18, 19, and X, suggesting an F1 hybrid between these strains as the most possible contaminant. As a third example, C57BLKS/J had been determined to be derived from C57BL/6J contaminated with DBA/2J (Naggert et al. 1995). In fact, an analysis with our SNP marker set revealed that not only did the C57BLKS/J genome have different size DBA/2J segments on every chromosome except Chromosomes 2 and 13, but it had regions on Chromosomes 4 (27–42 Mb and 96–106 Mb), 9 (18–30 Mb), 11 (23–26 Mb and 80–91 Mb), and 15 (96–103 Mb) that could not be explained solely by DBA/2J contributions on a C57BL/6J background. Although the different markers on Chromosomes 9 and 15 were present in other strains of the C57 group and may have been randomly fixed after C57BLKS/J separated in the 1940s, those on Chromosomes 4 and 11 suggest that C57BLKS/J had genetic segments from another strain, and BTBR T<sup>+</sup> tf/J best fits the pattern observed among the strains we tested. In yet another example, NOR/LtJ, a diabetes-free strain, was derived from the diabetic NOD/LtJ through an accidental outcross with C57BLKS/J. An analysis with our SNP marker set not only confirmed the presence of C57BLKS/J sequences on Chromosomes 1, 2, 4, 5, 7, 11, 12, and 18, as originally reported (Prochazka et al. 1992; Serreze et al. 1994), it also revealed additional C57BLKS/J regions on Chromosomes 10 (21–28 Mb) and 14 (77–88 Mb), and it precisely showed the regions of C57BLKS/J ancestry that were ultimately derived from either C57BL/6J or DBA/2J genetic backgrounds.

### Family Tree of the Mouse Strains

A better understanding of the genetic relationships among inbred strains of mice will improve experimental designs for mapping quantitative trait loci and choosing strategies for developing new genetic resources. The genealogy of inbred mouse strains is well documented (Simpson et al. 1997; Beck et al. 2000): some

share a common origin, some were either deliberately or accidentally crossed with pre-existing strains, and others are of entirely independent origin. Several genotypically based mouse family trees involving different sets of strains have been constructed using classical genotypes or SSLP markers (Atchley and Fitch 1993; Schalkwyk et al. 1999; Witmer et al. 2003). To further explore these relationships, we sought to reconstruct the phylogenetic relationships among the 102 inbred and wild-derived inbred strains tested in this study by using our SNP marker set (Fig. 3).

As discussed above, most of the SNPs we tested were either informative or highly informative. Moreover, their origins appear to predate the evolutionary divergence of *Mus* species and subspecies, suggesting that they were present long before the development of inbred mouse strains. However, any tree we construct will be biased, because our markers were originally selected for being polymorphic among a small subset of strains, and thus emphasize divergent relationships among these strains. It is not surprising then that our marker set assigned C57BL/6J (completely sequenced) to one branch, 129S1/SvImj (partially sequenced) to a second, and BALB/cByJ and C3H/HeJ (both partially sequenced) to a third branch of the tree, because a substantial number of SNPs in the set originated from and were thus polymorphic among these four strains. Accepting this caveat, our markers remain useful for assigning other strains to either existing or new tree branches, and for revealing the relationships among the strains within a branch. The large proportion (42%) of ancient SNPs in the set, being widely distributed among the 102 strains, may actually have resolved many of the tree's relationships quite well despite the "enhanced-resolution" bias for the four strains mentioned above.

Our phylogenetic tree distinguished seven groups. Group 1 has two branches anchored, respectively, by two of the sequenced strains, BALB/c and C3H. The BALB/c branch includes A/J, SEA/GnJ, and SEC/1ReJ (both derived from crosses of BALB/cBy with other strains; Festing 1996) and almost all albino strains



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