

Susan Tang, Fiona C.L. Hyland, Francisco M. De La Vega.
Applied Biosystems, Foster City, CA 94404, USA

INTRODUCTION

Single-nucleotide polymorphisms (SNPs) are increasingly being used in mouse genetics for several applications, including both genome-wide phenotype-genotype association studies and genetic monitoring of laboratory mice strains. While within an inbred mouse strain there is little genetic variation, single nucleotide differences exist between the common laboratory mice strains, and these can be detected with SNP genotyping assays and exploited using several experimental strategies. Genome-wide mapping of loci affecting a trait of interest in the mouse is performed by crossing different inbred strains that differ for the phenotype of interest (inherently or due to mutagenesis), following the inheritance of chromosomal blocks from the parental strains of origin in succeeding generations, and correlating this with the phenotype. Inheritance of parental chromosomal segments can be followed by genotyping an informative panel of SNPs. Another application of SNPs in the mouse is genetic monitoring, or strain QC, which allows researchers to identify individual mice strains and to detect mice genetic contamination by genotyping a specific panel of SNPs and using the allelic distribution to distinguish all the strains. We thus developed the Mouse SNPbrowser™ Software to aid researchers in selecting informative panels of mouse SNPs directed towards those genetic applications.

MATERIALS AND METHODS

The mouse SNP database used by our software as a starting point for selection includes about 10,000 evenly spaced SNPs loci genotyped across 48 inbred mouse strains by Pletcher et al [1]. This data is included in the software distribution.

Our software was developed in C++ utilizing the Qt GUI software toolkit and Microsoft Visual Studio v6, and is currently implemented for the MS Windows platform only.

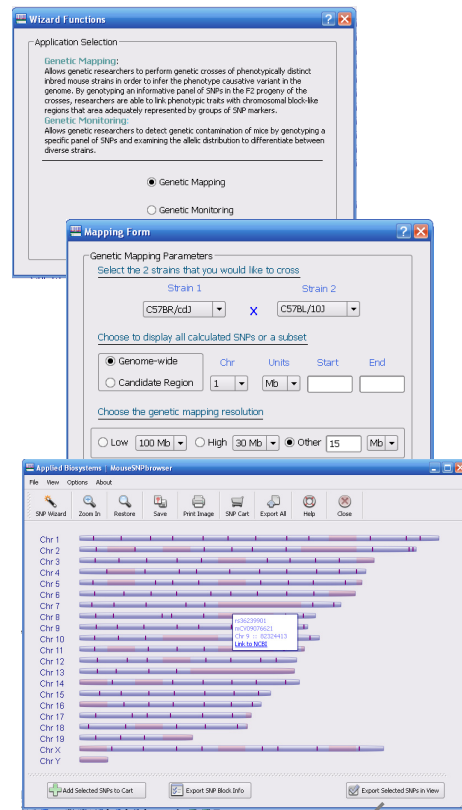
For genetic mapping, our software segments each chromosome into evenly sized blocks according to the mapping resolution specified by user. Then it searches for a distinguishing SNP (one that has contrasting alleles for the two strains that are crossed) starting from the center of each block. The search progressively deviates from the center of the block, without directional bias, until a distinguishing SNP is found. Some blocks may not be covered by a distinguishing SNP, and the likelihood of such an event increases with the search resolution.

For genetic monitoring, we used the Lossless Mode of a previously described haplotype tagging algorithm that selects the optimal set of SNPs to distinguish between any number of strains [2]. Two user input fields, *SNPs to Exclude* and *SNPs to Preferentially Include*, may influence the calculation process. Excluded SNPs are immediately removed from the input set of SNPs. Preferential SNPs are given priority during the selection process such that these SNPs are used when feasible. SNPs can be selected for each chromosome, or globally across the genome.

RESULTS

The *wizard* feature of the software can be used to easily select SNPs either for genetic mapping or for genetic monitoring in the most common mouse strains. Users are prompted for various SNP selection preferences, depending on the application of interest. SNPs are visualized on the main chromosomal display to establish distance relationships, highlight uncovered regions of the genome, and contrast SNP sets with different properties. Users can right click on a displayed SNP to obtain relevant information such as mCV ID, refSNP ID, chromosome number, physical position, and link to the NCBI Cluster Report for that SNP. After performing a genetic mapping calculation, user can click the *Export SNPs in View* button to export the selected SNPs in a tab-delimited file. Relevant SNP ID's, location, and allelic information for the appropriate strains are found in the export file. User can also click the *Add to Cart* button to add the selected SNPs from this calculation to existing SNPs in the cart.

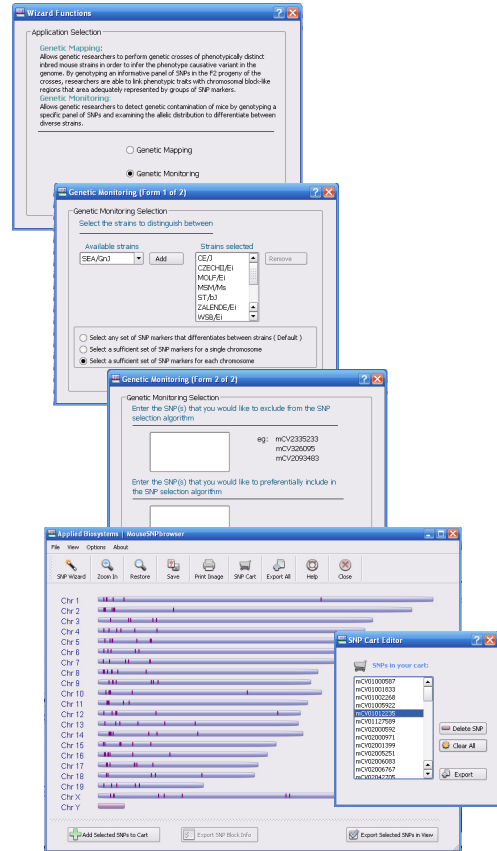
Fig 1. Mouse SNPbrowser Workflow: Genetic Mapping



Results generated by MouseSNPbrowser version 1.0 on 12-19-2006 17:16
Copyright: Applera Corporation
Application: genetic mapping
Cross selected: C57BL/6J X C57BL/10J

For genetic mapping, the workflow includes specifying the pair of strains, the mapping resolution, and global (genome-wide) vs. local selection. Mapping resolution can be selected in terms of physical or genetic distance. User may choose a pre-selected resolution (HIGH or LOW) or specify their own resolution. For definition of a candidate region, the user can enter a chromosome number and the desirable start/end positions on that chromosome.

Fig 2. Mouse SNPbrowser Workflow: Genetic Monitoring



For genetic monitoring, the workflow includes specifying the list of strains to differentiate between, SNPs to exclude, and SNPs to preferentially include in the selection algorithm. The latter can be particularly useful if the researchers have already developed a library of SNP genotyping assays that they want to reuse.

CONCLUSIONS

We have developed a software tool that allows efficient and easy selection of appropriate sets of SNPs to discriminate between strains of interest, with specific applications in genotype/phenotype mapping and strain verification. In the near future, we envision that all SNPs included in our database the corresponding TaqMan® SNP Genotyping Assays will be readily available. The Mouse SNPbrowser Software will allow these genotyping reagents to be ordered directly from the user interface, thus expediting the set-up of mouse genetic studies.

REFERENCES

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