Published in final edited form as:

Genet Epidemiol. 2003 May ; 24(4): 243–252. doi:10.1002/gepi.10227.

Genetic Maps of Microsatellite and Single-Nucleotide Polymorphism Markers: Are the Distances Accurate?

Suzanne M. Leal*

Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

Abstract

Genetic maps play an important role in gene mapping. Inaccurate genetic maps can hinder gene mapping by biasing lod scores and reducing the power to map a trait to a particular region. Although sequence-based physical maps can provide a unique order for markers, they do not provide information on genetic map distances. By simulation studies, I investigated how many meioses are necessary to accurately estimate genetic map distances for maps constructed from microsatellite and single-nucleotide polymorphism (SNP) markers for various intermarker distances and marker heterozygosity. To evaluate the accuracy of the generated genetic maps, the length of the 95% confidence interval for intermarker genetic distances was examined. In addition, the power to separate two adjacent markers by a nonzero map distance was investigated. The number of meioses necessary to accurately estimate map distances depends greatly not only on intermarker distances but also on marker heterozygosity. For example, for a genetic map with intermarker distances of 0.5 cM generated with 1,000 meioses, when marker heterozygosity was high (0.90), for 96% of the markers there was a nonzero map distance between adjacent markers. However, when marker heterozygosity was low (0.32), only 48% of the markers mapped to a unique position. For identical numbers of meioses and intermarker distances, genetic maps constructed from microsatellite markers will be more precise than maps assembled from SNP markers, due to the higher levels of heterozygosity for microsatellite markers.

Keywords

confidence intervals; genetic maps; map distances; recombination fractions; SNP markers; microsatellite markers

INTRODUCTION

With the completion of the sequence of the human genome near, it should be possible to know the exact order of all marker loci within the next few years. However, sequence-based physical maps will not give accurate information on genetic map distances. Genetic map distances are dependent on rates of recombination which are known to vary across the genome [Lichten and Goldman, 1995; Yu et al., 2001; Kong et al., 2002]. Therefore, it is not possible to interpolate from physical map distances to genetic map distances. Inaccuracies in

*Correspondence to: Dr. Suzanne M. Leal, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Alkek Building N1619.01, Houston, TX 77030. sleal@bcm.tmc.edu.

genetic maps can be due to genotyping errors that can dramatically inflate map distances [Morton and Collins, 1990; Buetow, 1991; Tomfohrde et al., 1992; Brzustowicz et al., 1993; Goldstein et al., 1997] as well as generating maps using a limited number of informative meioses [Broman et al., 1998; Kong et al., 2002]. Constructing genetic maps using information from sequence-based maps can aid in ordering markers [Tapper et al., 2001; Ke et al., 2001; DeWan et al., 2002a]. Currently, caution must be used when ordering markers based upon sequence-based physical maps, since these maps are not error-free [DeWan et al., 2002a,b; Katsanis et al., 2001; Kong et al., 2002]. Errors in marker order on sequence-based physical maps can be due to problems with assembly or in-silico mapping. At this time, information from both sequence-based physical and genetic maps may provide the most accurate information on marker order [Tapper et al., 2001; Ke et al., 2001; DeWan et al., 2002a; Kong et al., 2002].

The position of markers on commonly used genetic maps [e.g., Marshfield: Broman et al., 1998; CEPH: Dib et al., 1996; CHLC: Murray et al., 1994; Sheffield et al., 1995] are based on a limited number of meioses [Yu et al., 2001], which can lead to incorrect marker order and poor estimates of recombination fractions [Terwilliger et al., 1992]. In most cases, the markers that were used to generate these maps have only been genotyped in 8 of the largest Centre d'Etude du Polymorphisme Humain (CEPH) families that consist of 184 meioses [Yu et al., 2001]. Although 61 CEPH families are available for map construction [Dausset et al., 1990] with the advent of microsatellite markers [Weber, 1990], genotyping of marker loci for genetic maps was for the most part carried out on only 8 families, since all samples from these families could be run on two electrophoresis gels [Weissenbach et al., 1992].

The problem of correctly ordering markers is a particular dilemma for closely linked markers where there is a low order of support for their relative map position [Keats et al., 1991]. Recently, a genetic map was constructed by deCode Genetics using Icelandic families [Kong et al., 2002]. This map consists of 1,257 meioses, although in most cases, unlike the 8 CEPH pedigrees, there are no grandparental genotypes; thus, the data are phase-unknown. It is estimated that despite the fact that the deCode genetic map has 6 times the number of meioses, it only provides 5 times the average resolution of the Marshfield map [Kong et al., 2002]. Of the 5,012 markers shared by the Marshfield and deCode genetic maps, 42.82% of the markers on the Marshfield map did not have a distinct position. Even with the wealth of meioses used to construct the deCode map, 26.38% of these markers also did not map to a unique position [Kong et al., 2002].

Genetic maps play an important role in gene mapping. Errors in genetic maps can hinder the mapping and isolation of genes for complex and Mendelian traits [Risch and Giuffra, 1992; Feakes et al., 1999; Göring and Terwilliger, 2000]. For linkage studies, inaccurate recombination fractions can lead to loss of power and can bias the map position for the trait locus as well as the lod score [Clerget-Darpoux et al., 1986; Ott et al., 1988; Risch and Giuffra, 1992; Hanis et al., 1996; Feakes et al., 1999; Halpern and Whittemore, 1999; Daw et al., 2000; Stringham and Boehnke, 2001]. The effect of errors in genetic maps becomes increasingly serious as more marker loci are analyzed jointly [Göring and Terwilliger, 2000]. Multipoint linkage analysis has been shown to improve the power to map trait loci [Lathrop et al., 1984]. If single-nucleotide polymorphism (SNP) markers are used for gene mapping,

it will be essential that either multipoint methods are employed, or “super” loci which are composed of a cluster SNP loci are used for two-point analysis due to the low heterozygosity (maximum heterozygosity (H)=0.5) and informativeness of these diallelic markers [Kruglyak, 1997; Wilson and Sorant, 2000; Göring and Terwilliger, 2000; Goddard and Wijsman, 2002].

The deCode map placed SNP markers on the genetic map using interpolation. However, there were far fewer microsatellite markers (5,136) on the genetic map than SNP markers (~2,000,000). Using interpolation will not allow for the majority of SNP markers to be placed to a distinct position nor enable the estimation of the recombination fraction between most SNP markers, since the genetic microsatellite maps are much sparser than the SNP maps. For SNP markers, how feasible will it be to estimate recombination fractions using these less polymorphic, closely spaced markers? Here I examine how many meioses are necessary to accurately estimate map distances/recombination fractions for both microsatellite and SNP marker maps. The necessary number of meioses depends on the spacing of the markers, in addition to marker heterozygosity. A useful way to evaluate the accuracy of a point estimate is through the examination of its confidence interval (CI). The power to map markers to a unique map position is also examined for varying numbers of meioses, map distances, and marker heterozygosity.

MATERIALS AND METHODS

SIMULATION

Linked sets of markers were generated for CEPH format pedigrees that consisted of 4 grandparents, 2 parents, and 10 children. For each simulation study, the number of families, marker heterozygosity, and recombination fractions between markers were varied. The number of families generated ranged between 10–250, for a total of 200–5,000 meioses. It was of interest to simulate markers that resembled multiallelic microsatellite and diallelic SNP markers. In order to create a “microsatellite” marker map, 12 markers with a heterozygosity of 0.67 (three alleles of equal frequency), 0.8 (five alleles of equal frequency), and 0.9 (10 alleles of equal frequency) were generated. Twelve markers with a heterozygosity of 0.5 (two alleles with equal frequency) and 0.32 (common allele frequency = 0.8) were generated for the “SNP” marker map. For each simulation study, identical allele frequencies were used for each marker. The markers were generated with intermarker distances of 10 cM, 5 cM, 2 cM, 1 cM, 0.5 cM, 0.25 cM, and 0.01cM. These map distances were converted to recombination fractions using the Haldane mapping function [Haldane, 1919]. The simulation of data was facilitated through the use of the SIMULATE computer program [Terwilliger et al., 1993; Terwilliger and Ott, 1994]. In total, 1,000 replicates were generated and analyzed for each study.

ANALYSIS

The intermarker recombination fraction was estimated for each generated set of markers, using the Gemini algorithm as implemented in CILINK [Lathrop et al., 1984]. In addition, the variance-covariance matrix was calculated. The recombination fractions between the two middle markers (markers 6 and 7) were converted to a map distance, using the Haldane map

function [Haldane, 1919]. A 95% confidence interval was calculated for the intermarker map distance between these two markers, using the variance-covariance matrix. The number of equivalent meioses was calculated [Edwards, 1976], in cases where the estimated recombination fraction was 0 and the variance was also therefore 0. Based on the number of equivalent meioses, the binomial distribution was used to calculate a 95% CI. The lower and upper bounds of the CI and its length were calculated for each replicate. The lower and upper bounds of the CI, and CI length, were averaged over the 1,000 replicates. The standard deviation (SD) for the average length of the CI was also calculated. The t-test was used to evaluate if there was a statistically significant difference in the average length of the 95% CI for genetic maps generated using different marker heterozygosities, while holding intermarker map distances and the number of meioses constant. In addition, the power to detect a nonzero recombination fraction between the two adjacent middle markers was estimated as the number of replicates where the intermarker recombination fraction between markers 6 and 7 differed from 0, divided by the total number of replicates. The binomial distribution was used to calculate CIs for the power point estimates.

RESULTS

The accuracy of the point estimate of inter-marker map distance can be evaluated by examining its CI, with a longer CI indicating a less accurate point estimate. Several factors play a role in influencing the accuracy of the point estimate: these include genotyping errors, intermarker distances, marker heterozygosity, and number of meioses. Here is examined the effect of inter-marker distances, marker heterozygosity, and number of meioses. With increasing numbers of meioses, the CI becomes tighter around the point estimate. Table I displays the results for “micro-satellite” markers with heterozygosity ($H=0.67$) and $H=0.9$. For a map distance of 10 cM and a marker heterozygosity of 0.9, the length of the 95% CI shrinks from 8.51 cM (SD, 0.94 cM; 95% CI, 5.92–14.43 cM) for a genetic map constructed using 200 meioses to 1.70 cM (SD, 0.05 cM; 95% CI, 0.15–10.85 cM) for a map generated using 5,000 meioses. Although for microsatellite markers ($H=0.9$) it is not possible to accurately estimate map distances for fine maps generated using 200 meioses where the intermarker distances are 0.25 cM (95% CI, 0.00–1.90 cM), there is vast improvement for 2,000 meioses (95% CI, 0.04–0.45 cM), and quite accurate estimates are provided for a map constructed using 5,000 meioses (95% CI, 0.10–0.33 cM). It can be seen that when the marker heterozygosity is reduced from 0.9 to 0.67, the ability to accurately estimate the map distance is diminished. For example, for a map constructed from 200 meioses ($H=0.9$) for a 1-cM map, the average length of the 95% CI is 2.55 cM. When the marker heterozygosity was reduced to 0.67, the average 95% CI length increased to 2.87 cM. The difference in the average length of these two CI is statistically significant ($P<0.001$). In fact, for all map distances and numbers of meioses displayed in Table I, there is a statistically significant difference in the average length of the 95% CI, when comparing maps generated using markers with $H=0.9$ to those maps constructed from markers with $H=0.67$.

For maps with intermarker distances of 1 cM that are generated using markers with $H=0.67$ and 1,000 meioses, the power to separate markers with a nonzero map distance is high (>0.96). For maps generated with 200 meioses, the power to detect a nonzero recombination fraction between adjacent markers is much lower and is greatly influenced by

marker heterozygosity. For example, for a 1-cM map, the power to observe a nonzero recombination fraction between two adjacent markers is 0.56 (95% CI, 0.53–0.60 cM) when marker $H=0.67$; and the power increases to 0.75 (95% CI, 0.72–0.78 cM) when the marker heterozygosity is increased to 0.9. When the intermarker distance is reduced to 0.5 cM for genetic maps generated with 200 meioses, the power is always <0.34 to separate adjacent markers with a nonzero map distance.

For microsatellite markers, very accurate maps can be constructed. For example, for a 2-cM microsatellite marker ($= 0.8$) map constructed using 2,000 meioses, all markers could be mapped to a unique position, and the 95% CI (1.33–2.71 cM) for the map distance was narrow. For a 1-cM map built using 5,000 meioses, only 0.2% of the markers could not be mapped to a unique position. This map also provides accurate estimates of map distances (95% CI, 0.69–1.31 cM).

Table II presents the results for “SNP” markers. The effects of reducing the marker heterozygosity even further to 0.5 and 0.32 greatly reduces the ability to accurately estimate intermarker distances compared to maps which are generated using “microsatellite” markers with a higher heterozygosity. For a 1-cM map generated using 200 meioses, the power to separate two adjacent markers by a nonzero map distance falls even further for markers with lower heterozygosity. The power is 0.45 (95% CI, 0.42–0.48) for a map of markers with a heterozygosity of 0.5, and the power falls to 0.27 (95% CI, 0.24–0.30) for a map of markers with a heterozygosity of 0.32. The length of the CI is decreased by 54% when marker heterozygosity is increased from 0.32 to 0.9 (Tables 1, 2). There is a statistically significant difference in the average length of the 95% CI for those SNP linkage maps that were generated with markers with $H=0.32$ compared to those generated with markers with $H=0.5$ when the number of meiosis and the intermarker distance were kept constant for all examples shown in Table II. Although the power is good (0.82) to detect a nonzero map distance between adjacent markers for maps created with 5,000 meioses, $H=0.5$, and an intermarker spacing of 0.25 cM, the power falls to <0.68 when marker heterozygosity is reduced to 0.32. Once the intermarker map distance reaches 0.1 cM ($H=0.32$), the power is low (0.44) to observe a nonzero recombination fraction between two adjacent markers, and the 95% CI of the average length is wide, ranging from 0.01–0.25 cM.

DISCUSSION

For gene mapping using linkage analysis methods (“parametric” and “nonparametric”), it is vital to have accurate genetic maps, with the markers ordered correctly and with precise estimates of map distances. Incorrect estimates of map distances can produce either a positive or negative bias of lod scores. In the absence of linkage, a positive bias of lod scores can occur which can lead to an increase in the false-positive rate. In addition, incorrect estimates of map distances can reduce the ability to map a trait locus to its correct map position [Clerget-Darpoux et al., 1986; Ott et al., 1988; Risch and Giuffra, 1992; Feakes et al., 1999; Halpern and Whittemore, 1999; Daw et al., 2000; Göring and Terwilliger, 2000].

It has also been demonstrated that there is great variability in the rates of female and male recombination rates across the genome, with on average higher rates of recombination in

female meioses [Renwick and Schulze, 1965; Weitkamp et al., 1973; Lamm, 1973; Donis-Keller et al., 1987; Tanzi et al., 1992; Straub et al., 1993; Broman et al., 1998; Li et al., 1998; Mohrenweiser et al., 1998; Ashley-Koch et al., 1999; Yu et al., 2001; Kong et al., 2002; Matise et al., 2002a]. Regions around the centromeres usually display an excess of female recombination [Mohrenweiser et al., 1998; Broman et al., 1998], while the telomeric regions have higher rates of male recombination [Weber et al., 1993; Shen et al., 1994; Zahn and Kwiatkowski, 1995; Broman et al., 1998]. Although sex-specific map distances are rarely used in gene mapping, it has been demonstrated that inappropriate use of sex average maps can bias lod scores and can lead to either an increase in type I error or a loss of power [Ott et al., 1988; Cleves and Elston, 1997; Halpern and Whittemore, 1999; Daw et al., 2000]. For the examples presented, only equal male and female map distances were used. For equivalent accuracy in the estimate of sex-specific maps, additional data are required [Kong et al., 2002]. The amount of increase in data will depend on the proportions of male:female meioses.

Weber [2002] used the binomial distribution to calculate confidence intervals for various recombination fractions and numbers of meioses. These confidence intervals were calculated without taking into consideration the effects of marker heterozygosity. Here it is demonstrated that marker heterozygosity plays a very important role in the ability to estimate intermarker distances as well as the ability to map markers to a distinct genetic map position. Although marker heterozygosity gives information on whether a particular marker locus will have two different alleles, it does not supply complete information on whether or not a marker is informative. In order for a marker to be informative, it must be possible to determine from which parent a marker allele was obtained. The measure that provides this information is the polymorphism information content (PIC) [Botstein et al., 1980]. Thus, for two markers each with two alleles of equal frequency ($H=0.5$; $PIC=0.375$), for a data set which contains 5,000 meioses, on average 700 of these meioses would be informative. If the rate of recombination between the two markers is 0.01, an approximately 1-cM map distance, based upon the binomial distribution, the length of the 95% CI is 1.67 cM (95% CI, 0.41–2.08 cM) when marker $H=0.5$ for the two markers which are adjacent to the interval for which the map distance is being estimated. The length of the 95% CI is reduced by approximately one-half (0.82 cM) for the multi-point example provided in Table II. Likewise, for the same example, if the two markers each have 10 alleles of equal frequency ($H=0.9$; $PIC=0.891$), on average 3,970 meioses will be informative. For this example, the length of the binomial 95% CI is 0.65 cM, and is reduced to 0.58 cM for the multipoint example (Table I). If two completely informative markers are used (5,000 informative meioses) to estimate the intermarker recombination fraction, the length of the 95% CI would be 0.57 cM [Weber, 2002]. It should be noted that genetic maps are always generated in a multipoint context. Additional information is obtained in the multipoint situation compared to the example given above, when recombination fractions are estimated using only two adjacent markers. For markers with low heterozygosity (e.g., $H=0.5$), the accuracy of the estimate of the map distance is greatly improved for the multipoint situation. For markers with high heterozygosity (e.g., $H=0.9$), there is a slight improvement in the accuracy of the estimate of the genetic map distance for the multipoint situation compared to when only two

adjacent markers are used to estimate map distances, and the length of the 95% CI is almost equivalent to the case where all 5,000 meioses are completely informative.

The map distances and CI presented in this article have been estimated under the assumption of Hardy-Weinberg equilibrium (HWE). A deviation from HWE will affect the proportion of heterozygous genotypes and therefore also the proportion of informative meioses.

Consanguinity violates the assumptions of HWE and reduces the expected proportion of heterozygous genotypes [Wright, 1931, 1932; Buri, 1956; Cockerham, 1967, 1969; Hartl and Clark, 1989]. In addition, consanguinity has been shown to reduce the number of marker alleles [Cockerham, 1969; Hartl and Clark, 1989]; thus, for populations with high rates of consanguinity, the heterozygosity of markers can be lower than published values. Although a given set of pedigrees has a certain number of phase-known and -unknown meioses, the number of informative meioses is directly affected by marker heterozygosity and by whether the marker genotype frequencies are in HWE.

There is great interest in using SNP markers for gene mapping. The advantages of SNP markers are their density across the genome and their low mutation rates. There are SNP markers available which are placed approximately every 1.9 Kb [Sachidanandam et al., 2001]. In the future, the genotyping of SNP markers should also be both cost- and time-effective. One disadvantage of SNP markers is that due to their diallelic nature, they have a low heterozygosity ($H = 0.5$); therefore, they are less informative than microsatellite markers. For linkage disequilibrium (LD) mapping, haplotype-block maps (HapMap) will provide useful information on the extent of LD between SNP markers across the genome. It has been shown that haplotype blocks that range from 5–100 kb have very high levels of LD between marker pairs, and that these blocks are separated by recombination hot-spots that extend 1–5 kb [Daly et al., 2001; Jeffreys et al., 2001; Patil et al., 2001]. There is also interest in using dense maps of SNP markers for linkage analysis studies for both fine mapping and genome scans. Just as physical maps do not provide information on genetic map distances, neither will haplotype-block linkage disequilibrium maps. There are several parameters that influence LD between markers, including rates of recombination, gene conversion, marker allele frequency, mutation rates, natural selection, and population demographic factors (e.g., in breeding, population stratification, or bottlenecks) [Slatkin, 1994; Broman and Weber, 1999; Pritchard and Przeworski, 2001]. Genetic distances are influenced only by rates of recombination and gene conversion. In order for SNP markers to be truly useful for gene mapping, good estimates of recombination fractions are necessary. This information will not only be important for multipoint linkage analysis, but also in forming “superloci” to be used in two-point analysis. A “superlocus” is formed by using information from a cluster of two or more SNP markers, thus creating a marker that is more informative (i.e., higher heterozygosity) than its individual marker locus components. These “superloci” may be advantageous when using SNP markers for linkage analysis, due to the low heterozygosity of SNP markers [Görling and Terwilliger, 2000; Wilson and Sorant, 2000; Goddard and Wijsman, 2002].

It is not feasible to create a SNP genetic map ($H=0.5$) with markers placed every 2–5 Kb (assuming intermarker maps distances of 0.002–0.005 cM), due to recombination events being extremely rare. However, unlike the SNP maps, which will be used for LD mapping,

extremely dense marker maps of SNP markers should not be necessary for gene mapping using linkage analysis methods. Even with their low heterozygosity, a much less dense map of markers should suffice for linkage analysis. Kruglyak [1997] suggested that an SNP map of ~3,000 markers spaced approximately every 1 cM would provide more information than a 5-cM map of multiallelic marker loci. Others have proposed using genome scan linkage maps consisting of “superloci” [Göring and Terwilliger, 2000; Wilson and Sorant, 2000; Goddard and Wijsman, 2002]. The markers within these “superloci” should be within close physical proximity to each other (e.g., 100 kb), and therefore display very low levels of recombination. In addition, “superloci” should exhibit low levels of intermarker linkage disequilibrium [Wilson and Sorant, 2000; Goddard and Wijsman, 2002]. A number of biotech companies are currently developing sets of SNP markers and performing genotyping for linkage genome scans. Some biotech firms are going the route of developing SNP markers sets with SNP markers distributed uniformly across the genome, while the SNP Consortium Linkage Map Project developed a SNP marker set using clusters of SNPs. For example, Illumina developed a set of over 2,300 SNP markers that are approximately uniformly spaced across the genome (http://www.illumina.com/snp_linkage.htm). On the other hand, the SNP Consortium Linkage Map Project constructed a 4-cM linkage map consisting of 2,772 SNPs markers which are distributed as single SNP markers and clusters of 2-4 SNP markers in regions which are <100 kb [Matise et al., 2002b]. The SNP markers were genotyped in 609–661 individuals from 48-50 CEPH families. To date, it is not clear whether clusters of SNP loci or SNP loci distributed uniformly across the genome will be more beneficial for linkage analysis studies [Kruglyak, 1997; Wilson and Sorant, 2000; Goddard and Wijsman, 2002]. One SNP linkage map may not be advantageous in all situations; pedigree structure and analysis methods may play a role in which SNP linkage map is more powerful.

This study demonstrates that it is feasible to generate 1-cM SNP linkage maps. Constructing a map of SNP markers ($H=0.32$) using 2,000 meioses led to small CI values around the point estimates of the genetic map distance. In addition, the power is >0.8 to separate adjacent markers with a nonzero map distance (see Table II). When “superloci” are used, it will be difficult to accurately estimate genetic map distances between SNP loci within a cluster. For the SNP Consortium Linkage Map, if a one-to-one correspondence is assumed between physical and genetic map distances, then the intermarker distance within a cluster is at most 0.1 cM. For such a small distance, even when the genetic map is generated using 5,000 meioses, the 95% CI for the point estimate of the genetic map distance is more than twice the length of the point estimate. In addition, the power to separate adjacent markers with a nonzero map distance is low (<68%). The situation becomes worse for smaller map distances, which would usually be the case for clusters of SNP markers. For example, for a 0.01-cM map distance, the power to separate two adjacent markers with a nonzero map distance is <0.07, and the length of the CI is more than 10 times the length of the point estimate of the map distance (see Table II). The SNP Consortium Linkage Map does not report estimates of map distances between markers within a cluster. However, due to the selection of markers having low levels of intermarker linkage disequilibrium within a cluster, these markers may lay in regions enriched for recombination events. It is not clear

how the false assumption of zero map distance between SNP markers within a cluster will affect the ability to map trait loci.

It should be feasible to construct genetic linkage maps using a large number of meioses. Currently, a genetic map is in the process of being constructed, using the 10-cM genome scan markers from Marshfield panels 9 and 10, using genotyped data generated by the National Heart Lung and Blood Institute Mammalian genotyping service (<http://compugen.rutgers.edu/newmaps/>). Once SNP markers are used to carry out genome scans, genotype data generated at genotyping services (e.g., the Center for Inherited Disease Research) could be used to construct genetic maps. Currently, several genetic studies are being carried out, using a large number of samples from special populations to study a variety of genetic traits [Williams-Blangero et al., 2002; Han et al., 2002]. These samples could potentially be used to construct genetic maps. A recent example where this was done was for the construction of the deCode genetic map that was generated using pedigree data from Iceland [Kong et al., 2002].

Besides being useful for linkage studies, the generation of genetic maps from large numbers of meioses will be beneficial in helping to understand the nature of recombination across the genome. Genetic maps will also help answer questions about the varying rates of recombination across the genome, interference, positions of jungles and deserts, and how they vary in males and females. They should also help explain the effect of parental age, environment, and ethnicity on recombination events. The current genetic maps have given insights into some of these questions, but much still needs to be learned [Renwick and Schulze, 1965; Lamm, 1973; Weitkamp, 1974; Weitkamp et al., 1973; Donis-Keller et al., 1987; Tanzi et al., 1992; Straub et al., 1993; Weber et al., 1993; Lichten and Goldman, 1995; Broman et al., 1998; Li et al., 1998; Mohrenweiser et al., 1998; Ashley-Koch et al., 1999; Broman and Weber, 2000; Yu et al., 2001; Matise et al., 2002a; Kong et al., 2002]. Genetic, radiation hybrid, cytogenetic, sequence-based physical, and haplo-type-block linkage disequilibrium maps will each provide unique information to help solve the puzzle of the human and other genomes.

ACKNOWLEDGMENTS

The author thanks Kai Yan for programming assistance. In addition, the author thanks Andrew DeWan, Bertram Müller-Myhsok, and Dale Nyholt for useful suggestions and comments.

Grant sponsor: NIH; Grant number: DC03594.

REFERENCES

- Ashley-Koch A, Wolpert CM, Menold MM, Zaeem L, Basu S, Donnelly SL, Ravan SA, Powell CM, Qumsiyeh MB, Ayslworth AS, Vance JM, Gilbert JR, Wright HH, Abramson RK, DeLong GR, Cuccaro ML, Pericak-Vance MA. 1999 Genetic studies of autistic disorder and chromosome 7. *Genomics* 61:227–36. [PubMed: 10552924]
- Botstein D, White RL, Skolnick MH, Davies RW. 1980 Construction of a genetic linkage map in man using restriction fragment length polymorphisms. *Am J Hum Genet* 32:314–31. [PubMed: 6247908]
- Broman KW, Weber JL. 1999 Long homozygous chromosomal segments in reference families from the Centre d'Etude du Polymorphisme Humain. *Am J Hum Genet* 65:1489–92. [PubMed: 10577901]

- Broman KW, Weber JL. 2000 Characterization of human crossover interference. *Am J Hum Genet* 66:1911–26. [PubMed: 10801387]
- Broman KW, Murray JC, Sheffield VC, White RL, Weber JL. 1998 Comprehensive human genetic maps: individual and sex-specific variation in recombination. *Am J Hum Genet* 63:861–9. [PubMed: 9718341]
- Brzustowicz LM, Mérette C, Xie X, Townsend L, Gilliam TC, Ott J. 1993 Molecular and statistical approaches to the detection and correction of errors in genotype databases. *Am J Hum Genet* 53:1137–45. [PubMed: 8213837]
- Buetow KH. 1991 Influence of aberrant observations on high-resolution linkage analysis outcomes. *Am J Hum Genet* 49: 985–94. [PubMed: 1928104]
- Buri P 1956 Gene frequencies in small populations of mutant *Drosophila*. *Evolution* 10:367–402.
- Clerget-Darpoux F, Bonaiti-Pellie C, Hochez J. 1986 Effects of misspecifying genetic parameters in lod score analysis. *Biometrics* 42:393–9. [PubMed: 3741977]
- Cleves MA, Elston RC. 1997 Alternative test for linkage between two loci. *Genet Epidemiol* 14:117–31. [PubMed: 9129958]
- Cockerham CC. 1967 Group inbreeding and coancestry. *Genetics* 56:89–92. [PubMed: 6035597]
- Cockerham CC. 1969 Variance of gene frequencies. *Evolution* 23:72–84. [PubMed: 28562963]
- Daly MJ, Rioux JD, Schaffner SF, Hudson TJ, Lander ES. 2001 High-resolution haplotype structure in the human genome. *Nat Genet* 29:229–32. [PubMed: 11586305]
- Dausset J, Cann H, Cohen D, Lathrop M, Lalouel JM, White R. 1990 Centre d'Etude du Polymorphisme Humain (CEPH): collaborative genetic mapping of the human genome. *Genomics* 6:575–7. [PubMed: 2184120]
- Daw EW, Thompson EA, Wijsman EM. 2000 Bias in multipoint linkage analysis arising from map misspecification. *Genet Epidemiol* 19:366–80. [PubMed: 11108646]
- DeWan AT, Parrado AR, Matise TC, Leal SM. 2002a Map error reduction: using genetic and sequence-based physical maps to order closely linked markers. *Hum Hered* 54:34–44. [PubMed: 12446985]
- DeWan AT, Parrado AR, Matise TC, Leal SM. 2002b The map problem: a comparison of genetic and sequence-based physical maps. *Am J Hum Genet* 70:101–7. [PubMed: 11706388]
- Dib C, Faure S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, Marc S, Hazan J, Seboun E, Lathrop M, Gyapay G, Morissette J, Weissenbach J. 1996 A comprehensive genetic map of the human genome based on 5,264 microsatellites. *Nature* 380:152–4. [PubMed: 8600387]
- Donis-Keller H, Green P, Helms C, Cartinhour S, Weiffenbach B, Stephens K, Keith TP, Bowden DW, Smith DR, Lander ES. 1987 A genetic linkage map of the human genome. *Cell* 51: 319–37. [PubMed: 3664638]
- Edwards JH. 1976 The interpretation of lod scores in linkage analysis. *HGM* 3:289–93.
- Feakes R, Sawcer S, Chataway J, Coraddu F, Broadley S, Gray J, Jones HB, Clayton D, Goodfellow PN, Compston A. 1999 Exploring the dense mapping of a region of potential linkage in complex disease: an example in multiple sclerosis. *Genet Epidemiol* 17:51–63. [PubMed: 10323184]
- Goddard KA, Wijsman EM 2002 Characteristics of genetic markers and maps for cost-effective genome screens using diallelic markers. *Genet Epidemiol* 22:205–20. [PubMed: 11921081]
- Goldstein DR, Zhao H, Speed TP. 1997 The effects of genotyping errors and interference on estimation of genetic distance. *Hum Hered* 47:86–100. [PubMed: 9097090]
- Göring HH, Terwilliger JD. 2000 Linkage analysis in the presence of errors III: marker loci and their map as nuisance parameters. *Am J Hum Genet* 66:1298–309. [PubMed: 10731467]
- Haldane JBS. 1919 The combination of linkage values and the calculation of distances between the loci of linked factors. *J Genet* 8:229–309.
- Halpern J, Whittemore AS. 1999 Multipoint linkage analysis. A cautionary note. *Hum Hered* 4:194–6.
- Han Z, Heath SC, Shmulewitz D, Li W, Auerbach SB, Blundell ML, Lehner T, Ott J, Stoffel M, Friedman JM, Breslow JL. 2002 Candidate genes involved in cardiovascular risk factors by a family-based association study on the island of Kosrae, Federated States of Micronesia. *Am J Med Genet* 110:234–42. [PubMed: 12116231]

- Hanis CL, Boerwinkle E, Chakraborty R, Ellsworth DL, Concannon P, Stirling B, Morrison VA, Wapelhorst B, Spielman RS, Gogolin-Ewens KJ, Shepard JM, Williams SR, Risch N, Hinds D, Iwasaki N, Ogata M, Omori Y, Petzold C, Rietzch H, Schroder HE, Schulze J, Cox NJ, Menzel S, Boriraj VV, Chen X. 1996 A genome-wide search for non-insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2. *Nat Genet* 13:161–6. [PubMed: 8640221]
- Hartl DL, Clark AG. 1989 Principles of population genetics, 2nd ed. Sunderland, MA: Sinauer Associates, Inc.
- Jeffreys AJ, Kauppi L, Neumann R. 2001 Intensely punctate meiotic recombination in the class II region of the major histocompatibility complex. *Nat Genet* 29:217–22. [PubMed: 11586303]
- Katsanis N, Worley KC, Lupski JR. 2001 An evaluation of the draft human genome sequence. *Nat Genet* 29:88–91. [PubMed: 11528399]
- Ke X, Tapper W, Collins A. 2001 LDB2000: sequence-based integrated maps of the human genome. *Bioinformatics* 17:581–6. [PubMed: 11448876]
- Keats BJB, Sherman SL, Morton NE, Robson EB, Buetow KH, Cartwright PE, Chakravarti A, Francke U, Green PP, Ott J. 1991 Guidelines for human linkage maps: an international system for human linkage maps (ISLM 1990). *Genomics* 9:557–60. [PubMed: 2032725]
- Kong A, Gudbjartsson DF, Sainz J, Jonsdottir GM, Gudjonsson SA, Richardsson B, Sigurdardottir S, Barnard J, Hallbeck B, Masson G, Shlien A, Palsson ST, Frigge ML, Thorgeirsson TE, Gulcher JR, Stefansson K. 2002 A high-resolution recombination map of the human genome. *Nat Genet* 31:241–7. [PubMed: 12053178]
- Kruglyak L. 1997 The use of a genetic map of biallelic markers in linkage studies. *Nat Genet* 17:21–4. [PubMed: 9288093]
- Lamm LU. 1973 The relation of parental sex and age to recombination fraction in the HLA-A system. *Hum Hered* 23:197–205. [PubMed: 4760577]
- Lathrop GM, Lalouel JM, Julier C, Ott J. 1984 Strategies for multilocus linkage analysis in humans. *Proc Natl Acad Sci USA* 81:3443–6. [PubMed: 6587361]
- Li W, Fann C, Ott J. 1998 Low-order polynomial trends of trends of female-to-male map distance ratio along human chromosomes. *Hum Hered* 48:266–70. [PubMed: 9748696]
- Lichten M, Goldman AS. 1995 Meiotic recombination hotspots. *Annu Rev Genet* 29:423–44. [PubMed: 8825482]
- Matise TC, Porter CJ, Buyske S, Cuttichia AJ, Sulman EP, White PS. 2002a Systematic evaluation of map quality: human chromosome 22. *Am J Hum Genet* 70:1398–410. [PubMed: 11992248]
- Matise TC, Sachidanadam Clark A, Kruglyak L, Wijisman E, Chui B, Cohen C, Detoma C, Ehm M, Glanowski S, He C, Heil J, McMullern I, Stein L, Wagner M, Winik J, Winn-Deen ES, Cann HM, Kai E, Holder HL. 2002b A high resolution human SNP linkage map. *Am J Hum Genet* [Suppl] 71:215.
- Mohrenweiser HW, Tsujimoto S, Gordon L, Olsen AS. 1998 Regions of sex-specific hypo- and hyper-recombination identified through integration of 180 genetic markers into the metric physical map of human chromosome 19. *Genomics* 47:153–62. [PubMed: 9479487]
- Morton NE, Collins A. 1990 Standard maps of chromosome 10. *Ann Hum Genet* 54:235–51. [PubMed: 2221826]
- Murray JC, Buetow KH, Weber JL, Ludwigsen S, Scherpbier-Heddema T, Manion F, Quillen J. 1994 A comprehensive human linkage map with centimorgan density. Cooperative Human Linkage Center (CHLC). *Science* 265:2049–54. [PubMed: 8091227]
- Ott J, Lehner T, Sandkuyl LA. 1988 Fallacies of the technique of “haplotyping” two apparently linked loci in multipoint linkage analysis. *Am J Hum Genet* 43:154.
- Patil N, Berno AJ, Hinds DA, Barrett WA, Doshi JM, Hacker CR, Kautzer CR, Lee DH, Marjoribanks C, McDonough DP, Nguyen BT, Norris MC, Sheehan JB, Shen N, Stern D, Stokowski RP, Thomas DJ, Trulson MO, Vyas KR, Frazer KA, Fodor SP, Cox DR. 2001 Blocks of limited haplotype diversity revealed by high-resolution scanning of human chromosome 21. *Science* 294:1719–23.
- Pritchard JK, Przeworski M. 2001 Linkage disequilibrium in human: models and data. *Am J Hum Genet* 69:1–14. [PubMed: 11410837]

- Renwick J, Schulze J. 1965 Male and female recombination rates for nail-patella: ABO linkage in man. *Ann Hum Genet* 28: 379–92.
- Risch N, Giuffra L. 1992 Model misspecification and multipoint linkage analysis. *Hum Hered* 42:77–92. [PubMed: 1555848]
- Sachidanandam R, Weissman D, Schmidt SC, Kakol JM, Stein LD, Marth G, Sherry S, Mullikin JC, Mortimore BJ, Willey DL, Hunt SE, Cole CG, Coggill PC, Rice CM, Ning Z, Rogers J, Bentley DR, Kwok PY, Mardis ER, Yeh RT, Schultz B, Cook L, Davenport R, Dante M, Fulton L, Hillier L, Waterston RH, McPherson JD, Gilman B, Schaffner S, Van Etten WJ, Reich D, Higgins J, Daly MJ, Blumenstiel B, Baldwin J, Stange-Thomann N, Zody MC, Linton L, Lander ES, Altshuler D, International SNP Map Working Group. 2001 A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 15:928–33.
- Sheffield VC, Weber JL, Buetow KH, Murray JC, Even DA, Wiles K, Gastier JM, Pulido JC, Yandava C, Sunden SL. 1995 A collection of tri- and tetranucleotide repeat markers used to generate high quality, high resolution human genome-wide linkage maps. *Hum Mol Genet* 4:1837–44. [PubMed: 8595404]
- Shen Y, Kozman HM, Thompson A, Phillips HA, Holman K, Nancarrow J, Lane S, Chen LZ, Apostolou S, Doggett NA. 1994 A PCR-based genetic linkage map of human chromosome 16. *Genomics* 22:68–76. [PubMed: 7959793]
- Slatkin M 1994 Linkage disequilibrium in growing and stable populations. *Genetics* 137:331–6. [PubMed: 8056320]
- Straub RE, Speer MC, Luo Y, Rojas K, Overhauser J, Ott J, Gilliam TC. 1993 A microsatellite genetic linkage map of human chromosome 18. *Genomics* 15:48–56. [PubMed: 8094374]
- Stringham HM, Boehnke M. 2001 Lod scores for gene mapping in the presence of marker map uncertainty. *Genet Epidemiol* 21:31–9. [PubMed: 11443732]
- Tanzi RE, Watkins PC, Stewart GD, Wexler NS, Gusella JF, Haines JL. 1992 A genetic linkage map of human chromosome 21: analysis of recombination as a function of sex and age. *Am J Hum Genet* 50:551–8. [PubMed: 1347193]
- Tapper WJ, Morton NE, Dunham I, Ke X, Collins A. 2001 A sequence-based integrated map of chromosome 22. *Genome Res* 11:1290–5. [PubMed: 11435412]
- Terwilliger JD, Ott J. 1994 Handbook of human genetic linkage Baltimore: Johns Hopkins University Press.
- Terwilliger JD, Ding Y, Ott J. 1992 On the relative importance of marker heterozygosity and intermarker distance in gene mapping *Genomics* 13:951–6. [PubMed: 1505986]
- Terwilliger JD, Speer M, Ott J. 1993 Chromosome-based method for rapid computer simulation in human genetic linkage analysis. *Genet Epidemiol* 10:217–24. [PubMed: 8224802]
- Tomfohrde J, Wood S, Schertzer M, Wagner MJ, Wells DE, Parrish J, Sadler LA, Blanton SH, Daiger SP, Wang Z. 1992 Human chromosome 8 linkage map based on short tandem repeat polymorphisms: effect of genotyping errors. *Genomics* 14: 144–52. [PubMed: 1427821]
- Weber JL. 1990 Human DNA polymorphisms and methods of analysis. *Curr Opin Biotechnol* 1:166–71. [PubMed: 1367853]
- Weber JL. 2002 The Icelandic map. *Nat Genet* 31:225–226. [PubMed: 12053179]
- Weber JL, Wang Z, Hansen K, Stephenson M, Kappel C, Salzman S, Wilkie PJ, Keats B, Dracopoli NC, Brandriff BF, Olsen AS. 1993 Evidence for human meiotic recombination interference obtained through construction of a short tandem repeat-polymorphism linkage map of chromosome 19. *Am J Hum Genet* 53:1079–95. [PubMed: 8213834]
- Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, Vaysseix G, Lathrop MA. 1992 A second-generation linkage map of the human genome. *Nature* 359:794–801. [PubMed: 1436057]
- Weitkamp LR. 1974 Population differences in meiotic recombination frequency between loci on chromosome 1. *Cytogenet Cell Genet* 13:179–82. [PubMed: 4208017]
- Weitkamp LR, Van Rood JJ, Thorsby E, Bias W, Fotinio M, Lawler SD, Dausset J, Mayr WR, Bodmer J, Ward FE, Seignalet J, Payne R, Kissmeyer-Nielsen F, Gatti RA, Sachs JA, Lamm LU. 1973 The relation of parental sex and age to recombination in the HLA system. *Hum Hered* 23:197–205. [PubMed: 4760577]

- Williams-Blangero S, VandeBerg JL, Subedi J, Aivaliotis MJ, Rai DR, Upadhayay RP, Jha B, Blangero J. 2002 Genes on chromosomes 1 and 13 have significant effects on *Ascaris* infection. *Proc Natl Acad Sci USA* 99:5533–8. [PubMed: 11960011]
- Wilson AF, Sorant AJ. 2000 Equivalence of single- and multilocus markers: power to detect linkage with composite markers derived from biallelic loci. *Am J Hum Genet* 66:1610–5. [PubMed: 10762546]
- Wright S 1931 Evolution in Mendelian populations. *Genetics* 16:97–159. [PubMed: 17246615]
- Wright S 1932 The role of mutation, inbreeding, crossbreeding and selection in evolution. *Proc 6th Int Cong Genet* 1:356–66.
- Yu A, Zhao C, Fan Y, Jang W, Mungall AJ, Deloukas P, Olsen A, Doggett NA, Ghebranious N, Broman KW, Weber JL. 2001 Comparison of human genetic and sequence-based physical maps. *Nature* 409:951–3. [PubMed: 11237020]
- Zahn LM, Kwiatkowski DJ. 1995 A 37-marker PCR-based genetic linkage map of human chromosome 9: observations on mutations and positive interference. *Genomics* 28:140–6. [PubMed: 8530019]

TABLE I.

Results of simulation studies for “microsatellite” markers^a

Map distance	200 meioses				1,000 meioses			
	H=0.67		H=0.9		H=0.67		H=0.9	
	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power
10 cM	10.625, 1.816 4.704, 15.329	0.998	8.513, 0.935 5.917, 14.430	1	4.794, 0.324 7.614, 12.408	1	3.794, 0.191 8.075, 11.869	1
5cM	7.451, 1.705 1.439, 8.890	0.983	6.183, 1.068 1.983, 8.166	1	3.431, 0.286 3.286, 6.717	1	2.801, 0.197 3.607, 6.408	1
2.5 cM	4.843, 1.638 0.355, 5.198	0.897	4.282, 1.286 0.481, 4.763	0.977	2.452, 0.298 1.283, 3.735	1	2.023, 0.204 1.507, 3.530	1
1 cM	2.867, 1.026 0.027, 2.894	0.564	2.553, 0.911 0.033, 2.586	0.749	1.447, 0.403 0.259, 1.706	0.963	1.264, 0.252 0.363, 1.627	0.983
0.5 cM	2.318, 0.845 0.006, 2.324	0.296	1.954, 0.429 0.002, 1.956	0.339	0.959, 0.366 0.066, 1.025	0.861	0.858, 0.267 0.084, 0.942	0.958
0.25 cM	2.196, 0.990 0, 2.196	0.139	1.897, 0.818 0, 1.897	0.115	0.630, 0.253 0.007, 0.637	0.684	0.571, 0.238 0.015, 0.586	0.844
Map distance	2,000 meioses				5,000 meioses			
	H=0.67		H=0.9		H=0.67		H=0.9	
	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power
10 cM	3.382, 0.155 8.333, 11.715	1	2.688, 0.094 8.651, 11.339	1	2.140, 0.068 8.941, 11.081	1	1.702, 0.048 9.146, 10.848	1
5cM	2.433, 0.143 3.753, 6.186	1	1.979, 0.100 3.998, 5.977	1	1.538, 0.059 4.214, 5.752	1	1.253, 0.041 4.366, 5.619	1
2.5 cM	1.737, 0.137 1.628, 3.365	1	1.430, 0.103 1.785, 3.215	1	1.099, 0.058 1.945, 3.044	1	0.903, 0.041 2.036, 2.939	1
1 cM	1.082, 0.195 0.452, 1.534	0.987	0.905, 0.113 0.536, 1.441	0.996	0.695, 0.085 0.652, 1.347	0.992	0.581, 0.042 0.714, 1.295	1
0.5 cM	0.697, 0.238 0.127, 0.824	0.928	0.623, 0.152 0.180, 0.803	0.968	0.432, 0.160 0.231, 0.663	0.925	0.371, 0.112 0.268, 0.639	0.95 7
0.25 cM	0.476, 0.194 0.031, 0.507	0.873	0.404, 0.148 0.044, 0.448	0.928	0.286, 0.127 0.075, 0.361	0.898	0.233, 0.102 0.096, 0.329	0.92 8

^aFor each simulation study, 1,000 replicates were generated. Average length of 95% confidence interval (length) and its standard deviation (Std), average lower and upper bound of the 95% confidence interval (CI), and power to separate two adjacent markers with a nonzero map distance are shown for various map distances and marker heterozygosities (H).

TABLE II.Results of simulation studies for “SNP” markers^{aa}

Map distance	200 meioses					1,000 meioses			
	H=0.32		H=0.5		H=0.32		H=0.5		
	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power	
1 cM	4.712, 2.473 0.022, 4.734	0.271	3.339, 1.366 0.022, 3.361	0.449	1.885, 0.977 0.129, 2.014	0.671	1.620, 0.648 0.199, 1.819	0.859	
0.5 cM	4.072, 1.381 0.006, 4.078	0.118	2.858, 0.672 0.006, 2.864	0.203	1.214, 0.591 0.039, 1.253	0.478	1.010, 0.472 0.045, 1.055	0.717	
0.25 cM	3.840, 1.181 0.002, 3.842	0.066	2.766, 0.889 0.001, 2.767	0.109	0.927 0.325 0.016, 0.943	0.315	0.720, 0.350 0.011, 0.731	0.510	
0.1 cM	3.797, 1.359 0, 3.797	0.035	2.741, 0.826 0, 2.741	0.035	0.791, 0.158 0.003, 0.794	0.148	0.571, 0.285 0.001, 0.572	0.229	
0.01 cM	3.786, 1.072 0, 3.786	0.001	2.723, 0.385 0, 2.723	0.006	0.755, 0.092 0, 0.755	0.017	0.534, 0.048 0, 0.534	0.018	
Map distance	2,000 meioses					5,000 meioses			
	H=0.32		H=0.5		H=0.32		H=0.5		
	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power	Length, Std, CI	Power	
1 cM	1.513, 0.710 0.226, 1.739	0.827	1.202, 0.429 0.312, 1.514	0.910	0.999, 0.469 0.377, 1.376	0.849	0.818, 0.207 0.564, 1.382	0.965	
0.5 cM	0.899, 0.502 0.083, 0.982	0.622	0.766, 0.342 0.103, 0.869	0.842	0.604, 0.352 0.118, 0.722	0.740	0.511, 0.216 0.195, 0.706	0.878	
0.25 cM	0.619, 0.338 0.031, 0.650	0.468	0.519, 0.252 0.028, 0.547	0.727	0.419, 0.231 0.041, 0.460	0.684	0.332, 0.161 0.056, 0.388	0.822	
0.1 cM	0.444, 0.226 0.005, 0.449	0.256	0.337, 0.149 0.004, 0.341	0.448	0.239, 0.141 0.014, 0.253	0.438	0.207, 0.121 0.014, 0.220	0.666	
0.01 cM	0.376, 0.037 0, 0.376	0.017	0.268, 0.112 0, 0.268	0.038	0.149, 0.017 0, 0.149	0.018	0.112, 0.094 0.002, 0.114	0.062	

^aFor each simulation study, 1,000 replicates were generated. Average length of 95% confidence interval (length) and its standard deviation (Std), average lower and upper bound of 95% confidence interval (CI), and power to separate two adjacent markers with a nonzero map distance are shown for various map distances and marker heterozygosities (H).