

available is not an upper limit. But it may be increased significantly through the introduction of seismic moment tensor information and estimates of stress from geological and geodetical investigations as well as from past earthquakes.

Our results indicate that only about one-third of the strong earthquakes are preceded by foreshocks that are separated in time from an independent shock by more than t_M . For other modern catalogs of earthquakes that are similar in quality to the central California CALNET catalog, the number of failures-to-predict is about the same, that is, of the order of two-thirds (1, 3, 4).

A modification of the above strategy for prediction is called for in the case of the occurrence of strong earthquakes. Strong earthquakes have the potential for serving as foreshocks of even stronger earthquakes, or they may be the main shock in the sequence, just as weaker earthquakes can serve both functions. However, the coda time t_M is about 15 minutes for an earthquake with $m_L = 5$, and this time increases by a factor of about $\sqrt{10}$ for a unit increase in earthquake magnitude. If an earthquake with $m_L = 6$ were to occur, with or without prior warning according to the scenario above, no alarm for a possibly even stronger earthquake would be sounded for about $t_M = 50$ minutes, which might be an unacceptably long delay for issuing a warning. This difficulty is circumvented if we reduce the dead time for large earthquakes to a value less than the coda time.

This modification for strong earthquakes indicates that response strategies can also be developed with time delays of the order of seconds. As suggested by Heaton (20), it may be possible to predict some large earthquakes through the analysis of small starting phases of complex events that later blossom into large earthquakes. These small starting phases are genuine earthquakes whose signals overlap with those of their successors and raise the probability level for a short time, thereby triggering an alarm for the larger event. The number of these preshocks should increase as $t_b^{-3/2}$, where t_b is the time before the start of the main phase of a strong earthquake (2-4). In the present method, we are not restricted to dead times of the order of rupture times, but instead we are able to use longer delays of the order of a few minutes. With this procedure there should be far fewer failures-to-predict for very strong earthquakes. Automated response strategies could take advantage of these predictions in a well-developed technology.

The differences between our proposed forecasting technique and methods that use

empirically derived probabilities of fore-shock-main shock occurrence may be summarized as follows. (i) Since our model is based on a formulation derived from a multidimensional stochastic process, it is not necessary to use arbitrary windows to analyze seismicity, nor is it necessary to delete aftershocks from a catalog to make the catalog amenable to statistical analysis. Therefore, our forecasts are not dependent on a post-factum classification of earthquakes into fore-, main, and aftershocks, a subdivision that may not be possible in real time. (ii) Since the parameters of our seismicity model are obtained through a maximum likelihood procedure, the model is optimal in a quantitative way. The choices of the parameters can be justified on the basis of a well-defined theoretical model of earthquake occurrence (2, 10, 19). Furthermore, the model itself is consistent with all of the other aspects of statistical seismicity that have been well documented, and it has not been derived for the sole purpose of developing the foreshock-main shock relations. The model has only three parameters that are adjusted to the properties of the local seismicity: the rate of occurrence of independent earthquakes and the coefficients that specify the occurrence of dependent earthquakes, μ and σ . In one sense the exponent 2/3 in Eq. 4 is also an adjustable parameter, but since this can be derived on formal grounds (3), we have considered it as fixed. (iii) The likelihood function we have derived allows us to estimate the effectiveness of the proposed prediction scheme in terms of information content of an earth-

quake catalog. The procedures outlined here can be adapted to predicting schemes other than the one we have used, as soon as the quality and quantity of the data describing these precursors reach the stage where they can be processed by similar multidimensional statistical techniques.

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Homozygosity Mapping: A Way to Map Human Recessive Traits with the DNA of Inbred Children

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An efficient strategy for mapping human genes that cause recessive traits has been devised that uses mapped restriction fragment length polymorphisms (RFLPs) and the DNA of affected children from consanguineous marriages. The method involves detection of the disease locus by virtue of the fact that the adjacent region will preferentially be homozygous by descent in such inbred children. A single affected child of a first-cousin marriage is shown to contain the same total information about linkage as a nuclear family with three affected children. Calculations show that it should be practical to map a recessive disease gene by studying DNA from fewer than a dozen unrelated, affected inbred children, given a complete RFLP linkage map. The method should make it possible to map many recessive diseases for which it is impractical or impossible to collect adequate numbers of families with multiple affected offspring.

IN HIS CLASSIC STUDY OF INBORN ERRORS of metabolism, Garrod (1) noted that an unusually high proportion of patients with alkaptonuria were progeny of consanguineous marriages. Almost immedi-

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ately, Bateson (2) supplied the Mendelian explanation, providing an early success for the then newly rediscovered theory of heredity. Theory subsequently predicted and observation has confirmed that the rarer the disease, the more pronounced is the effect (3).

Our strategy for gene mapping relies on the related fact that in a child of a consanguineous marriage affected with a recessive genetic disease, a region of many centimorgans (cM) spanning the disease locus is almost always homozygous by descent. A few other regions may also be homozygous by descent in any given child, but these regions will vary from one child to another. Searching for regions that are consistently homozygous by descent would be expected to provide a powerful strategy for mapping a recessive gene (4).

A complete restriction fragment length polymorphism (RFLP) linkage map of the human genome (5) may soon be available. We suspected that such a map might make it feasible to detect homozygosity by descent (by looking for regions in which a number of adjacent RFLPs were all homozygous) and thereby to map recessive traits in humans without the need for family studies. Below, we provide a rigorous justification for this intuition.

Consider a child with coefficient of inbreeding F , defined (6) as the chance that a given locus will be found homozygous by descent or, equivalently, the fraction of the child's genome expected to be homozygous by descent; for sibling, first-cousin, and second-cousin marriages, $F = 1/4$, $1/16$, and $1/64$, respectively. Imagine a disease caused by a recessive allele at a single Mendelian locus, where disease alleles have frequency q in a population in Hardy-Weinberg equilibrium. If the child is affected, then homozygosity by descent at the disease locus is almost surely at fault; the probability is $\alpha = Fq/[Fq + (1 - F)q^2]$. To see this, note that Fq of all inbreds will be homozygous by descent at the disease locus and affected, while $(1 - F)q^2$ will not be homozygous by descent at the disease locus but will be affected due to random meeting of disease alleles. Provided that q is small compared to F , α is very close to 1.

While the region actually around the disease locus is homozygous by descent with probability $\alpha \approx 1$, unlinked regions are homozygous by descent with a probability of only F ($\ll 1$). Consider an RFLP so polymorphic that homozygosity for any allele implies homozygosity by descent. Each time that such an RFLP were observed to be homozygous in an inbred affected child, one would obtain an odds ratio of $\alpha:F$ in favor of the hypothesis that the disease gene is tightly linked to the marker, as compared to

the hypothesis that it is unlinked. For example, finding homozygosity for such an RFLP in the affected progeny of a first-cousin marriage ($F = 1/16$) yields odds of 16:1 in favor of linkage. If the RFLP is in fact tightly linked, then homozygosity will be consistently observed and odds of $16^3:1$ in favor of linkage—well over the accepted threshold (7) of 1000:1 required for proving linkage—will be obtained after studying only three such affected children.

While one cannot count on having a single highly polymorphic RFLP exactly at the disease locus, a similar effect can be accomplished by the use of a genetic map of adequately polymorphic RFLPs spaced throughout the human genome.

Specifically, homozygosity mapping would be performed as follows. To test the hypothesis that the disease gene maps to a given interval, we would examine the DNA of each affected inbred child for homozygosity at (say) six consecutive RFLPs—three to the left and three to the right of the interval. There are 64 possible outcomes at the six loci denoted HHH.HHH, HHH.HH-, HHH.H-., and so on, where "H" denotes homozygosity, "-" denotes heterozygosity, and "." indicates the interval being tested for linkage. For each outcome, we would compute the probability P_1 that the outcome would occur if the disease actually maps to the interval and P_2 that the outcome would occur if the disease is actually unlinked. The odds ratio in favor of linkage is then $P_1:P_2$. Odds ratios from independent cases can then be multiplied until the threshold of 1000:1; for the customary "LOD score" (\log_{10} of the odds ratio) the threshold is 3.

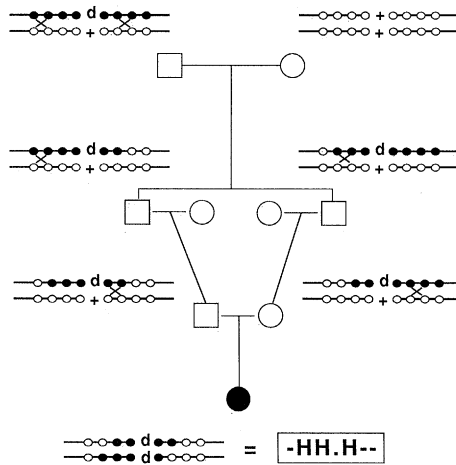


Fig. 1. Sample pedigree showing a first-cousin marriage producing a child affected with a recessive disease, due to homozygosity by descent for a disease-causing allele (d). For the purpose of homozygosity mapping, one is only assumed to observe the pattern of homozygosity and heterozygosity in the child; in the case shown, examining six RFLPs flanking the region would yield the pattern -HH.H--.

Computing P_1 and P_2 constitutes multilocus linkage analysis of seven loci (six markers and the disease gene) in a pedigree (Fig. 1) with a great deal of missing information. These calculations can be performed by standard programs that compute multilocus likelihoods (8), although they might be quite time-consuming. Recently, however, Lander and Green (9) introduced an efficient algorithm that makes it convenient to perform the analysis in seconds. A computer program, called HOMMAP, has been written implementing this algorithm for progeny of sibling or cousin marriages.

Consider, for example, a child of a first-cousin mating affected with a rare recessive disease. By rare, we mean that the frequency q of the disease allele is small enough so that $\alpha \approx 1$. Suppose that a genetic map were available consisting of RFLPs spaced every 10 cM throughout the human genome, each with a probability $b = 0.5$ of being found homozygous at random in the population from which the child is drawn. For each outcome, we used HOMMAP to compute the probabilities of observing an outcome given that the disease gene lies in the center of the region (P_1) and given that the disease gene is unlinked (P_2). A partial list (given in order of LOD score) is shown in Table 1.

In order to estimate the power of the method, it is necessary to compute the expected LOD score (ELOD). If the interval actually contains the disease gene, the ELOD will be $\sum P_1(\omega)z(\omega)$, which turns out to be 0.31. Thus, to achieve an LOD score of 3, about ten ($\approx 3/0.31$) such inbred affected children will on average be required.

If the interval under study is unlinked to the disease gene, however, the ELOD will be $\sum P_2(\omega)z(\omega)$, which turns out to be -0.35; about six children will be needed to achieve the customary threshold (6) of -2 for exclusion.

The results of many similar calculations are summarized in Fig. 2, which displays the expected number of inbred offspring [progeny of brother-sister (Fig. 2A), first-cousin (Fig. 2B), or second-cousin (Fig. 2C) marriages] required to map recessive diseases with RFLP linkage maps of different powers. With a map of RFLPs that is only modestly polymorphic ($b = 0.5$) and spaced every 15 cM, about 15 such inbreds should suffice for linkage mapping. With more highly polymorphic RFLPs, more densely spaced RFLPs, or both, between five and ten such individuals should suffice. Of course, other instances of close inbreeding (for example, uncle-niece, $F = 1/8$) are also useful and results are intermediate. The analysis above assumes no crossover interference; the presence of positive interference would tend to increase the power

Table 1. Probability of different patterns of homozygosity given that the disease gene lies in the center of the region [$P_1(\omega)$] or is not linked to the region [$P_2(\omega)$]. Markers are spaced every 10 cM and are homozygous 50% of the time at random. "H," homozygosity; "-", heterozygosity; ".,," the interval being tested for linkage. Probabilities are shown as percents.

Outcome, ω	$P_1(\omega)$	$P_2(\omega)$	LOD, $(z)(\omega)$
HHH.HHH	21.5	3.3	+0.81
HHH.HH-	9.0	2.2	+0.62
-HH.HHH	9.0	2.2	+0.62
HHH.H-H	5.4	2.0	+0.43
H-H.HHH	5.4	2.0	+0.43
HHH.H--	4.7	2.0	+0.37
--H.HHH	4.7	2.0	+0.37
-HH.HH-	3.8	1.7	+0.35
HHH.---	1.3	1.6	-0.09
---.HHH	1.3	1.6	-0.09
H--.HHH	1.4	1.7	-0.08
HHH.--H	1.4	1.7	-0.08
---.---	0.07	1.3	-1.24

of the method.

It might seem that more distant inbreeding (for example, a mating of second cousins rather than of siblings) would yield more information about linkage, since unlinked regions would be even less likely to be homozygous by descent. However, two serious problems limit the usefulness of more distant consanguinity: (i) Because of the increased number of opportunities for recombination, a denser RFLP map is required to extract the full information (Fig. 2). (ii) As the coefficient of inbreeding F falls relative to the allele frequency q , so too does the probability that the disease is actually the fault of homozygosity by descent. Eventually, the disease locus will not be homozygous by descent frequently enough to make detection possible. This effect is shown in Fig. 2D, which displays the relative increase in the number of inbred affected children required for homozygosity mapping, as q increases, for different degrees of inbreeding.

The following prescription, for example, will ensure at most a doubling of the required numbers in Fig. 2, A to C: the allele frequency q must be less than about 0.07 for progeny of sibs to be useful; $q < 0.02$ for progeny of first cousins; $q < 0.008$ for progeny of second cousins. Since most recessive diseases have $q < 0.02$ [this being roughly the frequency of the cystic fibrosis allele in the United States (10)], progeny of first-cousin matings and closer should be generally quite efficient for homozygosity mapping. Progeny of second-cousin matings should be collected for relatively rarer diseases.

We should emphasize that LOD scores obtained via homozygosity mapping are authentic LOD scores, as used in human genetics: they may be directly added to LOD

scores obtained from traditional family studies, since each represent likelihood ratios obtained by comparing the same two hypotheses. In this connection, it is striking to note that the ELOD obtained from a single affected child from a first-cousin marriage is equal to that of an outbred nuclear family with three affected, in the limit of a dense RFLP map; in both cases, six meioses are under study, with two being used to infer phase of the recessive disease allele.

The main advantage of homozygosity mapping is thus that it provides a way to map a recessive disease, even when—as is frequently the case—families with multiple affecteds are scarce. Since inbred children are overrepresented among those affected with a recessive disease (and since the overrepresentation is more pronounced the rarer the disease), it should often be easier to gather enough inbreds for homozygosity mapping than to gather enough families with multiple affecteds for traditional family studies (11).

Bloom's syndrome (12), for example, affects roughly 100 living individuals, but there are only eight known families with two living affecteds and one with three

affected (13). These resources are insufficient for traditional linkage analysis. By contrast, at least 24 affecteds are children of marriages between cousins (with $F \leq 1/64$). Even for a more common recessive disease such as Werdnig-Hoffmann syndrome [$q \approx 0.006$ in England (14)], multiplex families may be difficult to collect because affected children die at a very young age.

Homozygosity mapping may therefore be the method of choice for mapping the chromosomal location of most of the 1420 suspected recessive disorders listed in McKusick's catalog *Mendelian Inheritance in Man* (12). Of course, multiplex families should also be collected where available, since LOD scores can be combined.

Cases of affected inbreds can be collected in the United States and Britain, even though overall consanguinity rates are low. However, population geneticists have extensively studied many regions in which geographic isolation or cultural norms have led to a considerably higher rate of consanguineous marriages (15). Among the regions deserving special attention for homozygosity mapping are: parts of Italy, where con-

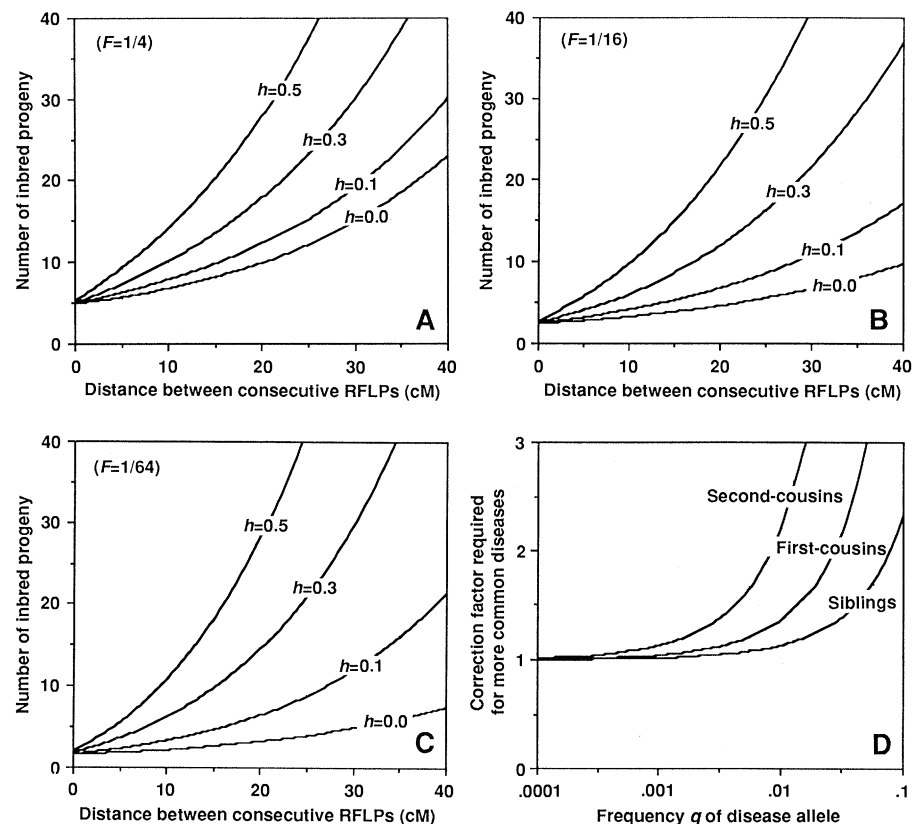


Fig. 2. Number of inbred progeny needed to map a rare ($q \approx 0$) recessive disease via homozygosity mapping, as a function of the spacing between consecutive RFLPs and the degree of polymorphism of each RFLP. The four curves refer to RFLPs that are found homozygous with probability 50%, 30%, 10%, and 0% (limiting case) in the general population. (A) Progeny of a sibling mating; (B) progeny of a first-cousin mating; (C) progeny of a second-cousin mating. If the disease is not rare, the required numbers must be multiplied by the approximate correction factor in (D). [The correction factor given is exact when the distance between consecutive markers $d = 0$ and the rate of homozygosity $b = 0$; it differs, but only slightly, for other cases.]

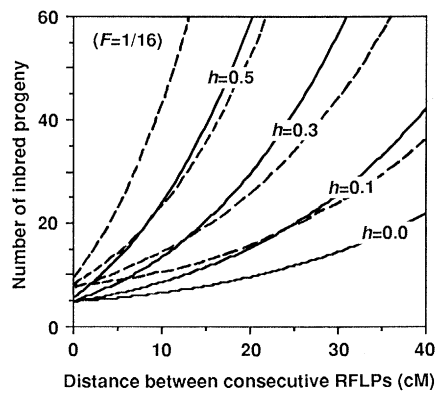


Fig. 3. Homozygosity mapping of a heterogeneous rare recessive trait by the method of simultaneous search (19). Number of first-cousin progeny required to identify a set of two loci at which disease alleles can occur, by means of RFLPs homozygous 50%, 30%, 10%, and 0% in the population, is shown in solid curves. Analogous result for a set of three loci is shown in dashed curves (unlabeled). Frequency of disease alleles at each of the loci is assumed to be equal.

sanguineous marriages are not uncommon and can be traced through records of the special dispensation that such marriages require from the Catholic Church (16, 17); Andhra Pradesh in India, where one-third of all Hindu marriages are between a niece and her maternal uncle ($F = 1/8$) (18); and many Middle Eastern populations (15). Note that the homozygosity rate h for an RFLP refers to the population from which the inbred is ascertained (19).

Homozygosity mapping clearly requires a reasonably complete genetic map of the human genome. An adequate map might consist of about 330 RFLPs evenly spaced every 10 cM, each homozygous at most 50% of the time in the population. Less dense maps would still be useful, while denser maps would allow linkage mapping with even fewer cases. Since more than 1000 RFLPs have already been discovered (in a human genome of about 3300 cM), such a map seems within reasonable prospect. Although the ideal map for homozygosity mapping is perhaps twice as dense as that for traditional family-based linkage studies (20), the smaller number of affected cases required for mapping should compensate for any increased effort in applying more markers. Moreover, one may first screen by means of a subset of the RFLPs and then confirm a suggestion of linkage by using a higher density of RFLPs in the region of interest.

The DNA of affected inbred children offers advantages not just for the initial detection of linkage, but also for the molecular cloning of the disease gene. While the surrounding region of homozygosity by descent is fairly large in any given child (median length ≈ 28 cM for the affected progeny

of a first-cousin marriage), the search for the gene may be confined to the overlap of these regions (median length $\approx 28/n$ cM, if n affected first-cousin progeny are studied).

Finally, we have assumed above that the disease is homogeneous (is caused by mutations at a single locus), although it is hard to know this in advance. If linkage is not found under the assumption of homogeneity, however, one may adapt the strategy of simultaneous search, which we recently proposed elsewhere (21). Briefly, simultaneous search would consist of searching for a set of several loci with the property that at least one is homozygous by descent in most of the inbreds. Figure 3 shows the number of inbred individuals needed to map a heterogeneous trait by means of homozygosity mapping; for maximum efficiency, a higher resolution RFLP map would be preferred.

The study of inbred children will be more likely than traditional family studies to reveal rare trait-causing loci in the case of a heterogeneous trait, since loci will be represented in proportion to their allele frequency ($q_1:q_2:\dots:q_k$) among inbreds, but in proportion to the square of the allele frequency ($q_1^2:q_2^2:\dots:q_k^2$) among the general population.

Homozygosity mapping may greatly extend the range of recessive diseases amenable to linkage mapping, because affected inbreds are not uncommon and relatively few are needed. Homozygosity mapping becomes practical only with the advent of a human genetic map. It exemplifies the sort of strategies for human genetics that will become available, we believe, as the human genome becomes more thoroughly explored (20).

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Thrombospondin Promotes Cell-Substratum Adhesion

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The physiological role of the platelet-secreted protein thrombospondin (TSP) is poorly understood, although it has been postulated to be involved in platelet aggregation and cellular adhesion. In this report, TSP isolated from human platelets was found to promote, *in vitro*, the cell-substratum adhesion of a variety of cells, including platelets, melanoma cells, muscle cells, endothelial cells, fibroblasts, and epithelial cells. The adhesion-promoting activity of TSP was species independent, specific, and not due to contamination by fibronectin, vitronectin, laminin, or platelet factor 4. The cell surface receptor for TSP is protein in nature and appears distinct from that for fibronectin.

THE PLATELET-SECRETED PROTEIN thrombospondin (TSP) is thought to participate in platelet aggregation and cellular adhesion. TSP was first de-

scribed by Baenziger *et al.* (1) and later shown to have a molecular weight of

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