to phosphorylate itself and its downstream targets, and this could be part of its mechanism for inhibiting the activation of DNA-repair complexes both at telomeres and at double-strand breaks. The demonstration by Bradshaw *et al.* that TRF2 is rapidly recruited to generic double-strand breaks will initiate a mutually productive period of interaction between the fields of DNA repair and telomere biology, as the roles for telomeric factors in the choreography of repair come into the spotlight.

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The beauty of admixture

Ariel Darvasi & Sagiv Shifman

Admixture mapping is an old concept that has only now been applied with markers across the entire genome. Such a study scanning an African American population identified two chromosomal regions affecting susceptibility to hypertension.

Anecdotally, children of parents of mixed ethnicities are exotically beautiful. More scientifically established is the merit of admixed populations for gene mapping purposes. The potential value of admixed populations was suggested more than half a century ago[1]. Substantial theoretical and practical aspects have been developed since then (reviewed by McKeigue[2]). A genome scan to identify genes affecting a complex trait is now presented for the first time to our knowledge by Xiaofeng Zhu and colleagues on page 177 of this issue[3].

The admixed population

The concept behind admixture mapping is simple (**Fig. 1**). In essence, admixture mapping is most similar to linkage analysis in experimental crosses with inbred strains, with specific similarity to advanced intercross lines[4]. An advanced intercross line is a population derived from two inbred strains that were randomly intercrossed for several generations. An advanced intercross line constitutes the ideal admixed population: all variations can be identified in one of the two progenitors, the mean ancestral composition is 50% for each progenitor, allele frequencies in the progenitor populations are either 1 or 0, and random mating is followed after a single generation of intercrossing the progenitors. In a human admixed population, these ideal conditions will never be met, resulting in decreased power for mapping purposes. Except for gene effect, which has a strong influence on power, the parameter that mostly affects power, specifically in admixture mapping, is the extent of difference in allele frequency between the ancestral populations[5].

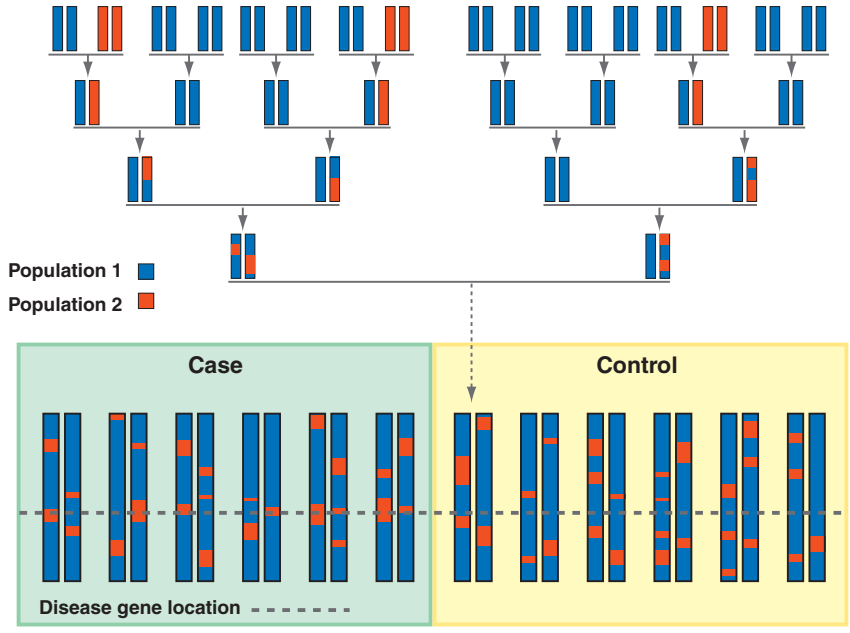

Figure 1 Schematic of one chromosome pair from each of several individuals in an admixed population. A group of cases (for a given disease) and a group of controls are separately presented at the bottom left and the bottom right, respectively. For one of the control individuals (arrow), a schematic presentation of all its ancestors in the last four generations is shown in the upper part of the figure. Admixture mapping can be ideally applied if population 1 (blue) and population 2 (red) carry a different allele at the disease locus (dashed line). Whole-genome scanning under the admixture mapping strategy consists of scanning the genome and identifying the regions with an excess of 'red' ancestry in the cases versus the controls, assuming that the 'red' population carries the predisposition allele. The size of the blocks from different ancestors will depend on the number of generations since the populations were mixed.

Ariel Darvasi is in The Life Sciences Institute, The Hebrew University, Jerusalem 91904, Israel. Sagiv Shifman is in the Wellcome Trust Centre for Human Genetics, Oxford OX3 7BN, UK. e-mail: arield@cc.huji.ac.il, sagiv@well.ox.ac.uk

For example, in the extreme case where the allele affecting a disease has the same frequency in both ancestral populations, admixture mapping cannot be efficiently applied. In contrast, the power of admixture mapping will be only mildly affected by the percentage contributed by each population to the admixture, as long as that proportion is between 20% and 80% (ref. 5).

Table 1 Main characteristics of mapping strategies

	Linkage analysis	Admixture mapping	Association analysis
Statistical power	Low	High*	High
Number of SNPs required for whole genome scan	Low	Low	High
Sensitivity to genetic heterogeneity	Low	Moderate	High
Mapping resolution	Poor	Intermediate	Good

*Power diminishes to zero with equal allele frequencies in the ancestral population.

Genome scan for hypertension

In an effort to identify chromosomal regions affecting hypertension, Zhu *et al.*[3] carried out a genome scan with 269 microsatellite markers and a total of 737 cases (hypertensives) and 573 controls (normotensives). Cases and controls were selected from the African American population. African Americans are an admixed population with ~75% African ancestry and ~25% European ancestry[6] and are thus appropriate for admixture mapping. All individuals were sampled from three networks (GenNet, GENOA and HyperGEN) in geographically distinct locations participating in the Family Blood Pressure Program.

Zhu *et al.*[3] initially explored hypertensive cases only, independently in the three networks, and found an excess of African ancestry in more than one network on chromosomes 4, 6 and 21. In particular, two markers around 6q24 showed an excess of African ancestry in all three populations. To validate the significance of these results, they compared the excess of African ancestry found in the cases with that found in controls. The excess of African ancestry was shifted upwards in cases relative to controls. The entire shift can be attributed to two chromosomal regions at 6q24 and 21q21 where the excess of African ancestry was significant in cases but not in controls. Therefore, these findings suggest that the chromosomal regions 6q24 and 21q21 contain genes affecting predisposition to hypertension. Support for the chromosome 6q24 findings can be drawn from previous linkage studies that found evidence for linkage between this chromosomal region and hypertension or related traits[7,8]. The large size of this chromosomal region (37 cM, including all markers with Z score >2.5) may suggest that more than one gene affecting hypertension is present. This is not unexpected, as *cis*-acting linked genes will behave as a single gene with a larger effect (the combined effect of the two genes) in an admixture mapping experiment, hence having greater power of being picked up in a genome scan. The 21q21 region needs further replication to establish its validity, as this region has not previously been suggested to be associated with hypertension.

A complementary approach

Two main approaches have been used to search for genes affecting complex traits: linkage analysis and association analysis[9]. Linkage analysis has two key disadvantages: relatively low statistical power for detecting modest effects[10], and low mapping resolution, which prevents gene identification even after a region has been detected[9]. Association analysis also has two key disadvantages. Because this approach is based on linkage disequilibrium or on testing the potential functional polymorphisms, the number of polymorphisms that need to be scanned in the entire genome is painfully high (>100,000)[11]. The second disadvantage is the diminishing power that occurs with high genetic heterogeneity[12]. Admixture mapping is a strategy that falls between linkage analysis and association analysis in many respects (**Table 1**).

Although admixture mapping has a substantially lower mapping resolution than association analysis, as long as genotyping costs are a limiting factor, admixture mapping will be a good approach for the initial genome scan. Admixture mapping is particularly appropriate for traits for which there is a large difference in the phenotypic prevalence in the ancestral populations of the admixture. Nevertheless, admixture mapping is not limited to those traits and will still work if the allele frequencies of the disease locus are different in the ancestors of the admixed population. This is more likely to occur when the disease prevalence varies in the ancestral populations.

Given the advantages of admixture mapping, it is notable that this experiment has only now been done. One reason for this might be the notion (which might be correct) that more markers are required for an adequate whole-genome scan with admixture mapping[5] than were used in the current experiment. In addition, admixture mapping is efficient only if the allele frequencies of the markers are substantially different in the ancestral populations. In that respect, it now seems that microsatellite panels might be more informative than originally thought[13]. Consequently, a standard panel of markers, normally used in linkage experiments, successfully served Zhu *et al.*[3] in their admixture mapping study. A word of caution is appropriate, though. The unexpected success might be due to the specific constellations particular to the current experiment, including chance. Therefore, the study of Zhu *et al.*[3], which applied admixture mapping to hypertension and concluded with successful and robust results, will still require some replications in other traits and with other samples before its generality can be established. The current results, however, are undoubtedly promising enough to encourage the scientific community to carry out these essential replications.

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