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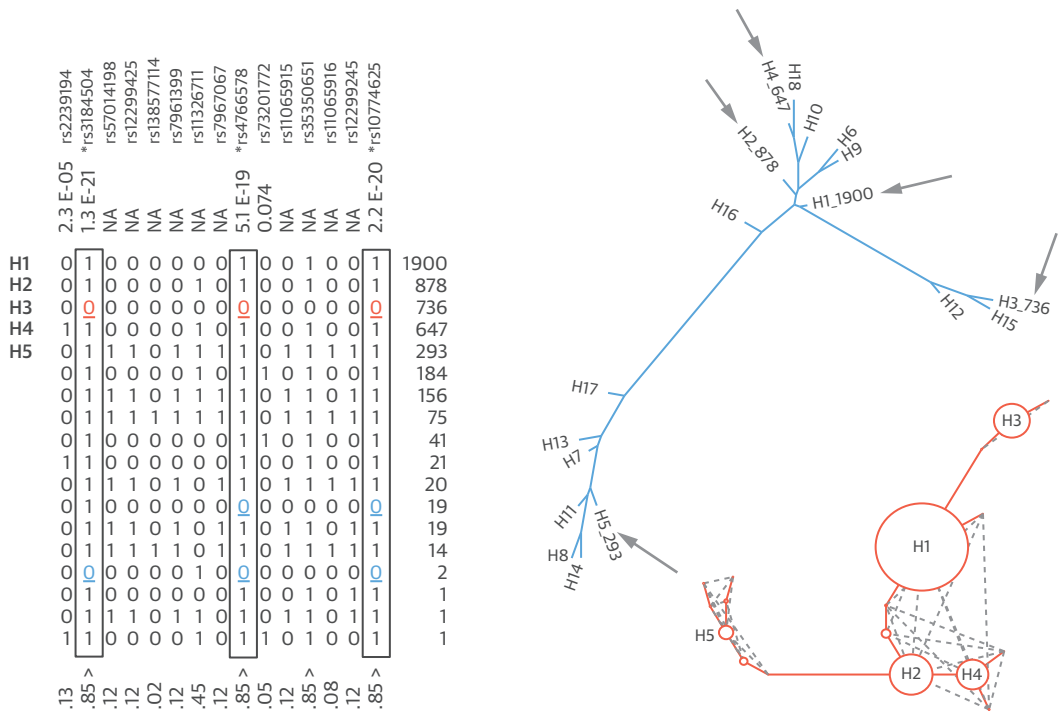
Toward Multiple SNP Motif Analyses of Loci Associated With Phenotypic Traits

A recent paper in the *Journal* (1) and other studies (2) are greatly improving our overview of candidate genetic codeterminants of cardiovascular risk or blood pressure and are also raising curiosity about sources of consistently strong (e.g., $p < 10^{-15}$) observed associations. In 12q24, a single nucleotide

FIGURE 1 Human Local Common SNP Haplotype Motifs/Clusters Including 12q24 SNP rs3184504



Each row of the matrix is a motif, that is, a vector of bi-allelic single nucleotide polymorphism (SNP)_ states observed in the 1000 Genomes Project Consortium (4). **Asterisks** denote SNPs **(columns)** with diastolic blood pressure associations of $p < 10^{-15}$ in Ehret et al. (2) (**top:** p values, SNP rs numbers; **right:** motif instances observed; **bottom:** frequencies of allele 1). Motif networks are plotted from difference (Hamming distance) matrixes by programs Phylip/neighbor **(top)** and R/pegas **(bottom)**; **arrows** indicate the 5 most frequent motifs (H1 to H5).

polymorphism (SNP) (rs3184504) (1) in 1 of 6 loci associated with coronary artery disease was also strongly associated with blood pressure (2); an Internet summary (3) noted its associations with 17 diseases or disease-related characteristics.

From the 1000 Genomes Project Consortium (4), we extracted 15 SNPs, <30-kb haplotype-motif views around rs3184504 for individual and pooled world populations. The world view revealed strong population structure of the 15-SNP motifs (**Figure 1**) ($n = 2 \times$ 2,504 haplotypes). At least 2 of the giant components and their master motifs (H1 to H4; encoded as in the 1000 Genomes Project Consortium study) (4) also appeared in individual populations, including some (e.g., Great Britain, GBR) that are generally not considered appreciably admixed or structured. Two dominating consensus motifs (H1+H2+H4 and H3) account for 83% of the 5,008 haplotypes worldwide.

Statistical significance can occur also when individual SNPs have no adaptive significance; if 1 drug is administered to cats and another to horses, efficacy differences may just reflect cat–horse differences (5). In 3 (boxed) columns (SNPs) in **Figure 1** with lowest p value, allele 0 appears exclusively in the null motif H3 (red) and 2 lower frequency variants of its component (blue), thus best exposing an underlying motif component structure that explains observable variation and covariation.

SNP-by-SNP associations can be profitably complemented by (~30 kb) *k*-SNP motif associations in which ≥2 giant components dominate, even if the reasons for their presence are uncertain.

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