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Why Do Complex Traits Resist DNA Analysis ?

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ABSTRACT The etiology of many human diseases is complex. The number of factors involved, the importance of their individual effect and the level of heterogeneity are unknown. To unravel the genetic etiology of these diseases, a popular strategy is to search for genetic risk factors by testing linkage systematically over the entire genome. The power of such an approach very much depends on the unknown characteristics of the genetic factors and the main difficulty is to establish a good trade off between false positives and false negatives. Avoiding a high rate of false positives will lead to low power for detecting a genetic factor with a moderate effect. In addition, when a genetic factor is detected, the precise localisation of this factor is generally not possible under this method. To go further in the identification of factors involved in the disease process, one has to set up a candidate gene strategy. If the candidate gene polymorphism is not directly available, information may be obtained through closely linked markers. In such a case, we may expect, in addition to linkage, allelic association between the candidate gene and marker alleles. However, the choice of candidate genes as well as markers showing allelic association is not simple. Some have proposed to consider every gene as a candidate and to screen the whole genome using the Transmission Disequilibrium Test. However, the problems of multiple testing and of heterogeneity between populations may cripple this approach. Despite extraordinary advances in molecular and computer techniques, it is likely that for multifactorial diseases the only genetic risk factors that can be detected are those with fairly strong effect. Even in this case, it is important to design strategies that increase the power of detection.

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