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From QTL to QTG: Are we getting closer?

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In spite of the significant progress in identification of genes responsible for Mendelian genes, similar success regarding quantitative trait loci (QTL) still awaits. Various reasons have been raised to explain the current hurdles in QTL analysis, together with suggestions for overcoming them. Analysis may be conducted from a functional angle, such as ENU mutagenesis, knockouts, etc., or via genetic analysis, or by a combination of both approaches. Here, we shall discuss recent advances for the use of inbred strains of mice as a mapping resource. The shared ancestry of inbred mouse strains, together with the availability of sequence and phenotype information, constitutes a resource which can be used to map QTLs. The difficulty in using sequence information exclusively, lies in the fact that in most instances the allelic state of the QTL cannot be unambiguously determined in a given strain. To overcome this difficulty, it has been suggested that multiple crosses between various inbred strains should be performed. We proposed and evaluated a general approach which consists of making crosses between the two strains, used initially to map the QTL, and any new strain. We have termed these crosses "Yin-Yang", their being complementary in the sense that the QTL will necessarily segregate in only one of the crosses. We used the publicly available SNP database of chromosome 16 to evaluate the mapping resolution achievable with this approach. Although on average the mapping contribution of only four inbred strains was relatively small, we found a great degree of variability among different chromosomal regions. This suggests that with a large number of strains in hand, selecting a small number of strains may provide a significant contribution to the fine mapping of QTLs. The exact resolution attainable through this approach requires additional studies once sequence information for a larger number of strains becomes available. With such information in hand, however, it will be possible to establish resolution maps for each chromosomal region and thus optimally select the strains to be used according to the chromosomal region of the QTL intended for mapping. It should be noted that although this approach may prove of significant value, specific crosses to map specific QTLs will still be required. This is of particular interest when evaluating alternative strategies, such as the suggested 1K RI resource which, while requiring significant setup and maintenance work, carries incomparable potential for QTL analysis.