Genetic dissection of complex genetic traits with chromosome substitution strains of mice

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An extraordinary variety of naturally-occurring phenotypic traits involving physiology, cancer, immunology, development and neurobiology vary between the C57BL/6J and A/J inbred strains of mice. These traits are controlled by multiple genes, most of which have eluded detection with conventional methods of complex trait analysis. The recent development of B6.A chromosome substitution strains (CSSs), a panel of 22 strains in which each A/J chromosome is substituted for the corresponding C57BL/6J chromosome on the C57BL/6J background, provides a new and powerful paradigm for dissecting multigenic genetic traits and complex gene-environment interactions. To demonstrate the broad power of this approach, we performed a preliminary screen of 53 traits associated with both metabolism and behavior in this CSS panel and discovered evidence for at least 150 quantitative trait loci (QTLs), most of which are novel. Of these, 18 were associated with resistance to diet-induced obesity. For example, we discovered that 17 A/J-derived chromosomes conferred resistance to diet-induced obesity, 4 A/J-derived chromosomes did not confer resistance, and chromosome X conferred a more extreme obesity phenotype. With only 440 mice, we detected at least 18 novel genetic variants associated with diet-induced obesity, many of which result in a 40-50% reduction in weight gain on the diet when compared to C57BL/6J. Studies of resistance to diet-induced obesity in F2 intercross progeny derived from B6.A6 identified multiple, significant QTLs on the substituted chromosome. We are currently pursuing a novel whole genome scan approach to narrow the QTLs on each of the A/J substituted chromosomes. With the sequencing of these two inbred strains nearly complete and the availability of BAC libraries that can be utilized for transgenic studies in genetically-engineered mice, the B6.A chromosome substitution strains are emerging as powerful tools for studying complex genetic traits, such as diet-induced obesity.

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