BUGS, GUTS AND FAT - A SYSTEMS APPROACH TO THE METABOLIC 'AXIS OF EVIL'

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Rapidly growing evidence suggests that complex and variable interactions between host genetic and systems factors, diet, activity and lifestyle choices, and intestinal microbes control the incidence, severity and complexity of metabolic diseases. The dramatic increase in the world-wide incidence of these diseases, including obesity, diabetes, hypertension, heart disease, and fatty liver disease, raises the need for new ways to maintain health despite inherited and environmental risks. We are pursuing a comprehensive approach based on diet-induced models of metabolic disease. During the course of these studies, new and challenging statistical, analytical and computational problems were discovered. We pioneered a new paradigm for genetic studies based on chromosome substitution strains of laboratory mice. These strains involve systematically substituting each chromosome in a host strain with the corresponding chromosome from a donor strain. A genome survey with these strains therefore involves testing a panel of individual, distinct and non-overlapping genotypes, in contrast to conventional studies of heterogeneous populations. Studies of diet-induced metabolic disease with these strains have already led to striking observations. We discovered that most traits are controlled by a many genetic variants each of which has unexpectedly large phenotypic effects and that act in a highly non-additive manner. The non-additive nature of these variants challenges conventional models of the architecture of complex traits. At every level of resolution from the entire genome to very small genetic intervals, we discovered comparable levels of genetic complexity, suggesting a fractal property of complex traits. Another remarkable property of these large-effect variants is their ability to switch complex systems between alternative phenotypic states such as obese to lean and high to low cholesterol, suggesting that biological traits might be organized in a small number of stable states rather than continuous variability. Moreover, by studying correlations between non-genetic variation in pairs of traits (the genetic control of non-genetic variation), we discovered a new way to dissect the functional architecture of biological systems. Finally, a neglected aspect of these studies of metabolic disease involves the intestingal microbes. Early studies suggest that diet and host physiology affect the numbers and kinds of microbes, and that these microbes in turn affect host metabolism. These interactions between 'bugs, guts and fat' extend systems studies from conventional aspects of genetics and biology to population considerations of the functional interactions between hosts, diet and our microbial passengers. With these models of diet-induced metabolic disease in chromosome substitution strains, we are now positioned find ways to tip complex systems from disease to health.