chromosomal subregions are inactivated? Is the genome so replete with genes whose products are required for progression through pachynema that inactivation of nearly any region would trigger a meiotic arrest? A key issue is the minimal size of unpaired or unsynapsed DNA required to trigger MSUC. Can interstitial chromosome deletions, duplications and insertions be sufficiently large to trigger this mechanism, and would the silencing extend beyond the unpaired regions? If so, then those deletions that are capable of being transmitted in mice, humans or other organisms with MSUC would presumably not contain or abut genes whose activity is required for the successful completion of meiosis. The various existing transgenes and chromosomal aberrations now sitting in mouse rooms around the world, coupled with genomic sequence and expression data, probably contain the answers to many of these questions.

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# A global view of epistasis

## Jason H Moore

**Epistasis is a phenomenon whereby the effects of a given gene on a biological trait are masked or enhanced by one or more other genes. A new study documents epistasis among 890 metabolic genes in yeast, providing one of the largest data sets of its kind in any model organism.**

In addition to elucidating the basic mechanisms of biology, genetic studies offer insights into genotype- phenotype relationships that have the potential to improve our ability to diagnose, prevent and treat human diseases. Some of the difficulty we will face while sifting through vast quantities of genetic data is that the relationship between genotype and phenotype is expected to be nonlinear for most common human diseases, such as cancer or cardiovascular disease[1]. Part of this complexity can be attributed to epistasis or gene-gene interactions[2]. Deciphering vast interconnected networks of genes and their relationships with disease susceptibility will be possible in the future, given the availability of methods for measuring all relevant information, coupled with bioinformatic strategies for making sense of the data. While we wait for all the pieces to fall in place for human studies, we can learn a great deal from studying epistasis in simpler organisms, where many of the appropriate tools are now becoming available. On page 77 of this issue,

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Daniel Segrè and colleagues[3] describe a systems-level approach to the study of epistasis in yeast, which has important implications for understanding basic biology and human genetics.

### Epistasis is an old idea
The idea that the effects of a given gene on a trait can be dependent on one or more other genes has been around for at least 100 years. William Bateson[4] used the term 'epistasis' to describe distortions of mendelian segregation ratios that were due to one gene masking the effects of another. Not long after, Sir Ronald Fisher described epistasis as deviations from additivity in a linear statistical model[5]. These two somewhat different definitions of epistasis have prevailed and are still discussed today[6]. The difference is that Bateson's definition is a biological one whereas Fisher's is purely statistical. **Figure 1** illustrates the differences between statistical, biological and genetical epistasis. An important question is whether statistical evidence of epistasis at the population level can be used to infer biological or genetical epistasis in an individual. Conversely, does biological evidence of epistasis imply that statistical evidence will be found? The relationship between biological and statistical epistasis has been discussed[7], but there are only a few observational and experimental studies that directly address the issue[8]. This question is perhaps best addressed in simple organisms such as yeast where different types of epistasis are more likely to converge[7].
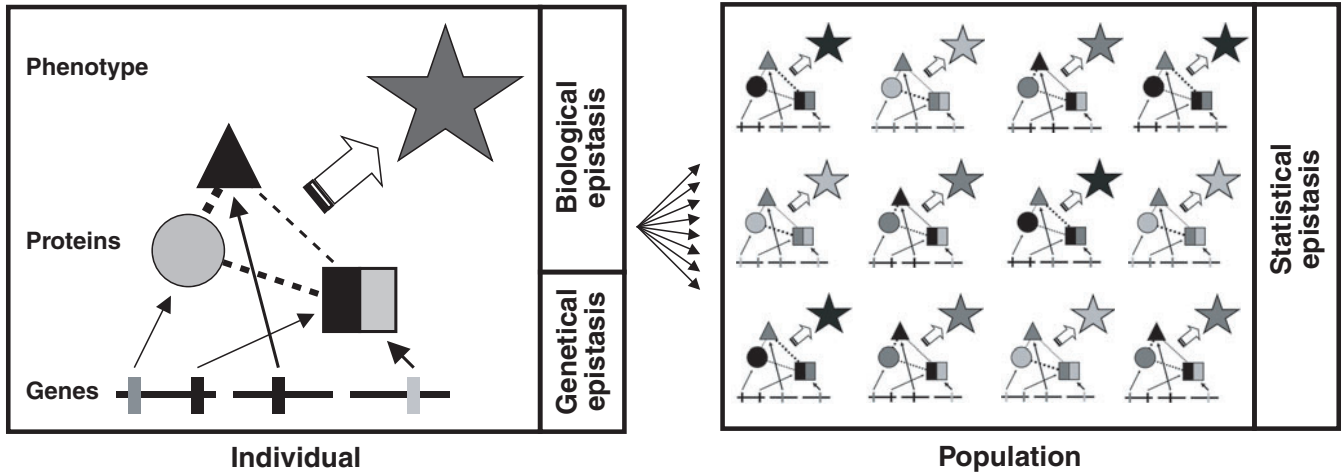
### Why is there epistasis?
No one knows for sure why epistasis exists or why it is an important component of the genetic architecture of many biological traits. But evolutionary theory and developmental biology provide some important clues through processes related to canalization and stabilizing selection. Canalization was described by Waddington[9] as the stability of complex developmental processes due to genetic buffering. From an evolutionary biology perspective[10], canalization has evolved to stabilize phenotypes through natural selection. The implication of this type of genetic buffering is that phenotypes are stable in the presence of mutations. For a phenotype to be buffered against the effects of mutations, it must have an underlying genetic architecture that is comprised of networks of genes that are redundant and robust. As a result, substantial effects on the phenotype are observed only when there are multiple mutational hits to the gene network. This sort of genetic buffering is realized as epistasis because it creates dependencies among the genes in the network. These ideas are supported by studies of yeast[3].

### Systems-level genetics
Evolutionary biology was revolutionized by the merger of mendelian genetics with darwinian evolution. Huxley[11] called this merger "the modern synthesis". Biology and genetics are undergoing a "new modern synthesis"[7] with the merger of population genetics and biotechnology into what has been called 'systems biology'[12]. Systems biology promises to

**Figure 1** Genetical, biological and statistical epistasis. Genetical epistasis can be thought of as the interaction among DNA sequence variations (vertical bars) that give rise to a particular phenotype in an individual. Genetic information affects phenotype through a hierarchy of proteins (circle, square, triangle) that are involved in biological processes ranging from transcription to physiological homeostasis. The physical interactions (dashed lines) among proteins and other biomolecules and their impact on phenotype (star) constitute biological epistasis. There is a very close relationship between genetical and biological epistasis, with each occurring at the level of the individual. Differences in genetical and biological epistasis among individuals in a population give rise to statistical epistasis. It is entirely possible for genetical and biological epistasis to occur in the absence of statistical epistasis. This can happen when the DNA sequence variations and biomolecules are the same for every individual sampled from a population. Thus, genetic and biological variation is crucial for the statistical detection of epistasis. But does evidence of statistical epistasis necessarily imply genetical or biological epistasis?

describe biological systems in detail using vast amounts of molecular and biochemical information gathered using the latest advances in biotechnology. Once the information is available, it can be modeled using computational and mathematical methods in the framework of population-level variability. For example, Davidson[13] has provided a preliminary gene network model for embryonic specification in the sea urchin. This network was constructed from experimental data with the aid of bioinformatic tools and includes nearly 50 genes that are organized into functional modules. Understanding how genetic variation in this network affects embryonic development will provide important insights into canalization and, ultimately, epistasis.

The study by Segrè et al.[3] opens the door to systems-level analysis of epistasis in model organisms such as yeast. Here, 890 metabolic genes were perturbed through single and double knockouts. Growth phenotypes of all knockouts were estimated using metabolic flux analysis. The authors found that pairs of genes buffered growth, aggravated growth or had no effect on growth. Notably, epistasis seemed to extend beyond individual genes to functional modules of genes. For example,

perturbing respiratory genes consistently aggravated glycolysis. This observation may have important implications for the detection, characterization and interpretation of epistasis in other model organisms and, especially, studies of human health and disease, in which genes in a particular pathway or functional group are often measured. These results challenge the common assumption that interactions between genes will be stronger within a functional group than between functional groups.

## A look into the future

The ultimate usefulness of systems-level genetic studies of yeast[3] and other model organisms such as bacteria[14] will be an increased understanding of epistasis as a fundamental component of genetic architecture. The path for human studies is quite different and heavily dependent on genetic epidemiology. In the near future, we will be implementing whole-genome association studies with thousands of measured genetic variations with the goal of identifying those polymorphisms that predict disease susceptibility. This starting point in humans does have its own analytical challenges[15]. The long-term

goal will be to merge knowledge from genetic studies in human populations with detailed descriptions of transcriptional networks, biochemical pathways and physiological systems in individuals. Only then will the 'new modern synthesis' provide a comprehensive view of human disease etiology that changes the course of healthcare.

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