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EVOLUTIONARY CONSERVATION OF METABOLISM EXPLAINS HOW *DROSOPHILA* NUTRIGENOMICS CAN HELP US UNDERSTAND HUMAN NUTRIGENOMICS

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ABSTRACT: ***While large populations in the third world are enduring famine, much of the developed world is undergoing an obesity epidemic. In addition to reflecting an unbalanced distribution of food, the "epidemic of overabundance" is ironically leading to a decrease in the health and longevity of the obese and improperly nourished in the first world. International consortia, such as the European Nutrigenomics Organization (NuGO), are increasing our knowledge of nutrient-gene interactions and the effects of diet and obesity on human health. In this review, we summarize both previous and ongoing nutrigenomics studies in Drosophila and we explain how these studies can be used to provide insights into molecular mechanisms underlying nutrigenomics in humans. We will discuss how quantitative trait locus (QTL) experiments have identified genes that affect triglyceride levels in Drosophila, and how microarray analyses show that hundreds of genes have altered gene expression under different dietary conditions. Finally, we will discuss ongoing combined microarray-QTL studies, termed "genetical genomics," that promise to identify "master modulatory loci" that regulate global responses of potentially hundreds of genes under different dietary conditions. When "master modulatory loci" are identified in Drosophila, then experiments in mammalian models can be used to determine the relevance of these genes to human nutrition and health.***

KEY WORDS: *Drosophila*, Genetical Genomics, Metabolism, Nutrigenomics

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INTRODUCTION

The current century has seen rapid progress in physiology, and it is now becoming possible to trace physiological evolution just as classical evolutionists traced its morphological aspect. Some biologists even believe that "our final theory of evolution will see it largely as a biochemical process" (Haldane, 1954). (Dobzhansky, 1955)

We open this review with an excerpt from a classic textbook on evolution, "Evolution, Genetics, & Man" (Dobzhansky, 1955). The recent sequencing of several genomes confirm what has long been predicted by the biochemists, that the enzymes involved in most aspects of intermediary metabolism are highly conserved from yeast, to worms, to flies, to man. Developmental genetics in *Drosophila* and other model organisms have contributed enormously to our understanding of the molecular mechanisms of development and cancer in humans, and nutrigenomic studies in these organisms will no doubt have a similar impact. In this review, because of the extensive evolutionary conservation of numerous metabolic pathways between flies and humans, we focus on the contribution that *Drosophila* will make on understanding the interactions between genes, nutrition, and health.

While *Drosophila* is primarily known for identifying and characterizing signaling pathways in eukaryotes, such as the Wingless (Wnt), Hedgehog (Hh), Notch, Transforming Growth Factor Beta (TGF-β, Epidermal Growth Factor Receptor (Egfr), Tumor Necrosis Factor Alpha (TNF-α), and many others, its genome sequence suggests that it can be used as a model for other aspects of physiology and intermediary metabolism. For example, *Drosophila* adults and larvae have fat cells containing triglycerides (Arrese et al., 2001; Canavoso et al., 1998; Canavoso et al., 2001; Canavoso and Wells, 2000; Ruden et al., 2005), and we and other laboratories have used this aspect to identify genes that modulate obesity (Clark and Keith, 1988; De Luca et al., 2005). In addition to fat cell developmental genes and fatty acid biosynthesis genes, most of the other metabolic genes found in humans are also found in *Drosophila* (Bier, 2005). In fact, over 70% of all known human disease genes are present in *Drosophila* and have conserved functions (www.homophila.sdsc.edu).

Drosophila is an ideal organism for studying gene-nutrient interactions because of its small size, small and well characterized genome, and because of the available mutations and deficiencies

that have been collected over the past century (Ruden et al., 2005). Furthermore, several years ago, Mackay and colleagues generated a large collection of recombinant inbred lines from divergent *Drosophila* strains *Oregon R* (*ORE*) and *Russian 2b* (*2b*) and they have used these to map numerous quantitative traits (Mackay, 1995; Mackay, 1996; Mackay, 2001; Mackay, 2002; Mackay et al., 1996; Mackay and Langley, 1990; Mackay and Lyman, 1998). Quantitative traits are phenotypes that are not all-or-none, such as those caused by most single-gene disorders, but rather differ in a normal distribution in a population, such as blood pressure or triglyceride levels.

Recently, the biotech company Exelixis, Inc., made available to the scientific community a large collection of *Drosophila* stocks that contain "isogenic" transposon insertions and deficiencies that mutate or uncover over half of the genes (Parks et al., 2004; Thibault et al., 2004). "Isogenic" means that they are in exactly the same genetic background, which is important because most quantitative phenotypes, such as triglyceride levels, are exceedingly affected by different genetic backgrounds. These new *Drosophila* strains will likely have a significant impact in nutrigenomics and other genetic studies (Ruden et al., 2005).

In the past few years, "genetical genomics" approaches have been developed that combine QTL analyses with microarray studies and have identified "master modulatory loci" that regulate hundreds of genes in the same tissue (Carlborg et al., 2005; Li et al., 2005; Page and Ruden, 2005). "Genetical genomics" is the term coined to indicate the process in which the levels of every mRNA, protein product, or metabolite is used as a quantitative trait in massive QTL analyses of potentially every molecule in a tissue (Page and Ruden, 2005). In this review, we describe how utilizing high-dimensional genetic and bioinformatic resources allow one to conduct sophisticated studies on the interactions among nutrients and genes.

NUTRIGENOMICS APPROACHES

Nutrigenomics is the convergence of three areas of research – health, diet, and genomics – and has been reviewed by numerous researchers (Bauer et al., 2004; Chadwick, 2004; Fenech, 2005; Gillies, 2003; Junien and Gallou, 2004; Kaput and Rodriguez, 2004; Muller and Kersten, 2003; Ommen and Groten, 2004; Ordovas and Mooser, 2004; Peregrin, 2001; Ruden et al., 2005; Trayhurn, 2003; van Ommen, 2004; van Ommen and Stierum, 2002). Health and diet converge in the field of nutrition, diet and genomics converge in the emerging fields of expression profiling, proteomics, and metabolomics, whereas health and genomics converge in the field of identifying biomarkers to classify and understand diseases (Ruden et al., 2005).

Diet-gene interactions are complex and require large human populations for adequate statistical power (Kaput, 2005; Kaput and Rodriguez, 2004). Therefore, the primary focus for future *Drosophila* nutrigenomic studies should be to identify molecular targets for gene-nutrient interactions using a variety of genetics, proteomics and metabolomics approaches. When candidate genes are identified in *Drosophila*, they can be verified in model organisms more closely related to humans, such as transgenic or knockout mice. While only ~70% of human disease genes have *Drosophila* homologs (Bier, 2005), over 99% have mouse homologs (Pennacchio, 2003). Also, unlike *Drosophila*, obesity-induced diabetes occurs in mice (Hribal et al., 2002; Rossmeisl et al., 2003). Nevertheless, *Drosophila* is an excellent starting point for beginning nutrigenomic studies in most other areas.

In this review we will discuss the progress made in *Drosophila* in the following four areas associated with nutrigenomics: (1) quantitative trait locus (QTL) mapping obesity genes, (2) microarrays and nutrition studies, (3) genetical genomics and nutrition, and (4) progressing from QTL to quantitative trait gene (QTG) to quantitative trait nucleotide (QTN). Few of these investigations have yet been done in nutrigenomics, but we will describe how they were conducted in related fields to stimulate research in these areas. Many of the complex genetic terms will be unfamiliar to readers of this journal, so they will be defined and described in more detail in the following sections.

QTL Mapping Obesity Genes in *Drosophila*

To begin a QTL mapping study, one starts with two parental strains that are in the same species, but are widely divergent in DNA sequence, in this case *Oregon R* (*ORE*) from Oregon, USA, and *Russian 2b* (*2b*) from the former Soviet Union. *ORE* and and *2b* have numerous single nucleotide polymorphisms (SNPs) between them. The F_1 hybrids between these isogenic strains are also genetically identical because they contain one set of chromosomes from *ORE* and one set from *2b* (Fig. 1) (Mackay, 2001). In the F_2 flies, however, there is a "shuffling of the decks" of the *ORE* and *2b* genomes, and each of the progeny contains a random combination of genetic material from each of the parental lines (Fig. 1).

There are two general approaches used in QTL analyses: 1) directly analyzing F_2 recombinant individuals, and 2) the more laborious method of generating "recombinant inbred" (RI) lines. In many mouse studies, the first approach has been used, whereby hundreds of F_2 mice are individually phenotyped and genotyped (Cheung et al., 2004; Devor et al., 2005; Kim et al., 2005; Kleeberger, 2005; Welton et al., 2005). For the second approach, Trudy Mackay's laboratory has developed a collection of *Drosophila* RI lines (Mackay, 2001) that our laboratory and others have used to identify obesity QTLs (Clark and Keith, 1988; De Luca et al., 2005). In the BXD and other mouse RI lines, as in the *Drosophila* RI lines, at least 20 generations of brother-sister matings were conducted to generate nearly isogenic RI lines.

The F_2 and RI lines are genotyped typically by analyzing hundreds of evenly-spaced single nucleotide polymorphisms (SNPs) that are specific for one parental strain or the other. However, the *Drosophila* RI lines were characterized prior to the completion of the genome sequence, and the cytological locations of the abundant roo transposon were used to characterize each line (Nuzhdin et al., 1997). QTL analyses

in mice have the further advantage that both parental strains in the BXD lines have been sequenced, so potentially millions of SNPs can be used for very fine-scale characterization of the lines. Many of the mouse and *Drosophila* RI lines are available from stock centers and individual investigators.

We note, rather counter intuitively, that it is not critical for the two parental strains to differ in a particular trait, such as triglyceride levels, before one chooses them for a QTL experiment to identify genes that affect the levels of that trait. In the case of *ORE* and *2b*, for instance, despite the fact that the parental strains have nearly identical triglyceride levels, the F_2 recombinant inbred lines display a broad distribution of triglyceride levels (De Luca et al., 2005). The parental strains have nearly the same triglyceride levels because combinations of different "high- and low-activity QTLs" netted nearly the same over-all triglyceride level. When different "high- and low-activity QTLs" are found in each parental line, the appearance of so-called "transgressive recombinants" appear in the segregating F_2 population (De Luca et al., 2005; Masojc and Milczarski, 2005).

How does one decide whether to use F_2 recombinants or RI lines in a QTL experiment? RI lines require many additional generations of brother-sister matings, whereas, F_2 individuals are generated, by definition, in only two generations. The advantage of using RI lines, however, is that many of them already exist, and one could theoretically keep them forever. In principle, one could use RI lines for QTL mapping experiments on an unlimited number of projects. In contrast, the F_2 lines can only be used once for phenotype and genotype analyses before being discarded. In actual practice, however, it is not known how long RI lines will be of practical use because each generation of inbreeding decreases the fitness of most of the lines. Also, the RI lines accumulate recessive-lethal mutations over time, which further decrease their viability.

Therefore, for the above reasons, new RI lines will undoubtedly need to be generated every few years. However, at least in *Drosophila*, the current advantages of using RI lines overcome this potential future inconvenience. Advances in global mapping of single nucleotide polymorphisms (SNPs), such as with "SNP Chips" (Drazinic et al., 2005; Du et al., 2003; Tebbutt et al., 2004; Tonisson et al., 2000), might obviate the need to use RI lines and encourage the further utilization of directly analyzing F_2 lines. A "SNP Chip" can be a microarray-type platform that contains oligos specific for many or all of the SNP differences between two parental strains. Non-microarray platforms have also been developed for global-SNP mapping studies (Drazinic et al., 2005; Du et al., 2003; Tebbutt et al., 2004; Tonisson et al., 2000). Rapid and inexpensive DNA genome-size sequencing technologies will also likely increase the practicality of directly genotyping and phenotyping F_2 individuals for QTL mapping studies (Church, 2006).

The principle of QTL analyses is that quantitative traits can be mapped to large (10-100 Mbp) sub-chromosomal genomic regions by correlating the phenotype in question (such as triglyceride levels in *Drosophila*) with the genotype. For example, in the simplest possible scenario, assume that there is one allelic variation of a gene that causes flies to have low triglyceride levels, *i.e.*, a "Thin Gene" (Fig. 1). Also, in the simplest scenario, if this is the only gene polymorphism that affects triglyceride levels, then F_2 individuals that inherit both thin genes will have low triglyceride levels, whereas F_2 individuals that are homozygous for the other allelic variation, *i.e.*, the "Fat Gene," will have high triglyceride levels. Individuals with one "Fat Gene" and one "Thin Gene" will have intermediate triglyceride levels. In our studies, there were numerous QTLs that affect triglyceride levels, and epistatic (non-linear) interactions have been identified among several of the loci (De Luca et al., 2005). However, the basic principle is the same whether there is a "single-affect locus" or whether there are "multiple-affect loci" (Mackay, 2001).

Figure 1. QTL Analyses in *Drosophila*. Two parental strains, *Oregon R* (*ORE*) and *Russian 2b* (*2b*) have differing triglyceride levels (De Luca et al., 2005). The F_1 hybrids have DNA from both of the parents and have intermediate triglyceride levels between that of the parents. The F_2recombinant flies have "shuffled" chromosomes. If there is a single "Thin Gene," then flies with both thin allelic varients (*/*) would be thin, whereas flies lacking the thin alleles would be fatter. In actual fact, this is a simplification of the QTL approach because there are numerous "thin genes" and "fat genes" spread throughout the genome (De Luca et al., 2005).

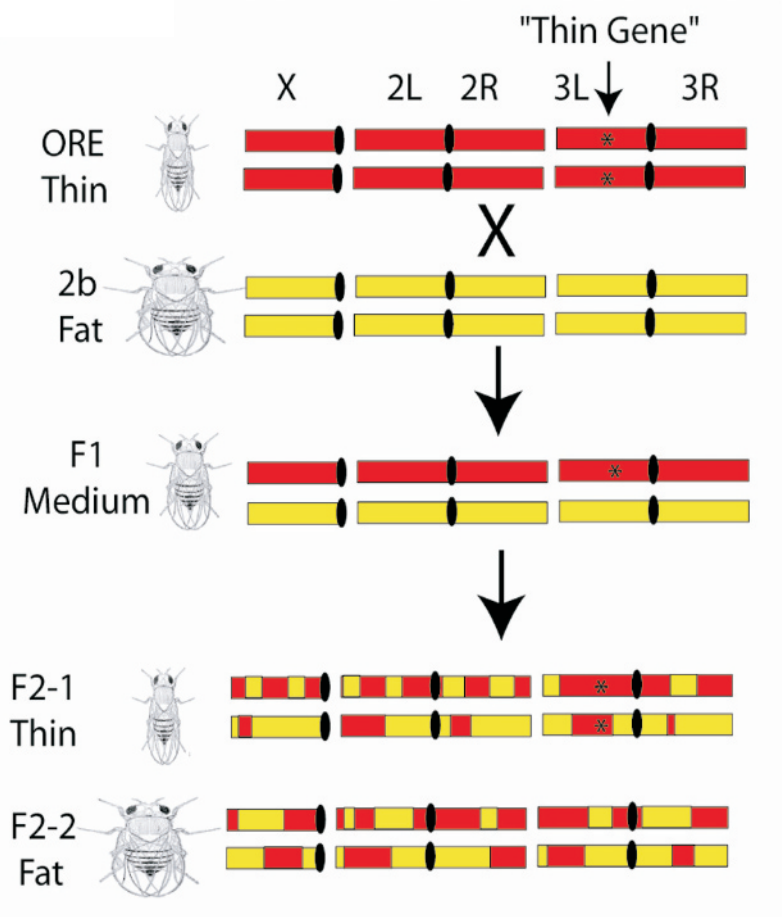


Figure 2. Genetical Genomics in *Drosophila*. Based on work done with mouse RI lines (Carlborg et al., 2005; Li et al., 2005; Reyes-Valdes and Williams, 2005; Tsaih et al., 2005), there will likely be four classes of QTLs in combined microarray-QTL analyses: 1) "cis-QTL" (red dots), that are polymorphisms in the transcriptional regulatory regions of the genes; 2) "simple tran-QTL" (blue dots), that are single loci that trans-regulate the expression level of other genes; 3) "modulatory loci" (purple dots), which are loci that trans-regulate the expression levels of several other genes; and 4) "master modulatory loci" (green dots), which are loci that trans-regulate the expression of thousands of other genes (Li et al., 2005).

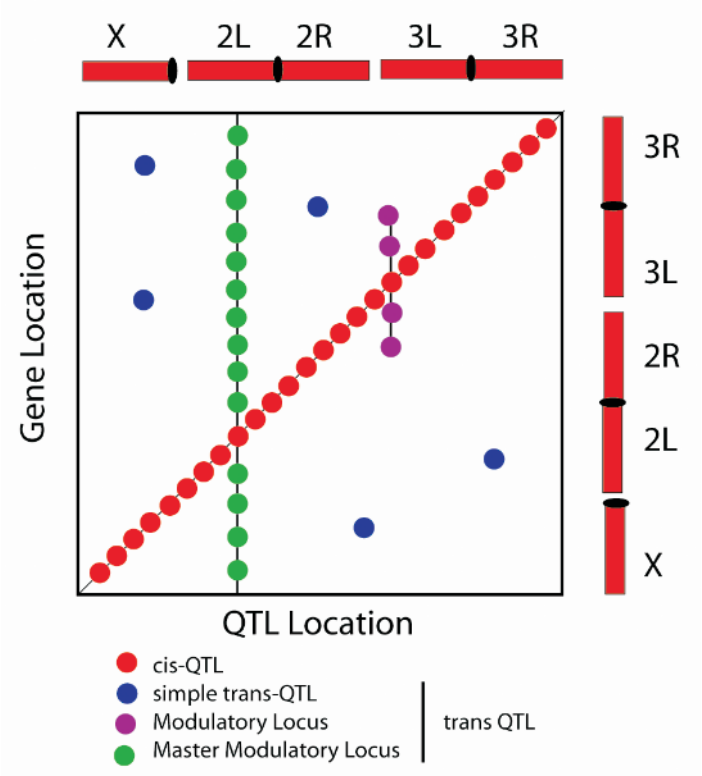
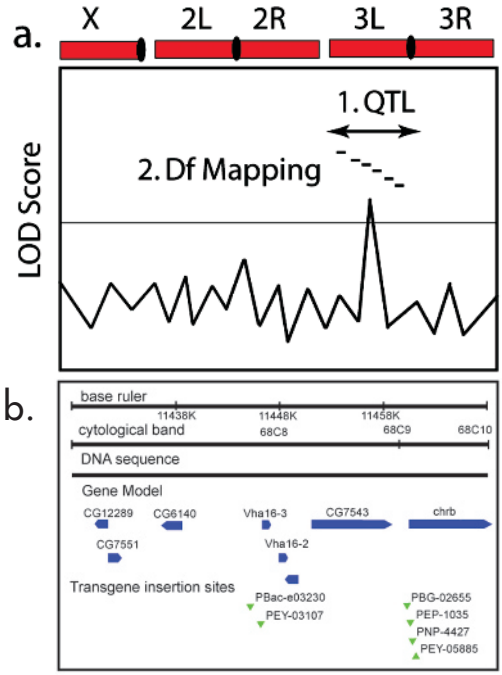


Figure 3. From QTL to QTG in *Drosophila*. a, QTL analysis can identify a locus that is 1-10 Mbp in size (1). The x-axis indicates the position in the genome and the y-axis indicates the log probability score (LOD). If a QTL peak is above the grey line, which is determined by permutation analyses, then it is considered significant and worthy of further fine-mapping studies. Deficiency mapping can refine the QTL to ~100,000 bp (2). The deficiencies are indicated with small horizontal lines. b, FlyBase (www.flybase.org) can be used to analyzed the annotated genome in the refined QTL region. The transposon insertions are indicated by green triangles. The genes are indicated by blue bars and the direction of transcription is indicated on the bars. The transposon insertion stocks can be ordered from the Bloomington, IN stock collection by clicking on the green triangle and following the links.



Microarrays and Nutrition Studies in *Drosophila*

There are an estimated 18,000 genes in *Drosophila* and 36,000 genes in humans. The number of gene products, via alternative RNA splicing and post translational modifications, is less well known, but it is certainly much higher. *Drosophila* does not have DNA rearrangements that occur during immune cell development in humans. However, the *Drosophila* immune system utilizes alternative splicing of the Ig-domain protein DSCAM which has over 18,000 alternative-splice isoforms (Schmucker et al., 2000; Schmucker and Flanagan, 2004; Watson et al., 2005; Worby et al., 2001). All in all, there are likely well over 100,000 protein products in both humans and *Drosophila*, but the precise numbers are not yet known.

Microarrays, such as the "whole genome" arrays from Affymetrix, which we currently use in our laboratory, contain oligonucleotide probes for ~18,000 *Drosophila* genes and ~36,000 human genes (www.affymetrix.com). We have used similar *Drosophila* "whole-genome" arrays to determine the number and types of genes that have altered expression patterns when the flies are reared under various dietary conditions (Ruden et al., 2006). We have found, for instance, that when flies are fed a diet in which the sucrose found in standard fly food is replaced "isocalorically" (the same overall number of calories) with either beef or soy, over 400 genes have significantly altered expression patterns ($P < 0.05$) (Ruden et al., 2006). Interestingly, only about 40 of these genes are commonly altered in expression by both beef and soy (Ruden et al., 2006). In a book chapter on this subject, we describe several statistical and visualization approaches to further describe these and other microarray data and analyses (Ruden et al., 2006).

Most *Drosophila* studies investigate the effects of caloric restriction on longevity (Helfand and Rogina, 2003; Partridge et al., 2005a; Partridge et al., 2005b). Other types of nutrigenomics studies in *Drosophila*, albeit much less common, involve studying the effects of micronutrients, such as selenium levels (Guo et al., 2001), or macronutrients, such as purified fatty acids (Driver, 1988). Because of the over-emphasis on caloric restriction studies in *Drosophila*, we argue that *Drosophila* has been underutilized for nutrigenomic studies and many more types of studies can be conducted (Ruden et al., 2005).

What sorts of genes does diet regulate? The genes that are positively altered in expression by both soy and beef, for instance, are those involved in fatty acid catabolism (Ruden et al., 2006). This makes sense because both beef and soy have ~30% of their calories in the form of fat, albeit beef is primarily saturated fat whereas soy has healthier unsaturated fats such as omega-3 and omega-6 fatty acids. There are also several unexpected genes that go up in one diet and go down in the other diet, such as several genes in the olfactory sensory pathway. Based on this result, it is likely that the *Drosophila* olfactory sensory system actually changes depending on the diet (Ruden et al., 2006).

That the olfactory-sensory system might be altered by diet is one of several novel hypotheses that probably would not have been considered if it were not for such microarray analyses. One might expect, for instance, that adaptation to a new diet would more likely involve a change in gut microflora (Marteau et al., 2004; Parracho et al., 2005), rather than a change in gene expression in the sensory neurons. It would be interesting to determine whether different diets induce similar long-term or short term changes in human sensory behavior. Because of the often overwhelming quantity of data generated, microarray analyses, while powerful, are predictably more important in hypothesis generating than hypothesis testing. Multi-dimensional studies that combine microarray analyses with other types of genome-wide analyses promise to have more power in generating useful data.

Genetical Genomics and Nutrition

In this section, we describe recent studies that have combined microarray and QTL analyses. This approach has been called "genetical genomics" because it merges classical QTL genetics studies with whole-genome microarray analyses (Bystrykh et al., 2005; Carlborg et al., 2005; de Koning et al., 2005; de Koning and Haley, 2005; Jansen and Nap, 2001; Li et al., 2005; Perez-Enciso and Misztal, 2004). We have described approaches to utilize genetical genomics approaches to nutrigenomic studies in *Drosophila* (Page and Ruden, 2005).

In addition to pioneering studies in yeast and *Arabidopsis*, genetical genomics studies were also recently conducted with several isolated cell types in mice (Bystrykh et al., 2005; Carlborg et al., 2005; de Koning et al., 2005; de Koning and Haley, 2005; Jansen and Nap, 2001; Li et al., 2005; Perez-Enciso and Misztal, 2004). In yeast and *Arabidopsis* genetical genomics studies, it was found that the great majority of QTLs identified are "*cis*-QTL," which are polymorphisms in the promoter and enhancer regions that alter the expression levels. Less common QTLs found in yeast and Arabidopsis are "*trans*-QTLs," which alter the expression of another gene or as many as a dozen or so other genes.

Interestingly, studies with mouse cells, such as fluorescent-activated cell sorter (FACS)-purified hematopoetic stem cells, identified large-effect *trans*-QTLs that the authors called "master regulatory genes" because they can alter the expression of over 1,000 genes (Bystrykh et al., 2005). Different tissues, such as purified brain cells or immune cells have large-effect *trans*-QTLs in different regions of the genome, suggesting that "master regulatory genes" are numerous and tissue specific (Bystrykh et al., 2005).

Unfortunately, the genomic localization of a *cis*- or a *trans*-QTL in mice is necessarily crude because 10 Mbp region is typically used as a window to classify *cis*- and *trans*-QTLs (Bystrykh et al., 2005). Consequently, the gene underlying a large-effect *trans*-QTL identified in mice, whether a transcription factor or a signaling molecule, will require enormous efforts. In *Drosophila*, however, because of its much smaller genome and sophisticated genetics, the gene underlying a *cis*- or *trans*-QTL will be much more easily identified. Figure 2 shows a simplification of a typical genetical genomics experiment and demonstrates the visualization of *cis*-and trans-QTLs.

"Genetical genomics" is also a potentially powerful technique in the field of nutrigenomics. One could, for instance, identify *cis*- and *trans*-QTLs that are only present when an animal is fed a particular nutrient. As described in the next section, the genes corresponding to the *trans*-QTLs can be relatively rapidly identified in *Drosophila*, and, once identified, these genes would be candidates for "validation" in mice. "Validation" means that mice are generated with a loss-of-function mutation in a gene identified in *Drosophila*, and then fed the nutrient in question to determine the physiological responses. By using a combined approach of identifying candidate genes in *Drosophila* and then validating their importance in mice, one can more quickly identify candidate diet-specific master regulatory loci in humans.

In the future, comparing diet-specific master-regulatory loci with those that modulate longevity or cancer survival, one could have a better idea of the dietary conditions that better promote longevity and good health in humans. We emphasize that master-regulatory *genes* have not yet been identified in mice, *Drosophila*, or any other organism. Rather they exist only as broad peaks with significant "LOD scores" on QTL analyses. Identifying the genes underlying the nutrient-specific master-modulatory loci in *Drosophila*, and then validating them in mice, is an exciting area of nutrigenomics research.

From QTL to QTG to QTN in *Drosophila*

In mice, it is difficult to identify quantitative trait genes (QTGs), such as the above described master-regulatory genes. A QTG is a gene that underlies a QTL. In other words, the strain variation in the QTG, such as expression level or activity, is the basis behind the QTL. If this strain variation did not exist, then there would be no QTL peak. The reason for the difficulty in identifying QTGs in mice is that QTLs are typically on the order of 10-100 Mbp and this region can contain hundreds or thousands of candidate genes.

Fortunately, in *Drosophila*, genetic resources are now available to quickly identify smaller regions of 100,000 or fewer bases that correspond to a QTL. One could then test individual mutations in candidate genes delineated by these small QTLs to determine if they are the QTGs responsible for the phenotypic variation. The detailed technique of going from QTL to QTG in *Drosophila* is described in Figure 3 and in several papers (Mackay, 2001; Mackay, 2002; Mackay and Fry, 1996; Mackay et al., 1994).

A further advantage to doing QTL analyses in *Drosophila* is that, after a QTG is identified, it is theoretically possible to identify quantitative-trait nucleotides (QTNs) that contribute to the quantitative phenotype (De Luca et al., 2003). The rationale of QTN analyses is that one could identify the *exact nucleotide polymorphism* that causes the quantitative trait. Typically QTNs are in regulatory regions, and therefore presumably affect transcription factor binding sites, or are missense mutations in protein coding regions (Curtsinger, 2003). In this respect, QTN polymorphisms resemble mendelian mutations in metabolic genes, but they differ in that they are natural polymorphisms with altered, and not absent, activity.

Unfortunately, QTN analyses cannot be conducted in humans because the human population has not gone through as many meiotic divisions as *Drosophila*. Consequently, the human genome is subdivided into individual "haplotype blocks" which consist of large regions (100,000 to several million base pairs) that usually do not differ between individuals. Human "Hap-map" studies typically analyze only one or two SNPs per haplotype block (Kaput, 2005), so the resolution that can be obtained is much less than that obtained in *Drosophila* and other models.

QTN analyses are conducted by measuring the quantitative traits in outbred populations, or more specifically in "chromosome-substitution lines" (De Luca et al., 2003). Chromosome-substitution lines, which have been constructed in both flies and mice, consist of one chromosome from strains obtained in the wild, and the remaining chromosomes from an isogenic laboratory strain. By sequencing a gene from a large number of chromosome-substitution lines, and then phenotyping them, one can correlate particular SNPs with the quantitative phenotype.

Currently, the most thorough example of a QTN analysis was on the effects of SNPs in the dopa decarboxylase (DDC) gene on longevity in *Drosophila* (De Luca et al., 2003). However, further validation of the QTNs by showing that they affect DDC gene expression levels or enzyme activities has not yet been completed. In principle, QTN analyses can also be done with a nutrient-dependent quantitative trait in *Drosophila*. The QTN technique is so-far unique to *Drosophila* because, for instance, the relatively small number of recombination events in mice precludes these studies in this model.

The QTN technique has high power in *Drosophila* because outbred populations in a small area, such as near a farmers market in Raleigh, North Carolina, contain potentially millions of individual flies and multiple generations (De Luca et al., 2003). In fact, adjacent SNPs, or SNPs just a few nucleotides from each other, can often be in "genetic equilibrium," which means that multiple recombination events has occurred between the adjacent SNPs (De Luca et al., 2003). QTN mapping in *Drosophila* outbred populations is arguably almost equivalent to the classic recombination experiments in the 1960's at the RIIB locus in T4 bacteriophage, wherein, it is now known, recombination events were recovered at almost adjacent nucleotide positions (Parma et al., 1979).

DISCUSSION

It is a commonplace observation that every living being is so constructed that it is able to live in a certain environment. A fish is adapted to live in water, a bird is an efficient flying machine, a cow and a deer have digestive organs which enable them to feed on herbage and foliage, the human mind permits man to acquire and transmit culture (Dobzhansky, 1955).

As we began this review, we end this review with another quote from "Evolution, Genetics, & Man" (Dobzhansky, 1955). Almost two decades after he published this seminal textbook, less than two years before his death in 1975, Dobzhansky wrote a famous article entitled, "Nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973). The title is a pithy version of a longer excerpt he wrote in his 1955 textbook that begins: "But homology suggests evolution; the facts of homology make sense if they are supposed to be due to evolution of now different organisms from a common stock. *They do not make sense otherwise*." (emphasis added) (Dobzhansky, 1955).

In this review, we argue that further nutrigenomics studies in *Drosophila* are needed because certain genetic techniques, such as "genetical genomics," QTL, QTG, and QTN analyses, are far more efficient and less expensive than comparable experiments in mice. The evolutionary homology of metabolic pathways between humans and *Drosophila* is such that we will certainly gain knowledge through nutrigenomics studies in *Drosophila*, and this knowledge will likely lead to further advances in human health.

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