

Meeting report

Evolution enters the genomic era

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A report on the 18th Congress of the European Society for Evolutionary Biology (ESEB), Aarhus, Denmark, 20-25 August, 2001.

The congress covered all aspects of evolution, from the molecular and the genomic to the morphological, and only a small sample of the talks will be discussed here. As was apparent in many talks, genomics is starting to bring together research on ecological forces, morphological innovations, and other kinds of phenotype, with molecular genotypes. This convergence was approached from two directions: by starting with phenotypic differences and looking for a genetic cause, and by starting with genomic sequence differences between organisms and searching for either functional effects or for the signatures of adaptation.

There were several very different plenary addresses at the meeting. Nancy Moran (University of Arizona, Tucson, USA) spoke on the genomic evolution of bacterial symbionts. She concluded that the genome reduction often seen in symbionts is driven not by a selective pressure for genome reduction but by a reduction in selection for gene maintenance. She has found large deletions removing many genes, with no evidence for strong selection to increase gene density (the gene density remained similar as the gene number decreased). Michael Donoghue (Yale University, New Haven, USA) spoke on the value of considering phylogeny when examining historical biogeography, in order to understand the evolution of species distributions. Deborah Charlesworth (University of Edinburgh, UK) gave an overview of the importance of polymorphism and classical population genetics in the genome era for addressing questions central to biology.

The power of selection

Following the theme that genomics is unifying evolutionary biology, a new US National Science Foundation forum in

evolutionary and ecological functional genomics was presented [<http://pondside.uchicago.edu/~feder/EEFG.html>]. This forum, bringing together research and researchers in evolution, ecology, functional analysis (for example *in vitro* biochemistry), and genomics, is intended to promote understanding of the evolutionary origin and functional significance of genomic variation in populations of species and was represented by two sessions - one on laboratory evolution and a second on evolution in natural populations.

Several talks from the laboratories of David Botstein (Stanford University, USA) and R. Frank Rosenzweig (University of Florida, Gainesville, USA) demonstrated the power of selection on yeast growing in a chemostat. Changes in gene expression after evolution in the laboratory were measured and traced to specific genes acting in specific pathways; these genes may be responsible for adaptation of the cells to their environment. For example, the genes that are upregulated or downregulated as yeast cells adapt to glucose limitation are shown in Figure 1; they are involved in glycolysis, the tricarboxylic acid cycle, oxidative phosphorylation, and metabolite transport. Clifford Zeyl (Wake Forest University, Winston-Salem, USA), also working in yeast, found that only about four mutations over 2,000 generations were responsible for 75% of the increase in fitness observed during selection in glucose-limiting conditions in his experiments.

While many researchers are working with yeast and other model organisms, Douglas Crawford (University of Missouri, Kansas City, USA) emphasized the ease of cDNA cloning for the analysis of variation in gene expression in non-model organism species, including the fish *Fundulus* that he studies. He offers a comparative functional genomics course [<http://sgi.bls.umkc.edu/funnylab/cfgcourse.html>] that teaches molecular biologists how to clone cDNAs in the non-model organisms they are interested in. Discussion of this topic showed a general interest in increased availability of cDNA sequences from non-model organisms.

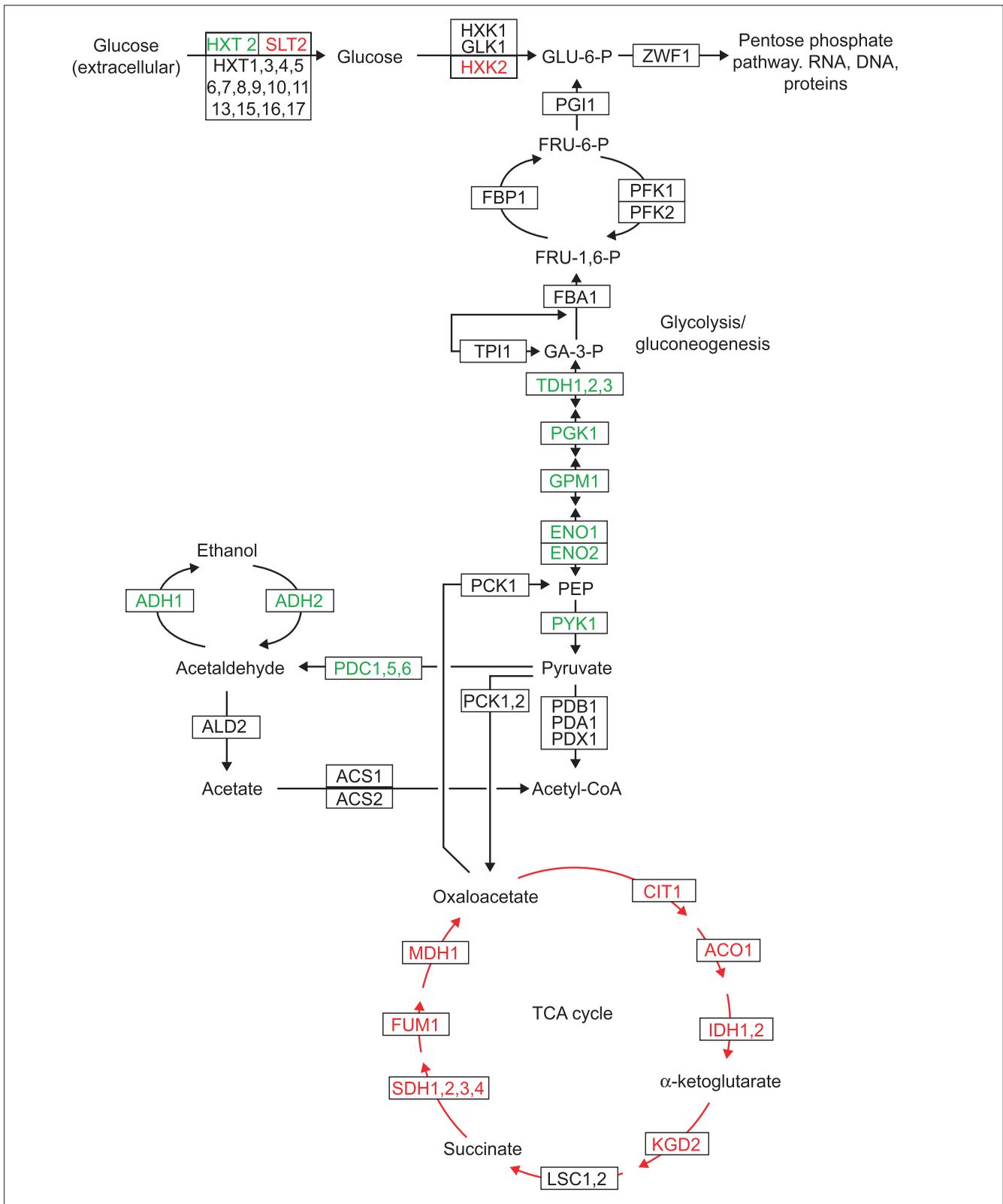


Figure 1 Metabolic maps of central carbon metabolism in yeast. Enzymes whose genes were significantly upregulated and downregulated in gene expression during laboratory evolution are indicated in red and green, respectively. Adapted from Ferea et al.: *Proc Natl Acad Sci USA* 1999, **96**:9721-9726.

In the symposium on natural populations, Thomas Mitchell-Olds (Max Planck Institute of Chemical Ecology, Jena, Germany) analyzed *Arabidopsis* and its relatives to identify genes responsible for variation in metabolism, using mapping and statistical tests such as the Tajima D statistic (which compares the number of pairwise fixed differences between species with the number of polymorphic sites as an indication of selective pressures on a gene). Robert Feldman (Molecular Dynamics Inc., Sunnyvale, USA), one of the few corporate speakers, described a large number of his academic collaborations, which range from examination of genomic sequences from deep-sea microbes to the sequencing of mitochondrial genomes from various mammalian species (the latter in collaboration with researchers from the San Diego Zoo). Nicholas Mundy (University of Oxford, UK) and Michael Nachman (University of Arizona, Tucson, USA) discussed selection on coat color mediated by specific mutations to the melanocortin-1 receptor in bananaquits (passerine birds) and in desert mice, respectively. Phenotypic adaptation in different species has resulted from selection at the same gene and, in some cases, even the same amino-acid position; multiple paths within a species have also given the same phenotypic effect. These approaches, which start from phenotypes and move on to look for genes and mutations, are complemented by lists of genes with nonsynonymous substitution rates (K_a) much greater than their synonymous substitution rates (K_s), indicating positive selection.

Sessions on the genetics of adaptation, gene and genome duplication, and Hox gene evolution extended the conference further into a molecular understanding of evolutionary mechanisms. In comparing substitutions between *Drosophila melanogaster* and *Drosophila simulans*, Adam Eyre-Walker (University of Sussex, Brighton, UK) presented some dramatic results. Using the McDonald-Kreitman test (in which the numbers of nonsynonymous and synonymous polymorphisms are compared with the number of fixed nonsynonymous and synonymous substitutions) on a large set of genes, he concluded that at least 35% of all amino-acid substitutions are adaptive substitutions fixed by selection, representing one substitution event every 56 years.

Evolution of novel gene functions

Wen-Hsiung Li (University of Chicago, USA) presented a database of the gene families found in the *D. melanogaster*, *Saccharomyces cerevisiae*, and *Caenorhabditis elegans* genomes. The families with the most members in each species were trypsin and the trypsin-like genes, the hexose transporters, and olfactory receptors, respectively. Li found 139 very recently duplicated genes in worm, 41 in yeast, but only seven in fruitfly; the latter is surprisingly low. It will be interesting to see how these data develop as the genomes are better characterized and as more metazoan genomes are completed.

Andreas Wagner (University of New Mexico, Albuquerque, USA) showed an analysis of robustness and redundancy in

large protein-interaction networks in yeast. He found that networks can be robust without being redundant, through epistatic, non-additive, non-linear interactions among unrelated genes. In fact, genes that are the most closely related by sequence and expression pattern produced the largest phenotypic effect when knocked out. Among the most recent duplicates, only about half have similar sets of interactions with other proteins, as measured by the yeast two-hybrid protein-protein interaction assay. This fits with a model presented recently by Lynch and Force (*Genetics* 2000, **154**:459-473), in which many duplicated genes that are not lost from a genome undergo subfunctionalization (retaining only a fraction of their original functions) or neofunctionalization (developing new functions) while they diverge.

Axel Meyer and Yves Van de Peer (University of Konstanz, Germany) and Marc Robinson-Rechavi (Ecole Normale Supérieure de Lyon, France) discussed models for gene, chromosome, and genome duplications in fish. Using subsets of the genes available from various fish species, they presented phylogeny-based models for the divergence times of various gene families; they disagreed on the scale and timing of duplication, however (see Figure 2). Meyer analyzed the evolutionary history of the Hox genes in fish, and presented a model in which several duplications of the Hox gene clusters, coupled with loss of specific genes, have driven body-plan evolution.

In a session on the evolution of noncoding DNA, Jürgen Brosius (University of Münster, Germany) spoke on the importance of retrotransposition in mammalian genomes. He has shown that some small RNAs, such as Alu elements, appear to be more efficient than mRNAs at retrotransposition. Retrotransposition of small RNAs has resulted in the formation of novel protein-coding genes, novel regulatory elements (for example, for transcription and mRNA splicing), as well as some novel small RNAs. One example Brosius presented was a novel RNA whose presence in transgenic mice appears to be correlated with a fear of open spaces. The genes encoding Leptin and its receptor appear to be other interesting examples of loci undergoing divergent evolution through several different mechanisms: both genes have an elevated ratio of nonsynonymous to synonymous nucleotide substitutions in the coding sequence in primates (as published in 1998 by S.A. Benner and colleagues), and thus appear to be undergoing positive selection. Brosius described a repetitive element that seems to have inserted into the regulatory region for Leptin transcription in the primate lineage. This example of evolution through multiple interacting mechanisms will probably turn out to be increasingly important as genotype-phenotype correlations are studied at genomic scale. The design of frameworks that can accommodate correlations between different events (such as coding-sequence evolution, gene-expression changes, changes in alternative-splicing patterns, and others) driving phenotypic divergence under selective pressure along specific

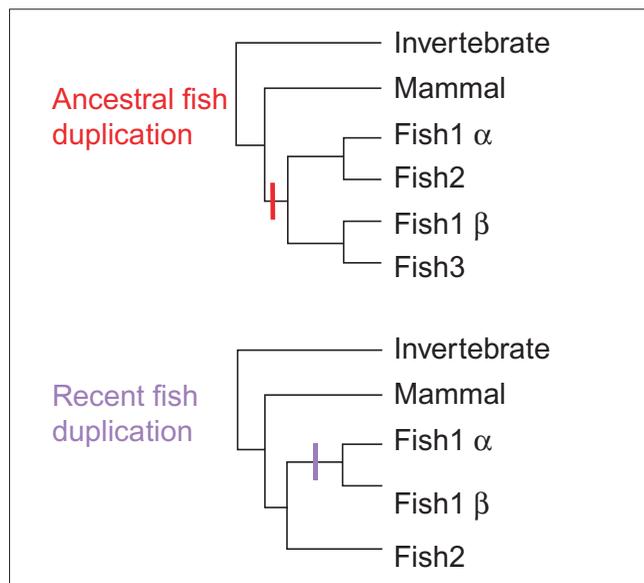


Figure 2

A phylogenetic methodology for determining gene duplication times showing how recent and ancestral gene duplication events can be differentiated. Marc Robinson-Rechavi (Ecole Normale Supérieure de Lyon, France) has found four gene families that give the top tree, in which two duplicated genes in one species (Fish1, genes α and β) group with different genes from other species (Fish2 and Fish3), and eleven families that give the bottom tree, in which the two duplicated genes from the same species group together. The time of gene duplication is indicated by a bar on each tree. According to their two talks at this meeting, Robinson-Rechavi believes that this analysis does not support a genome duplication in the fish lineage, whereas Yves Van de Peer (University of Konstanz, Germany), who has undertaken a similar analysis, believes that it does. Figure kindly provided by Marc Robinson-Rechavi.

branches of the tree of life will therefore become increasingly important as the big picture emerges.

Population genetics and epidemiology

Andrew Clark (Pennsylvania State University, University Park, USA) showed the power of population-genetic approaches applied to genomic sequences. He stressed the importance of linkage-disequilibrium mapping in model organisms and humans. Describing an analysis of single-nucleotide polymorphisms (SNPs) in the human genome, he emphasized that different regions of the genome have different periods to common ancestry, depending upon the timing and population dynamics of original individual substitutions, and that different isochores (regions with nonrandom G+C content, also called gradichores because of their nondiscrete boundaries) have different mutation rates. From his modeling, he estimated the expected sampling of SNPs in different genomic sequencing projects, which was in very close agreement with an analysis of sequence data from the

two human genome sequencing projects themselves. Finally, he presented a comparison between orthologs from the dog, mouse, and human and identified genes that appear to be under positive selective pressure along the three different lineages. Some of these were clear examples of where there is likely to have been selection for high mutation rates that has led to modified gene function. (A similar sample list of genes can be found in the TAED database [<http://www.sbc.su.se/~liberles/TAED.html>].) Clark concluded from substitution rates that dog and human are more closely related to each other than either is to mouse. He discussed the similarity between disease models in human and dog and the understanding of phenotypic variation in the dog, concluding that a dog genome project would be valuable.

Mikkel Schierup (University of Aarhus, Denmark) demonstrated the effect of sequence recombination on reconstruction of phylogenies. He showed that recombination within the sequence being analyzed can cause a loss of clocklike behavior and cause overestimation of the length of a tree and its terminal branches, coupled with underestimation of the time to the true common ancestor. These effects can be caused by other phenomena, such as exponential population growth, but recombination and exponential growth can be differentiated by Tajima's D statistic, which yields significantly negative values when exponential growth has occurred and values close to zero when recombination has occurred.

A plenary lecture from Andrew Read (University of Edinburgh, UK) examined the evolution of malaria. The benefits of virulence are increased efficiency of parasite transmission and, surprisingly, increased host success, whereas the main cost of virulence is a reduction of transmission because of death of the host. This model does not, according to Read, fully estimate the cost of increased virulence. He compared it with epidemiological models that do not consider evolution, concluding that when evolution is ignored, an improvement in survival rates after incomplete vaccination can be falsely predicted.

The very early evolution of life

Daniel Jeffares (University of Copenhagen, Denmark) speculated on the 'RNA world', an era when RNA is thought to have been the dominant genetic material before DNA took over, and its vestiges in the modern world. He proposed that introns were the original functional units, and mRNA was 'junk'; this situation left its mark in the form of intron-encoded small nucleolar RNAs. Further, Jeffares argued that prokaryotic cells are derived from eukaryotic ancestors (in which RNA plays a greater role in metabolism). The question-and-answer period after the talks also produced some interesting speculation; for example, I presented a hypothesis, based on the *in vitro* evolution of catalytic DNA, that an original 'DNA world' evolved into a 'DNA+RNA world' before encoded proteins were produced.

Speculations on the origins of life were a good place to emerge after a long conference covering many different aspects of evolutionary biology. From this diverse conference, the power of genomics and genomic biology to approach evolutionary questions was clear. The resulting increased convergence of research in molecular and morphological evolution, tied to the convergence of statistical and molecular methods, links multiple evolutionary mechanisms with the 'big picture' of organismal evolution.

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