

Abstracts First BAPGC, Stanford, 10/22/1009:

Graham Coop, UC Davis, Coop Lab " "Meiotic recombination hotspots in humans and mice"

Abstract: Meiotic recombination events cluster into narrow regions of the genome (1-2Kb), defined as hotspots, the molecular basis of which remain unknown. These hotspots are known to differ in location within and between species. I'll outline our work to identify the genetic and molecular causes of this variation.

Dan Kvitek, Stanford, Gavin Sherlock Lab, "Molecular characterization of the fitness landscape in asexually evolving populations of *Saccharomyces cerevisiae* "

Abstract: Using fluorescent markers, we have visualized the population dynamics of yeast evolving asexually in a glucose-limited environment, in eight independent populations. Our data show that adaptive evolution under these conditions does not occur by clonal replacement, and that an adaptive event is typically not built upon the previous one. From one of these evolving populations, we have isolated adaptive clones from throughout the evolution and used Solexa sequencing to identify the underlying mutations. The PKA-dependent and independent glucose-signaling pathways are frequent targets of adaptive mutation under these conditions, with three independent nonsense mutations occurring in MTH1 (which encodes a repressor of hexose transporter genes), three independent amplifications of HXT6/7 (which encodes a high affinity hexose transporter), and mutations in three different genes whose products function in the Ras-cAMP/PKA pathway (which integrates nutrient signaling with cell division). Additionally, we find that the MTH1 and HXT6/7 mutations are mutually exclusive, as they never co-occur in the same clone, and when forced to co-occur, produce a severe fitness disadvantage. This mutual exclusivity is an example of sign epistasis, and may be a determinant of the evolutionary trajectory on this limiting-glucose fitness landscape. These data provide the most detailed molecular characterization of an experimental evolution to date, and show a strong candidate for evolutionary trajectory-determining mutations.

David Goode, Stanford, Arend Sidow Lab, "Evolutionary constraint facilitates interpretation of genetic variation in resequenced human genomes"

Abstract: We here demonstrate how comparative sequence analysis facilitates genome-wide base-pair level interpretation of individual genetic variation, and address two questions of importance for human personal genomics: First, whether an individual's functional variation

comes mostly from noncoding or coding polymorphisms; second, whether population-specific or globally present polymorphisms contribute more to functional variation in any given individual. Neither has been definitively answered by analyses of existing variation data because of a focus on coding polymorphisms, ascertainment biases in favor of common variation, and a lack of base-pair level resolution for identifying functional variants. We resequenced 575 amplicons within 432 individuals at genomic sites enriched for evolutionary constraint, and also analyzed variation within three published human genomes. We find that high-resolution, single-site measures of evolutionary constraint are strongly predictive of reductions in modern-day genetic diversity across multiple annotation categories and across the allele frequency spectrum from rare ($< 1\%$) to high-frequency ($> 10\%$ MAF). Furthermore, we show that putatively functional variation in an individual genome is dominated by polymorphisms that do not change protein sequence, and which originate from our shared ancestral population and commonly segregate in human populations. These observations show that common, noncoding alleles contribute substantially to human phenotypes and that constraint-based analyses will be of tremendous value to identify phenotypically-relevant variants in individual genomes.

Qi Zhou, Berkeley, Doris Bachtrog Lab, "Deciphering neo-sex and B chromosome evolution by the complete genome of *Drosophila albomicans*"

Abstract: We report the first *Drosophila* genome assembled completely from ultrashort (45-75bp) reads. *Drosophila albomicans* is a unique model for studying sex chromosome and B chromosome evolution. A pair of its autosomes comprising 40% genome became sex-linked ~ 0.12 million years ago, creating the youngest and largest 'neo-sex' system reported to date. It also possesses recently derived B chromosomes that can influence fertility. We provide genome-wide evidence for surprisingly rapid evolution on the neo-X, and for the early degeneration of the neo-Y. In particular, we observed an excess of tandem duplications in coding regions along the neo-Y. Finally, we characterized non-repetitive and transcriptional sequence features of B chromosomes. These results provide important and novel insights into Y chromosome degeneration and the origin and function of B chromosomes.

Hunter Fraser, Stanford, Hunter Fraser Lab, "Widespread adaptive evolution of gene expression in budding yeast"

Abstract: Changes in gene expression have been proposed to underlie many, or even most, adaptive differences between species. Despite the increasing acceptance of this view, only a handful of cases of

adaptive gene expression evolution have been demonstrated. To address this discrepancy, we introduce a simple test for lineage-specific selection on gene expression. Applying the test to genome-wide gene expression data from the budding yeast *Saccharomyces cerevisiae*, we find that hundreds of gene expression levels have been subject to lineage-specific selection. Comparing these findings with independent population genetic evidence of selective sweeps suggests that this lineage-specific selection has resulted in recent sweeps at over a hundred genes, most of which led to increased transcript levels. Examination of the implicated genes revealed a specific biochemical pathway—ergosterol biosynthesis—where the expression of multiple genes has been subject to selection for reduced levels. In sum, these results suggest that adaptive evolution of gene expression is common in yeast, and that regulatory adaptation can occur at the level of entire pathways.