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ABSTRACTS

HGM 2008 population genetics and natural selection in man symposium abstracts

030: Natural Selection in Biological Networks: Towards Evolutionary Systems Biology

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Molecular and cell biology are providing key features to understand basic biological functions, to which cellular and animal models have added a wealth of new knowledge. Nonetheless, evolutionary analysis may provide new tools to biology, which may help in advancing at a higher pace on the basic understanding of function at the gene-product (or protein) level. First, comparative analysis of selective pressures on sets of genes involved in a complex pathway or functional network may help disentangle the fine tuned purifying selection pressures that may be converted in terms of "biological importance" or relative dispensability in sets of genes. Results in functional networks and gene families show differences in selective pressures (and thus in function) that are not being detected by standard experimental methods. An example of serotonin function will be presented. Second, the evolutionary analysis among humans may unravel the specific role of genetic variants in different populations having been exposed to different selective forces. When looking at genes that may be related to the pathogenic environment (of strong stratification in humans), not only genes related to immunity or inflammation are of interest, but also those related to glycosylation of the membrane proteins. Where in the functional network these forces are shown may help to understand the basic forces of adaptation and genotype-phenotype relationships. An analysis of genes involved in glycosylation, both in a world wide variation study and in a case–control study in pregnancy malaria will be presented, along another on the genetic variation of genes related to cell adhesion. These evolutionary studies are nothing but the analysis of the results of long term adaptation through selective forces and thus of functional analysis of variation naturally produced by mutation and natural selection having shaped the resulting phenotypes.

031: Signatures of Natural Selection on Genes of the Human Innate Immune System

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The innate immune system developed before the separation of the vertebrates and invertebrates. The adaptive immune system is dependent on the innate immune system. The TLRs and the defensins are the two major gene families known to regulate innate immune responses; there are also other genes, such as Cathelicidins and the Mannose-binding lectin, that play important roles in the innate immune system. We have documented extensive variation, that included the discovery of 259 novel variants, in 12 innate immunity genes (cathelicidin antimicrobial peptide, *CAMP*; α-defensins, *DEFA4*, *DEFA5* and *DEFA6*; β-defensin, *DEFB1*; mannose binding lectin, *MBL2*; and *TLRs 1*, *2*, *4*, *5*, *6* and *9*) in an Indian population resident in a region with high microbial load and have shown that the haplotype structures of these genes differ markedly in this population compared to the HapMap populations. The geographic distribution of haplotype frequencies in the *TLR4* gene correlates well with the prevalence of various infectious diseases. There is debate whether these genes are continuing to evolve or whether being evolutionarily ancient they have been highly optimized by natural selection. We have assessed the nature and extent of the operation of natural selection in maintaining the genetic diversity of these genes. Our analyses of DNA sequence data on these 12 genes included (a) tests of deviation of allele frequency spectra from those expected under neutrality, (b) extended haplotype homozygosity tests, (c) estimation of the extent of synonymous and non-synonymous changes in various regions of these genes, and (d) determination of haplotype networks. Based on the results of our analyses, we find that balancing selection is the major signature of natural selection on these genes and, for some of them, specifically overdominant selection seems to be the dominant mode of operation of balancing selection in those genomic regions that are involved in microbial recognition. (Acknowledgements: I thank all members of the TCG-ISI Centre for Population Genomics, in particular Neeta Sarkar Roy and Souvik Mukherjee, for rendering help at all stages of this work. This work has been funded by the National Institute of Allergy and Infectious Disease, National Institutes of Health, USA, under contract No. HHSN266200400067C.)

032: Global distribution of genomic diversity underscores rich complex history of continental human populations

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Characterizing patterns of genetic variation within and among human populations is important for understanding human evolutionary history and for careful design of medical genetic studies. Here, we analyze patterns of variation across 443,434 SNPs genotyped in 3,845 individuals from over 80 countries. This unique resource allows us to illuminate patterns of diversity in previously under studied populations at the genome-wide scale including Latin America, South Asia, and Southern Europe. Key insights a? orded by our analysis include quantifying the degree of admixture in a large collection of individuals from Guadalajara, Mexico; identifying language and geography as key determinants of population structure within India; and elucidating a North–South gradient in haplotype diversity within Europe. We also present a novel method for identifying long-range tracts of homozygosity indicative of recent common ancestry. Application of our approach suggests great variation within and among populations in the extent of homozygosity suggesting both demographic history (such as population bottlenecks) and recent ancestry events (such as consanguinity) play an important role in patterning variation in large modern human populations.

33: Searching for the footprints of pathogen pressures in the human genome

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Inferences concerning the action of natural selection in the human genome provide a powerful tool for predicting regions of the genome potentially associated with disease. Genetic variants influencing human susceptibility to disease are likely to affect the fitness of the organism, unless the disease concerned begins late in the life. There is therefore an intimate relationship between disease and selection that can be exploited for the identification of candidate disease loci. This relationship is evident in the case of infectious diseases, as, before the advent of antibiotics and vaccines, infectious diseases have been paramount among the threats to health and survival for most of human evolutionary history. To date, some of the strongest evidence for selection in the human genome has been obtained for human genes involved in the immune response or host-pathogen interactions. However, very few studies have investigated the extent to which pathogens have exerted selective pressure on the innate immune system. The phylogenetically ancient innate immune system governs the initial detection of pathogens and stimulates the first line of host defence. The innate immune system therefore provides the biological context for the adaptive immune response, which requires signals providing information about the origin of the antigen and the type of response to be induced. The genes encoding the Toll-like receptors, the C-type lectins and the scavenger receptors are the principal innate immunity genes involved in pathogen recognition, and the crucial roles of the proteins they encode make them ideal targets of natural selection. I will review our most recent data on natural selection acting on human genes involved in immune-related processes or host-pathogen interactions. These studies, which go from global genomewide scans to more fine-tuned analyses in specific genes or gene families, highlight how the identification of selected loci or variants of immunity-related genes may provide insight into host genes or pathways playing an important role in pathogen resistance. Finally, using the human Toll-like receptor gene family as a paradigm, I will show how the integration of our data into a clinical and epidemiological framework clearly illustrates the value of adopting an evolutionary perspective to biological questions, such as the relevance of genes in immunity to infection.