NATURAL SELECTION IN HUMANS

UNDERSTANDING OUR ADAPTATIONS

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July 17th and 18th, 2017

WELCOME

Dear Speakers and Participants,

It is our pleasure to welcome you for the meeting "Natural Selection in Humans: Understanding our adaptations". This event is possible thanks to the great support of B·Debate, an initiative of Biocat and Obra Social "la Caixa", and of the Institute of Evolutionary Biology (IBE), a joint CSIC-Universitat Pompeu Fabra (UPF) research institute.

Understanding the genetic bases of our uniqueness as humans or the distinctiveness of human populations is a permanent open question in biology that may be addressed through the detection of specific adaptations. This goal is now possible through the analysis of full genome sequencing data and by detecting and interpreting the footprints that adaptive (positive) natural selection has left in our genomes. However, in order to effectively reveal the specific adaptations that happened in our common ancestors and that characterize different human populations, the field needs more powerful statistical methods as well as novel experimental molecular approaches and a variety of interdisciplinary methodologies. Understanding our adaptation requires uncovering not only hard selective sweeps but also polygenic adaptation and soft sweeps. The final goal should be the interpretation of adaptive phenotypes, with experimental approaches that can demonstrate the functional impact of the adaptive variants.

With the participation of leading investigators in human adaptation, we aim to analyze the present and future of methods for understanding adaptive selection including the detection of hard selective sweeps but also soft sweeps, selection on standing variation and polygenic adaptation. Additionally, we hope to provide a general overview on the use of functional approaches to understand the biology behind the signatures detected. We expect that the invited talks and open debates will stimulate the discussion and will provide guidelines for future research on human adaptation.

We encourage you to actively participate in the discussions and wish you a fruitful meeting over the next two days.

Yours sincerely,

Jaume Bertranpetit, Elena Bosch, and B·Debate

PROGRAM

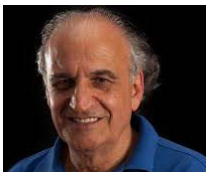
Monday, July 17th, 2017

8:30	**Registration**
9:00	**Welcome** **Jordi Portabella**, La Caixa Foundation **Jordi Fàbrega**, Biocat **Jaume Bertranpetit**, Pompeu Fabra University and Institute of Evolutionary Biology (CSIC-UPF) **Elena Bosch**, Pompeu Fabra University and Institute of Evolutionary Biology (CSIC-UPF)
9:15	**SESSION 1:** **The detection and interpretation of adaptive selection in human populations: an introduction** **Jaume Bertranpetit,** UPF and IBE (CSIC-UPF), Barcelona, Spain **Archaic inheritance: facilitating adaptations to new environments** **Emilia Huerta-Sanchez,** University of California, Merced, California, USA
10:45	**Coffee break**
11:15	**SESSION 2:** **Adaptations to high altitude in human populations** **Anna Di Rienzo,** University of Chicago, Chicago, USA **Diverse origins of human adaptive alleles** **Aida Andrés,** EVA-Max Planck Institute, Lepzig, Germany
12:45	**Lunch & networking**
14:00	**SESSION 3:** **The Genomic Basis of Human Physiological Adaptation** **Rasmus Nielsen,** UC Berkeley, Copenhagen, Denmark **Detecting selection in human biological pathways** **Laurent Excoffier,** University of Bern, Bern, Switzerland
15:30	**Coffee break**
16:00	**SESSION 4:** **Polygenic adaptation and the role of archaic introgression in complex human phenotypes: the case of bone mineral density and attention deficit hyperactivity disorder** **Oscar Lao,** CNAG/CRG, Barcelona, Spain
16:45	**Round table**
18:00	**Adjourn**

Tuesday, July 18th, 2017

9:30	**SESSION 5:** **Human adaptation to pathogen pressures: genetic and non-genetic factors driving immune response variation** **Lluís Quintana-Murci,** Institut Pasteur, Paris, France **Sources of variation in human immune responses: genes, evolution and environment** **Mihai Netea,** Radboud University Medical Center, Nijmegen, The Netherlands
11:00	**Coffee break**
11:30	**SESSION 6:** **The path from signatures of selection to adaptive phenotypes: an unpassable road?** **Elena Bosch,** UPF and IBE (CSIC-UPF), Barcelona **Finding and validating classic selective sweeps** **Chris Tyler-Smith,** Sanger Institute, Cambridge, UK
13:00	**Lunch & networking**
14:00	**SESSION 7:** **Selective sweeps on the X chromosome, genetic conflict and speciation** **Mikkel Heide Schierup,** Aarhus University, Aarhus C, Denmark **The contribution of transposable element insertions to environmental adaptation** **Josefa González,** IBE (CSIC-UPF), Barcelona
15:30	**Round table**
16:30	**Meeting closure**

SCIENTIFIC COMMITTEE



Jaume Bertranpetit, Professor at **Pompeu Fabra University and Institute of Evolutionary Biology (CSIC-UPF),** Barcelona, Spain.

Researcher unique identifier(s): http://www.researcherid.com/rid/F-8550-2012

URL for web site: http://biologiaevolutiva.org/jbertranpetit/

Professor of Biology at the Pompeu Fabra University (Barcelona). Group leader in the Evolutionary Biology and Complex Systems Program in this University. Promoter of the Institute for Evolutionary Biology, IBE (UPF-CSIC). His research field is in different aspects on the study of the human genome variation and diversity: human population genetics, molecular evolution, comparative genomics and the interaction between human evolutionary biology and other fields, including medicine, genetic of complex diseases, statistical genetics and others. Recent publications are mainly on the footprint of natural selection in the human genome and the emerging field of Evolutionary Systems Biology, with the relationship of molecular networks and adaptation in genome-wide perspective. Director of ICREA (Institució Catalana de Recerca i Estudis Avançats) till 2015.

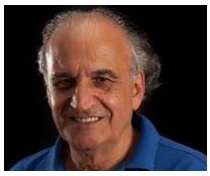
Elena Bosch Fusté, Associate Professor at **Pompeu Fabra University and Institute of Evolutionary Biology (CSIC-UPF)**, Barcelona, Spain.

Elena Bosch graduated in Biology at the Universitat de Barcelona in 1995 and, after pursuing her doctoral research on population genomics of the North African populations, she obtained her PhD at the Universitat Pompeu Fabra. In February 2000, she moved to the UK, where she was appointed Research Assistant at the University of Leicester to work on the human Y chromosome diversity and dynamics, at the laboratory of Dr. Mark Jobling. In 2004, thanks to a "Ramón y Cajal" contract, she established her own research group on Evolutionary Population Genetics at the Universitat Pompeu Fabra. In 2008, she was granted tenure with an Associate Professor position that changed to Assistant Professor in February 2012. In 2008, she was one of the founding members of the Institute of Evolutionary Biology (CSIC-UPF). She lectures on Human Evolution and Health within the bachelor degrees of Human Biology and Medicine within the Universitat Pompeu Fabra. In the last years, her research work has focused on investigating different aspects of human genetic diversity including human adaptation and the architecture of the genetic predisposition to complex disease. Beyond the detection of the footprint of natural selection into the genome itself, her group aims to elucidate the genetic variants and molecular phenotypes underlying the genetic basis of different human adaptations presumably related to immunity and pathogen interaction, diet, and micronutrient content.

DETAILED PROGRAM AND INVITED SPEAKERS

Monday, July 17th, 2017

Session 1



Jaume Bertranpetit, Professor at **Institute of Evolutionary Biology, CSIC-Universitat Pompeu Fabra,** Barcelona, Spain.

(See his CV at the Scientific Committee section)

The detection and interpretation of adaptive selection in human populations: an introduction

The information contained in the diversity of the human genome can shed light on multiple aspects of our past, including the adaptive processes, by detecting regions where selection left a footprint in the genome. An initial step is the evaluation of the different tests for detecting selective sweeps and the compound statistics, like the "hierarchical boosting". Some cases will be presented of specific adaptations.

Beyond the cases clearly described of selective sweeps, now we can begin undertaking the analysis of adaptive selection when it targets the molecular basis of complex adaptations by coupling the scans of selection with the results of GWAS. Data for height and academic attainment will be presented.

Gene products function in molecular networks, as such, the position within the network may determine the strength of selection applied to the gene. It is possible to interrogate how selection is distributed across the molecular networks. This analysis indicates how evolution is shaping the complex interactions inherent to molecular pathways and networks. This analysis may be applied to the pathway level, the entire metabolome, or even the whole interactome. We present here all these cases.

At the level of the human interactome, selection has not acted equally throughout evolutionary history: genes with higher number of interactions are more likely to have been targeted by recent positive selection during recent human evolution. Our results indicate that the relationship between centrality and the impact of adaptive evolution highly depends on the evolutionary time-scale. Most likely, network adaptation occurs through intraspecific adaptive leaps affecting key network genes, followed by the fine tuning of adaptations in less important network regions.

These analyses goes beyond the identification of single cases of adaptation and opens the scope of understanding how natural selection works within the biomolecular complexity of life. Nonetheless most of the analysis of selection have not reached the expected goals and the complexity of the relationship between genotype and phenotype prevents more success in the field.

Emilia Huerta-Sanchez, Assistant Professor at **University of California Merced**, US.

Emilia is an Assistant Professor in the Department of Molecular Cell Biology at the University of California Merced. She received her PhD in Applied Mathematics from Cornell University under the supervision of Carlos Bustamante and Rick Durrett. After her PhD, she joined the laboratory of Rasmus Nielsen as a postdoctoral fellow. Her current research interests involve detecting and characterizing natural selection in human populations and estimating human demographic histories.

Archaic inheritance: facilitating adaptations to new environments

As humans settled around the world, they encountered and adapted to many diverse and challenging environments. The genetic changes that facilitated our adaptations are still present in our genome sequence, and can be discovered by looking for specific signatures derived from evolutionary models. In this talk I describe my recent work that has revealed signatures of past evolutionary events: the discovery of the genetic basis for high altitude adaptation in Tibetans, and the characterization of archaic adaptive introgression in non-African populations.

Session 2

Anna Di Rienzo, Professor at **University of Chicago**, Chicago, USA.

Anna was trained in Human Genetics and Medical Genetics at the University of Rome "La Sapienza", Italy. After a postdoctoral training period at the Institute of Cell Biology of the National Research Council, she moved to the US where she did further postdoctoral training at University of California in Berkeley and in UC San Francisco.

In 1993, she took an Assistant Professor position in the Department of Anthropology at Northwestern University, moving to the University of Chicago in 1996. She is now a Professor in the Department of Human Genetics and a member of the Institute for Genomics and Systems Biology, the Committee on Genetics, Genomics and Systems Biology, the Committee on Clinical Pharmacology and Pharmacogenomics, and the Committee on Molecular Metabolism and Nutrition.

Anna has had a long-standing interest in using genetic data to make inferences about human demography, with a particular focus on the history of population size changes. In addition, she has been interested in detecting signatures of genetic adaptations to local environments especially at susceptibility genes for common diseases or genes coding for drug and steroid hormone metabolizing enzymes. More recently, her group has combined population genetic approaches and functional genomic analyses to elucidate the genetic bases of inter-individual and inter-ethnic variation in transcriptional response phenotypes.

Adaptations to high altitude in human populations

The ascent to high altitude presents formidable challenges to physiological processes, including hypoxia as well as cold stress and resource-poor habitats; these environmental features pose severe constraints on work capacity and reproduction. Therefore, the history of initial settlement at high altitude and subsequent population movements is intertwined with the history of adaptations. Studies of human populations from the Tibetan region have revealed a complex history of mixing among modern human populations as well as evidence that a key adaptive allele was introduced into the Tibetan genome through admixture with a Denisova-like population. This history provides novel opportunities for mapping locally beneficial alleles and for learning about the genetic architecture of high altitude adaptations. We are studying a large cohort of Tibetans and Sherpa from Nepal using approaches to detect selective sweeps as well as polygenic adaptation signals. We complement these approaches with standard genome-wide association mapping of physiological and reproductive phenotypes measured at high altitude, to gain insights into the phenotypes and the genetic variation that is causally related to improved fitness outcomes. The challenges and rewards of conducting field studies in the era of genomics will be discussed along with avenues for functional validation of genetic variants with signals of adaptation.

Aida Andrés, Group Leader at **Max Planck Institute for Evolutionary Anthropology**, Leipzig, Germany.

Aida Andrés studied Biology at the Universitat de Barcelona and obtained her PhD from the Universitat Pompeu Fabra, also in Barcelona. After postdoctoral positions at Cornell University and the USA National Institutes of Health, in 2010 she moved to Leipzig (Germany) to join the Max Planck Institute for Evolutionary Anthropology. Her group studies genomes, both ancient and modern, to understand how humans and other primates have biologically adapted to their particular natural environments. Her group investigates different aspects of genetic adaptation, but she is particularly interested in the selection mechanisms that create genetic and phenotypic differences among individuals of the same population (balancing selection) and among populations of the same species (local adaptation).

Diverse origins of human adaptive alleles

Human evolution is interesting from a number of reasons. Among them is the fact that human ancestors lived in Africa for millions of years, but they successfully colonized non-African environments only in the last 50,000 years or so. Many of these areas differ substantially in ecological terms, and their colonization was accompanied by selective pressures to adapt locally. Analyzing modern and ancient genomes we infer that local adaptation has significantly contributed to the (otherwise modest) genic differences that exist among human groups. Some of these adaptations result in population differences in important phenotypes, including disease.

The origin of the adaptive alleles remains debated, with new and neutral standing alleles being classically accepted sources, and alleles borrowed from archaic humans being an interesting additional source. I will discuss the diverse origin of human adaptive alleles, including these cases. I will also discuss how previously selected alleles could, through shifts in selection, mediate fast, local adaptation in small ancestral human groups. I will present data showing that long-term balancing selection (an important type of natural selection that maintains advantageous diversity within populations) may have favored several Eurasian adaptations, and has great potential to promote local adaptation in populations of low effective size. Overall, the diversity in origins calls for diversity in methods to identify human adaptive alleles.

Session 3

Rasmus Nielsen, Professor at **UC Berkeley**, Berkeley, USA.

Dr. Nielsen's work is on statistical and population genetic analyses of genomic data, in particular methods for detecting natural selection, describing population genetic variation, inferring demography, and methods for association mapping. Much of his current research concerns statistical analyses of next-generation sequencing data, both in the context of medical genetics and population genetics. Many of the methods he has developed are heavily used by other researchers, including the phylogeny based methods for detecting positive selection implemented in PAML, the methods for inferring demographic histories implemented in the IM and IMa programs, the method for detecting selective sweeps implemented in SweepFinder, and the methods for analysing Next Generation Sequencing (NGS) data implemented in ANGSD. He has published >200 peer reviewed papers, invited book chapters and review papers since 1997 (including 36 in Science or Nature) with a total H-index of 101, and many of these papers focus on methods development and theory. However, much of his recent research has also focused on the application of evolutionary genetics for understanding molecular function, for example for understanding the genetic basis of the regulation of haemoglobin concentration in high-altitude adapted or diet and cold adaptation in Inuit of Greenland.

The Genomic Basis of Human Physiological Adaptation

As the first anatomically modern humans spread around the globe, they had to adapt to a new and diverse set of environments. Today we can find the traces of this evolutionary process in the genomes of modern humans. In this talk, I will give two examples of human physiological adaptation to the local environment. The first example concerns physiological adaptation to the hypoxic environment of high-altitude. Tibetans harbor adaptive genetic variants in two genes, EPAS1 and EGLN1, that affect hemoglobin production. Recently, we have shown that the adaptive EPAS1 haplotype was transferred into humans by introgression from Denisovans – an archaic hominin group. I will discuss recent progress on understanding the process of adaptive introgression in humans and its role in altitude adaptation.

The second example is adaptation of the indigenous people of Greenland, the Inuit, to life in the Arctic, including low temperatures and a diet based primarily on fish and marine mammals and rich in ω-3 polyunsaturated fatty acids (PUFAs). Studies of Inuit have been used to argue for the benefits of a high dietary intake of ω-3 PUFAs. We recently performed the first scan of Inuit genomes for signatures of adaptation and found extreme signals in several loci, relating to metabolism of fatty acids, particularly PUFAs. Using association mapping, we show that the selected alleles have strong effects on a number health-related phenotypes, and we replicate the findings in Europeans. Our results show that Inuit have unique physiological adaptions to life in the artic, in particular a diet rich in ω-3 PUFAs.

Laurent Excoffier, Professor at **Institute of Ecology and Evolution, University of Bern,** Bern, Switzerland.

Laurent Excoffier is interested in the development of computational methods to understand evolutionary processes at the population and species level. He has been studying the effect of complex demography on the molecular genetic diversity of a species, with the aim of designing better tests of selective neutrality. Recent work has also focused on the effect of spatial range expansion on non-neutral (functional) diversity, evidencing the buildup of a mutation load during range expansions due to inefficient purifying selection on wave fronts. He has also developed methods to detect individual loci or gene networks under selection. Laurent Excoffier is also involved in the development of statistical methods to reconstruct the past demography of a species from its genetic diversity, and to test among alternative evolutionary scenarios, with recent applications to humans and other primate species.

Detecting selection in human biological pathways

Most studies of human adaptation have aimed at detecting selection at the level of single genes, whereas most phenotypic traits are controlled by several genes with small effects, implying that selection is essentially polygenic. In order to find evidence of polygenic adaptation in the genome, we have developed tests of selection at the level of whole biological pathways, which include dozens to hundreds of genes involved in a given biological process. Our first analyses of patterns of polymorphism within humans have revealed that most significantly differentiated pathways were involved in immunity and resistance to pathogens. The comparison of polymorphism and divergence between humans and chimps revealed more complex patterns, with pathways showing signals of positive, balancing, or purifying selection but also others showing an ancient relaxation of selective constraints. The study of polygenic adaptation at a higher level in the primate lineages ancestral to humans have identified signals of positive selection in several pathways involved in immune response, sensory perception, metabolism, and energy production. Interestingly, in pathways that are significant at several levels in the phylogeny, different genes were involved in adaptive events. However, these previous analyses have tested whole pathways, whereas it is more likely that only at subset of genes are involved in an adaptive response. To overcome this problem, we have developed a new algorithm (signet) to find subnetworks of biological pathways showing evidence of adaptation. Its application to the detection of convergent adaptation to altitude in humans identifies connected subsets of genes that are involved in the response to hypoxia. Our approach has been extended to analyse large networks with thousands of genes, and could therefore be applied to large protein-protein interaction databases or to gene expression networks.

Session 4

Oscar Lao, Team Leader at Population Genomics, **CRG-CNAG**, Barcelona, Spain.

Oscar Lao holds a degree in Biology from the University of Barcelona and a PhD in Health Sciences from the Universitat Pompeu Fabra. Between 2005 and 2014 he worked as a postdoctoral fellow at the Forensic Molecular Biology Department at Erasmus Medical Centre University in Rotterdam, The Netherlands. Since 2015 he is the Population Genomics team leader at the CNAG.

He focuses on the analysis and interpretation of the genetic variation present in human populations, the development of new statistical and bioinformatic tools for the detection of hidden population substructure and the evolutionary processes that shaped our genome.

As result of this work, Oscar Lao has co-authored over 60 articles published in prestigious scientific journals and encyclopedias.

Polygenic adaptation and the role of archaic introgression in complex human phenotypes: the case of bone mineral density and attention deficit hyperactivity disorder

Anatomically modern humans (AMH) appeared and adapted in Africa ~200 kilo years ago (kya); during the human Diaspora out of the African continent, AMH biologically adapted to the new environments they encountered. This adaptive process could have been fuelled by interbreeding with homo archaic species -such as Neanderthal and Denisovan- present at that time in Eurasia.

Nowadays, thanks to the technological advances and the detailed description of the genetic variation in large human datasets, the identification of the fingerprint of classical positive selection events in the human genome and the identification of archaic introgressed regions in the genome is living a golden age of scrutiny.

However, as new evidences accumulate, it is obvious that i) currently developed demographic models are too simplistic to properly describe the complex demographic history of humans, ii) the so far identified genomic regions under positive selection are likely the tip of the process of human adaptation iceberg because most of the human phenotypes are complex in nature, involving many genes, and iii) knowing which is the environmental factor trigging the adaptive response is hard in most of the cases because most phenotypes are pleiotropic.

In this presentation I will describe the latest models of human demography that we are developing at my group; furthermore, I will provide the evidences of polygenic adaptation that we have identified in two phenotypes of medical and evolutionary interest: a physiological phenotype such as bone mineral density (BMD) and a complex behavior phenotype such as attention deficit hyperactivity disorder (ADHD). Both phenotypes are associated to several impairing conditions in current populations; a main question is why Darwinian selection has not removed the alleles associated to these phenotypes from human populations.

Tuesday, July 18th, 2017

Session 5

Lluís Quintana-Murci, Laboratory Head at **Institut Pasteur**, Paris, France.

Lluís Quintana-Murci, a Director of Research of the CNRS, heads the Unit of Human Evolutionary Genetics at the Institut Pasteur (Paris). He earned his Ph.D. in Population Genetics at the University of Pavia (Italy), and his MSc in Biology at the University of Barcelona (Spain). His laboratory explores how natural selection, human demography and lifestyle have shaped human genome diversity, focusing on immune-related traits. In particular, they study the respective contribution of genetic, epigenetic and evolutionary factors to immune response variation, between individuals and populations. To this end, his laboratory combines population genetics and cellular genomic approaches, with computational modelling and development of new statistical fraeworks, often working closely to theoretical population geneticists, immunologists, epidemiological geneticists as well as anthropologists.

Human adaptation to pathogen pressures: genetic and non-genetic factors driving immune response variation

Pathogens have been a major cause of human mortality, so natural selection is expected to act strongly on immune response genes. However, the extent to which selection have affected immune-related genes, and how genetic and non-genetic factors drive immune response variation have remained elusive. In this presentation, I will summarize different cases of innate immunity genes and pathways that have been targeted by selection, in its different forms and intensities, helping to delineate essential mechanisms of host defense, with respect to those exhibiting higher immunological redundancy. I will discuss different forms of genetic adaptation to pathogen pressures and, specifically, how population admixture can also represent a new source of adaptive variation. I will also present data on how host genetic variation can profoundly impact immune molecular phenotypes, such as gene expression upon infection (eQTL), contributing to marked differences in immune responses between human populations. Notably, we have recently shown that immune-responsive eQTLs are enriched in population-specific signals of positive selection, suggesting their important role in human adaptation, and found that admixture with Neandertals introduced regulatory variants into European genomes, affecting preferentially responses to viral challenges. Finally, I will discuss the respective contribution of genetic, epigenetic (DNA methylation) and intrinsic (age and sex) factors to the observed individual and population variation of immune responses to microbial challenges. The presentation will attempt to provide a glimpse into how population and functional genomic approaches can help to pinpoint evolutionarily important determinants of host immune responsiveness and the mechanisms underlying the diversity of immune phenotypes in health and disease.

Mihai G. Netea, Head Laboratory Experimental Medicine at **Radboud University Medical Center,** Nijmegen, the Netherlands.

Mihai Netea was born and studied medicine in Cluj-Napoca, Romania. He completed his PhD at the Radboud University Nijmegen, The Netherlands, on studies investigating the cytokine network in sepsis. After working as a post-doc at the University of Colorado, he returned to Nijmegen where he finished his clinical training as an infectious diseases specialist, and where he currently heads the division of Experimental Medicine, Department of Internal Medicine, Nijmegen University Nijmegen Medical Center. He is mainly interested in understanding the factors influencing variability of human immune responses, the biology of sepsis and immunoparalysis, and the study of the memory traits of innate immunity.

Sources of variation in human immune responses: genes, evolution and environment

Variability of immune system determines host defense and susceptibility to immune-mediated diseases. To understand the sources of variability influencing innate immune responses, we have investigated host genetic and non-genetic factors, as well as microbiome effects, on cytokine responses in two cohorts of 500 and 200 healthy volunteers of European ancestry from the Human Functional Genomics Project. We demonstrate a strong impact of genetic heritability on cytokine production capacity after challenge with bacterial, fungal, viral, and non-microbial stimuli. In addition to 17 novel genome-wide significant cytokine production QTLs, our study provides a comprehensive list of genetic variants that influence both direct cytokine production capacity as well as trained immunity (innate immune memory). Important taxonomical and biological pathways related to microbiome that influence cytokine responses are also reported. The cytokine QTLs are more often located in regions under positive selection, and are significantly enriched among SNPs associated with infections and immune-mediated diseases. In addition, we show that many of the genes involved in host defense, and in particular innate immunity, are under positive selection in populations of different ancestries living in Europe.

Session 6

Elena Bosch, Associate Professor at **Pompeu Fabra University and Institute of Evolutionary Biology (CSIC-UPF)**, Barcelona, Spain.

(See his CV at the Scientific Committee section)

The path from signatures of selection to adaptive phenotypes: an unpassable road?

While we know how to identify targets of natural selection under different selective scenarios few human adaptive alleles and phenotypes have been fully characterized to date. Once signatures of positive selection are detected in our genomes different strategies can be used to identify candidate adaptive variants and phenotypes. Such strategies usually take into account the nature of the selection signatures, the potential functional role of all linked variants and the allele frequency differences among populations with and without the detected signals, respectively. However, given our current limited knowledge on the biological role of many annotated genes in the human genome, the pleiotropic nature of particular genes, the inconsistency and diversity of in silico methods for predicting functionality on coding and non-coding variants, and without an a priori idea about the potential adaptive phenotypes or particular selective pressures on the populations studied, the complete validation of human adaptive alleles from genome scans of selection will probably remain a long and difficult task. During my talk I will present the insights gained as well as the limitations suffered during such endeavor for several ongoing projects and putative adaptive cases already characterized in my lab:

i) The CD5 case. Clear signals for a classical hard selective sweep were initially identified from genotype data around the CD5 gene. Sequencing data confirmed the detected signals in East Asians and pointed out to a non-synonymous substitution for which we demonstrated differential molecular phenotypes related to the immune response.

ii) The ZIP4 case. We detected an extreme pattern of population differentiation when comparing Africans with non-Africans (yet absence of other classical signatures of positive selection) for a non-synonymous SNP for which we demonstrated functional differences in surface protein expression, basal intracellular levels of zinc and zinc uptake. Although the adaptive phenotype is unknown, these functional results may indicate differences in zinc homeostasis among modern human populations with possible relevance for disease risk.

iii) Zinc transporter genes. Zinc homeostasis is tightly kept by 10 zinc efflux transporters and 14 zinc influx transporters encoded by the SLC30A and SLC39A gene families, respectively. We are analyzing signatures of polygenic selection and classical selective sweeps in different geographical areas and identifying highly differentiated non-synonymous SNPs and eQTLs, which will be functionally validated in an effort to understand the adaptive variants and phenotypes behind such signatures.

iv) Finally, we also are exploring potential adaptive variants and phenotypes in the Andamanese.

Chris Tyler-Smith, Group leader at **The Wellcome Trust Sanger Institute**, Hinxton, UK.

I am a team leader at The Wellcome Trust Sanger Institute in the UK. My team, Human Evolution, generates data on worldwide genetic variation in humans and closely-related species such as gorillas and chimpanzees, and uses this information to investigate the human past. We are interested in the way humans have spread around the world, diverged, mixed, and also adapted to their environments throughout prehistoric and historic times.

We have contributed to large international projects such as the 1000 Genomes Project and African Genome Variation Project. Now, our focus is on understanding genetic variation in Africa more thoroughly, as well as variation in other parts of the world including the Middle East, the Himalayas, the Pacific and the Americas.

We also want to understand the functional consequences of genetic variants, including knockouts of human genes in healthy people, and advantageous human variants, which we model in mice.

Population-genetic and functional studies of classic selective sweeps in humans

Classic selective sweeps have probably been rare in human history, but are of exceptional interest, and we would like to discover additional examples starting from genetic data. Two approaches to this are investigating new populations, and refining methods to identify classic sweeps. Following the first approach, we have studied 49 Himalayan populations inhabiting a wide range of altitudes to explore their adaptations to living at high altitude. We rediscover the known EPAS1 and EGLN1 loci, plus eight additional candidate genomic regions. Following the second approach, we have developed a method, Fine-Mapping of Adaptive Variation (FineMAV), which combines population differentiation, derived allele frequency and a measure of molecular functionality to prioritize candidate positively-selected variants for functional follow-up, and applied it to the 1000 Genomes Project populations. In addition to the expected signals, we find many novel candidates and are in the process of modelling some of them in mice. A striking example is PRSS53, where parallel evolution on different variants in East and South Asia appear to influence hair morphology.

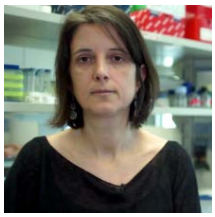
Session 7

Mikkel Heide Schierup, Professor of Bioinformatics at **Aarhus University**, Aarhus, Denmark.

Mikkel Heide Schierup is an evolutionary geneticists developing models for comparative population genomics and applying them to whole genome sequences of humans and other primates. He has been analysing incomplete lineage sorting patterns among great apes species and what they can tell about the population genetics of ancestral species including the evolution of recombination landscapes and speciation processes. Current main interest is to decipher why the X chromosome is the target of very strong natural selection.

Selective sweeps on the X chromosome, genetic conflict and speciation

The X chromosome is disproportionally involved in speciation in humans and other great apes. We recently reported that the X chromosome has been the target of independent very strong selective sweeps in several great apes species targeting overlapping regions. These regions associate with the location of multicopy, testis-expressed genes (so-called ampliconic genes) and also with deserts of Neanderthal introgression into humans suggesting that they contain reproductive incompatibilities between human and Neanderthal. We speculated that competition between X and Y in male meioses, i.e. meiotic drive, by these ampliconic genes and their non homologous counterparts on the Y chromosome is responsible for these observations, and that such drive may be a major contributor to speciation. We present new results based on the Simons genome diversity data and the Danish pangenome data showing extensive variation in ampliconic gene number within and among human populations both on the X chromosome and on the Y chromosome. We also show evidence for independent very strong selective sweeps targeting specific human populations. We find that these sweeps are particularly devoid of Neanderthal introgression and speculate that they represent the remnants of a first out-of-Africa population that were later replaced by the main out-f-Africa population except for these putatively driving parts of the X chromosome.



Josefa González, CSIC Tenured Scientist at **Institute of Evolutionary Biology, CSIC-Universitat Pompeu Fabra,** Barcelona, Spain.

I did my PhD in Biology in Prof. Alfredo Ruiz lab at the Universitat Autònoma de Barcelona (UAB). After a first postdoctoral stay at UAB, I moved to Stanford University to work with Prof. Dmitri Petrov. While at Stanford, I was first a Fulbright Postdoctoral fellow and then a Research Associate at the Department of Biology. In 2010, I was awarded a Ramon y Cajal fellowship to join the Institute of Evolutionary Biology (IBE) in Barcelona. Since March 2017, I am a CSIC Tenured Scientist at IBE.

Our lab focuses on understanding how organisms adapt to their environments. We combine -omics approaches with detailed molecular and phenotypic analyses to get a comprehensive picture of adaptation.

The contribution of transposable element insertions to environmental adaptation

Identifying the genomic basis of environmental adaptation is a growing field of research. Advances in whole genome sequencing and other high-throughput technologies allow us now to identify and characterize the genes and traits more relevant for environmental adaptation. Most of our knowledge so far comes from the analysis of one type of genetic variant: single nucleotide polymorphisms (SNPs). Other types of variants such as transposable element insertions, that are complex mutations likely to play a role in adaptation, are largely ignored. We are currently focusing on elucidating the contribution of transposable to adaptation in the model species Drosophila melanogaster. We are analysing a worldwide sample of D. melanogaster natural populations, and we have functionally validated a subset of the adaptive mutations identified. Besides, we are also starting to investigate the role of transposable elements in re-wiring and fine-tuning stress regulatory networks in humans.

PRACTICAL INFORMATION

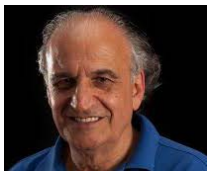
Venue: Palau Macaya

Palau Macaya
Pg. de Sant Joan, 108
08037 Barcelona, Spain

Room: Auditorium

Free Wi-Fi: wifi_palau_macaya

Contact persons during the event



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OUTCOMES

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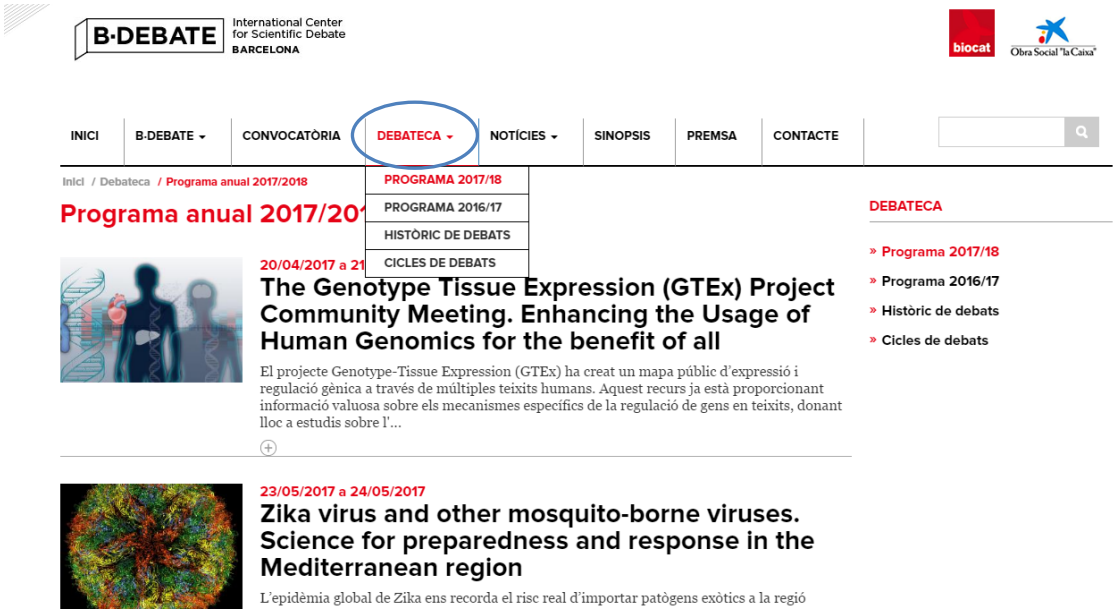
Contents of the meeting "Natural Selection in Humans: Understanding our adaptations"



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