Genetic Diversity and Origins of Europeans

Closing conference of COST Action BM0803

15-16 January 2013 University of Geneva - Sciences II

Conference Abstracts

Tuesday 15 January 2013

Session 1 **The peopling history of Europe: non-genetic background**
Chair: Dr Laurent Sagart, CRLAO, Paris, France

09h30 **Bioarchaeological assessments of the spread of farming into Europe**
Dr Ron Pinhasi
Smurfit Institute of Genetics, Dublin, Ireland

The emergence of the first agricultural societies in the Near East and Anatolia was a long and complex process which entailed major economic, social, technological and behavioural transformations. During the 7th millennium BC, the Neolithic way of life appeared in southeast Europe and then spread across the continent.

The neolithisation process entailed both the spread of farmers by demic diffusion and other dispersal mechanisms, and the adoption of farming via the acculturation of indigenous Mesolithic hunter-gatherers. The array of processes led to a single outcome-- the eventual disappearance of European Mesolithic societies as farming became the preferred way of life across Europe. The analysis of genetic, archaeological and anthropological data, and a range of other proxies, yielded in some cases conflicting results regarding the demographic history of this process. The fact that no single model can provide a best fit for these data reaffirms that the Neolithic transition in Europe was a complex multi-phased process which varied in mode and intensity across time and space.

This paper focuses on the anthropological data with the aim to provide an overview of some of the results obtained from the analyses of dental and cranial metric data, and other aspects, in order to elucidate (a) the contribution of these proxies to the study of the neolithisation process in Europe, and (b) the implication of these on the context of genetic studies of both ancient and modern European populations.

10h25 **Early domestic animals in the Near East and Europe: what relationship with the peopling history?**
Dr Jean-Denis Vigne
Muséum national d'Histoire naturelle - CNRS, Paris

Except for dogs which have been domesticated much earlier, the process of domestication of mammals was first initiated in a large area of the Near East starting from 12-11 ka BP. It resulted in the apparition of new typical domestic phenotypes for several species ca. 10.5-10 ka BP, then to the birth of animal husbandry ca. 9.5 ka BP, creating a new way of life (Neolithic). Between 8.8 and 5.5 ka BP, domestic species and husbandry spread from Anatolia to the most remote areas of Northwest Europe in a slow and arrhythmic complex process. The talk aims to assess how these phenomena shed light on the processes of exchanges and migrations of people during these times.

10h25 **Mapping the origins and expansions of the Indo-Europeans**
Prof. Russell Gray
University of Auckland - School of Psychology, New Zealand

Languages, like genes, are documents of history. The rich history of humanity's speech communities is inscribed in the remarkable diversity of linguistic forms we see today. This diversity is generated by evolutionary processes that, like biological evolution, take place in space and time. In this talk I show how evolutionary methods designed to analyse the spread of viral outbreaks can be used to model the spread and diversification of languages. Bayesian phylogeographic models will be used to test two hypotheses for the origin of the Indo-European language family. The conventional view places the homeland in the Pontic steppes about 6000 years ago. An alternative hypothesis claims that the languages spread from Anatolia with the expansion of farming 8000 to 9500 years ago. I will show that that the inferred timing and root location of the Indo-European language trees fit with an agricultural expansion from Anatolia beginning 8000 to 9500 years ago. These results highlight the critical role that evolutionary models can play in resolving debates about language origins and human history.

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Session 2 **Genetic diversity of Europeans: past and present**
Chair: Dr Estella S. Poloni, University of Geneva, Switzerland

14h00 **Ancient DNA: a window to the past of Europe**
Dr Marie-France Deguilloux
CNRS UMR PACEA, Bordeaux, France

The history of European populations is characterized by numerous migrations or demographic events that are likely to have had major impacts on the European gene pool patterns. The presentation will focus on how ancient DNA (aDNA) data contribute to our understanding of past populations dynamics in Europe. Offering valuable insights into the evolution of the European gene pool composition at key moments of its history, palaeogenetic evidence actually plays a primary role in gaining a deeper understanding of the European populations' evolution.
Technological challenges of the palaeogenetic approach will be first discussed. Studies using ancient DNA are plagued by a unique set of methodological challenges, including template degradation, contamination with modern exogenous DNA or lack of representativeness of samples studied. However, the recent development of second-generation sequencing technologies, that has greatly benefited the field of ancient DNA, will be pointed out.
With these limitations in mind, it will be shown that the acquisition of aDNA data at different dates and places across the continent now permits to catch a glimpse of how human genetic diversity has changed spatially and temporally in Europe, from the Palaeolithic through the present-day. Although determination of early modern human DNA sequences are confined to rare exceptionally well-preserved specimens, genetic samples of reasonable size are becoming available for the Mesolithic and the Neolithic periods. This accumulation of data allows a direct comparison of the gene pool composition in the last hunter-gatherers, the early farmers, and the current local populations, and already permits to discuss regional variation in the inferred mode of the spread of farming. Palaeogenetic data are also collected for more recent periods and regularly demonstrate genetic discontinuity between past and present populations. Thus, palaeogenetic evidence clearly indicates that contemporary European ancestry is not a living fossil of the Palaeolithic or Neolithic maternal deme. Only large diachronic aDNA datasets from throughout Europe will permit researchers to reliably identify all demographic and evolutionary events which shaped the modern European gene pool.

14h55 **Origins, admixture and population structure in European Romani: insights from the genome**

Prof. David Comas
Universitat Pompeu Fabra, Barcelona, Spain

Despite the large efforts performed to unravel the population history of Europeans through genetic markers, there are still some European minorities and isolates that have not been properly studied. This is the case of the Romani, also known as Gypsies, the largest minority group in Europe that consists of approximately 11 million people. The Romani people lack written historical records on their origins and dispersal. Linguistic and anthropological data have pointed to a southern Asian origin of the Romani who arrived to Europe in historical times.

The analysis of uniparental inherited genomes, mitochondrial DNA and Y-chromosome markers, has shown a mixture of European lineages and lineages frequent in India, suggesting an Indian origin of the Romani with subsequent admixture with non-Romani Europeans. In addition, the genetic diversity of the uniparental lineages is reduced, which points to a founder effect of the Romani groups.

The analyses of genome-wide data from several Romani groups collected across Europe confirm an Indian origin for European Romani, consistent with the data from uniparental lineages and linguistic studies. The genome-wide evidence specifies the geographic origin of Romani towards the north/northwestern parts of India and provides a date of origin of about 1,500 year ago. After limited gene flow from the Middle East, the Romani people settled in the Balkan region and began spreading across Europe about 900 years ago through serial bottlenecks that have modeled the genetic architecture of the Romani groups.

16h05 **Dissecting the genetic history of a human population: A decade of research about Icelanders**

Prof. Agnar Helgason
DeCode Genetics, Reykjavík, Island

Iceland was settled 1100 years ago, during the Viking age, as a part of an expansion of Norse invaders across much of Northwestern Europe, which had a particularly long-lasting cultural and genetic impact on the populations in the North Atlantic. My talk will summarize the outcome of just over a decade of research at deCODE Genetics focusing on the genetic history of the Icelandic population. I will explain how genealogies and genetic data from modern and ancient Icelanders have been used to shed light on questions about the origins of the first settlers 1100 years ago and the subsequent evolutionary history of the population, including its brief foray to Greenland and Newfoundland (Vinland). My talk will also explore the settlement of Iceland in the context of other populations in the North Atlantic region, such as Shetland, Orkney and the Faroe Islands, and what this can tell us about the behaviour of the Norse during the Viking age.

Wednesday 16 January 2013

Session 3 **Genetic history of Europe: current hypotheses**

Chair: Prof. David Comas, Universitat Pompeu Fabra, Barcelona, Spain

09h00 **Genetic evidence for prehistoric demographic changes in Europe**

Prof. Guido Barbujani

Università di Ferrara - Dipartimento di Biologia ed Evoluzione, Ferrara, Italy

It is not clear yet to what extent DNA diversity in modern Europeans reflects either a genetic continuity since Paleolithic times, or a discontinuity associated with the expansion of early Neolithic farmers from the Levant. The genetic gradients encompassing much of the continent are generally viewed as supporting a model of Neolithic demic diffusion; the ancient coalescence times of most European mitochondrial lineages have long been regarded as evidence of a population structure established in the Paleolithic period. Both views have been seriously challenged recently. On the one hand, it has become apparent that the European clines do not necessarily correspond to those expected under Neolithic demic diffusion; on the other, studies of ancient DNA have shown that mtDNA variants labeled as Paleolithic were common among Neolithic people as well, proving that the ages of molecules do not contain information on demographic changes.

The above models are schematic outlines of phenomena that must have been more complex, with both Paleolithic and Neolithic processes shaping genetic diversity in different parts of Europe. Still, at the mtDNA level, modern Europeans have closer genealogical relationships with Neolithic than with Paleolithic people, above and beyond what would be expected given their distance in time, suggesting that a significant demographic change accompanied the Neolithic shift from hunting-gathering to agriculture. Questions that need be addressed include: (1) Are the two main models different enough to be distinguished in genetic analyses? (2) While we wait for sufficiently large ancient DNA nuclear datasets to accumulate, how much can we trust inference from mitochondrial DNA? and (3) Do we already have sufficient archaeological information to construct a mixed model, incorporating at various locations either genetic continuity since Paleolithic times or Neolithic demographic shifts?

09h55 **Investigating European genetic history through computer simulations**

Dr Mathias Currat
University of Geneva - Department of Genetics and Evolution, Switzerland

The genetic diversity of current Europeans has been shaped by various factors, among which one of the most significant is the demographic history of their ancestors. During prehistory, human were highly mobile, they colonized new areas at different time periods and once those new lands have been settled, populations still exchanged migrants at various rates, depending on the geographic landscape and on their cultural affinities. Due to their complexity, those movements over space and time are hardly taken into account in the analyses of genetic data. Fortunately, the computer simulation approach offers a powerful tool to study complex models and it has been increasingly applied to European prehistory recently. During this talk, we are going to present and explain how past population demographic variation and migration can be simulated using a specific computer program, and how the resulting genetic consequences can be investigated. We are going to highlight the main advantages of this approach over alternative methods. For instance, various source of information (genetics, archaeological, environment) may be easily integrated in the models, which is particularly useful to get insight about the prehistory of Europe. We will then summarize the main results obtained with computer simulations regarding European genetic history, with a focus on the main phases of population expansions and contractions which potentially occurred in that continent since the arrival of modern humans. Finally, we will present current and future improvements of the method, such as the incorporation in the simulations of ancient DNA extracted from bone remains. We are convinced that the kind of approach presented in our paper has a huge potential for drawing inferences about human evolution.

11h05 **HLA in Europe: immunogenetic diversity of Europeans from an evolutionary point of view**

Prof. Alicia Sanchez-Mazas
University of Geneva - Department of Genetics and Evolution, Switzerland

HLA genes are known to exhibit a particularly high level of polymorphism in the human genome. The largest part of this molecular variation lies in the exons encoding the peptide-binding region (PBR) of the HLA molecules, and is thus likely to be functionally significant. The crucial role played by HLA in the defense of our organism against pathogens may also explain why the majority of individuals are heterozygous for HLA genes in human populations and why significant associations are found between HLA alleles and many autoimmune and infectious diseases. On the other hand, HLA genetic patterns explored at the worldwide or at continental levels have always shown clear signatures of human demographic and migrations' history, e.g. significant correlations with geography and reduced diversity in small stationary populations like Taiwanese Aborigines or Amerindians. Actually, the few studies that tried to disentangle the effects of selective and stochastic forces shaping HLA genetic diversity concluded to a rather small effect of natural selection.

Thanks to our initiative to collaborate with many HLA laboratories worldwide and at the European level through several International HLA workshops and the COST *HLA-NET* Action, we were recently able to bring together a large collection of HLA molecular data for European and pan-European populations, including newly investigated regions like the Balkans and the Russian areas. For the first time, we provide a fine description of HLA variation across Europe and its surroundings, which reveals, among other results, a remarkable differentiation of Southeastern populations. Given the complex evolution of the HLA polymorphism, we propose to discuss these results in relation to European peopling history (e.g. the role of the Alps as a geographic barrier to gene flow), immune adaptation (e.g. the effect of heterozygous advantage in pathogen-rich environments) and associations to diseases (e.g. cœliac disease in relation to wheat consumption). A take-home message of our presentation is that the great genetic diversity observed in Europe contradicts the widespread idea that Europeans share a homogeneous « Caucasian » genetic pool. Besides its possible contribution to change our views on human racial classifications, this final conclusion is most important for epidemiological research where disease-association studies need really reliable control populations.

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Session 4 **European genetic diversity in relation to public health**
Chair: Prof. Gottfried Fischer, Medical University of Vienna, Austria

13h30 **European genetics in relation to tissue transplantation**
Prof. Frans Claas
Leiden University Medical Center/ Eurotransplant Reference Laboratory, Leiden, the Netherlands

Genes within the HLA complex code for the very polymorphic HLA class I and Class II molecules, which are the main targets for alloimmune responses leading to graft rejection. The best transplant results are obtained with a fully HLA matched donor but the chance to find such a donor in an unrelated situation if rather low. Expanding the potential donor pool will increase the chance to find a well-matched donor for a patients. This was the basis for the foundation of Eurotransplant by Jon van Rood in 1967. Currently, all renal transplant candidates from Austria , Belgium, Croatia, Germany, Luxemburg, Slovenia and the Netherlands (and in the near future Hungary) are put on common waiting list and kidneys from all deceased donors from these countries are allocated via a transparent point system. This collaboration has led to a degree of HLA matching, which would not have been possible without this policy. However, current immunosuppressive drugs are very potent and graft survival of mismatched transplants has improved significantly. This international collaboration is currently more relevant for highly sensitized patients. The presence of antibodies against the HLA antigens of the donor is a contra-indication for transplantation as this may lead to hyperacute rejection. A serological crossmatch is performed in order to prevent this. The problem is that highly sensitized patients, who have antibodies against many HLA antigens , will often have a positive crossmatch and remain on the waiting list. A special strategy has been developed to enhance transplantation of these highly sensitized patients, which is based on the definition of those HLA antigens toward which the patient did not make antibodies. By giving priority to a highly sensitized patient when a donor with the so called acceptable mismatches becomes available , the transplantation rate of this difficult patient group has increased significantly within Eurotransplant. The results of these transplants are excellent. However for about 30% of the highly sensitized patients this strategy does not work as the HLA phenotype of the patient does not occur in the Eurotransplant donor population. Similar situations occur in other transplant organizations within Europe. As HLA phenotype frequencies differ enormously between the different European populations, an FP7 project called EUROSTAM has recently been initiated in order to look for suitable donors in other populations outside Eurotransplant taking advantage of the achievement of the HLA-NET consortium. It is to be expected that this approach will be of benefit for this subgroup of highly sensitized patients.

14h25 **Genetics of European populations in allogenic stem cell transplantation**

Dr Jean-Marie Tiercy
Lab. Immunologie Transplant. Geneva, Switzerland

Allogenic hematopoietic stem cell transplantation (HSCT) is a well recognized treatment for a number of hematological malignancies, including leukemias, lymphomas, and other disorders of the immune system. More than 50% of the transplantations are now performed with HSC from volunteer unrelated donors registered in 66 donor registries and 47 cord blood banks connected through the international Bone Marrow Donor Worldwide organisation. The success of transplantation has improved with the higher degree of patient/donor matching allowed by the implementation of DNA-based high resolution HLA typing techniques. However the extremely high level of HLA allele and haplotypic polymorphism has increased the difficulties in identifying a perfectly matched donor. In particular, because most donors in the Bone Marrow Donor Worldwide (BMDW) registry are of European descent, searches for patients of other ethnic backgrounds have a lower success rate, particularly for those patients with a mixed origin. Overall still 5% patients do nat have a single HLA-A,B,DRB1 matched donor in BMDW. Among those patients for whom at least one potential donor is listed in the BMDW database, about 50% will eventually find a highly matched donor, and another 20% a donor with a single HLA compatibility. More than 8 million HLA-typed volunteer donors are now available in European registries, which show a large diversity of allele/haplotype frequencies that correlate best with geography. In view of the large diversity of HLA haplotypes present in patients treated in individual centers it is of utmost importance to support recruitment strategies that include the largest possible number of regions in Europe. Even small registries allow a representation of rare HLA haplotypes that might not be found in national registries of several million donors each. Disclosure of regional variability in HLA haplotypes (e.g. HLA-B-C associations) as detected by high resolution typing has an impact on donor search algorithms.

15h35 **Individualized and population genomics**

Prof. Emmanouil Dermitzakis
Dept of Genetic Medicine and Development, University of Geneva Medical School, Switzerland

Molecular phenotypes are important phenotypes that informs about genetic and environmental effects on cellular state. The elucidation of the genetics of gene expression and other cellular phenotypes are highly informative of the impact of genetic variants in the cell and the subsequent consequences in the organism. In this talk I will discuss recent advances in three key areas of the analysis of the genomics of gene expression and cellular phenotypes in human populations and multiple tissues and how this assists in the interpretation of regulatory networks and human disease variants. I will also discuss how the recent advances in next generation sequencing and functional genomics are bringing closer our hopes for personalized medicine.