

# JASs Research news

## A Cover Story for a Nature cover: genetic signature of human expansions into Eurasia revealed by a panel of worldwide high coverage genomes

**Luca Pagani**

Dipartimento di Biologia, Università di Padova, Italia; Estonian Biocentre, Tartu, Estonia  
e-mail: lp.lucapagani@gmail.com



We are an African species, and as such it is clear that in order for *Homo sapiens* to be present in all habitable lands worldwide, some major expansion must have occurred at some point during our evolutionary history. The so called “Out of Africa” expansion (OoA), being crucial to the formation of all modern non-African human populations, has long been subject of study and debate in the broader field of Human Evolution. Understanding the dynamics and timing of such an event is therefore a major challenge to shed light on the human peopling of Eurasia.

According to the fossil human remains available so far, our species was present in West Asia at least since 120 thousand years ago (kya) (Groucutt *et al.*, 2015; Grove *et al.*, 2015). However it is unclear whether these remains should be interpreted as the beginning of OoA, or as a failed expansion (Mellars *et al.*, 2013) or just as a simple extension of the African occupation due to favourable climatic conditions. In light of craniometrical studies of African and Eurasian populations (Reyes-Centeno *et al.*, 2014) and recent availability of additional fossil data from eastern Asia (Groucutt *et al.*, 2015; Liu *et al.*, 2015), one may see these as preliminary evidence of an early dispersal.

From a genetic viewpoint, previous analyses of living populations have revealed a steady decline in genetic diversity with distance from Africa, which is consistent with a serial founder event model (Prugnolle *et al.*, 2005; Ramachandran *et al.*, 2005; Li *et al.*, 2008). Furthermore the genetic landscape emerging from uniparental markers such as mitochondrial DNA (mtDNA) and Y chromosome would point to a single expansion event that took place not earlier than 70kya (Soares *et al.*, 2012). Furthermore, the most recent genomic evidence pointed to a Northern route (i.e. through Sinai, rather than across the Red Sea and South Arabia) (Pagani *et al.*, 2015) as the predominant path followed by the ancestors of Eurasians when expanding from Africa after 70kya (Schiffels & Durbin, 2014).

The resolution of this emerging picture was increased by the availability of archaic human sequences, which revealed how all non-Africans derive from an admixture episode between humans and Neanderthal, at around 55kya (Green *et al.*, 2010), while modern Papua New Guineans and Australians also display genetic traces from another, recently characterized archaic hominin (Denisova) (Reich *et al.*, 2011). Therefore, before our research begun, the available evidence were pointing towards a model (Gravel *et al.*, 2011; Meyer *et al.*, 2012) depicting modern humans outside of Africa as the result of a single dispersal event that was followed by admixture with archaic humans (Green *et al.*, 2010; Meyer *et al.*, 2012).

As it appears clear from the geographical distribution of the collected samples, our study (Pagani *et al.*, 2016) was not explicitly designed for refining current knowledge of the OoA. When it started, the main scientific aim of the international collaboration coordinated by the Estonian Biocentre of Tartu was to provide a comprehensive catalogue of the Eurasian human genomic diversity, to serve as the starting point for future spatially explicit analyses and detection of regional signatures of natural selection. To achieve this in a budget-aware manner, we followed an innovative sampling strategy aimed at maximizing the number of sampled populations (we ended up gathering 125 human groups worldwide), at the expenses of the number of sequenced individuals per group (on average three to four samples per population). That said, the researchers at the EBC had been part of a large collaborative study led by Dr. Eske Willerslev at the Centre for GeoGenetics of Copenhagen, which sequenced the first complete genome of a native Australian individual in 2011 (Rasmussen *et al.*, 2011). This study suggested that the genetic history of native Australians has a chapter that is different from that of the Eurasians. We were of course keen to follow this up and there for made sure that we had Papuan and native Australian samples in the panel.

Soon after work started toward assembling of our sample panel we were approached by Dr. David Reich from Harvard with an offer to join into a similar sequencing effort he was leading. The panels were to be sequenced with different technologies and also the sampling schemes were not entirely duplicating each other but also complementary so EBC was happy to join. We decided early on to synchronize our scientific submissions, to avoid racing our scientific work at the expenses of quality and accuracy. During later stages of the project Dr. Eske Willerslev, who was leading a study that concentrated on sequencing a large number of Papuan and specifically native Australian genomes, suggested to enlarge the synchronized collaboration effort and to coordinate the submission of all three studies. Both Tartu and Harvard saw this as a great opportunity to draw more attention to human evolutionary genomics as a discipline. This effort led to the simultaneous publications of our work together with other two papers led by Anna Sapfo Malaspina (Malaspina *et al.*, 2016) and Shop Mallick (Mallick *et al.*, 2016), respectively. All three papers confirmed with an astonishing amount of genomic data that all modern non-Africans derive their genome from a single expansion performed by a human group that diverged from West Africans at around 75kya. At a closer inspection, though, we noticed a minor exception to this otherwise clear scenario: the modern Papua New Guinean samples we analysed seemed to have traces of a more ancient human expansion! Our Papua New Guineans indeed displayed a genetic divergence from modern Africans that was at least 15kya deeper than the one detected from all other non-African samples. We initially thought that the documented presence of an additional archaic human (Denisova) component in Oceania (Reich *et al.*, 2010) could explain the observed phenomenon, making our samples looking more “ancient” at those sites where their genome was derived from Denisova. Surprisingly, after correcting for this bias via effectively removing these archaic sequences from the dataset, we noticed that the signal remained as clear and as puzzling as before. We then inspected the genetic features of the Papuan sequences we thought responsible for this signal and found that these were compatible with the signature of a now extinct modern human population that probably have left Africa as early as 120ky ago. We then concluded that modern Papua New Guineans, while deriving the vast majority of their genome from the already described OoA event, have also incorporated within their genes the presence of an early human group they may have encountered on their way to the island, and that had left Africa much earlier, as part of an otherwise extinct OoA expansion.

Due to its mysterious and now extinct nature, we dubbed this expansion “xOoA” and we speculate these people may help explain who left a genetic trace in the genome of some Neanderthals at around 100kya (Kuhlwilm *et al.* 2016), or who left fossil remains in China some ~80kya (Liu *et al.*, 2015). However it is important to note that, perhaps due to differences in the adopted statistical approaches, the other two international consortia mentioned above did not find evidence in support for this extinct expansion, while they also did not rule out a potential minor contribution of such earlier migration. As with any scientific debate, I am confident that additional analyses aided by adequate advances in available software may help clarifying our results.

Another challenge we faced during our work was the need to represent results in a graphic and intelligible way. We wanted to keep as much information as possible on the described OoA expansion(s), with particular attention to the time and spatial dimensions. An established way of representing human movements through space and/or time is to trace arrows on a map followed by annotations of relevant time check-points. In our case an arrow starting from Africa and expanding all the way to Papua New Guinea would represent “xOoA”, while another arrow all over Eurasia would be the major OoA. We realized, however, that besides the beginning and the endpoint of these expansions, we had no clear evidence on the path followed by these early human populations. The arrow shafts, therefore, would have risked delivering the erroneous meaning of “exact trajectory followed by”, while our intention was simply to represent a “point A and point B connected by some movement of people in between”. We therefore got inspired by the topological intuition that led Harry Beck to developing the first London Tube diagram, and called it a “Subway plot”. The Subway plot designed by Mait Metspalu, senior author of our work, represents human dispersals as “subway lines”, leading from one point to another in a way that is agnostic to the actual path they follow, and it shows admixture events as “exchange stations”, where two lines cross and exchange genes. I must say we are very proud of this artistic solution and we hope this may provide useful when describing additional events of our evolutionary history.

## References

- Gravel S., Henn B.M., Gutenkunst R.N., Indap A.R., Marth G.T., Clark A.G., Yu F., Gibbs R.A. & Bustamante C.D. 2011. Demographic history and rare allele sharing among human populations. *Proc. Natl. Acad. Sci. USA*, 108: 11983-11988.
- Green R.E., Krause J., Briggs A.W., Maricic T., Stenzel U., Kircher M. *et al.* 2010. A draft sequence of the Neandertal genome. *Science*, 328: 710-722.
- Groucutt H.S., Petraglia M.D., Bailey G., Scerri E.M., Parton A., Clark-Balzan L., Jennings R.P., Lewis L., Blinkhorn J., Drake N.A. *et al.* 2015. Rethinking the dispersal of Homo sapiens out of Africa. *Evol. Anthropol.*, 24: 149-164.
- Grove M., Lamb H., Roberts H., Davies S., Marshall M., Bates R. & Huws D. 2015. Climatic variability, plasticity, and dispersal: A case study from Lake Tana, Ethiopia. *J. Hum. Evol.*, 87: 32-47.
- Kuhlwilm M., Gronau I., Hubisz M.J., de Filippo C., Prado-Martinez J., Kircher M., Fu Q., Burbano H.A., Lalueza-Fox C., de la Rasilla M. *et al.* 2016. Ancient gene flow from early modern humans into Eastern Neanderthals. *Nature*, 530: 429-433.

- Li J.Z., Absher D.M., Tang H., Southwick A.M., Casto A.M., Ramachandran S., Cann H.M., Barsh G.S., Feldman M., Cavalli-Sforza L.L. & Myers R.M. 2008. Worldwide human relationships inferred from genome-wide patterns of variation. *Science*, 319: 1100-1104.
- Liu W., Martinon-Torres M., Cai Y.J., Xing S., Tong H.W., Pei S.W., Sier M.J., Wu X.H., Edwards R.L., Cheng H. *et al.* 2015. The earliest unequivocally modern humans in southern China. *Nature*, 526: 696-699.
- Malaspinas A.S., Westaway M.C., Muller C., Sousa V.C., Lao O., Alves I., Bergström A., Athanasiadis G., Cheng J.Y., Crawford J.E. *et al.* 2016. A genomic history of Aboriginal Australia. *Nature*, 538: 207-214.
- Mallick S., Li H., Lipson M., Mathieson I., Gymrek M., Racimo F., Zhao M., Chennagiri N., Nordenfelt S., Arti Tandon A. *et al.* 2016. The Simons Genome Diversity Project: 300 genomes from 142 diverse populations. *Nature*, 538: 201-206.
- Mellars P., Gori K.C., Carr M., Soares P.A. & Richards M.B. 2013. Genetic and archaeological perspectives on the initial modern human colonization of southern Asia. *Proc. Natl. Acad. Sci. USA*, 110: 10699-10704.
- Meyer M., Kircher M., Gansauge M-T., Li H., Racimo F., Mallick S., Schraiber J.G., Jay F., Prüfer K., de Filippo C. *et al.* 2012. A High-Coverage Genome Sequence from an Archaic Denisovan Individual. *Science*, 338: 222-226.
- Pagani L., Lawson D.J., Jagoda E., Mörseburg A., Eriksson A., Mitt M., Clemente F., Hudjashov G., DeGiorgio M., Saag L. *et al.* 2016. Genomic analyses inform on migration events during the peopling of Eurasia. *Nature*, 538: 238-242.
- Pagani L., Schiffels S., Gurdasani D., Danecek P., Scally A., Chen Y., Xue Y., Haber M., Ekong R., Oljira T. *et al.* 2015. Tracing the Route of Modern Humans out of Africa by Using 225 Human Genome Sequences from Ethiopians and Egyptians. *Am. J. Hum. Genet.*, 96: 986-991.
- Prugnolle F., Manica A. & Balloux F. 2005. Geography predicts neutral genetic diversity of human populations. *Curr. Biol.*, 15: R159-R160.
- Ramachandran S., Deshpande O., Roseman C.C., Rosenberg N.A., Feldman M.W. & Cavalli-Sforza L.L. 2005. Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa. *Proc. Natl. Acad. Sci. USA*, 102: 15942-15947.
- Rasmussen M., Guo X., Wang Y., Lohmueller K.E., Rasmussen S., Albrechtsen A., Skotte L., Lindgreen S., Metspalu M., Jombart T. *et al.* 2011. An Aboriginal Australian Genome Reveals Separate Human Dispersals into Asia. *Science*, 333: 94-98.
- Reich D., Green R.E., Kircher M., Krause J., Patterson N., Durand E.Y., Bence Viola B., Briggs A.W., Stenzel U., Johnson P.L.F. *et al.* 2010. Genetic history of an archaic hominin group from Denisova Cave in Siberia. *Nature*, 468: 1053-1060.
- Reich D., Patterson N., Kircher M., Delfin F., Nandineni M.R., Pugach I., Ko A.M., Ko Y.C., Jinam T.A., Phipps M.E. *et al.* 2011. Denisova admixture and the first modern human dispersals into Southeast Asia and Oceania. *Am. J. Hum. Genet.*, 89: 516-528.
- Reyes-Centeno H., Ghirotto S., Detroit F., Grimaud-Hervé D., Barbujani G. & Harvati K. 2014. Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia. *Proc. Natl. Acad. Sci. USA*, 111: 7248-7253.
- Schiffels S. & Durbin R. 2014. Inferring human population size and separation history from multiple genome sequences. *Nat. Genet.*, 46: 919-925.

Soares P., Alshamali F., Pereira J.B., Fernandes V., Silva N.M., Afonso C., Costa M.D., Musilova E., Macaulay V., Richards M.B. *et al.* 2012. The Expansion of mtDNA Haplogroup L3 within and out of Africa. *Mol. Biol. Evol.*, 29: 915-927.



This work is distributed under the terms of a Creative Commons Attribution-NonCommercial 4.0 Unported License <http://creativecommons.org/licenses/by-nc/4.0/>