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Ancient human migrations

Alte Völkerwanderungen

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Abstract: *Humans show a remarkable ability to adapt to various climates and environments. Today they can be found on almost every continent, from the coastlines of Arctic Greenland to the tropical Amazon rainforests. Their ability for innovation and exploration lead them to inhabit and adapt to almost every possible place on earth. However this is a rather recent development within the last 5 million years. Only about 50 000 years ago, with the spread of anatomically modern humans from Africa into the rest of the world, humans started to explore rapidly almost every possible environment, including Australia and the New World. Other regions, such as Europe and Asia, however, were already settled by other hominins (humans and their ancestors) such as Neandertals, when modern humans first migrated in those regions. Based on results from various disciplines I will here discuss our current understanding about the spread of modern humans from Africa into the world as well as potential interactions with archaic hominins during those ancient migrations. In particular I will focus on the contribution of genetic studies to reconstruct our recent evolutionary past and to identify biological changes that are potentially responsible for the rapid spread and large success of anatomically modern humans. Before going into detail I will start with a short introduction to some of the various disciplines that study human evolution and our current understanding of the first 5 million years of our evolutionary past. By default this will be far from complete.*

Zusammenfassung: *Menschen zeigen eine bemerkenswerte Fähigkeit, sich verschiedenen Klimazonen und Umgebungen anzupassen. Heute findet man sie auf fast jedem Kontinent, von der arktischen Küste Grönlands bis zum tropischen Amazonas-Regenwald. Ihre Fähigkeit zu Innovation und Entdeckungen führte sie dazu, fast jeden Ort der Welt zu besiedeln. Dies ist aber ein relativ junges Kapitel der Menschheitsgeschichte. Erst vor ca. 50.000 Jahren mit der Ausbreitung des anatomisch modernen Menschen aus Afrika in den Rest der Welt, begann der Mensch schnell fast jede mögliche Umwelt zu erforschen, einschließlich Australien und die „Neue Welt". Andere Regionen wie Europa und Asien wurden zuvor bereits von anderen Homininen, wie dem Neandertaler, besiedelt, bevor modernen Menschen in diese Gebiete einwanderten. Basierend auf den Ergebnissen aus verschiedenen Disziplinen, soll unser gegenwärtiges Verständnis über die Ausbreitung des modernen Menschen aus Afrika in die Welt, als auch die möglichen Wechselwirkungen mit archaischen Hominien vorgestellt werden. Insbesondere wird der Fokus auf den Beitrag genetischer Studien liegen, um unsere jüngste evolutionäre Vergangenheit zu rekonstruieren und biologische Veränderungen, die möglicherweise für die rasche Ausbreitung und den großen Erfolg des anatomisch modernen Menschen verantwortlich sind zu ergründen.*

Human evolution in a nutshell

Since the discovery of the first human fossils in the Neander Valley, close to Duesseldorf in Germany, in 1856, thousands of human fossils have been unearthed. They have triggered much debate, first questioning our divine creation and later leading to various hypotheses about the origin of our lineage. Many hypotheses, however, remain contested, often due to the fact that the fossil record is far from complete. This is best illustrated by the variable number of species assigned to the human lineage by different authors ranging from four to greater than twenty. Large gaps gape in our ancestry tree, and what was once thought as a straight line connecting apes and humans has turned out to be a thicket of branches with modern humans as the only remaining hominin (KRAUSE 2012). It is therefore important to complement paleoanthropology, the study of human fossils, with other approaches to study our evolutionary past. Disciplines such as archaeology for example focus on the cultural artifacts left behind by early humans, such as stone tools. Archaeologists try to understand the cultural evolution of hominins and the spread of innovations throughout space and time. Geologists are working on the age of archeological sites and hominin fossils to put them in a temporal context, whereas archaeozoologists and archaeobotanists are reconstructing the environment and food resources to which early hominins had access.

The picture that emerges from these various disciplines suggests that the early evolution of humans started in Africa about 5 to 7 million years ago when early hominins diverged from a common ancestor with chimpanzees. In the first few million years of hominin evolution our ancestors were more similar to apes than to modern humans. Even though upright walking, e.g. *Ardipithecus ramidus* that lived around 4.5 million years ago, their cranial capacity and body shape was more similar to that of the modern great apes (WHITE 2009). For most of our early evolutionary history, fossil evidence further suggests that several different forms of hominins roamed Africa simultaneously. They were likely adapted to different ecological niches, such as *Paranthropus robustus* as a robust herbivore or *Australopithecines* as diverse omnivores adapted to arboreal or savannah life (WOOD/CONSTANTINO 2007). There is no indication that any of the early hominins left Africa before 2 million years ago. That changed, however, when the first hominins of the genus *Homo* appear. This is usually marked by the appearance of *Homo habilis* around 2.1 million years ago (LEAKEY/TOBIAS/NAPIER 1964). Even though the designation of this hominin to our own genus is contentious, it marks the beginning of a transition from the ape like body type to anatomical features more similar to our own, e.g. a narrow pelvis, physical changes adapted for long distance travel and an increased brain size (BRAMBLE/LIEBERMAN 2004). It is thus not surprising that just a few hundred thousand years after the appearance of *Homo*, the first hominin forms called *Homo erectus* appear outside Africa in what is now Georgia and the island of Java around 1.9 million years ago (WOOD/COLLARD 1999; GABUNIA et al. 2000). Within a relatively short time *Homo erectus* spread from Africa to various parts of Asia. Also within Africa this hominin spread throughout the continent so that by 1.5 million years before present, all other African hominins disappear from the fossil record. *Homo erectus* is thus probably the most successful hominin in our evolutionary history: it can be found for more than 1.5 million years in large parts of Africa and Eurasia long before anatomically modern humans appear, and its range spans half the world from tropical environments to temperate mountainous regions of the Caucasus.

Around 500,000 years ago *Homo erectus* evolves in Africa into *Homo heidelbergensis*, a hominin with a larger brain capacity that is usually referred to as the last common ancestor of anatomically modern humans and Neandertals (WOOD/LONERGAN 2008). From Africa *H. heidelbergensis* spreads into Europe and evolves there into Neandertals starting around 400,000 years ago (STRINGER/HUBLIN 1999). In Africa *H. heidelbergensis* gives rise to

anatomically modern humans, with the oldest fossil remains from Ethiopia that are around 200,000 years old (WHITE et al. 2003). From the fossil record it is rather unclear how long *H. erectus* survived in Asia. Early claims that suggested a late survival on the island of Java were recently refuted (INDRIATI et al. 2011). The discovery of *Homo floresiensis* suggests that at least some archaic *Homo erectus*-like hominins survived in Asia (BROWN et al. 2004). This enigmatic hominin with a chimpanzee-sized brain and small stature that is thought to be a dwarfed form of early homo still existed on the island of Flores, in what is now Indonesia, when modern humans first appeared there. Other fossils such as the Dali and Maba skulls from southern China that are both less than 200,000 years old show a morphology rather similar to *H. heidelbergensis* (WOOD/LONERGAN 2008).

The oldest fossils of anatomically modern humans discovered outside Africa were surprisingly found in Lake Mungo in Australia and are about 45,000 years old, thus thousands of years older than fossils attributed to modern humans found in Europe and Asia (BOWLER et al. 2003). This lead to the theory that there were at least two migration routes from Africa into Eurasia, one along the coast lines called the "southern route" and one throughout central Asia called the "northern route" *(Fig. 1)* (WELLS 2002).

At the same time when the modern human morphology appears in fossils in Eurasia the archaic body type, e.g. as presented by Neandertals, disappears. Archaeological evidence also suggests that around 60,000 to 40,000 years ago a major transition occurred in human behavior. This is based on the sudden appearance of new types of stone tools, such as micro blades as well as evidence for symbolic art such as figurines and pendants outside Africa (CONARD/BOLUS 2003). Until recently it remained contentious as to whether those cultural innovations were transported with people leaving Africa or whether they represented an evolutionary process that was happening in parallel in many regions in the world. The latter hypothesis is referred to as the "multi-regional model" and the former the "out of Africa model". Both models were intensely debated for almost two decades at the end of the 20th century. The result is, however, not contested with either hypothesis. In the last 30,000 years, modern humans have spread into every habitable place on Earth and the question of whether this was accomplished via a worldwide parallel evolution, a replacement, or an assimilation of other archaic hominins was best answered not by the physical analysis of new fossils or stone tools, but rather by the seemingly unrelated field of molecular biology.

Ancient molecular studies

Molecular investigations have a different approach to study the fossil record by comparing structural differences in organic molecules such as proteins and nucleic acids that have been not yet completely degraded. Under ideal preservation conditions such molecules can survive several hundred thousand years, thus allowing a direct comparison and an establishment of the phylogenetic relationships between past and present populations. The main reason is the stability of DNA in time: since it is used by all living organisms as the blue print for all its building blocks, it is thus extremely stable and can survive hundreds of thousands of years (PAABO 2004). With more than 3 billion positions in most mammals it is also comprised of long strings of information that can be decoded and compared between closely related organisms. Each of the 3 billion positions can be found in four different states that are usually depicted with A, C, T or G, which reflect different molecular building blocks called bases. The more bases in common, the more closely related two organisms are.

There are two structures in a normal animal cell that contain DNA: the cell nucleus and the mitochondrion. The former carries both sets of chromosomes that mammals receive from their parents, whereas the mitochondrial DNA (mtDNA) is passed on by the female line only

and shows hundreds of identical copies in each cell, dozens in each mitochondrion. This is also the reason why mtDNA is still the most popular genetic region studied from fossil remains, simply because there is more of it in each piece of fossil bone.

Due to a process called mutation, the sequence of bases in a string of DNA can change. Those mutations rain down on the genome in every generation in a rather constant rate. Every human passes about 40 to 60 changed bases on to its progeny. Most of those mutations have no negative effect on the carrier. This is mostly due to the fact that only about 1.5% of our genome consists of what we consider genes, a region of the genome that is coding for a building block of our cells, either proteins or structural RNA (LANDER 2011). The rest of the genome might be important for the regulation of gene activity and structural organization. However, the vast majority of the genome does not fulfill any known purpose (LANDER 2011). Most of our DNA can therefore change without negative consequences for the carrier (NEI/SUZUKI/NOZAWA 2010). Those changes are passed on over generations and accumulate over time. Changes in these non-coding portions of the DNA that are shared between two individuals indicate often a closer relationship of the two compared to the rest of the population, since it is rather unlikely that the same change would occur in 3 billion positions randomly at the same place in the genome, especially when every base can change into three other bases. Hence DNA is the perfect organic molecule to reflect relationships in a quantifiable and directed way.

The first attempt to study DNA from archaic human fossils was made in the mid 1990s when a team led by Svante Pääbo managed for the first time to decipher a short region of Neandertal DNA from the type specimen discovered in 1856. The retrieved mtDNA sequence was different from all modern human mtDNAs on the planet today and the Neandertal mtDNA formed a separate branch on the human phylogenetic tree, suggesting that Neandertals are an extinct side branch and not the direct ancestors of modern humans (KRINGS et al. 1997). This finding provided direct support for the controversial hypothesis of a recent African origin of anatomically modern humans. Over the last 25 years more than a dozen Neandertals ranging from the Iberian Peninsula to southern Siberia were genetically studied confirming the initial results. Together with modern genetic data from worldwide contemporary modern populations and additional fossil evidence it became commonly accepted over the last years that modern humans left Africa around 50-60,000 years ago and spread into Asia, Australia and Europe within the following 10,000 years. Only the beginning of the last big glacial period between 28k and 12k years BP stopped modern humans from exploring even further into the new world; however, as soon as the glaciers melted away, the first modern humans spread rapidly into North and South America. As a result, modern humans had settled in every large landmass except Antarctica by 1000 years BP.

What makes modern humans?

Much was speculated about the reason why anatomically modern humans were so successful in rapidly colonizing the world, spreading from Africa and replacing all other hominins that had lived for hundreds of thousands of years in Eurasia. Some scientists believe that a few mutations in our DNA suddenly gave rise to modernity (KLEIN 2009) others think about it as a slow process that took largely place in Africa over a period of 100.000 years crossing a certain threshold around 50.000 years ago that enabled early modern humans to leave Africa with a complete modern cultural package (MCBREARTY/BROOKS 2000). In principle genetics should be able to address at least the first hypothesis by studying genetic changes that are unique to modern humans when compared to archaic humans such as Neandertals.

One of the first such candidate genes considered to explain cultural modernity in modern humans is a gene related to language abilities. It was first discovered in an English family were several family members showed a specific language disorder that does not allow the affected individuals to articulate proper words. They furthermore suffer from major difficulties with grammar, word order, and fine motor skills. The same severe phenotype was also found in other non-related patients. A genome wide study showed that all affected individuals carry mutations in a gene called FOXP2. All patients carried only a single functional version of the gene, where the second allele was disrupted or the resultant protein structure altered, producing a non functional protein (FISHER et al. 1998). It could be furthermore shown that the FOXP2 gene, despite being largely conserved between mammals, had acquired two amino acid changes in the last 5 million years of human evolution (ENARD et al. 2002). As a result the human and chimpanzee FOXP2 version show two amino acid differences whereas chimpanzee and mouse show only a single amino acid difference, despite the fact that both are rather distantly related. Functional studies with transgenic mice, where the mouse FOXP2 gene was replaced by the human FOXP2 gene, furthermore showed an effect of the human version on mouse vocalization as well as neuron growth patterns. Those findings support the idea that the human FOXP2 gene had changed on the human lineage to enable the evolution of language (ENARD et al. 2009). Such a mutation would thus be a prime candidate to explain cultural modernity and the rapid spread of anatomically modern humans. The analysis of the FOXP2 gene in two Spanish Neandertals showed, however, that Neandertals carried the same version of the FOXP2 gene as modern humans do (KRAUSE et al. 2007), suggesting that the mutations in the FOXP2 gene are at least 400.000 years old. Thus, at least from the point of this gene, nothing speaks against the notion that Neandertals already possessed the same language skills as modern humans.

Even though the approach as described for the FOXP2 gene provides information about certain candidate genes in archaic humans that might have changed recently in our evolution, it is like looking for the needle in the hay stack to test each gene in order to find mutations that might explain the cognitive differences between Neandertals and anatomically modern humans and thus the biological basis of human modernity. More promising is a genome-wide comparison to compare modern human genomes with archaic human genomes, e.g. the Neandertal genome, in order to catalogue all changes between modern and ancient hominins.

The Neandertal Genome

In 2010 the first draft genome of an archaic human, the Neandertal, was published. It was a composite genome of seven Neandertal fossils from the original type site in Germany, the Caucasian mountains in Russia, a Northern Spanish cave and a cave from Croatia in Southern Europe (GREEN et al. 2010). The archaic genome represents a tremendous achievement that was made possible by the development of next generation sequencing (NGS) technologies. The throughput of those machines increased by seven orders of magnitude within the last seven years, allowing dozens of contemporary human genomes to be sequenced within a few days, on a single machine, for less than a thousand dollars (STONEKING/KRAUSE 2011). This is a stark contrast to the first human genome that was sequenced, taking almost 13 years and costs of more than 2 billion dollars. Besides having a remarkable impact on modern genetics NGS machines also revolutionized the field of ancient DNA, allowing millions of DNA fragments to be sequenced from ancient fossils.

The DNA fragments sequenced from the Neandertals were found to be rather short in length, only about 50 positions in average. It was furthermore shown that the vast majority of DNA (more than 95%) retrieved from the Neandertal fossils was rather of microbial ori-

gin than actual human DNA (GREEN et al. 2006). It was thus necessary to sequence more than a billion DNA fragments in order to obtain a first draft overview of the Neandertal genome. In total more than 4 billion bases of Neandertal DNA could be reconstructed covering more than 60% of the genome (GREEN et al. 2010). In order to show that those DNA fragments were indeed of Neandertal origin and would not present potential contamination from modern human DNA of archaeologists or lab workers, regions of the mtDNA and nuclear DNA that are unique to Neandertals were compared to thousands of DNA fragments that overlapped those differences. It was found that at least 99.2% of the human DNA from the fossils represents authentic Neandertal DNA.

The comparison of the Neandertal genome to that of various modern humans revealed that both populations had separated between 240,000 and 420,000 years BP (GREEN et al. 2010). It could furthermore be shown that only a small number of amino acid differences, fewer than 200, distinguish modern humans from Neandertals (BURBANO et al. 2010). This might be expected since both hominins are relatively closely related. It was, however, surprising that the genes that carried more than one amino acid change were related to pigmentation, suggesting phenotypic differences between modern humans and Neandertals in skin morphology (GREEN et al. 2010).

The Neandertal genome furthermore allowed to analyze regions in the modern human genome that have changed more than expected after the divergence from the common ancestor with the Neandertal. Such regions likely underwent a selective sweep, which is caused by a mutation that arises in an individual and spreads due to positive selection in the whole population. If present in a high frequency in modern humans and absent in Neandertals, it might indicate a certain selective advantage and those regions would be prime candidates to explain the success of modern humans in comparison to Neandertals. The region that showed the strongest signal of being under selection in modern humans, after separation from the Neandertal, carries a gene called THADA (GREEN et al. 2010). Mutations in this gene are well-known to increase the risk of type II diabetes. One might, therefore, speculate that this gene, that obviously plays a major role in human metabolism, has changed during our recent evolution, potentially as an adaptation to dietary changes. Surprisingly among the top 20 regions with the strongest signal of such a selective sweep, three regions carry genes that are known to be involved in neurological disease in modern humans such as schizophrenia, Down syndrome, and autism (GREEN et al. 2010). Mutations in those genes that caused the selective sweep might have played a role during the evolution of cognitive abilities in modern humans and could be thus responsible for the success and rapid spread of modern humans. It remains however to be tested in functional or association studies that the modern human version of those genes is indeed causing a different phenotype compared to the Neandertal version, like described above for the FOXP2 gene.

Another region that carried a strong selection signal carried a gene called RUNX2. Mutations in this gene are known to cause a severe disease called cleidocranial dysplasia. Patients with this rare disease show frontal bossing, a curved clavicle bone, and a bell-shaped rib cage, all three of which constitute morphological traits that distinguish Neandertals from modern humans. It is rather unlikely that the selective sweep that points to this gene is caused by selection of the modern human body type, however, this might be a side effect and may partially explain the differences in morphological features between modern humans and Neandertals (GREEN et al. 2010).

The Neandertal genome sequence has thus produced a number of potential candidate genes that will be tested in the future in animal models and cell lines in order to understand the functional consequences of certain genetic differences between Neandertals and ourselves. Some of those genes might explain the tremendous success of modern humans in comparison to Neandertals and other extinct hominins. It should, however, be mentioned that cul-

tural changes to the exclusion of biological differences may be responsible for the rapid expansion of modern humans outside of Africa. It is entirely likely that contributions were made from both, and it will however be hard to disentangle how cultural and biological adaptations have influenced each other.

Genetic admixture with Neandertals

The Neandertal genome allowed for an evaluation of the amount of genetic admixture between archaic humans and early modern humans after the latter left Africa some 50,000 year BP. This was achieved by sequencing genomes of modern humans from various populations in Africa and Eurasia and testing for the extent of genetic similarity between each individual population and the Neandertal. If all modern humans are equally related to the Neandertal, this would suggest that Neandertals made no genetic contribution to any one modern human population. Admixture of a modern human population with a Neandertal, however, would be reflected in a closer genetic distance of this particular population and the archaic human, and would thus permit the computation of the amount of Neandertal DNA in their genomes. The comparative analysis revealed that all populations outside Africa carry about 2.5% Neandertal DNA in their genome (GREEN et al. 2010). Since the same amount of admixture was found in modern Europeans, Chinese as well as people from Papua New Guinea, this surprising finding suggests that modern humans and Neandertals admixed with each other in the early stage of the out of Africa movement, likely around 50,000 years BP, most probably somewhere in the Near East (GREEN et al. 2010; STONEKING/KRAUSE 2011). The Neandertal contribution that modern humans received was subsequently distributed throughout the world and is now present in all populations outside Africa *(Fig. 1)*.

It is, however, surprising that even though Neandertals and early modern humans overlapped in Europe for almost 10,000 years, no additional admixture of Neandertals and modern Europeans was observed, despite them being biologically compatible. It remains to be shown if this might be explained by the fact that contemporary Europeans are not the direct descendants of the first early modern humans that settled in Europe some 40,000 years BP. Instead, modern Europeans may be a product of later migrations and a local replacement of the native European population at the end of the last ice age, e.g. during the Neolithic period, some 7000 years BP, when agricultural technologies spread throughout Europe. To address this question it will be necessary to test the amount of Neandertal DNA in the ancient genomes of the first modern humans that migrated into Europe before the last ice age. This, however, is rather challenging since contemporary contamination will be difficult to distinguish from ancient modern human DNA.

The Denisova hominin

Neandertals represent only a single hominin group that could be genetically linked to modern humans and there are numerous other human fossil groups. Unfortunately most of them are too old to have DNA preserved or they were discovered in warm and moist environments close to the equator that are not conducive to DNA survival (PAABO et al. 2004). In 2010 a new hominin group was described solely based on genetics (KRAUSE et al. 2010). The DNA fragments were retrieved from a tiny finger bone that likely once belonged to the distal phalanx of a pinky finger from a 5-7 year old girl. The bone was discovered in 2008 in the Denisova cave in the Altai Mountains in southern Siberia. A genetic analysis of the DNA recovered from this specimen revealed that the girl belonged to a hominin population that was

neither a Neandertal nor a modern human (KRAUSE et al. 2010; REICH et al. 2010). Instead it became clear that this hominin population was a sister group of Neandertals that diverged from the Neandertal lineage around 200,000 years ago (REICH et al. 2010). Based on the name of the cave where the fossil was discovered the population was named the "Denisovans", analogous to the "Neandertals" discovered in the Neander Valley.

The Denisovans likely derived from the same migration of hominins that left Africa around 500,000 years ago and gave rise to Neandertals in Europe. This hominin is mostly referred to as *H. heidelbergensis*. In Europe *H. heidelbergensis* evolved into Neandertals whereas in Asia it evolved into Denisovans (REICH et al. 2010). Surprisingly, the Denisovans mtDNA shows quite a different relationship to Neandertals and modern humans than the rest of their genome. Based on the two individuals that have been studied so far, their mtDNA is twice as different when compared to a modern human then when compared to a Neandertal mtDNA (KRAUSE et al. 2010; REICH et al. 2010).

A phylogeny reconstructed from the Denisova mtDNA suggests a separation time of more than a million years for modern humans and Denisovans, unlike the rest of the genome that suggests a separation time of around 350,000 years. Such inconsistencies were observed before and could be potentially explained by a rather large population size of hominins over the last 1 million years. However, modern genetic data as well as archaeological and anthropological data suggests a rather small population size of hominins in this time window. The alternative explanation for the discrepancy of mtDNA and nuclear DNA could be that the mtDNA is yet the product of another hybridization event between early Denisovans and another hominin that roamed Asia when Denisovans arrived in this region (REICH et al. 2010). This hominin would have left Africa around 1 million years BP and would indicate that hominins left Africa at least four times: first *H.erectus* 2 million years ago, second the unknown hominin that contributed its mtDNA to Denisovans, third *H. heidelbergensis* and fourth anatomically modern humans (KRAUSE et al. 2010). It will remain, however, difficult to show genetic admixture of an unknown hominin with the Denisovans in the absence of genetic data from both.

Genetic admixture with Denisovans across the Wallace line

A genome wide comparison of Denisovans and modern humans from different worldwide populations may quantify the amount of genetic admixture between those two hominin groups. Since the layer in the cave in which the Denisova bones were discovered is only about 50,000 years old, it is rather likely that Denisovans have interacted with modern humans after they later migrated into Eurasia (REICH et al. 2010). In order to test if those interactions left a genetic signal, the Denisova genome was compared to the genome of 13 humans to test for genetic similarities as described above for Neandertals. It was found that most populations inside as well as outside Africa do not carry any Denisova DNA in their genome, one group was an exception. Melanesians from Papua New Guinea and Bougainville were shown to carry around 5% Denisova DNA in their genome (REICH et al. 2010). So, in addition to the 2.5% Neandertal DNA in their genome those populations also carry 5% Denisova DNA *(Fig. 1)*.

In a subsequent study more than 200 individuals from 22 South East Asian populations were tested for the amount of admixture with Denisovans (REICH et al. 2011). The surprising result was that of all populations tested those from Eastern Indonesia, the Philippines, Oceania, Australia and Melanesia carry up to 5% Denisova DNA in their genome. It is surprising that all populations showing ancient admixture with Denisovans can be found today across the so-called "Wallace line", an imaginary line first described in 1859 by Alfred Russel Wallace *(Fig. 1)*. This line separates the fauna and flora of Asia and Wallacea, a transi-

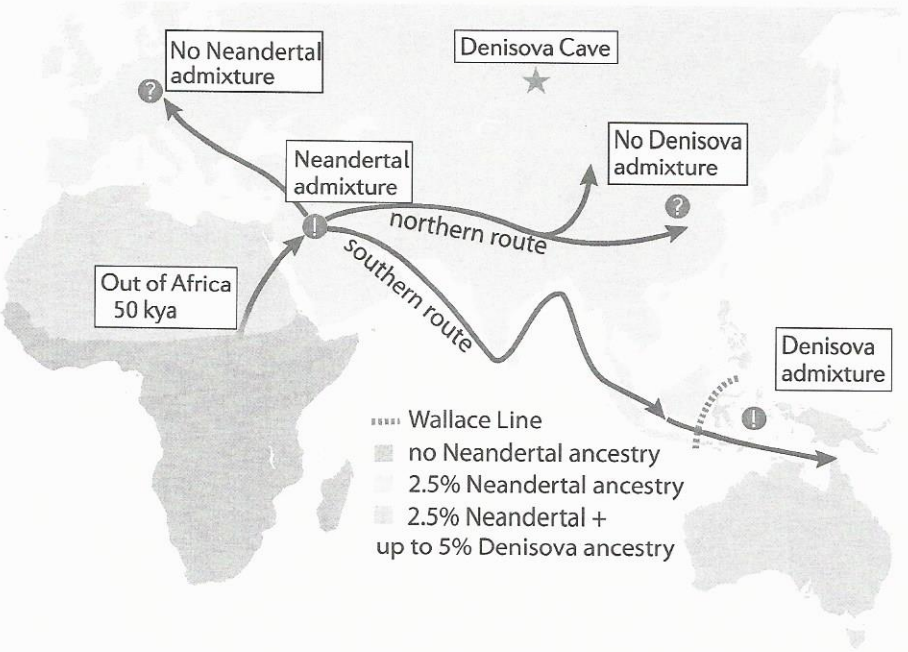

Fig. 1
Ancient Migration routes of modern humans from Africa
A map adapted from STONEKING/KRAUSE 2011, illustrating the dispersal routes of modern humans from Africa about 50,000 years BP, followed by admixture with Neandertals in the ancestry of all non-Africans, followed by admixture with Denisovans in the ancestry of New Guineans. Arrows indicate general directionality and not specific migration routes – in general we only know for sure the endpoints of migrations, not the routes. The red star indicates the location of Denisova cave. The exclamation marks indicate admixture, but there is extreme uncertainty as to where the Neandertal and Denisova admixture occurred. Question marks indicate regions where no additional admixture was detected even though archaeological findings suggest that Neandertals and Denisovans overlapped with modern human populations in those regions, e.g. Central Europe. Colors indicate the amount of archaic human admixture detected in modern populations from those larger world areas.
It should be noted that Northern Africa experienced a drastic genetic exchange over the last 10,000 years with Europe and the Near East. This likely caused a certain amount of Neandertal DNA in Northern African populations.

tional zone between Asia and Australia. During the last ice ages, all larger islands west of the Wallace line, such as Java, Bali, Sumatra and Borneo were connected to the mainland. This landmass is usually called Sundaland, whereas all major islands in the east were connected to Australia a landmass referred to as Sahul. The transitional zone between Asia and Australia is called Wallacea. The ecosystems of the two major landmasses were separated by deep water trenches that even during the last glacial maximum did not connect Sahul and the mainland. Thus fauna and flora east and west of the Wallace line remained quite distinct for millions of years, with placental mammals west and marsupials and giant lizards east.

Until some years ago it was thought that no other hominin except modern humans had ever crossed the Wallace line, mostly due to the fact that no archaic human fossils or archaeological remains older than 50,000 years were discovered in Wallacea or Australia. However, the discovery of *H.floresiensis* drastically changed the theories in 2003. This distinct and remarkable dwarf hominin was discovered on the island of Flores in the middle of Wallacea and well across the Wallace line (BROWN et al. 2004). Furthermore archaeological remains were discovered on the island that suggests the presence of some form of human more than a million years ago on Flores (BRUMM et al. 2010). In 2011 skeletal remains were discovered on the Philippine islands that are older than 65,000 years, thus making them too old to be of modern human origin (MIJARES et al. 2010). Evidence continues to accumulate that suggests that humans were present in Wallacea before the arrival of anatomically modern humans.

The presence of Denisova DNA in all modern human populations east of the Wallace line opens the possibility that also Denisovans may have been present in those regions when modern humans arrived. The detected admixture can be explained by two competing scenarios: either admixture with Denisovans happened in Wallacea, or it occurred on the mainland and was brought to the islands with migrating modern human populations. The analysis of the 200 South East Asians revealed that the Denisova admixture detected in modern Melanesians and Aborigines in Australia is distinct from the Denisova DNA that was detected in inhabitants of the Philippine islands. It was suggested that this is evidence for two independent hybridization events of modern humans and Denisovans (REICH et al. 2011). It is thus unlikely that the admixture of Denisovans and modern humans would have happened somewhere on the Eurasian mainland, since it is close to impossible that the admixed Denisova DNA would have segregated differently into two distinct populations after anatomically modern humans settled Wallacea. The most parsimonious explanation would thus be that the admixture happened on the islands in Wallacea. One admixture event occurred between Denisovans and the ancestors of modern Melanesians, such as Australian Aborigines and Papua New Guineans and a second event happened with the ancestors of Aboriginal people from the Philippines, such as the Mamanwa.

The genetic evidence thus suggests that, in addition to *H.floresiensis* and his ancestors, Denisovans likely also crossed the Wallace line. Based on this scenario, at least two different human groups have migrated into the Indonesian archipelago and the Philippines over the last million years, before the arrival of modern humans. Yet interestingly there is no evidence that they ever set foot on Sahul, the continent that united Australia and Papua New Guinea when the sea levels were up to 130m lower than they are today. To migrate within Wallacea, e.g. from Sundaland to Flores, one would have to cross half a dozen deep water trenches, whereas there is just two between Flores and Australia. Archaic humans were obviously capable of crossing open water, the question is what kept them from crossing those two last water lines?

Timor, the next island from Flores towards Australia, is visible from the other islands, thus it was likely settled by archaic humans as were the other larger islands in the Archipelago. Australia is not visible from Timor, despite it being only an 80 km distance between the Indonesian archipelago and Sahul during the maximum of the ice age. This is due to the fact that the Sahul shelf, unlike the Indonesian islands, shows little volcanic activity and therefore has no elevated land (Volcanoes). One explanation for the lack of early humans in Australia might therefore be that they never crossed in larger numbers to Sahul in order to establish a larger self sustaining population, since they did not see land on the horizon. Unlike modern humans, they may also have never crossed onto the Pacific Islands. It might be that they simply lacked the technology to do so. On the other hand, a large part of Sahul is today under sea level, thus potential settlements of archaic humans along the coast of Sahul might be found under water.

It thus remains a possibility that archaic humans within the last one million years did cross from Wallacea to Sahul in smaller groups but we are as yet lacking the anthropological and archaeological evidence, partially because some of it might simply be submerged.

Summary

The tendency for humans to explore and migrate seems to be a rather ancient trait that goes back more than two million years, when the first hominins left Africa to explore new environments. They subsequently colonize large parts of Asia and later also Europe. These largely mobile and adventurous migrants from Africa are usually referred to as *Homo erectus*. They were highly adapted for long distance travel and already displayed a rather modern body stature, quite distinct to earlier hominins. They were a quite successful group and roamed most parts of Africa and Eurasia for more than 1.5 million years. Eventually around 500,000 years ago they evolved probably somewhere in Africa into *H. heidelbergensis* and spread into Europe and Asia, replacing or admixing with the local *H.erectus* populations. In Europe *H. heidelbergensis* slowly evolved into Neandertals, a hunter gatherer that was quite well adapted to extreme ice age conditions. In Asia *H. heidelbergensis* evolved into Denisovans, a hominin of which we have very limited knowledge, though its genetic traces are found in fossils from Siberia and in modern humans in South East Asia, suggesting that Denisovans were common in large parts of East Asia throughout the last few hundred thousand years before the arrival of modern humans.

The last big hominin migration starts again in Africa, where *H. heidelbergensis* evolved into our direct ancestors, anatomically modern humans. After at least one failed attempt around 120,000 years ago (BAR-YOSEF 1998), anatomical modern humans finally leave Africa about 50,000 years ago and within a few thousand years spread all over the planet *(Fig. 1)*. They show a remarkable adaptation to various environments and for the first time clear evidence of symbolic art, such as ornaments, figurines, cave paintings and even musical instruments appear (CONARD 2009; CONARD/MALINA/MUNZEL 2009). Within just 10,000 years they either replace or to a small extend assimilate all other archaic humans on the planet. They are extraordinary explorers and seem to be driven by a remarkable curiosity while going on open sea voyages beyond visible land and settling even on remote islands in the pacific as well as Australia and Papua New Guinea. It remains to be shown though if modern humans were indeed the first hominins that settled Australia or if archaic humans had already crossed from Wallacea to Sahul millennia before. Around 15,000 years ago when the Northern American glaciers retreat, humans rapidly settle North- and South America (DILLEHAY et al. 2008).

It remains to be also shown if the driving force of human expansion and modernity was of biological or cultural nature or a combination of both. Genome comparisons with archaic humans such as Neandertals and Denisovans have the potential to reveal potential genetic changes that happened in our recent past, after the divergence from Neandertals. Some interesting candidate genes were already identified and the more we learn about the function of our genes, the more we will know about how those functions evolved. What seems clear is that some part of the archaic genetic heritage from Neandertals and Denisovans has survived in small parts in some modern human populations, such as Europeans and Asians. Some of the genes contributed from Denisovans can be found even in a high frequency in modern humans in South East Asia today, suggesting that those genes were beneficial when humans migrated into those regions and admixed with the local population. All archaic humans were either eventually replaced by modern humans or were absorbed into their gene pool, though with at least 90% of all human genetic makeup showing a recent African origin. The future

will surely determine whether indeed the remaining 10% of archaic DNA in some populations have played an important role for modern human adaptation. Regardless, the fact that modern humans were biologically compatible with Neandertals as well as Denisovans questions our concept of anatomically modern humans as a distinct species.

With the initial settlement of all large landmasses by modern humans, the drive for human exploration does not abate. There is archaeological and genetic evidence for various large pre-historic migrations often associated to the spread of agriculture and domestic animals, such as the Neolithic expansion into Europe around 7000 years BP or the Bantu Expansion in Africa around 5000 years BP. Large parts of the population get replaced or assimilated by incoming populations. New cultural innovations allow the human population to grow and expand. This inevitably leads to aggravating conflicts over land and resources. War and colonization often follow this imbalance of power and wealth, causing large population admixture. This process continues throughout history until today.

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