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1 **The demographic and adaptive history of central African hunter-**
2 **gatherers and farmers**

3

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19

1 **Abstract**

2 Central Africa, a forested region that supports an exceptionally high biodiversity, hosts the
3 world's largest group of hunter-gatherers, who live in close proximity with groups that have
4 adopted agriculture over the past 5,000 years. Our understanding of the prehistory of these
5 populations has been dramatically hampered by the almost total absence of fossil remains in this
6 region, a limitation that has recently been circumvented by population genomics approaches.
7 Different studies have estimated that ancestors of rainforest hunter-gatherers and Bantu-speaking
8 farmers separated more than 60,000 years ago, supporting the occurrence of ancient population
9 structure in Africa since the Late Pleistocene. Conversely, the Holocene in central Africa was
10 characterized by large-scale population migrations associated with the emergence of agriculture,
11 and increased genetic interactions between autochthonous rainforest hunter-gatherers and
12 expanding Bantu-speaking farmers. Genomic scans have detected numerous candidate loci for
13 positive selection in these populations, including convergent adaptation for short stature in
14 groups of rainforest hunter-gatherers and local adaptation to endemic malaria in western and
15 central Africans. Furthermore, there is recent increasing evidence that adaptive variation has been
16 acquired by various African populations through admixture, suggesting a previously
17 unappreciated role of intraspecies gene flow in local adaptation. Ancient and modern DNA
18 studies will greatly broaden, and probably challenge, our view on the past history of central
19 Africa, where introgression from yet uncharacterized archaic hominins and long-term adaptation
20 to distinct ecological niches are suspected.

21

1 **Introduction**

2 The central African belt — a vast territory that extends from the Congo Basin in its western part
3 to Lake Victoria in its easternmost part — is mostly covered by dense rainforests and supports
4 one of the highest levels of biodiversity worldwide. This region is key to understand African
5 prehistory, population structure and dynamics as it harbours both the largest living group of
6 active hunter-gatherers, the rainforest hunter-gatherers, as well as Bantu-speaking, agriculturalist
7 communities [1-3]. These two groups differ not only in their subsistence patterns (i.e., broadly,
8 although not exclusively, hunting and gathering *versus* farming) but also in their lifestyle,
9 ecologies and exposure to environmental pressures [4] and diseases [5]. While most farming
10 communities are sedentary and live in rural or urban areas, rainforest hunter-gatherers
11 traditionally live in huts in the rainforest, moving regularly from one camp to another.

12
13 African rainforest hunter-gatherers (RHG) — collectively known by the historical and derogatory
14 term “Pygmies” — are broadly subdivided into two groups that reflect their geographic location
15 [6]. Western RHG inhabit the Congo Basin and include multiple populations such as the Baka,
16 Aka, Koya or Bongo, whereas Eastern RHG live close to the Ituri rainforest and Lake Victoria
17 and comprise groups such as the Asua, Sua, Efe or BaTwa. In addition to a forest-dwelling mode
18 of subsistence, Western and Eastern RHG share distinctive cultural and phenotypic traits, such as
19 specific hunting and honey-gathering techniques and a trait known as the “pygmy phenotype”,
20 i.e., small adult body size distinctive of certain African, Southeast Asian and South American
21 populations [7]. African RHG, particularly those of the Ituri rainforest, show the lowest average
22 adult stature worldwide, of < 155 cm [8].

23

1 Bantu-speaking, agriculturalist populations of central Africa are thought to descend from early
2 farming communities that recently expanded across sub-Saharan Africa [9]. The central African
3 belt is also key in this respect, as it is adjacent to the postulated homeland of Bantu languages,
4 where agriculture possibly emerged 3-5 Ky ago, in the area that corresponds today to Southeast
5 Nigeria and Western Cameroon [3]. The appearance of pottery and polished stone tools within
6 this time frame, together with the shared languages and oral traditions of farmers and hunter-
7 gatherers, indicates an early and extensive history of economic and technological exchanges
8 between the ancestors of these two communities [1-3,8,10]. These contacts have been maintained
9 until today; for example, some groups of rainforest hunter-gatherers remain sedentary for some
10 time due to strong socioeconomic dependence on neighbouring farmers.

11
12 The lacks of archaeological data for central Africa, in particular for the Congo Basin owing to the
13 rapid disintegration of fossil remains in the rainforest's acidic soils, have hampered the
14 understanding of demography and adaptation of populations inhabiting this region. How the
15 increasing availability of genomic data from populations of the region has counteracted this
16 limitation is the goal of this review. We focus on how genomic studies of rainforest hunter-
17 gatherers and farmers have been of paramount importance to infer their past demography —
18 population splits, sizes changes and gene flow — as well as their history of biological adaptation,
19 highlighting the importance of admixture as a possible source of new adaptive variation.

20 21 **Deep divergence of central African populations in the Late Pleistocene**

22 While the late Pleistocene is thought to have witnessed modern human diversification within
23 Africa [11], the human fossil record of central Africa is exceptionally sparse for this period [12].

1 The oldest samples studied have been dated at 20-25 Ky, and suggest that the biological and
2 cultural diversity of central Africa during this period was considerable [13]. However, it is
3 currently unknown if such diversity was a local exception, or a general rule in the diverse
4 ecological regions composing central Africa.

5
6 The study of the genetic diversity of present-day populations represents an alternative, powerful
7 approach to infer past population histories and ecologies. Population genetic studies have shown
8 that present-day RHG and farming populations are characterized by one of the deepest splits in
9 human evolution [14,15]. The combined modelling of 16 high-coverage whole genomes supports
10 a separation of the ancestors of RHG and the west African Yoruba 90 Ky (85–92) or 155 Ky
11 (139–164) ago, assuming either instantaneous or continuous asymmetric gene flow between the
12 two groups [14]. A similar approach recently applied on 300 exomes of RHG and Bantu-
13 speaking farmers has estimated that their ancestors diverged 135 Ky (57–259) ago [15] (**Figure**
14 **1**), assuming the most recent estimations of mutation rate [16] and generation time [17]. Under
15 the same assumptions, the former study supports a population split as old as 300 Ky ago, while
16 previous studies based on independent autosomal regions support a separation ~110 Ky ago
17 [18,19]. Despite discrepancies between estimates, which may be due to imperfections in the
18 models, low sample sizes, or the effects of background selection, they all support ancient
19 structure among the ancestors of rainforest hunter-gatherer and farmer populations, in agreement
20 with the proposed human diversification within Africa during the Late Pleistocene [11].

21
22 Seminal ancient genomic studies have revealed that Neanderthals contributed ~2% of the genetic
23 variation of present-day non-Africans [20-22], while Denisovans contributed ~5% of genetic
24 variation to modern Melanesians [23-25]. Despite the coexistence throughout Africa of diverse

1 forms of *Homo* with both archaic and modern traits during the Pleistocene [26], few studies have
2 yet provided robust evidence of archaic introgression in Africa. Reference-free methods have
3 nonetheless identified in RHG genomes hundreds of candidate introgressive loci, which are
4 strongly depleted in genic regions [27-29]. Whether these observations reflect archaic admixture
5 or ancestral structure [30] remains to be determined.

6

7 **Demographic transitions and admixture during the Holocene**

8 The Holocene in central Africa was characterized by a global warming after the Last Glacial
9 Maximum, and the increase of forested areas followed by short episodes of forest contraction
10 from 4 Ky onward [31,32]. These deforestation events were concomitant with the well-
11 documented expansion of Bantu languages from the modern-day Nigeria-Cameroon border
12 [3,33,34]. The Bantu expansion is thought as one of the most influential cultural events of
13 African prehistory, as it spread a new, more sedentary lifestyle that ultimately led to the diffusion
14 of agriculture and iron-smelting technology across sub-Saharan Africa. Population genetic
15 studies have revealed that present-day Bantu-speaking populations (BSP) of central, eastern and
16 southern Africa present little differentiation [35-37], supporting their recent separation during the
17 Bantu expansion. Haplotype-based approaches, together with linguistics [34] and archaeoclimate
18 data [9], all support a model in which early BSP first moved southward through the rainforest,
19 before migrating toward eastern and southern Africa [37-39]. Interestingly, the signal of
20 population growth observed in BSP genomes cannot be solely explain by an expansion occurring
21 3-5 Ky ago, suggesting that their ancestors were already a demographically successful group
22 prior to agriculture emergence [40,41].

23

1 As they dispersed throughout central Africa, BSP encountered local RHG populations. Several
2 studies indicate that admixture occurred between the ancestors of these two groups [18,35-37,41-
3 45]. Model-based methods have estimated that gene flow from BSP to RHG was greater than the
4 opposite [14,15] (**Figure 1**), resulting in high BSP ancestry among some RHG groups [18,41,43-
5 45]. Furthermore, uniparentally-inherited and X-linked markers have revealed that gene flow
6 from BSP to RHG was male-biased [41,44,46]. However, asymmetrical male-biased gene flow is
7 not systematically observed across western RHG groups [41,44], suggesting variable
8 intermarriage customs. While modelling approaches based on the site frequency spectrum have
9 estimated a time of admixture as old as ~ 7 Ky [14,15] (**Figure 1**), decay of admixture linkage
10 disequilibrium is compatible with admixture occurring mostly during the last millennium [37,41].
11 We anticipate that methodological improvements allowing parameter estimation under both
12 instantaneous and continuous admixture models [47] will help resolving these apparent
13 discrepancies.

14

15 **Population size changes and the burden of deleterious mutations**

16 Understanding how demographic events such as explosive growth or bottlenecks have affected
17 the ability of populations to purge deleterious variants is crucial for the dissection of the genetic
18 architecture of diseases [48-50]. Fuelled by the availability of population sequencing data, there
19 has been increased interest on whether human populations carry differential burdens of
20 deleterious alleles (i.e. mutational load). Despite some initial controversy, the consensus today is
21 that the demographic events experienced by the majority of human populations have not been
22 long or severe enough to impact, at least to a detectable extent, mutational load under an additive
23 model of dominance, whereas they may impact load under a recessive model [51-53].

1
2 The question of how population size changes affect mutational load is especially relevant in
3 hunter-gatherer history, as their subsistence patterns are expected to be associated with a unique
4 demography [15,18,19,41]. Based on exome sequencing data from RHG and BSP from western
5 and eastern central Africa, a recent study has explored, using simulations, the trajectories of
6 mutational load across populations, and examined the model of dominance that is most
7 compatible with the patterns of deleterious variation [15]. Despite the marked population
8 collapses and expansions experienced by RHG and BSP, respectively (**Figure 1**), both groups
9 exhibit similar load under an additive model. Furthermore, the historically large effective
10 population size of RHG, together with the gene flow received from neighbouring farmers, have
11 counteracted the predicted effect of the recent and strong population decline of RHG on their
12 recessive load.

13
14 In the absence of knowledge of the average distribution of dominance coefficients across the
15 genome and full consideration of rare variants located in both coding and non-coding regions, the
16 question of the extent of mutational load differences between hunter-gatherers and farmers, and
17 more generally among human populations, remains open.

18
19 **Signatures of local adaptation in rainforest hunter-gatherers and farmers**
20 Despite rainforest hunter-gatherers and farmers cohabit along the central African belt, their
21 history of population divergence dates back to > 60 Ky ago [14,15,18,43]. Their differences in
22 effective population sizes appear to result from demographic events that predate the first farmers'

1 expansions 3-5 Ky ago [41], suggesting a long — and probably different — history of biological
2 adaptation.

3
4 The “pygmy phenotype” [7] appears to have a genetic basis, at least in Africa [45,54,55], and its
5 adaptive nature — proposed to be associated with higher fitness in rainforest environments
6 through thermoregulation, food limitation, improved mobility or earlier reproduction [7,8,56,57]
7 — is increasingly supported [58]. Population genetic studies have detected signatures of positive
8 selection targeting a largely non-overlapping set of genes in various RHG groups
9 [14,29,45,55,59-62], possibly reflecting false positives. The relevance of some candidate loci is
10 nonetheless supported by functional and epidemiological studies; for example, *FLNB* and *EPHBI*
11 present not only robust signatures of positive selection but also variation that affect body size in
12 model organisms or is associated with human height [14,29,45] (**Figure 2**). That studies of
13 different RHG groups detect different candidate genes for the pygmy phenotype may also reflect
14 convergent adaptation within Africa, as supported by population genetics data [55] and analysis
15 of longitudinal growth rates in western and eastern RHG groups [63].

16
17 Functional categories of candidate genes evolving adaptively among RHG also involve
18 reproduction, cell signalling, neural development and immune functions [14,29]. Beside all these
19 cases of candidate selective sweeps, signals of polygenic adaptation [64] have been also detected
20 among RHG, related to the pygmy phenotype [55] and immunity-related processes (i.e. antigen
21 binding and pattern recognition receptor activity) [14].

22
23 Genetic adaptation related to host defence against pathogens has been pervasive among African
24 populations [65,66]. The pressure imposed by *Plasmodium* — the causative agent of malaria —

1 largely characterises the history of positive selection of sub-Saharan Africans [67], particularly
2 that of western and central African farming communities [36,37]. Highly supported cases of
3 genes that have evolved adaptively in response to malaria include *HBB*, *DARC (ACKR1)*, *G6PD*,
4 *CR1* and *CD36* [36,68-74] (**Figure 2**), variation in which confers protection against *falciparum*
5 or *vivax* malaria [67]. Other cases of genetic adaptation include *APOLI*, conferring resistance to
6 *Trypanosoma brucei* [75], *LARGE*, implicated in Lassa virus infectivity and immunity [76],
7 *TLR5*, associated with decreased NF- κ B activity [77], as well as several loci putatively involved
8 in adaptation to temperature and osmoregulation [36]. All these studies have collectively
9 broadened our understanding of the ecological pasts of populations of central Africa that differ in
10 their carrying capacities and modes of subsistence.

11

12 **Admixture as a vehicle of genetic adaptation**

13 Recent studies have highlighted a previously unappreciated role of admixture and gene flow as an
14 important source of adaptive genetic variation, from ancient hominins such as Neanderthals or
15 Denisovans [30,78,79], or between modern human populations [37,80,81].

16

17 Within Africa, BSP rapidly dispersed in less than 3 Ky, and had to adapt to new ecosystems.

18 Recent data has shown that during their dispersals, BSP acquired advantageous genetic variation
19 via admixture with the local populations they encountered [37]. For example, BSP from western
20 central Africa acquired adaptive variants at the *HLA-D* gene locus through admixture with RHG,
21 and BSP from eastern Africa acquired the lactase persistence trait through gene flow from east
22 African pastoralists [37] (**Figure 2**). Another study has reported strong changes in local ancestry
23 in the genome of the Fula population from west Africa; the region overlapping the lactase

1 persistence trait (*LCT/MCM6*) exhibits the highest proportion of Eurasian ancestry, while *DARC*,
2 where the Duffy null allele confers almost complete resistance to *vivax* malaria, exhibits the
3 highest proportion of African ancestry [81]. That adaptation can be accelerated by gene flow is
4 also supported by studies of African-descent, admixed populations of Madagascar and Pakistan,
5 where the Duffy null allele is, again, observed at higher frequencies than expected [82-84].

6

7 **Conclusions and perspectives**

8 Human evolutionary genomics in central Africa has contributed new knowledge of the history
9 and evolution of human groups inhabiting this ecologically unique region. Deep population
10 divergence between populations with historically distinct subsistence strategies, as well as
11 compelling signatures of local adaptation, suggest an early prehistory of central Africa
12 characterized by isolation between populations relying on different ecosystems. Conversely, the
13 Holocene witnessed the geographical expansion of demographically-successful, sedentary Bantu-
14 speaking peoples, resulting ultimately in asymmetric and male-biased admixture with several
15 groups of rainforest hunter-gatherers.

16

17 Despite these new insights, important aspects of the evolutionary past of central Africans remain
18 unclear, because of inherent limitations of modern population genomics and the scarcity of high-
19 quality genomic data for both modern and ancient human DNA. Uncertainties in the geographic
20 distribution of ancestors of present-day populations and in mutation rates impede the
21 interpretation of the demographic models fitted on the available genetic data [85]. The overall
22 genetic diversity of central Africans remains to be fully characterized, as the geographic
23 distribution of sampled populations is still fragmented, particularly in the Democratic Republic

1 of Congo where several hunter-gatherer groups live, such as the Twa and the Cwa [1] (**Figure 2**).

2 The extreme scarcity of human fossils and the low preservation of ancient DNA in these regions

3 also hamper ancient genomics, yet this field is essential to confirm that archaic admixture with

4 ancient hominins did occur in Africa, and if so, to determine which modern populations were

5 mostly introgressed.

6

7 Finally, the contrasted demographic histories and ecologies of central African populations are

8 expected to impact their present-day phenotypic diversity, both benign and disease-related. While

9 compelling evidence support that a number of distinctive traits of rainforest hunter-gatherers and

10 farmers are adaptive, the genetic architecture of such traits, as well as that of diseases endemic of

11 this region, is yet to be determined. Future studies combining rich phenotype data with innovative

12 methodological tools to detect the footprints of polygenic selection and adaptive introgression

13 will provide invaluable insights into the determinants of human biological diversity.

14

1 **BOX 1 - The genetic legacy of the Transatlantic Slave Trade**

2
3 Millions of individuals from western and central Africa were forcibly brought to the Americas by
4 slave traders from the 16th to the 19th centuries. Subsequent admixture between the descendants
5 of slaves and European- or Native-American-descent Americans impacted greatly the genetic
6 landscape of the New World. Contemporary American populations of African descent show
7 considerable variation in African ancestry proportions, ranging from <5% in Puerto Ricans to
8 more than 95% in the Noir Marron from north-eastern South America [86-91]. Within North
9 America, innovative approaches modelling ancestry and recent relatedness estimated that
10 admixture occurred in the first half of the 19th century mainly in the South, followed by ancestry-
11 biased migration towards the North [90].

12
13 Although rich historical records documented slave embarkations from different coastal regions of
14 western and central Africa [92], they could not inform the precise geographical origins of
15 African-descent Americans. These origins were recently revealed by genetic surveys that
16 estimated the relative genetic contribution of western and central African populations to African-
17 Americans [37,91], highlighting Angola as an important source of slaves in both South and North
18 America [93].

19
20 Leveraging the rich genealogical and genetic records of Iceland, a seminal study reconstructed
21 the African genome of Hans Jonatan, an Icelandic immigrant born in the Caribbean in 1784 to an
22 enslaved African mother and European father, from the genomes of 182 of his descendants in
23 Iceland, and inferred his mother originated from western central Africa [94].

1 **Conflict of interest statement**

2 Nothing declared.

3

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9

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Figures

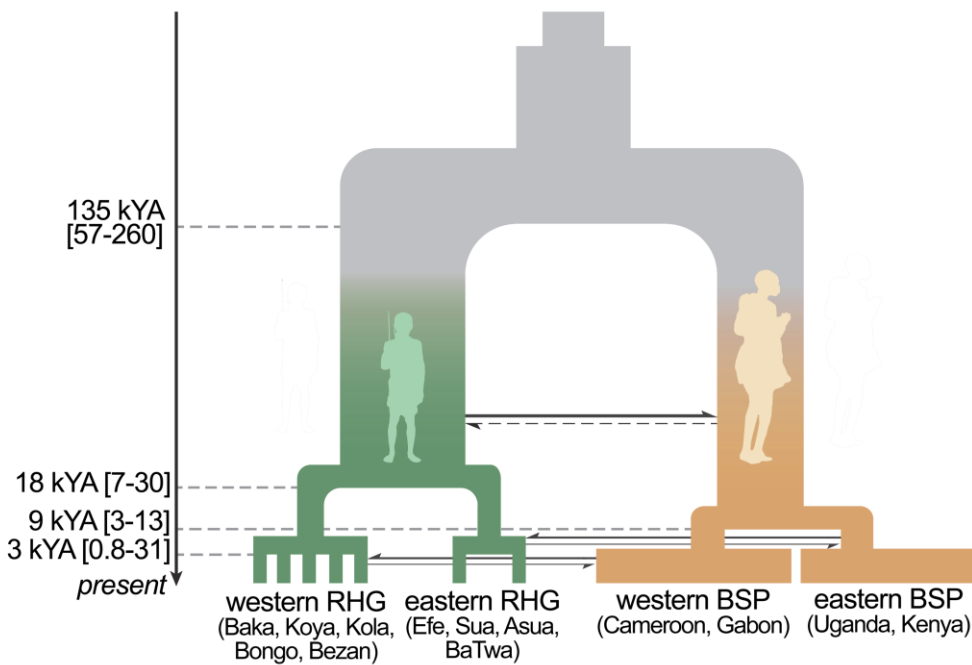


Figure 1. A general demographic model of rainforest hunter-gatherer and farmer

populations. This model recapitulates estimations of the demographic history of rainforest

hunter-gatherers (RHG) and neighbouring Bantu-speaking farmer populations (BSP) of central

Africa [15,41,43]. Times are given in thousands of years from present (kYA). Inferred changes in

effective population size are shown by changes in branch width, and gene flow by arrows.

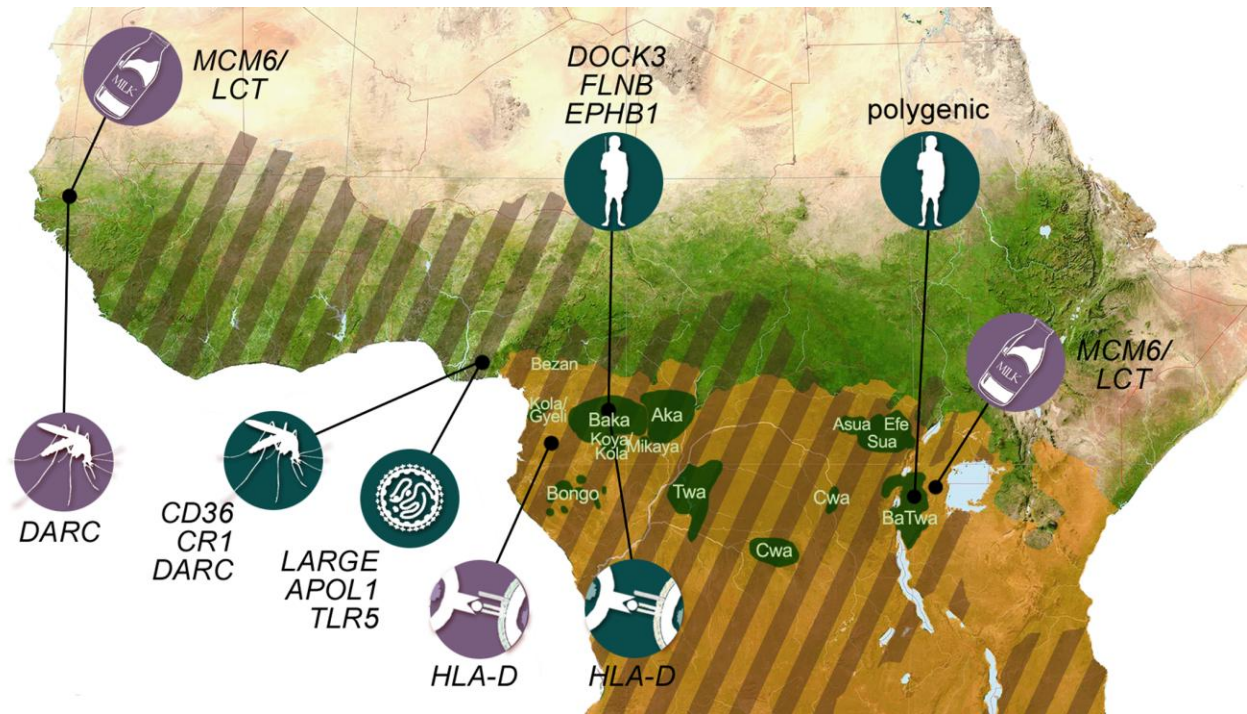


Figure 2. A map of human local adaptations in central Africa. Blue circles indicate case examples of candidate local adaptations and corresponding positively-selected genes in western/central Africa. Violet circles indicate candidate cases of adaptive admixture, when adaptive variation was acquired through admixture or gene flow. The orange area shows where Bantu languages are spoken today (adapted from [3]). Dark green areas indicate the geographic areas that the different RHG groups occupy (adapted from [1]). The maroon hatched areas indicate predicted areas of high *Plasmodium falciparum* malaria endemicity [95].