

Network analysis of the hominin origin of Herpes Simplex virus 2 from fossil data

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ABSTRACT

Herpes simplex virus 2 is a human herpesvirus found worldwide that causes genital lesions and more rarely causes encephalitis. This pathogen is most common in Africa, and particularly in central and east Africa, an area of particular significance for the evolution of modern humans. Unlike HSV1, HSV2 has not simply co-speciated with humans from their last common ancestor with primates. HSV2 jumped the species barrier between 1.4 and 3 MYA, most likely through intermediate but unknown hominin species.

In this paper, we use probability-based network analysis to determine the most probable transmission route between intermediate hosts of HSV2, from the ancestors of chimpanzees to the ancestors of modern humans, using paleo-environmental data on the distribution of African tropical rainforest over the last 3 million years and data on the age and distribution of fossil species of hominin present in Africa between 1.4 and 3 MYA. Our model identifies *Paranthropus boisei* as the most likely intermediate host of HSV2, while *Homo habilis* may also have played a role in the initial transmission of HSV2 from the ancestors of chimpanzees to *P. boisei*.

Keywords network analysis; human evolution; infectious disease; epidemiology; archaeology

Introduction

Herpes simplex virus 2 (HSV2) is a sexually transmitted human pathogen that causes genital lesions and, rarely, encephalitis (eg Tang et al. (2003)), and is associated with increased risk of HIV acquisition (Freeman et al., 2006). After primary infection, the virus adopts a life cycle of latency punctuated by periods of lytic replication when new hosts can be infected through genital contact. The virus is related to the human oral pathogen herpes simplex virus 1 (HSV1). Both HSV1 and HSV2 are alphaherpesviruses, which are found in many primates (Wertheim et al., 2014). HSV1 primarily causes infection, and sporadic lesions, within the oral cavity and establishes latency in the trigeminal ganglia, while HSV-2 is associated with infection of the genitalia and surrounding skin, and establishes latency in the sacral ganglia (Whitley2007). Both simplex viruses can infect either body cavity, although there is viral shedding data from co-infected individuals to suggest that HSV1 is a more successful oral and HSV2 a more successful genital pathogen (Kim2006). The genetic basis of this difference in tropism isn't fully understood: some studies of recombinant HSV1 x HSV2 strains have highlighted the importance of the latency-associated transcript (LAT) in how successfully the two simplex viruses reactivate from latency within different nerve types (Bertke2007). HSV1 and 2 also differ in the length of the glycoprotein G (US4) open reading frame, which may play a role in tropism (Baines2007).

HSV2 was originally thought to have co-speciated with humans when our lineage diverged from that of the ancestors of chimpanzees and bonobos (anc-chimps). Comparisons of the HSV1, HSV2 and chimpanzee herpes virus 1 (ChHV1) genomes (Tang et al., 2003) suggest that HSV2 is more closely related to ChHV1 than HSV1 (Wertheim et al., 2014). This analysis also found that ChHV1 and HSV2 diverged from one another between 1.4 and 3 MYA, and the authors inferred that an unknown hominin (or hominins) was infected with HSV2 before it switched host to the ancestors of modern humans.

We hypothesise that by combining fossil data on when and where different hominin species were likely to be present in Africa, the geographical range of modern chimpanzees and bonobos, and the reconstructed distribution of tropical rainforest habitat as a proxy for the past range of the chimpanzee/bonobo ancestor (anc-chimps) it will be possible to develop a model to statistically infer the species that facilitated the host-switch of HSV2 in the modern human lineage defined here as beginning with *Homo erectus* (Anton et al., 2016).

Before *Homo erectus* it is unclear which hominins are the direct ancestors of anatomically modern humans. However, once HSV2 has reached *Homo erectus*, no further host-switches are required for HSV2 to be considered present in the ancestors of modern humans.

HSV2 is found in all living populations (Looker et al., 2015), is accepted as having an African origin (Koelle2017; Burrell, Boutolleau, et al., 2017), and has patterns of genetic divergence consistent with having diverged with human populations as they spread out of Africa (Koelle2017). Current genetic, archaeological and fossil evidence suggests 100 KYA as a plausible (although not universally accepted) earliest date for anatomically modern humans (AMH) to have left Africa (Mirazón Lahr et al., 2016). We therefore infer that HSV2 must have been in the population of AMH before they left Africa, in order to take it with them when migrating to the rest of the world.

Methods

HSV2 prevalence data, hominin fossil data and chimpanzee and tropical rainforest geographic range data

HSV2 is most closely related to ChHV1 which infected the ancestors of modern chimpanzees. The GIS data on the range of modern *Pan troglodytes* and *Pan paniscus*, provided by the IUCN Red List (Oates et al., 2008), is shown in fig. 3a. Only one ancestral chimpanzee fossil, dated to c. 500 KYA, is currently known (McBrearty2005). This means that the habitat range of anc-chimps is not directly measurable from the fossil record but is inferred to be a larger geographical range. Therefore, we have used the paleo-tropical rainforest range during the period of 1.4 - 3 MYA Köppen-Geiger climate classification dataset Peel, Finlayson, and McMahon, 2007 as a proxy for the ancient range of chimpanzees and combined this with data based on modern great ape distribution patterns and range size estimates (Thompson2003), and is shown in fig. 3b.

To identify which species could have been involved in the host-switch of HSV2 from the ancestors of chimpanzees to the ancestors of modern humans, we collated spatio-temporal data on African hominin fossil species extant between 100 KYA and 3 MYA. Latitude and longitude of site location was used to provide a spatial data point for each species. Temporally, published fossil dating evidence was used to provide a first appearance datum (FAD) and last appearance datum (LAD) for each species (see supplementary Table 1).

Data on the prevalence of herpes simplex virus 2 between 2000 and 2015 CE was taken from the supplementary materials of (Looker et al., 2015), and plotted to demonstrate the distribution of HSV2 across Africa (Supplementary Figure A. 1).

Network analysis

To establish the most probable transmission route of HSV2 from anc-chimps to modern humans, it is important to identify potential species that may have been intermediary hosts. Initially, all hominins in Africa with temporal ranges within the 1.4 - 3 MYA confidence window (Wertheim et al., 2014) of the chimp-hominin transmission were identified (see Supplementary Table 1). Their distance to ancient tropical rainforest was calculated, and only those species whose fossil remains were found within 400 km of tropical rainforest were considered as putative species for initial ancestral-chimp-hominin HSV2 transmission. This reflects the distance that would have been covered by hominins employing three possible strategies: (a) a broadly omnivorous subsistence strategy based on scavenging, (b) hunting using carnivore and herbivore movement patterns and (c) modern hunter-gatherer range sizes (Foley1978; Grant1992). A matrix of spatio-temporal distances was then calculated to map the distances between the nearest neighbours of each species and also to calculate the temporal overlap between species using the fossil record. Fossils from four genera (*Ardipithecus*, *Kenyanthropus*, *Orrorin* and *Sahelanthropus*) were excluded from the analysis on the basis that there is no fossil evidence that they persisted after 3 MYA.

A network of possible transmission routes of HSV2 from anc-chimps to humans through different hominins was developed as a directed acyclic graph (DAG) $G = (V, E)$ comprising of a set of nodes (V), representing potential intermediary hosts, and edges (E) connecting the nodes, which represents the direction of transmission between species (See Figures 1 and 2). The DAG comprised of the anc-chimps as the start node, *H. erectus* as the target node, and other potential species forming secondary nodes in the graph. The edges are typically weighted; in this analysis, the weights are based on the inverse probability of transmission.

If HSV2 was transmitted to *Homo erectus*, no further cross-species transmission event is needed to explain the infection of modern humans. Simple vertical mother-to-child or horizontal (sexual) transmission of the virus through the genus *Homo* from this point would be sufficient as the ancestor-descendent path from *Homo erectus* to *Homo sapiens* is relatively secure (Maslin, Shultz, and Trauth, 2015).

Bayesian inference

A Bayesian network or a belief network is a graphical structure that allows us to represent and reason about an uncertain domain. In a Bayesian network, the species (nodes) are variables, and the transmission routes (edges) represent direct links between species. The process of conditioning (also called probability propagation or inference) is performed via a “flow of decisions” through the network, which involves computing the posterior probability distribution for a set of query nodes, given values for some evidence (or observation) nodes. An important consideration in all Bayesian-based methods is the choice of a prior. An empirical Bayesian method that estimates the likelihood of HSV2 infection using a prior beta distribution is adopted, which is an approximation to a hierarchical Bayesian approach (Farine and Strandburg-Peshkin, 2015; Murphy, 2012).

Bayesian networks provide full representations of probability distributions over their variables, which allows us to infer upon any subset of variables. A Bayesian network is created using the DAG described above. Each node on the graph represents a potential intermediary host that has a probability of transmitting HSV2. The probability of infection transmission is represented as a beta distribution, with shape parameters α representing the time period of the species in 100,000 years and β representing the distance to the neighbour in kilometres. A Conditional Probability Table (CPT) is generated for all possible combinations of a dichotomous outcome for each variable (HSV2 infection is true or false). The “Combined Inference” approach is adopted to evaluate the probability of intermediary hosts transmitting HSV2, by conditioning the ancestral-chimpanzee and *Homo erectus* nodes for the presence of HSV2 (Korb and Ann E. Nicholson, 2003). The Bayesian inference analysis was performed using the AI space decision network tool (Poole and Mackworth, 2010).

Optimal path traversal

A network of possible transmission routes of HSV2 from ancestral-chimpanzees to humans through different potential hominins was developed as a Directed Cyclic Graph (DAG) $G = (V, E)$ comprising of a set of nodes (V), representing potential intermediary hosts, and edges (E) connecting the nodes, which represents the direction of transmission between species. Infection Prevalence (HSV2-IP) and Infection Transmission (HSV2-IT) models assign probability value (edge costs) to the DAG utilising the temporal overlap between hominin species and their geographic proximity to rainforest habitat and one another. More details about the probability models are discussed in the next section. A Conditional Probability Table (CPT) is calculated to determine the nodal heuristics. Ancestral-chimpanzees and *Homo erectus* formed the start node and the target node of the DAG.

The A* pathfinding algorithm Hart, Nilsson, and Raphael, 1968 was used on the DAG to identify the most probable transmission (optimal path) route for HSV2. The A* algorithm is the most widely used path-finding algorithm. A* is an informed search algorithm that searches through all possible paths to the target that yields the smallest cost. This is done by combining information on favouring vertices that are close to the starting point and information on favouring vertices that are close to the goal. At each time-step A* algorithm selects the path at a given vertex n that has the lowest $f(n) = g(n) + h(n)$. Where $g(n)$ represents the exact cost of the path from the starting point to any vertex n , and $h(n)$ represents the heuristic estimated cost from vertex n to the goal. A* balances the two as it moves from the starting point to the goal. The A* algorithm evaluates the most probable transmission route, by minimising the traversal costs based on the edge cost and nodal heuristics of the transmission network graph.

HSV2-Infection Prevalence (HSV2-IP) model

This model describes the probability of HSV2 infection based on the proximity to the rain forest habitat and the duration (difference between the first and the last appearance datum) using a beta distribution. The probability density function is defined as:

$$PDF : \frac{x^{\alpha-1}(1-x)^{\beta-1}}{B(\alpha, \beta)} \quad \text{where} \quad B(\alpha, \beta) = \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha + \beta)} \quad (1)$$

Where, Γ defines a gamma distribution function, α is the time period of existence of the species in 100,000 years and β is the spatial distance of the fossil from the rainforest in kilometres. Monte-carlo simulations were performed to sample from the distributions to populate the edge costs. A minimum overlap threshold of 10% is considered for possible transmission of HSV2 from one species to another.

Stochastic modelling of infection transmission

The Susceptible - Infection - Recovered (SIR) is one of the most widely used model in epidemiological system. In the stochastic version of the SIR model, the continuous variables are replaced by discrete numbers, and the process rates are replaced by process probabilities. At time ‘t’ the probability of a new susceptible host is infected is modelled as an exponential distribution, which is epidemiologically incorrect for most diseases Wearing, Rohani, and Keeling, 2005; Bailey, 1975; Sartwell et al., 1950,

of infectives at time (t) = Initial number of infectives who are still infectious at time (t) + Those who have acquired the infection in the time interval $[0, t]$ and are still infectious at time (t)

Table 1. Probable HSV2 transmission routes

Disease Transmission Route	HSV2-IP route ranking (normalised path cost)	HSV2-IT route ranking (normalised path cost)
anc-chimp \Rightarrow <i>P. boisei</i> \Rightarrow <i>H. erectus</i>	1 (1.0)	3 (1.14)
anc-chimp \Rightarrow <i>H. habilis</i> \Rightarrow <i>P. boisei</i> \Rightarrow <i>H. erectus</i>	4 (1.13)	1 (1.0)
anc-chimp \Rightarrow <i>H. habilis</i> \Rightarrow <i>H. erectus</i>	2 (1.20)	2 (1.05)
anc-chimp \Rightarrow <i>H. rudolfensis</i> \Rightarrow <i>H. erectus</i>	3 (1.24)	4 (1.54)

* The most probable route has a cost of 1. The path costs are normalised to the shortest path.

i.e., the rate of leaving the exposed is independent of the time spent on the host. Wearing et al Wearing, Rohani, and Keeling, 2005 suggested a more realistic distribution of latent and infectious periods, with a stronger central tendency:

More realistic distributions can be obtained by choosing probability density function of the infectious period, $p(t)$ to be a gamma probability density function Blythe and Anderson, 1988; Lloyd, 2001.

Infection Transmission (HSV2-IT) model

This model utilising the temporal overlap between hominin species and their geographic proximity to one another to determine the probability of transmission using a gamma distribution. The probability density function of a gamma distribution is given as:

$$PDF : \frac{\beta^\alpha}{\Gamma(\alpha)} x^{\alpha-1} \exp^{-\beta x} \quad (2)$$

in terms of shape α and rate β . The parameters shape is defined as the ratio of the time period in 1000 years / distance in kilometers and rate is defined as the normalised time period Y/x , where x is the time period of the species in 1000 years and Y is the time period of anc-chimpanzees. Monte-carlo simulations were performed to evaluate the combined probability of transmission between species is evaluated as mutually exclusive events based on the probability distributions.

Results

The A* optimal graph traversal algorithm was used to evaluate the most probable intermediary host(s) of HSV2 between the ancestors of modern chimpanzees and bonobos (ancestral-chimpanzees or anc-chimps) and the ancestors of modern humans. Directed Acyclic Graphs (DAGs) linking potential HSV2 transmission hominins were developed, with edges representing the possible direction of transmission between different hominins. Two mathematical models: the Infection Prevalence (HSV2-IP) model and the Infection Transmission (HSV2-IT) model, were developed for estimating the probability of HSV2 infection/transmission between species based on their geo-spatial and temporal distributions and their proximity to rainforest. These probability models were used to populate the DAG edge costs and node heuristics. Bayesian network inference of the DAG was also used to determine the most probable intermediary hosts. Both the A* algorithm figs. 1 and 2 and the Bayesian network inference identified *Homo rudolfensis* as the most probable intermediary host that transmitted HSV2 from ancestral-chimpanzees to the ancestors of modern humans. Table 1 shows the probable HSV2 intermediary routes and their rankings based on the infection transmission models and Bayesian network inference.

Fossils from four genera (Ardipithecus, Kenyanthropus, Orrorin and Sahelanthropus) were excluded from the analysis on the basis that there is no fossil evidence that they persisted after 3 MYA. Our range of candidate species can be restricted to those in supplementary Table A.1.

We then used further data on geo-temporal proximity of one species to another to develop mathematical models to quantify the probability of HSV2 infection transmission so as to assess the likelihood that each of these species further transmitted HSV2 to another hominin (see methodology section for further detail of the model). If HSV2 was transmitted to *Homo erectus*, parsimony militates against the need for a further cross-species transmission event to be invoked to explain the infection of

Table 2. Sobol indices of transmission paths for HSV2-IT model using gamma distribution

Disease Transmission Route	Sobol total-order indices	Sobol first-order indices
anc-chimp \Rightarrow <i>P. boisei</i>	0.640	0.454
anc-chimp \Rightarrow <i>H. habilis</i>	0.519	0.334
<i>P. boisei</i> \Rightarrow <i>H. erectus</i>	0.0262	0.0262

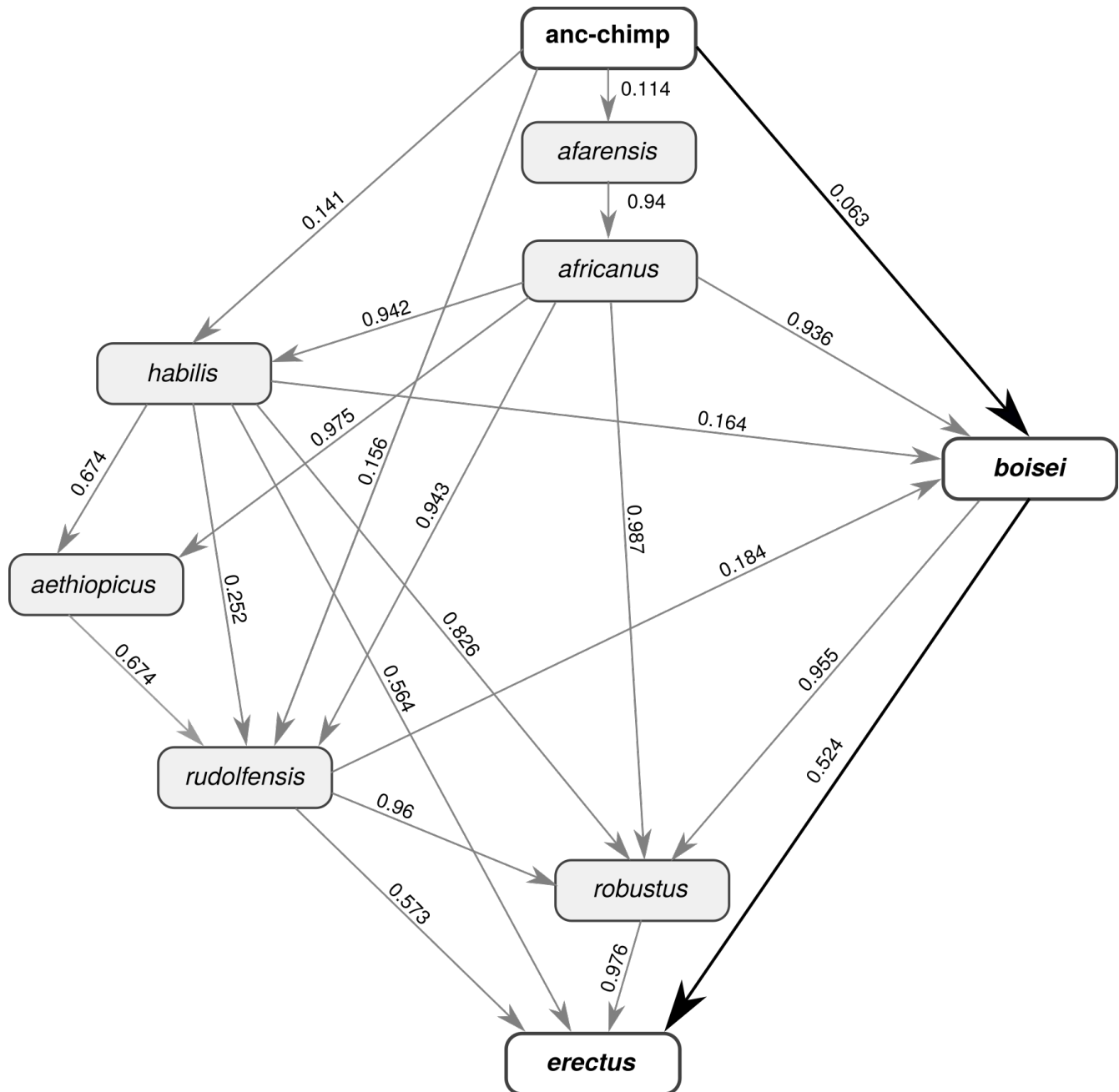


Figure 1. the A* shortest path route(s) for the Infection Prevalence model. The lines with arrows are the possible transmission paths. The values on the lines are the edge costs (inverse probability of transmission). This model predicts that the host switch of HSV2 occurred through the route ancestral-chimps, *P. boisei* and *H. erectus*. The route remained unchanged in the sensitivity analysis.

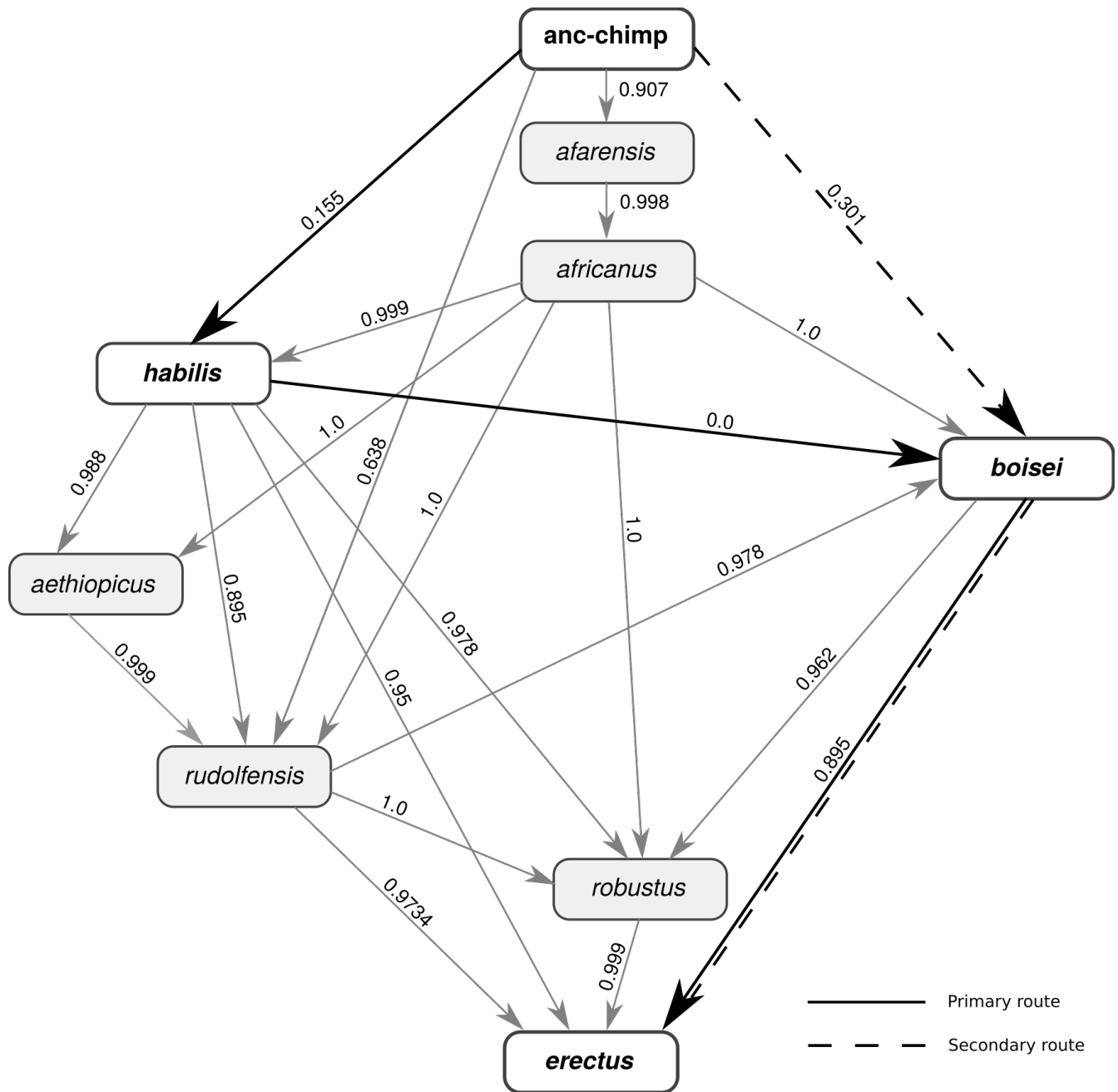
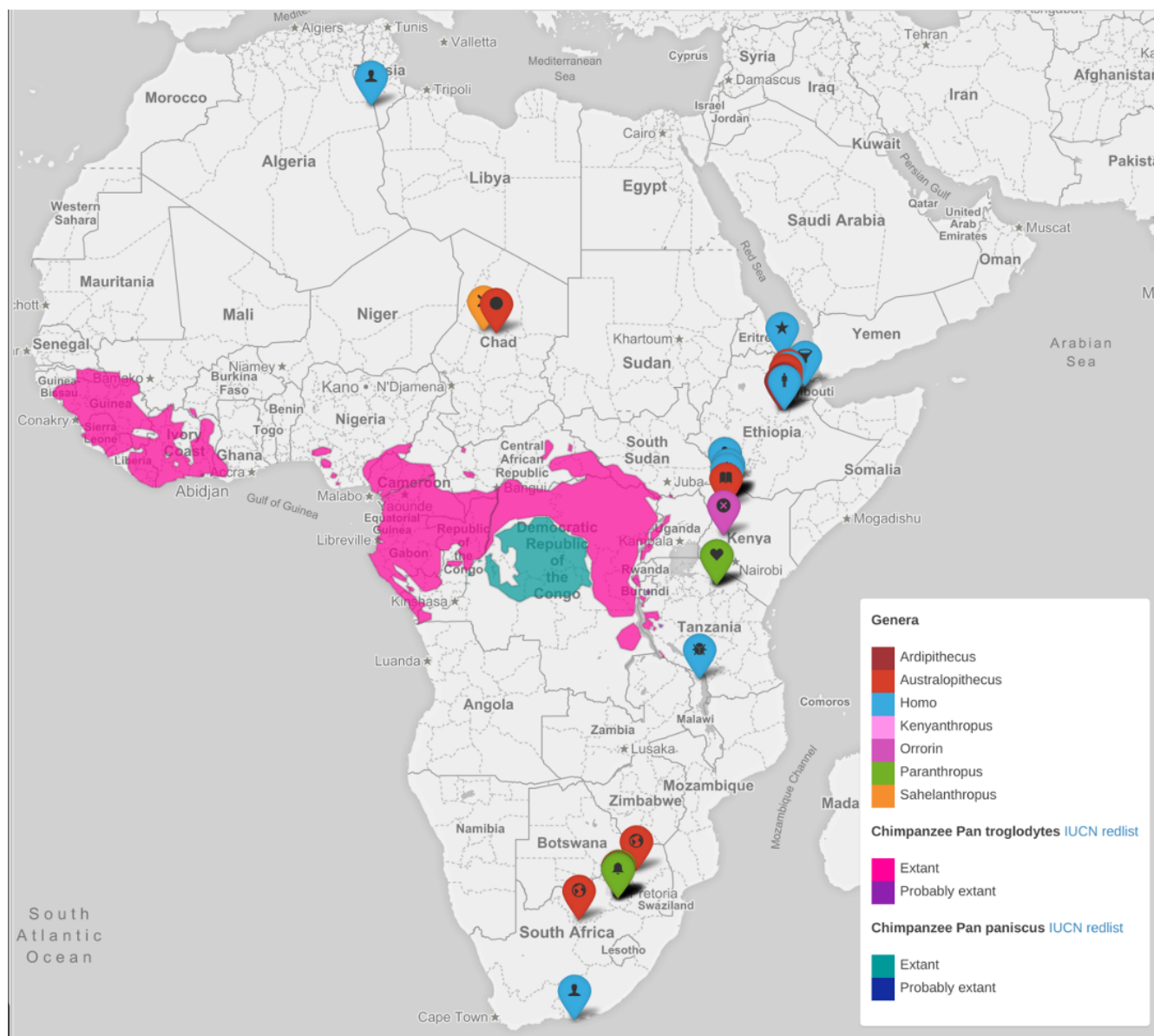
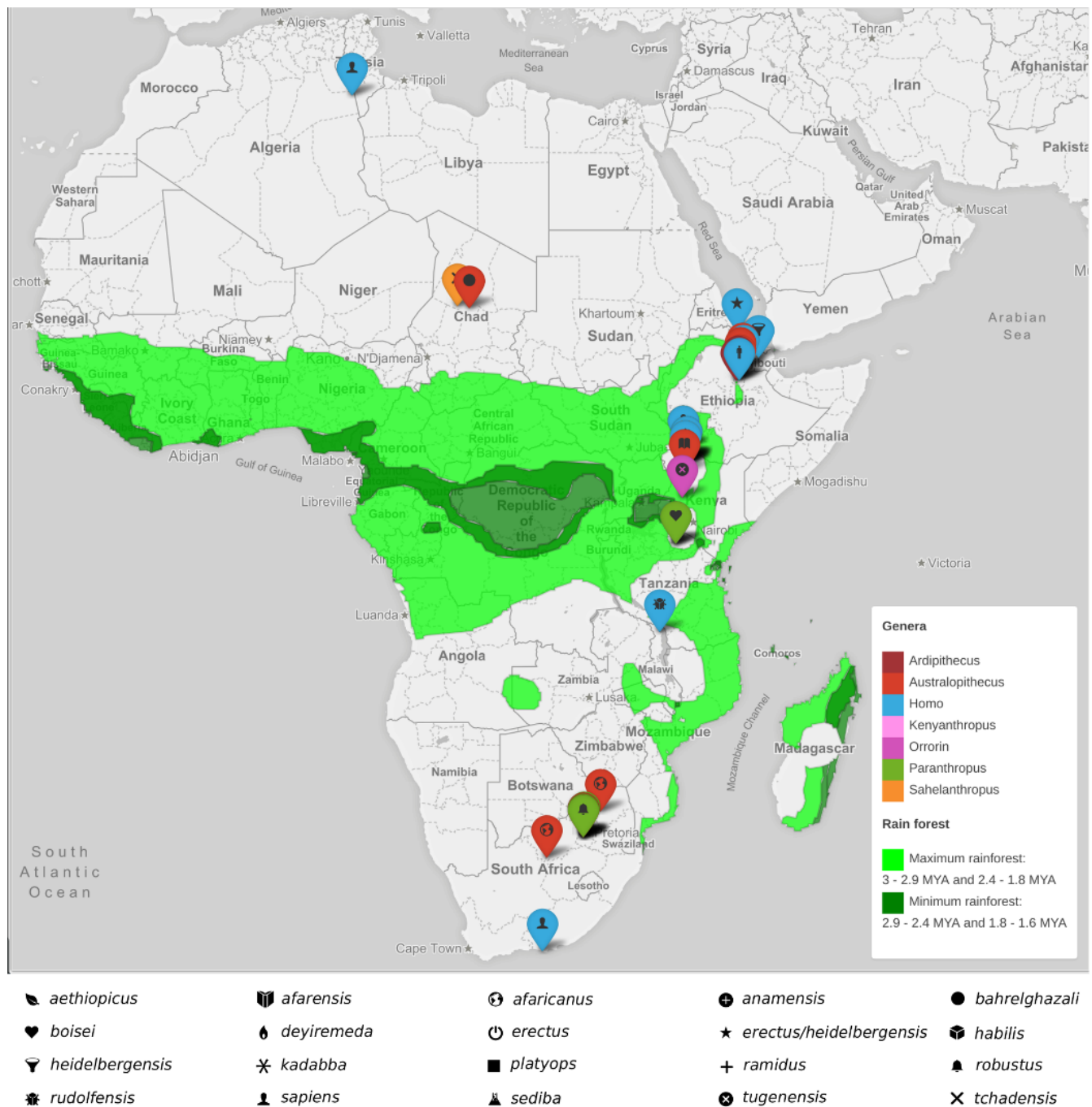


Figure 2. the A* shortest route for the Infection Transmission model. The lines with arrows are the possible transmission paths. The values on the lines are the edge costs (inverse probability of transmission). This model predicts that the host switch of HSV2 occurred through the primary route of ancestral-chimps, *H. Habilis*, *P. boisei* and *H. erectus*. Sensitivity analysis revealed the primary route occurred 60% as opposed to the secondary route of ancestral-chimps, *P. boisei* and *H. erectus* (which occurred the remaining 40%).



- | | | | | |
|------------------------|-------------------|-------------------|--------------------------------|----------------------|
| <i>aethiopicus</i> | <i>afarensis</i> | <i>afaricanus</i> | <i>anamensis</i> | <i>bahrelghazali</i> |
| <i>boisei</i> | <i>deyiremeda</i> | <i>erectus</i> | <i>erectus/heidelbergensis</i> | <i>habilis</i> |
| <i>heidelbergensis</i> | <i>kadabba</i> | <i>platyops</i> | <i>ramidus</i> | <i>robustus</i> |
| <i>rudolfensis</i> | <i>sapiens</i> | <i>sediba</i> | <i>tugenensis</i> | <i>tchadensis</i> |

(a) Distribution of extant chimpanzee (*Pan troglodytes*) and bonobo (*Pan paniscus*) populations [IUCN redlist <http://maps.iucnredlist.org/map.html?id=15933>, <http://maps.iucnredlist.org/map.html?id=15932>]. The locations of hominin fossils [supplementary table 1] are shown with markers. The colour of the marker indicates the hominin genus; the symbol represents the species.



(b) Location of hominin fossils relative to ancient minimum and maximum rainforest distributions (Peel, Finlayson, and McMahon, 2007). These figure are available interactively: <https://wadhamite.github.io/hsv-mapping/>.

Figure 3. Location of hominin fossils, extant chimpanzees, and ancient minimum and maximum rainforest distributions.

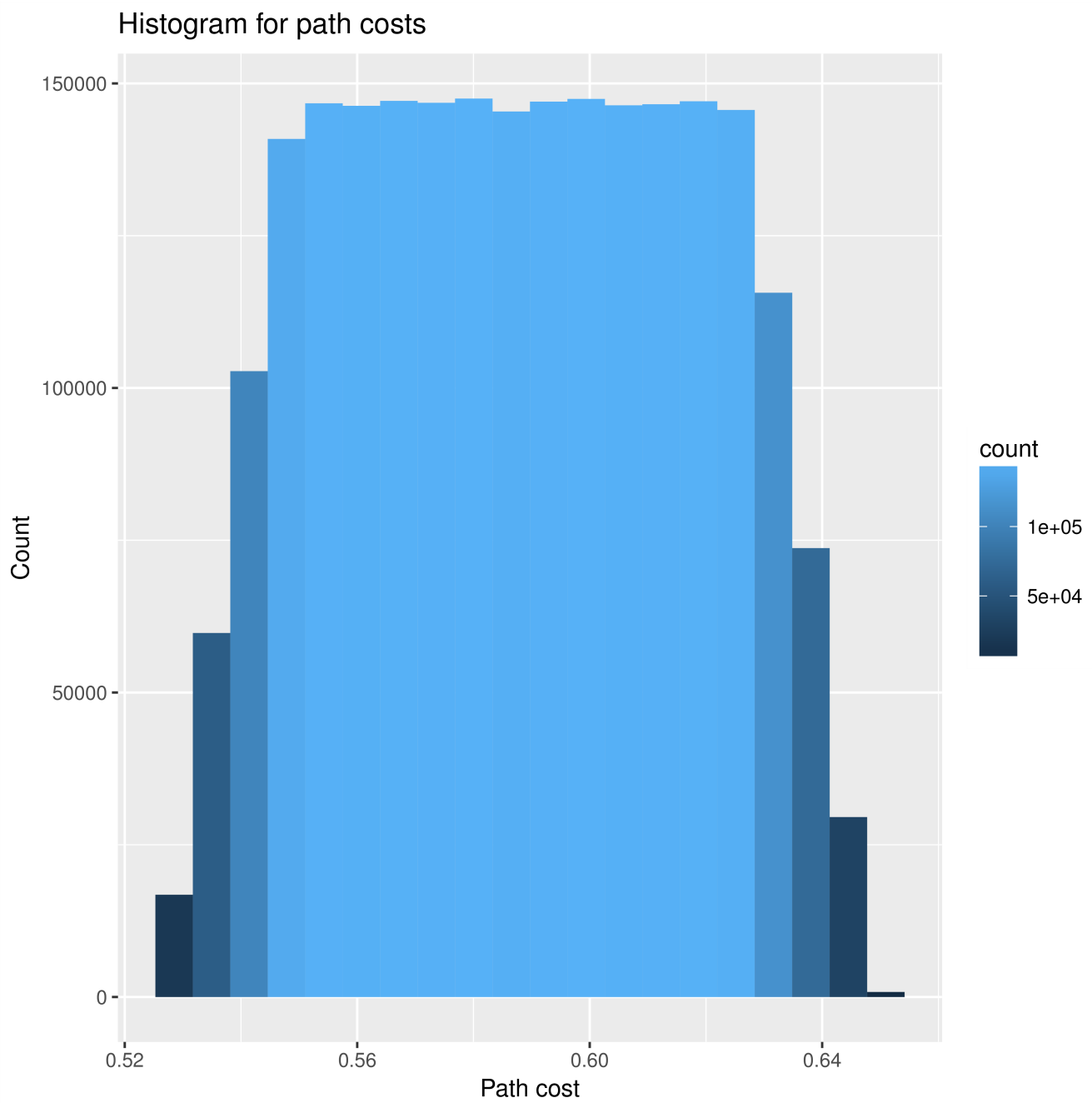


Figure 4. Path costs distribution for Infection Prevalence model. The shortest path is ‘anc-chimp \Rightarrow *P. boisei* \Rightarrow *H. erectus*’ with an average path cost 0.587.

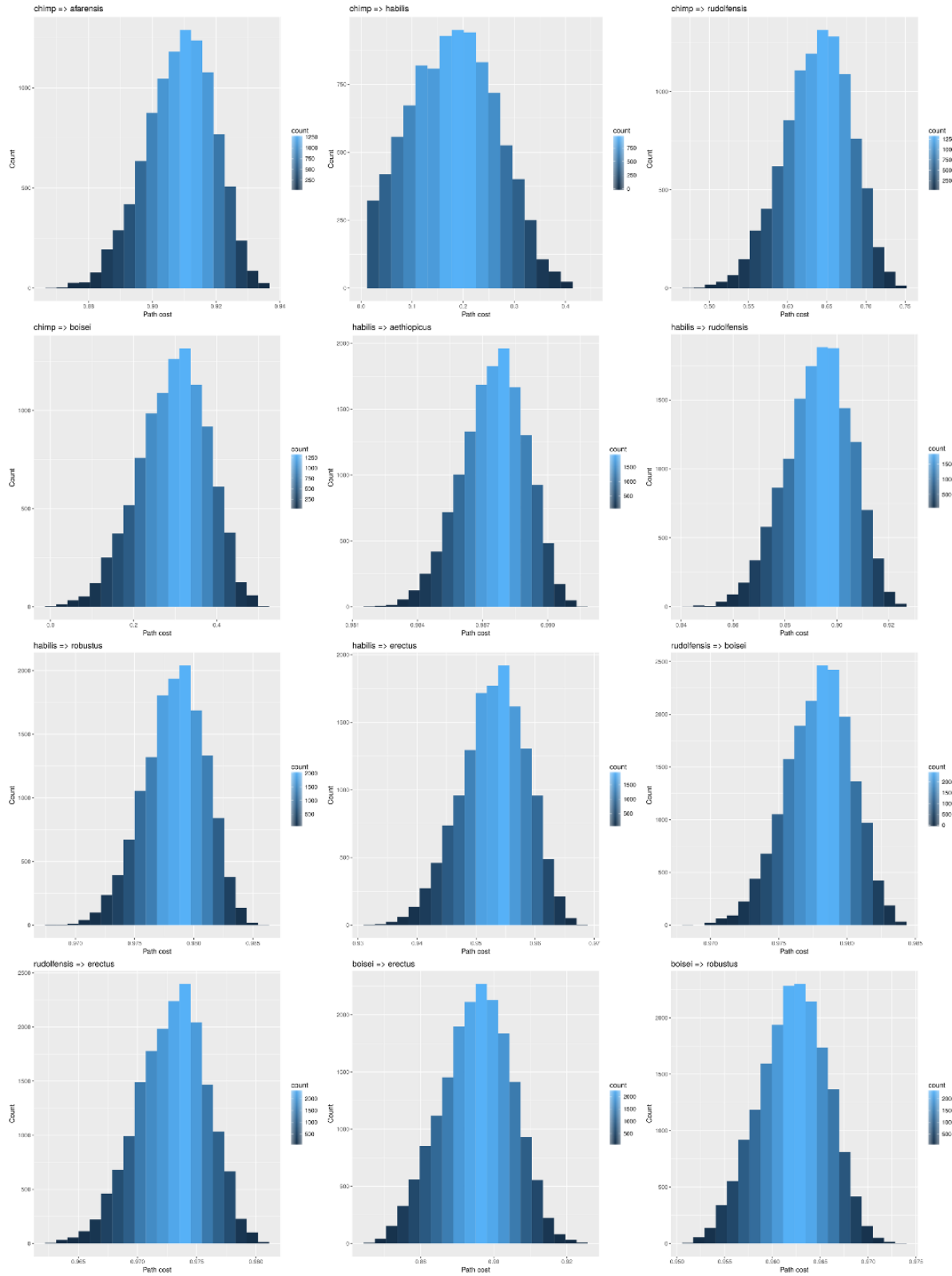
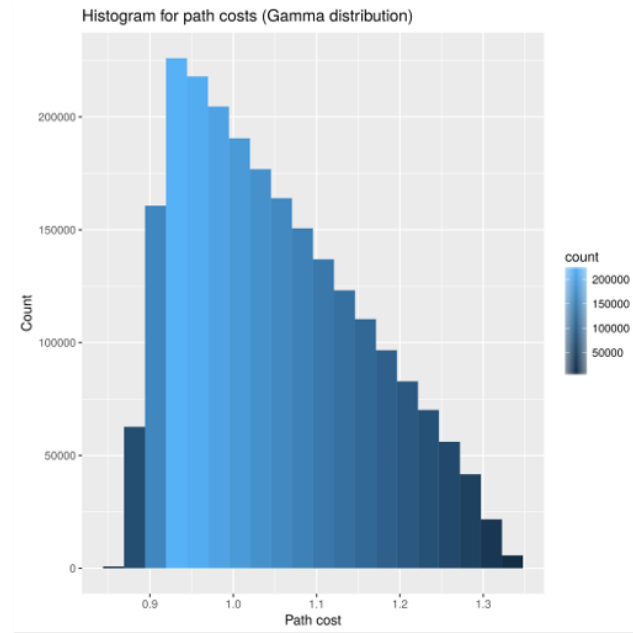
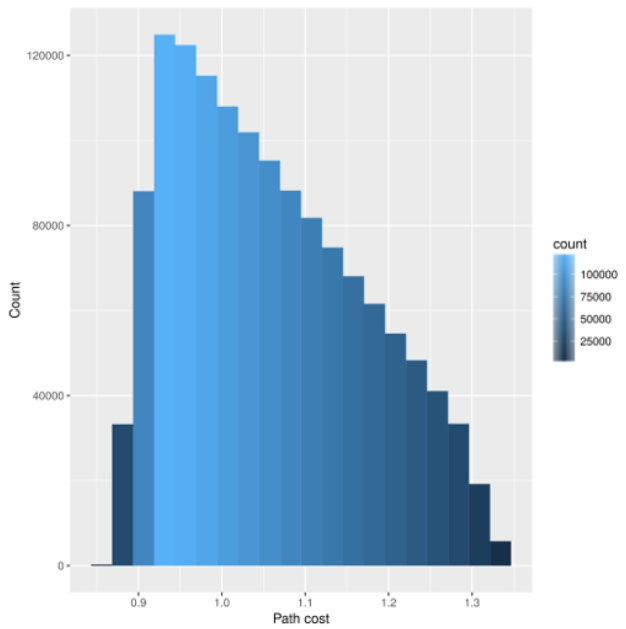


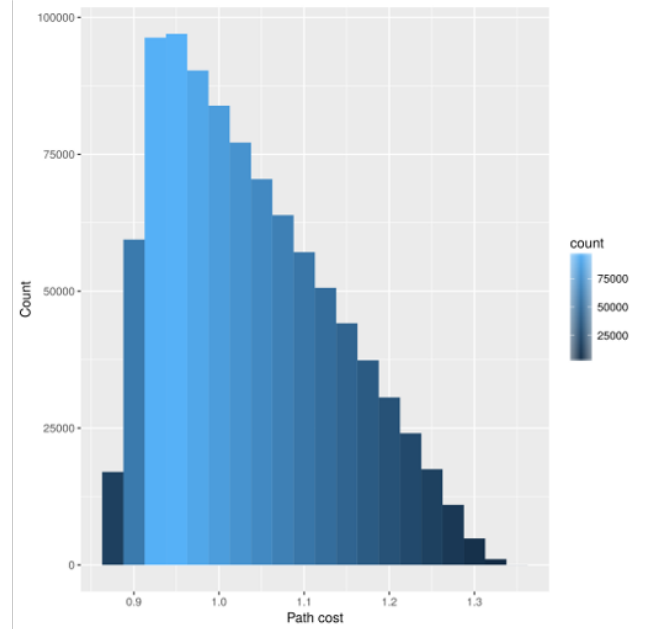
Figure 5. Distribution of selected edge costs for Infection Transmission model. Each histogram shows the distribution of edge costs for the IT model of HSV2 transmission. Colour contours indicate the number of occurrences of a path cost in the sensitivity analysis. The lowest edge costs are seen for ‘anc-chimp \Rightarrow *H. habilis*’, ‘anc-chimp \Rightarrow *P. boisei*’ and ‘*P. boisei* \Rightarrow *H. erectus*’.



(a) Infection Transmission model (all routes)



(b) Primary transmission route



(c) Secondary transmission route

Figure 6. Path costs distribution for Infection Transmission model. Each histogram shows the distribution of path costs for the IT model of HSV2 transmission. Colour contours indicate the number of occurrences of a path cost in the sensitivity analysis. The optimal transmission route is ‘anc-chimp \Rightarrow *H. habilis* \Rightarrow *P. boisei* \Rightarrow *H. erectus*’. (a) Total distribution of path costs for HSV2-IT model, (b) distribution path costs for the primary transmission route (‘anc-chimp \Rightarrow *H. habilis* \Rightarrow *P. boisei* \Rightarrow *H. erectus*’), and (c) distribution path costs for the secondary transmission route (‘anc-chimp \Rightarrow *P. boisei* \Rightarrow *H. erectus*’).

modern humans by HSV2. Simple vertical mother-to-child or horizontal (sexual) transmission of the virus through the genus *Homo* from this point would be sufficient as the ancestor-descendent path from *Homo erectus* to *Homo sapiens* is relatively secure Maslin, Shultz, and Trauth, 2015.

Discussion

Transmission of HSV2

Our analysis suggests that *Homo rudolfensis* was the most likely intermediate host of HSV2 between chimpanzees and the ancestors of *Homo sapiens*. The combined inference analysis of a Bayesian Network, considering the presence of HSV2 in both ancestral-chimpanzees and *Homo erectus*, revealed *A. afarensis* (90.33%), *H. habilis* (60.85%), *P. boisei* (57.3%), and *H. rudolfensis* (42.6%) to be the likely intermediary hosts. However, *A. afarensis* could only transmit to *A. africanus*, which had a mere 6% chance of being infected by HSV2. This narrowed the possibility of transmission through *H. habilis*, *P. boisei* and *H. rudolfensis*, either directly or as intermediary hosts. Infection Prevalence (HSV2-IP) describes the probability of HSV2 infection based on the proximity to the rain forest habitat and the duration (difference between the first and the last appearance datum) using a beta distribution. While, the Infection Transmission (HSV2-IT) model assigns probability values (edge costs) to the DAG utilising the temporal overlap between hominin species and their geographic proximity to one another. The A* algorithm estimated the minimum path costs of 0.252 and 0.87 for the transmission route through *Homo rudolfensis* for both HSV2-IP and HSV2-IT based DAGs, respectively. Bayesian network inference analysis estimated the highest probability of HSV2 transmission (11.6%) to the ancestors of *Homo sapiens* through *rudolfensis*. Transmission through *boisei* and *habilis* was estimated to be 9.3% and 7.8% probable. A* optimal path traversals also predicted *boisei* and *habilis* to be the second (5% less likely than *rudolfensis*) and the third (7% less likely than *rudolfensis*) most probable routes. These algorithms predict a single intermediate hominin to be more likely than multiple-levels of transmissions. The A* algorithm and the Bayesian network inference have clearly demonstrated that *Homo rudolfensis* is the most likely intermediate hominin host.

Tropical refugia during hot dry periods may have driven chimpanzees into higher concentrations in certain areas, driving them into contact and competition with *Homo rudolfensis*. Violent confrontation or predation in combination with hunting and butchery practices would have provided a viable route of transmission for HSV2. While no stone tools have to date been found in the same archaeological strata as *Homo rudolfensis* fossils it is a logical assumption that they would have been extensively used by this species Ungar, Grine, and Teaford, 2006; Torre et al., 2003 as Oldowan or Mode 1 stones tools are widely distributed in the same spatial-temporal localities as *Homo rudolfensis* fossils Stern et al., 1993; Leakey et al., 2012. *Paranthropus aethiopicus*, *P. boisei*, and *P. robustus* are associated with the Oldowan stone tool complex De Heinzelin et al., 1999, and *P. boisei* explicitly with butchery Domínguez-Rodrigo, Pickering, Baquedano, et al., 2013 lending support to the hypothesis that bushmeat hunting and butchery may have led to the initial transmission of HSV2 to the hominins. *A. afarensis*, although a tool user, can be excluded both on statistical grounds and by the lack of evidence for hunting and butchery within this species which instead used tools to scavenge the carcasses left behind by savannah predators Domínguez-Rodrigo, Pickering, and Bunn, 2010; Domalain, Bertin, and Daver, 2016.

Although ChHV1 causes outbreaks of oral and pharyngeal lesions in chimpanzees in a manner similar to HSV1, in hominins contracting the virus which was to become HSV2, the oral niche was already occupied by HSV1. This may have protected the hominin first infected with HSV2: pre-existing infection with HSV1 reduces the likelihood that subsequent infection with HSV2 will be symptomatic Langenberg et al., 1999, and also reduces the risk of HSV2 meningitis Aurelius et al., 2012. HSV2 may have been forced to adapt to a different mucosal niche in order to reduce competition from the co-evolved, native HSV1.

We suggest that the mode of transmission of HSV2 into hominins was most likely through hunting injuries (eg chimpanzee bites or cuts sustained during meat processing), although onwards transmission into the ancestors of *Homo sapiens* could have been sexual (horizontal) or a result of hunting injuries (vertical). There are many reports of transmission of B virus (*Cercopithecine herpesvirus 1*), the cercopith homolog of HSV1 and ChHV1, to humans, where disease ranges from mild to fatal. Transmission has occurred from bites and scratches, needle sticks and even scratches from cage bars that are contaminated with B virus-positive bodily fluids Huff and Barry, 2003. Onwards transmission between humans has been reported to occur Centers for Disease Control (CDC), 1987. Human herpesvirus 1 can infect other primates, from gorillas Gilardi et al., 2014 to owl monkeys Melendez et al., 1969, typically causing fatal disease in species more distantly related to *Homo sapiens*, while causing oral lesions and milder disease in great apes such as *Gorilla beringei graueri* Gilardi et al., 2014. We therefore infer that herpes simplex-like viruses spread relatively easily between individuals even across species barriers, increasing the chances of transmission between hominins and other primates from close contact such as hunting, butchery, inter-personal violence or sexual contact. Evidence for close hominin-hominid contact is also found in other 'heirloom' human pathogens Houldcroft et al., 2017.

The high prevalence of HSV2 in central and eastern Africa (see Figure A.1) and interactive maps at <https://wadhamite.github.io/hsv-mapping>) is consistent with the limited genetic data available from African HSV2 isolates. A study from Burrell and colleagues Burrell, Desire, et al., 2015 showed that HSV2 can be divided into African and worldwide

lineages on the basis of diversity in gene UL30. Furthermore, they found evidence of gene flow from HSV1 into HSV2, and speculate that the flow of HSV1 loci into the worldwide HSV2 lineage may have helped this lineage of HSV2 to further adapt to human hosts, and so spread more successfully around the world from around 41kya Burrell, Boutolleau, et al., 2017. Two recent studies have significantly increased the number of whole HSV2 genomes available for analysis, contributing to our knowledge of HSV2 diversity Szpara et al., 2014; Kolb et al., 2015, however precise geographic origins of each sample are not available. More whole HSV2 genomes from central and east Africa, with clear country of origin data, are needed to enrich this picture, as our model predicts that individuals from east Africa are also likely to carry ancient HSV2 lineages.

The time-depth of ancient DNA analysis is dually limited by technology and preservation of DNA. Similarly the archaeological and fossil records suffer from differential rates of preservation and gaps that can never be filled because the material has simply not survived. Our analysis has allowed the reconstruction of hominin/human-disease interaction well beyond the horizon of ancient DNA and at a level that is invisible to the fossil and archaeological records. Demonstrating the potential for using modern disease genetics to better understand the evolutionary interaction between humans and disease in deep time.

Data presentation

The distribution maps were created with custom JavaScripts codes using Leaflet.js library [<http://leafletjs.com/>] and interactive maps can be found at <https://wadhamite.github.io/hsv-mapping>

Author contributions

SJU and CH conceived the study and contributed data. SJU, KK and CH performed the analyses. SJU, KK and CH wrote the paper. All authors approved the publication of the manuscript.

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Supplementary material

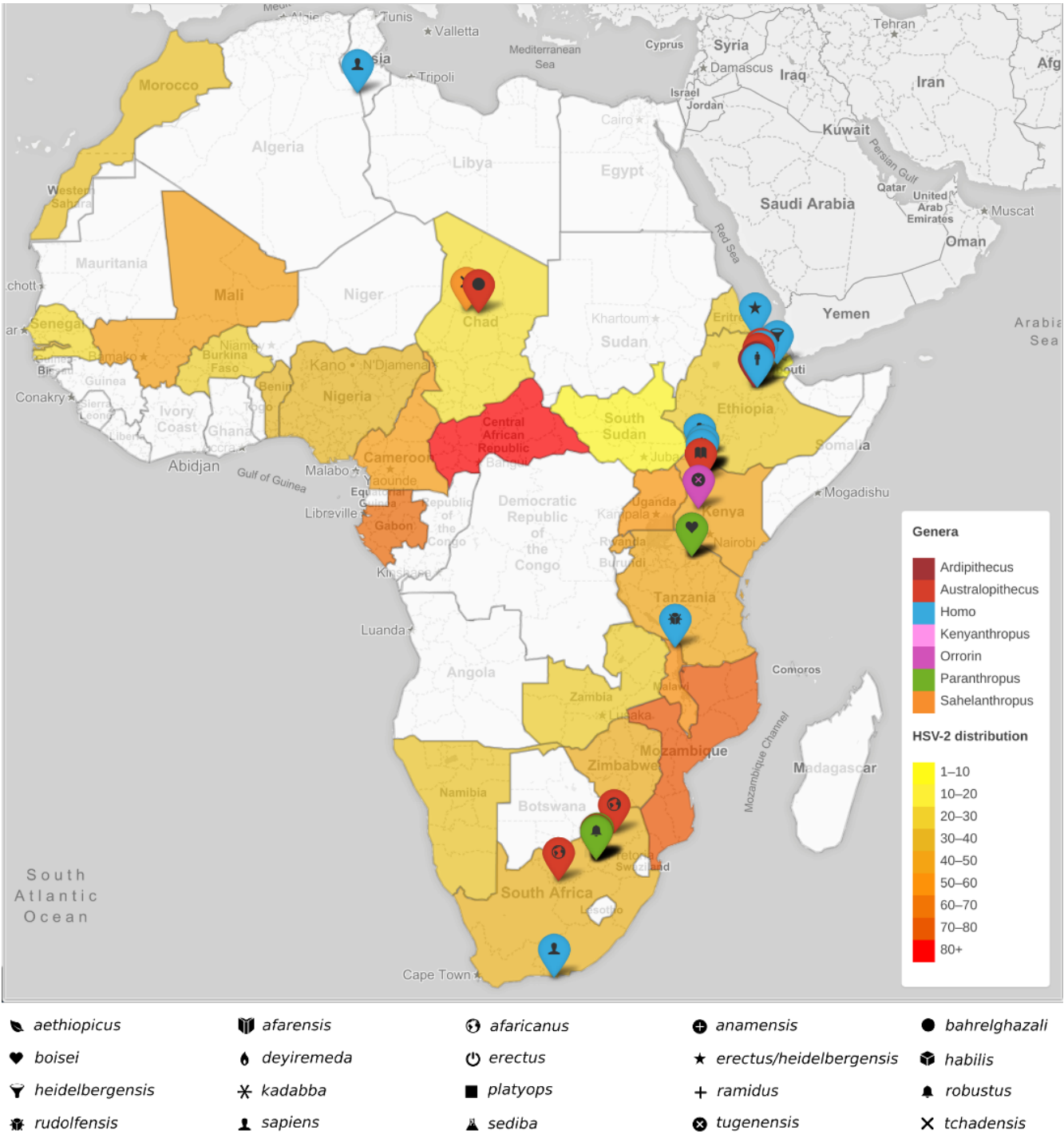


Figure A.1. Prevalence of HSV2 in Africa

Table A.1. Fossil hominins with the potential to acquire - HSV2 from ancestral chimpanzee

Species	Type specimen	Locations (type specimen)	Age (000s BP)	Publication (suggesting a new species)
<i>Australopithecus afarensis</i>	LH4 (mandible)	East Africa (Laetoli, Tanzania)	3900 - 2800	Johanson DC, White TD and Coppens Y 1978 A new species of the genus <i>Australopithecus</i> (Primates: Hominidae) from the Pliocene of eastern Africa. <i>Kirtlandia</i> 28: 2-14.
<i>Australopithecus africanus</i>	Taung 1 (cranium)	Southern Africa (Taung, SA)	2800 - 2300	Dart RA 1925 <i>Australopithecus africanus</i> : The man-ape of South Africa. <i>Nature</i> 115: 195-199.
<i>Australopithecus gahri</i>	BOU-VP-12/130 (cranium)	East Africa (Bouri, Ethiopia)	2500	Asfaw B, White T, Lovejoy O, Latimer B., Simpson S and Suwa G 1999 <i>Australopithecus garhi</i> : A new species of early hominid from Ethiopia. <i>Science</i> 284: 629-635.
<i>Paranthropus aethiopicus</i>	Omo 18-1967-18 (mandible)	East Africa (Omo, Kenya)	2700 - 2300	Arambourg C and Coppens Y 1967 Sur la découverte, dans le Pléistocène inférieur de la vallée de l'Omo (Éthiopie), d'une mandibule d'australopithécien. <i>Comptes Rendus de l'Académie des Sciences, Paris, series D</i> , 265: 589-590.
<i>Paranthropus robustus</i> (including <i>Paranthropus crassidens</i> , SK 48)	TM 1517 (various)	Southern Africa (Kromdraai, SA)	1800 - 1000	Broom R 1938 The Pleistocene anthropoid apes of South Africa. <i>Nature</i> 142: 377-379.
<i>Paranthropus boisei</i>	OH 5 (cranium)	East Africa (Olduvai Gorge, Tanzania)	1750 - 1200	Leakey LSB 1959 A new fossil skull from Olduvai. <i>Nature</i> 184: 491-493.

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Species	Type specimen	Locations (type specimen)	Age (000s BP)	Publication (suggesting a new species)
<i>Homo habilis</i> (Australopithecus?)	OH 7 (mandible)	East Africa (Olduvai Gorge, Tanzania)	2500 - 1600	Leakey LSB, Tobias PV and Napier JR 1964 A new species of the genus <i>Homo</i> from Olduvai Gorge, Tanzania. <i>Nature</i> 202: 308-312.
<i>Homo rudolfensis</i> (Kenyanthropus?)	KNM-ER 1470 (cranium)	East Africa (Koobi Fora, Kenya)	2400 - 1800	Leakey RE 1973 Evidence for an advanced Plio-Pleistocene hominid from east Rudolf, Kenya. <i>Nature</i> 242: 447-450.
<i>Homo erectus</i>	KNM-ER 992 (mandible)	Africa (Koobi Fora, Kenya)	2000 - 600	Groves CP and Mazák V 1975 An approach to the taxonomy of the Hominidae: Gracile Villafranchian hominids of Africa. <i>Casopis pro Mineralogii Geologii</i> 20: 225-247.