Evolution of *Homo sapiens* in Asia: an alternative implication of the "Out-of-Africa" model based on mitochondrial DNA data

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ABSTRACT

Cann *et al.* [1] have claimed on the basis of mitochondrial DNA (mtDNA) data that our direct ancestral *Homo sapiens* evolved in the African continent and spread to other continents, followed by the total replacement of the indigenous population. Their "Out-of-Africa" model is based on the assumption that mtDNA inheritance is simply maternal. Recent findings suggest the possibility that in between-population, e.g. African and Asian, mating, the African paternal mtDNA was transferred to the egg cell of an Asian together with Y-chromosomal DNA in the human past. Considering that Y-chromosomal DNA and mtDNA sequences of African origin coexist together with Asian X-chromosomal and autosomal DNA sequences in a current Asian, the observations by Cann *et al.* suggest the full/near full replacement of mtDNA in the human past, but do not necessarily imply the total replacement of indigenous populations with African migrants.

Keywords: Out-of-Africa Model; Origin of Asian; Paternal mtDNA Inheritance; mtDNA Transmission/ Recombination

1. INTRODUCTION

Evidence has accumulated that the *Homo* lineage originally appeared in Africa, followed by its successful global expansion. The view of "Out-of-Africa" that our direct ancestral *H. sapiens* evolved in the African continent and spread to other continents, has been popularly received among researchers [1-8]. On the other hand, there have been significant fossil records in non-African continents, supporting the "regional continuity" model [9]. This model claims that our direct ancestral *H. sapiens* evolved locally in the widespread regions of major con-

tinents, e.g. Africa, Europe and Asia [10-12]. In fact, morphological continuity in East Asian traits from East Asian *Homo erectus* during the middle-late Pleistocene transition can be seen in these fossil records [12-14]. However, most of these records have neither definitely refuted nor supported one of the models for or against the origin of *H. sapiens*, particularly in Asia. Furthermore, most genetic evidence, such as simulated dendrograms, genetic diversity and ancient DNA sequences can argue for either model of human origin [15].

In 1987, a crucial observation was made by Cann *et al.*, who examined the human mitochondrial DNA (mt DNA) diversity of globally dispersed populations. They concluded that modern humans simply spread to other continents, e.g. East Asia, from Eastern Africa around 200,000 years to 50,000 years (200 KY to 50 KY) ago, followed by the total replacement of pre-inhabited indigenous populations [1,2]. The "Out-of-Africa" model, reconstructed with mtDNA data, is primarily based on a few assumptions. One of the key assumptions is that animal mtDNA does not undergo homologous recombination. This is because of past failure to observe the clear cases of mtDNA recombination in natural populations. However, recent findings have raised a new insight into mtDNA inheritance and the behaviours of mtDNA in a fertilised egg [16,17]. In this study, an attempt was made to integrate the interdisciplinary information obtained in the research fields, not only anthropology and mitochondrial genetics but also other areas, such as developmental biology, ecology and social sciences. A meta-analysis of these findings has raised the need of careful scrutiny in the interpretation of Cann *et al.* [1,2].

2. CRITICAL VIEW OF MITOCHONDRIAL DNA INHERITANCE: STRICTLY MATERNAL?

Two sibling bat species, European *Myotis myotis* and newly migrated *M. blythii* to Europe from Asia, share

multiple identical or very similar haplotype in mitochondrial genomes when they occur in sympasy. However, they show a strikingly different pattern of nuclear DNA diversity. On the other hand, allopatric *M. blythii* in Asia possesses mtDNA divergent from those of two species in Europe, postulating that the mtDNA of European *M. blythii* has been replaced with that of *M. myotis* [18]. Similar mtDNA (full/near-full/partial) replacement has been observed in a wide variety of other species in an animal kingdom, for example, nematodes [19], molluscs [20], insects [21], fishes [22] and mammals other than bats, such as vole [23]. As opposed to the popular belief, all of these observations suggest that paternal mtDNA inheritance occurs widely in the animal kingdom. In fact, paternal mtDNA inheritance has been observed even in humans [24,25]. At present, no specific information has been reported, which strongly favours the notion that these human cases were really exceptional and that human mtDNA replacement, similar to the cases of *Myotis*, has never taken place in evolution when two "sibling" human populations met and lived in sympasy. Furthermore, evidence has shown that the segregation and transmission of mtDNA sequences [26-28] play a crucial role in the inheritance of human mitochondrial diseases [16].

Molecular and cellular events at an early stage of fertilisation would also provide us with more information which we can not ignore the view of paternal mtDNA inheritance in human. During the process of fertilisation in mammals, up to 100 sperm mitochondria actually enter an egg cell, together with the sperm head [17,29, 30]. However, these paternal mtDNAs are soon destroyed by a selective elimination mechanism, including ubiquitination of paternal mitochondria [30]. However, the elimination mechanism in the fertilised egg cell is not always highly stringent and fails to destroy all of the inserted paternal mitochondria, causing paternal leakage [30]. Such leakage was observed in mice progeny at a frequency of around one in 10,000 [31]. An interesting observation was that when "non-self" paternal mitochondria—in terms of the population/subspecies/species, to which the mating partner belongs—are inserted into the egg cell, such as in the mating between cow and gaur, these mitochondria are not eliminated and remain active in the fertilised egg cell [30]. In the mating between two inbred mouse strains, *Mus musculus* and *M. spretus*, a similar escape of paternal mitochondria through the elimination mechanism was observed as well [32]. These leakages would lead to a heteroplasmic offspring and thereby enhance the opportunity of transmission or recombination. It has been shown that human mitochondrial particles are fully equipped with the toolkits required for recombination [33-35]. Furthermore, each mitochondrial organelle holds the mechanisms, leading from heteroplasmy to the transmission of mtDNA [16, 28]. The detailed molecular mechanisms for paternal mtDNA inheritance and replacement might differ from one case to the other [36] and, at present, remain to be examined in each case.

3. THE POSSIBLE FULL/NEAR-FULL REPLACEMENT OF MTDNA SEQUENCES IN THE HUMAN PAST

It is highly likely that the anatomically modern humans that originated in Africa were different from those who inhabited in allopasy in the Asian continent for a long evolutionary period [37]. Furthermore, different populations have differing variation in biological responses [38]. Therefore, African migrants and indigenous inhabitants in Asia were likely to show different recognition responses to the partner's paternal mitochondria in their "between-population" mating although they were sibling and hybridisable. Thus, the ubiquitin-tagged paternal mitochondria, which were inserted in the egg cell, would not be subject to stringent mitochondrial elimination and could survive in the fertilised egg cell, as seen in the case of cow and gaur pairing [30]. There would be a huge difference in recognition response between Palaeolithic African migrant and inhabited Asians, who had never exposed to Africans and thus much more paternal (African) mtDNA molecules might had remained active without any damages in Asian egg cells in their "between-population" mating. Since current human populations have already mixed each other in some degree, I believe that much more African paternal mtDNA molecules had survived in Palaeolithic Asian egg cells than those we suspect in current "between-population" mating.

Most, if not all, of advocates for the "Out-of-Africa" model based on mtDNA data often argue against the alternative model of human origine on the following basis: The alternative model has not based on the conclusive evidence showing the recombination/paternal transmission of mtDNA in the human past. However, we should realise that the "Out-of-Africa" model has been standing on the shaky—recently much more shaky—ground without any explicit and conclusive evidence, showing that any recombination/paternal transmission of mtDNA had not taken place in the human past. In fact, Wilson [39] has mentioned that many puzzles have remained between Y-chromosome and mtDNA data in the conservative interpretation of the complex data in human migration. In the present paper, I have already mentioned the new findings, which include the paternal mtDNA behaviours in the fertilised eggs and the recombination/paternal transmission of mtDNA in the wide

range of animal kingdom. In fact, taking all of these new findings into consideration, it is much more difficult to prepare a reasonable explanation for the notion that a series of the events, leading to the replacement of maternal mtDNA with the paternal DNA, had never taken place in the human past. As already mentioned, the transmission or recombination of mtDNA in the animal kingdom has occurred more frequently and more widely than we have previously suspected. Therefore, the limited human cases that have been currently reported so far on the replacement of mtDNA should not be claimed against the argument for the possible replacement events in the human past.

Cann *et al.* [1] have shown that the mtDNA itself of current humans in the Asian continent is really of African origin. However, their claim that indigenous inhabitants in Asia became completely extinct and were totally replaced with African migrants is confusing. As will be discussed in the next section, the present meta-analysis shows that ironically, their result together with chromosomal DNA sequences can nicely account for the possible paternal mtDNA inheritance in the human past. Thus, this novel view does not necessarily imply the extinction of Asian indigenous inhabitants, followed by the *total* replacement of the human population in Asia.

4. DISCUSSION AND CONCLUSION

The estimated ages of the most recent common ancestor (MRCA) of Y-chromosomal DNA sequences, such as several sites on SRY and YAP regions, were around 150 KY ago [40]. Current non-African men carry the M168 mutation, which arose in Africa during the period of 89 KY to 35 KY ago [41-43]. All of these sequences on Y-chromosome were much younger than those (1,860 KY to 535 KY ago) of X-chromosomal DNA sequences, e.g. gene coded for pyruvate dehydrogenase E1α [44] and non-coding sequences Xq [45], and autosomal DNA sequences, e.g. gene coded for β-globin [46] and non-coding sequences on chromosome 22 [47]. It should be noted that the MRCA ages of Y-chromosomal DNA sequences roughly correspond to the time (200 KY-100 KY ago) of human migration to Asia and thus that the Y-chromosomal and mtDNA sequences were likely to arise in the ancestor who lived in Africa around < 200 KY ago [2]. On the other hand, the DNA sequences on X-chromosome and autosomes could be traced back to the era of *H. erectus* in Asia [10,48-50]. Therefore, these results clearly suggest that the current Asians would be the offspring of the hybrids resulting from the mating between migrated Africans and indigenous Asian inhabitants. However, it appears likely that African migrants brought only African Y-chromosomal and mt D-NA sequences to Asia [51] and most of Asian X-chromosomal and autosomal DNA sequences remained in the hybrid offspring. The most plausible scenario of the event in Palaeolithic Asia would be as follows: In the "between-population" mating, African Y-chromosomal DNA entered an Asian egg cell, accompanying with his mtDNA. The newly inserted paternal mtDNA remained intact without any significant damage/elimination in the fertilised egg cell and then formed heteroplasmy in the hybrid. After a series of transmission or recombination processes, the maternal mtDNA of Asian origin was fully/near-fully replaced with the paternal (African) mtDNA. Considering the possibility that the dilution-out and/or selective sweep of African X-chromosomal and autosomal DNA sequences might have occurred for evolutionary advantage, the X-chromosomal and autosomal DNA sequences of Asian origin would tend to be preserved more often and finally would be maintained as a major component in the East Asian population [52]. Therefore, the male offspring, including a current Asian male, would not necessarily be the direct descendant of a replaced African, but would be the hybrid offspring possessing the mitochondrial and Y-chromosomal DNA sequences of African origin, together with Asian X-chromosomal and autosomal DNA sequences. The sequence data, if possible, of chromosomal DNA and mtDNA of Palaeolithic Asian remains and the comparison with those of current humans in different populations should give a brighter view on this issue. The view raised in this paper would open a new research field of biological interactions, particularly in "between-population" reproduction in the human past.

5. ACKNOWLEDGEMENTS

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