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Review

A history of you, me, and humanity: mitochondrial DNA in anthropological research

Jada Benn Torres*

Laboratory of Genetic Anthropology, Department of Anthropology, Vanderbilt University, Nashville, TN 37325, USA

*** Correspondence:** Email: j.benntor@vanderbilt.edu; Tel: +615-343-6120.

Abstract: Within genetic anthropology, mitochondrial DNA (mtDNA) has garnered a prominent if not enduring place within the anthropological toolkit. MtDNA has provided new and innovative perspectives on the emergence and dispersal of our species, interactions with extinct human species, and illuminated relationships between human groups. In this paper, I provide a brief overview of the major findings ascertained from mtDNA about human origins, human dispersal across the globe, interactions with other hominin species, and the more recent uses of mtDNA in direct to consumer ancestry tests. Relative to nuclear DNA, mtDNA is a small section of the genome and due to its inheritance pattern provides a limited resolution of population history and an individual's genetic ancestry. Consequently, some scholars dismiss mtDNA as insignificant due to the limited inferences that may be made using the locus. Regardless, mtDNA provides some useful insights to understanding how social, cultural, and environmental factors have shaped patterns of genetic variability. Furthermore, with regard to the experiences of historically marginalized groups, in particular those of African descent throughout the Americas, mtDNA has the potential to fill gaps in knowledge that would otherwise remain unknown. Within anthropological sciences, the value of this locus for understanding human experience is maximized when contextualized with complementary lines of evidence.

Keywords: mitochondrial DNA (mtDNA); genetic ancestry; human origins; human evolution; migration; direct-to-consumer tests

1. Introduction

Situated within nucleated cells, mitochondria are organelles that are primarily responsible for energy production. Beyond their capacity to produce energy, mitochondria also have a role within apoptosis, or programmed cell death, cellular metabolism, and intracellular messaging [1]. Within human cells there are multiple copies of mitochondria and within each mitochondria, there are 2 to 10 copies of the circular 16,569 base pair genome. This extra-nuclear DNA results in hundreds to thousands of copies of the mitochondrial genome within a cell [2]. The high copy number of mitochondrial genomes within cells makes mtDNA a methodologically advantageous genetic locus to genotype. The mitochondrial genome itself contains 37 genes that code for different types of RNAs and proteins. Conventionally, only small portions of the mitochondrial genome have been utilized in genetic anthropological research. These regions are known as hypervariable region I and II (HVS I and HVS II), corresponding to nucleotide positions 16024-576 in addition to certain single nucleotide polymorphisms found throughout the coding region. Increasingly however, more recent studies utilize the whole mitochondrial genome rather than just the coding region polymorphisms and hypervariable regions. MtDNA also has a unique inheritance pattern that is unlike the inheritance of nuclear DNA. MtDNA is inherited from mother to child generally unchanged generation after generation. Only women pass their mtDNA to offspring and only female offspring pass the same mitochondrial lineage to subsequent generations. Due to this uni-parental inheritance pattern, mtDNA is particularly useful for examining questions about female migration as well as sex-biased gene flow between populations [1].

In addition to its inheritance pattern, mtDNA also has a distinct geographic distribution across global populations. Mitochondrial lineages, or haplotypes, differ in sequence from one another. The differences between the haplotypes are primarily based upon nucleotide variability in the hypervariable regions as well as polymorphisms found throughout the coding region. Phylogenetically related haplotypes can be grouped together to form haplogroups. These mitochondrial haplogroups are considered continentally specific. This means that certain haplogroups are found at high frequency among populations in one geographic region but the same haplogroup is virtually absent in other geographically distant populations. The number of mitochondrial haplogroups currently stands at 5400 [3].

MtDNA was first sequenced in 1981 [4], and the published sequence was dubbed the Cambridge Reference Sequence (CRS). However, due to errors in the original sequence, a corrected version, now referred to as the revised Cambridge Reference Sequence (rCRS), was published in 1999 [5]. The CRS/rCRS sequences have since been used as the baseline to which other sequences are compared and to which phylogenetic assessments are made to determine haplotype and haplogroup membership [6]. However, this reference sequence is not representative of the ancestral mitochondrial human sequence but instead a derived sequence belonging to haplogroup H2a2a1. The fact that the rCRS is not ancestral to known mitochondrial lineages has created complications in making assessments about the phylogenetic relationships between mitochondrial lineages. To address this issue, a new reference sequence has been published which is more representative of the root of all human mitochondrial sequences and was also constructed in relation to Neanderthal mtDNA [7]. This new reference sequence is known as the RSRS or Reconstructed Sapiens Reference Sequence. Though some researchers and direct-to-consumer (DTC) genetic testing companies have adopted the RSRS and use it adjacent to rCRS, other scientists are not as resolute in its implementation [6,8]. The primary criticism to the use of RSRS is that with the discovery of novel mitochondrial sequences the

RSRS may not actually represent the root mitochondrial lineage and consequently will need to be modified. In addition, the potential for confusion and miscommunication may increase with a transition from rCRS to the RSRS [9].

Nonetheless, as will be discussed in subsequent sections, regardless of which reference sequence is used, mtDNA has refined anthropological understandings surrounding questions of human origins, relationships with now extinct human species, and human migration. With regard to DTC genetic tests, mtDNA has proven invaluable to genetic genealogists and others interested in utilizing genetic data to learn more about familial relationships as well as long-term, or 'deep' ancestry. In addition to addressing conventional anthropological and genetic genealogic questions, mtDNA has also proven crucial in adding new perspectives to understanding how the genetics of marginalized populations have been shaped by historical processes. These insights into the 'bio-histories' of marginalized populations are best understood within the social, historical, and political contexts in which they emerged. Thus, as mtDNA and genetic data more broadly, becomes more firmly established as relevant anthropological tools, the new data may challenge old ideas about the human condition, including ideas about our origins, evolution, and human variation.

2. Mitochondrial studies of human origins

MtDNA was featured in the 1987 seminal paper by Rebecca Cann, Mark Stoneking, and Allan Wilson [10]. This paper became the foundation that helped to establish that the most recent common mitochondrial ancestor to all living humans lived in Africa roughly 200,000 years ago. In this study, Cann and colleagues examined mtDNA from 147 individuals sampled from five different regions of the world. They concluded that all mitochondrial lineages coalesced to one woman that lived about 200,000 years ago, most likely in Africa. The media later dubbed this common mitochondrial ancestor "Mitochondrial Eve" [11]. This study elicited criticism due to issues regarding the study design and the statistical merit of the analyses. Specifically, Cann and colleagues had sampled African Americans instead of Africans and failed to emphasize alternative but equally plausible analyses that suggested a non-African origin of our species. Four years later, a follow-up study by Vigilant et al., was published in Science [12]. This paper directly addressed some of the criticisms aimed at the Cann et al. study. Like the earlier analysis, Vigilant and colleagues also concluded that Africa was the geographic origin of *Homo sapiens*. Both the Cann et al. and Vigilant et al. papers became very influential genetics based papers to support the idea that Africa was central to the origin and evolution of our species. Within the next decade additional supporting studies that examined both mitochondrial and nuclear DNA were published [13-16]. These subsequent publications helped to solidify mtDNA as an informative marker within anthropological genetics.

Studies using mtDNA were also crucial in evaluating competing theories regarding the temporal and geographic origin of our species. The two primary human origin hypotheses, dubbed, the "Recent Out of Africa" and "Multiregionalism" theories posit different scenarios of how our species emerged. The first hypothesis, promoted by Chris Stringer and other researchers, posits that modern humans originated in Africa, migrated out into other regions of the world and completely replaced other human species with virtually no gene exchange between *Homo sapiens* and the other encountered human species [17]. The second hypothesis, advocated by Milford Wolpoff among others, also posits an African origin, but not of anatomically modern humans. According to this hypothesis, anatomically modern humans evolved from an earlier related species, *Homo erectus* that emerged from Africa and populated the world 1–2 million years ago. As a result of genetic exchange,

or gene flow, between geographical regions, anatomically modern humans emerged in several regions of the world beyond the African continent [18]. While ultimately, the details of the human origins debate remained unresolved, the work of Cann et al., Vigilant et al., and others lent support to the Recent Out of Africa hypothesis. However, additional questions about our species origins, specifically regarding the relationship between anatomically modern humans and now extinct hominins, remained unsettled [19-21].

3. Human migration and settlement

In addition to delineating human origins, mtDNA has also been used to trace human migration and settlement of the world. With a starting point in east Africa, humans migrated throughout the African continent as well as out into southwest Asia, Europe, Eastern Asia, and into the Americas. Mitochondrial analyses generally indicate that these dispersals began around 70,000 years ago [16,22]. The current understanding is that the initial dispersions out of Africa occurred in two routes, an earlier southern route that resulted in human presence in western and southern Asia and Australia by around 50,000 years ago [23]. The northern route was an expansion into North Africa, eastern and northern Asia and Europe. This second migration out of Africa is believed to have occurred around 40,000 years ago [24]. The final major dispersion of human groups was into the Americas and is estimated to have occurred 30,000 to 15,000 years ago [25]. In addition to movement out of Africa, mitochondrial data also support back migrations to Africa from different regions of the world [26,27].

4. *Homo sapiens* and other hominins

As human populations expanded beyond the African continent, they encountered other types of, now extinct, human species. According to taxonomic classifications based upon genetic data, the term hominins refers to humans and extinct human ancestors whereas the term hominids refer to human, extinct human ancestors, chimpanzees, gorillas, and orangutans [28]. Early studies analyzing mtDNA from extinct hominins, specifically Neanderthals, indicated that the variation observed among Neanderthals consistently fell outside of the variation observed for anatomically modern humans [29,30]. This suggested that, based upon mtDNA, anatomically modern humans and Neanderthals, while sharing a common ancestor that dates to 550,000 to 690,000 years ago, were not part of the same breeding population [29]. Subsequent studies analyzed mtDNA extracted from other Neanderthal specimens and also concluded that Neanderthals did not make genetic contributions to modern human populations [31,32]. However, based on studies completed within the last ten years, the finding that Neanderthals and humans did not exchange genes has been challenged with the inclusion of nuclear genomic data. The general conclusion from these studies is that for populations outside of Sub-Saharan Africa, extinct hominins including Neanderthals and Denisovans, interbred with anatomically modern humans [33-35]. In fact, low levels of genetic contributions from these species have been found in Eurasians. Around 1%–2% Neanderthal ancestry has been observed among Eurasian populations while Melanesians have 6%–8% ancestry from Denisovans [32,36-38]. Additionally, newer studies are also suggesting that genetic exchange between anatomically modern humans and now extinct hominins was not restricted to Europe and Asia, but likely occurred within African populations as well [39,40]. More data from both mitochondrial and nuclear DNA will be useful in further elucidating the nature of the relationships between our species and extinct hominins.

5. Direct to consumer genetic testing

Within the last twenty years, the number of companies offering mtDNA and other genetic tests to paying consumers has risen dramatically, with nearly 40 companies currently offering services [41]. These types of companies generally provide a variety of genotyping services including tests for genetic ancestry, relatedness, and disease risk [42-44]. Adding to the popularity of these services are both Internet and television advertisements in addition to media attention such as that featured in television documentaries like 'Who do you think you are?' or 'African American Lives' [45].

Beyond popular and media interest, DTC genetic tests have garnered the attention of scholars that seek to understand social impacts of these technologies. These scholars generally focus on why and how people engage with DTC technologies [46-48]. In these studies, many researchers report a variety of individual experiences, ranging from life-changing positive outcomes to confusion, anger, and regret about what genetic tests reveal [49-51]. Such studies reflect the uncertainties that surround uses of genetic tests including questions about privacy, consent, and appropriate interpretation of the results. In addition to documenting idiosyncratic experiences of DTC genetic test users, some researchers also examine the variety of ways that genetic information from DTC genetic tests impact historically marginalized communities [52-54]. For many members of historically marginalized communities, information about family and community histories are unavailable due to generations of systematic discrimination that has resulted in an obscuring of their histories. Genetic testing, consequently, potentially opens an avenue to obtaining previously unavailable information. In the case of people with African descent throughout the Americas, mitochondrial tests in addition to other ancestry informative markers illuminate the biological impacts of the Trans-Atlantic Slave trade highlighting ancestral geographic origins and evidencing admixture [55-58]. In the Spanish-speaking Caribbean islands, for example, genetic ancestry data has been referenced as support for the continued presence of indigenous Caribbean peoples. As a result, DTC ancestry tests have helped to shape the ongoing indigenous resurgence movements seen in these islands [59,60].

As part of the examination of social impacts of DTC genetic tests, researchers also have commented on the nature of the DTC testing industry. Despite the popularity of such tests, the DTC industry is unregulated and this laissez-faire approach has resulted in a wide variety of companies offering different tests that range in quality. While 'buyer-beware' is the current guiding principle to the DTC industry, increasingly, academics and federal agencies, such as the FDA, are making efforts to influence if not regulate DTC testing [41,69-71]. Accordingly, geneticists and social scientists that study the interactions between science and society are voicing concern over the lack of transparency and standardization of laboratory and statistical methods for ancestry estimations. The primary critique of DTC companies is that while genetic data, may appear precise, there are limitations to what may be inferred, in particular from genetic markers like mtDNA, and these limitations are not consistently provided to potential consumers.

6. The limitations of mitochondrial genetic data

Genetic anthropologists and genetic genealogists alike have lauded the advent of the Genomic age. Genetic technology has allowed for renewed investigational questions about human origins and migration, hominin species, and inter/intra regional relationships between populations. However, there are some technological and interpretive limitations of mtDNA. MtDNA does not recombine

and therefore is ideal for understanding the particular migratory histories of human groups. However, the lack of recombination also means that the scope and resolution of any interpretation based on mtDNA is comparatively limited relative to nuclear genetic markers [72]. For the purposes of genetic histories, mtDNA is essentially one genetic marker and cannot necessarily be considered as representative of the entire genome. The opposing conclusions regarding the relationship between Neanderthals and *Homo sapiens* based on mtDNA and nuclear DNA, illustrate the limitations of formulating theories about major evolutionary events using only one genetic marker. Secondly, with regard to genetic ancestry, due to the uni-parental inheritance of mtDNA, this genetic marker is only informative about the maternal lineage and not at all reflective of the entirety of an individual's genealogy. Citing a lack of substantive information content, some researchers devalue mtDNA regarding it as minimally informative [73]. However, on the scale of a population, rather than the individual, mtDNA still is quite informative about the demographic and migratory history of a population [74]. Thirdly, the assignment of genetic lineages to a specific continent is based on a frequency of how common the genetic lineage is in a particular region. In theory, this means that lineages are not stringently restricted to particular regions but instead can be found, albeit, at low frequencies, across the world. This semi-ubiquitous quality to genetic lineages can lead to an erroneous identification of an individual's geographic origin [73]. Despite these limitations, as discussed above, mtDNA have proven useful for making inferences about past evolutionary and historical processes. In addition to the general knowledge about broader questions surrounding human origins and evolution that mtDNA analyses have garnered, mtDNA data have also proven useful for addressing questions about local populations that would otherwise be left unaddressed.

7. MtDNA and local histories

Because of the unique maternal inheritance pattern of mtDNA, genetic genealogists, in addition to anthropologists, have found mtDNA particularly informative for tracing maternal ancestry. Considerations of mtDNA can serve as an analog to both paternally inherited Y chromosome DNA and paternally inherited surnames. Beyond tracing maternal lineages far back in time or 'deep ancestry', mtDNA can also be used to identify maternally related members of a family. Individuals that share a maternal lineage share a common ancestor, however estimating the time to that recent common ancestor is complicated due to variability of reported mutation rates for the mitochondrial genome [75,76]. Nonetheless, for the purposes of genetic genealogies, mitochondrial haplotypes that are shared between individuals generally correspond to a common mitochondrial ancestor within one to hundreds of generations ago [77,78]. MtDNA has also been marketed as a tool to help people 'discover' unknown elements of their ancestry [79]. For example, despite controversies of equating a genetic profile with any particular ethnicity, some genetic genealogy companies market the prospect of discovering Native American ancestry while other companies advertise their ability to further elucidate African ancestry [42,47]. The general theme with these uses of DTC tests is to recover knowledge that was lost as a result of colonization, enslavement, migrations, and other historical events.

Crossing disciplines, mitochondrial data have been combined with historical, ethnographic, and archaeological data to provide new insights into local histories. At times, mtDNA has been used to confirm what is generally already known. This was the case, for example, with the last royal Russian family, the Romanovs. The leading narrative was that Ural Soviets executed the entire family in 1918. However, since the bodies were deposited into unmarked graves, some historians posited that not all of the family members had died [80]. In 1991 and again in 2007, the purported remains of the family

were recovered and genetically tested. The mitochondrial and nuclear DNA tests provided confirmation that the entire family had indeed been executed in 1918 [81-83].

In other cases, mtDNA helps to radically alter primary narratives about the past. In a study led by Juan Martínez Cruzado, published in 2001, [84], the extent of indigenous Caribbean ancestry among contemporary Puerto Ricans was shown to be considerably higher than expected. General narratives of the Caribbean note that indigenous Caribbean populations were driven to extinction at the hands of European colonists soon after the turn of the 16th century [85]. Martínez Cruzado's work, in addition to subsequent publications from other geneticists, historians, and activists on other contemporary populations in Puerto Rico, Cuba, Dominica, St. Vincent, and Trinidad, illustrate that the extinction narrative is not correct but instead requires a more nuanced and integrative understanding of Caribbean history [86-90].

This last example from the Caribbean highlights the importance of contextualizing genetic data within larger frameworks. Using information from relevant other sources helps to interpret the genetic record. Contextualization is particularly important as cultural, social, political, economic, and biological factors affect processes that result in specific patterns of genetic variation. Relying on only genetic information while ignoring factors that shape the genetic landscape, can provide very limited, at best, or erroneous, at worse, ideas about human biological histories. While genetic data can provide novel perspectives to human experience, the experience of being human extends beyond DNA. Anthropological approaches using DNA must therefore take a holistic approach and rely upon multiple perspectives when making sense of the data.

8. Conclusion

Though representative of only a small percentage of the human genome, mtDNA has been quite powerful in illuminating human evolutionary history. As genotyping technology improves and comparative databases grow, mtDNA will continue to be a cornerstone in the anthropological and genetic genealogical toolkit. In particular, as the ability to recover DNA from ancient remains improves, researchers will gain better understandings of both the processes of human evolution and hominin relationships. Moreover, with an increased inclusion of people from understudied communities, researchers can work towards a refined and expanded understanding of the evolutionary processes that have shaped human histories. Finally, in light of enhanced analytical techniques and databases, genetic data are still best understood and interpreted when contextualized using additional lines of evidence. Interdisciplinary research drawing on history, archaeology, and other relevant sources will remain critical for understanding and interpreting the genetic record.

Conflict of interest

The author declares there is no conflict of interest.

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