

Generations of genomes: advances in paleogenomics technology and engagement for Indigenous people of the Americas

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For decades, scientists have collected genomic information from Indigenous peoples and their ancestors with the goal of elucidating human migration events, understanding ancestral origins, and identifying ancestral variants contributing to disease. However, such studies may not have offered much benefit to the Indigenous groups who contributed DNA, and many have instead perpetuated stereotypes and other harms. With recent advances in genomic technology facilitating the study of both ancient and present-day DNA, researchers and Indigenous communities have new opportunities to begin collaboratively addressing important questions about human health and history. Yet, while there are increased efforts to ethically engage Indigenous communities, more work is still needed as the discipline struggles to absolve itself of the racialized science and extractive biocolonialism that defined its past.

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Introduction

Recent technological advancements in paleogenomics, the study of our ancestors and relations using ancient DNA (aDNA), have enabled more sequenced ancient human genomes in the past two years than in the entirety of human history [1,2]. Just six years ago, sequencing the complete genome of a Neanderthal woman was a major scientific achievement [3]. Sequencing technology continues to improve, enabling increased scale (number of ancient genomes analyzed), resolution (quality of aDNA assemblies), and infrastructure (number of laboratories). While paleogenomic studies permit unprecedented insights into the human past, this rapid trajectory has raised important concerns for Indigenous scientists and communities regarding the balance of technology with ethics and expectations for community engagement.

Scientists have analyzed genomes of current-day and ancient Indigenous peoples to connect them to a broader narrative of human dispersals out of Africa and into the Americas [4–7]. These studies have challenged Indigenous peoples' beliefs about their origins, for instance, by suggesting they are not originally from their ancestral lands. Further, past sampling portrayed Indigenous peoples as isolated groups, leading to problematic notions of racial purity (using local ancestry estimation methods) and conflations of biological classifications of race [8,9] with sociocultural and political designations of Indigeneity [10,11]. Certainly, improved methods and higher-resolution estimates of local and global ancestry make it possible to move away from race-based characterizations of genetic ancestry [12], but these methods should incorporate culturally respectful research collaborations with local communities who offer detailed accounts of their own local histories and ethnographical data.

Genomics has been divisive for many Indigenous people throughout the Americas [2,13,14], especially in cases lacking robust engagement and consultation. Building and establishing trust is paramount for conducting genomics research in Indigenous communities, especially as paleogenomics research expands and brings potential implications for future generations. For instance, engaging Indigenous communities in aDNA research can aid in the identification of their ancestors (which may be important for repatriation efforts [15,16]) and collaboration can

enrich our global understanding of diversity in ancient and contemporary populations [17].

Here, we examine current genomic research involving the collection of aDNA from Indigenous ancestors and its implications for present-day Indigenous people. Because of the volume of studies occurring in North, Central, and South America, we largely focus on Indigenous people of the Americas. Throughout this piece, we use the term ‘Indigenous’ to describe first peoples generally and encourage researchers to cease using ‘Amerind’ or ‘Amerindian’ since those terms are closely tied to outdated racial ideologies [18]. The term ‘Native American’ should be reserved as a political designation in the US. We urge scientists to defer to communities to designate how they wish to be referred.

Recent insights into old questions

When considering how people moved across the globe, Gneccchi-Ruscione *et al.* states that ‘the history of Native American populations is one of the most debated topics in the study of ancient human migrations’ [19]. Much of recent paleogenomics research is centered on determining when the Americas were originally populated and by whom [20]. North American studies, for instance, continue to use genetic, archeological, and paleoecological evidence to elucidate the timing of Pacific coastal and inland migrations [21,22*,23,24]. In contrast, many paleogenomic studies in Central and South America have focused on a different part of the peopling of the Americas narrative [25], such as investigating genetic differences [4] that typify pre-Columbian peopling of the Andes versus the Amazon region, or the ‘Andes-Amazonia Divide,’ both at the continent-wide scale [19,26,27] or more locally within populations [28–31].

Some aDNA studies throughout the Americas have examined other kinds of questions, such as recent population histories or patterns of movement and interaction. While some researchers see a potential divide between aDNA research and other fields [1], there has been an increasing ‘multidisciplinary dialogue’ [32] that allows researchers to layer multiple forms of complementary data (e.g. genomic, linguistic, archeological, and sociocultural experiences) to create a higher resolution understanding of our shared history. For instance, Gomez-Carballa *et al.* analyzed variations in mtDNA and the nonrecombining portion of the Y-chromosome to reveal sex-specific genetic trends in gender demography. They found that women historically exhibited a larger effective population size presumably due to linguistic exogamy, a cultural practice requiring men to marry women speaking a different language [30]. These multidisciplinary questions increasingly involve analysis of living descendants, not just ancestors, and thus could benefit from more collaboration with Indigenous communities.

Caring for our ancestors and their DNA

Indigenous people have raised concerns about the open accessibility of their genomic sequence data. Much of the apprehension stems from concerns about biocolonialism [33], or the commodification of Indigenous peoples’ biological information. Additionally, there is considerable pluralism in the ability of Indigenous people to exercise autonomy in governing their genomic data [34]. In the US, for example, some tribes exert their sovereign authority by instituting their own research regulations [35,36]. While we cannot comment on the sovereign status or degree of research oversight by Indigenous people in Central and South America, we express concern that research oversight from government agencies alone may effectively bypass direct engagement with communities. Rather than depositing data in openly assessable databases, some researchers take proactive approaches to act as data stewards to make data available upon request with restrictions [37]. However, we must ultimately empower Indigenous peoples to become data stewards themselves to enforce safeguards around the use of data [38].

Beyond genomic data, recent studies show greater attentiveness to the care, identification, and return of ancestors to descendant communities. Many Indigenous peoples assert that their ancestors should remain in ancestral lands near kin to maintain their connections to land and relatives [39], which is essential for ancestors’ spirits to rest [13**]. Importantly, we can learn from the collaboration and consultation that Wright *et al.* had with Aboriginal Australian Traditional Owners to integrate knowledge from elders and communities in a study showing that mitochondrial DNA (mtDNA) is a poor identifier of descentancy, resulting in an estimated 7% return of ancestors to the wrong Indigenous group [40**]. This is important for future efforts that may rely on mtDNA to repatriate ancestors.

Amidst long-standing concerns about destructive sampling of aDNA [41], there is hope and excitement over emerging non-invasive technologies, a trend that has been implemented increasingly in laboratories [42]. For instance, in contrast to traditional ZooMS (Zooarchaeology by Mass Spectrometry) techniques that require destructive analysis of samples, non-destructive ZooMS was applied to bone points from pre-contact St. Lawrence Iroquoian village sites in southern Quebec, Canada [43]. Additionally, metagenomic soil analysis of burial sites has the potential to yield sequence ‘reads’ by deconvoluting bacterial DNA in soil from human aDNA [44]. These emerging non-invasive techniques offer the potential to generate impactful paleogenomic data without destroying sacred Indigenous items or ancestors. However, new ethical questions are raised related to the provenance of Indigenous aDNA collected from soil ten meters below an excavation site. For instance, the

question of who ‘owns’ or has stewardship over digital sequence information (DSI) from soil microbiomes should be decided in collaboration with Indigenous partners.

Balancing risks and benefits

We caution that repatriation should not be oversold as a benefit to Indigenous communities [45] as each community has its own unique cultural history and diaspora. For instance, as the Australian diaspora predates the Polynesian diaspora (respectively ~50 versus ~2–7 thousand years ago, or kya), there is less genetic diversity among Polynesian populations, making it more difficult to repatriate Polynesian ancestors to specific communities or islands due to a lack of high aDNA resolution. Further, for US tribes, the Native American Graves Protection and Repatriation Act (NAGPRA) does not enforce the provenance of Indigenous ancestors stored in museum collections worldwide, especially for those curated before the law was enacted in 1990. Also, NAGPRA’s definition of ‘human remains’ is not defined, thus human teeth or hair containing aDNA have been sold [Christie’s Auction House, URL: <https://www.christies.com/lotfinder/Lot/a-necklace-lei-niho-palaoa-hawaiian-islands-6230024-details.aspx>] and sequenced without consideration of Indigenous descendants. Repatriation under NAGPRA will likely be further limited as it does not reflect current technological advancements related to storage and access of DSI from Indigenous ancestors.

Paleogenomic techniques can also enable our understanding of past human genetic variation and inform current medical knowledge [46]. Exome sequencing of a First Nations ancestor [47] suggest that decreased effective population size and gene flow events due to European contact, intermarriage, introduction of diseases, and genocide led to changes in HLA variant frequencies among Indigenous peoples in British Columbia, thus potentially informing our understanding of immune-related selection pressures in present-day Indigenous peoples. Such temporally cross-sectional genomic analyses of both ancient and present-day Indigenous genome sequence data could profoundly impact the development of treatments for autoimmune disorders. However, in investigating these potential linkages, scientists must ensure their use of language does not exacerbate existing negative stereotypes and become normalized in peer-reviewed publications. For example, a study of the biomedical implications of recent admixture described a Colombian Andean population as having ‘escaped from complete admixture given their warrior nature and persistent culture’ [29]. Indigenous communities should be consulted about culturally sensitive language in final research products before dissemination.

Just as aDNA can be used to inform our current understanding of disease phenotypes, geneticists are studying

recent admixture in Latin American descendent communities to understand variation inherited from Indigenous ancestors. For instance, investigators concluded that a gene variant associated with lighter skin pigmentation in Eurasia was carried into the Americas through migrations into the New World some 15 kya [48^{*}]. While this could contribute to our larger understanding of genetic and phenotypic variation [49] and maybe even challenge simplistic notions of ancestry and phenotype [50], such studies should take care not to inadvertently contribute to already divisive viewpoints that conflate race and skin pigmentation [51–53] or other physical traits [48^{*},54]. Exercising cognizance of these larger social and cultural dynamics is important, particularly if one is conducting research with historically disempowered communities.

Similarly, using Indigenous ancestors for genetic ancestry estimation can have consequences for present-day Indigenous descendants. The politics of what constitutes Indigenous identity and ancestry are complex, and the issue is further complicated when lay individuals falsely equate biological constructs with Indigeneity. For instance, Leroux [55] accounts an ongoing controversy in which individuals lacking lineal evidence of an Indigenous ancestor are misinterpreting mtDNA to claim First Nation Métis identity, and points to a 149% increase in Métis self-identification claims from 2006 to 2016. This movement has been exacerbated by direct to consumer testing that does not account for lived experiences in cultural practices, developing traditional kinship relations, and connections with the land [56–58]. Genetic testing for the purposes of establishing an Indigenous ancestor is not supported among Indigenous communities because DNA does not determine identity [11].

In general, scientists must remember that categories of race, ethnicity, and ancestry are not neutral. Furthermore, scientists must be careful not to ‘equate those who are more admixed as being less Indigenous than ‘non-admixed’ Indigenous people’ [55] because Indigeneity and kinship are socially and politically determined, and Indigenous people retain the right to define them for themselves. To modify these structures would mean undermining their sovereignty.

Empowering Indigenous people

It is incumbent upon researchers to empower Indigenous people to serve as stewards of their ancestors and be more collaborative to ensure bi-directional benefits [15,59]. Indigenous communities have a long history of being subjected to research with unethical dimensions, little to no benefit, or in inappropriate or unapproved areas. To mitigate these harms, Indigenous scholars and policy makers have developed new guidelines, protocols, and frameworks for ethical engagement [60^{••}], while also

advocating for ways to implement and enforce existing regulations [61,62,63**,64]. Emergence of Indigenous data sovereignty or the right of Indigenous peoples and nations to govern the collection, ownership, methods, and application of data about their peoples, lands, and resources [65–69], has prompted Indigenous peoples to assert their collective rights to control interests in biological materials [70**], develop laws and policies, use emerging technologies to direct population genetics narratives for themselves [71], and build capacity to house and oversee materials. Formal tribal approval through research review boards [72,73] or government-to-government consultation with tribes is essential to seek input and approval [74**]. Most tribes in the US have sovereign status to uphold their own laws and research codes.

In the frameworks and guidelines about ethical engagement in research, a greater emphasis is being placed on finding ways to avoid exacerbating stereotypes or harmful assumptions that challenge tribal affiliation [57] and ancestral familial connections [56]. First, researchers should consult with the community about important questions that can be answered using genomic techniques, then proceed with permission to carry out respectful methods while maintaining transparency, and finally collaboratively work to interpret the results with culturally-appropriate viewpoints [75]. Research collaboration with community informants can enable diverse interpretations and offers opportunities to delve deeper and uncover new insights about human evolutionary history.

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Conflict of interest statement

The authors do not declare any conflicts.

CRedit authorship contribution statement

Krystal S Tsosie: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Rene L Begay:** Conceptualization, Writing - original draft, Writing - review & editing. **Keolu Fox:** Conceptualization, Writing - original draft, Writing - review & editing. **Nanibaa' A Garrison:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

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