Advances in Clinical and Medical Research

Genesis-ACMR-4(4)-66
Volume 4 | Issue 4
Open Access
ISSN: 2583-2778

Thanks Mom! The Evolution-Health Disparities Link Through Mitochondrial Genetic Disease

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Citation: Jackson F, Mingo E, Caldwell J, Batson N, Mohammed M, et al. (2023) Thanks Mom! The Evolution-Health Disparities Link Through Mitochondrial Genetic Disease. Adv Clin Med Res. 4(4):1-20.

Received: August 14, 2023 | **Published:** September 28, 2023

Abstract

Anatomically modern humans evolved in Africa ~300,000 years ago. For this reason, the evolution of mtDNA genetic variants tracks the migratory histories of humanity worldwide. With these genetic variants have come corresponding diversity in mtDNA-associated genetic diseases. These tend to aggregate in ethnic and regional groups in conjunction with the concentration of specific mtDNA haplotypes in these same groups. Given the ubiquity of mtDNA in every human cell, the fact that mtDNA molecules encode genes for the mitochondrial respiratory chain, protein synthesis, and regulation, are of primarily maternal heritage, and do not undergo recombination, it is not surprising that mtDNA genetic diversity in combination with environmental factors influences health disparities.

DOI: https://doi.org/10.52793/ACMR.2023.4(4)-66

We provide a model for this interaction and a comprehensive overview of the range of genetic diseases impacted by specific mtDNA variants "95 cases were reviewed" covering 29 clinical conditions. 62% of all cases were in patients of European descent, 34% in individuals of East Asian descent, and only 1% were among people of recent African descent. mtDNA-associated diseases included diverse cancers, neurodegenerative diseases, and metabolic diseases. Many more adverse associations were reported than preventative. These findings are discussed within an evolutionary context.

Keywords
Human evolution; mtDNA cancer; Neurodegenerative; Metabolic diseases.

Introduction

Genomic evolution in the homeland of humanity

Africa presents the most complex genetic picture of any continent, with a time depth for mitochondrial DNA (mtDNA) lineages >100,000 years [1]. Studies of human mtDNA genomes demonstrate that the root of the human phylogenetic tree is solidly in Africa [2] and comparison of the intra population sequence divergence in African and non-African populations confirms that African populations exhibit the largest extent of mtDNA variation. This observation supports the hypothesis that Africans represent the most ancient human group and that all modern humans have a common and recent African origin [3].

While humankind's origins in Africa are thus well established in the scientific literature, the intra-continental migrations of these early humans around the African continent are less well documented. Most migration studies are one-dimensional and refer to the migration out of Africa of a subset of African humans approximately 60,000 years ago [4]. Studies of mtDNA phylogeny within continental Africans suggest that the L0-L1'6 split occurred at about 140,000-160,000 years ago and may represent also an early sub-structuring of small, isolated, but increasingly mobile African communities [5]. As indigenous communities grew and dispersed geospatially within the African continent, regional variation accumulated over the following millennia, with L2 and L3 lineages arising in Central and East Africa ~100,000-75,000years ago. Their sub-Saharan dispersal prior to~60,000, largely overwhelmed the L0'1 distribution [5]. We still see evidence of this pattern of replacement in the early 21st century Ely-Jackson database of African and African American mtDNA variants [6].

It has been suggested that cyclic expansions and retractions of the equatorial forests in Africa between 40,000 years ago and the Last Glacial Aridity Maximum (21,000 years ago) caused in Africa a major expansion of existing deserts [7] along with a large drop in sea levels. These induced significant climatic shifts and reduced the genetic diversity of modern humans. Surviving regional-specific lineages emerged from the Sahelian refuge areas, including the Nile Valley [8], repopulating the region and contributing to the overall pattern of genetic similarity in West Africans. Subsequently, particular L1- L3 lineages expanded in range due to the substantial population growth made possible by moister and warmer conditions of the African humid period.

The African humid period extended over the Sahara as well as the entirety of eastern, southeastern and equatorial Africa [86] During this period, important technological advances to subsistence patterns emerged and were associated with the development of agriculture and implementation of iron smelting techniques that supported population growth and increased survival. During the African humid period, lakes, rivers, wetlands and vegetation including grass and trees covered the Sahara and Sahel [85, 10, 11] creating a Green Sahara with forests and woodlands expanding through the entire African continent. As recently as6,000 years ago the vast Sahara Desert was covered in grassland that received an abundance of rainfall. However, shifts in the world's weather patterns precipitated by fluctuations in the orientation of the orbit of the earth and changes in climate that abruptly transformed the well vegetated region into some of the most arid land on the planet. V. Černý and colleagues [12] suggested that the mtDNAL3 sub lades L3f2 and L3e5 are unique to the Chad Basin. The Bantu expansion of agriculturalists occurred towards the end of the periods, perhaps stimulated in part by the climatic changes. The diffusion of these farmers from West Central Africa toward South Africa around 3,000 years ago accelerated the replacement of much of the pre-existent mtDNA lineages among previously hunter-gatherer communities [13].

Critical to the retention of mtDNA diversity and the promotion of new variants has been the improved community carrying capacities associated with the shift from hunter-gatherer subsistence to agriculture. Researchers have observed changes in the pair wise sequence distributions, patterns of coalescence events, and numbers of variable positions relative to the mean sequence difference that suggest that Africans who remained hunter gatherers retained population sizes that stayed constant over time whereas those who embraced agriculture expanded in size [14]. We can also envision that those groups that remain as foragers would have been less likely to experience admixture [15] and in their relative isolation, retained more of the original genetic signatures. This hypothesis appears to be supported by recent studies of aDNA in Africa [15] that infer foragers have retained more of the original mtDNA sequences than agriculturalists and that within the last 5,000 years, population demographics in Africa have undergone significant rearrangements mediated by technological developments.

Natural selection and nonrandom mating practices alter mtDNA mutational loads

There are hundreds to thousands of copies of mitochondrial DNA (mtDNA) in each human cell in contrast to only two copies of nuclear DNA [16]. Molecular variants of mtDNA have three origins [17]: inherited variants, which run in families, somatic mutations arising within each cell or individual, and variants that are also associated with ancient mtDNA lineages (haplogroups) and are thought to permit adaptation to changing tissue or geographic environments. High-frequency pathogenic mtDNA mutations have been found in patients with classic mitochondrial diseases, premature aging, cancers, and neurodegenerative diseases [18-23].

Mitochondrion harbors its own DNA (mtDNA), which encodes many critical proteins for the assembly and activity of mitochondrial respiratory complexes. mtDNA is packed by many proteins to form a nucleoid that uniformly distributes within the mitochondrial matrix, which is essential for mitochondrial functions. Defects or mutations of mtDNA result in a range of diseases [24]. Indeed, the small circle of mitochondrial DNA (mtDNA) present in all human cells is a rich source of pathogenic mutations and rearrangements

[25]. It is known that mtDNA is susceptible to environmental perturbations and that natural selection likely selected for certain mtDNA lineages [26] while selecting against less well adapted mtDNA variants. Additionally, these selective events may have produced multiple functionally important amino acid changes in ATP6, cytochrome b, and cytochrome oxidase [26].

The preservation of a functional mitochondrial genome over an individual's lifetime requires faithful replication, segregation, and expression of appropriate function during development and in all subsequent mitotic cell divisions. Preservation also requires protection from and efficient repair of mtDNA damage [27]. It may be that genetic disease results when the number of pathogenic mtDNA mutations exceeds a certain threshold. Mitochondrial and heteroplasmy tend to show high pathogenicity, and is significantly overrepresented in disease-associated loci [16]. Purifying selection may limit the viability of these mutations and genomically standardize and lock-in specific haplotypes at the population level. This, plus the tendency toward consanguinity within ethnic groups would decrease their mtDNA genetic variability and increase within-group molecular consistency.

mtDNA variation produces increased risk of genetic disease

In the Ely-Jackson database we observed aggregations of specific mtDNA haplotypes within regionally specific ethnic groups but also unanticipated genetic variation within each of the African mitochondrial DNA (mtDNA) haplotypes expressed. Apparently most, if not all, humans contain multiple mtDNA genotypes (heteroplasmy). Specific patterns of variants accumulate in different tissues, including cancers, over time. Some molecular variants are preferentially passed down to the next generations or are suppressed in the maternal germ line [29]. This piqued our curiosity about the potential evolutionary significance of these findings. It takes energy to produce a complex mtDNA genomic environment. We anticipate that low levels of mtDNA heteroplasmy must be of evolutionary benefit, perhaps protecting against viral, fungal, or bacterial infections [30]. Whereas high levels of mtDNA mutations may increase the risk of developing common late-onset human diseases [31]. This variability within haplotypes also challenges the conventional view that high percentages of a mutation are required before a new variant has functional consequences [29].

Concentration of limited number of mtDNA haplotypes in specific human communities' results in the aggregation of their associated genetic diseases

The population estimates of early prehistoric and historical periods are imprecise but our assumption has been that the initial populations of "Homo sapiensnumbered" in the hundreds. Emphasis has recently focused on what was happening within the African continent before modern humans expanded their range globally [32]. Over time, the initial groups of foraging humans proliferated and at some point, early modern humans' fission into smaller groups. A recent article [33] has suggested that the most plausible reticulated African population history is one in which present-day population structure dates back to 130,000 and 80,000 years ago. According to their calculations, the earliest population divergence among contemporary populations occurred 120,000 to 135,000 years ago and was preceded by links between two or more weakly differentiated ancestral Homo populations connected by gene flow over hundreds of thousands of years. As these smaller entities migrated from the original for aging regions, they may have encountered new selective forces that differently impacted on their existing genetic variation and

changed the survival values associated with mutated mtDNA. Additionally, as these weakly affiliated smaller groups expanded, they moved farther from each other and the potential for regular admixture with other groups diminished. In such instances we anticipate a constriction of gene pools and a greater proportion of consanguineous reproductive mating. This would tend to concentrate the diversity of mtDNA haplogroups within the group, particularly if the in-migration of females was limited.

Since mutations in the maternally inherited mitochondrial genome (mtDNA), contribute essential protein subunits to the enzyme complexes of oxidative phosphorylation, mutations in this genome are an important cause of genetic disease. Specific mtDNA haplotypes will tend to cluster in specific ethnic groups, it is easy to see how geospatial redundancy in mtDNA haplotypes could emerge as a precursor to ethnic and regional patterns of mtDNA-associated genetic disease that would, when previously divergent groups are reunited, influence the pattern of health disparities.

Aggregated genetic disease can display as a health disparity

Health and health care disparities refer to differences in health and health care between groups that stem from broader inequities [34-35]. A health disparity is a health difference that adversely affects disadvantaged populations in comparison to a reference population (usually in the US, upper-middle and upper-class European Americans), based on one or more health outcomes. Genetic disease can cause differential health outcomes [36]. The tricky aspect of health disparities is determining the contribution due to genetic disease. While all populations with health disparities are socially disadvantaged due in part to being subject to past racist or discriminatory actions by the larger society, they are also usually underserved in health care, thus compounding their disadvantage and reducing their survival value. Add to these volatile socio-economic circumstances the small fraction of health disparities that are due to genetic disease, and you have an amalgamation of interacting gene-environment causes that can not only amplify the extent of health disparities, it can make them seen intractable. (Figure 1) depicts the interplay of human evolution, mtDNA genetic variations, population dynamics over time, and the emergence of health disparities.

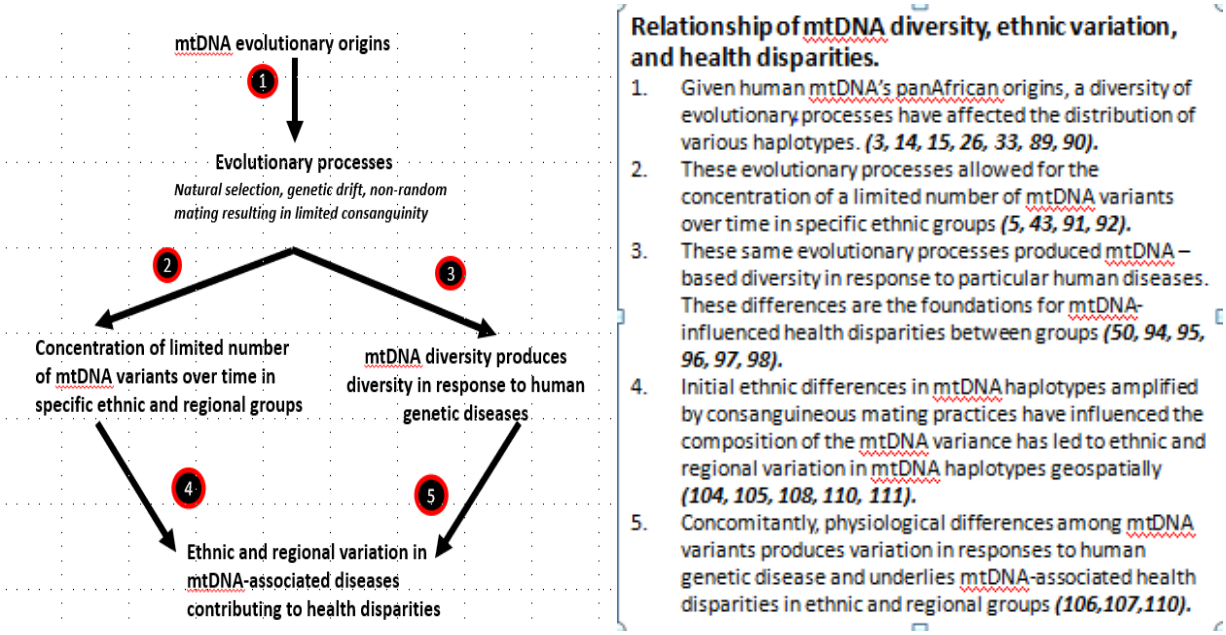

Figure 1: Depicts the interplay of human evolution, mtDNA genetic variations, population dynamics over time, and the emergence of health disparities.

Methods and Materials

Using the Ely-Jackson Database of African mtDNA variants [6] coupled with an extensive review of the scientific literature on mtDNA genetic variation and genetic disease; we researched the interrelationship between mtDNA and health disparities and have tried to place this in an evolutionary context. The databases reviewed included the following:

- AmtDB (https://amtdb.org/)
- GenBank (https://isogg.org/wiki/GenBank)
- Helix mitochondrial DNA database (https://www.helix.com/pages/mitochondrial-variant-database)
- mtDB [37]
- MSeq DR Consortium (https://mseqdr.org/)
- Ely-Jackson Database of African and African American mtDNA variants

The Ely-Jackson Database is a specialized, expertly curated database with information on sequenced HVS1 and HVS2, detailed ethnographic, and geospatial information on all 4291 samples. Named after senior biologists Bert Ely (University of South Carolina) and the late Bruce Jackson (University of Lowell), the database was collected in the early 2000s and was used initially to determine the number of African ethnic groups that matched the mtDNA haplotypes observed in African Americans [6]. Since then, we have developed a phylogenetic tree of African American mtDNA variants linked to specific African ethnic and regional groups. We also developed an inclusive phylogenetic tree of African mtDNA variants associated with specific African linguistic, ethnographic, and geospatial groups. These efforts familiarized us with the range of molecular variation in mtDNA and the phylogenetic relationships between the different haplotypes.

In the Ely-Jackson database we observed unanticipated genetic variation within each of the 85African mitochondrial DNA (mtDNA) haplotypes. Apparently most, if not all, humans contain multiple mtDNA genotypes (heteroplasmy) and specific patterns of variants accumulate in different tissues, including cancers, over time. “Some of these molecular variants are preferentially passed down or suppressed in the maternal germ line [29]. This piqued our curiosity about the evolutionary significance of these findings. While these findings” suggest that there must be a benefit cast light on the origin and spread of mtDNA mutations at multiple scales, from the organelle to the human population, and challenge the conventional view that high percentages of a mutation are required before a new variant has functional consequences.

For this report, the published scientific literature was comprehensively search for mtDNA variants known to be correlated with specific types of genetic disease. These databases included:

- PubMed PubMed(https://pubmed.ncbi.nlm.nih.gov/)
- Embase (https://www.elsevier.com/solutions/embase-biomedical-research)
- LILACS (https://lilacs.bvsalud.org/en/)
- ScienceDirect (https://www.sciencedirect.com/)
- Google Scholar (https://scholar.google.com)

Bibliometric searches were conducted using these reference databases using the following keywords: mtDNA, genetic disease, evolution, physiology, and health disparities. The resulting documents were then organized by presumed genetic disease association and/or by mtDNA haplotype. A table was created (Table 1) that summarizes the core data needed to recognize the depth and breadth of the numerous associations between mtDNA and specific genetic diseases.

Results

mtDNA Haplotype	Associated Genetic Disease	Physiological Consequences of mtDNA variant on genetic disease	Effects of mtDNA variant on genetic disease	Affected Population	*Reference*
A	T2DM	Unknown	RIsk	Meta	*(45)*
A	AIDS susceptibility	Possible differences in max. temp, ROS	Risk	Han Chinese, Southwestern China	*(51)*
A	MS	ROS	Risk	Iranian Persian	*(52)*
A	atherothrombotic cerebral	Unknown	Risk	Japanese Females	*(53)*
B	Knee Osteoarthritis	Unknown, but mitochondria play a critical role in bone homeostasis	Risk	Korean	*(84)*
B4	Oral lichen planus	Unknown	Protection	Chinese	*(54).*
B4b′d′e′j	Gallstone disease	Unknown	Risk	Shanghainese	*(55).*
B5	Alzheimer's	Increased ROS	Risk	Southern and East China	*(56)*
D	End stage renal	Unknown	Risk	Han Chinese	*(57)*
D	HTN	Unknown	Risk	Han Chinese	*(57)*
D	Low Total Cholestero	Unknown	Risk	Han Chinese	*(57)*
D	Low Total Cholesterol (Young)	Unknown	Risk	Han Chinese	*(57)*
D	Lung CA	Unknown	Protection	Han Chinese, Southwestern	*(57)*
D4a	Thyroid	Unknown	Risk	Wenzhou,	*(58)*
D4	AML	Unknown	Risk	Korean	*(59)*
M, (Subgroup D5)	Breast CA	Unknown	Risk	Wenzhou, China	*(58)*

D5 (Supergroup M)	T2DM	Unknown	Protection	Taiwan	*(60)*
D5 (Supergroup N)	T2DM	Unknown	Protection	Taiwan	*(60)*
F	Lung CAm	Unknown	Protection	Han Chinese, Southwestern China	*(57)*
F	T2DM	Unknown	Risk	Meta	*(45.*
F4 (Supergroup M)	T2DM	Unknown	Protection	Taiwan	*(60)*
F4 (Supergroup N)	T2DM	Unknown	Protection	Taiwan	*(60)*
F4 (D5)	HTN	Increased ROS	Risk	Taiwan	*(60)*
F4 (Supergroup M)	HTN	Increased ROS	Risk	Taiwan	*(60)*
F4 (Super group N)	HTN	Increased ROS	Risk	Taiwan	*(60)*
F4 (D5)	Obesity	Unknown, but mitochondria control conversion of adipose into brown fat	Risk	Taiwan	*(60)*
F4 (Macro group M)	Obesity	Unknown, but mitochondria control conversion of adipose into brown fat	Risk	Taiwan	*(60)*
F4 (Macro group N)	Obesity	Unknown, but mitochondria control conversion of adipose into brown fat	Risk	Taiwan	*(60)*
G	Lung CA	Unknown	Risk	Han Chinese, Southwestern China	*(57)*
H	Alzheimer's	Elevated ROS	Risk of Disease	Meta Analysis, mostly European;	*(45); (61); (62)*
H	LHON-associated visual failure	Unknown	Protection	European	*(63)*

DOI: https://doi.org/10.52793/ACMR.2023.4(4)-66

H5	Alzheimer's	Increased ROS (recall heterogeneity	Risk	Northern + Southern Italy	*(64)*
H5 (synergy with	Alzheimer's	Unknown	Risk	Poland	*(62)*
H5, in the presenc	Alzheimer's	Increased ROS (recall heterogeneity in J)	Risk	Northern + Southern Italy	*(64)*
H5a	Alzheimer's	Increased ROS (recall heterogeneity	Risk	Northern + Southern Italy	*(64)*
H6A1A	Alzheimer's	Unknown	Protection	Utah (Cache County Cohort)	*(65)*
H6A1B	Alzheimer's	Unknown	Protection	Utah (Cache County Cohort)	*(9)*
HV	Schizophrenia	Increased ROS	Risk of Disease	Israeli Arabs	*(66)*
HV	Alzheimer's	Increased ROS (recall heterogeneity	Risk	Poland	*(62)*
HV	Parkinson's	Elevated ROS	Risk	Meta Analysis,	*(45*
Pre-HV	Bipolar (unspecified type) and	Possible Coupling Differences	Risk	U.S. citizens	*(67)*
J	Parkinson's	Decreased ROS	Protection	Meta Analysis, mostly	*(45)*
J	3MS score decline (8-year	High ROS for some subtypes	Risk	Memphis and Pittsburg	*(68)*
J	Alzheimer's	Unknown	Protection	Poland	*(62)*
J	Longevity	ROS	Associated	Meta	*(45)*
J	LHON-associated visual failure	Unknown	Risk	European	*(63)*
J1 (Compared	LHON-associated visual failure	Unknown	Risk	European	*(63)*
J2 (Compared to J1)	LHON-associated visual failure	Unknown	Risk	European	*63)*
J1b	Parkinson's	Decreased ROS	Protection	UK	*(63)*
JK	Parkinson's	Decreased ROS	Protection	U.S. Caucasians	*(69)*
JT	Parkinson's	Decreased ROS	Protection	UK	*(63)*
JT	Alzheimer's	Reduced ROS, possibly higher activity of catalases	Protection	Poland	*(62)*
JT	Schizophrenia	Unknown, recall heterogeneity in J	Risk of early onset of	Italy	*(70)*
JT	Parkinson's	Decreased ROS	Protection	Meta	*(63)*
UKJT	Parkinson's	Unknown	Delayed Onset	Cypriot Greek	*(71)*
UKJT	Alzheimer's	Decreased ROS	Protection	Western Europe	*(72)*

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K	Alzheimer's	Unknown	Protection—especially from APOE4	Poland	*(62)*
K	Schizophren	Unknown	Risk	European, UK	*(66)*
K	Parkinsons	Decreased ROS	Protection	Meta Analysis, mostly	*(45); (69); (61)*
K	Breast Cancer	Unknown	Risk	North American European	*(73)*
K	Breast CA	Unknown	Risk	European	*(74)*
K	MS	ROS	Risk	Iranian Persian	*(52)*
K	LHON-associated visual failure	Unknown	Risk	European	*(63)*
K1	Childhood Acute Lymphoblast	Unknown	Risk	Finland	*(75)*
K1A1B and K1A1B2A1	Decreased Temporal Pole	Unknown	Risk	US + Canada	*(65)*
KU	Alzheimer's	Unknown	Protection	Poland	*(62)*
L	Colorectal Cancer	Unknown	Risk	Multi ethnic cohort from Hawaii and	*(88)*
L1	Alzheimer'	Unknown	Risk	African Americans	*(68)*
LMN	Parkinson'	Unknown	Protection	Cypriot Greek	*(71)*
M	Breast CA	Unknown	Risk	Wenzhou, China	*(58)*
M7	Lung CA	Unknown	Risk	Han Chinese, Southwestern	*(57)*
N9a (Super group N)	HTN	Increased ROS	Risk	Taiwan	*(60)*
N9a	Bipolar (Unspecified	Unknown	Risk	Japan	*(38)*
N9a	Schizophr	Unknown	Risk	European, UK	*(63)*
N9a	T2DM	Unknown	Protection	Asians	*(76); (60)*
N1a1	Schizophr	Unknown	Risk	European, UK	*(63)*
NWXI	Parkinson'	Unknown	Protection	Cypriot Greek	*(71)*
T	Parkinson's	Decreased ROS, better response to	Protection	Meta Analysis, mostly	*(45); (61)*
T	Dementia	Unknown	Risk	Memphis and Pittsburg	*(68)*
T	Alzheimer'	Decreased ROS	Protection	Poland	*(62)*
T	Bipolar (unspecified	Possible Coupling Differences	Protection	U.S. citizens	*(67)*
T	Colorectal Cancer	Unknown	Risk	Multi ethnic cohort from Hawaii and	*(88)*
T	T2DM	Unknown	Risk	Asians	*(76)*
U	Bipolar-Associated	Unknown	Risk	European, UK	*(77)*

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U	T2DM Vascular	Unknown	Protection	Finland	*(78)*
U	T2DM maternal	Unknown	Association	Finland	*(78)*
U	Breast CA	Unknown	Protection	European	*(74)*
U	Breast Cancer	Unknown	Protection	North American Caucasian	*(73)*
U	Prostate Cancer	Unknown	Risk	North American Caucasian	*(79)*
U	Renal Cancer	Unknown	Risk	North American Caucasian	*(79)*
U	Atheroscle	ROS	Risk	Polish	*(80)*
U5	Schizophr	Unknown	Risk	European, UK	*(31)*
U9	Schizophr enia	Unknown	Risk	European, UK	*(31)*
U5a	Schizophr enia	Unknown	Risk	European, UK	*(31)*
U5a1	Schizophr	Unknown	Risk	European, UK	*(31)*
U5B1 or U5B1B2	Decrease d Temperal	Unknown	Risk	US + Canada	*(65)*
V	T2DM	Unknown	Protection	Polish	*(80)*
W	Longevity	ROS	Not Associated	Meta	*(45)*
Branch 155	Decrease d Whole	Unknown	Risk	US + Canada	*(83)*
Branch 184	Decrease d Whole	Unknown	Risk	US + Canada	*(83)*
Branch 184	Left Hippocam pal	Unknown	Risk	US + Canada	*(65)*
p.G166G; m.15244A>G	Decline in DSST score	Unknown	Risk	Memphis and Pittsburg	*(68)*
p.I166V; m.14178T>C	3MS score decline	Unknown	Risk	Memphis and Pittsburg	*(68)*
Disagreeing studies	Alzheimer's, Parkinson'	NONE	NONE	Spanish	*(81); (82)*

Table 1: A cross-section of articles from the published scientific literature detailing the associations of mtDNA haplotypes and genetic disease.

Discussion

Encoding only 37 genes, mitochondria have evolved to become an essential organelle within the cell [31]. The mitochondrion's compact structure and minimal redundancy results in mutations on the mitochondrial genome being an important cause of genetic disease. Our search of the literature revealed numerous associations between mtDNA variants and genetic disease with many of these diseases displaying important health disparities.

The comprehensive literature search results displayed in Table 1show that the numbers of risk association variants (N=59) are much greater than the number of protective associations variants (N=33). This is likely a reflection of our pathology driven biomedical research paradigm [39]. Abnormalities are more likely to gain the attention of the clinical community and Big Pharma than are mtDNA variants that are deterrents to genetic disease. In spite of the literature's emphasis on disease risk alleles, very few explicit physiological consequences of specific variants have been identified in the literature. This likely reflects the still early stage of the research on the associations of specific mtDNA types and particular genetic diseases.

Our survey suggests that only 3 out of 95 entries are from "megahaplo group" L, even though this is the oldest haplogroup in our species and could, therefore, provide the greatest evolutionary information about the complex association of mtDNA variants, genetic disease, and current health disparities. Low coverage of "megahaplo group" L is consistent with the general underrepresentation in the scientific literature of studies on genetic variants more commonly observed in peoples of recent African descent. While there have been many calls for parity in research [40-41],this has not yet translated into adequate representation of African mtDNA variants in either disease association studies or cell culture experiments [42].In one of the few studies of molecular and bioenergetic differences between regionally diverse mtDNA haplogroups [43] the L "megahaplo group", common in peoples of recent African descent, showed lower mtDNA copy numbers, but higher expression levels for nine mtDNA-encoded respiratory complex genes, decreased ATP (adenosine triphosphate) turnover rates and lower levels of reactive oxygen species production, parameters which were considered consistent with more efficient oxidative phosphorylation. In a more recent study, comparisons between megahaplo group L and haplogroup H (common in Europeans) showed important physiological differences including variations in (i) responses to exogenous stressors (Amyβ and UV radiation), (ii) epigenetic status, and (iii) modulation profiles of methylation-mediated downstream complement, inflammation, and angiogenesis genes [44]. These latter differences are commonly associated with various human diseases, many of which display important health disparities.

In our study, we identified 29 clinical conditions associated with mtDNA mutations. The most commonly encounter pathologies were cancer, neurodegenerative diseases, and metabolic disorders. The cancers included lung, thyroid, breast, lymphoblastic, and colorectal. Several mutations in nuclear genes encoding for mitochondrial components have been associated with an increased cancer risk [23]. Previous studies have associated a range of mtDNA abnormalities, including mutations, deletions, inversions and copy number alterations, with mitochondrial dysfunction and these changes may be the biogenesis of hampered cellular bioenergetics in diverse cancer cell types [23].

Neurodegenerative diseases were a second target of mtDNA dysfunction. These include Alzheimer's, Schizophrenia, Parkinson's, bipolar, MS, Leber hereditary optic neuropathy, and dementia. Several symptoms were reported that may be precursors to these neurodegenerative malfunctions, including left hippocampus atrophy, decreased temporal pole thickness, decreased whole brain volume, migraine, and declines in performance on the digital symbol substitution test. Mitochondrial dysfunction is directly

implicated in several neurodegenerative diseases, and is potentially related to increased oxidative damage and amyloid-β (Aβ) formation in Alzheimer's disease [46].

Metabolic disorders reported in our search of the literature included reports of Type 2 diabetes mellitus, gallstone disease, low total cholesterol, and obesity. It has been reported that European mtDNA haplogroups may play an important role in susceptibility to metabolic disturbance and cardiovascular disease [47,48]. It is likely that our lists of disruptive mtDNA genetic disease conditions (metabolic, carcinogenic, and neurodegenerative) are largely a reflection of the sampled base populations. This presents a dilemma for making solid correlations to existing health disparities.

In the scientific literature, the populations sampled for mtDNA genetic disease associations are in inverse proportion to the patterns of current health disparities. The US groups with persistently disproportionate health disparities include African Americans/Blacks, American Indians and Alaska Natives, Asians, Native Hawaiians/other Pacific Islanders and Hispanics/Latinos. The literature focused 59 out 95 cases (62%) in Europeans and peoples of European descent although worldwide, Europeans are estimated to comprise only 12% of the world's population. There were 32/95 cases (34%) in the literature that considered Asians although Asia represents 30% of the world's land mass and over 60% of the world's current population are Asians. In our review of the literature, the overwhelming majority of the represented Asians were East Asians. The mtDNA genetic disease associations in peoples of African descent represented only 1% of all studies we reviewed. "YetAfrica" is the second most populous continent in the world and there are approximately 150 million African-descended people worldwide, according to the United Nations. Additionally, the high genetic diversity observed in peoples of recent African descent and the antiquity of the human presence in continental Africa, mandates that more than 1% of our scientific effort be focused on the disease consequences of molecular variation observed in these populations.

To increase parity in genetic disease studies, we must intentionally collect from the underrepresented populations using big data storage, processing, exchange and curation [87]. Once researchers commit to including more diversity in mtDNA genetic disease studies, increasing the bibliometric databases to include, for example, Web of Science (WoS), Google Scholar, Microsoft Academic, Crossreff, Dimensions and Cite Seer [49] will enhance the catchment area of relevant publications. Right now, however, we are at the beginning of understanding the complex relationships of mtDNA haplotypes, genetic disease incidence, and the contribution to health disparities. Since mtDNA mutations may cause unanticipated, extended phenotypes and have reproductive implications [50] it is imperative that we systematically broaden the sampling database of these studies so that the evolutionary and biomedical inferences can be anticipated.

Competing Interests

The authors declare no competing interests.

Author Credits

The manuscript was initiated, figure 1 conceived, and the text was written by FJ. Table 1 was compiled by LM with input from JC, NB, MM, and KK. All authors collaborated on the final manuscript.

Acknowledgements

We thank the All of Us Researcher Academy and RTI for support of this study and the QuadGrid Data Lab Research Group for bibliometric assistance throughout the project. We thank Dr. Bert Ely, University of South Carolina for access to the Ely-Jackson Database of African and African American mtDNA variants." This work is supported by the Division of Engagement and Outreach, All of Us Research Program, National Institutes of Health under award number 1OT20D028395-01."

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