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Health and genetic ancestry testing: time to bridge the gap

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Abstract

Background: It is becoming increasingly difficult to keep information about genetic ancestry separate from information about health, and consumers of genetic ancestry tests are becoming more aware of the potential health risks associated with particular ancestral lineages. Because some of the proposed associations have received little attention from oversight agencies and professional genetic associations, scientific developments are currently outpacing governance regimes for consumer genetic testing.

Main text: We highlight the recent and unremarked upon emergence of biomedical studies linking markers of genetic ancestry to disease risks, and show that this body of scientific research is becoming part of public discourse connecting ancestry and health. For instance, data on genome-wide ancestry informative markers are being used to assess health risks, and we document over 100 biomedical research articles that propose associations between mitochondrial DNA and Y chromosome markers of genetic ancestry and a wide variety of disease risks. Taking as an example an association between coronary heart disease and British men belonging to Y chromosome haplogroup I, we show how this science was translated into mainstream and online media, and how it circulates among consumers of genetic tests for ancestry. We find wide variations in how the science is interpreted, which suggests the potential for confusion or misunderstanding.

Conclusion: We recommend that stakeholders involved in creating and using estimates of genetic ancestry reconsider their policies for communicating with each other and with the public about the health implications of ancestry information.

Keywords: Direct-to-consumer genetic tests, Genetic ancestry, Disease/Health risk, Regulation, Social implications, Public understanding

Background

While genetic ancestry tests marketed to consumers do not currently claim to provide information about disease risk, it is becoming increasingly difficult to keep information about ancestry separate from information about health. In this article, we consider the recent and unremarked upon growth in genetic tests and biomedical studies linking markers of genetic ancestry to various diseases and medical conditions. These developments are becoming part of public discourse connecting ancestry and health, but because genetic testing companies, oversight agencies, and professional genetic associations have largely treated health and ancestry genetic tests as independent and distinct, little guidance is available to help consumers understand and interpret the reported connections between genetic ancestry and disease risk. Consequently, when such findings circulate in the public realm, consumers learn that there may be health risks tied to their genetic ancestry even though companies do not report those associations. There is therefore potential for confusion or misunderstanding that is problematic for both consumers and the scientific community. We argue that the various stakeholders in genetic ancestry testing need to reconsider what they communicate about the health implications of ancestry information, both to the public and to each other, in order to effectively bridge the gap that currently exists in policies and consumer guidance regarding genetic tests for ancestry and health.

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The gap between genetic tests for health and ancestry

Genetic ancestry tests were first marketed directly to consumers in 2000, for the purpose of reconstructing genealogies and investigating personal genetic heritage. They quickly became the most popular of all consumer genetic testing services, and more than three million individuals have reportedly purchased these tests to date [1, 2]. Over the last 15 years, companies [3], regulators [4] and professional scientific associations [5, 6] have treated ancestry genetic tests differently than medical or health-oriented genetic tests. Tests that make health-related claims or have implications for the prevention, diagnosis, or treatment of disease have been subject to greater scrutiny and oversight, as regulators have sought to ensure that potentially life-changing healthcare decisions are not made on the basis of poor quality information or with a lack of appropriate medical knowledge, advice, and support [7]. Genetic ancestry tests have received less attention from legislators, policy makers and regulatory agencies because they are not marketed explicitly for disease diagnosis, treatment, or prevention, and have thus been seen as more "recreational", less consequential, and less ethically problematic. This differentiation between ancestry and health genetic testing has seemed appropriate because the two types of tests have had such different applications.

However, recent developments demonstrate that the boundary between ancestry-related and health-related genetic testing is more porous than previously suggested [8], and it is being transgressed in a variety of ways. When genetic testing company 23andMe suspended its 'health reports' in 2013, following a warning from the US Food and Drug Administration (FDA), it continued to provide customers with ancestry information and their raw genetic data [9, 10]. With these ancestry testing data, consumers could still obtain an assessment of their health risks using independent online 'interpretation-only' services for as little as $5 [11]. More explicit links between genetic ancestry and health are evident in 23andMe's relaunched Health + Ancestry Service, which was approved by the FDA as a 'medical device' and provides both ancestry and health information. This service directly connects ancestry to health in its 'wellness' reports for traits like lactose intolerance and in its 'carrier status' reports for medical conditions like cystic fibrosis and sickle cell anemia, as both link risk estimates to named racial/ethnic groups. At least one other leading genetic testing company (Ancestry.com) is in discussions with the FDA about expanding its service to include similar carrier status reports [12]. Furthermore, as we show in this article, even when genetic ancestry tests report only an individual's ancestry, consumers can become aware of possible health risks tied to their genetic ancestry via media coverage of scientific studies and online discussion groups.

This blurring of the line between genetic ancestry and health accentuates the gaps that currently exist in policy and in the available guidance for consumers because little attention has been given to the health implications of genetic ancestry testing. However, as others have noted, it may become common for consumers to share their ancestry test results or ancestry-related estimates of disease risk with their physicians, expecting such information to inform their healthcare decisions and improve their quality of care [13, 14]. It is therefore crucial that we bridge these gaps to ensure that genetic testing information is used appropriately in health-related decisions and clinical care. This is especially important because most physicians lack the expertise needed to interpret and contextualize the results of genetic tests: only 29% of US clinicians surveyed rate their knowledge of genetics as excellent, very good, or good [15], and less than a third of the physicians surveyed in five European countries were confident or very confident in their ability to carry out basic medical genetic tasks [16]. Given these findings, there is a real risk that consumers or their physicians could make problematic and potentially irreversible healthcare decisions based on inaccurate, misleading, or misinterpreted genetic testing results. Genetic ancestry information has been misinterpreted or over-interpreted in the past [17–19], and it has been used in ways that reach far beyond the intended or anticipated scientific applications — for example, in controversial attempts to use genetic ancestry tests to support Native American tribal membership claims [20] and to infer nationality in asylum cases [21].

Thus, it is critical that we recognize and address the increasingly porous boundary between genetic tests for ancestry and health because (1) genetic ancestry tests can provide information that has consequences for health decision-making, (2) test-takers may have unrealistic expectations about the scientific and medical certainties offered by the tests they have purchased, (3) many physicians are not prepared to interpret and apply the genetic test results that their patients may bring into the clinic, and (4) better guidance for consumers is needed to ensure that health-related information from genetic ancestry tests is interpreted and applied in valid ways. This is especially important because, as we show in the next section, scientific and biomedical studies have been drawing ever more connections between ancestry and health, and there is evidence that these connections are beginning to affect consumer interpretations of their genetic ancestry test results.

Mounting evidence of connections between genetic ancestry and disease risk

Genetic ancestry plays an important role in contemporary biomedical science. Medical genetic studies, for instance,

commonly use ancestry inferences derived from autosomal markers (typically single nucleotide polymorphisms or "ancestry informative markers") to control for population stratification, a practice that underpins the now routine reporting of population-specific or ancestry-specific estimates of disease risks and drug response in genetic epidemiology [13, 22]. Far less attention has been given to the fact that studies using uniparental genetic markers have uncovered connections between ancestry and health. These tests have been a mainstay of the direct-to-consumer ancestry-testing marketplace, but have been widely considered to have little biomedical value [13].

Over the last decade, hundreds of biomedical studies have been published that suggest that certain mitochondrial DNA (mtDNA) and Y chromosome variants (and the haplogroups defined by those variants) are associated with an increased risk of disease and other health complications [23]. These variants and haplogroups have been linked to a diverse array of common diseases and medical conditions, including coronary artery disease, myocardial infarction, ischaemic stroke, heart transplant complications, Leber hereditary optic neuropathy, advanced age-related macular degeneration, hearing loss, osteoarthritis, osteoporosis, multiple sclerosis, Alzheimer's and Parkinson's disease, complications from type 2 diabetes (especially retinopathy, neuropathy, nephropathy, and renal failure), several types of cancer (breast, thyroid, pancreatic, esophageal, colorectal, prostate, renal, and lung cancer), and the rate of AIDS progression in HIV patients (an additional table shows examples of associations discussed in the biomedical literature [see Additional file 1]). The exact causes of these associations are not always clear, but it is thought that the associated genetic variants alter the expression of key gene pathways [24] or, in the case of mtDNA, contribute to the development and progression of disease by affecting energy metabolism and important cellular processes, including ATP synthesis, reactive oxygen species (ROS) production, oxygen consumption efficiency, calcium signaling, and apoptosis [25–27].

It is important to note that the quality of studies reporting associations between mtDNA/Y chromosome haplogroups and disease susceptibility is quite variable. Some haplogroup-disease associations are supported by multiple independent studies with rigorous statistical designs, but many others are not. The biomedical literature includes a large number of studies that suffer from small sample sizes, inappropriate controls for population stratification, and/or problematic statistics (for example, *P*-values that have not been corrected for multiple comparisons), so some of the reported haplogroup-disease associations are almost certainly false positives. Other researchers have also drawn attention to these problems [23, 28]. However, regardless of the quality of these studies, many publications present possible associations between mtDNA/Y haplogroups and disease risk, and consumers are becoming aware of these reports as they garner media attention and enter public discourse.

In 2012, for example, a study published in *The Lancet* found that British men belonging to Y chromosome haplogroup I have a 50% higher age-adjusted risk of coronary artery disease (CAD) than other British men, with haplogroup I being the most significant predictor of CAD after HDL cholesterol and lipid-lowering treatment [24]. This finding was widely reported by the media in the UK, US, and Australia, under headlines about heart disease risk being inherited along paternal lines (Tables 1 and 2). This coverage demonstrated the potential for raised consumer expectations about the value of genetic ancestry information to health, and the future possibilities of acting on that information. One article, for example, suggested that: "when a screening test is developed to find those Y chromosome gene clusters and researchers have a better understanding of how they act, it may be possible to protect some [unlucky men] from having heart attacks." [29] The UK National Health Service added an extensive discussion of ancestral haplogroups and CAD to their patient information website, *NHS Choices*, after the study was published — albeit to argue that this information was not of immediate use for tackling CAD in the UK because, among other reasons, "men are unlikely to know their specific haplogroup, so are unlikely to know whether they may be at increased risk of CAD" [30]. Ancestry testing consumers discussed this *Lancet* study (along with other reports of haplogroup-associated disease susceptibilities) in online forums (in threads entitled, for example, "Medical conditions associated with Y-chromosome haplogroups" and "Do not read if you are a hypochondriac…"), and a Principal Scientist at 23andMe blogged about the study, expressing skepticism about the study's conclusions and offering an alternative analysis using his company's data (Table 3). Thus, by following the circulation of this study in public domains, we can see variation in how the study was understood, disagreement over the robustness of its conclusions, and a lack of clarity about the significance of genetic ancestry markers like haplogroups to health.

While similar observations can be made about studies of autosomal or genome-wide markers and disease risk, we have focused here on uniparental genetic markers because mtDNA and Y chromosome tests are the two types of genetic ancestry tests that companies, policymakers, regulators, and professional scientific associations have invariably treated as less relevant to health. However, as we have shown, there is public interest in the extensive biomedical literature investigating the associations between mtDNA/Y chromosome haplogroups

Table 1 Coverage of Charchar et al. [24] in mainstream news media

Outlet	Author	Date	Headline	Section	URL	Quoted
BBC News Online (UK)	Michelle Roberts	09/02/12	Men can inherit a form of heart disease from father via Y chromosome	Health	www.bbc.co.uk/news/health-16931585	Dr Maciej Tomaszewski (University of Leicester); Dr Hélène Wilson (British Heart Foundation)
The Independent (UK)	Jeremy Laurance	09/02/12	Male gene increases risk of hereditary heart disease for one in five	Health	www.independent.co.uk/life-style/health-and-families/ health-news/male-gene-increases-risk-of-hereditary-heart-disease-for-one-in-five-6676537.html	Dr Maciej Tomaszewski (University of Leicester); Dr Virginia M. Miller (Mayo Clinic)
The Daily Telegraph (UK)	Rebecca Smith	09/02/12	One in five men have DNA that puts them at greater risk of a heart attack: research	Health	www.telegraph.co.uk/health/healthnews/9068859/One-in-five-men-have-DNA-that-puts-them-at-greater-risk-of-a-heart-attack-research.html	Dr Hélène Wilson (British Heart Foundation); Dr Maciej Tomaszewski (University of Leicester); Dr Virginia M. Miller (Mayo Clinic)
The Daily Mail (UK)	Sadie Whitelocks	09/02/12	Men can inherit higher risk of heart attack from father - and can pass danger on to their sons	Health	www.dailymail.co.uk/health/article-2098314/Fathers-common-gene-variant-50-cent-higher-risk-heart-disease–pass-sons.html	Dr Hélène Wilson (British Heart Foundation); Dr Maciej Tomaszewski (University of Leicester)
The Daily Mirror (UK)	Lachlan MacKinnon	09/02/12	Close to men's hearts: Y chromosome link to coronary risk	Technology and science	www.mirror.co.uk/news/technology-science/science/close-to-mens-hearts-y-chromosome-678644	Dr Hélène Wilson (British Heart Foundation); Dr Maciej Tomaszewski (University of Leicester)
Time (USA)	Alexandra Sifferlin	09/02/12	Like Father like Son? Y Chromosome Linked to Heart Disease	Heart Disease	healthland.time.com/2012/02/09/like-father-like-son-y-chromosome-linked-to-heart-disease/	Scientific American Dr Maciej Tomaszewski (University of Leicester)
CBS News (USA)	Brenda Goodman	09/02/12	Some men may inherit a higher risk of heart disease from dad	News	http://www.cbsnews.com/news/some-men-may-inherit-a-higher-risk-of-heart-disease-from-dad/	Lisa Bloomer (University of Leicester); Dr Virginia M. Miller (Mayo Clinic)
The New York Times (USA)	Gina Kolata	08/02/12	Male Genes May Explain Higher Heart Disease Risk	Health	www.nytimes.com/2012/02/09/health/research/heart-disease-risk-may-be-tied-to-y-chromosome.html?_r=0	Dr Virginia M. Miller (Mayo Clinic); Dr Sekar Kathiresan (Massachusetts General Hospital); Dr. Daniel J. Rader (University of Pennsylvania)
Scientific American (USA)	Katherine Haron Courage	08/02/12	Y Chromosome Can Raise Heart Disease Risk by 50%	Blogs	http://blogs.scientificamerican.com/observations/2012/02/08/y-chromosome-can-raise-heart-disease-risk-by-50-percent/	Prof F Charchar (University of Ballarat); Dr Virginia M. Miller (Mayo Clinic)
Forbes (USA)	Larry Husten	09/02/12	The Y Chromosome May Explain Why Men Have Earlier Coronary Disease	Pharma and Healthcare	http://www.forbes.com/sites/larryhusten/2012/02/09/the-y-chromosome-may-explain-why-men-have-earlier-coronary-disease/	The Lancet paper; Dr Virginia M. Miller (Mayo Clinic)

Table 1 Coverage of Charchar et al. [24] in mainstream news media *(Continued)*

The Age (Australia)	Deb Anderson	27/03/12	Does the Y chromosome influence men's health?	Education		Prof F Charchar (University of Ballarat)
The Chronicle (Australia)	Tom McIlroy	13/02/12	UB releases heart disease research	News	http://www.thecourier.com.au/story/62162/ub-releases-heart-disease-research/	Prof F Charchar (University of Ballarat); Dr Hélène Wilson (British Heart Foundation)
International Business Times (Australia)	Lawrence Villamar	10/02/12	Heart Disease Risks Linked to Genes in Men: study	Articles		Prof F Charchar (University of Ballarat)
The Times of India (India)	Kounteya Sinha	10/02/12	Sons can inherit heart disease from dad: Study	India	http://timesofindia.indiatimes.com/india/Sons-can-inherit-heart-disease-from-dad-Study/articleshow/11829916.cms	The Lancet paper; Dr Pramod Kumar (Fortis Hospital); Dr Virginia M. Miller (Mayo Clinic)

Table 2 Coverage of Charchar et al. [24] in online sources of medical news

Site	Author	Date	Headline	URL	Quoted
NHS Choices		09/02/12	One in five men 'carries heart risk gene'	www.nhs.uk/news/2012/02February/Pages/y-chromosome-heart-disease-risk.aspx	BBC News
Medical News Today	Jospeh Nordqvist	09/02/12	Male Gene Linked To Coronary Artery Disease Risk	www.medicalnewstoday.com/articles/241441.php	The Lancet paper; Dr Virginia M. Miller (Mayo Clinic)
WebMD	Brenda Goodman	08/02/12	Some Men May Inherit a Higher Risk of Heart Disease From Dad	www.webmd.com/heart-disease/news/20120208/some-men-may-inherit-higher-risk-heart-disease-from-dad	Lisa Bloomer (University of Leicester); Dr Virginia M. Miller (Mayo Clinic)
Medscape	Lisa Nainggolan	10/02/12	Like Father, Like Son: Y-Chromosome Variant May Explain CAD	http://webcache.googleusercontent.com/search?q=cache:RhYvNynICn4J:www.medscape.com/viewarticle/758437+&cd=1&hl=en&ct=clnk&gl=uk	Lisa Bloomer (University of Leicester); Dr Virginia M. Miller (Mayo Clinic); Dr Sekar Kathiresan (Massachusetts General Hospital)
News Medical	AnayaMandal	12/02/12	Y chromosome may be the link that passes heart disease risk from father to son	www.news-medical.net/news/20120 212/Y-chromosome-may-be-the-link-that-passes-heart-disease-risk-from-father-to-son.aspx	The Lancet paper; Dr Sekar Kathiresan (Massachusetts General Hospital); Dr Virginia M. Miller (Mayo Clinic)
The Naked Scientist	Kat Arney	12/02/12	Y Chromosome yields heart disease clues	www.thenakedscientists.com/HTML/news/news/2485/	
MyDr		09/02/12	Heart disease risk passed from father to son		Dr Virginia M. Miller (Mayo Clinic)
Cure Talk	Priya Menon	undated	Coronary Artery Disease Linked To Y Chromosome: Study By Fadi J. Charchar	trialx.com/curetalk/2012/03/coronary-artery-disease-linked-to-y-chromosome-study-by-fadi-j-charchar/	
Men's Health		09/02/12	Y chromosome may increase risk of coronary artery disease	www.drharryfisch.com/y-chromosome-may-increase-risk-of-coronary-artery-disease/	
drholdright.co.uk		02/12	The Y male sex chromosome and risk of heart disease	http://www.drholdright.co.uk/dynamicpage.php?pg=news&pageid=OTk=	

Table 3 Coverage linking haplogroups and health online in blogs and forums

Site	Author	Date	Headline	Type	URL	Includes Charchar et al. (2012) [24]
23andMe	Dave Hinds	04/04/12	Second Opinion: Haplogroup I Likely Not Linked to Heart Disease	blog	blog.23andme.com/news/second-opinion-haplogroup-i-likely-not-linked-to-heart-disease/	Yes
Improving Population Health	David A. Kindig	07/10/12	Are Male Genetic Health Differences Disparities or Inequities	blog	www.improvingpopulationhealth.org/blog/2012/07/are-male-genetic-health-differences-disparities-or-inequities.html	Yes
Dienekes Anthropology Blog		09/02/12	Y-chromosomes and coronary artery disease in Britain	blog	dienekes.blogspot.co.uk/2012/02/y-chromosomes-and-coronary-artery.html	Yes
Fight Aging		05/11/13	Those Lucky Haplogroup H Bearers	blog	www.fightaging.org/archives/2013/11/those-lucky-haplogroup-h-bearers.php	No
Mathilda's Anthropolgy Blog		03/11/08	Mitochondrial DNA and survival after sepsis	blog	mathildasanthropologyblog.wordpress.com/2008/11/03/mitochondrial-dna-and-survival-after-sepsis/	No
Eupedia		28/01/09 – 23/09/13	Medical conditions associated with Y-chromosome haplogroups	forum	www.eupedia.com/forum/threads/25199-Medical-conditions-associated-with-Y-chromosome-haplogroups	Yes
familytreeDNA		09/02/12 – 10/02/12	Do not read if you are a hypochondriac…	forum	forums.familytreedna.com/showthread.php?t = 30303&highlight = haplogroup + health + risk	Yes
Rootschat		22/05/13 – 01/06/13	Utter Confusion: please help me choose DNA test	forum	www.rootschat.com/forum/index.php?topic=647807.54	Yes (via ref to Hinds blog)
Eupedia		26/07/07 – 26/04/14	Medical conditions and risk factors associated with mtDNA haplogroups	forum	www.eupedia.com/forum/threads/24801-Medical-conditions-and-risk-factors-associated-with-mtDNA-haplogroups	No
Zetaboards		12/01/13 – 12/01/13	Examples of diseases associated with a haplogroup	forum	s1.zetaboards.com/anthroscape/topic/5045507/1/	No
WorldFamilies		14/06/11 – 20/03/12	At last some FGS-s for R0a2 from Tuscany and The Marche	forum	www.worldfamilies.net/forum/index.php?topic=9937.0	No

and disease, and some consumers of genetic ancestry tests are already trying to understand how their ancestry is relevant to their health and disease prognosis in light of these research findings. Other consumers are also likely to encounter the results of these biomedical studies in the popular press, in online forums, in literature from their healthcare provider, or in well-known medical journals, and they too may grapple with the possible health implications of their genetic ancestry test results. Therefore, even when genetic ancestry tests report only an individual's ancestral lineage or uniparental haplogroup, consumers can become aware of the possible relationship with genetic health risks because scientists have linked haplogroup ancestry to health outcomes.

Conclusions

Like the repurposing of genome-wide ancestry test data to assess health risks, and like the use of autosomal genetic markers in genetic epidemiology to identify population-specific disease risks and drug response, the reported associations between uniparentally-inherited haplogroups and various diseases represent another blurring of the line between genetic information on health and ancestry. Developments in scientific knowledge and commercial practice appear to be outpacing the current oversight and governance regimes that largely treat genetic tests for ancestry and health as separate and distinct.

We therefore suggest that it is time for the various stakeholders in genetic ancestry testing to reconsider what they communicate about the health implications of ancestry information, both to the public and to each other. This will require considering some difficult questions. For example, can and should consumer genetic testing companies take responsibility for the ways in which test-takers connect ancestry test results with other publicly available information? Can and should genetic testing companies, alongside scientific associations and consumer advocates, provide guidance to consumers about the accuracy and reliability of the various postulated associations between haplogroups (or other genetic markers) and health risks? How can those who communicate about the relevant science (scientific researchers, journal editors, science journalists, genetic testing companies, consumer advocates, policy advisors, etc.) achieve maximum clarity regarding the potential health implications of genetic ancestry (or the lack of them), and make effective use of the published critiques of the putative links between uniparental haplogroups and health risks [23, 28]? Should there be any changes to policies governing the regulation or oversight of consumer genetic testing, or additions to guidelines being developed by professional associations like the American Society of Human Genetics (ASHG)?

To help address the issues raised here, we make five recommendations for stakeholders in consumer genetic testing to consider:

(1) The ASHG or another respected professional genetics society should organize a roundtable to bring the various stakeholders together to produce authoritative guidance that will inform and benefit consumers, and help create a set of standards for the industry to follow. This guidance should make clear what we can and cannot know from genetic ancestry testing, and provide guidance regarding the accuracy and reliability of associations between genetic markers and health risks. Industry representatives, consumer advocates, policy and legal advisors, biomedical researchers, social scientists, and regulators should all be involved in drafting this guidance.
(2) Consumer advocates, scientific organizations, companies, science journalists, and government agencies should play a role in making this information available to consumers.
(3) Genetic ancestry testing companies should report only associations between genetic markers and diseases/medical conditions that have been scientifically validated. They should also provide information about the limitations of their tests (as 23andMe now does as part of their 'carrier status' and 'wellness' reports; [31]) and include information about how to interpret the connections between ancestry and health among their FAQs.
(4) Medical schools and continuing medical education (CME) programs should discuss the potential health implications of genetic ancestry information so that physicians can help their patients to interpret and contextualize their genetic testing results.
(5) Policy-makers and government agencies may wish to reconsider current oversight regimes for direct-to-consumer genetic testing in light of the increasingly porous boundaries between tests for health and ancestry.

Our recommendations are aimed at encouraging novel and timely interventions into ongoing debates about direct-to-consumer genetic tests, especially since the US FDA, European Commission, ASHG, and high-profile ancestry testing companies are all considering scientific, ethical, and regulatory issues regarding health-related genetic testing. Now is the time to start bridging the gap in our current approaches to health and ancestry genetic testing.

Additional file

Additional file 1: Examples of associations between mitochondrial DNA (mtDNA) or Y chromosome variants and diseases/medical traits discussed in the biomedical literature. Description of data: an extensive list of published associations between mitochondrial DNA (mtDNA) or Y chromosome variants and diseases/medical traits. Organised by disease/medical traits, and including: mtDNA or Y Chromosome Variant; Proposed Association (or Lack of Association); Study Location; and Reference. (DOCX 58 kb)

Abbreviations

ASHG: American Society of Human Genetics; CAD: Coronary artery disease; CME: Continuing medical education; FDA: Food and Drug Administration; mtDNA: Mitochondrial DNA; PGS: Personal genome service; ROS: Reactive oxygen species

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Authors' contributions

All authors contributed substantively to the argument developed in this paper and to the drafting and editing of the manuscript. AS initiated the collaboration, and collated and reviewed evidence from print and online media sources. RT advised on ethical and legal frameworks. AS and DB collated evidence of scientific work in the field, and DB reviewed and evaluated these. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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References

1. Kaiser J. Who has your DNA—or wants it. Science. 2015;349:1475.
2. Wells S. Paper presented at the International Conference for Genetic Genealogy. 2014.
3. Wagner J, et al. Tilting at windmills no longer: a data-driven discussion of DTC DNA ancestry tests. Genet Med. 2012;14:586–93.
4. Kalokairinou L, et al. Changes on the horizon for consumer genomics in the EU. Science. 2014;346:296–8. doi:10.1126/science.1256396.
5. Hudson K, et al. ASHG Statement on Direct-to-Consumer (DTC) Genetic Testing in the United States. Am Soc Hum Genet. 2007;81:635–7.
6. The American Society of Human Genetics. ASHG Ancestry Testing Statement and Recommendations: guidelines for Understanding the issues and implications involved. 2008. Available: www.ashg.org/pages/policy_statements.shtml.
7. National Human Genome Research Institute. Regulation of genetic tests. 2014. Available: www.genome.gov/10002335.
8. Lee S, et al. The illusive gold standard in genetic ancestry testing. Science. 2009;325:38–9.
9. U.S. Food and Drug Administration. Warning letter: 23andMe, Inc. 2013. Available: www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm.
10. Seon-Hee Y, Chung Y-J. Reflections on the US FDA's Warning on Direct-to-Consumer Genetic Testing. Genomics Inform. 2014;12(4):151–5. doi:10.5808/GI.2014.12.4.151.
11. Regalado A. How a wiki is keeping direct-to-consumer genetics alive. MIT technology review. 2014. Available: www.technologyreview.com/featuredstory/531461.
12. Duhaime-Ross A. Ancestry.com is talking to the FDA about using DNA to estimate people's risk of disease. The Verge. 2015. Available: http://www.theverge.com/2015/10/12/9487685/ancestry-com-dna-test-kit-disease-risk-fda.
13. Royal C, et al. Inferring genetic ancestry: opportunities, challenges, and implications. Am J Hum Genet. 2010;86:661–73.
14. Cherkas L, et al. A survey of UK public interest in internet-based personal genome testing. PLoS One. 2010;5(10):e13473.
15. Bonham V, et al. Physicians' knowledge, beliefs, and use of race and human genetic variation: new measures and insights. BMC Health Serv Res. 2014;14:456.
16. Nippert I, et al. Confidence of primary care physicians in their ability to carry out basic medical genetic tasks—a European survey in five countries—Part 1. J Community Genet. 2011;2(1):1–11.
17. Richards M. Beware the gene genies. The Guardian. 2003. Available: http://www.theguardian.com/education/2003/feb/21/highereducation.uk.
18. Bolnick D, et al. Genetics. The science and business of genetic ancestry testing. Science. 2007;318(5849):399–400.
19. Sense about Science. Sense about genetic ancestry testing. 2013. Available: http://archive.senseaboutscience.org/pages/genetic-ancestry-testing.html.
20. Tallbear K. DNA, blood, and racializing the tribe. Wicazo Sa Review. 2003;18(1):81–107.
21. Tutton R, Hauskeller C, Sturdy S. Suspect technologies: forensic testing of asylum seekers at the UK border. Ethnic Racial Stud. 2014;37:738–52.
22. Yu J-H, et al. What are our AIMs? Interdisciplinary perspectives on the use of ancestry estimation in disease research. AJOB Prim Res. 2012;3:87–97.
23. Salas A, Elson JL. Mitochondrial DNA as a risk factor for false positives in case–control association studies. J Genet Genomics. 2015;42:169–72.
24. Charchar F, et al. Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. Lancet. 2012;379:915–22.
25. Santoro A, et al. Evidence for sub-haplogroup H5 of mitochondrial DNA as a risk factor for late onset Alzheimer's disease. PLoS One. 2010;5:e12037. doi:10.1371/journal.pone.0012037.
26. Ebner S, et al. Mitochondrial haplogroups, control region polymorphisms and malignant melanoma: a study in Middle European Caucasians. PLoS One. 2011;6:e27192. doi:10.1371/journal.pone.0027192.
27. Palacín M, et al. Mitochondrial DNA and TFAM gene variation in early-onset myocardial infarction: evidence for an association to haplogroup H. Mitochondrion. 2011;11:176–81.
28. Raule N, et al. Association studies on human mitochondrial DNA: methodological aspects and results in the most common age-related diseases. Mitochondrion. 2007;7:29e38.
29. Kolata G. Male genes may explain higher heart disease risk. The New York Times. 2012. Available: http://www.nytimes.com/2012/02/09/health/research/heart-disease-risk-may-be-tied-to-y-chromosome.html.
30. Choices NHS. One in five men 'carries heart risk gene'. 2012. Available: www.nhs.uk/news/2012/02February/Pages/y-chromosome-heart-disease-risk.aspx.
31. 23andMe. Learn how your DNA may affect your health. 2016. Available: www.23andme.com/service/.

Additional File 1. Examples of associations between mitochondrial DNA (mtDNA) or Y chromosome variants and diseases/medical traits discussed in the biomedical literature.

Note: Published associations were included regardless of the quality of statistical analysis or the robustness of the reported association. Some of the associations listed here are likely false positives. This is not a comprehensive listing of all relevant studies and does not include all reported associations.

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Longevity			
mtDNA haplogroup D4	longevity	China	X. Y. Cai, *et al.*, Association of mitochondrial DNA haplogroups with exceptional longevity in a Chinese population. PloS ONE **4**, e6423 (2009), 10.1371/journal.pone.0006423.
mtDNA haplogroups M9, N9, B4a	reduced longevity	China	X. Y. Cai, *et al.*, Association of mitochondrial DNA haplogroups with exceptional longevity in a Chinese population. PloS ONE **4**, e6423 (2009), 10.1371/journal.pone.0006423.
mtDNA 150T	longevity	Costa Rica	L. Castri *et al.*, Mitochondrial polymorphisms associated with differential longevity do not impact lifetime-reproductive success. *Am J Hum Biol* **23**, 225-227 (2011).
mtDNA 5178A in haplogroup D	reduced longevity	Costa Rica	L. Castri *et al.*, Mitochondrial polymorphisms associated with differential longevity do not impact lifetime-reproductive success. *Am J Hum Biol* **23**, 225-227 (2011).
mtDNA haplogroups D4a, D5, D4b2b	longevity	Japan, Korea	Y. Nishigaki, N. Fuku, M. Tanaka, Mitochondrial haplogroups associated with lifestyle-related diseases and longevity in the Japanese population. *Geriatr Gerontol Int* **10 Suppl 1**, S221-235 (2010).
mtDNA haplogroup F	longevity	China	J. Feng *et al.*, Association of mtDNA haplogroup F with healthy longevity in the female Chuang population, China. *Exp Gerontol* **46**, 987-993 (2011).
mtDNA 150T	no association with longevity	China	H. Pan *et al.*, Absence of association between mitochondrial DNA C150T polymorphism and longevity in a Han Chinese population. *Exp Gerontol* **46**, 511-515 (2011).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Longevity (cont.)			
mtDNA haplogroups	no association with longevity	Spain	T. Pinos *et al.*, Are mitochondrial haplogroups associated with extreme longevity? A study on a Spanish cohort. *Age (Dordr)* **34**, 227-233 (2012).
mtDNA haplogroup X	successful aging	USA	M. D. Courtenay *et al.*, Mitochondrial haplogroup X is associated with successful aging in the Amish. *Hum Genet* **131**, 201-208 (2012).
mtDNA haplogroup J	less successful aging	USA	M. D. Courtenay *et al.*, Mitochondrial haplogroup X is associated with successful aging in the Amish. *Hum Genet* **131**, 201-208 (2012).
mtDNA 150T, 73G	longevity	Turkey	O. Guney *et al.*, Mitochondrial DNA polymorphisms associated with longevity in the Turkish population. *Mitochondrion* **17**, 7-13 (2014).
mtDNA haplogroup D4b2 and 1382C	longevity	Japan	N. Fuku *et al.*, The mitochondrial-derived peptide MOTS-c: a player in exceptional longevity? *Aging Cell* **14**, 921-923 (2015).
mtDNA haplogroups	no association with longevity	China	Y.-H. He *et al.*, Mitochondrial DNA plays an equal role in influencing female and male longevity in centenarians. *Exp Geront* **83**, 94-96 (2016).
mtDNA haplogroup M9	reduced longevity	China	L. Li *et al.*, Mitochondrial genomes and exceptional longevity in a Chinese population: the Rugao longevity study. *Age* **37**, 14 (2015).
mtDNA haplogroups A4h, R11a1a1a	longevity	China	L. Li *et al.*, Mitochondrial genomes and exceptional longevity in a Chinese population: the Rugao longevity study. *Age* **37**, 14 (2015).
mtDNA haplogroup C	reduced longevity	Costa Rica	L. Castri *et al.*, A mitochondrial haplogroup is associated with decreased longevity in a historic New World population. *Hum Biol* **86**, 251-259 (2014).
Cancer			
mtDNA 239C, 263G, 16207T, haplogroup I	breast cancer	Poland	A. M. Czarnecka *et al*, Mitochondrial genotype and breast cancer predisposition. *Oncol Rep* **24**, 1521-1534 (2010).
mtDNA 73G, 150T, 16183C, 16189C, 16223T, 16362C	reduced risk of breast cancer	Poland	A. M. Czarnecka *et al*, Mitochondrial genotype and breast cancer predisposition. *Oncol Rep* **24**, 1521-1534 (2010).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Cancer (cont.)			
linked mtDNA 16183C, 16189C, 16192T, 16270T, 195T	malignant melanoma	Middle Europe	S. Ebner *et al.*, Mitochondrial haplogroups, control region polymorphisms and malignant melanoma: a study in middle European Caucasians. *PLoS One* **6**, e27192 (2011), 10.1371/journal.pone.0027192.
mtDNA haplogroups M, D5	breast cancer	China	H. Fang *et al.*, Cancer type-specific modulation of mitochondrial haplogroups in breast, colorectal and thyroid cancer. *BMC Cancer* **10**, 421 (2010).
mtDNA haplogroup D4a	thyroid cancer	China	H. Fang *et al.*, Cancer type-specific modulation of mitochondrial haplogroups in breast, colorectal and thyroid cancer. *BMC Cancer* **10**, 421 (2010).
mtDNA haplogroup Uk	vulvar squamous cell carcinoma	Poland	A. Klemba *et al*., Mitochondrial genotype in vulvar carcinoma - cuckoo in the nest. *J Biomed Sci* **17**, 73 (2010).
mtDNA haplogroup H	reduced risk of vulvar squamous cell carcinoma	Poland	A. Klemba *et al*., Mitochondrial genotype in vulvar carcinoma - cuckoo in the nest. *J Biomed Sci* **17**, 73 (2010).
various rare mtDNA variants	pancreatic cancer	USA	E. T. Lam *et al.*, Mitochondrial DNA sequence variation and risk of pancreatic cancer. *Cancer Res* **72**, 686-695 (2012).
mtDNA haplogroup D (especially D4a, D5)	esophageal cancer	China	X. Y. Li *et al.*, Association of mitochondrial haplogroup D and risk of esophageal cancer in Taihang Mountain and Chaoshan areas in China. *Mitochondrion* **11**, 27-32 (2011).
mtDNA haplogroup U	prostate cancer	USA	L. M. Booker *et al*, North American white mitochondrial haplogroups in prostate and renal cancer. *J Urol* **175**, 468-472 (2006).
mtDNA haplogroup U	no association with prostate cancer	Middle Europe	E. E. Mueller *et al.*, Mitochondrial haplogroups and control region polymorphisms are not associated with prostate cancer in Middle European Caucasians. *PLoS One* **4**, e6370 (2009), 10.1371/journal.pone.0006370.
mtDNA haplogroup M	breast cancer	China	L. Shen *et al.*, Evaluating mitochondrial DNA in cancer occurrence and development. *Ann N Y Acad Sci* **1201**, 26-33 (2010).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Cancer (cont.)			
mtDNA haplogroup M5	breast cancer	India	N. R. Tipirisetti *et al.*, Mitochondrial genome variations in advanced stage breast cancer: a case-control study. *Mitochondrion* **13**, 372-378 (2013).
mtDNA 752A, 1440A, 4770A	colorectal cancer	Scotland	E. Theodoratou *et al.*, Association between common mtDNA variants and all-cause or colorectal cancer mortality. *Carcinogenesis* **31**, 296-301 (2010).
mtDNA haplogroups D, F	reduced risk of lung cancer	China	S. Zheng *et al.*, Association of mitochondrial DNA variations with lung cancer risk in a Han Chinese population from southwestern China. *PLoS One* **7**, e31322 (2012), 10.1371/journal.pone.0031322.
mtDNA haplogroups G, M7	lung cancer	China	S. Zheng *et al.*, Association of mitochondrial DNA variations with lung cancer risk in a Han Chinese population from southwestern China. *PLoS One* **7**, e31322 (2012), 10.1371/journal.pone.0031322.
mtDNA haplogroup JT	myelodysplastic syndromes	USA	J. N. Poynter *et al*., Association between mitochondrial DNA haplogroup and myelodysplastic syndromes. *Genes Chromosomes Cancer* **55**, 9 (2016), 10.1002/gcc.22370.
mtDNA haplogroups	no association with prostate cancer	Colombia	D. Cano *et al*., Mitochondrial DNA haplogroups and susceptibility to prostate cancer in a colombian population. *ISRN Oncol*. 530675 (2014), 10.1155/2014/530675.
mtDNA	no association with prostate cancer	USA	E. E. Giorgi *et al*., No Association between the Mitochondrial Genome and Prostate Cancer Risk: The Multiethnic Cohort. Cancer Epidemiol Biomarkers Prev. **25**, 6 (2016), 10.1158/1055-9965.
mtDNA haplogroup T	colorectal cancer	USA	Y. Li *et al.,* Association of Genes, Pathways, and Haplogroups of the Mitochondrial Genome with the Risk of Colorectal Cancer: The Multiethnic Cohort. PLoS One **10**, e0136796 (2015), 10.1371/journal.pone.0136796.
mtDNA haplogroup H	breast cancer	Uruguay	C. Bonilla *et al*, Breast cancer risk and genetic ancestry: a case-control study in Uruguay. *BMC Womens Health*. **15**, 11 (2015) 10.1186/s12905-015-0171-8.

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Cancer (cont.)			
mtDNA haplogroups R9, F1	nasopharyngeal carcinoma	China	S. P. Hu, J. P. Du, D. R. Li, Y. G. Yao, Mitochondrial DNA haplogroup confers genetic susceptibility to nasopharyngeal carcinoma in Chaoshanese from Guangdong, China. PLoS One **9**, e87795 (2014), 10.1371/journal.pone.0087795.
Coronary Conditions			
mtDNA haplogroups N9b, M7c	reduced risk of myocardial infarction	Japan, Korea	Y. Nishigaki, N. Fuku, M. Tanaka, Mitochondrial haplogroups associated with lifestyle-related diseases and longevity in the Japanese population. *Geriatr Gerontol Int* **10 Suppl 1**, S221-235 (2010).
mtDNA haplogroup G1	myocardial infarction	Japan, Korea	Y. Nishigaki, N. Fuku, M. Tanaka, Mitochondrial haplogroups associated with lifestyle-related diseases and longevity in the Japanese population. *Geriatr Gerontol Int* **10 Suppl 1**, S221-235 (2010).
mtDNA 16189C	coronary artery disease & myocardial infarction	Saudi Arabia	K. K. Abu-Amero *et a.l*, The mitochondrial DNA variant 16189T>C Is associated with coronary artery disease and myocardial infarction in Saudi Arabs. *Genet Test Mol Bioma* **14**, 43-47 (2010).
mtDNA haplogroup H	reduced risk of left ventricular hypertrophy	Russia	S. V. Buikin, M. V. Golubenko, V. P. Puzyrev, Genes for mitochondria in arterial hypertension and left ventricular hypertrophy. *Mol Biol* **44**, 23-27 (2010).
mtDNA haplogroup T	left ventricular hypertrophy	Russia	S. V. Buikin, M. V. Golubenko, V. P. Puzyrev, Genes for mitochondria in arterial hypertension and left ventricular hypertrophy. *Mol Biol* **44**, 23-27 (2010).
Y chromosome haplogroup I	coronary artery disease	UK	F. J. Charchar *et al.*, Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. *Lancet* **379**, 915-922 (2012).
mtDNA haplogroup K	reduced risk of transient ischaemic attack, & ischaemic stroke	UK	P. F. Chinnery *et al.*, Mitochondrial DNA haplogroups and risk of transient ischaemic attack and ischaemic stroke: a genetic association study. *Lancet Neurol* **9**, 498-503 (2010).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Coronary Conditions (cont.)			
mtDNA haplogroup H	end-stage heart failure	Europe	M. E. Gallardo *et al.*, Mitochondrial haplogroups associated with end-stage heart failure and coronary allograft vasculopathy in heart transplant patients. *Eur Heart J* **33**, 346-353 (2012).
mtDNA haplogroup Uk	cardiac allograft vasculopathy	Europe	M. E. Gallardo *et al.*, Mitochondrial haplogroups associated with end-stage heart failure and coronary allograft vasculopathy in heart transplant patients. *Eur Heart J* **33**, 346-353 (2012).
mtDNA haplogroup W	coronary artery disease	Lebanon	M. Haber *et al.*, mtDNA lineages reveal coronary artery disease-associated structures in the Lebanese population. *Ann Hum Genet* **76**, 1-8 (2012).
mtDNA haplogroup T	coronary artery disease	Austria	B. Kofler *et al.*, Mitochondrial DNA haplogroup T is associated with coronary artery disease and diabetic retinopathy: a case control study. *BMC Med Genet* **10**, 35 (2009), 10.1186/1471-2350-10-35.
mtDNA 16189C	coronary artery disease	Austria	E. E. Mueller *et al.*, The mitochondrial T16189C polymorphism is associated with coronary artery disease in Middle European populations. *PLoS One* **6**, e16455 (2011), 10.1371/journal.pone.0016455.
mtDNA haplogroup H	early-onset myocardial infarction	Spain	M. Palacin *et al.*, Mitochondrial DNA and TFAM gene variation in early-onset myocardial infarction: evidence for an association to haplogroup H. *Mitochondrion* **11**, 176-181 (2011).
mtDNA haplogroups A, M7a	coronary atherosclerosis	Japan	M. Sawabe *et al.*, Mitochondrial haplogroups A and M7a confer a genetic risk for coronary atherosclerosis in the Japanese elderly: an autopsy study of 1,536 patients. *J Atheroscler Thromb* **18**, 166-175 (2011).
Y chromosome haplogroup K	atherosclerotic plaque occurrence	Cyprus	K. Voskarides, D. Hadjipanagi, L. Papazachariou, M. Griffin, A. G. Panayiotou, Evidence for contribution of the Y chromosome in atherosclerotic plaque occurrence in men. *Genet Test Mol Biomarkers* **18**, 552-556 (2014).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Coronary Conditions (cont.)			
Y chromosome haplogroup YAP	reduced risk of atherosclerotic plaque	Cyprus	K. Voskarides, D. Hadjipanagi, L. Papazachariou, M. Griffin, A. G. Panayiotou, Evidence for contribution of the Y chromosome in atherosclerotic plaque occurrence in men. *Genet Test Mol Biomarkers* **18**, 552-556 (2014).
Y chromosome haplogroups	no association with cardiovascular risk	Poland	G. Kostrzewa, G. Broda, M. Konarzewska, P. Krajewki, R. Płoski. Genetic polymorphism of human Y chromosome and risk factors for cardiovascular diseases: a study in WOBASZ cohort. *PLoS ONE* **8**, e68155 (2013), doi:10.1371/journal.pone.0068155.
mtDNA haplogroup H	hypertrophic cardiomyopathy	Denmark	C. M. Hagen *et al.*, Mitochondrial haplogroups modify the risk of developing hypertrophic cardiomyopathy in a Danish population. *PLoS One* **8**, e71904 (2013), 10.1371/journal.pone.0071904.
Y chromosome haplogroups	no association with recurrent venous thrombosis	Holland	H. G. de Haan *et al*., Male-specific risk of first and recurrent venous thrombosis: a phylogenetic analysis of the Y chromosome. *J Thromb Haemost*. (2016), doi: 10.1111/jth.13437.
mtDNA haplogroup D4b	reduced risk of ischemic stroke	China	D. Yang *et al*., Mitochondrial DNA haplogroup D4b is a protective factor for ischemic stroke in Chinese Han population. *Mol Genet Genomics.* **289**, 6, 1241-6 (2014).
mtDNA haplogroup N9	facilitates neurological recovery after ischemic stroke	China	B. Cai *et al*., Mitochondrial DNA haplogroups and short-term neurological outcomes of ischemic stroke. *Sci Rep* **20**, 5, 9864 (2015), 10.1038/srep09864.
mtDNA haplogroup H	subclinical carotid atherosclerosis	Russia	A. Zhelankin *et al.,* 1A.06: Mitochondrial DNA haplogroup H is associated with subclinical carotid atherosclerosis in Russian population. *J Hypertens* **33** suppl 1:e2 (2015), 10.1097/01.hjh.0000467356.04711.5
mtDNA haplogroups J, Uk	reduced risk of hypertrophic cardiomyopathy	Denmark	C. M. Hagen *et al.*, Mitochondrial haplogroups modify the risk of developing hypertrophic cardiomyopathy in a Danish population. *PLoS One* **8**, e71904 (2013), 10.1371/journal.pone.0071904.

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Type 2 Diabetes			
mtDNA haplogroups F, D4b	type 2 diabetes	Japan, Korea	Y. Nishigaki, N. Fuku, M. Tanaka, Mitochondrial haplogroups associated with lifestyle-related diseases and longevity in the Japanese population. *Geriatr Gerontol Int* **10 Suppl 1**, S221-235 (2010).
mtDNA haplogroups H, H3, U3, V	complications from diabetes	Italy	A. Achilli *et al.*, Mitochondrial DNA backgrounds might modulate diabetes complications rather than T2DM as a whole. *PLoS One* **6**, e21029 (2011), 10.1371/journal.pone.0021029.
mtDNA haplogroup N9a	reduced risk of type 2 diabetes	Japan, Korea	Y. Nishigaki, N. Fuku, M. Tanaka, Mitochondrial haplogroups associated with lifestyle-related diseases and longevity in the Japanese population. *Geriatr Gerontol Int* **10 Suppl 1**, S221-235 (2010).
mtDNA haplogroup J1	type 2 diabetes	Europe, North Africa	J. Feder *et al.*, Parental diabetes status reveals association of mitochondrial DNA haplogroup J1 with type 2 diabetes. *BMC Med Genet* **10**, 60 (2009), 10.1186/1471-2350-10-60.
mtDNA 16189C	no association with type 2 diabetes	China	L. Zhong *et al.*, Reappraising the relationship between mitochondrial DNA variant m.16189t > c and type 2 diabetes mellitus in East Asian populations. *Curr Mol Med* **14**, 1273-1278 (2014).
mtDNA 16390A	type 2 diabetes	Tunisia	S. Hsousa, *et al.*, Association study of mitochondrial DNA polymorphisms with type 2 diabetes in Tunisian population. *Mitochondr DNA* **26**, 367-372 (2015).
mtDNA haplogroups M8a, N9a	type 2 diabetes	China	Q. Niu *et al.*, Effects of mitochondrial haplogroup N9a on type 2 diabetes mellitus and its associated complications. *Exp Ther Med* **10**, 1918-1924 (2015).
mtDNA 3243G, 16189C	type 2 diabetes	Asia	S. H. Kwak, K. S. Park, Role of mitochondrial DNA variation in the pathogenesis of diabetes mellitus. *Front Biosci (Landmark Ed.)* **21**, 1151-1167 (2016).
mtDNA haplogroups and mutations	no association with type 2 diabetes	Denmark	S. Li *et al.*, Variation and association to diabetes in 2000 full mtDNA sequences mined from an exome study in a Danish population. *Eur J Hum Genet* **22**, 1040-1045 (2014).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Hearing Loss			
mtDNA haplogroup L1	noise-induced hearing loss	Brazil	R. S. Abreu-Silva *et al.*, The search of a genetic basis for noise-induced hearing loss (NIHL). *Ann Hum Biol* **38**, 210-218 (2011).
mtDNA 1555G	aminoglycoside-induced, non-syndromic hearing loss	China	Y. Bai *et al.*, A six-generation Chinese family in haplogroup B4C1C exhibits high penetrance of 1555A > G-induced hearing Loss. *BMC Med Genet* **11**, 129 (2010), 10.1186/1471-2350-11-129.
mtDNA 1555G	non-syndromic sensorineural hearing loss	Morocco	H. Nahili *et al.*, Prevalence of the mitochondrial A 1555G mutation in Moroccan patients with non-syndromic hearing loss. *Int J Pediatr Otorhinolaryngol* **74**, 1071-1074 (2010).
mtDNA 1555G	aminoglycoside-induced, non-syndromic hearing loss	China	J. Lu *et al.*, Mitochondrial haplotypes may modulate the phenotypic manifestation of the deafness-associated 12S rRNA 1555A>G mutation. *Mitochondrion* **10**, 69-81 (2010).
mtDNA 1555G, haplogroup B	higher risk, penetrance, & expressivity of hearing loss	China	J. Lu *et al.*, Mitochondrial haplotypes may modulate the phenotypic manifestation of the deafness-associated 12S rRNA 1555A>G mutation. *Mitochondrion* **10**, 69-81 (2010).
mtDNA 1555G, 961G	non-syndromic sensorineural hearing loss	Italy	V. Guaran *et al.*, Association between idiopathic hearing loss and mitochondrial DNA mutations: a study on 169 hearing-impaired subjects. *Int J Mol Med* **32**, 785-794 (2013).
mtDNA 1555G, 3243G, 3595G, 6204G	non-syndromic hearing loss	Japan	T. Yano *et al.*, Frequency of mitochondrial mutations in non-syndromic hearing loss as well as possibly responsible variants found by whole mitochondrial genome screening. *J Hum Genet* **59**, 100-106 (2014).
mtDNA 1222G	non-syndromic sensorineural hearing loss	China	Q. Wei *et al.*, Genetic mutations of GJB2 and mitochondrial 12S rRNA in nonsyndromic hearing loss in Jiangsu Province of China. *J Transl Med* **11**, 163 (2013).
mtDNA 1555G, haplogroup B	aminoglycoside-induced, non-syndromic hearing loss	China	Z. Ying *et al.*, Mitochondrial haplogroup B increases the risk for hearing loss among the Eastern Asian pedigrees carrying 12S rRNA 1555A>G mutation. *Protein Cell* **6**, 844-848 (2015).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Hearing Loss (cont.)			
mtDNA haplogroups D4a, M22, H2	aminoglycoside-induced, non-syndromic hearing loss	China	X. Tang *et al.*, Mitochondrial tRNA(Ser(UCN)) variants in 2651 Han Chinese subjects with hearing loss. *Mitochondrion* **23**, 17-24 (2015).
mtDNA haplogroups and mutations	no association with age-related hearing impairment	Belgium	S. Bonneaux *et al.*, Inherited mitochondrial variants are not a major cause of age-related hearing impairment in the European population. *Mitochondrion* **11**, 729-734 (2011).
mtDNA 7505C	non-syndromic hearing loss	China	X. Tang *et al.*, Maternally inherited hearing loss is associated with the novel mitochondrial tRNA Ser(UCN) 7505T>C mutation in a Han Chinese family. *Mol Genet Metab* **100**, 57-64 (2010).
Hypertension			
mtDNA 4291C	hypertension, hypercho-lesterolemia, hypomagnesemia	USA	F. H. Wilson *et al.*, A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. *Science* **306**, 1190-1194 (2004).
mtDNA 4401G	hypertension	China	R. Li *et al.*, Failures in mitochondrial tRNAMet and tRNAGln metabolism caused by the novel 4401A>G mutation are involved in essential hypertension in a Han Chinese Family. *Hypertension* **54**, 329-337 (2009).
mtDNA 4435G	hypertension	China	Z. Lu *et al.*, The tRNAMet 4435A>G mutation in the mitochondrial haplogroup G2a1 is responsible for maternally inherited hypertension in a Chinese pedigree. *Eur J Hum Genet* **19**, 1181-1186 (2011).
mtDNA 4295G	hypertension	China	Z. Li, Y. Liu, L. Yang, S. Wang, M. X. Guan, Maternally inherited hypertension is associated with the mitochondrial tRNAIle A4295G mutation in a Chinese family. *Biochem Biophys Res Commun* **367**, 906-911 (2008).
mtDNA haplogroup H	not associated with hypertension	Russia	A. Zhelankin *et al.,* 1A.06: Mitochondrial DNA haplogroup H is associated with subclinical carotid atherosclerosis in Russian population. *J Hypertens* **33** suppl 1:e2 (2015), 10.1097/01.hjh.0000467356.04711.5 B.

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Hypertension (cont.)			
mtDNA haplogroups M, HV, JT, UK	pulmonary arterial hypertension	USA	S. Farha *et al*., Mitochondrial Haplogroups and Risk of Pulmonary Arterial Hypertension. *PLoS One* **11**, e0156042 (2016).
mtDNA haplogroup L	reduced risk of pulmonary arterial hypertension	USA	S. Farha *et al*., Mitochondrial Haplogroups and Risk of Pulmonary Arterial Hypertension. *PLoS One* **11**, e0156042 (2016).
mtDNA 4263G	hypertension	China	S. Wang *et al*., Maternally inherited essential hypertension is associated with the novel 4263A4G mutation in the mitochondrial tRNAIle gene in a large Han Chinese family. *Circ Res* **108**, 862-870 (2011).
Infertility			
Y chromosome haplogroup K	male infertility	Latvia	A. Puzuka *et al.*, Y chromosome—a tool in infertility studies of Latvian population. *Russian Journal of Genetics* **47**, 347-353 (2011).
Y chromosome haplogroups F, K, P, N1	male infertility	China	J. Ran *et al.*, Association study between Y-chromosome haplogroups and susceptibility to spermatogenic impairment in Han People from southwest China. *Genet Mol Res* **12**, 59-66 (2013).
Bone Disease			
mtDNA haplogroup U	increased severity of knee osteoarthritis	Spain	I. Rego-Perez, M. Fernandez-Moreno, C. Fernandez-Lopez, J. Arenas, F. Blanco, Mitochondrial DNA haplogroups: role in the prevalence and severity of knee osteoarthritis. *Arthritis Rheum* **58**, 2387-2396 (2008).
mtDNA haplogroup J	reduced risk of knee osteoarthritis	Spain	I. Rego-Perez, M. Fernandez-Moreno, C. Fernandez-Lopez, J. Arenas, F. Blanco, Mitochondrial DNA haplogroups: role in the prevalence and severity of knee osteoarthritis. *Arthritis Rheum* **58**, 2387-2396 (2008).
mtDNA haplogroup J	reduced risk of hip osteoarthritis	Spain	I. Rego, *et al*., Role of european mitochondrial DNA haplogroups in the prevalence of hip osteoarthritis in Galicia, Northern Spain. *Ann Rheum Dis* **69**, 210-213 (2010).
mtDNA haplogroup X	lower hip bone mineral density (osteoporosis)	USA	Y. Guo *et al.*, Mitochondria-wide association study of common variants in osteoporosis. *Ann Hum Genet* **75**, 569-574 (2011).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Bone Disease (cont.)			
mtDNA 4823C	lower hip bone mineral density (osteoporosis)	USA	Y. Guo *et al.*, Mitochondria-wide association study of common variants in osteoporosis. *Ann Hum Genet* **75**, 569-574 (2011).
mtDNA haplogroup G	knee osteoarthritis	China	H. Fang *et al.*, Role of mtDNA haplogroups in the prevalence of knee osteoarthritis in a southern Chinese population. *Int J Mol Sci* **15**, 2646-2659 (2014).
mtDNA haplogroups B, B4	reduced risk of knee osteoarthritis	China	H. Fang *et al.*, Role of mtDNA haplogroups in the prevalence of knee osteoarthritis in a southern Chinese population. *Int J Mol Sci* **15**, 2646-2659 (2014).
mtDNA haplogroups J, T	reduced risk of osteoarthritis	UK, Spain	A. Soto-Hermida *et al.*, mtDNA haplogroups and osteoarthritis in different geographic populations. *Mitochondrion* **15**, 18-23 (2014).
mtDNA haplogroups J, TJ	osteoarthritis	Spain	J. M. Shen, *et al.,* Role of mtDNA haplogroups in the prevalence of osteoarthritis in different geographic populations: a meta-analysis. *PLoS One* **9**, e108896 (2014). doi:10.1371/journal.pone.0108896
mtDNA haplogroup TJ	slower osteoarthritis progression	Spain	A. Soto-Hermida *et al.*, Mitochondrial DNA haplogroups modulate the radiographic progression of Spanish patients with osteoarthritis. *Rheumatol Int* **35**, 337-344 (2015).
mtDNA haplogroup H	more joint surgery for osteoarthritis	Spain	A. Soto-Hermida *et al.,* Mitochondrial DNA haplogroups modulate the radiographic progression of Spanish patients with osteoarthritis. *Rheumatol Int* **35**, 337-344 (2015).
mtDNA haplogroups	no association with osteoarthritis	UK	G. Hudson *et al*., No evidence of an association between mitochondrial DNA variants and osteoarthritis in 7393 cases and 5122 controls. *Ann Rheum Dis* **72**, 136-139 (2013).
AIDS/HIV Antiviral Therapy Complications			
mtDNA haplogroups U5a, J	accelerated AIDS progression	USA	S. L. Hendrickson *et al.*, Mitochondrial DNA haplogroups influence AIDS progression. *AIDS* **22**, 2429-2439 (2008).
mtDNA haplogroups I, W, X, H3	delayed onset of AIDS	USA	S. L. Hendrickson *et al.*, Mitochondrial DNA haplogroups influence AIDS progression. *AIDS* **22**, 2429-2439 (2008).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
AIDS/HIV Antiviral Therapy Complications (cont.)			
mtDNA haplogroup Uk	reduced risk of AIDS	USA	S. L. Hendrickson *et al.*, Mitochondrial DNA haplogroups influence AIDS progression. *AIDS* **22**, 2429-2439 (2008).
mtDNA haplogroup L1c	peripheral neuropathy during HIV antiretroviral therapy	USA	J. A. Canter *et al.*, African mitochondrial DNA subhaplogroups and peripheral neuropathy during antiretroviral therapy. *J Infect Dis* **201**, 1703-1707 (2010).
mtDNA haplogroup L2	slower CD4 T-cell recovery during HIV antiretroviral therapy	USA	B. J. Grady *et al.*, Mitochondrial genomics and CD4 T-cell count recovery after antiretroviral therapy initiation in AIDS clinical trials group study 384. *J Acquir Immune Defic Syndr* **58**, 363-370 (2011).
mtDNA haplogroup I	lipoatrophy during HIV antiretroviral therapy	USA	T. Hulgan *et al.*, European mitochondrial DNA haplogroups and metabolic changes during antiretroviral therapy in AIDS Clinical Trials Group Study A5142. *AIDS* **25**, 37-47 (2011).
mtDNA haplogroup J	reduced risk of neuroretinal disorder during HIV antiretroviral therapy	USA	S. L. Hendrickson *et al.*, Genetic variants in nuclear-encoded mitochondrial genes influence AIDS progression. *PLoS One* **5**, e12862 (2010), 10.1371/journal.pone.0012862.
mtDNA haplogroup L2	slower CD4 T-cell recovery during HIV antiretroviral therapy	USA	B. Aissani *et al.*, Mitochondrial DNA variation and virologic and immunological HIV outcomes in African Americans. *AIDS* **28**, 1871-1878 (2014).
mtDNA haplogroups J, T	slower CD4 T-cell recovery during HIV antiretroviral therapy	Spain	M. Guzman-Fulgencio *et al.*, European mitochondrial haplogroups are associated with CD4+ T cell recovery in HIV-infected patients on combination antiretroviral therapy. *J Antimicrob Chemother* **68**, 2349-2357 (2013).
European mtDNA haplogroups	not associated with hepatitis C virus treatment response	Spain	M. Guzmán-Fulgencio *et al*., European mitochondrial haplogroups are not associated with hepatitis C virus (HCV) treatment response in HIV/HCV-coinfected patients. *HIV Med* **15**, 425-430 (2014).
mtDNA haplogroup A	susceptibility to AIDS	China	H. W. Wang, *et al.,* Mitochondrial DNA Haplogroup A may confer a genetic susceptibility to AIDS group from Southwest China.*Mitochondrial DNA A DNA Mapp Seq Anal* **27**, 2221-2224 (2016).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
AIDS/HIV Antiviral Therapy Complications (cont.)			
mtDNA haplogroup B	less neurocognitive impairment during HIV antiretroviral therapy	USA	T. Hulgan *et al.,* Mitochondrial DNA Haplogroups and Neurocognitive Impairment During HIV Infection. *Clin Infect Dis* **61**, 1476-1484 (2015).
mtDNA haplogroup H	faster CD4 T-cell recovery during HIV antiretroviral therapy	Spain	M. Guzman-Fulgencio *et al.*, European mitochondrial haplogroups are associated with CD4+ T cell recovery in HIV-infected patients on combination antiretroviral therapy. *J Antimicrob Chemother* **68**, 2349-2357 (2013).
Neurodegenerative Conditions/Treatment Response			
mtDNA haplogroup H (7028C)	earlier onset of Huntington's disease	Germany	L. Arning *et al.*, Mitochondrial haplogroup H correlates with ATP levels and age at onset in Huntington disease. *J Mol Med (Berl)* **88**, 431-436 (2010).
mtDNA haplogroup H (7028C)	late onset Alzheimer's disease	Spain	E. Coto *et al.*, Late-onset Alzheimer's disease is associated with mitochondrial DNA 7028C/haplogroup H and D310 poly-C tract heteroplasmy. *Neurogenetics* **12**, 345-346 (2011).
mtDNA haplogroups J1c, J2, U4, U5a1, K	reduced risk of Parkinson's disease	Poland	K. Gaweda-Walerych *et al.*, Mitochondrial transcription factor A variants and the risk of Parkinson's disease. *Neurosci Lett* **469**, 24-29 (2010).
mtDNA haplogroup H	Alzheimer's and Parkinson's diseases	Spain	A. Gomez-Duran *et al.*, Unmasking the causes of multifactorial disorders: OXPHOS differences between mitochondrial haplogroups. *Hum Mol Genet* **19**, 3343-3353 (2010).
mtDNA haplogroup Uk	reduced risk of Alzheimer's and Parkinson's disease	Spain	A. Gomez-Duran *et al.*, Unmasking the causes of multifactorial disorders: OXPHOS differences between mitochondrial haplogroups. *Hum Mol Genet* **19**, 3343-3353 (2010).
mtDNA haplogroup Uk	Alzheimer's disease	USA, Canada	A. Lakatos *et al.*, Association between mitochondrial DNA variations and Alzheimer's disease in the ADNI cohort. *Neurobiol Aging* **31**, 1355-1363 (2010).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Neurodegenerative Conditions/Treatment Response (cont.)			
mtDNA haplogroups	no association with Alzheimer's disease	N.A.	M. Mancuso, V. Calsolaro, D. Orsucci, G. Siciliano, L. Murri, Is there a primary role of the mitochondrial genome in Alzheimer's disease? *J Bioenerg Biomembr* **41**, 411-416 (2009).
mtDNA haplogroup E1	Parkinson's disease	Guam	D. M. Reiff *et al.*, Inherited and somatic mitochondrial DNA mutations in Guam amyotrophic lateral sclerosis and parkinsonism-dementia. *Neurol Sci* **32**, 883-892 (2011).
mtDNA haplogroup E2	reduced risk of Parkinson's disease	Guam	D. M. Reiff *et al.*, Inherited and somatic mitochondrial DNA mutations in Guam amyotrophic lateral sclerosis and parkinsonism-dementia. *Neurol Sci* **32**, 883-892 (2011).
mtDNA haplogroup H5	Alzheimer's disease	Italy	A. Santoro *et al.*, Evidence for sub-haplogroup h5 of mitochondrial DNA as a risk factor for late onset Alzheimer's disease. *PLoS One* **5**, e12037 (2010), 10.1371/journal.pone.0012037.
mtDNA haplogroups	no association with Parkinson's disease	USA	D. K. Simon *et al.*, Maternal inheritance and mitochondrial DNA variants in familial Parkinson's disease. *BMC Med Genet* **11**, 53 (2010), 10.1186/1471-2350-11-53.
mtDNA haplogroup H	Parkinson's disease	UK	G. Hudson *et al*., Two-stage association study and meta-analysis of mitochondrial DNA variants in Parkinson disease. *Neurology* **80**, 2042-2048 (2013).
mtDNA haplogroups J, K, T	reduced risk of Parkinson's disease	UK	G. Hudson *et al*., Two-stage association study and meta-analysis of mitochondrial DNA variants in Parkinson disease. *Neurology* **80**, 2042-2048 (2013).
mtDNA haplogroup D	Parkinson's disease	China	Y. F. Chen *et al*., Mitochondrial DNA Haplogroups and the Risk of Sporadic Parkinson's Disease in Han Chinese. *Chin Med J (Engl)* **128**, 1748-1754 (2015).
mtDNA haplogroup B	reduced risk of Parkinson's disease	China	Y. F. Chen *et al*., Mitochondrial DNA Haplogroups and the Risk of Sporadic Parkinson's Disease in Han Chinese. *Chin Med J (Engl)* **128**, 1748-1754 (2015).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Neurodegenerative Conditions/Treatment Response (cont.)			
mtDNA haplogroup B5	Alzheimer's disease	China	R. Bi *et al*., Mitochondrial DNA haplogroup B5 confers genetic susceptibility to Alzheimer's disease in Han Chinese. *Neurobiol Aging* **36**, 1604.e7-16 (2015).
mtDNA haplogroup L1	Alzheimer's disease	USA	G. J. Tranah *et al.*, Mitochondrial DNA sequence associations with dementia and amyloid-beta in elderly African Americans. *Neurobiol Aging* **35**, 442 e441-448 (2014).
Opthalmic Diseases/Conditions			
mtDNA 10609C, 10663C	Leber's hereditary optic neuropathy	Kuwait	R. Behbehani *et al*., ND4L gene concurrent 10609T > C and 10663T > C mutations are associated with Leber's hereditary optic neuropathy in a large pedigree from Kuwait. *Brit J Ophthalmol* **98**, 826-831 (2014).
mtDNA haplogroups H, R	keratoconus	Saudi Arabia	K.K. Abu-Amero *et al*., Association of mitochondrial haplogroups H and R with keratoconus in Saudi Arabian patients. *Invest Ophth Vis Sci* **55**, 2827-2831 (2014).
mtDNA haplogroup T	increased risk of diabetic retinopathy	Austria	B. Kofler et al., Mitochondrial DNA haplogroup T is associated with coronary artery disease and diabetic retinopathy: a case control study. *BMC Med Genet* **10**: 35 (2009), 10.1186/1471-2350-10-35.
mtDNA 14484C	Leber's hereditary optic neuropathy	Various	T. M. Bosley, K. K. Abu-Amero, Assessing mitochondrial DNA nucleotide changes in spontaneous optic neuropathies. *Ophthalmic Genet* **31**, 163-172 (2010); N.A. Khan *et al*., Haplogroup heterogeneity of LHON patients carrying the m.14484T > C mutation in India. *Invest Ophth Vis Sci* **54**, 3999-4005 (2013).
mtDNA haplogroup T2	age-related macular degeneration	USA, Australia	J. P. SanGiovanni *et al.*, Mitochondrial DNA variants of respiratory complex I that uniquely characterize haplogroup T2 are associated with increased risk of age-related macular degeneration. *PLoS One* **4**, e5508 (2009), 10.1371/journal.pone.0005508.
mtDNA haplogroup L	primary open-angle glaucoma	Saudi Arabia	K. K. Abu-Amero *et al*., Mitochondrial DNA lineages of African origin confer susceptibility to primary open-angle glaucoma in Saudi patients. *Mol Vis* **17**, 1468-1472 (2011).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Opthalmic Diseases/Conditions (cont.)			
mtDNA haplogroup N1	reduced risk of primary open-angle glaucoma	Saudi Arabia	K. K. Abu-Amero *et al*., Mitochondrial DNA lineages of African origin confer susceptibility to primary open-angle glaucoma in Saudi patients. *Mol Vis* **17**, 1468-1472 (2011).
mtDNA haplogroups L2, T	pseudoexfoliation glaucoma	Saudi Arabia	K. K. Abu-Amero *et al*., Eurasian and Sub-Saharan African mitochondrial DNA haplogroup influences pseudoexfoliation glaucoma development in Saudi patients. *Mol Vis* **17**, 543-547 (2011).
mtDNA haplogroup N1	reduced risk of pseudoexfoliation glaucoma	Saudi Arabia	K. K. Abu-Amero *et al*., Eurasian and Sub-Saharan African mitochondrial DNA haplogroup influences pseudoexfoliation glaucoma development in Saudi patients. *Mol Vis* **17**, 543-547 (2011).
mtDNA 11778A	Leber's hereditary optic neuropathy	Various	T. M. Bosley, K. K. Abu-Amero, Assessing mitochondrial DNA nucleotide changes in spontaneous optic neuropathies. *Ophthalmic Genet* **31**, 163-172 (2010).
mtDNA 3460A	Leber's hereditary optic neuropathy	Various	T. M. Bosley, K. K. Abu-Amero, Assessing mitochondrial DNA nucleotide changes in spontaneous optic neuropathies. *Ophthalmic Genet* **31**, 163-172 (2010).
mtDNA haplogroup B5a1	Leber's hereditary optic neuropathy	Thailand	S. Kaewsutthi *et al*., Mitochondrial haplogroup background may influence Southeast Asian G11778A Leber hereditary optic neuropathy. *Invest Ophth Vis Sci* **52**, 4742-4748 (2011).
mtDNA haplogroup F	reduced risk of Leber's hereditary optic neuropathy	Thailand	S. Kaewsutthi *et al*., Mitochondrial haplogroup background may influence Southeast Asian G11778A Leber hereditary optic neuropathy. *Invest Ophth Vis Sci* **52**, 4742-4748 (2011).
mtDNA haplogroup U	reduced risk of exfoliation glaucoma	Germany	C. Wolf *et al.*, Mitochondrial haplogroup U is associated with a reduced risk to develop exfoliation glaucoma in the German population. *BMC Genet* **11**, 8 (2010), 10.1186/1471-2156-11-8.
mtDNA haplogroups A2, C	later onset/reduced impact of Leber's hereditary optic neuropathy	Chile	P. Romero *et al.,* Pan-American mDNA haplogroups in Chilean patients with Leber's hereditary optic neuropathy. *Mol Vis* **14,** 334-40 (2014).

mtDNA or Y Chromosome Variant	*Proposed Association (or Lack of Association)*	*Study Location*	*Reference*
Opthalmic Diseases/Conditions (cont.)			
mtDNA 14502C, 11778A	Leber's hereditary optic neuropathy	China	P. Jiang *et al.,* Biochemical evidence for a mitochondrial genetic modifier in the phenotypic manifestation of Leber's hereditary optic neuropathy-associated mitochondrial DNA mutation. *Hum Mol Genet* **Jul 17**. pii: ddw199 (2016).
mtDNA 3635A, 14502C	Leber's hereditary optic neuropathy	China	X. Jin *et al.*, Leber's Hereditary Optic Neuropathy is Associated with Compound Primary Mutations of Mitochondrial ND1 m.3635G > A and ND6 m.14502 T > C. *Ophthalmic Genet* **36**, 291-298 (2015).
mtDNA 16111, 16362, 16319, 1736, 12007	age-related macular degeneration	USA	N. A. Resrepo, *et al.*, Mitochondrial variation and the risk of age-related macular degeneration across diverse populations. *Pac Symp Biocomput.* 243-54 (2015).
mtDNA haplogroups J, T, U	age-related macular degeneration	USA	M. C. Kenney *et al*., Mitochondrial DNA haplogroups confer differences in risk for age-related macular degeneration: a case control study. *BMC Med Genet* **14** (2014), 10.1186/1471-2350-14-4.