Racial and Ethnic Disparities in Genetic Testing for Hearing Loss: a Systematic Review and Synthesis

Stephanie L Rouse

UCSF: University of California San Francisco

Michelle M Florentine

UCSF: University of California San Francisco

Emily Taketa

UCSF: University of California San Francisco

Dylan K Chan (✉ Dylan.chan@ucsf.edu)

University of California San Francisco <https://orcid.org/0000-0003-0836-3730>

Research Article

Keywords: Hearing loss, Genetic testing, Health disparities

Posted Date: May 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-484764/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Human Genetics on September 7th, 2021.

See the published version at <https://doi.org/10.1007/s00439-021-02335-7>.

Abstract

Racial/ethnic disparities in the diagnostic efficacy of genetic testing for hearing loss has been described. These disparities may relate to differences in variant classification between different racial/ethnic groups, which may in turn derive from disparate representation of these groups in the published literature. We sought to quantify racial/ethnic disparities in the published literature on the human genetics of hearing loss. We conducted a search of PubMed for articles describing single-gene, multiple-gene, or whole-exome sequencing for individuals with sensorineural hearing loss. Data on the populations studied, including race/ethnicity and/or region of origin, subjects tested, and method of testing, were extracted. 1,355 unique populations representing 311,092 subjects from 1,165 studies were included. Overall, White and Asian populations and subjects were equivalently represented, but Latinx, Black, and Native American/Hawaiian groups were significantly underrepresented; over 96% of all subjects in the published literature were White or Asian. Within racial/ethnic groups, the majority of subjects derived from a small subset of countries. The observed racial/ethnic disparity was greater for multiple-gene and whole-exome sequencing than for single-gene sequencing.

These findings illustrate the large disparity in published literature on the genetics of hearing loss, and demonstrate the need for increased representation of Latinx, Black, and Native American populations.

Introduction

Sensorineural hearing loss (SNHL) is the most common congenital sensory disorder, affecting 1 in 500 newborns, and over 80% of those 85 years of age and older.^{1,2} Identifying a genetic etiology of hearing loss provides valuable prognostic information, allows early detection of syndromic forms of SNHL prior to overt syndromic phenotypes, and facilitates time-sensitive counseling.^{3–5} Establishing etiologic diagnoses for deafness, however, is challenging due to the multitude of potential causes, clinical variability, phenotypic overlap and extreme genetic heterogeneity of hearing loss.⁶ The advance of next-generation sequencing (NGS) technologies has made genetic testing cost-effective, increasing availability of testing and transforming clinical diagnostic practice. Comprehensive genetic testing (CGT) has rapidly become a valuable tool for the identification of a genetic cause of hearing loss in deaf and hard-of-hearing (D/HH) patients.⁷ As genetic testing expands, it is important to ensure it is conducted equitably.

There is growing acknowledgement of disparities in genetic testing in hearing loss based on race and ethnicity. Multiple groups have found that the rate of molecular diagnosis as well as the spectrum of genes implicated by CGT for SNHL varies widely by ethnic group, with Asian and White populations having higher diagnostic rates compared with Blacks and Hispanics.^{8–10} While it is possible that true differences exist between these groups in the incidence of genetic hearing loss, it is also possible that the decreased diagnostic efficacy of genetic testing among Blacks and Hispanics derives from the relative paucity of knowledge on the genetics of hearing loss in these populations, both in terms of undiscovered deafness genes in these groups and uncertain interpretation of variants found in known hearing-loss

genes. Indeed, GJB2, the most frequently studied gene in hearing-loss genetics, is commonly affected in White and Asian populations, but rarely in Blacks.^{11,12}

Because interpretation of sequence variants is a crucial element of accurate genetic diagnosis and discrepancies in variant interpretation can have serious, harmful implications for patient care, standards designated by the ACMG for classification of variants require substantial evidence to categorize a variant as disease-causing.^{13–15} Therefore, underrepresentation of groups in genetic studies, and the resultant underrepresentation in the knowledge base upon which variant classification is performed, may constrain diagnostic power for these populations. Indeed, the proportion of known pathogenic/likely pathogenic variants is greater in White and Asian groups, whereas the rate of variants of unknown significance (VUSs) is high among people of African or Central American descent.^{9,10}

In this study, we sought to quantify the racial/ethnic disparity in published literature on the genetics of hearing loss. In doing so, we aim to describe the extent to which racial/ethnic groups may be underrepresented in the hearing-loss genetic literature, which may underlie disparities in the diagnostic efficacy of genetic testing for hearing loss and our understanding of deafness across all populations. Understanding how the efficacy and limitations of genetic testing are affected by demographic, racial and ethnic disparities is a critical concern when considering health equity.

Methods

Systematic Review

Systematic review was performed in accordance with PRISMA guidelines.¹⁶ Three searches were performed to compile the studies included in this systematic review. First, a PubMed search was conducted on March 30, 2021 using the search parameter “COL11A1 OR MYO7A OR MYH14 OR USH2A OR OTOG OR TNC OR MCM2 OR MYH9 OR CDH23 OR COL11A2 OR TCOF1 OR TECTA OR PCDH15 OR SCL26A4 OR STRC OR TJP2 OR KCNQ4 OR OTOF OR TMC1 OR ALMS1 OR COCH OR DFNA5 OR DFNB59 OR EYA1 OR MYO15A OR PAX3 OR PDZD7 OR CHD7 OR COL4A3 OR DIAPH3 OR EYA4 OR FGFR3 OR MITF OR MYO6 OR OTOGL OR POU4F3 OR SEMA3E OR SLC17A8 OR SOX10 OR TMPRSS3 OR (“genetic testing”) OR (exome) AND (hearing OR deafness) NOT (review) NOT (screening)” with the “human only” filter. These parameters were chosen to identify studies in which either WES, multiple-gene testing (including CGT), or single-gene testing for common genes involved in hearing loss, excluding GJB2, was performed. The list of individual genes was assembled by examining a database of pediatric patients with SNHL who underwent CGT at UCSF.¹⁰ Genes that were possibly causative for hearing loss in two or more patients within a racially and ethnically diverse cohort were included; this list comprised the 41 genes included in our search. This search identified 1,635 articles.

Two separate searches were performed on GJB2 given the large number of publications related to this gene and the existence of a prior large systematic review.¹¹ First, information on GJB2 was extracted from a database compiled by the corresponding author (DKC) on July 18, 2012 with the search criteria

“(GJB2 OR Connexin 26 OR Cx26) AND (hearing OR deafness),” which included studies through 2012. The 245 articles evaluated for this systematic review were re-reviewed according to the inclusion and exclusion criteria for this study, and data extracted as described below. A second, separate search for GJB2 was conducted on April 15, 2021 to additionally identify studies published during or after 2013 while avoiding duplicates from the global search, as follows: “(GJB2) AND (hearing or deafness) NOT (screening OR review OR COL11A1 OR MYO7A OR MYH14 OR USH2A OR OTOG OR TNC OR MCM2 OR MYH9 OR CDH23 OR COL11A2 OR TCOF1 OR TECTA OR PCDH15 OR SCL26A4 OR STRC OR TJP2 OR KCNQ4 OR OTOF OR TMC1 OR ALMS1 OR COCH OR DFNA5 OR DFNB59 OR EYA1 OR MYO15A OR PAX3 OR PDZD7 OR CHD7 OR COL4A3 OR DIAPH3 OR EYA4 OR FGFR3 OR MITF OR MYO6 OR OTOGL OR POU4F3 OR SEMA3E OR SLC17A8 OR SOX10 OR TMPRSS3 OR (“genetic testing”) OR (exome))” with the “human only” filter. This search identified 165 articles.

Studies were included based on title, abstract, and full-length paper (when necessary) according to these criteria:

A. Inclusion criteria:

- i. Primary report of human subjects with hearing loss
- ii. Single-gene, multiple-gene, or whole-exome sequencing was performed.
- iii. Race/ethnicity or country of origin of subjects, region where the study was performed, or the country of the corresponding author was identifiable.

b. Exclusion criteria:

- i. Review or screening studies
- ii. Studies in which specific variants were studied rather than complete gene sequencing performed

Search Results

In total, from these 3 searches, a total of 2,045 studies were identified, of which 1,165 were included, after applying inclusion/exclusion criteria and eliminating duplicate entries. From these studies, we collected data including article identifiers (author, year, PMID) and, for each distinct, identifiable population within the study, the race/ethnicity if stated, region of origin of subjects if stated, region of subjects inferred from the region where the study was performed, country of corresponding author, genetic testing method (multiple gene testing, exome sequencing, or single gene testing), as well as sample size of those who underwent genetic testing, including controls. Three reviewers each independently reviewed one third of the 1,635 articles from the broad search results. A fourth reviewer independently reviewed 410 articles from the two GJB2 search results. When questions arose about study inclusion or data extraction, at least one additional author reviewed the study and decision made after discussion. Data were extracted from abstracts when available, and from the full-text review when necessary. We did not explicitly assess risk of bias for each individual article given the large numbers of studies and case study/case series design for all.

Race/Ethnicity Categorization

The primary outcome measure in this systematic review and synthesis is the racial/ethnic group, based primarily on U.S. Census definitions, of populations described within included studies. Each study was reviewed to identify unique populations, each being defined by the following attributes:

1. Racial/ethnic group of the population
2. Region of origin of the population (country, when available, and/or region as defined by United Nations Geoscheme)
3. Country of the corresponding author
4. Number of subjects in the population
5. Type of genetic testing performed.

Subjects were classified as White, Asian, Black, Latinx or Native American/Native Hawaiian when explicitly stated in the article. When race/ethnicity was not explicitly stated, the region of origin of the population was determined as follows: region of origin (for example, Pakistani population living in UK would be classified as Pakistani); if unavailable, the population was assigned to the region where the study took place (for example, a population described in a study from China without race, ethnic, or country of ancestral origin explicitly stated would be classified as Chinese). Whether a population had an explicitly defined race/ethnicity/region of ancestral origin, or whether the region was inferred from the study site, was documented. The defined unique region of origin was then assigned to a racial/ethnic group as described below.

1. Subjects were considered “White” when explicitly stated as “Caucasian” or “White.” If the region assigned to the population was located in North America (United States or Canada), Oceania (Australia or New Zealand), or Europe, participants were considered “White.” Participants whose race/ethnicity was stated as Ashkenazi Jews were also assigned White race/ethnicity.
2. Subjects were considered “Black” when explicitly stated as “Black” or “African American.” If the region assigned to the population was located in Africa, participants were considered “Black.”
3. Subjects were considered “Asian” when explicitly stated, or if the region assigned to the population was located in Asia, including the Middle East (i.e. Western Asia, as defined by the United Nations Geoscheme).
4. Subjects were considered “Latinx” when explicitly stated as “Hispanic” or if the region assigned to the population was located in South or Central America. “Latinx,” which refers to people of Latin-American ethnicity, is distinct from the U.S. Census designation “Hispanic,” which refers to people originating from Spanish- or Portuguese-speaking countries. The “Latinx” designation was used intentionally here to distinguish between people of Spanish, Portuguese or Sephardic Jewish origin, who were assigned to White given their European origin, in order to focus this category on people of Central and South American origin and be more representative of indigenous American ancestry.

5. Subjects were considered “Native American” or “Native Hawaiian” when explicitly stated. These two groups, while distinct, were grouped together due to the very small number of studies and subjects addressing them.
6. Subjects of defined mixed race/ethnicity were assigned once to each racial/ethnic group to reflect their contribution to the literature for each group.

The number of individual subjects comprising the unique population was recorded. In cases where sample size information was limited to the number of families rather than individual participants, each family was considered as a sample size of one. Finally, studies were only included if, at a minimum, sequence analysis of a single gene was performed. The broad type of genetic testing performed was recorded for each population as single-gene testing, multiple-gene testing, or whole exome sequencing.

Statistical Analysis and Human Subjects Protection

Stata MP 16 was used for descriptive analysis. The retrospective review to identify the 41 common hearing-loss genes to be included in the search was approved by the Institutional Review Board of UCSF. The literature review is exempt from IRB review.

Results

Systematic Review

The three search criteria identified 2,045 articles, of which 1,165 of which met the criteria for inclusion and data synthesis (Figure 1). These studies encompassed 1,355 unique populations and 311,092 subjects who underwent genetic testing across 87 countries and 6 continents from 1992 to 2021. The majority of studies were performed in the United States (20%), Europe (32%), China (16%), and Japan (7%), with relatively few studies originating from Central and South America, and from Africa (Figure 2).

Race/Ethnicity Distribution

We sought to identify the racial/ethnic makeup of published literature on the genetics of hearing loss. Race, ethnicity, and/or region of origin of subjects was explicitly stated for 953 (70%) of studies and inferred based on the region where the study was performed for the remaining 402 (30%) studies. Of the 1,355 unique populations, 43% were White, 46% were Asian, 5% were Black, 5% were Latinx, and 0.7% were Native American/Native Hawaiian (Figure 3, left). Of the 311,092 subjects included, 53% were White, 43% Asian, 1% Latinx, 2% Black, and 0.1% Native American/Native Hawaiian (Figure 3, right). These findings demonstrate that, compared with White populations, Asian populations are represented roughly equivalently, but Latinx populations are underrepresented in genetic testing literature by a factor of 9.5 to 1, Black populations by 8.3 to 1, and Native American/Native Hawaiian populations by 65 to 1. White subjects outnumber Latinx subjects by 37:1, Blacks by 26:1, and Native American/Hawaiian by 565:1. Overall, Whites and Asians comprise 96.4% of all reported subjects in publications on genetic testing for hearing loss.

Geographic Distribution

Within racial/ethnic groups, the distribution of countries of origin for the included populations introduces yet another element of bias in the representation with each group. The distribution of countries/regions of origin within racial/ethnic groups is described for both unique populations and subjects (Figure 4). 34 studies that did not explicitly state a single specific country of origin for the included populations were not included in this geographic analysis.

The majority of White subjects originated from the United States (66%) or Europe (33%), and the majority of Asian subjects from Asian subjects from East (80%) and Western (10%) Asia, especially China (56%) and Japan (21%), with limited representation from Southern (7%) and Southeastern (1%) Asia. The majority of Latinx participants originated from Brazil (37%) and the United States (27%), with scant contribution from Central America (8%) or other parts of South America outside of Brazil and Argentina. Finally, the majority of Black participants originated from the United States (26%) and Northern Africa (24%), including Tunisia and Morocco, despite the majority of the African population living outside these regions, particularly sub-Saharan Africa. Finally, there were extremely few studies on Native American, Alaskan, Hawaiian, and Pacific Islander populations, with the majority of subjects reported from a single study from Greenland (89%).

Studies over time

The number of populations described for each racial/ethnic group was studied over time to understand trends in studied racial/ethnic groups between 1992-2020. On average, 20 studies are published per year on White populations, 21 on Asians, 2 on Hispanic, 2 on Black, and 0.3 on Native Americans, with Asian studies overtaking White studies since 2010 (Figure 5).

Genetic Testing Method

Genetic testing method for each population was categorized as single-gene testing (45% of all subjects), multiple-gene testing (47%), and whole-exome sequencing (8%). While White and Asian subjects were roughly equally represented in all three testing modalities, the magnitude of the disparity between White and Latinx, Black, or Native American/Hawaiian subjects varied significantly by testing type. Whereas White subjects outnumbered Latinx and Black subjects in single-gene testing reports by 18- and 13-fold, respectively, they outnumbered Latinx and Black subjects in multiple-gene testing by 250- and 113-fold, and whole-exome sequencing by 39- and 29-fold.

Discussion

Recent advances in technology, decrease in expense, and broadening of insurance coverage has made NGS more accessible and ubiquitously used. While CGT is one of the strongest tools in the clinical evaluation of SNHL, there is a need to establish that it is equivalently accessible and informative across all populations, lest it exacerbate existing disparities. Several studies have found that Latinx and Black

populations are currently less served by genetic testing, with higher numbers of VUSs and poorer diagnostic rates.^{9,10} In an attempt to understand and address the source of this disparity in genetic testing, we reviewed the distribution of studies on genetic testing in hearing loss.

In a systematic review of 1,165 studies describing 1,355 unique populations and 311,092 subjects, we found striking differences in the number of studies, participants, and populations based on racial/ethnic group. Studies originated predominantly from Europe, North America, and East Asia, with over 82% of corresponding authors from these regions. White and Asian populations were represented 10 times more than Latinx or Black populations, and over 70 times more than Native Americans. When considering number of individual subjects, the disparity was even larger: compared with White subjects, there were 37-fold fewer Latinx, 26-fold fewer Black, and 565-fold fewer Native Americans/Hawaiians. Even within broad racial/ethnic groups, the distribution of countries from which these populations were derived is uneven; for example, 57% of subjects in the Latinx category are from Brazil and Argentina, and 77% of subjects in the Asian category are from China and Japan, suggesting limited representation of other groups. While trends over time suggest a slow increase in representation of Black and Latinx populations, and Asian populations overtaking White groups in the literature, the gap remains large. Furthermore, compared with single-gene testing, more advanced genetic testing strategies, such as multiple-gene testing and whole exome sequencing, which carry greater potential for genetic discovery, are subject to far greater disparities, with Whites and Asians comprising nearly 96% of all subjects who underwent whole-exome sequencing and over 99% of all subjects who underwent multiple-gene testing, including CGT. Expansion of more advanced genetic testing technology in intentional ways may offer an opportunity to close the gap in understanding normal variation, identifying pathogenic variants, and discovering new deafness genes in underrepresented populations.

The racial/ethnic disparity in published literature on hearing-loss genetics is stark. Though Black and Latinx people make up 26% of global populations, they comprise only 3% of subjects in hearing-loss genetics studies. In contrast, White individuals comprise 15% of global populations and 53% of reported subjects. This underrepresentation in the literature likely underlies the previously reported poor diagnostic efficacy of genetic testing for hearing loss in sub-Saharan African (4%) and Guatemalan (0%) probands, compared to a 28% diagnostic rate for all probands from non-sub-Saharan African countries.⁹ These findings accord with previous reports on genetic testing in general¹⁷; a 2009 analysis revealed 96% of participants in genome-wide association studies (GWAS) were of European descent. A 2016 update showed that White participants continued to make up 81% of all samples in GWAS studies while comprising only 16% of global population; in comparison, Black and Latinx subjects comprised only 2% and <0.5%, respectively.¹⁸ Indigenous American and Pacific Islander populations experience particular challenges in accessing testing; we found that Native American and Native Hawaiian populations are barely represented at all in the literature, comprising a mere 0.01% of all subjects reported.¹⁹

This trend in racial/ethnic disparities has been well described in genetic testing for other diseases. Broadly, patients of African and Asian ancestry are more likely than those of European ancestry to receive

ambiguous genetic test results after exome sequencing, or be told that they have VUSs.²⁰ Cardiomyopathy suffers from similar diagnostic inequity, in which genetic testing is more likely informative for those with well-characterized variants predominantly from White populations, as current standards prioritize limiting false-positive rates over test sensitivity.^{21,22} As a result, patients of African ancestry are more likely than those of European ancestry to be falsely told their variant increases their risk of developing life-threatening hypertrophic cardiomyopathy.^{23,24} These analyses illustrate how unequal representation of genetic variation can negatively affect present genomic interpretation in individuals of non-European ancestry.²⁰ In contrast with studies in other conditions, Asians are well represented in the hearing-loss genetics literature, with 46% of populations of Asian origin and the number of studies conducted in Asian populations surpassing the number of studies in White populations in 2010. The majority of this representation, however, is from East Asia, and China in particular; representation from other Asian regions, especially Southeast Asia, is still very poor.

This study has several limitations. First, there was considerable heterogeneity in descriptions of race, ethnicity, and ancestry. Many of the studies included in this analysis made no explicit mention of the racial or ethnic background of populations, and if they did, they did not specify whether the categorization was self-identified by patients/populations, inferred by the study investigators, or determined based on genetic ancestry analysis. Thus, multiple assumptions were made to assign a racial/ethnic group to each population. Furthermore, these assignments were based on a United States-centric definition of race/ethnicity, largely based off of continent of origin, which can lack complexity, underrepresent certain groups, and may not align with how these populations identify themselves, particularly outside of the United States. We adjusted the use of Hispanic to Latinx in an attempt to specifically focus on populations of Central and South America, which are more likely representative of indigenous American ancestry as opposed to European ancestry. However, this category does not encompass the extent of the genetic complexity of these populations.

The structure of our search and method of data extraction from articles had limitations. Search terms, while intended to generate a thorough and representative sampling of studies pertaining to genetic testing and hearing loss, were not necessarily comprehensive. Additionally, we introduced a potential source of bias as we only queried one database (PubMed). While we attempted to address systemic bias by performing comparative analysis of studies and populations against each other, we did not explicitly address bias on an article-by-article basis. As all articles were case studies or case series, only 2 of 7 domains (Selective Reporting and Complete Data) are potentially relevant from Cochrane guidelines, and our goal of comparative analysis of studies and their respective study populations against each other mitigates the impact of these potential biases on our analysis.²⁵ We further mitigated systematic bias by including non-English studies. Data extraction was systematic, but imperfect given incomplete data. Despite these methodological limitations, none are expected to systemically bias the comparisons or the conclusions, particularly given the large magnitude of the effects seen.

Consideration of race/ethnicity in scientific research and medicine is complex. This study does not address issues of race/ethnicity as a social construct or a biological construct relating to genetic ancestry, but merely is intended to illustrate the disparities in the literature and underrepresentation of broadly-defined groups.^{26,27} While there may be conflicting perspectives on the inclusion of race as a factor in the study of medicine and science, more information on underrepresented groups, as defined by genetic ancestry, country of origin, or self-identification, is clearly needed. Patient populations represented in studies directly inform clinical interpretation, decision making, and outcomes. Advances in screening and increases in availability have the potential to help ameliorate disparities present in hearing loss, but for that to be a reality, genetic testing must be equally informative for all groups.²⁸ If applications of new technology, like NGS, continue to be applied disproportionately in overrepresented populations, the models generated from newly available data risk perpetuating and exacerbating health disparities.²⁹

Finally, while it is commonplace to compare the percent of subjects studied to the percent of global population of a particular racial/ethnic group, even distribution of studies along these population proportions is likely not the best approach for allocation of future research. These subgroups do not represent homogenous populations, and genetic diversity within single racial/ethnic groups is often larger than between groups. For example, while our findings suggest that Asians are well represented in the literature, and therefore do not need to be specifically targeted in future research, the “Asian” group aggregates many divergent populations into one group that is very heterogeneous. 77% of studies of Asian populations only included Chinese and Japanese participants; Cambodian and Hmong immigrants have poorer overall health outcomes than other Asian Americans and are not represented by these works.³⁰ Additionally, several studies indicate greater genetic diversity between individuals of the same race than between individuals of different races.^{31–33} This has been especially noted among individuals of African ancestry.³⁴ It is estimated that because of shorter linkage disequilibrium, a GWAS of African population would require approximately 1.5 million SNPs to achieve the same resolution as a study of a European population using 0.6 million SNPs.³⁵ Therefore, allocating research to European and African populations proportional to their populations would underserve the genetic diversity of African populations.

Conclusion

This systematic review and synthesis demonstrates a wide racial/ethnic disparity in published literature on the genetics of hearing loss, with Latinx, Black, and Native American/Hawaiian populations vastly underrepresented compared to White and Asian groups. Increasing representation of these groups in future clinical testing and research efforts is necessary to improve the efficacy and equity of genetic testing for hearing loss.

Declarations

Funding: This study was funded by an award from the Claire Giannini Fund, and by NIDCD R01DC018583 to DKC.

Conflicts of interest/Competing interests: The authors declare no competing interests.

Availability of data and material: All relevant data are included in this manuscript

Code availability: N/A

Authors' Contributions:

MMF, SLR, and DKC contributed to the study conception and design. All authors contributed to material preparation, data collection and analysis. The first draft of the manuscript was written by MMF and SLR, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent: This study was approved by the Institutional Review Board at UCSF.

References

1. Morton CC, Nance WE. Newborn Hearing Screening — A Silent Revolution. *New England Journal of Medicine*. 2006;354(20):2151-2164. doi:10.1056/NEJMra050700
2. Lin FR, Thorpe R, Gordon-Salant S, et al. Hearing loss prevalence and risk factors among older adults in the United States. *J Gerontol A Biol Sci Med Sci*. 2011;66(5):582–590.
3. Kimberling WJ, Hildebrand MS, Shearer AE, et al. Frequency of Usher Syndrome in Two Pediatric Populations: Implications for genetic screening of Deaf and Hard of Hearing Children. *Genet Med*. 2010;12(8):512-516. doi:10.1097/GIM.0b013e3181e5afb8
4. Brodie KD, Moore AT, Slavotinek AM, et al. Genetic Testing Leading to Early Identification of Childhood Ocular Manifestations of Usher Syndrome. *Laryngoscope*. Published online October 28, 2020. doi:10.1002/lary.29193
5. Shearer AE, Shen J, Amr S, Morton CC, Smith RJ. A proposal for comprehensive newborn hearing screening to improve identification of deaf and hard-of-hearing children. *Genet Med*. 2019;21(11):2614-2630. doi:10.1038/s41436-019-0563-5
6. Hilgert N, Smith RJH, Van Camp G. Function and expression pattern of nonsyndromic deafness genes. *Curr Mol Med*. 2009;9(5):546-564. doi:10.2174/156652409788488775
7. Pandya A. Genetic hearing loss: the journey of discovery to destination – how close are we to therapy? *Molecular Genetics & Genomic Medicine*. 2016;4(6):583-587. doi:https://doi.org/10.1002/mgg3.260
8. Sloan-Heggen CM, Bierer AO, Shearer AE, et al. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. *Hum Genet*. 2016;135:441-450. doi:10.1007/s00439-016-1648-8

9. Yan D, Tekin D, Bademci G, et al. Spectrum of DNA variants for nonsyndromic deafness in a large cohort from multiple continents. *Hum Genet.* 2016;135(8):953-961. doi:10.1007/s00439-016-1697-z
10. Florentine MM, Rouse SL, Stephans J, Conrad D, Czechowicz J, Matthews IR, Meyer AM, Nadaraja GS, Parikh R, Virbalas J, Weinstein JE, Chan DK. Racial and Ethnic Disparities in Diagnostic Efficacy of Comprehensive Genetic Testing for Sensorineural Hearing Loss. Presented at the American Society of Pediatric Otolaryngology Spring Meeting, April 11, 2021.
11. Chan DK, Chang KW. GJB2-associated hearing loss: systematic review of worldwide prevalence, genotype, and auditory phenotype. *Laryngoscope.* 2014;124(2):E34-53. doi:10.1002/lary.24332
12. Lebeko K, Bosch J, Noubiap JJN, Dandara C, Wonkam A. Genetics of hearing loss in Africans: use of next generation sequencing is the best way forward. *Pan Afr Med J.* 2015;20. doi:10.11604/pamj.2015.20.383.5230
13. Amendola LM, Jarvik GP, Leo MC, et al. Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. *Am J Hum Genet.* 2016;98(6):1067-1076. doi:10.1016/j.ajhg.2016.03.024
14. Booth KT. Unraveling the genotypic and phenotypic complexities of genetic hearing loss. Published online December 1, 2018. doi:10.17077/etd.h3om-klhg
15. Harrison SM, Riggs ER, Maglott DR, et al. Using ClinVar as a Resource to Support Variant Interpretations. *Curr Protoc Hum Genet.* 2016;89:8.16.1-8.16.23. doi:10.1002/0471142905.hg0816s89
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. doi:10.1016/j.jclinepi.2009.06.005
17. Suther S, Kiros G-E. Barriers to the use of genetic testing: A study of racial and ethnic disparities. *Genetics in Medicine.* 2009;11(9):655-662. doi:10.1097/GIM.0b013e3181ab22aa
18. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nature Genetics.* 2019;51(4):584-591. doi:10.1038/s41588-019-0379-x
19. D'Angelo CS, Hermes A, McMaster CR, et al. Barriers and Considerations for Diagnosing Rare Diseases in Indigenous Populations. *Front Pediatr.* 2020;8. doi:10.3389/fped.2020.579924
20. Petrovski S, Goldstein DB. Unequal representation of genetic variation across ancestry groups creates healthcare inequality in the application of precision medicine. *Genome Biol.* 2016;17. doi:10.1186/s13059-016-1016-y
21. Walsh R, Mazzarotto F, Whiffin N, et al. Quantitative approaches to variant classification increase the yield and precision of genetic testing in Mendelian diseases: the case of hypertrophic cardiomyopathy. *Genome Med.* 2019;11(1):5. doi:10.1186/s13073-019-0616-z
22. Ho CY, Day SM, Ashley EA, et al. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy. *Circulation.* 2018;138(14):1387-1398. doi:10.1161/CIRCULATIONAHA.117.033200

23. Gerhard GS, Fisher SG, Feldman AM. Genetic Testing for Inherited Cardiac Diseases in Underserved Populations of Non-European Ancestry: Double Disparity. *JAMA Cardiol.* 2018;3(4):273. doi:10.1001/jamacardio.2017.5345
24. Manrai AK, Funke BH, Rehm HL, et al. Genetic Misdiagnoses and the Potential for Health Disparities. *N Engl J Med.* 2016;375(7):655-665. doi:10.1056/NEJMs1507092
25. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook
26. Burchard EG, Ziv E, Coyle N, et al. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med.* 2003;348(12):1170-1175. doi:10.1056/NEJMs025007
27. Cooper RS, Kaufman JS, Ward R. Race and genomics. *N Engl J Med.* 2003;348(12):1166-1170. doi:10.1056/NEJMs022863
28. Bush ML, Kaufman MR, McNulty BN. Disparities in Access to Pediatric Hearing Healthcare. *Curr Opin Otolaryngol Head Neck Surg.* 2017;25(5):359-364. doi:10.1097/MOO.0000000000000388
29. Popejoy AB, Fullerton SM. Genomics is failing on diversity. *Nature News.* 2016;538(7624):161. doi:10.1038/538161a
30. Srinivasan S, Moser RP, Willis G, et al. Small is essential: importance of subpopulation research in cancer control. *Am J Public Health.* 2015;105 Suppl 3:S371-373. doi:10.2105/AJPH.2014.302267
31. Baye TM. Inter-chromosomal variation in the pattern of human population genetic structure. *Human Genomics.* 2011;5(4):220. doi:10.1186/1479-7364-5-4-220
32. Lewontin RC. The Apportionment of Human Diversity. In: Dobzhansky T, Hecht MK, Steere WC, eds. *Evolutionary Biology.* Springer US; 1972:381-398. doi:10.1007/978-1-4684-9063-3_14
33. Kaessmann H, Wiebe V, Weiss G, Pääbo S. Great ape DNA sequences reveal a reduced diversity and an expansion in humans. *Nat Genet.* 2001;27(2):155-156. doi:10.1038/84773
34. Mersha TB, Abebe T. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. *Human Genomics.* 2015;9(1):1. doi:10.1186/s40246-014-0023-x
35. Jallow M, Teo YY, Small KS, et al. Genome-wide and fine-resolution association analysis of malaria in West Africa. *Nat Genet.* 2009;41(6):657-665. doi:10.1038/ng.388

Figures

Figure 1

Flowchart of systematic review and racial/ethnic group assignment.

Figure 2

Home country of corresponding author. The number of studies with a corresponding author from each country is indicated. Darker blue indicates more studies (range as indicated in legend); yellow indicates no studies originating from that country. Note: The designations employed and the presentation of the

material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 3

Racial/ethnic distribution of published hearing-loss genetic testing data. The number of unique populations (left) and subjects (right) attributable to the indicated racial/ethnic groups is described for 1,165 included studies, comprising 1,355 populations and 311,092 subjects.

Figure 4

Countries/regions of origin for populations (A) and subjects (B) contributing to each racial/ethnic group.

Figure 5

Representation of racial/ethnic groups in published studies over time.

Figure 6

Representation of subjects from different racial/ethnic groups in published studies by genetic testing type