

Racial and Ethnic Disparities in Diagnostic Efficacy of Comprehensive Genetic Testing for Sensorineural Hearing Loss

Michelle M Florentine

University of California San Francisco

Stephanie L Rouse

UCSF: University of California San Francisco

Jihyun Stephans

UCSF: University of California San Francisco

David Conrad

UCSF: University of California San Francisco

Josephine Czechowicz

UCSF: University of California San Francisco

Ian R Matthews

UCSF: University of California San Francisco

Anna K Meyer

UCSF: University of California San Francisco

Garani S Nadaraja

UCSF: University of California San Francisco

Rajan Parikh

UCSF: University of California San Francisco

Jordan Virbalas

UCSF: University of California San Francisco

Jacqueline E Weinstein

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>

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Abstract

Understanding racial/ethnic disparities in diagnostic rates of genetic testing is critical for health equity. We sought to understand the extent and cause of racial/ethnic disparities in diagnostic efficacy of comprehensive genetic testing (CGT) for sensorineural hearing loss (SNHL). We performed a retrospective cohort study at two tertiary children's hospitals on a diverse cohort of 240 consecutive pediatric patients (76% publicly insured, 82% non-White) with SNHL of unknown etiology who underwent CGT. Definite and possible molecular diagnoses were assigned for each patient, representing the likelihood of a genetic cause of hearing loss. Associations between race/ethnicity and diagnostic rates were examined. 3.8 ± 2.1 variants were detected per patient; this frequency did not vary between White/Asian and Hispanic/Black cohorts. Overall, 82% of variants were Variants of Unknown Significance (VUS). Compared with White/Asian subjects, variants identified among Hispanic/Black children were less likely to be known (15% vs. 24%, $p < 0.001$), and Hispanic/Black children were less likely to have a definite molecular diagnosis (10% vs. 37%, $p < 0.001$). Expanding molecular diagnostic criteria to include predicted deleterious VUSs reduced these disparities between White/Asian and Hispanic/Black children, with comparable molecular diagnostic rates (41% vs. 35%, $p = 0.46$). The adjusted odds ratio for definite genetic diagnosis in Black/Hispanic children compared with White/Asian children was 0.18. These results demonstrate the extent of racial/ethnic disparities in diagnostic efficacy of comprehensive genetic testing. Consideration of deleterious VUSs reduced these disparities, highlighting the need for increased inclusion of underrepresented groups in genetic hearing-loss studies to clinically validate these variants.

Introduction

Hearing loss is the most common congenital sensory deficit, affecting one in 500 newborns.^{1,2} Over 60% of sensorineural hearing loss (SNHL) is estimated to be caused by genetic factors.^{3,4} Identifying an etiology for childhood SNHL can assist in prognosis and guide management in deaf and hard-of-hearing (D/HH) children.^{5,6} Additionally, early identification of syndromic forms of SNHL, prior to the development of overt syndromic phenotypes, can significantly affect management and counseling.⁷ Recently, comprehensive genetic testing (CGT) has become a standard-of-care tool for the identification of a genetic cause of hearing loss in D/HH children.⁸

Though genetic testing is valuable in the clinical management and understanding of pediatric hearing loss, the diagnostic rate has been reported to vary widely, from 10-83%.⁹ This is in part due to the discrepancy between the vast increase in the amount of genetic information readily available with the advancement and increasing availability of next-generation sequencing (NGS) and our ability to interpret the clinical significance of identified variants. With over 150 genes implicated in NSHL, testing routinely yields a large number of novel variants, the majority of which are caused by single nucleotide changes, a small number of indels, or copy number variants, complicating interpretation of results.^{4,10,11} The interpretation of sequence variants is a crucial element of accurate genetic diagnosis, and discrepancies in variant interpretation can have serious implications for patient care.¹²⁻¹⁴ The American College of

Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) have published recommendations for the interpretation of sequence variants.¹⁵ These guidelines are intentionally broad and conservative, requiring substantial evidence to categorize a variant as disease-causing,¹⁶ which may constrain diagnostic power for populations that are historically underrepresented in genetic studies. Understanding how the efficacy and constraints of genetic testing are affected by demographic disparities is a critical concern when considering health equity.

SNHL is in many ways an ideal human genetic disease model in which to explore complexities of genetic testing – it is a common, narrowly defined, quantifiable clinical entity with a precisely delineated group of highly penetrant genes associated with a clear phenotype. Lessons learned in the study of SNHL may be applicable to the treatment of a range of genetic disorders. Disparities in genetic testing in hearing loss have been observed. The rate of diagnosis as well as spectrum of genes and variants varies widely by ethnic groups, but the underlying cause of this disparity is not well described.^{17,18} The majority of studies have focused on GJB2, yet causative variants in these genes are mostly found in people of European and Asian descent.¹⁹ In contrast, GJB2 variants are rarely the cause of SNHL in Black populations.²⁰

In recent years, CGT has become more accessible due to decrease in expense and broadening of insurance coverage, increasing the opportunity to examine genetic testing outcomes in historically underrepresented populations. In this study, we report on the molecular diagnostic efficacy of CGT for SNHL in a diverse pediatric population, with a focus on examining the extent and cause of disparities in diagnostic rate and variant distribution among children from different racial/ethnic populations.

Methods

Study Population

We performed a retrospective chart review of 240 consecutive pediatric patients with an unknown etiology of SNHL at two tertiary children's hospitals (UCSF Benioff Children's Hospital Oakland, UCSF Benioff Children's Hospital San Francisco) who underwent comprehensive hearing-loss gene panel testing from 2018-2020. Samples were obtained by blood draw or cheek swab. Patients were not excluded based on physical exam, imaging, or other findings. This study was approved by the Institutional Review Board at UCSF.

Demographics

Gender and insurance were extrapolated from the patients' electronic medical record. Ethnicity, race and primary home language were based on parents' self-report, with children categorized as Non-Hispanic White (White), Non-Hispanic Black (Black), Non-Hispanic Asian (Asian), Hispanic, any race (Hispanic), and Other or Unknown (which included Pacific Islander, Native American, Mixed/Multi-race, or Declined to State).

Clinical history

Clinical data were collected from otolaryngology and audiology reports. This included newborn hearing screening (NHS) results as well as earliest and most recent audiogram results. Hearing-loss onset was considered congenital if the patient referred on their NHS and post-natal if the patient passed their NHS. In cases where an NHS result was unavailable, hearing loss onset was categorized as unknown. Baseline audiogram results are reported from the earliest audiogram report available. Hearing loss symmetry, laterality, and baseline hearing loss level were determined using pure tone average (PTA) for thresholds between 0.5-4 kHz. Hearing loss was defined as follows: unilateral (PTA > 15 dB in one ear only); bilateral (PTA > 15 dB in both ears); asymmetric: PTA difference > 15 dB between ears; progressive: difference > 15 dB between baseline and most recent audiograms; hearing level (based on worse-ear level): normal (PTA < 15 dB HL), slight-mild (15-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90 dB), and profound (> 90 dB).

Genetic data

Hearing-loss gene panel testing (GeneDx) was conducted by targeted gene capture followed by massively parallel sequencing. Details on genetic testing and variant classification are provided in the Supplemental Material.

Statistical analyses

Descriptive statistics are presented as percentages or means \pm standard deviations. Univariate ANOVA and two-way ANOVA were used to identify predictors of our outcomes of interest. Binomial logistic regression was used to assess for predictors and confounding variables.

Results

Sample Population and hearing-loss gene panel testing outcomes

Data were collected from 240 children, 0-22 years old, with SNHL (Figure 1). The study population was ethnically and linguistically diverse, with a majority publicly insured (76%). 36% had congenital hearing loss. Children were evenly split between congenital and postnatal onset and represented a wide range of hearing levels, but were predominantly bilaterally affected.

All 240 children underwent comprehensive hearing-loss gene panel testing. 944 variants were identified in our study population, with an average of 3.8 ± 2.1 variants identified per patient. The majority of variants were Variants of Unknown Significance (VUSs; 82%). Of the remainder, 14% were identified as Pathogenic (PV) and 5% Likely Pathogenic (LPV); we analyzed these together as Known Variants (Supplemental Table 1).

Of the 240 patients involved in this study, 23% overall received a definite genetic diagnosis (Patient MD = 4, see Supplemental Methods), representing the highest likelihood of a genetic cause of hearing loss and requiring either two known PV/LPVs in a gene with an autosomal recessive inheritance pattern or one PV/LPV in an autosomal dominant gene.

Racial and ethnic disparities in genetic testing outcomes

We sought to assess for differences in definite genetic diagnostic rates across race/ethnicity groups. We found that White and Asian children had a higher rate of definite genetic diagnoses (29% and 44%, respectively) when compared to Hispanic and Black children (10% and 13%, respectively) (Figure 2).

For subsequent analyses, we dichotomized race/ethnicity into a group of Black and Hispanic children and a group of White and Asian children to reflect this disparity. On one-way ANOVA, there was a significant association between definite genetic diagnosis and race/ethnicity, with 37% of White/Asian children receiving a genetic diagnosis compared with only 10% of Black/Hispanic children ($p < 0.001$). In order to control for clinical factors, univariate analysis was performed to determine the association of definite genetic diagnostic rate with hearing loss onset, baseline hearing level and hearing loss laterality (Table 1). Hearing loss laterality was the only clinical variable significantly associated with definite genetic diagnosis ($p = 0.02$). We then performed a two-way ANOVA to explore the association between hearing loss laterality and race/ethnicity on definite genetic diagnoses. Both main effects were significant, and the interaction between hearing loss laterality and dichotomized race/ethnicity was not significant. Because there was no significant difference in hearing loss laterality between both racial/ethnic groups on one-way ANOVA ($p = 0.71$), dichotomized race/ethnicity was used as our primary predictive variable for all subsequent analyses.

We sought to understand why the definite genetic diagnostic rate varies by race/ethnicity. One possible contributor to this disparity is a difference in the number of rare variants identified between the two groups. After NGS, rare variants are identified by filtering based on racial/ethnic-group-specific mean allele frequency. One-way ANOVA demonstrated no significant difference between White/Asian and Black/Hispanic groups in the number of variants identified per patient (3.8 vs 3.6 variants, $p = 0.47$; Figure 3A). Therefore, the number of rare variants detected was unlikely to contribute to the association between race/ethnicity and definite genetic diagnostic rate.

We then probed the hypothesis that the variants identified in our White/Asian population were better studied and therefore, were more likely to lead to a genetic diagnosis. In order to assess this, we identified Known Variants, defined as variants that have been described as P/LPV or B/LBV and therefore have a known relationship with hearing loss. Overall, only 18% of the variants were classified as Known Variants, with the remainder (82%) classified as VUSs. One-way ANOVA demonstrated that Known Variants were more common in White/Asian children than in Black/Hispanic children (23.8% vs 15.0%, $p = 0.002$; Figure 3B).

This disparity in Known Variants suggests that the body of knowledge contributing to variant classification is biased according to race and ethnicity. Alternatively, White/Asian children may simply have a higher proportion of deleterious variants in hearing-loss genes. To probe this further, we analyzed variants that were categorized as VUSs and segregated them based upon PROVEAN prediction. Because the PROVEAN predictions are based on the *in silico* predicted effect of the genetic variant on protein function, they should be less dependent on prior literature, and therefore less biased on race and

ethnicity. We dichotomized VUSs into deleterious VUSs and non-deleterious VUSs, which included benign and unknown VUSs, and found no significant difference between racial/ethnic groups ($p=0.94$; Figure 3C).

In order to explore the impact of this less racially/ethnically biased method on genetic diagnostic rate, we created a new genetic diagnosis category (“possible genetic diagnosis”, Patient MD = 3). For this category, a “possible genetic diagnosis” was made based on the classification of deleterious VUSs as possibly diagnostic (Supplemental Figure 2). A Patient MD of less than 3 was considered an unlikely genetic diagnosis. For this analysis, Patient MDs of 4 (defined based upon the presence of Known Variants) were excluded, so as to assess the isolated effect of the unbiased VUS classification scheme on genetic diagnostic rate. Using this less biased classification scheme, White/Asian children and Black/Hispanic children had comparable possible genetic diagnostic rates (41% vs 35%, $p=0.46$; Figure 4). Reconfiguring the patient-level diagnostic criteria to rely on less-biased PROVEAN prediction rather than prior studies thus eliminated the disparity in genetic diagnostic rate between White/Asian and Hispanic/Black children.

Finally, binomial logistic regression was performed in order to assess for additional predictors of genetic testing outcomes. The logistic regression analysis included demographic variables found to have a significant association with either definite and possible genetic diagnoses on univariate analysis, as well as clinical variables (hearing loss laterality, hearing loss onset, and baseline hearing loss level) (Supplemental Table 2). The odds of a Black/Hispanic child receiving a definite genetic diagnosis is 0.18 that of a White/Asian child receiving a definite genetic diagnosis (95% CI: 0.08-0.37, $p<0.001$). When the diagnosis is based on PROVEAN prediction using the possible genetic diagnosis model, race/ethnicity no longer affects the overall distribution of genetic diagnoses ($p=0.51$).

Discussion

Identifying genetic etiology of hearing loss can improve clinical care. With the advent of NGS, genetic testing is readily available and has become a clinical standard of care,⁶ but this approach has its limitations. Access to CGT is often limited by economic factors, and variants are difficult to interpret. The development of massively parallel sequencing technologies has made genetic data more readily available than ever before, shifting the bottleneck in identifying molecular etiology from acquisition of data to meaningful variant interpretation that is accurate, disease-specific, and equitably representative.

We present here an analysis of the clinical efficacy of CGT in a diverse pediatric population. From 240 pediatric patients with SNHL of unknown etiology, 944 variants were identified in 132 genes. Overall, 23% of patients were diagnosed by CGT, with significant variability seen across racial and ethnic groups. Asian (44%) and White (29%) groups had significantly higher diagnostic rates than Black (13%) and Hispanic (10%) children. Though diagnostic rates were overall lower than previous reports, the trend in differences in between racial/ethnic group rates was similar.¹⁷ We observed different rates of Known

Variant interpretation and definite molecular diagnosis across racial/ethnic groups. The difference in diagnostic rate was neither attributable to clinical covariates nor numbers of variants identified.

Instead, we found that the disparity was related to a significantly higher rate of Known Variants among White/Asian subjects. This bias in variant classification is likely due to a higher rate of prior genetic studies performed on White and Asian populations compared to Black and Hispanic ones, an inequity that has been demonstrated repeatedly.²¹ Specific to hearing loss, most SNHL genes have been identified in families from consanguinity belts in the Middle East and India.²² On the other hand, few studies have been done in people of African or indigenous American descent, due to a combination of decreased access to care as well as cultural differences, historic stigmatization and discrimination that have contributed to avoidance of genetic testing and research.^{23,24}

We tested to see whether using a less biased method of variant classification – *in silico* prediction of deleterious versus benign VUSs – would eliminate the disparity in genetic diagnostic rate. Indeed, these *in silico* predictions were not significantly biased, and when we compared the “possible molecular diagnosis” rate, based solely on the *in silico* variant classification, the racial/ethnic disparities were eliminated. These findings highlight the gap in understanding of variants across these populations and the critical need for increased inclusion of underrepresented groups in genetic hearing-loss studies. Accumulating diverse population data will allow us to better classify VUSs as pathogenic or benign, decreasing the rate of false positives and negatives and increasing the CGT diagnostic value.

Such a classification scheme based on *in silico* predictions alone without additional clinical validation is not sufficient to make actionable genetic diagnoses. This need for significant evidence to classify variants, however, skews definitive classifications toward populations that are better represented in the literature and variant databases.^{25,26} Thus, the clinical value of genetic testing is higher amongst these groups, exacerbating disparities in treatment and understanding of disease. This is well documented in the study of genetic testing in breast cancer, cardiomyopathy, and chronic kidney disorders, in which racial and ethnic health disparities persist despite the rapid increase in genetic information.^{27–29}

Our study is unique in that 76% of our study population is publicly insured. While Black and Hispanic patients are generally less likely to have private insurance coverage and therefore less access to genetic testing, access to genetic testing was not a barrier for the Black and Hispanic patients in our study. Additionally, the clinical indications for testing, and clinical features themselves, were comparable across all groups. Because access to testing and clinical indications for obtaining testing was consistent across race/ethnic groups, differences in diagnostic rate are likely reflective of the disparity in Known Variants rather than differences in patients’ clinical features.

There are several limitations to our study. Family history was not available for the majority of patients, so designation of inheritance was not based on family pedigree but instead on clinical report or OMIM classification. Thus, the VUS reclassification we designed and tested may disproportionately inflate the role of dominant variants. We mitigated this effect by defaulting to a recessive pattern when inheritance

was in question for a VUS. Due to limited family history and parental testing, we cannot confirm biallelic (in trans) variants for most subjects. Pre-clinical syndromic associations may have been missed in clinical evaluations.

Finally, while our cohort includes many patients underrepresented in studies of genetic HL, only 15 of 240 of our patients were Black, showing the limits to inclusivity and representation even in this relatively large study. Overall, the categorization of race/ethnicity in studies of genetics is complex. Health disparities between vulnerable social groups such as racial/ethnic minorities are frequently based in nonbiologic characteristics such as socio-economic status. Race/ethnicity itself is a sociocultural construct and is treated as such in this study. It is important to consider disparities within the context of these socially defined categories, as these are the same classifications that lead to disparate treatment. As such, race and ethnicity were self-reported in our study. However, this classification can lead to imprecise designations and limitations in interpretation.

We found that current CGT for SNHL is nearly 3 times less effective in Black and Hispanic children compared to White and Asian ones. This decreased hit rate may lead clinical providers to utilize this resource less often in these populations. Compared to White children, Black children with SNHL in the US are already half as likely to receive genetic testing.³² If applications of new technology, such as CGT, continue to be utilized disproportionately, the models generated from newly available data risk perpetuating and exacerbating health disparities.³³ This has been seen in the genetic diagnosis of cancers, in which disparities in genetic testing of cancer predisposition have increased disparities in clinical management.^{34,35} Similarly, misclassification of hypertrophic cardiomyopathy has been demonstrated in African Americans due to lack of accessible genetic data from appropriate control populations.²⁵

The gap in diagnostic utility between racial/ethnic groups highlights the need for expansion of genetic knowledge among traditionally underrepresented groups of D/HH individuals. Targeted studies of underrepresented groups to understand these hearing-loss genes and variants, as well as acquisition of large-scale sequencing data from diverse populations, is necessary to close this gap. Expanding the scope of testing to involve whole exome sequencing will allow better identification of novel variants in genes not currently represented in existing panels. While CGT is one of the strongest tools in the clinical evaluation of HL, there is a need to establish that it is equivalently useful and clinically valid across all populations, or else it threatens to exacerbate existing disparities.³⁶ As efforts increase to develop gene therapy for hearing loss, ensuring an inclusive basis of genetic diagnosis is critical to avoid propagation of historical inequities from testing to treatment.

Declarations

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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.

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Table

	White/Asian	Black/Hispanic	p value
Number of variants per child (mean, SD)	3.8 (2.1)	3.6 (2.1)	0.47
Variant MD (mean, SD)	2.4 (0.8)	2.2 (0.6)	0.02
Known variants (% Known)	23.7	15.0	0.002
VUS (%)	75.1	84.4	0.82
Dichotomized VUS (% Deleterious)	33.4	33.2	0.94
Gene MD (mean, SD)	1.7 (1.1)	1.6 (0.8)	0.04
Patient MD (mean, SD)	2.7 (1.3)	2.2 (1.0)	0.001
Definite Genetic Diagnosis (%)	37.1	10.3	<0.001
Possible Genetic Diagnosis(%)	41	35.0	0.46

Table 1. Descriptive analysis of genetic outcomes of both race/ethnicity cohorts with reported p-value of one-way ANOVA.

Figures

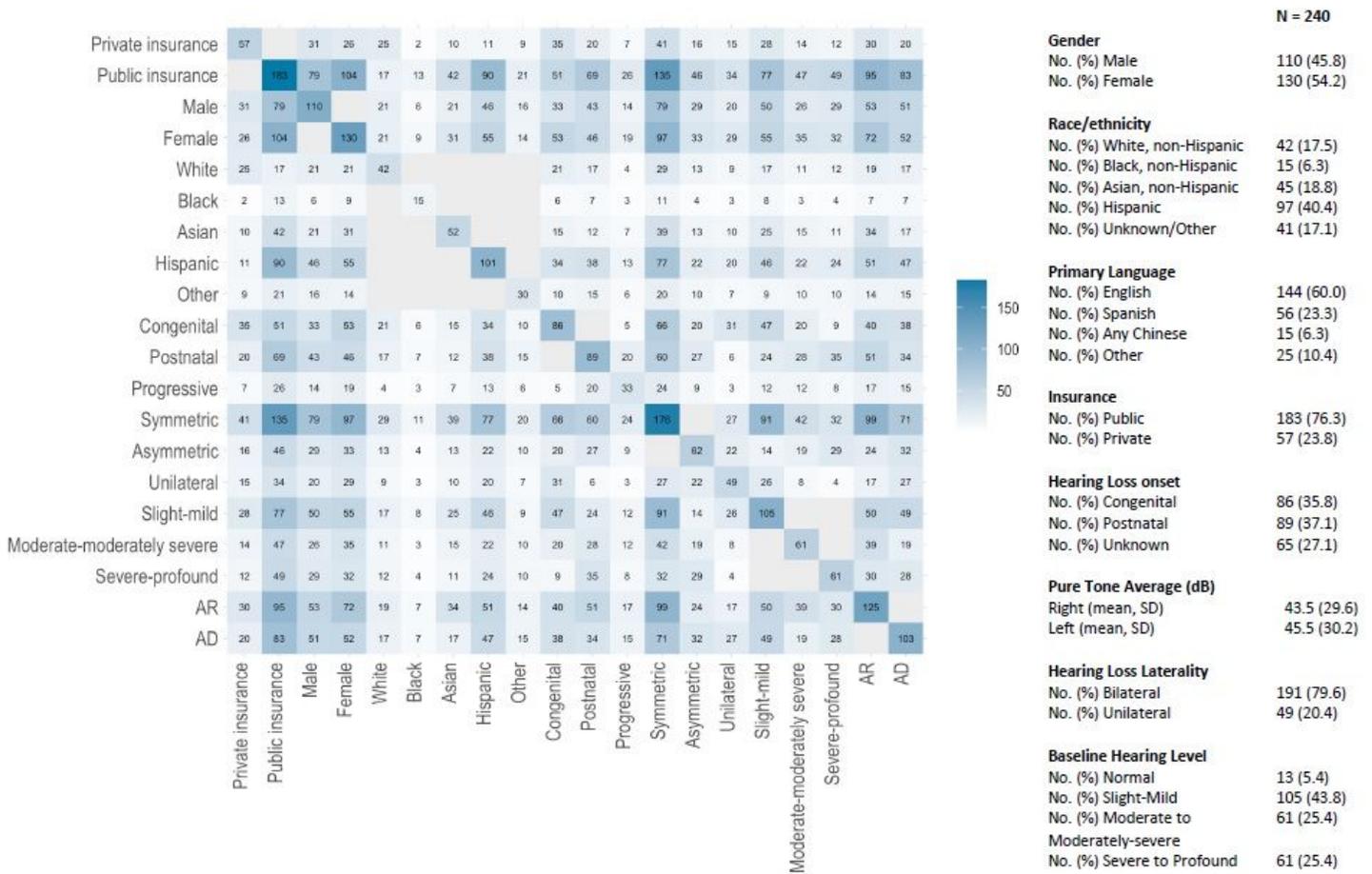


Figure 1

Study population demographic and clinical characteristics. A. Blue shading and numbers reported in individual boxes indicate the number of patients with the paired criteria delineated by row and column. B. Categorical variables were reported as both a number and percentage. Descriptive analysis of continuous variables is reported as a mean and standard deviation for normally distributed variables.

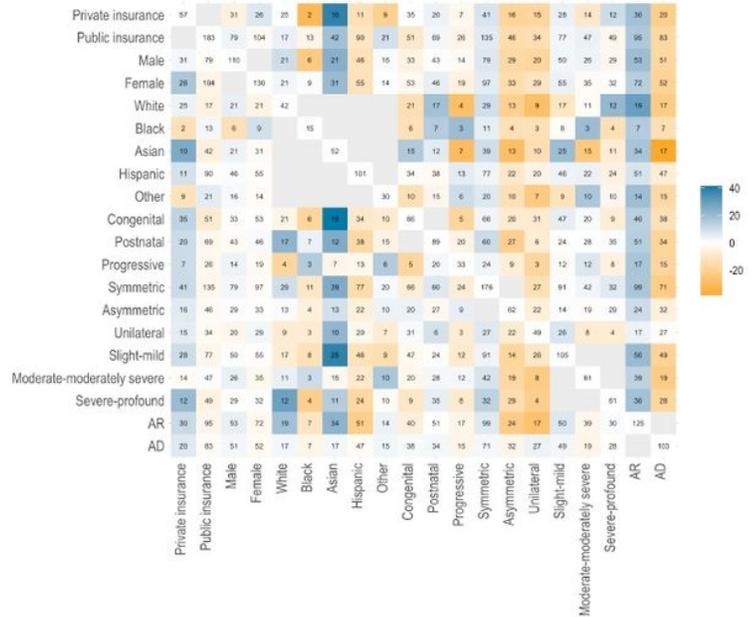
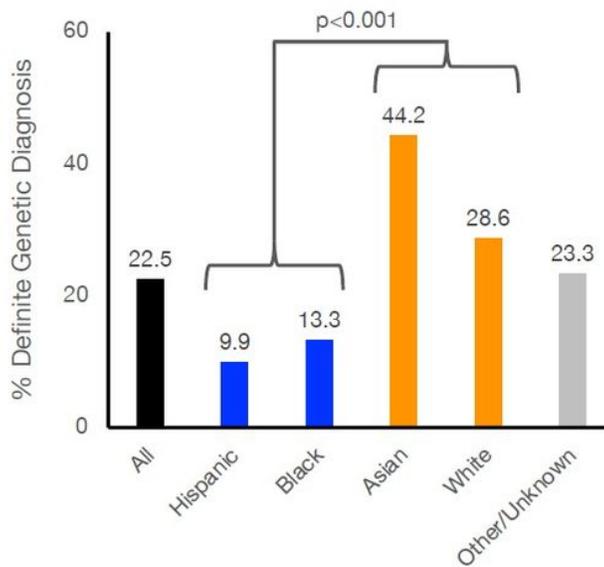


Figure 2

Definite genetic diagnostic rate. A. Distribution of definite genetic diagnoses (Patient MD = 4) across race/ethnicity groups. Definite genetic diagnostic rate was compared by ANOVA between dichotomized race/ethnicity groups (White/Asian and Black/Hispanic). B. Distribution of definite genetic diagnosis across insurance, sex, racial-ethnic group, onset, severity, laterality, and inheritance characteristics. Coloring/shading is indicative of difference of diagnostic rate from the average diagnostic rate adjusted by row: orange indicates below the average diagnostic rate for patients with the characteristic defined by the row, white indicates a diagnostic rate average for patients with the characteristic defined by the row, and blue indicates higher diagnostic rate for patients with the characteristic defined by the row. Numbers in boxes indicate the number of patients who received a definite genetic diagnosis, defined as Patient MD of 4, with paired characteristics of the column and row.

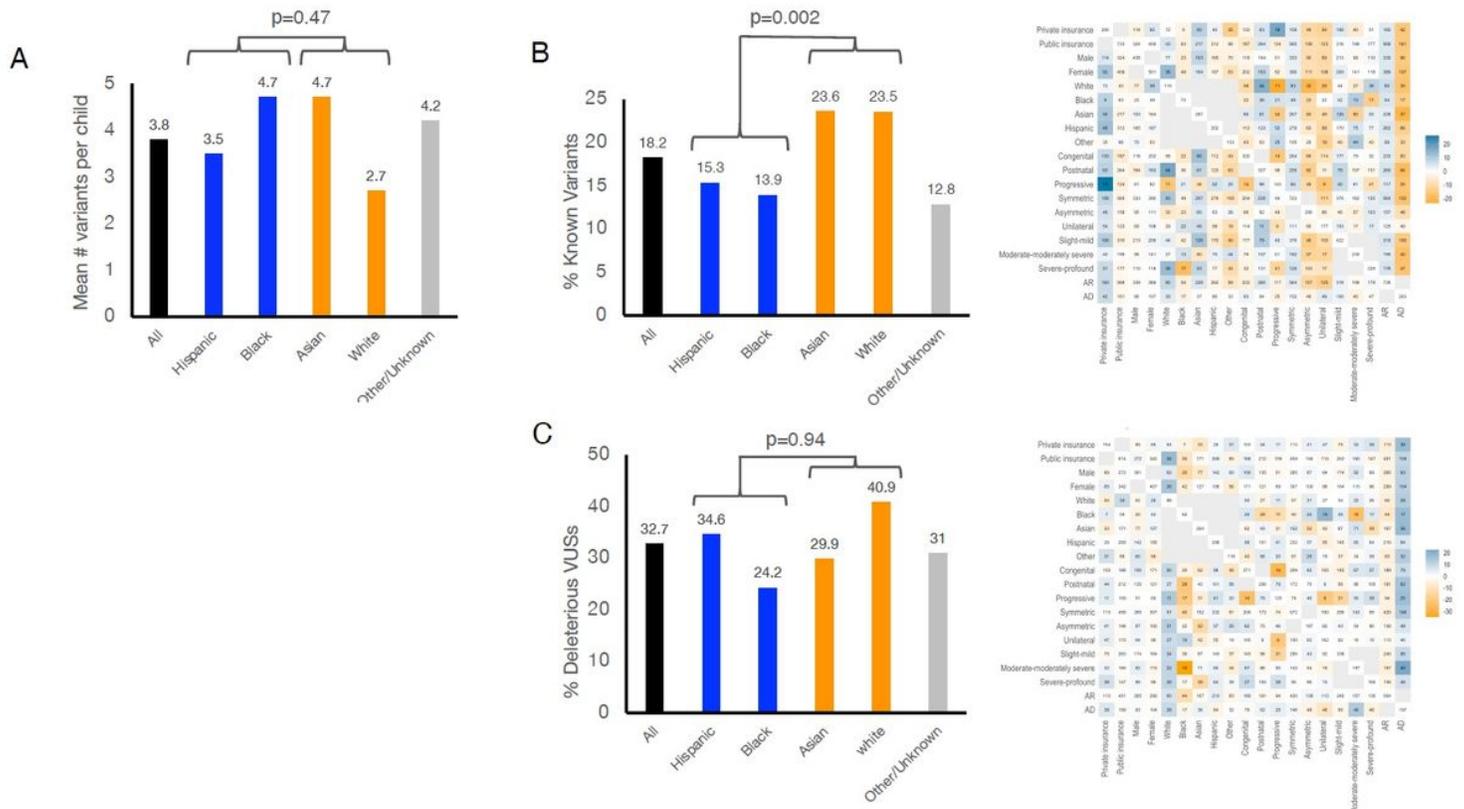


Figure 3

Variant distribution. A. Mean number of variants identified per child across race/ethnicity groups with reported p-value of ANOVA for mean number of variants vs dichotomized race/ethnicity (White/Asian and Black/Hispanic). B. Known Variant rate. Left: Distribution of Known Variants across race/ethnicity groups. Known Variant rate was compared by ANOVA between dichotomized race/ethnicity groups (White/Asian and Black/Hispanic). Right: Distribution of Known Variants across characteristics is shown. Color scheme is as described in Figure 2. C. Predicted deleterious VUS rate. Left: Distribution of predicted deleterious VUSs (by PROVEAN prediction) across race/ethnicity groups. Deleterious VUS rate was compared by ANOVA between dichotomized race/ethnicity groups (White/Asian and Black/Hispanic). Right: Distribution of deleterious VUSs across characteristics is shown. Color scheme is as described in Figure 2.

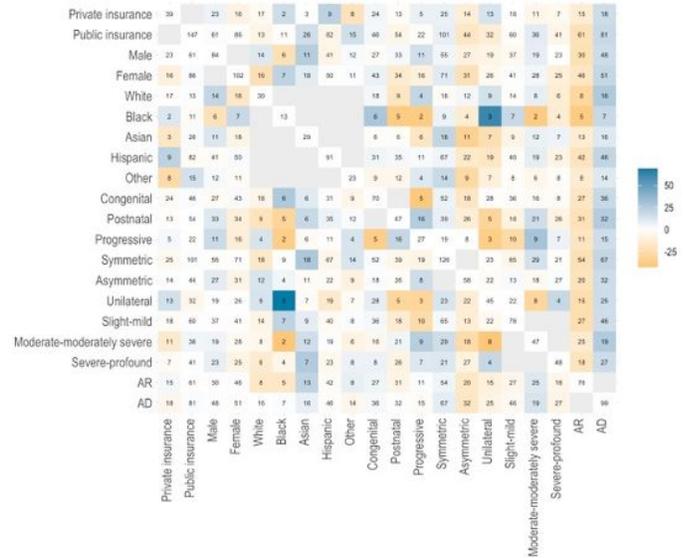
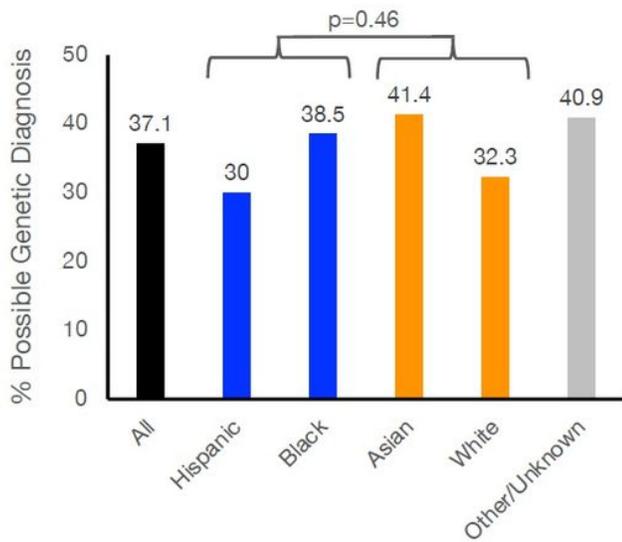


Figure 4

Possible genetic diagnostic rate. A. Distribution of possible genetic diagnoses (Patient MD = 3) across race/ethnicity groups. Possible genetic diagnostic rate was compared by ANOVA between dichotomized race/ethnicity groups (White/Asian and Black/Hispanic). B. Distribution of possible genetic diagnosis across characteristics is shown. Color scheme is as described in Figure 2.

Supplementary Files

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- [SupplementalFigure1.pdf](#)
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- [SupplementalFigure3.pdf](#)
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