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Audiologic Measures in an Indigenous Community with *A2ML1*- and *FUT2*-Related Otitis Media

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Background: Many indigenous peoples are at elevated risk for otitis media, however there is limited information on hearing loss due to OM in these communities. An Indigenous Filipino community that has previously been described with an elevated prevalence of OM that is due to rare *A2ML1* variants and a common *FUT2* variant underwent additional phenological testing. In this study, we describe the audiologic profiles in *A2ML1*- and *FUT2*-related otitis media and the validity of otoscopy and genotyping for *A2ML1* and *FUT2* variants in screening for otitis media and hearing loss.
Method: We analyzed *A2ML1* and *FUT2* genotypes together with demographic, otologic and audiologic data from tympanometry and hearing level assessments of 109 indigenous individuals.
Results: We confirmed previous findings of a spectrum of nonsyndromic otitis media as associated with *A2ML1* variants. *A2ML1* and *FUT2* variants were associated with high-frequency hearing loss at 4000 Hz. As expected, young age was associated with flat tympanograms, and eardrum perforations due to chronic otitis media were associated with severe-to-profound hearing loss across frequencies. Adding *A2ML1* or *FUT2* genotypes improved the validity of otoscopy as a screening test to rule out moderate-to-profound hearing loss.
Conclusion: Continued multi-disciplinary management and audiologic follow-up using tympanometry and screening audiometry are needed to document and treat otitis media and prevent permanent hearing loss in the indigenous community.

Keywords: *A2ML1*, audiology, *FUT2*, hearing loss, otitis media, tympanometry

Introduction

Otitis media (OM) or middle ear (ME) inflammation that is usually due to infection is one of the most common diseases of childhood. Hearing loss (HL) from OM affects communicative development, causing developmental delay and behavioral changes (Rovers et al, 2004). Thus, screening for ME function and HL is important in children with OM. Tympanometry is a simple objective tool in assessing eardrum mobility and ME function (Rovers et al, 2004). Determination of hearing thresholds, tympanometry, and otoscopy altogether provides adequate information and should be included in the hearing screening protocol for OM (Jacob et al, 1997).

Worldwide, acute and chronic OM increased in prevalence over two decades, though age-standardized rates for chronic OM have decreased (Acuin, 2004; GBD, 2018). In the Philippines, OM has a 9.6% prevalence among ≤12-year-old children, of whom 3.7% have OM with effusion (OME), while 3.1% have chronic suppurative OM (Caro et al, 2014).

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OM is particularly prevalent (3–30%) in Indigenous populations, such as in the Inuit, Native American, Aboriginal Australian, and Maori populations (Bhutta, 2015; Jensen et al, 2013).

An Indigenous Filipino population ($N \sim 250$) has a $\sim 50\%$ prevalence of OM (Santos-Cortez et al, 2016b). In this population, variants in the genes *A2ML1*, *FUT2*, and *SPINK5* were previously associated with susceptibility to acquiring OM (Frank et al, 2021; Larson et al, 2019; Santos-Cortez et al, 2018; Santos-Cortez et al, 2015). *A2ML1* and *SPINK5* encode protease inhibitors that are expressed in the ME mucosa and are essential for the integrity of the epithelial barrier (Frank et al, 2021; Larson et al, 2019; Nielsen et al, 2022; Santos-Cortez et al, 2015; Williams et al, 2020).

Meanwhile the fucosyltransferase encoded by *FUT2* regulates expression of A antigen and subsequently pathogen or commensal binding on the mucosal epithelial surface; *FUT2* also regulates expression of genes that are involved in the immune response during ME infection as well as the maintenance of the epithelial surface mucus barrier and thereby mucociliary transport (Elling et al, 2022; Ma et al, 2018; Santos-Cortez et al, 2018).

A2ML1 and *FUT2* variants were also associated with shifts in the ME, nasopharyngeal, and oral microbiotas (Elling et al, 2022; Frank et al, 2021). Based on our previous cross-sectional microbiota studies on this Indigenous Filipino population, carriage of the rare *A2ML1* variants was associated with altered microbiota composition and increased *Leptotrichia* sp. in the ME, whereas a rare *SPINK5* variant was associated with altered overall microbiota of the oral cavity and increased relative abundance of *Microbacteriaceae* sp. in the ME (Frank et al, 2021).

Moreover, in a cohort of children with OM in the United States, the patients who carried a common stop variant within *FUT2* had increased bacterial richness in the ME (Elling et al, 2022; Santos-Cortez et al, 2018). However, the latter finding was not replicated in the Indigenous Filipinos, which is potentially due to the stronger effects of the rare *A2ML1* variants that obscure the weaker effect of the common *FUT2* variant identified in the Indigenous population (Santos-Cortez et al, 2018).

To determine the effect of OM-associated genetic variants on hearing function, in this report we described audiologic measures in *A2MLI*- and *FUT2*-related OM, and tested the validity of otoscopy and genotyping as screening tools for OM and HL.

Materials and Methods

Ethical considerations

The University of the Philippines Manila Research Ethics Board, the National Commission on Indigenous Peoples, and the Colorado Multiple Institutional Research Board approved the study. In addition to community consent, individual informed consent was obtained from study participants.

Clinical evaluation

Ear specialists visited the community biannually and performed otoscopy, ear cleaning, and hearing screening using tympanometry and audiometry. Free medications were distributed for treatment, however, ME surgeries were not performed due to logistic difficulties. Based on microbiota studies (Santos-Cortez et al, 2018; Santos-Cortez et al, 2016a), oral antibiotics included coverage for *Haemophilus influenzae* for acute OM or OME while aminoglycoside–steroid otic drops were given for chronic OM.

Otoscopy was performed by at least two otologists. The following OM types were diagnosed: *chronic*, smooth-edged perforations ± mucoid/mucopurulent ME discharge and thickened ME mucosa; *acute*, usually erythematous eardrums ± small pinpoint perforations with pulsating ME discharge; *effusive*, intact eardrums with dullness, limited mobility, or visible fluid behind the eardrum; and *healed*, scarred eardrum (e.g., tympanosclerosis, healed perforations) or normal otoscopy after OM diagnoses from previous visits. A comprehensive review of systems during history taking was also performed.

Audiologic testing

Two audiologists performed all tests, with no significant differences in results between testers. Tympanometry was performed using the easyTymp Pro (MAICO, Berlin, Germany) with results as follows: *A*, normal; *Ad*, high static compliance suggesting ossicular disarticulation or scarred thin eardrum; *As*, low static compliance indicating potential ossicular dysfunction resulting in ME stiffness; *B*, flat tympanogram due to ME fluid or eardrum perforation; or *C*, some fluid behind the eardrum. Audiometry using SHOEBOX equipment (Ottawa, ON, Canada) that is designed for use in the community setting was performed in a relatively quiet room.

Statistical analyses

Available genotypes from previous exome and Sanger sequencing studies for the variants *A2ML1* c.2478_2485dupGCTAAAT (p.Ser829Trpfs*), *A2ML1* c.4061+1G>C, and *FUT2* c.604C>T (p.Arg202*), along with gender, age, and OM status were included for analysis (Table 1) (Santos-Cortez et al, 2018; Santos-Cortez et al, 2015; Larson et al, 2019). A *SPINK5* variant (Frank et al, 2021) had a lower prevalence and no significant association with audiologic measures, and was, therefore, excluded from further analyses. Carriage of *A2ML1* or *FUT2* variants (whether homozygous, compound heterozygous for variants in the same gene, or heterozygous only; Table 1) was the main determinant variable and each gene was analyzed independently in association analyses.

Standard bivariate tests were performed using Fisher exact, Mann–Whitney–Wilcoxon, Kruskal–Wallis, or Spearman correlation in R. Standard validity measures (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were estimated for OM diagnosis by otoscopy versus [1] tympanometry, [2] audiometry, and [3] *A2ML1* or *FUT2* genotypes. Lastly, validity was also estimated for otoscopy and genotypes combined versus [1] tympanometry and [2] audiometry.

Results

Nonsyndromic OM due to A2ML1 variants

Prevalence of active OM (i.e., acute, OME, and chronic) decreased from 47.1% to 30.2% over 12 years (Fig. 1). Chronic OM prevalence decreased from 43.9% to 22–26%,

Table 1. Demographics, Genotypes, and Audiologic Results According to Otitis Media Status

Variables	*Chronic*	*Acute*	*Effusive*	*Healed*	*Normal*	*Total*
	OM status					
Median age (years)	11	9	9	16	12	12
Female (%)	69	33	42	76	54	59
A2ML1+ (*n* ID)[a]	20	1	10	18	17	66[b]
Homozygous or compound heterozygous[c]	2	0	4	2	4	12
Heterozygous	18	1	6	16	13	54
FUT2+ (*n* ID)[a]	11	0	6	9	18	44
Homozygous	1	0	1	3	1	6
Heterozygous	10	0	5	6	17	38
Tympanometry (counts by ear)						
A	0	0	9	26	50	85
Ad	0	0	1	3	6	10
As	2	0	5	9	15	31
B	31	4	11	7	18	71
C	0	0	3	1	0	4
Total	33	4	29	46	89	201
SHOEBOX audiometry (median dB per ear for 500–4000 Hz)						
n	12	0	5	11	30	58
Average	53.5	—	33.5	37	36.8	40
Median	48.8	—	32.5	35	37.5	37.5
Range	27.5 to beyond test limits[a]	—	30–37.5	25–75	15–50	15 to beyond test limits[d]

[a]The worse ear per genotype was counted for IDs with unilateral or asymmetric OM.
[b]Out of 66 IDs who carried *A2ML1* variants, 20 IDs also carried the *FUT2* variant.
[c]Homozygous or compound heterozygous for the *A2ML1* variants c.2478_2485dupGCTAAAT (p.Ser829Trpfs*) and c.4061 + 1G>C.
[d]For one ear with hearing threshold beyond the audiometer testing limits, a default value of 120 dB was assigned.
OM, otitis media.

which include individuals who no longer heal spontaneously with medical treatment and will require surgery. The prevalence rates for each OM type were higher in the Indigenous community than in the general Filipino population (Fig. 1) (Caro et al, 2014). Female gender (Fisher exact $p = 0.003$) and older age (Wilcoxon $p = 0.007$) were associated with healed OM. Females in this population are known to have better health-seeking behavior or greater participation in health activities (Cutiongco-de la Paz et al, 2019).

Among 127 individuals with detailed history, the most common extraotologic complaint was nasal discharge (72.1%), followed by productive cough (24.0%), nasal congestion (8.5%), diarrhea (8.5%), abdominal pain (4.7%), and skin itchiness (4.7%). Nasal discharge was associated with young age (Wilcoxon $p = 0.0001$), whereas skin problems (11.9%) were common in females (Fisher exact $p = 0.05$). History of cough or lung disease (e.g., tuberculosis and asthma) was observed in 15.9%, usually in females (Fisher

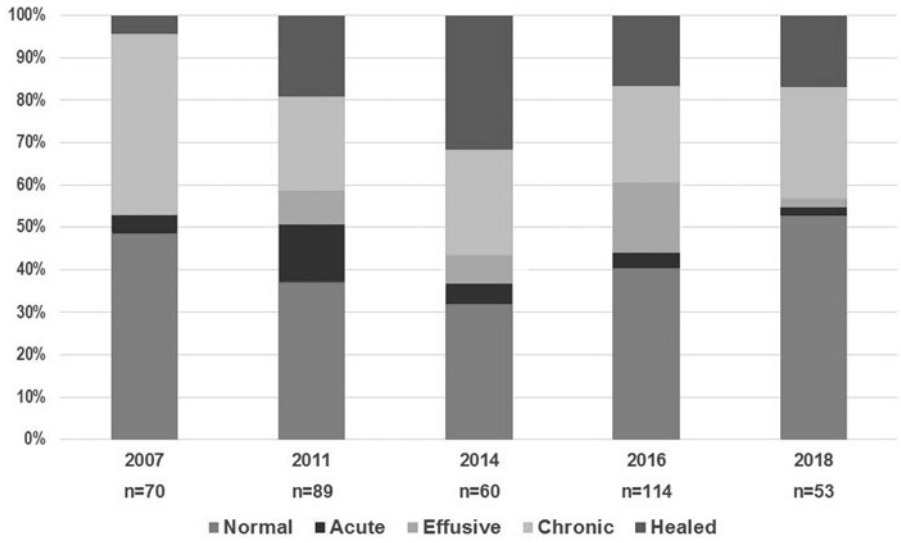

FIG. 1. Relative frequency of OM types by year. OM, otitis media.

exact $p = 0.047$) and those without OM (Fisher exact $p = 0.03$). None of these complaints was associated with genetic variants, consistent with previous assessment of nonsyndromic OM without additional clinical features.

Among those with audiologic results ($n = 109$), carriage of an *A2ML1* variant (Table 1) was associated with previous or current OM (Fisher exact odds ratio = 2.74; 95% CI: 1.51–5.03; $p = 0.0004$) but was not specific to any OM type (Table 1), consistent with previous findings that all OM types were observed in *A2ML1* variant carriers. In contrast, a lower proportion of genotyped individuals carry the *FUT2* variant, and 20 individuals carry both *A2ML1* and *FUT2* variants (Table 1). The overlap of *FUT2* and *A2ML1* variants resulted in no association between the *FUT2* variant and OM in these analyses.

HL due to genetic variants and chronic OM

Of 109 individuals with audiologic results, 58.7% were female and the average age was 16.7 years (Table 1). Of 218 ears, 41 (18.8%) had chronic OM, 4 (1.8%) had acute OM, 29 (13.3%) had OME, 48 (22.0%) had healed ME, and 96 (44.0%) had normal ears. In 33 (30.3%) participants, ear diagnoses were unilateral or asymmetric with various combinations of OM diagnoses.

Tympanometry was performed in 201 ears from 104 participants (Table 1). As expected, type B, which is usually due to eardrum perforation or ME fluid, was associated with presence of OM (Fisher exact $p = 0.00006$), occurrence of eardrum perforations (Fisher exact $p < 2.2 \times 10^{-16}$), and young age (Wilcoxon $p = 0.0006$). Conversely healed OM with an intact eardrum was negatively associated with a type B tympanogram (Fisher exact $p = 0.001$).

Bilateral audiometric results were available for 58 ears from 29 individuals (Table 1). *A2ML1* and *FUT2* variants were associated with increased hearing thresholds at 4000 Hz (Wilcoxon $p = 0.02$). Older age and chronic OM were also associated with higher thresholds at 4000 Hz (Wilcoxon $p = 0.02$), but only chronic OM was associated with worse median thresholds at 500–4000 Hz (Wilcoxon $p = 0.0008$; Fig. 1).

Validity of otoscopy and genotyping

For otoscopy versus tympanometry, normal ears were first compared against all OM types. Using B tympanometry as gold standard, detection of OM based on otoscopy alone had 75% sensitivity (true positive rate), 55% specificity (true negative rate), 47% PPV (diseased who test positive), and 80% NPV (nondiseased who test negative). If normal and healed ears were lumped together versus all other OM, validity was better overall: 65% sensitivity, 85% specificity, 70% PPV, and 81% NPV. These results indicate that otoscopy was good for community-based screening of ME function, particularly if healed ears were treated like normal. In addition, the likelihood of having ME pressure issues in healed ears was low.

When compared with median hearing thresholds >40 dB (moderate-to-profound HL), otoscopy had 56% sensitivity, 55% specificity, 36% PPV, and 73% NPV. If the cutoff was increased to ≥50 dB (Table 1), otoscopy had 88% sensitivity, 58% specificity, 25% PPV, and 97% NPV. Therefore, otoscopy was good at ruling out HL ≥50 dB, but poor at identifying who had HL.

For the validity of *A2ML1* or *FUT2* genotypes in predicting OM per ear, *A2ML1* genotype has 33% sensitivity, 40% specificity, 32% PPV, and 43% NPV, and *FUT2* genotype has 46% sensitivity, 55% specificity, 42% PPV, and 59% NPV. These results suggest that genotyping for *A2ML1* and *FUT2* variants is not good as a sole screening test for OM status. When comparing normal plus healed ears versus all other OM, the combination of otoscopy and any *A2ML1*+ or *FUT2*+ genotypes had the following results: for type B tympanometry—48% sensitivity, 85% specificity, 64% PPV, and 75% NPV; and for median hearing threshold ≥50 dB—75% sensitivity, 78% specificity, 35% PPV, 95% NPV. The latter estimates revealed that adding *A2ML1* or *FUT2* genotyping to otoscopy increased the ability to rule out HL ≥50 dB.

Discussion

Within this Indigenous Filipino population, *A2ML1* variants were strongly associated with nonsyndromic OM. *A2ML1* genotypes may be used to predict early onset, protracted progression, and longitudinal risk for OM (Santos-Cortez et al, 2016b), but cannot be used alone to predict OM diagnosis. In contrast, otoscopy performed quite well as a screening test to determine OM-related ME fluid or perforation and to rule out moderate-to-profound HL at ≥50 dB, and adding *A2ML1* or *FUT2* genotypes to otoscopy increased test performance for HL detection.

Prevalence rates of normal and healed ears (Fig. 1) increased with medical treatment, awareness of OM as a disease, and prevention strategies including better ear hygiene (Cutiongco-de la Paz et al, 2019). Families were counseled that OM risk given genotypes may be modified by multiple factors, for example, age, prevention strategies such as breastfeeding, vaccination, and early treatment, variability in disease presentation including recurrence or spontaneous resolution, or additional genetic risk factors. The common *FUT2* variant is also a risk factor for OM in this population, however, the effect of this variant is being concealed by rare *A2ML1* variants that have higher prevalence and stronger effects (Larson et al, 2019; Santos-Cortez et al, 2018; Santos-Cortez et al, 2015).

Eardrum perforation due to chronic OM was the strongest risk factor for both poor ME function and HL (Fig. 2; Table 1). Younger age was associated with type B tympanograms, whereas older age was a risk factor for HL. Tympanometry and SHOEBOX audiometry are useful to detect fluid behind an intact eardrum and HL, respectively. However, our community-based hearing screening methods have important limitations, such as the discontinuity of otologic care, lack of a soundproof booth, small sample size, other potential cause of HL, for example, noise, and the unavailability of bone conduction audiometry to determine air-bone gap levels and temporal bone imaging to detect ossicular chain defects or cholesteatoma.

Nevertheless, we demonstrated the necessity for prevention and early intervention for OM to prevent permanent HL. In the Indigenous Inuit population of Greenland, ~40% of teenagers and young adults with >25 dB thresholds had HL due to chronic OM, and another 18–35% of HL was due to OME or healed OM (Jensen et al, 2013). It is known that recurrent acute OM in childhood tends to result in

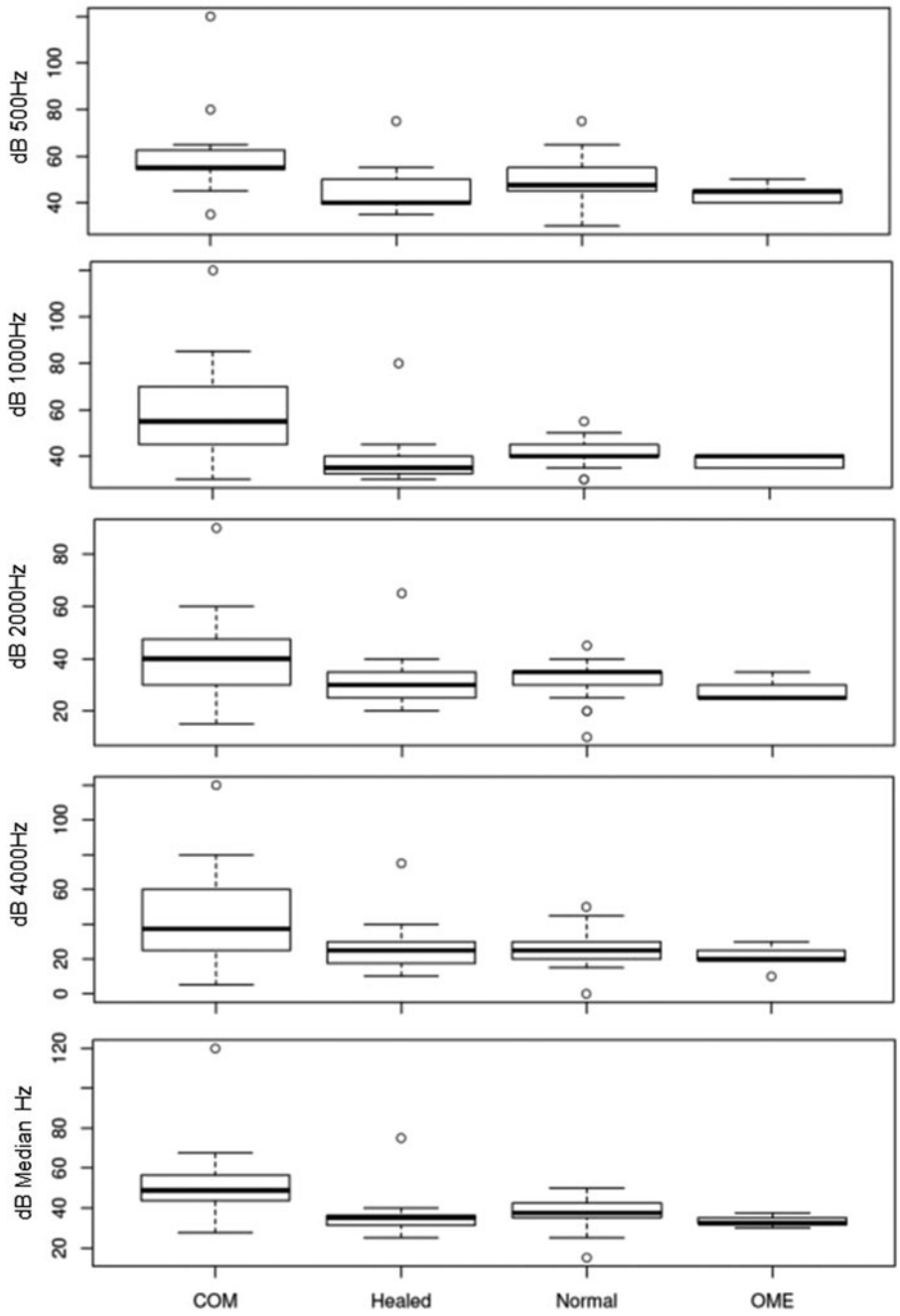

FIG. 2. Hearing thresholds in dB at 500–4000 Hz by OM type. *COM*, chronic otitis media; *OME*, otitis media with effusion.

high-frequency HL in adulthood (Krakau et al, 2017). In this report, *A2ML1* and *FUT2* genotypes were associated with high-frequency HL; however chronic OM was more strongly associated with HL, with chronically infected ears having median hearing thresholds ≥40 dB across frequencies and higher thresholds at the low frequencies 500–1000 Hz (Fig. 1).

Conclusion

The Indigenous Filipino population has greater HL risk due to *A2ML1*- and *FUT2*-related OM susceptibility. Multidisciplinary services including otology, audiology, genetic counseling, and primary and dental care must be improved to address gaps in OM and HL management (Cutiongco-de la Paz et al, 2019; Larson et al, 2019). Frequent audiologic screening using tympanometry and audiometry and proper otologic care are necessary to identify individuals at risk and prevent HL due to OM.

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Disclaimer

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Authors' Contributions

Conceptualization, funding acquisition, and supervision were carried out by M.R., C.C., and R.S.; data curation and project administration were done by R.S., T.Y., M.P., C.C., and M.R.; formal analysis was carried out by R.S. and K.O.; investigation, methodology, and resources were taken care by R.S., K.O., A.C., M.T., T.Y., M.S., M.P., T.C., E.C., G.A., E.L., A.C., C.C., and M.R.; writing original draft was done by R.S., K.O., and A.C. All authors read, critically appraised, and approved the article.

Author Disclosure Statement

The authors declare no conflict of interest.

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