Medical Hypotheses 114 (2018) 19–22

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Are human ATP-binding cassette transporter C11 and earwax associated with the incidence of cholesteatoma?

Hiroshi Nakagawa[a,b,*,1], Yu Toyoda[c,1], Tobias Albrecht[d], Megumi Tsukamoto[a], Mark Praetorius[d], Toshihisa Ishikawa[e], Kazusaku Kamiya[b], Takeshi Kusunoki[f], Katsuhisa Ikeda[b], Serkan Sertel[d,g,*]

[a] Department of Biological Chemistry, College of Bioscience and Biotechnology, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi 487-8501, Japan
[b] Department of Otorhinolaryngology, Juntendo University Faculty of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
[c] Department of Pharmacy, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[d] Department of Otorhinolaryngology, Head & Neck Surgery, University of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany
[e] NGO Personalized Medicine & Healthcare, Yokohama 226-0016, Japan
[f] Department of Otorhinolaryngology, Juntendo University of Medicine, Shizuoka Hospital, 1129 Nagaoka Izunokuni-shi, Shizuoka 410-2295, Japan
[g] HNO Praxis Prof. Sertel, Rottstraße 39, 67061 Ludwigshafen am Rhein, Germany

ARTICLE INFO

Keywords:
Cholesteatoma
ATP-binding cassette (ABC) transporter
ABCC11
Cerumen
Earwax

ABSTRACT

Cholesteatoma is an ear disease based on a locally destructive noncancerous conglomerate of epidermis and keratin debris. Abnormal growth of stratified keratinized squamous epithelium in the temporal bone causes destruction of the outer and middle ear, potentially leading to hearing impairment, facial palsy, vertigo, lateral sinus thrombosis, and intracranial complications. Although cholesteatoma is effectively treated by surgical resection (mastoidectomy), the lack of effective and nonsurgical therapies potentially results in fatal consequences, establishing the need for a comprehensive investigation of cholesteatoma pathogenesis. Although its etiology is still being debated, interestingly, we found that the trend associated with the 538G allele frequency of the *adenosine triphosphate-binding cassette transporter C11* (*ABCC11*) gene, the determinant of wet-type earwax, and ethnic groups was similar to that between the incidence of cholesteatoma and ethnic groups (countries). The incidences of cholesteatoma in Europe (Denmark, Finland, and Scotland) are higher than in East Asia (Japan), and the frequencies of the *ABCC11* 538G allele in African, American, and European (Finland and Scotland) populations are higher than those in East Asian populations (Japan). Additionally, a single-nucleotide polymorphism in the *ABCC11* gene (rs17822931, 538G > A; Gly180Arg) is closely related to earwax morphotypes. While earwax is often beneficial to ear health, it is sometimes harmful in cases where it causes hearing impairment. Based on independent findings of associations between *ABCC11* and the physiological environment of the auditory canal, we hypothesize a possible link between ABCC11, earwax, and the incidence of cholesteatoma.

Introduction

Cholesteatoma is an ear disease that can arise in any age group and gender. Although initially reported as a pearly tumor [1], it is histologically characterized as a noncancerous conglomerate of epidermis, keratin debris with cholesterin, and lipids [2]. Cholesteatoma can be classified into congenital and acquired types, with the congenital type defined as a cholesteatoma mass behind an intact eardrum in children. Although several theories have been proposed to explain the pathogenesis of congenital cholesteatoma [3–5], none of these have thus far been convincingly proven, supplemented, or supported by further research. Regarding the pathogenesis of the latter type of cholesteatoma, four theories have been histologically suggested and accepted to date: 1) invagination of the tympanic membrane (retraction-pocket cholesteatoma) [6,7], 2) basal-cell hyperplasia [8,9], 3) epithelial ingrowth through a perforation (migration theory), and 4) squamous metaplasia of middle-ear epithelium [10–12]. However, neither the molecular mechanisms nor the risk factor(s) underlying the pathogenesis of the acquired type of cholesteatoma are sufficiently understood.

What is clearly known about cholesteatoma pathogenesis is that abnormal growth of stratified keratinized squamous epithelium is observed in the temporal bone of cholesteatoma patients [13], in whom

* Corresponding authors at: Department of Applied Biological Chemistry, College of Bioscience and Biotechnology, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi 487-8501, Japan (H. Nakagawa). HNO Praxis Prof. Sertel, Rottstraße 39, 67061 Ludwigshafen am Rhein, Germany (S. Sertel).
E-mail addresses: hnakagaw@isc.chubu.ac.jp (H. Nakagawa), praxis@prof-sertel.de (S. Sertel).
[1] Authors contributed equally to the study.

https://doi.org/10.1016/j.mehy.2018.02.030
Received 11 October 2017; Accepted 23 February 2018
0306-9877/ © 2018 Elsevier Ltd. All rights reserved.

the adjacent auditory canal wall is often eroded and destroyed. These comprise destruction of the outer and middle ear, including the external auditory canal, ossicles, and mastoid, potentially leading to hearing impairment, facial palsy, vertigo, lateral sinus thrombosis, and possible intracranial complications, such as meningitis and epidural, subdural, and intracranial abscesses. The only effective therapy for cholesteatoma is surgical resection by mastoidectomy and, secondarily, reconstruction of the middle ear to improve hearing. Cholesteatoma has a high recurrence rate; therefore, a comprehensive investigation is needed for deeper understanding of the molecular mechanisms and the risk factor (s) underlying cholesteatoma pathogenesis.

Hypothesis

The risk of disease is affected by both genetic and environmental factors, except in the case of single gene disorders. Because there is no report describing cholesteatoma as a single gene disorder, here, we focused on a single-nucleotide polymorphism (SNP) in the *adenosine triphosphate (ATP)-binding cassette transporter C11* (*ABCC11*) gene and earwax as genetic and environmental factors, respectively. Recent studies clearly linked *ABCC11* to human earwax morphotypes (wet or dry type) [14] and demonstrated one end of the underlying mechanism by which ABCC11 determines the earwax morphotypes [15]. Based on these findings, we focused on the potential association between ABCC11, earwax, and the risk of cholesteatoma. To validate this speculation, we researched available scientific information linking the three, finding that the trend associated with the *ABCC11* 538G allele frequency and ethnic groups was similar to that between the incidence of cholesteatoma and ethnic groups (countries). Based on two aspects of earwax (beneficial and harmful) [16,17], as well as independent findings on the association between ABCC11 and the physiological environment of the auditory canal, we propose the possibility that ABCC11 is associated with the incidence of cholesteatoma.

Hypothesis evaluation and consequences

Beneficial and harmful aspects of earwax

In the outer third portion of the auditory canal, earwax is naturally generated as a mixture of epithelial cells and secretions from the apocrine glands in the auditory canal [18]. Under physiological conditions, earwax represents a protective barrier in the auditory canal, and old earwax is regularly transported from the inside toward the entrance of the ear canal and supported by the migration of cells formed in the center of the tympanic membrane to the walls of the ear canal [16]. However, excessive earwax is sometimes impacted in the auditory canal and associated with symptoms of earache, fullness in the ears, and hearing impairment [17].

Association between an ABCC11 allele and the physiological environment of the auditory canal

The human body expresses 48 ABC transporters, which are further divided into seven sub-families (ABCA–ABCG) based on sequence homology and protein organization [19], with some demonstrated as transporters of multiple endogenous and exogenous substrates across membranes in an ATP-dependent manner [20]. *ABCC11*, located on chromosome 16q12.1, encodes the 1382-amino acid-long human ABCC11 (known as multidrug-resistance-associated protein 8; MRP8), which reportedly transports cyclic nucleotides (cAMP and cGMP) and gender steroids (estradiol 17-beta-D-glucuronide and dehydroepiandrosterone 3-sulfate) in biochemical assays [21]. Although the physiological function of ABCC11 remains to be elucidated, previous studies reported that a nonsynonymous SNP in the *ABCC11* gene (rs17822931, 538G > A; Gly180Arg) is responsible for earwax morphotypes (wet or dry type) [14], and that ABCC11 is expressed in human apocrine glands [15,22,23], where the protein appears to be associated with the development of human apocrine glands [15,22,24,25]. Wet-type earwax and well-developed apocrine glands are observed in human auditory canals harboring an *ABCC11* 538G allele, whereas dry type earwax and poorly developed apocrine glands are observed in those harboring homozygous *ABCC11* 538A/A alleles [14,15,22]. However, it was also reported that earwax contains a complex mixture of volatile organic compounds, and that the concentrations of these compounds are higher in humans carrying homozygous 538G/G alleles than in those carrying homozygous 538A/A alleles [26]. Therefore, the SNP in the *ABCC11* gene (rs17822931, 538G > A; Gly180Arg) is suggested to be strongly associated with the physiological environment of the auditory canal.

Table 1
Summary of allelic frequencies of SNP 538G > A in human *ABCC11*.

No.	Population	Reference allele (538G) frequency	Alternative allele (538A) frequency
African		**0.988**	**0.012**
1	African Caribbean in Barbados	0.953	0.047
2	African ancestry in Southwest US	0.951	0.049
3	Esan in Nigeria	1.000	N.D.
4	Luhya in Webuye, Kenya	1.000	N.D.
5	Mandinka in The Gambia	0.996	0.004
6	Mende in Sierra Leone	1.000	N.D.
7	Yoruba in Ibadab, Nigeria	1.000	N.D.
American		**0.860**	**0.140**
8	Colombian in Medellin, Colombia	0.894	0.106
9	Mexican ancestry in Los Angeles, California	0.867	0.133
10	Peruvian in Lima, Peru	0.729	0.271
11	Puerto Rican in Puerto Rico	0.933	0.067
East Asian		**0.220**	**0.780**
12	Chinese Dai in Xishuangbanna, China	0.462	0.538
13	Han Chinese in Beijing, China	0.029	0.971
14	Southern Han Chinese, China	0.157	0.843
15	Japanese in Tokyo, Japan	0.120	0.880
16	Kinh in Ho Chi Minh City, Vietnam	0.364	0.636
European		**0.864**	**0.136**
17	Utah residents with Northern and Western European ancestry	0.869	0.131
18	Finnish in Finland	0.758	0.242
19	British in England and Scotland	0.890	0.110
20	Iberian populations in Spain	0.916	0.084
21	Toscani in Italy	0.883	0.117
South Asian		**0.518**	**0.482**
22	Bengali in Bangladesh	0.453	0.547
23	Gujarati Indian in Houston, TX	0.602	0.398
24	Indian Telugu in the UK	0.436	0.564
25	Punjabi in Lahore, Pakistan	0.630	0.370
26	Sri Lankan Tamil in the UK	0.466	0.534

Data acquired from 1000 Genomes Project phase 3 browser [28].
N.D., not detected.

Table 2
Summary of cholesteatoma incidence.

Region	Incidence/year (100,000)	Year reported	Author	Ref. No.
Denmark	6.8–15.5	1988, 2017	Tos, Britze et al.	[30,34]
Finland	9.2	1999	Kemppainen et al.	[32]
Japan	3.9	2015	Shibata et al.	[33]
Scotland	13.2	1989	Padgham et al.	[31]

Download English Version:

https://daneshyari.com/en/article/8515756

Download Persian Version:

https://daneshyari.com/article/8515756

Daneshyari.com