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# Wet Earwax Phenotype Determined by ABCC11 Polymorphism is a High-risk Factor for Acne

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## Abstract

**Background:** The type of earwax-wet or dry-is determined by a single nucleotide polymorphism (SNP)-538G>A (Gly180Arg)-in the ABCC gene (ABCC11), which encodes an ATP-binding cassette domain. Since axillary osmidrosis is closely related to earwax type, some dermatoses may be associated with earwax type.

**Objectives:** We analyzed the association between the prevalence of a series of dermatoses and earwax phenotype. Further, we investigated ABCC11 localization in the skin.

**Methods:** A total of 660 patients who visited Nopporo Dermatology Clinic in Hokkaido were enrolled in this study. The patients were interviewed to determine their earwax type-wet or dry-and a medical practitioner diagnosed dermatoses. The association between the prevalence of dermatoses and earwax type was analyzed statistically. ABCC11 localization in the skin was immunohistochemically evaluated using anti-ABCC11 antibody.

**Results:** Wet earwax type was more prevalent in patients with acne than in those without acne and the odds ratio was 5.36. On the other hand, dry earwax was more prevalent in patients with atopic dermatitis than in those without it, and the odds ratio was 1.86, which was non-significant. In the immunohistochemical staining, ABCC11 was found to be strongly expressed in the sebaceous glands of wet earwax type skin specimen.

**Conclusion:** Wet earwax phenotype is a high-risk factor for acne. Therefore, hyper-secretion of lipids from sebaceous glands elicited by ABCC11 may play an important role in the pathogenesis of acne.

**Keywords:** Earwax; ABCC11; ABC Transporter; Acne; Prevalence rate

## Introduction

The ATP-Binding Cassette (ABC) transporter super-family encodes a group of membrane proteins that are involved in energy-dependent transport of various substrates across the membrane. The ABCC11 (ABCC11) is a newly discovered member of the ABC transporter super-family; is also called Multi-drug Resistance Protein (MRP) 8 [1]. ABCC11 functions as an ATP-dependent efflux pump for conjugates such as steroid sulphates and bile acids [2]. A single nucleotide polymorphism (SNP)-538G>A (Gly180Arg)-in the ABCC gene (ABCC11) has been reported to determine earwax phenotype [3]. Earwax is of 2 types: wet and dry. Wet earwax is a natural secretory product of the ceruminous apocrine gland, while dry earwax develops because of the lack of ceruminous secretion. The genotypes G/G and G/A in the SNP (538G>A) are associated with wet earwax, whereas the genotype A/A is associated with dry earwax. Dry earwax is commonly found in East Asian populations (80-95%) but is rare in European and African populations (0-3%) [3]. Recently, it was reported that in Japan, dry earwax is found in 77.1% of the population [4]. A correlation between frequency of wet earwax and that of breast cancer has been reported [5]. Recent reports have also shown that axillary osmidrosis is closely related to wet earwax, which is determined by ABCC11 polymorphism [6]. These findings suggest that the study of earwax type would aid in identifying patients at risk for dermatoses. In the present study, we evaluated the frequency of wet earwax in patients with different types of dermatoses and found that acne is strongly associated with wet earwax.

## Patients and Methods

### Patients

A total of 660 patients (age, >18 years) who visited Nopporo Dermatology Clinic in Hokkaido (Japan) between March and April 2006 were included in this study. Atopic dermatitis was diagnosed on the basis of the criteria established by the Japanese Dermatological Association [7]. Other dermatoses were diagnosed by examination of medical history and visual observation of the skin lesions. The patients were grouped according to their disease (maximum of 3 diseases in 1 patient).

### Determination of earwax phenotype

There is a clear difference between the 2 types of earwax (wet and dry). Wet earwax is brownish and sticky, whereas the dry earwax lacks cerumen. In a previous report, earwax types were identified either by self-assessment by the patient or by examination by a medical practitioner [3]. In this study, the earwax type was determined by interviewing the patients. In order to avoid diagnostic bias, the earwax type of the patients was determined after diagnosis. Thirty-seven patients were excluded because they were unable to determine their earwax type. Thus, 623 patients with 759 diagnoses were finally studied.

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### Immunohistochemical analysis of ABCC11 expression

For immunohistochemical staining, paraffin-embedded skin sections were deparaffinized and rehydrated. After incubation in citrate buffer (10 mm, pH 6.0) with microwave treatment for 10 min, the sections were incubated with peroxidase-blocking solutions (K1390, DAKO Japan, Tokyo, Japan) for 10 min. After blocking, the skin sections were incubated with a 1:600 dilution of anti-ABCC11 antibody (HPA031980, SIGMA ALDRICH, MO, USA) overnight. These sections were washed twice in buffer and processed using the EnVision/HRP kit (K1390, DAKO Japan, Tokyo, Japan) according to manufacturer's instructions. Reaction products were visualized using diaminobenzidine. This clinical investigation was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Review Board of Shimane University Faculty of Medicine (Izumo, Japan; Approval No. 667).

### Statistical analysis and approval of the study

The relationship between skin disease and earwax type was determined by Fisher's exact test using Statistical Package for the Social Sciences (ver. 18.0).

The clinical investigation was conducted according to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Review Board of Shimane University Faculty of Medicine (Izumo, Japan; Approval No. 634).

## Results

### Wet earwax phenotype results in a high susceptibility of acne

Out of 660 patients, 37 were excluded from the analysis because they could not determine their earwax phenotype. The remaining 623 were divided into 2 groups according to their earwax type-wet or dry. The wet earwax group included 147 patients (66 men and 81 women) with 179 diagnoses, and the dry earwax group included 476 patients (204 men and 272 women) with 580 diagnoses. Wet earwax was found in 23.6% of the 623 patients. The mean ages of the patients in the wet and dry earwax groups were 48 years 6 months and 47 years 7 months, respectively. There was no significant difference in both age and sex between the groups.

We diagnosed 47 diseases, of which contact dermatitis/hand eczema was the most frequent. Further, 17 of the 47 were diagnosed in more than 6 patients and were analyzed to determine whether they were related to the earwax phenotype. The diseases and the number of patients with wet earwax are summarized in (Table 1). When the incidence of wet earwax according to each dermatosis was analyzed by Fisher's exact test, the incidence of wet earwax was found to be significantly higher in patients with acne and lower in those with atopic dermatitis as compared with the total patient population. No statistically significant differences in the incidence of wet earwax were found between patients with any other skin condition and the total patient population. The odds ratio for acne was 5.36 and it was statistically significant (Table 2A), whereas that for atopic dermatitis was 1.86 but it was not statistically significant (Table 2B).

### Sebaceous glands in the skin express ABCC11

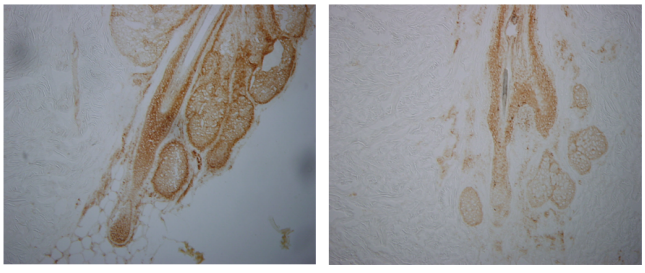
Because these observations led to the hypothesis that expression of ABCC11 in the skin results in susceptibility to acne, ABCC11 expression in the skin was investigated immunohistochemically using anti-ABCC11 antibodies. The results of ABCC11 staining in the skin are shown in (Figure 1). ABCC11 was found to be strongly expressed in the sebaceous glands of the wet skin type specimen (Figure 1A). The staining patterns were similar to those in The Human Protein Atlas (http://www.proteinatlas.org/ENSG00000121270/normal). Meanwhile, the expression of ABCC11 was weaker in the sebaceous glands of the dry skin type specimen than in the wet skin type specimen (Figure 1B).

| Dermatoses | Number | Wet type (%) | P value | *P<0.01 |
|---|---|---|---|---|
| Contact dermatitis and hand eczema | 129 | 31 (24.03) | 0.908 | |
| Asteatotic eczema | 104 | 19 (18.27) | 0.205 | |
| Tinea | 75 | 15 (20.0) | 0.472 | |
| Atopic dermatitis | 67 | 10 (14.93) | 0.093 | |
| Seborrhoeic dermatitis | 66 | 17 (25.8) | 0.648 | |
| Acne | 52 | 21 (40.4) | 0.006 | * |
| Urticaria | 47 | 11 (23.4) | 1 | |
| Viral wart | 37 | 6 (16.2) | 0.324 | |
| Herpes (zoster and simplex) | 30 | 10 (33.3) | 0.193 | |
| Skin tumour | 27 | 5 (18.5) | 0.647 | |
| Injury | 18 | 4 (22.2) | 1 | |
| Psoriasis vulgaris | 17 | 2 (11.8) | 0.385 | |
| Chelitis | 9 | 3 (33.3) | 0.477 | |
| Erythema multiforme | 9 | 3 (33.3) | 0.477 | |
| Nummular eczema | 8 | 3 (37.5) | 0.401 | |
| Alopecia | 7 | 3 (42.9) | 0.364 | |
| Prurigo | 7 | 2 (28.6) | 0.671 | |
| Others | 47 | 13 (27.7) | 0.487 | |
| Total diagnoses | 759 | 179 (23.6) | | |

**Table 1:** Summary of the frequency of wet earwax phenotype in various dermatoses (total 759 diagnoses in 623 patients).

| | Wet type | Dry type | Odds ratio | | CI | |
|---|---|---|---|---|---|---|
| (A) | | | | | | |
| Acne (n=52) | 21 | 31 | 5.36 | 2.9778 | - | 9.648 |
| Control (n=571) | 126 | 445 | | | | |
| (B) | | | | | | |
| Atopic dermatitis (n=67) | 10 | 57 | 1.86 | 0.9245 | - | 3.738 |
| Control (n=556) | 137 | 419 | | | | |

**Table 2:** Odds ratio analysis. (A) Odds ratio was determined between the patients with acne and those without acne (control). (2B) Odds ratio was determined between the patients with atopic dermatitis and those without atopic dermatitis (control).



A B

**Figure 1:** Expression of ABCC11 in the sebaceous glands. (a) Skin section of wet earwax type. ABCC11 is highly expressed in sebaceous gland. (b) Skin section of dry earwax type. Expression of ABCC11 is weaker than that of wet type.

## Discussion

The results of our study suggest that individuals with wet

earwax have a high risk of developing acne. This is supported by immunohistochemical data showing the strong expression of ABCC11 in the sebaceous glands of skin, since earwax type is determined by the ABCC11 genotype. The strong expression of ABCC11 in the sebaceous glands of a wet skin type specimen suggested that increased sebum excretion due to increased ABCC11 expression in the sebaceous glands of individuals with wet earwax induced acne, because increased sebum excretion causes the development of acne lesions [8]. Wet earwax is composed of different types of lipids, including cholesterol, which are secreted from the ceruminous apocrine gland, in which ABCC11 plays a pivotal role in lipid transport [9]. ABCC11 is similarly involved in lipid secretion from the sebaceous gland, as shown in our study. Thus, active ABCC11 function plays an important role in acne development. Patel and Nobel have shown that the composition of the skin surface lipids in patients with acne is different from that in patients with atopic dermatitis [10]. This suggests that acne is different from atopic dermatitis in terms of the composition of skin surface lipids, which is mediated by ABCC11. Dysfunction of ABCC11 also plays an important role in the development of atopic dermatitis.

Several studies have been conducted on ABC transporters in skin [11-13]. ABCA12 has been found to be responsible for harlequin ichthyosis [14,15]. Mutations in ABCA12 cause defective lipid transport in keratinocytes and impair skin barrier function. However, lipid secretion was normalized after corrective ABCA12 gene transfer into the keratinocytes of patients; thus, it can be said that ABC transporters in keratinocytes play an important role in lipid secretion.

Several surveys have been published on the prevalence of acne among ethnic groups [16-18]. Child et al. compared the annual percentage of adult acne among different ethnic groups, including blacks and whites and those of Asian, Oriental, and Arabic origin [16]. They found that fewer acne patients were of Asian, Oriental, and Arabic origins (8%) than blacks (51%) and whites (49%). Asian patients with acne comprised a smaller population than those with other diseases. The reason for this difference remains unclear. However, a previous report showed that almost all blacks and whites have wet earwax and 85-95% of East Asians have dry earwax [3]. Considering this finding and our data collectively, it is conceivable that the difference in the prevalence of acne among different ethnic groups is dependent on the incidence of wet earwax.

Since the occurrence of injury is not in any way influenced by earwax type, the frequency of injury among patients with wet earwax was expected to reflect the overall frequency of wet earwax in the population served by the clinic. This frequency was found to be 22%, which was, in fact, similar to the frequency of injury among all study patients. These values are more accurate than previously reported values [4]. The findings indicate that the frequency of wet earwax among the patients in this study may indicate the frequency of wet earwax in the general population in Japan.

This study has some limitations: the earwax type was determined by the patients themselves, and the patients were relatively few in number. In fact, 37 patients were excluded from the study because they were unable to determine their earwax phenotype. However, we believe that this study provides significant evidence of the association between wet earwax phenotype and the incidence of acne. An investigation carried out with a larger number of patients with dermatoses may reveal additional correlations between dermatoses and earwax phenotype. Our study found a low incidence of atopic dermatitis in individuals with wet earwax; however, the results of the odds ratio analysis did not reach a significant level, as shown in (Table 2).

In conclusion, our study showed that earwax type, determined by ABCC11 polymorphism, influences the risk of acne, which may be caused by unknown lipids secreted by sebaceous glands. To the best of our knowledge, this report is the first to show the relationship between earwax type and skin diseases. Determination of the type of earwax is extremely easy and provides useful information for assessing the clinical risk of acne. Moreover, the results indicate that inhibition of ABCC11 expression may serve as a new approach for acne therapy.

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