

wild-type *ABCC11* (538G) is related to drug resistance in breast cancer and high rates of mortality. In conclusion, the present study shows that Japanese women with wet earwax have a higher relative risk of developing breast cancer than those with dry earwax. Further examination of the *ABCC11* SNPs that determine these phenotypes may provide useful insights into the mechanisms by which breast cancer develops and progresses, including drug resistance and chemosensitivity.

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### References

- Gaudet MM, Milne RL, Cox A, Camp NJ, Goode EL, Humphreys MK, Dunning AM, Morrison J, Giles GG, Severi G, Baglietto L, English DR, Couch FJ, Olson JE, Wang X, Chang-Claude J, Flesch-Janys D, Abbas S, Salazar R, Mannervaa A, Kataja V, Kosma VM, Lindblom A, Margolin S, Heikkinen T, Kämpjärvi K, Aaltonen K, Nevanlinna H, Bogdanova N, Coinac I, Schürmann P, Dörk T, Bartram CR, Schmutzler RK, Tchatchou S, Burwinkel B, Brauch H, Torres D, Hamann U, Justenhoven C, Ribas G, Arias JI, Benitez J, Bojesen SE, Nordestgaard BG, Flyger HL, Peto J, Fletcher O, Johnson N, Dos Santos Silva I, Fasching PA, Beckmann MW, Strick R, Ekici AB, Broeks A, Schmidt MK, van Leeuwen FE, Van't Veer LJ, Southey MC, Hopper JL, Apicella C, Haiman CA, Henderson BE, Le Marchand L, Kolonel LN, Kristensen V, Grenaker Alnaes G, Hunter DJ, Kraft P, Cox DG, Hankinson SE, Seynaeve C, Vreeswijk MP, Tollenaar RA, Devilee P, Chanock S, Lissowska J, Brinton L, Peplonska B, Czene K, Hall P, Li Y, Liu J, Balasubramanian S, Rafii S, Reed MW, Pooley KA, Conroy D, Baynes C, Kang D, Yoo KY, Noh DY, Ahn SH, Shen CY, Wang HC, Yu JC, Wu PE, Anton-Culver H, Ziogas A, Egan K, Newcomb P, Titus-Ernstoff L, Trentham Dietz A, Sigurdson AJ, Alexander BH, Bhatti P, Allen-Brady K, Cannon-Albright LA, and Wong J; Australian Ovarian Cancer Study Group and Chenevix-Trench G, Spurdle AB, Beesley J, Pharoah PD, Easton DF and Garcia-Closas M: Breast Cancer Association Consortium: Five polymorphisms and breast cancer risk: results from the Breast Cancer Association Consortium. *Cancer Epidemiol Biomarkers Prev* 18: 1610-1616, 2009.
- Petrakis NL: Cerumen genetics and human breast cancer. *Science* 173: 347-349, 1971.
- Ing R, Petrakis L and Ho HC: Evidence against association between wet cerumen and breast cancer. *Lancet* 1: 41, 1973.
- Yoshiura K, Kinoshita A, Ishida T, Ninokata A, Ishikawa T, Kaname T, Bannai M, Tokunaga K, Sonoda S, Komaki R, Ihara M, Saenko VA, Alipov GK, Sekine I, Komatsu K, Takahashi H, Nakashima M, Sosonkina N, Mapendano CK, Ghadami M, Nomura M, Liang DS, Miwa N, Kim DK, Garidkhuu A, Natsume N, Ohta T, Tomita H, Kaneko A, Kikuchi M, Russomando G, Hirayama K, Ishibashi M, Takahashi A, Saitou N, Murray JC, Saito S, Nakamura Y and Niikawa N: A SNP in the *ABCC11* gene is the determinant of human earwax type. *Nat Genet* 38: 324-330, 2006.
- Toyoda Y, Sakurai A, Mitani Y, Nakashima M, Yoshiura K, Nakagawa H, Sakai Y, Ota I, Lezhava A, Hayashizaki Y, Niikawa N and Ishikawa T: Earwax, osmidrosis, and breast cancer: why does one SNP (538G>A) in the human ABC transporter *ABCC11* gene determine earwax type? *FASEB J* 23: 2001-2013, 2009.
- Yabuuchi H, Shimizu H, Takayanagi S and Ishikawa T: Multiple splicing variants of two new human ATP-binding cassette transporters, *ABCC11* and *ABCC12*. *Biochem Biophys Res Commun* 288: 933-939, 2001.
- Toyoda Y, Hagiya Y, Adachi T, Hoshijima K, Kuo MT and Ishikawa T: MRP class of human ABC transporters: Historical background and new research directions. *Xenobiotica* 38: 833-862, 2008.
- Matsunaga E: The dimorphism in human normal cerumen. *Ann Hum Genet* 25: 273-286, 1962.
- Nakano M, Miwa N, Hirano A, Yoshiura K and Niikawa N: A strong association of axillary osmidrosis with the wet earwax type determined by genotyping of the *ABCC11* gene. *BMC Genet* 10: 42, 2009.
- Inone Y, Mosi T, Toyoda Y, Sakurai A, Ishikawa T, Mitani Y, Hayashizaki Y, Yoshimura Y, Kurahashi H and Sakai Y: Correlation of axillary osmidrosis to a SNP in the *ABCC11* gene determined by the Smart Amplification Process (SmartAmp) method. *J Plast Reconstr Aesthet Surg* 63: 1369-1374, 2010.
- Miura K, Yoshiura K, Miura S, Shimada T, Yamasaki K, Yoshida A, Nakayama D, Shibata Y, Niikawa N and Masuzaki H: A strong association between human earwax-type and apocrine colostrum secretion from the mammary gland. *Hum Genet* 121: 631-633, 2007.
- Bera TK, Lee S, Salvatore G, Lee B and Pastan I: MRP8, a new member of ABC transporter superfamily, identified by EST database mining and gene prediction program, is highly expressed in breast cancer. *Mol Medicine* 7: 509-516, 2001.
- Bieche I, Girault I, Urbain E, Tozlu S and Lidereau R: Relationship between intratumoral expression of genes coding for xenobiotic-metabolizing enzymes and benefit from adjuvant tamoxifen in estrogen receptor alpha-positive postmenopausal breast carcinoma. *Breast Cancer Res* 6: R252-R253, 2004.
- Mitani Y, Lezhava A, Kawai Y, Kikuchi T, Oguchi-Katayama A, Kogo Y, Itoh M, Miyagi T, Takakura H, Hoshi K, Kato C, Arakawa T, Shibata K, Fukui K, Masui R, Kuramitsu S, Kiyotani K, Chalk A, Tsunekawa K, Murakami M, Kamataki T, Oka T, Shimada H, Cizdziel PE and Hayashizaki Y: Rapid SNP diagnostics using asymmetric isothermal amplification and a new mismatch-suppression technology. *Nat Methods* 4: 257-262, 2007.
- Aw W, Ota I, Toyoda Y, Lezhava A, Sakai Y, Gomi T, Hayashizaki Y and Ishikawa T: Pharmacogenomics of human ABC transporters: detection of clinically important SNPs by SmartAmp2 method. *Curr Pharm Biotech* 12: in press, 2011.
- Martin A, Saathoff M, Kuhn F, Max H, Terstegen L and Natsch A: A functional *ABCC11* allele is essential in the biochemical formation of human axillary odor. *J Invest Dermatol* 130: 529-540, 2009.

- 17 Chen ZS, Guo Y, Belinsky MG, Kotova E and Kruh GD: Transport of bile acids, sulfated steroids, estradiol 17-beta-D-glucuronide, and leukotriene C4 by human multidrug resistance protein 8 (ABCC11). *Mol Pharmacol* 67: 545-557, 2005.
- 18 Bortfeld M, Rius M, König J, Herold-Mende C, Nies AT and Keppler D: Human multidrug resistance protein 8 (MRP8/ABCC11), an apical efflux pump for steroid sulfates, is an axonal protein of the CNS and peripheral nervous system. *Neuroscience* 137: 1247-1257, 2006.
- 19 Honorat M, Mesnier A, Vendrell J, Guitton J, Bieche I, Lidereau R, Kruh GD, Dumontet C, Cohen P and Payen L: ABCC11 expression is regulated by estrogen in MCF7 cells, correlated with estrogen receptor alpha expression in postmenopausal breast tumors and overexpressed in tamoxifen-resistant breast cancer cells. *Endocr Relat Cancer* 15: 125-138, 2008.
- 20 Oguri T, Bessho Y, Achiwa H, Ozasa H, Maeno K, Maeda H, Sato S and Ueda R: MRP8/ABCC11 directly confers resistance to 5-fluorouracil. *Mol Cancer Ther* 6: 122-127, 2007.
- 21 Guo Y, Kotova E, Chen ZS, Lee K, Hopper-Borge E, Belinsky MG and Kruh GD: MRP8, ATP-binding cassette C11 (ABCC11), is a cyclic nucleotide efflux pump and a resistance factor for fluoropyrimidines 2',3'-dideoxycytidine and 9'-(2'-phosphonylmethoxyethyl)adenine. *J Biol Chem* 278: 29509-29514, 2003.
- 22 Kruh GD, Guo Y, Hopper-Borge E, Belinsky MG and Chen ZS: ABCC10, ABCC11, and ABCC12. *Pflugers Arch* 453: 675-684, 2007.

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