Osteoporosis International (2023) 34:2133–2135
https://doi.org/10.1007/s00198-023-06909-1

LETTER TO THE EDITOR

ALDH2 polymorphism rs671 and alcohol consumption: possible explanatory factors for race/ethnic differences in bone density

Mikiko Tokiya[1] · Takaomi Kobayashi[2,3] · Mizuho A. Kido[4] · Akiko Matsumoto[1]

Received: 19 July 2023 / Accepted: 31 August 2023 / Published online: 11 September 2023

Dear Editor,

We read the recently published article by Morin et al. with interest [1]. Fracture prevention in the elderly is an important concern for Japan, the world's oldest society. The authors analyzed the effect of race on bone mineral density (BMD) in Canadians. The linear regression model estimated that Black and South or Southeast Asian presented higher BMD values than White participants (model 4 in Table 4 [1]). The effect of East Asian ethnicity was less documented, yet this was the only race with inconsistent partial regression coefficients (β) across the four statistical models. Despite the positive β estimated for model 4, negative β was estimated for models 1 and 2 (β = −0.020 to −0.031 and −0.028 to −0.039 for femoral neck BMD [FNBMD] and total hip BMD [THBMD], respectively, compared to White participants).

We expected such association, which can be justified by rs671, a genetic polymorphism of aldehyde dehydrogenase 2 (ALDH2) unique to East Asians; approximately half the Japanese and southern Chinese population carry this variant [2, 3]. ALDH2's enzymatic activity is < 20% in heterozygous and 0% in homozygous carriers [4–7]. rs671 presents extremely strong and diverse phenotypes and is useful genetic information for personalized medicine [8–12].

Epidemiological studies have associated rs671 with an increased osteoporosis and hip fractures risk [13, 14], with supporting findings being reported in animal models. In *Aldh2* knockout mice bone metabolism in response to ethanol or mechanical stress differ from the wild-type mice [15–18]. Administration of an ALDH inhibitor also provoked bone loss in rats by inducing osteoblast apoptosis via G1 arrest, with a high degree of ALDH2 dependence in osteoblasts being a possible involved mechanism [19].

In the linear regression model 3 for BMD estimation in the report by Morin et al. [1], the effect of East Asian ethnicity disappeared (β = 0.019 [95% CI, −0.003 to 0.041] and 0.012 [−0.006 to 0.031] for FNBMD and THBMD, respectively). The β was estimated slightly more positively for model 4 with additional adjustment for grip strength and physical performance score (β = 0.022 [95% CI, 0.000 to 0.045] and 0.016 [−0.002 to 0.035] for FNBMD and THBMD, respectively). Among the additional factors, body mass index and grip strength have been negatively associated with the rs671 variant [20–26]. Therefore, the negative association between BMD and East Asian ethnicity could be obscured by adjustment for such rs671-related factors.

Ethanol loading decreases bone mass [27, 28] via mechanisms such as inhibition of osteoblast differentiation and calcification [28–31]; tobacco smoking is another risk factor [32]. In the study by Morin et al. [1], current smoking and alcohol intake (> 3 servings/day) were more prevalent in White participants than in other groups (Table S1), which may explain the low BMD in White participants. East Asians consume less alcohol [6, 33, 34] due to discomfort symptoms arising after its ingestion [35]. If alcohol consumption had been included in the models, BMD might have been estimated even lower for East Asians.

✉ Mikiko Tokiya
sx4932@cc.saga-u.ac.jp

Takaomi Kobayashi
takaomi_920@yahoo.co.jp

Mizuho A. Kido
kido@cc.saga-u.ac.jp

Akiko Matsumoto
matsumoa@cc.saga-u.ac.jp

1 Department of Social and Environmental Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

2 Department of Preventive Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

3 Department of Orthopaedic Surgery, Faculty of Medicine, Saga University, Saga 849-8501, Japan

4 Department of Anatomy and Physiology, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-023-06909-1.

Acknowledgements We would like to thank Miyuki Fuchigami for providing administrative support.

Funding This study was supported by a research grant 21K19652 from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Declarations

Conflicts of interest None.

References

1. Morin SN, Berger C, Papaioannou A, Cheung AM, Rahme E, Leslie WD, Goltzman D (2022) Race/ethnic differences in the prevalence of osteoporosis, falls and fractures: a cross-sectional analysis of the Canadian Longitudinal Study on Aging. Osteoporos Int 33:2637–2648. https://doi.org/10.1007/s00198-022-06539-z
2. Li H, Borinskaya S, Yoshimura K et al (2009) Refined geographic distribution of the oriental ALDH2*504Lys (nee 487Lys) variant. Ann Hum Genet 73:335–345. https://doi.org/10.1111/j.1469-1809.2009.00517.x
3. Goedde HW, Agarwal DP, Fritze G et al (1992) Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet 88:344–346. https://doi.org/10.1007/BF00197271
4. Kitagawa K, Kawamoto T, Kunugita N, Tsukiyama T, Okamoto K, Yoshida A, Nakayama K, Nakayama K (2000) Aldehyde dehydrogenase (ALDH) 2 associates with oxidation of methoxyacetaldehyde; in vitro analysis with liver subcellular fraction derived from human and Aldh2 gene targeting mouse. FEBS Lett 476:306–311. https://doi.org/10.1016/s0014-5793(00)01710-5
5. Lai CL, Yao CT, Chau GY, Yang LF, Kuo TY, Chiang CP, Yin SJ (2014) Dominance of the inactive Asian variant over activity and protein contents of mitochondrial aldehyde dehydrogenase 2 in human liver. Alcohol Clin Exp Res 38:44–50. https://doi.org/10.1111/acer.12215
6. Peng GS, Chen YC, Tsao TP, Wang MF, Yin SJ (2007) Pharmacokinetic and pharmacodynamic basis for partial protection against alcoholism in Asians, heterozygous for the variant ALDH2*2 gene allele. Pharmacogenet Genomics 17:845–855. https://doi.org/10.1097/FPC.0b013e3282609e67
7. Wang RS, Nakajima T, Kawamoto T, Honma T (2002) Effects of aldehyde dehydrogenase-2 genetic polymorphisms on metabolism of structurally different aldehydes in human liver. Drug Metab Dispos 30:69–73. https://doi.org/10.1124/dmd.30.1.69
8. Matsumoto A (2016) Fundamental properties of Aldehyde Dehydrogenase 2 (ALDH2) and the importance of the ALDH2 polymorphism. Nihon Eiseigaku Zasshi 71:55–68. https://doi.org/10.1265/jjh.71.55
9. Matsumoto A (2018) Importance of an aldehyde dehydrogenase 2 polymorphism in preventive medicine. Nihon Eiseigaku Zasshi 73:9–20. https://doi.org/10.1265/jjh.73.9
10. Matsumoto A (2019) The bidirectional effect of defective ALDH2 polymorphism and disease prevention. Adv Exp Med Biol 1193:69–87. https://doi.org/10.1007/978-981-13-6260-6_4
11. Matsumoto A, Hara M, Ashenagar MS, Tokiya M, Sawada T, Iwasaka C, Furukawa T, Kitagawa K, Miyake Y, Hirota Y (2022) Variant Allele of ALDH2, rs671, Associates with attenuated post-vaccination response in Anti-SARS-CoV-2 spike protein IgG: a prospective study in the Japanese general population. Vaccines (Basel) 10. https://doi.org/10.3390/vaccines10071035
12. Matsumoto A, Nakashima C, Kimura S, Sueoka E, Aragane N (2021) ALDH2 polymorphism rs671 is a predictor of PD-1/PD-L1 inhibitor efficacy against thoracic malignancies. BMC Cancer 21:584. https://doi.org/10.1186/s12885-021-08329-y
13. Yamaguchi J, Hasegawa Y, Kawasaki M, Masui T, Kanoh T, Ishiguro N, Hamajima N (2006) ALDH2 polymorphisms and bone mineral density in an elderly Japanese population. Osteoporos Int 17:908–913. https://doi.org/10.1007/s00198-006-0077-2
14. Takeshima K, Nishiwaki Y, Suda Y et al (2017) A missense single nucleotide polymorphism in the ALDH2 gene, rs671, is associated with hip fracture. Sci Rep 7:428. https://doi.org/10.1038/s41598-017-00503-2
15. Tajima T, Menuki K, Okuma KF, Tsukamoto M, Fukuda H, Okada Y, Kosugi K, Yamanaka Y, Uchida S, Sakai A (2018) Cortical bone loss due to skeletal unloading in aldehyde dehydrogenase 2 gene knockout mice is associated with decreased PTH receptor expression in osteocytes. Bone 110:254–266. https://doi.org/10.1016/j.bone.2018.02.020
16. Okuma KF, Menuki K, Tsukamoto M et al (2017) Disruption of the aldehyde dehydrogenase 2 Gene results in no increase in trabecular bone mass due to skeletal loading in association with impaired cell cycle regulation Through p21 expression in the bone marrow cells of mice. Calcif Tissue Int 101:328–340. https://doi.org/10.1007/s00223-017-0285-0
17. Tsuchiya T, Sakai A, Menuki K et al (2013) Disruption of aldehyde dehydrogenase 2 gene results in altered cortical bone structure and increased cortical bone mineral density in the femoral diaphysis of mice. Bone 53:358–368. https://doi.org/10.1016/j.bone.2012.12.049
18. Shimizu Y, Sakai A, Menuki K, Mori T, Isse T, Oyama T, Kawamoto T, Nakamura T (2011) Reduced bone formation in alcohol-induced osteopenia is associated with elevated p21 expression in bone marrow cells in aldehyde dehydrogenase 2-disrupted mice. Bone 48:1075–1086. https://doi.org/10.1016/j.bone.2011.01.008
19. Mittal M, Khan K, Pal S et al (2014) The thiocarbamate disulphide drug, disulfiram induces osteopenia in rats by inhibition of osteoblast function due to suppression of acetaldehyde dehydrogenase activity. Toxicol Sci 139:257–270. https://doi.org/10.1093/toxsci/kfu020
20. Kasai A, Jee E, Tamura Y, Kouzaki K, Kotani T, Nakazato K (2022) Aldehyde dehydrogenase 2 deficiency promotes skeletal muscle atrophy in aged mice. Am J Physiol Regul Integr Comp Physiol 322:R511-r525. https://doi.org/10.1152/ajpregu.00304.2021
21. Kato N, Takeuchi F, Tabara Y et al (2011) Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. Nat Genet 43:531–538. https://doi.org/10.1038/ng.834
22. Kikuchi N, Tajima T, Tamura Y, Yamanaka Y, Menuki K, Okamoto T, Sakamaki-Sunaga M, Sakai A, Hiranuma K, Nakazato K (2022) The ALDH2 rs671 polymorphism is associated with athletic status and muscle strength in a Japanese population. Biol Sport 39:429–434. https://doi.org/10.5114/biolsport.2022.106151
23. Wang T, Ma X, Peng D et al (2016) Effects of obesity related genetic variations on visceral and subcutaneous fat distribution in a Chinese population. Sci Rep 6:20691. https://doi.org/10.1038/srep20691
24. De Almeida KY, Saito M, Homma H, Mochizuki Y, Saito A, Deguchi M, Kozuma A, Okamoto T, Nakazato K, Kikuchi N (2022) ALDH2 gene polymorphism is associated with fitness in the elderly Japanese population. J Physiol Anthropol 41:38. https://doi.org/10.1186/s40101-022-00312-1
25. Saito A, Saito M, Almeida KY, Homma H, Deguchi M, Kozuma A, Kobatake N, Okamoto T, Nakazato K, Kikuchi N (2022) The association between the ALDH2 rs671 polymorphism and athletic performance in Japanese power and strength athletes. Genes (Basel) 13. https://doi.org/10.3390/genes13101735
26. Zhang Q, Zheng J, Qiu J, Wu X, Xu Y, Shen W, Sun M (2017) ALDH2 restores exhaustive exercise-induced mitochondrial

dysfunction in skeletal muscle. Biochem Biophys Res Commun 485:753–760. https://doi.org/10.1016/j.bbrc.2017.02.124
27. Mittal M, Bhagwati S, Siddiqi MI, Chattopadhyay N (2020) A critical assessment of the potential of pharmacological modulation of aldehyde dehydrogenases to treat the diseases of bone loss. Eur J Pharmacol 886:173541. https://doi.org/10.1016/j.ejphar.2020.173541
28. Maurel DB, Boisseau N, Benhamou CL, Jaffre C (2012) Alcohol and bone: review of dose effects and mechanisms. Osteoporos Int 23:1–16. https://doi.org/10.1007/s00198-011-1787-7
29. Rapuri PB, Gallagher JC, Balhorn KE, Ryschon KL (2000) Alcohol intake and bone metabolism in elderly women. Am J Clin Nutr 72:1206–1213. https://doi.org/10.1093/ajcn/72.5.1206
30. Dai J, Lin D, Zhang J, Habib P, Smith P, Murtha J, Fu Z, Yao Z, Qi Y, Keller ET (2000) Chronic alcohol ingestion induces osteoclastogenesis and bone loss through IL-6 in mice. J Clin Invest 106:887–895. https://doi.org/10.1172/jci10483
31. Torricelli P, Fini M, Giavaresi G, Borsari V, Rimondini L, Rimondini R, Carrassi A, Giardino R (2007) Intermittent exposure to ethanol vapor affects osteoblast behaviour more severely than estrogen deficiency does in vitro study on rat osteoblasts. Toxicology 237:168–176. https://doi.org/10.1016/j.tox.2007.05.010
32. Ward KD, Klesges RC (2001) A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcif Tissue Int 68:259–270. https://doi.org/10.1007/BF02390832
33. Hayashida H, Matsumoto A, Nanri H, Nishida Y, Takagi Y, Hara M (2023) ALDH2 rs671 variant allele is associated with higher energy intake in middle-aged and elderly Japanese who routinely consume alcohol. Environ Health Prev Med 28:29. https://doi.org/10.1265/ehpm.22-00276
34. Takeuchi F, Isono M, Nabika T et al (2011) Confirmation of ALDH2 as a Major locus of drinking behavior and of its variants regulating multiple metabolic phenotypes in a Japanese population. Circ J 75:911–918. https://doi.org/10.1253/circj.cj-10-0774
35. Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A (2009) The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. PLoS Med 6:e50. https://doi.org/10.1371/journal.pmed.1000050