Cinacalcet HCl therapy in East Asian patients and rs1042636 carriers

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To the Editor

In the July 2017 issue of the *Clinical Journal of the American Society of Nephrology*, Moe et al. [1] reported that the association of the calcium-sensing receptor (CaSR) gene single-nucleotide polymorphism (SNP) rs1042636 with "... baseline changes of PTH in the European ancestry (EA) population ... meet the threshold of $P < 0.01$ " in the EVOLVE trial study population, with the glycine allele being associated with lower PTH levels as compared with the arginine allele. It is important to note that allele frequencies of this SNP are reversed between East Asians and Blacks/Whites, i.e., 5–10% of Blacks and Whites carry the glycine allele, while 5–10% of East Asians carry the arginine allele [2]. Cell culture data back this up: in transfected HEK cells, Vezzoli et al. [3] showed that rs1042636 causes indeed a gain-of-function in the CaSR molecule, the allele dose of one glycine allele equalling about 30 mg once daily of cinacalcet. East Asian patients need lower cinacalcet HCl doses than Whites or Blacks. In their elaborate study of 2015 [4] with Japanese patients, Koda et al. had to exclude patients from analysis, because they did not tolerate the minimum dose of 12.5 mg and developed hypocalcemia, while 30 mg is the smallest dose available in most countries for Black and/or White patients.

In addition to being more sensitive to calcium ions, CaSR molecules of East Asian rs1042636 glycine allele carriers are also more sensitive to cinacalcet HCl as compared to East Asian rs1042636 arginine allele carriers [5]. This again corresponds with our patient who was referred to in the recent Moe paper and who was a Chinese rs1042636 glycine allele carrier: he showed a more dramatic PTH lowering response to cinacalcet as compared to Black and White rs1042636 arginine allele carriers [6].

How can we use these findings for clinical routine? There are two conclusions to be drawn:

1. Rs1042636 is in fact a surrogate marker for long-term cinacalcet therapy; in other words, it may be used for Mendelian randomization to study the effects of such a therapy in any condition, where CaSR activation might play a role, such as ADPKD [7].
2. In East Asian dialysis patient populations testing for rs1032636 (i.e., identifying the 5–10% arginine allele carriers) might help to titrate the correct cinacalcet dose faster and avoid side effects of hypocalcemia.

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