Calcium-Sensing Receptor Genotype and Response to Cinacalcet in Patients Undergoing Hemodialysis

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Abstract

Background and objectives We tested the hypothesis that single nucleotide polymorphisms (SNPs) in the calcium-sensing receptor (*CASR*) alter the response to the calcimimetic cinacalcet.

Design, setting, participants, & measurements We analyzed DNA samples in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial, a randomized trial comparing cinacalcet to placebo on a background of usual care. Of the 3883 patients randomized, 1919 (49%) consented to DNA collection, and samples from 1852 participants were genotyped for 18 *CASR* polymorphisms. The European ancestry (EA; $n=1067$) and African ancestry (AfAn; $n=405$) groups were assessed separately. SNPs in *CASR* were tested for their association with biochemical measures of mineral metabolism at baseline, percent change from baseline to 20 weeks, and risk of clinical fracture as dependent variables.

Results There were modest associations of *CASR* SNPs with increased baseline serum parathyroid hormone and bone alkaline phosphatase primarily with the minor allele in the EA group (all $P\leq0.03$), but not in the AfAn sample. In contrast, there was a modest association of decreased baseline serum calcium and FGF23 with *CASR* SNPs ($P=0.04$) primarily with the minor allele in the AfAn but not in the EA sample. The minor allele of two SNPs was associated with decreased percent reduction in parathyroid hormone from baseline to 20 weeks in the EA population ($P<0.04$) and this was not altered with cinacalcet. In both EA and AfAn, the same SNP (rs9740) was associated with decreased calcium with cinacalcet treatment (EA and AfAn $P\leq0.03$). Three SNPs in high linkage disequilibrium were associated with a higher risk of clinical fracture that was attenuated by cinacalcet treatment in the EA sample ($P<0.04$).

Conclusions These modest associations, if validated, may provide explanations for differences in CKD-mineral bone disorder observed in EA and AfAn populations, and for differential biochemical responses to calcimimetics.

human genetics | calcium sensing receptor | fracture | FGF23 | single nucleotide polymorphisms | Alkaline Phosphatase | Alleles | calcium | Chronic Kidney Disease-Mineral and Bone Disorder | Cinacalcet Hydrochloride | DNA | Genotype | Humans | Linkage Disequilibrium | Minerals | parathyroid hormone | Polymorphism, Single Nucleotide | Receptors, Calcium-Sensing | renal dialysis

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