

LETTER TO THE EDITORS

Dear Editors:

We read with great interest the article by Bachmann and coworkers on the gender-dependent association of the *GNAS1* T393C polymorphism with early aseptic loosening after total hip arthroplasty (THA).¹ The authors reported the association between single nucleotide polymorphism (SNP) *GNAS1* T393C and increased risk of premature aseptic loosening of THA in men. They concluded that presence this particular genotype in male patients represents an independent factor for time to aseptic loosening. We would like to add some comments regarding the methodology and interpretation of the results from this study.

- (1) In our experience and also according to the others,^{2,3} aseptic loosening in THA can be caused by heterogeneous factors and especially the premature failure should be analyzed with maximum attention. Here, median time to failure was 42 months (1–120 months), therefore particularly in the patients with shorter time to failure an alternative explanation for failure should be sought. In this line surgical inexperience, low-grade sepsis, and inconvenient implant seem to be more plausible cause of the failure than the role for IL-6 pathway influence on osteoclasts as suggested by the authors.
- (2) The study group consisted of 57 Caucasian patients with failed both the cups and stems in eleven of them, failed stems in 22 and cups in 24 of them, respectively. Such mismatch precludes obtaining valid conclusions on the association between genetic predisposition and outcome. Importantly, in addition to the above-mentioned criticism, there is also concern about the different mechanisms of failure at the site of cups and stems. Also differences in the cemented and cementless implants/interfaces or polyethylene origin/ manufacturing could play a role in the mechanism of aseptic loosening.⁴ In addition, several studies reported increased risk to premature failure in relation to the particular design of the prosthesis.⁵ As a result, one cannot make significant conclusions without adjusting for other risk factors potentially playing a role in THA failure.
- (3) Despite the extensive statistics used in this study we doubt that the approach to the data analysis is adequate. The study population comprised only patients operated for aseptic loosening within

first 10 years after THA. However, survivorship analysis related to the *GNAS1* genotypes would benefit from the usage of a systematic THA cohort which could better control for other relevant factors and competitive risks. Alternatively, appropriate control group comprising patients with the same THA that did not fail within the critical time period would provide base for the case-control study design.⁶ Having realized any such study design, the authors could consider the observed differences to be significant and possibly causal. In fact, the authors are aware that the presented data are limited by the size of their study population. Nevertheless, it should be further noted that the key observation from the study (association of *GNAS1* T393C SNP with time to aseptic loosening in males) is based just on the 20 THA patients among whom only four were *GNAS1* TT homozygotes. Such number of cases should be considered quite far from the optimum number for the analyses of genetic components of complex diseases and/or their complications.⁷

- (4) Regardless the *GNAS1* genotype, the authors reported apparent difference in THA survival between male and female THA patients. Because this finding may also be relevant for observed “contradictory” impact of *GNAS1* SNP on aseptic loosening in males and females, we missed any discussion of other possible causes of THA outcome being dependent on gender.

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