A research article by Jacq and colleagues [1], recently published in this journal, reported an association between rheumatoid arthritis (RA) and the rs3738919-C allele in the ITGAV gene, which encodes the αv subunit of the integrin αvβ3, in a European Caucasian population.

One feature of the pathophysiology of RA is the hyperangiogenesis observed in the synovial tissue and, along with excess macrophages and T lymphocytes, αvβ3 ligands are also abundant in synovial fluid [2]. As a key player in angiogenesis [3], it has been suggested that ITGAV may be a RA susceptibility gene. The linkage study also supports this view because the 2q31 region containing ITGAV exhibited linkage in a dense genome scan [4].

Although the European association study by Jacq and colleagues [1] indicated ITGAV to be a new minor RA susceptibility gene, a replication study conducted in a population of different ethnicity is helpful in exploring whether the association is caused by a common variance through various ethnic groups. We therefore undertook a large population-based study to investigate the association between ITGAV and RA in a Japanese population.

DNA samples were obtained from 1,504 Japanese RA patients and 449 population control individuals [5]. Genotypes were determined using the TaqMan method, in accordance with the manufacturer’s instructions (Applied Biosystems, Tokyo, Japan). Table 1 shows the genotype distributions and allelic frequencies of patients and control individuals. Unlike the European population, the rs3738919-C allele was more frequent in control individuals in our Japanese population, and no significant differences were observed in allele frequencies for Japanese RA patients and control individuals (0.908 and 0.922, respectively).

There are several factors that must be accounted for when a study fails to corroborate a previously identified association. One of these is an ethnicity-specific effect. Ethnic differences can result in differences in allele frequencies, and the genetic background of the disease itself may vary between ethnic groups. Another issue that must be considered is that, usually, negative association studies of a target gene outside the HLA region lack sufficient power to detect the genetic effect because the disease-associated genes outside the region may be associated with limited relative risk for disease susceptibility. While considering the odds ratio of Jacq et al.

Table 1

| Genotype | C versus A | CC + CA vs. AA |
|----------|------------|----------------|
| Genotype | CC | CA | AA | Total | MAF | OR (95% CI) | P* | OR (95% CI) | P* |
|----------|----|----|----|-------|-----|-------------|---|-------------|---|
| Patients | 1,221 | 259 | 8 | 1,488 | 0.092 | 1.20 (0.91 to 1.60) | 0.23 | 0.60 (0.16 to 2.72) | 0.49 |
| Controls | 380 | 62 | 4 | 446 | 0.078 | | | |

The distribution of the genotypes followed the Hardy-Weinberg equilibrium for both groups. *P values were obtained using Fisher’s exact test (R version 2.4.1). CI, confidence interval; MAF, minor allele frequency; OR, odds ratio.
al.’s study [1], our study was designed to have sufficient power to detect the effect of the ITGAV gene (>0.96; number of cases = 1504, number of controls = 449, OR in the original French study [1] = 1.94, frequency of rs3738919-A allele in the controls = 0.078, significance level = 0.05). However, when the odds ratio is under 1.67, the power is limited to below 0.8, and this may represent a study limitation.

Despite its association with RA in Caucasian populations, an association of the ITGAV gene with RA patients in the Japanese was not observed. Further studies in other ethnic groups are necessary to draw definite conclusions.

Competing interests
The authors declare that they have no competing interests.

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