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COMMENTARY

# A Commentary on genome-wide association study to identify genetic variants present in Japanese patients harboring intracranial aneurysms

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Despite the diagnostic and therapeutic developments of the past decades, subarachnoid hemorrhage (SAH) is fatal in approximately 50% of cases and causes significant disability in about 30% of the survivors. In Japan, the annual mortality rate from SAH is estimated to be 22.5 per 100 000 person-years. Rupture in intracranial aneurysm (IA) accounts for more than 90% of SAH cases. Genetic factors, female gender and lifestyle are associated with IA. IA is estimated to be prevalent in as many as 2% of the general Japanese population. Because IA is preventable and treatable, a strategy for its prevention has long been expected.

There are two traditional strategies used for the prevention of diseases: population strategy and high-risk strategy. For IA, it is well established that smoking and hypertension are the major risk factors. These factors have been considered as intervention tools for the population strategy. From the viewpoint of a cost–benefit balance, a focus on risks attributable to large populations and the contraindicated ratios of those risk factors can provide a practical approach. However, a more immediate preventive strategy has been anticipated. Under Japanese law, SAH is considered to be a work-related disease and workers who have SAH attack during working hours have often claimed workers' compensation. Thus, in the workplace, both population and high-risk strategies are desirable.[1] A difficult question to address is whether magnetic resonance angiography (MRA) should be used for screening for IA. MRA is expensive and is not usually recommended as a tool for screening general populations. However, if a genetic marker for IA is available, MRA screening may be used for persons identified as high risk.

In 2008, Helgadottir *et al.*[2] reported that the locus tagged by the single nucleotide polymorphism (SNP) rs10757278 is a risk factor for IA. Bilguvar *et al.*[3] reported a multistage genome-wide association study of European and Japanese populations and identified common SNPs associated with IA on chromosomes 2q, 8q and 9p. In 2010, three new loci (18q11.2, 13q13.1 and 10q24.32) were found and two previously identified loci (8q11.23 and 9p21.3) were confirmed by an international consortium that included a team from Japan.[4]

In this issue of the journal, the Japanese team, Akiyama *et al.*,[5] report five SNPs (rs1930095 of intergenic region (9q31), rs4628172 and rs7781293 of TMEM195 (7p21), rs7550260 of ARHGEF11 (1q23) and rs9864101 of IQSEC1 (3p25)) in a Japanese population. They speculate that, because the three genes may have a role in actin remodeling in the ELN/LIMK pathway, these genes may be IA susceptibility ones. This study indicates the presence of several susceptibility loci in the Japanese population that deserve further investigation. Clearly, this study has provided evidence of genetic factors for IA that are specific to the Japanese.

There are, however, two major problems. It has long been anticipated that more data would increase the statistical power of the information revealing genuine genetic factors. This seems not to be so. Although the international consortium has published more than three articles on IA, few loci have been replicated. In addition, the Japanese studies using overlapping populations did not replicate the risk loci. Thus, increased statistical power seems to enhance the effects of 'noise.' The other problem lies in the statistical approaches themselves. Traditionally, genome-wide significance levels are adjusted by Bonferroni's correction. In the current study by Aoyagi *et al.*, none of the SNPs had *P*-values smaller than $\alpha=0.05/250\ \ 507\approx 2\times 10^{-7}$. Further, most studies use a two-step strategy: identify SNPs in a population and validate the SNPs in a different population. Aoyagi *et al.* have not followed this strategy and thus the current study seems to suffer from statistical 'abuse.'

Joining an international consortium can be a good way to increase the data and enhance the statistical power of a study. However, if ethnicity-specific risk factors exist, these loci may impose a bias from population stratification and this may appear as 'noise' in a large study. Although the current study reported by Akiyama *et al.*[5] is ambitious and challenging, it may have various drawbacks. Particularly, the hypothesis of actin remodeling in the ELN/LIMK pathway is, as yet, unsubstantiated and requires a more substantial biological explanation. Further, the new genetic markers reported in this study do not select high-risk persons any more efficiently than do family histories. However, in spite of these deficiencies, the current study is an attempt to examine ethnicity-specific risk factors for IA and should be encouraged.[5]

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