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COMMENTARY

A Commentary on Identification of an autosomal dominant locus for intracranial aneurysm through a model-based family collection in a geographically limited area

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Prevalence of intracranial aneurysms (IAs) is relatively common, at 2–4% in the general population in Japan. Its natural course has been intensively studied. Its rapture rate per year is reported to be 0.05%[1] and results in subarachnoid hemorrhage (SAH). When SAH occurs, 50% of the SAH results in fatality and majority of the remaining 50% have decreased in activity of daily living and quality of life. Therefore, intervention program to prevent SAH is urgently needed. Although magnetic resonance angiography (MRA) is the gold standard, there has been no evidence as to whether application of MRA to the general population is effective or not in preventing SAH from a viewpoint of cost performance. Alternatively, as familial clustering has been well known for IAs, genetic markers have been expected to identify high-risk pedigrees by a high-risk strategy.

Since the 2000s, its genetic factors have been explored by genome-wide association study.[2,3] More than dozens of genetic loci for IAS have been reported. However, IA has defied identifying genetic markers with large risks (odds > 5). Case–control association study usually recruits unrelated cases and controls. In the case–control study design, degrees of contribution of genetic factors are heterogeneous and are reasonably assumed to be confounded by phenocopies. Thus, it is not expected to obtain large genetic factors. On the other hand, family-based approaches have also been hampered by difficulties in recruiting large families. In the family-based approach, linkage analysis has been conducted in families with familial IA clustering. There is a major caveat for this approach: locus heterogeneities. However, if we can increase the sizes of families by recruiting only three-generation large families, we can reduce noise significantly. Given the dense familial clustering, we can expect a large genetic risk factor.

Such analysis, however, has been confronted with another technical problems. Usually more than 100 genes are included in the 1-Mb size locus. Thus, it has been a quite heavy burden to sequence such a large number of candidate genes. However, recent progress in exome analysis (next generation-sequencing technology) has made it easy to sequence entire genome. Therefore, we can expect a gene pausing a large genetic risk.

A recent publication by Kim *et al.*[4] identified a locus of IA on chromosome 8p22.2, in which there are 23 candidate genes. The authors carefully recruited families in a small geographic region, by which they can minimize genetic heterogeneity among IA families. Exome analysis may be a good choice for identifying a brand new and large genetic risk factor. It may also be applicable for other family-based studies[4–6] too. Thus, we are now in an era when family-based study has become realistic.

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