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EDITORIAL COMMENT

Pathogenic *TSR1* Gene Variants in Patients With Spontaneous Coronary Artery Dissection*

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Spontaneous coronary artery dissection (SCAD) is increasingly recognized as a cause of acute coronary syndrome. During the last several years, larger cohorts of patients have become available, facilitating the study of comorbidities and risk factors, including contributory genetic variation (1). Development of new genomic methods, in particular of next-generation sequencing technology, now enables the comprehensive (i.e., genome-wide) detection of rare and common genetic variants in individual patients at rapidly decreasing costs. As a consequence, the genetics of coronary artery disease has gained new momentum, which is well illustrated in the study by Sun et al. (2) in this issue of the *Journal*.

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The authors performed a genome-wide search using whole exome sequencing for variants associated with SCAD risk in 85 Chinese cases compared with 296 non-SCAD control subjects; this is critically important because rare mutations may also be found at a low level in the general population. A further strength of the study is the addition of a second sample of 53 SCAD patients and 201 control subjects to provide further support. The authors observed an excess of rare or low frequency (minor allele frequency [MAF] <0.01) coding variants in the *TSR1* gene, encoding the TSR1 ribosome maturation factor, in SCAD cases compared with control subjects (2). The associated variants in the *TSR1* gene were predicted to be deleterious and were rare (MAF <0.0001) or low frequency (MAF 0.0001 to 0.01). Whereas the association of common genetic findings with a disease phenotype is typically not directly relevant to clinical care because of the typically weak effect size, the association with rare, pathogenic findings could potentially have direct clinical impact for the affected individuals and their families, depending on their penetrance. Whether *TSR1* should be added to the panel of candidate genes to be analyzed in SCAD patients within a clinical context will depend on whether these findings are confirmed in other studies. The TSR1 ribosome maturation factor, a nucleolar protein involved in RNA processing, could represent a new mechanism in the pathogenesis of SCAD.

This novel finding is exciting, but also raises several issues 1) the mechanisms behind the suggested causal role of *TSR1* in the etiology of SCAD remain unclear; and 2) the study sample, moreover, differs in several aspects from other published study samples, which may affect the generalizability of the findings. Although DNA sequencing studies of other cohorts of SCAD patients have consistently identified small numbers of patients with mutations causing known connective tissue disorders (e.g., *COL3A1*, *FBN1*, *TGFBR2*), such mutations were not found in the Chinese patients in the current investigation. Moreover, the baseline characteristics of the Chinese cohorts differ from published cohorts of European descent; in particular, the high proportion of male Chinese SCAD patients is in striking contrast to

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European cohorts, in whom a higher proportion of women have been noted. Interestingly, predominant male cohorts of SCAD patients have also been described in other Asian populations (3,4), which may indicate differences in the underlying pathogenesis of SCAD between Asian and European populations or could simplify reflect a greater proportion with atherosclerotic CAD and SCAD in the current study.

Other intriguing questions relate to the shared underlying pathologies of SCAD, cervical artery dissection, and fibromuscular dysplasia (5). Recent genome-wide association studies (GWAS) identified association of these vascular pathologies with a common variant in the *PHACTR1/EDN1* locus (rs9349379) in individuals of European descent (6). The same allele of this common polymorphism was also associated with migraine. Shared association of several nonatherosclerotic arterial phenotypes may indicate shared pathogenic processes of these different disorders (7). The absence of rare pathogenic mutations in genes known to underlie connective tissue disorders in the current Chinese SCAD cohort contrasts with the presence of such variants in a recent Chinese study of vertebral artery dissection (8). At the moment, the finding of rare *TSR1* variants in Chinese SCAD patients is therefore an outlier finding in 2 respects: it suggests a role for a new gene that was described previously neither in SCAD patients of European descent, nor in Chinese patients with other arterial pathologies that may be related pathologies.

Confirmation of the findings in an independent sample from another Chinese population is a major strength of the current study. Even if all 4 genes with suggestive association in the Wuhan discovery cohort were tested in the Beijing validation cohort, the findings in the Wuhan population remain suggestive after correction for multiple testing. Certainly, further replication in independent populations will be needed to strengthen the association of *TSR1* with SCAD. Linkage analysis in pedigrees with familial SCAD (9) would provide important support. If association is confirmed, characterization in animal or cellular models of the role of *TSR1* and arterial pathogenesis would be needed to understand whether any therapeutic potential exists.

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