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Editorial

New Prediction Model for Stroke in Korean

Jang-Whan Bae, MD, PhD[1,2]

[1]Department of Internal Medicine, College of Medicine, Chungbuk National University, Cheongju, Korea
[2]Regional Cardiocerebrovascular Center, Chungbuk National University Hospital, Cheongju, Korea

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Correspondence to
Jang-Whan Bae, MD, PhD
Department of Internal Medicine, College of Medicine, Chungbuk National University, 1 Chungdae-ro, Seowon-gu, Cheongju 28644, Korea.
E-mail: drcorazon@hanamil.net

ORCID iDs
Jang-Whan Bae
https://orcid.org/0000-0003-1362-9804

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Ischemic stroke (IS) is one of leading causes of death in developed countries and cerebrovascular disease (CVD) was the 3rd main cause of death in the year of 2016 in the Republic of Korea.[1] The classical main causes of CVD including IS are hypertension, dyslipidemia, diabetes mellitus, smoking, and premature CVD in the first relative familial members. Although the appropriate control of preventable risk factors for CVD, substantial part of incidence risk for myocardial infarction (MI) or IS still remains. One of those remained risks for IS can be the genetic predisposition for IS, this risks which is more important in IS occurs in premature age.[2][3] To reduce the incidence of primary IS, appropriate control of modifiable risk factors is the most important in daily practices, and the others might be early discovery of the high risk population for IS in epidemiological and genetical aspects.[4] Therefore, examinations to discover mutational genes associated with IS was continuously tried during last 2 decades. Lingren A specified several interest topics in stroke genetics, e.g., molecular genetic variations affecting risk of monogenic stroke or common stroke syndromes, genetic risks for stroke, including atrial fibrillation, hypertension or white matter hyperintensities, hereditary cause of familial stroke aggregation, epigenetic influences on protein expression in acute brain injury, genetic influences on stroke recovery and pharmacogenetics for stoke treatment drugs.[4] There are 3 main subtypes of IS, including large vessel disease (LVD), cardioembolic stroke (CS), and small vessel disease (SVD). Genetic studies for IS were performed to find the genetic affection for 3 main IS subtypes separately.[4] According to the genetic studies, IS is one of complex genetic disorders affected by multiple genetic and environmental factors. One genome-wide complex trait analysis using genome-wide association study (GWAS) data in 3,752 IS patients and 5,972 controls showed that genetic heritability for IS was 37.9%, and LVD showed more common hereditability (40.3%) than those of CS (32.6%) and SVD (16.1%), respectively.[5] In this study, *PHACTR1* gene showed significant relation with LVD, and *PITX2*, *ZFHX3* genes showed specific relation to CS subtype of IS.[5] Various genetic studies using GWAS revealed the association between IS subtypes and specific single nucleotide polymorphisms (SNP). For example, HDAC9 in 7p21, SUPT3H/CDC5L in 6p21.1, CDKN2A/CDKN2B/ANRIL in 9p21, and MMP12 in 11q22 had relation with LVD, ZFHX3 in 16q22 showed high risk in CS, and NINJ in 12p13.33, NAA25/C12orf30 in 12q24.12 were high risk gene in all 3 subtypes of IS.[4] Besides of SNPs for IS, there are specific diseases of monogenic stroke syndromes. For example, cerebral autosomal dominant subcortical infarcts and leukoencephalopathy have NOTCH3 region mutation in 19p13.2–p13.1, cerebral autosomal

recessive arteriopathy with subcortical infarcts and leukoencephalopathy is originated *HTRA1* gene alteration in 10q26.3 area, and hereditary endotheliopathy with retinopathy, nephropathy and stroke shows TREX1 gene abnormality in 3p21.31.[4] Stronger familial clustering of IS was observed more commonly in younger-onset IS compared to older-onset one. Seshadri et al.,[6] verified risk of stroke incidence in offspring with verified parental stroke status. After the adjustment with age, sex, sibship, and baseline stroke risk factors, they found that both all strokes and IS were associated with increased risk of incident of stroke of the same type in the offspring, documented parental stroke by 65 years of age was associated with a 3-fold increment of stroke for offspring in Framingham study cohort.[6] How we can predict risk of IS incidence in daily practice? Classical method is using the risk prediction models for IS obtained from general epidemiological data. There are excess of models predicting incident CVD including IS, e.g., Framingham Anderson model, QRISK Hippisley-Cox model, SCORE Conroy model, and Woodward model.[7] With these prediction models, we can crudely estimate specific forms of CVD incidence risk in certain geographic regions or human races. But, most of those models have not been externally validated or directly compared on their relative predicative performance; it makes uncertainty of risk estimation.[7] To overcome these limitations, refining of traditional epidemiological risk prediction models with optimal external validations, or addition of discovered genetic risk prediction models using polygenic risk scoring system (polyGRS) and merging model of traditional epidemiological risk prediction model and genetic risk model can be used. Recently, Hachiya et al.[8] adopted the polyGRS using GWAS to overcome the limitation of low predictability for IS of the weighted multilocus genetic risk scoring system in Japanese population. In this study, the polyGRS showed significantly superior prediction power for IS compared the weighted multilocus genetic risk scoring system, and the addition of the polyGRS to a traditional nongenetic risk model resulted in a significant improvement of the predictive ability.[8]

In this issue of the *Korean Circulation Journal*, Jung et al.[9] tried to develop precise genetic risk score (GRS) using genetic variants which are common and high predictable in stroke, and compare the predictability of GRS to traditional risk score (TRS). And they finally proposed the better prediction model using combining GRS on TRS for stroke in Korean population. Authors have analyzed the TRS and GRS using GWAS based on the Korean Chip obtained from the K-CHIP consortium in population of the Korean Cancer Prevention Study-II Biobank. They found that 16 of 72 SNPs in K-CHIP had strong association with incident of stroke, and GRS showed better prediction for stroke especially in younger population (<40 years old) than TRS, which had better prediction in older ones. More important thing is that the combined model using GRS and TRS showed better prediction power for the incidence of stroke. Up to now, the GRS showed better prediction power for premature or younger stroke and incidence, it was reproducible in this Korean data. To reduce stroke incidence, early discovery of high risk population and endeavors to control stroke risk factors are very important. With this clinical background, combined use of TRS and GRS will be reasonable approach to discover high risk population. As mentioned above, stoke is not single disease entity as like MI. At least, 3 subtypes of IS have been dealt in GRS works. But, authors could not check the GRS and TRS in each subtype of stroke, and hemorrhagic stroke was included in this analysis. Each subtype of stroke has own traditional and genetic risk profile, and hemorrhagic stroke can be biased with intracerebral hemorrhage. It can be a significant hurdle to introduce this new prediction model into daily practice of stroke care. CVDs including MI and IS are leading causes of mortality in Korea. We need more intensive works to make precise CVD prediction models using fine epidemiologic data and genetic studies to reduce the national burden of these drastic diseases.

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