The past decade witnessed substantial breakthroughs in the genetics of cardiovascular diseases. Particularly, genome-wide association studies (GWAS) identified hundreds of genomic variants that modulate the risk to develop stroke or coronary artery disease. A broad consensus from these studies is that particularly the numbers and effect sizes of common alleles, shared by all of us to a smaller or larger degree, add to the individual risk to develop such common disease. Whereas these findings stimulated basic research into disease mechanisms and might help to develop novel tools in risk prediction and prevention, the nature of genetic variants affecting long-term clinical outcomes after an event is still largely unclear (Figure 1). This is particularly disappointing for patients and physicians who hope for precision medicine in fostering the repair of damages left behind after a recent attack.

In this issue of *Circulation Research*, Mola-Caminal et al5 aimed at identifying genetic factors that associate with improvement in the modified Rankin scale (mRS) after ischemic stroke. This is important in several ways: first, there is a need to identify markers that help to personalize rehabilitation strategies to facilitate optimal convalescence, and second, there is a need for identification of molecular and cellular processes leading to better healing and thus improved functional recovery. Thus, from a clinical point of view, knowledge about the genetic modifiers of healing might lead to better treatment after a stroke.

Mola-Caminal et al5 performed a GWAS and gene-based burden test to identify variants associated with better recovery as determined by mRS at 3 months of follow-up. Such analysis requires serial and standardized measurements because the read out (phenotype) is a delta over time, rather than the case/control design used in GWAS thus far. In an ideal setting, one would study precisely functional changes between 2 presentations of a patient, for example, ejection fraction after a myocardial infarction at hospital discharge and 6 months later, and uncover by GWAS variants affecting the changes that occurred. Unfortunately, the authors could not exactly run such analysis and rather took the mRS at 3 months of follow-up and adjusted this for the National Institutes of Health stroke scale at discharge. The authors mindfully excluded patients with minor strokes (National Institutes of Health stroke scale, ≤4) and those with dependent status before the stroke from their sample to decrease the heterogeneity of the phenotype. Moreover, they defined for their replication strategy open and stringent inclusion criteria, to investigate whether a larger number of patients (open criteria, ie, particular covariates were not available, such as detailed mRS category, data on perfusion therapy, and National Institutes of Health stroke scale at baseline or discharge) or a better phenotyping (stringent criteria, ie, all covariates were available) might show the best results. Interestingly, in meta-analyses based on both open and stringent criteria, the authors detected variants at a single genomic locus to be associated with outcome (the analysis using stringent criteria performed slightly better).

The locus harbors the *PATJ* gene, which had not been associated with stroke (in the traditional case/control design) or any other cardiovascular phenotype before. *PATJ* encodes hINADL (human INAD-like protein), which has been described to colocalize with tight junctions in epithelial cells. Molecular functions that have been mainly investigated in *Drosophila* include regulation of epithelial polarity and interaction with transient receptor potential calcium channels. A hint that endothelial cell permeability might be an interesting cellular process is provided by the authors in preliminary experiments mentioned in the Online Data Supplement in the study by Mola-Caminal et al.5

The variants identified by Mola-Caminal et al5 are located without exception in intronic regions, which renders a regulatory mechanism linking genotype and phenotype likely. However, at least in data from the Genotype-Tissue Expression consortium, none of the variants are associated with expression of *PATJ* or any other gene. Additionally, *PATJ* is strongly expressed on RNA level in cerebellar tissue, whereas brain tissues only show weak expression (Genotype-Tissue Expression Portal, accessed on October 26, 2018). This and the lack of mechanistic data, which help explaining how these variants and this particular gene affect recovery after ischemic stroke, currently define future in vitro and in vivo studies needed to unravel a potential therapeutic potential (Figure 2).

Independent from a functional role, *PATJ* variants could also be used to identify patients at risk for poor recovery. However, it has to be taken into account that the risk variants are rather rare with allele frequencies of 2% and 3%. Given this
low frequency, the authors estimate the contribution of the lead single-nucleotide polymorphism to the outcome to be only 0.27%, indicating that the large part of the underlying genetic factors yet remains to be discovered. On the contrary, the effect size of the risk allele was substantial. Three months after the ischemic stroke, carriers of one risk allele were, on average, 0.4 higher on the mRS than the noncarriers. Thus, knowledge on the underlying mechanisms might be of enormous benefit for understanding cellular mechanisms of functional recovery and thus offer a starting point for the identification of novel treatment options. Another disappointment may be seen in the fact that despite the substantial size of the GWAS (>3700 patients were studied), only a single locus was discovered. Thus, it seems like with other cardiovascular phenotypes that hundred thousands of patients need to be studied to replicate the locus and to unravel the full potential of this approach.

Taken together, the work of Mola-Caminal et al exemplifies the potential of genetic analyses not only in the identification of risk genes for the development of diseases as stroke or coronary artery disease but also for functional recovery after an event. The formation of large international consortia will probably lead to the identification of further such variants. Nevertheless, as for risk genes predisposing for the disease, there is a long way of further research to elucidate the underlying molecular and cellular mechanisms and to understand whether and how this knowledge will help to improve risk prediction and therapy (Figure 2).

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Disclosures

None.

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