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Researchers find seventeen genetic abnormalities that cause brain aneurysms

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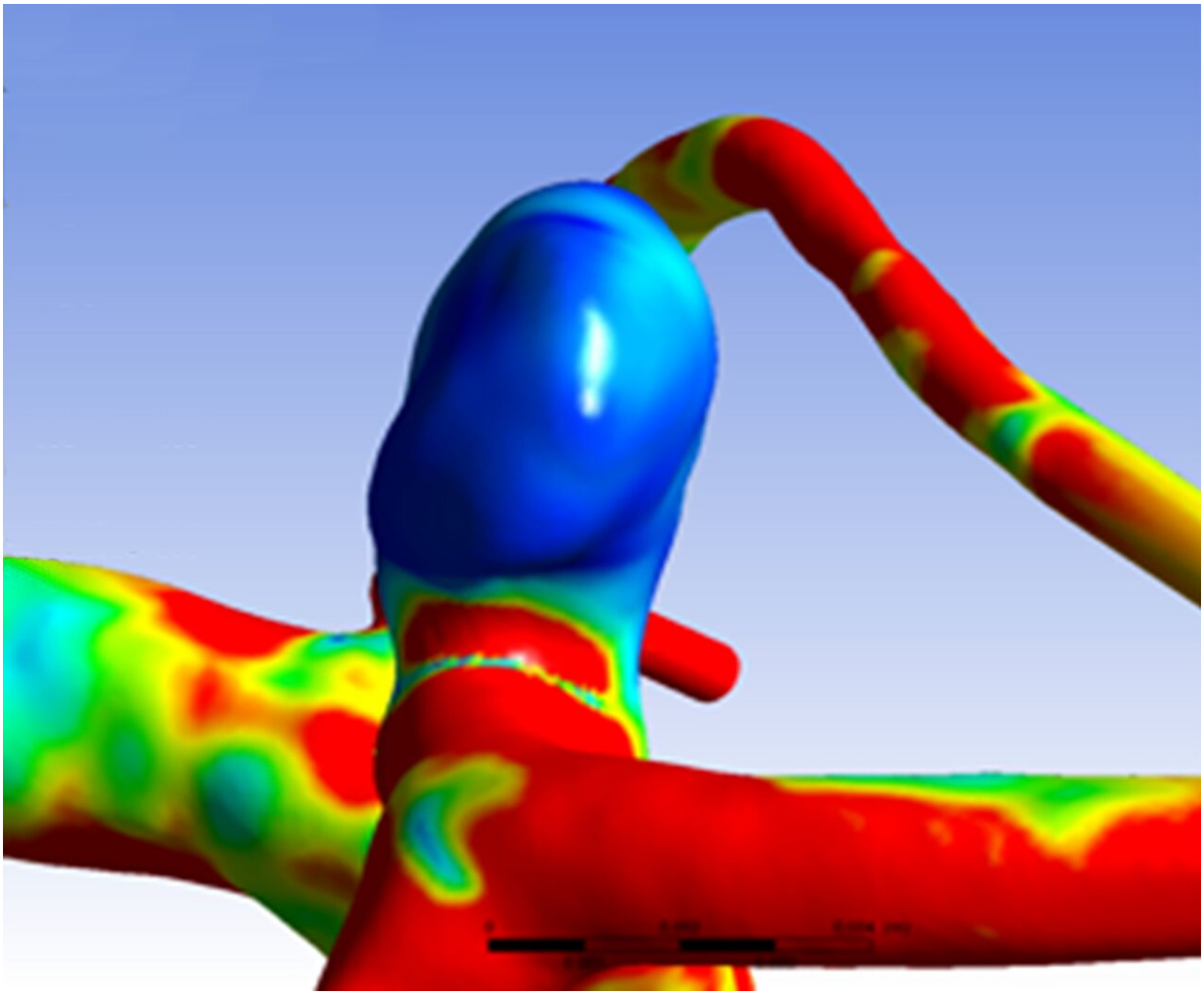

An aneurysm is a natural dome (in blue) that usually grows at an intracerebral arterial bifurcation aimed at decreasing the friction forces (in red) and thus allowing the vessel to heal. Multiple factors participate in the healing of the vessel wall; danger comes however from the risk of rupture. Credit: UNIGE-

HUG

Nearly three percent of the world's population is at risk of developing an intracranial aneurysm, a localized dilation of a blood vessel forming a fragile pocket. Rupture of this aneurysm results in extremely severe, and, in one-third of cases, fatal hemorrhage. In the framework of the International Stroke Genetics Consortium, a team led by the University of Geneva (UNIGE), the University Hospitals of Geneva (HUG) and the University of Utrecht is studying the genetic determinants of aneurysms in order to better understand the different forms of the disease and to assess individual risk. Through the examination of the genome of more than 10,000 people suffering from aneurysms compared to that of 300,000 healthy volunteers, 17 genetic abnormalities have been identified that are notably involved in the functioning of the vascular endothelium, the inner lining of blood vessels. In addition, the scientists discovered a potential link between these genetic markers and anti-epileptic drugs, making it possible to consider the use of certain drugs in the management of the disease. These results, to be read in the journal *Nature Genetics*, also highlight how the wise use of large databases containing genomic and phenotypic information can advance research.

Every year, five out of every 100,000 people experience a rupture of an intracranial aneurysm—as many as those injured in road accidents. And only very rapid and highly specialized surgical management can hope to save their lives. "It is therefore essential to better understand the genetic basis—inherited or otherwise—governing the risk of developing the disease, but also to distinguish between the different forms of the disease and its severity. This will allow us to detect people at risk and offer them the most appropriate treatment," explains Philippe Bijlenga, Assistant Professor in the Department of Clinical Neurosciences at UNIGE Faculty of Medicine and Senior Consultant at HUG Division of

Neurosurgery, who led the Swiss part of this study. This multipronged disease, whose evolution depends on genetic, congenital and environmental factors, is indeed complex to apprehend. "The tiny variations that make it up must therefore be deciphered," he adds.

A study of unprecedented scope

The work carried out in Geneva and Utrecht is the largest genetic study in the world in the field of intracranial aneurysms. The DNA of more than 10,000 patients was examined and compared with that of 300,000 volunteers: eleven new regions of the genome—compared with six previously—were found to be associated with the disease. "Each of these DNA variations causes a slight increase in the risk of an intracranial aneurysm," says Ynte Ruigrok, neurologist and associate professor at the University Medical Center of Utrecht University, who co-led the study. "Thus, their accumulation can, together, constitute a significant risk."

Most of these genetic abnormalities appear to be related to the functioning of the endothelial cells that line the inside of blood vessels and usually make them robust. "These cells have long been suspected of being responsible for aneurysms," says Philippe Bijlenga. "We now have evidence that leads us to work on possible markers of instability that could indicate whether the aneurysm is stable, healed, or at high risk of adverse outcomes."

In addition, this research shows that a genetic predisposition to high blood pressure and smoking play an important role in the development of an intracranial aneurysm. If these risk factors were already known from a clinical and epidemiological point of view, we now have the genetic evidence.

The scientists also made a surprising discovery: "It appears that the protein structures of some of the genes we identified are linked to

antiepileptic drugs. We do not yet know whether this effect is positive or negative, but it opens up the possibility for pharmacological treatments, potentially less invasive than the surgical approaches we are currently using," says Philippe Bijlenga. The scientists will now work on modeling the disease, both biologically and therapeutically, to offer physicians a medical decision support system that will help determine potential management protocols based on each person's genetic data.

Scientific advances and data protection

To carry out these studies, the research teams must have access to a very large number of patients, and therefore work in international consortia. "To achieve this, we have set up tools to standardize complex data. We had to find a common language, unify clinical evaluation criteria, imaging methods and their computer processing, and establish exchange structures while guaranteeing the protection of personal data," reports Philippe Bijlenga, who supervised this work on data.

The consortium has set up a structure capable of collecting, harmonizing and securing huge amounts of data. The Swiss Institute of Bioinformatics (SIB) manages the phenotypic data, while the University of Utrecht stores the genomic data. Both datasets are accessible through an approval process to research teams around the world. "However, proper use must be demonstrated. Our system allows scientific advances, but with protection of personal data," the authors conclude.

More information: undefined undefined et al. Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors, *Nature Genetics* (2020). DOI: 10.1038/s41588-020-00725-7