GENIUS: GENETIC INFLUENCES ON THE FUNCTIONAL OUTCOME OF STROKE

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1. Project Summary

In this project we wanted to study whether there are genetic variants that influence the level of disability of a patient after a stroke. We know that there is a lot of variability and we also know several factors that contribute to explain this variability, such as the stroke's location within the brain, the size of the area that has been left without blood supply, the patient's age, etc. However, even when comparing patients with the greatest possible similarity in these aspects, we continue to see variability in the degree of disability. Our hypothesis is that this variability could be explained in part by genetic differences, and that these differences would be found in genes that participate in the biological process of recovery from stroke. Therefore, knowing these variants will allow us to move towards personalized medicine for stroke patients, and to better understand the mechanisms that are activated in the body in response to stroke, and that are involved in its recovery.

To do this, we have started from previous data in which we had studied a small subgroup of 90 very well characterized patients, selected from the extremes of recovery (41 of those who recovered better and 49 of those with worse recovery) and closely matched in variables known to influence recovery. This study helped us to choose some 70 genes that could be interesting, to which we added other relevant genes and regions of the genome according to data on their function. From all these regions of the genome we have obtained the sequence in 700 patients with ischemic stroke of specific subtypes. From here we have identified the variants and we have performed a statistical analysis to see if any of these genes had more variants in patients who recover better (these would be protective variants) or those who recover worse (which would be risk variants).

For the statistical analysis, we wanted to develop a specific statistical tool for rare variant association analysis. This type of studies are performed by collapsing all the variants occurring in the same gene, instead of analyzing each variant separately. Although some tools and algorithms are already in use for this type of analysis, ours is based on a recent computational approximation (INLA) and it allows us to increase the statistical power of the analysis.

2. Results

Statistical analysis has identified a gene that has variants almost exclusively in patients who have a good recovery. These are very rare variants; among all the patients (those from the previous study and this study) we have only identified 11 with variants in this gene, and 10 of them have a good recovery. Although they seem very few (11 of 771 patients), the results are statistically significant. This gene produces a protein that is involved in the inflammatory response that occurs after a stroke. We are now trying to see the effect of the identified variants on the protein's function.

In addition, we have found another gene that presents more variants in patients with greater disability after stroke, but in this case the statistical analysis is not so clear and we would need to obtain data from more patients to be able to confirm this result. This gene would be involved in the formation of tight junctions, and probably in the permeability of the blood-brain-barrier, a process that has already been associated to stroke functional outcome in a genome-wide association study (GWAS).

As mentioned above, we developed a statistical tool for rare variant association analysis. This tool was developed within a collaborative project with other computational and statistical research groups, and is based on a novel computational method (INLA). In assays with simulated data, we have seen that our approximation (BATI) has more statistical power than other tools frequently used in rare variant association studies such as ours.

3. Relevance and possible future implications

Our results highlight the relevance of the inflammatory process in post-ischemia recovery, and could point to a possible therapeutic intervention: the function of this gene could be blocked to improve the prognosis of patients who have suffered a stroke. Very few stroke treatment options are currently available, and some of them can only take place in the first few hours. Therefore, it would be very important to be able to carry out a treatment that would reduce sequelae in a broader time range.

On the other hand, we believe that the tool that we developed, BATI, might be useful for other investigators in other rare variant association projects, and, therefore, we have made it available in the appropriate repositories.

4. Generated bibliography

The statistical method developed has been published:

Title: Efficient and flexible Integration of variant characteristics in rare variant association studies using integrated nested Laplace approximation
Authors: Susak, H., Serra-Saurina, L., Demidov, G., Rabionet, R., Domènech, L., Bosio, M., Muyas, F., Estivill, X., Escaramís, G., & Ossowski, S.
Reference: *PLoS Comput Biol*. 2021;17(2):e1007784 (2021)
doi:10.1371/journal.pcbi.1007784

We have presented our results in an international conference and are preparing a scientific article.

Title: Genetic influences on functional outcome after stroke
Authors: Estefanía Alcaide, Nuria Martínez-Gil, Geòrgia Escaramís, Uxue Lazcano, Marina Mola-Caminal, Caty Carrera, Cristòfol Vives-Bauza, Jordi Jiménez-Conde, Israel Fernández-Cadenas, Raquel Rabionet
Meeting of the European society of human genetics (virtual); abstract published at: European Journal of Human Genetics (2022) 30:88–608; P05.050.D