Fundació La Marató 3

23rd SOCIAL RETURN OF THE RESEARCH
Strokes and traumatic spinal cord and brain injury

EPIGENESIS PROJECT. EPIGENETIC AND GENETIC STUDY COMBINED WITH INTEGROMICA OF DATA AND FUNCTIONAL ANALYSIS TO FIND GENES ASSOCIATED WITH NEUROLOGICAL DETERIORATION FOLLOWING ISCHAEMIC STROKE

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1. Project summary

The objective of the EPIGENESIS project was to analyze if epigenetic factors such as DNA methylation affect the evolution of stroke. We also wanted to find new therapeutic targets to generate neuroprotective drugs to improve the outcome of a stroke. And finally we wanted to understand the most important biological factors associated with neurological deterioration and disability after suffering a stroke using massive epigenetic and genetic data.

We analyzed ischemic strokes with data on neurological deterioration, using the NIHSS scale and measuring the score difference between the initial phase of the stroke (first hours) and 24h post-stroke. We did an epigenome-wide association study (EWAS) to analyze the methylation pattern of 850,000 CpG islands using the EPIC-Infinium BeadChip. We analyzed blood samples obtained (<6h) from 500 ischemic strokes and performed a genome-wide association study (GWAS) in more than 5,000 stroke patients to detect 6,000,000 genotyped or imputed polymorphisms.

2. Results obtained

We have discovered that epigenetics is associated with neurological deterioration: specifically changes in the methylation of the EXOC4 gene are related to neurological deterioration during the first hours of suffering a stroke and until the patient's hospital discharge. We have also discovered that mutations in other genes, such as EXOC4 that participate in neuronal excitotoxicity are also associated with post-stroke neurological deterioration. In a genetic study with more than 5,000 patients, it was found that common genetic variations in the GRIA1 and ADAM23 genes could modulate neurological worsening. This information will be very useful to understand these processes and find drugs to improve the prognosis of stroke.

3. Relevance to possible future implications

In the Epigenesis study we have confirmed that epigenetic factors influence the long-term evolution of stroke and we discovered for the first time that during the acute

phase of stroke genetic factors also play a relevant role (Ibañez et al. Brain 2022), specifically ADAM23 and GRIA1 genes.

We have also found that epigenetics is a heritable factor influencing both stroke risk (Cullell et al. Thromb and Haem 2022 (In press)) and post-stroke outcomes (results in submission to Clinical Epigenetics).

For the first time we have observed that epigenetic changes are associated with the evolution of stroke during the acute phase. We have found a gene: EXOC4 in which changes in its methylation affect this neurological evolution. In addition, in studies using molecular pathway integromics with the genetic and epigenetic data available from our study, we have observed that neuronal excitotoxicity plays a very relevant role in post-stroke neurological deterioration. These results observed from two different angles (epigenetics and genetics) make us think that neuronal excitotoxicity may be a good pharmacological target to improve the prognosis of stroke. In fact, we are collaborating with a group of researchers from Washington University in St. Louis to analyze a mouse model and modulate the genes associated with excitotoxicity that we have found in this study (EXOC4, ADAM23 and GRIA1).

Regarding EXOC4, we should note that epigenetic changes are more easily modulated than genetic variations. In fact, there are drugs that change DNA methylation and are used in oncology. That is why we think that our epigenetic results are quite relevant and that they can lead to potential neuroprotective treatments in stroke.

On the other hand, our group has also developed a tool to predict the evolution of stroke patients using clinical data. It is a prediction result that uses simple, common data and is equal to or more powerful than other results that have been published. We believe that this result may help in clinical practice to predict patients with another probability of disability and to establish personalized medicine. This personalized medicine could consist of a more careful monitoring of the patient and also more intense rehabilitation therapies to improve the functionality of the patients and that cannot be applied to all strokes due to the high cost of these therapies.

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