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Examining the so-called Basque mutation of Parkinson's

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The relationship between genetics and Parkinson's has been investigated for more than a decade, but it is only over the last few years that significant results have begun to be obtained. The first mutations related to the development of this disease were found in 2004. A team from the UPV/EHU-University of the Basque Country came across a mutation of the LRRK2 gene, which is particularly prevalent among the population of Gipuzkoa. It is the R1441G mutation and is known as the Basque mutation. Now, Doctor Javier Ruiz, a doctor on the same team, has submitted a thesis in which he has studied this mutation; apart from the study of its prevalence, the study includes the calculation of its penetrance, the description of its clinical phenotype, its progression, and the neuropathological study of a patient carrying this mutation. The results have been published in the prestigious journals *Neurogenetics* and *Movement Disorders*.

In actual fact, it was no easy task relating Parkinson's with certain genes. "At first, one-off descriptions were made and they pointed to the old idea that Parkinson's was something sporadic, but this is not true," says Ruiz, the author of the study. When a decade ago people began to say that there were family forms, the genes were not these ones. They were genes that accounted for a type of Parkinson's that was slightly different, and which was somewhat removed from the classical Parkinson's that we could all see

The gene studied by Ruiz's team and which codifies the protein they called dardarina, does, however, explain a type of Parkinson's which is

the common one. Nevertheless, that gene is not the only one related to the disease. "Right now, genes continue to be discovered," explains Ruiz. "There is a list of about 15 or 16 genes involved in the monogenic forms of Parkinson's, in other words, forms of the disease that can be associated with a specific mutation. This gene is the most important from the point of view of frequency, it is the one most seen in the world population."

However, it is not known what dardarina, the protein that encodes the gene studied, actually does. One of the lines of research is seeking the function of dardarina from the point of view of neuronal death, since it is linked to this process in certain specific brain structures, but its exact role is not yet known. "Different mutations of the gene are known to cause the protein to do different things, but what the so-called Basque mutation actually does is not fully understood. There is another mutation that is more prevalent worldwide, the G2019S, which is the best known one. It has a more enzymatic activity; it is a kinase, in other words, a protein that transfers phosphate groups from one molecule to another," says Ruiz.

Questions and answers

In this thesis Ruiz studied four families in Gipuzkoa who have the R1441G mutation, and he did this from a range of perspectives. "Well, I've got families with Parkinson's and I want to know why. I do research, but I'm also a clinician, and I'm in contact with patients every day, and the questions I get from them I then transfer to the research," he says.

Ruiz says that the first question is about knowing what having a mutation means. It is the study of penetrance that he did in his thesis; "having a mutation means that by the time you're 80 you have an 83% chance of having Parkinson's," he explains.

Another question is whether the mutation is something by chance or is frequent in the Basque Country. What is more, Ruiz has studied whether the mutation only appears in the patients or whether it is common in the general population. That is why he took samples from people in Azpeitia and Azkoitia, which is where the highest number of patients are, and he found that 1.8% of the general population have it.

He also looked into whether the Parkinson's associated with this mutation, R1441G, is similar to that associated with the G2019S. "Studying the non-motor symptoms is very much in vogue in Parkinson's research," says Ruiz. The result of the study indicates that these symptoms are less present in the case of the Basque mutation.

"And armed with this, what can I contribute to science and to my patients? Well, an early diagnosis perhaps, and having a target population that could be the first to benefit from a future neuroprotective treatment, which, it has to be said, does not yet exist," says Ruiz. That is why another part of the research has focused on the quest for biomarkers in people carrying the mutation, since they indicate who has a greater risk of contracting the disease. The study proposes olfactory dysfunction and sympathetic dysfunction measured by cardiac gammagraphy as markers to be studied.

Besides the results obtained, the thesis also points to the lines along which the research needs to be continued. "You owe that to the population; the patients' relatives have altruistically donated their blood to enable us to do this study," explains Ruiz. "We will have to give them answers."

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