Study of rare cancer identifies patients at highest risk of metastasis and those who would respond to immunotherapy

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CNIO researchers Bruna Calsina (left) and Mercedes Robledo. Credit: Laura M. Lombardía, CNIO

Pheochromocytoma is a rare tumor, with an incidence of three to eight

cases per million population per year. The work published today, Feb 28, on Rare Disease Day 2023, in *Nature Communications*, is the largest study on this cancers' molecular causes and focuses on patients with metastatic pheochromocytomas, which account for 20% of all cases. Survival of patients with metastatic pheochromocytoma is 20–60% at five years.

Mercedes Robledo, head of the Hereditary Endocrine Cancer Group at the Spanish National Cancer Research Center (CNIO) and one of the two researchers who led the study, has been studying these tumors since 1996. He says, "One of the difficulties of working with rare diseases is to recruit large series of patients to reach robust conclusions. And this study stands out because the number of samples we worked with was outstanding." The CNIO belongs to the Spanish network of Rare Diseases (CIBERER).

CNIO researcher and co-author Bruna Calsina explains, "The number of patients with metastatic disease that our study gathers corresponds to a population of 100 million people." This has been possible thanks to the collaboration between 16 centers from six countries around the world, with which the CNIO has been collaborating for the last decade.

Such a large sample was necessary to achieve what they and their research colleagues have achieved with their work: to identify, at the time of diagnosis of the primary tumor, markers associated with an increased risk of metastasis. These markers can be added to other clinical and histological criteria for personalized clinical management.

As Robledo and Calsina explain, most patients with this type of tumor who develop metastasis do so one or two years after the diagnosis of the disease, but there are cases in which metastasis develops ten or twenty years after the initial diagnosis. The new molecular markers will help clinicians to follow more closely those patients at high risk of metastasis.

Patients who might respond to immunotherapy

Another problem with this rare disease is that the therapies do not always work, and the reason is unknown. "This is a hereditary disease in 40% to 50% of cases," explains Mercedes Robledo, "and very complex from a genetic point of view. Up to 22 genes related to the disease have been identified, of which five have been discovered in our laboratory."

The more genes involved in a disease, the more difficult it is to study and the more complex it is to find effective therapies. To date, several types of treatment have been tested, from chemotherapy to targeted therapies, but as Bruna Calsina explains, "It is not known a priori which patients might respond to one therapy or another."

For this reason, another part of the research consisted of searching for markers that would allow treatment to be personalized. The research led by Robledo and Calsina has identified a group of patients with pheochromocytoma who could benefit from immunotherapy treatments.

This work would not have been possible without the close collaboration between the CNIO Hereditary Endocrine Cancer Group and the CNIO Bioinformatics Unit, together with other CNIO researchers and international collaborators. "The study will be a benchmark in the field of metastatic pheochromocytoma," concludes Robledo.

More information: Bruna Calsina et al, Genomic and immune landscape of metastatic pheochromocytoma and 3 paraganglioma, *Nature Communications* (2023). DOI: 10.1038/s41467-023-36769-6. www.nature.com/articles/s41467-023-36769-6

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