LIQUID BIOPSIES FACTSHEET

An innovative method for better monitoring of rhabdomyosarcoma

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In rhabdomyosarcoma (RMS), the most common malignant mesenchymal tumor in children and adolescents, genetic alterations may be of different types, affecting the number, structure or sequence of chromosomes and the genes that they carry. How can we detect and identify those that may constitute appropriate therapeutic targets? Dr. Gaëlle Pierron, assistant head of Institut Curie's somatic genetics unit at Institut Curie, and her team, have found a solution: combining two tumoral DNA Next Generation Sequencing (NGS) techniques.

Combining exhaustive sequencing and targeted sequencing

The first will focus on a panel of around forty genes and areas of interest in RMS, to identify the mutations (part of the gene contains a writing error) but also the translocations (part of the gene has been moved to another area of the genome). Since few genes are sequenced in this first analysis, they can be sequenced a significant number of times, which provides a high level of sensitivity. The second, known as shallow sequencing, will be less sensitive, but will analyze the entire genome, thus identifying areas gained or lost in the sample studied.

"By combining these two methods we can identify different types of alterations and draw up a molecular identity map for each tumor," announces Dr. Gaëlle Pierron. The bioinformatics tools needed for the full analysis of this sequencing have been successfully developed and tested. **The method was applied to 35 tumors and helped identify mutations presented at diagnosis, as well as those that appeared at relapse.**

Monitoring the patient, anticipating relapse and adapting treatment

"This offers three opportunities: firstly, to obtain the tumor's properties at the time of diagnosis and thus define appropriate treatment targets; secondly, to observe the effects of the treatment via changes in the circulating tumor DNA; and lastly, to detect any relapse at a early stage", summarizes Dr. Gaëlle Pierron. **The method developed does not require direct access to the tumor, since it uses a liquid biopsy (via blood sample).** Any relapse can therefore de detected on the circulating tumor DNA isolated in the plasma, via a simple blood sample.

The next step will involve making these tools widely available: the new FAR-RMS protocol to be implemented on an international scale by the end of the year will aim to use the method in a clinical setting. Routine access to the molecular portrait of RMS, as well as monitoring throughout treatment of alterations identified, will enable clinicians to adapt treatment for each patient and offer innovative treatments.

Oral communication/SOFT TISSUE SARCOMAS Session - October 14, 2023 - Sequential genomic analysis using a multisample/multiplatform approach to better define rhabdomyosarcoma progression and relapse – last author: Dr. Gaëlle Pierron, Speaker Dr. Henri De Traux

Retinoblastoma: no demonstrated connection between molecular markers of aggressiveness and intensity of treatment

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Retinoblastoma affects one child in 15-20,000. This tumor of the retina can be easily treated if diagnosed on time, often via chemotherapy followed by ophthalmological treatment (laser, cryotherapy) or with ophthalmological treatment alone (sometimes with the need to remove the eye if the disease is advanced).

Today new options are becoming available, with the possibility for doctors to sample droplets of aqueous humor in the rear chamber of the eye to map the genetic anomalies of the tumor. Using this method, some scientists have proposed using this information to improve patient treatment: if molecular markers of aggressiveness are identified, they could be used to classify retinoblastomas and thus adapt the level of treatment.

The connection between molecular markers, a histological risk factor and use of additional treatment is in question

A leading national center for retinoblastoma, Institut Curie has studied the relationship between molecular markers of aggressiveness and the histological analysis of tumors sampled, in order to guide the intensity of post-operative treatment.

"We selected 87 patients with retinoblastoma who had already undergone enucleation", explains Dr. Yassine Bouchoucha, assistant chief resident in Institut Curie's pediatrics department "to map the molecular identity of the disease by sequencing fragments of the tumor DNA."

The study found no connection between the biomarkers and the necessary intensity of post-operative treatment. In particular, children whose tumor showed DNA fragments with aggressiveness markers (corresponding to amplification of the MYCN gene) did very well without the need for additional chemotherapy. Additional studies are therefore needed in order to use molecular markers in a new risk classification for retinoblastoma, and achieve better adaptation of treatments for each patient.

Usefulness of aqueous humor biopsy for genetic counseling

Sampling a few droplets of aqueous humor, now a routine practice at Institut Curie, is already helping to improve genetic counseling. These biopsies help identify children affected by retinoblastoma with a genetic predisposition, linked to a constitutional anomaly of the RB1 gene, and thus a higher risk of sarcoma in adulthood. "This systematic biopsy of aqueous humor in children's eyes (with the parents' consent), allows us to search for various markers of aggressiveness," concludes Dr. Yassine Bouchoucha. "These results provide the substrate necessary for the studies that will ultimately help reduce treatments for children whose retinoblastoma has no markers of aggressiveness, with the ultimate goal of reducing long-term after-effects. It is an avenue that merits exploration."

Poster presentation: Prognostic value of molecular markers in unilateral retinoblastoma treated by first-line enucleation. Yassine Bouchoucha, Jessica Le Gall, Alexandre Matet, Sarah Mezghani, Hrant Ghazelian, A. Savignoni, Meriam Mahmoudi, Clément Hua, Jennifer Carrière, Marion Gauthier-Villars, Arnaud Gauthier, Paul Fréneaux, Hervé Brisse, Nathalie Cassoux, Livia Lumbroso-Le Rouic, Isabelle Aerts, François Doz, François Radvanyi, Liesbeth Cardoen, Lisa Golmard.