Researchers unveil the origin of second pediatric cancers and chemotherapy-induced mutations in healthy tissues

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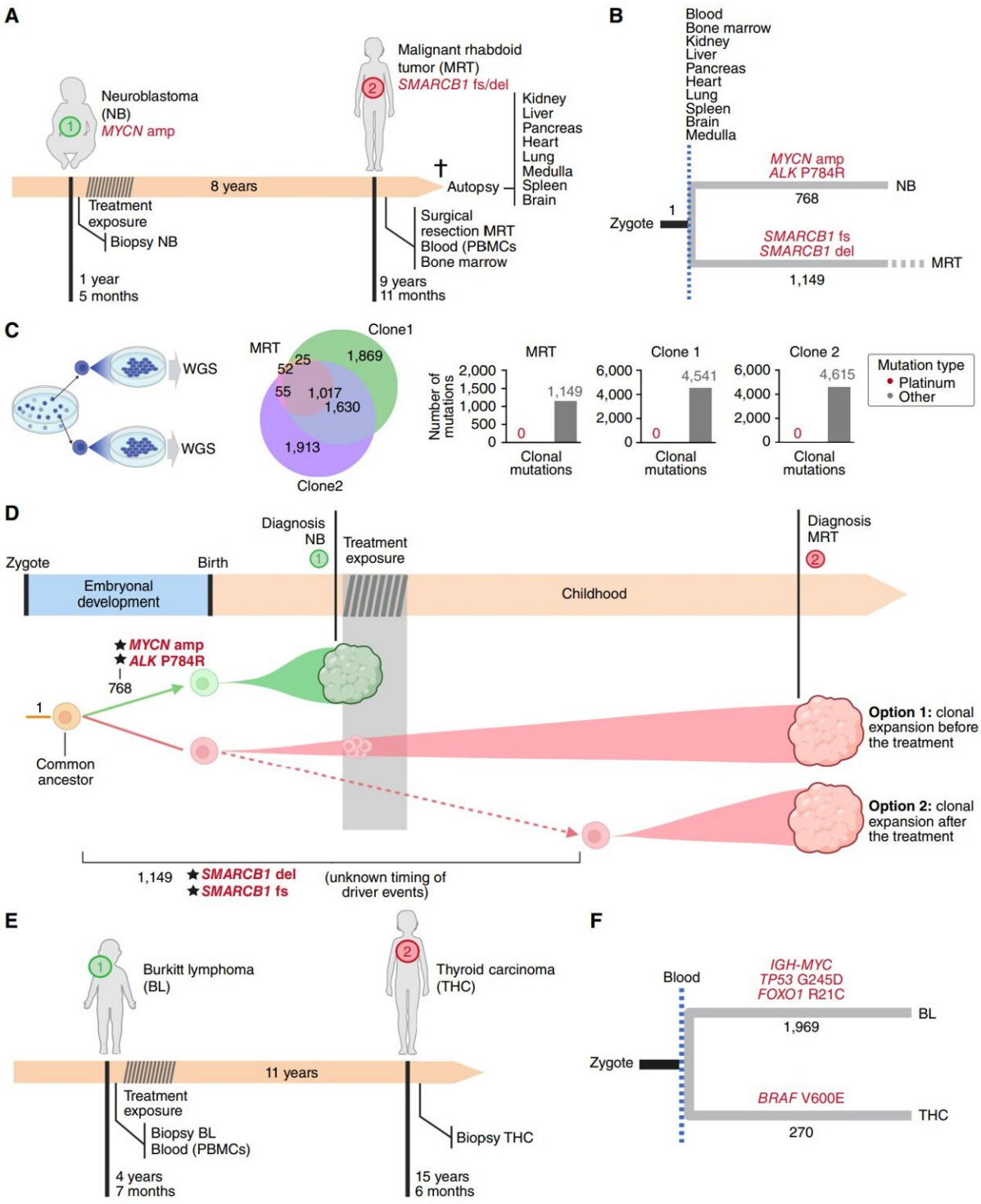

The origin of second solid tumors of cases 3 (A–D) and 4 (E–F). A, Eight years after the development of NB, the child presented with MRT. B, The comparison of whole-genome mutations in both tumors with those detected across samples of

10 normal tissues (some obtained during autopsy) revealed a completely independent origin of the NB and the MRT. C, No platinum-related mutations were detected in expanded single cells of the MRT. Therefore, there is apparently no mutagenic contribution of cisplatin to the mutational burden of the MRT. D, Schematic representation of the evolution of the two tumors of case 3. E, Eleven years after the development of BL, the child presented with THC. F, The analysis of whole-genome somatic mutations in both tumors revealed a totally independent origin of both tumors. Credit: *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-23-1186

Pediatric cancer, also known as developmental cancer, is rare. Around 400,000 new cases are diagnosed worldwide each year. The likelihood of a child developing two independent cancers during childhood is extremely low. However, such cases do occur, and studying the origin of these second neoplasms not only helps explain these specific cases but also contributes to a better understanding of the origin of pediatric cancer in general.

In a study published by the Institute for Research in Biomedicine (IRB Barcelona) and the PCCB-Sant Joan de Déu Hospital · Sant Joan de Déu Research Institute (HSJD—IRSJD) in the journal *Cancer Discovery,*, a team of scientists has made significant progress in understanding the origin of childhood cancer.

Dr. Monica Sánchez-Guixé, the first author of the work, is a member of the team led by ICREA researcher Dr. Núria López-Bigas and Dr. Abel González-Pérez, both at IRB Barcelona. Together with Dr. Jaume Mora, at PCCB-HSJD, they have carried out an exhaustive analysis of clinical cases with two tumors and have identified three distinct patterns that explain the occurrence of the second cancer.

"The study not only clarifies the origin of the highly improbable

conditions of these patients but also enhances our understanding of pediatric cancers in general. In the future, this knowledge could contribute to setting the treatment and monitoring of young patients," reflects Dr. Abel González-Pérez.

The mutational footprint of chemotherapy

The study focused on exploring the origin of these second cancers using advanced genome sequencing techniques. The results revealed that cancer therapies, specifically those based on platinum, introduce mutations—changes in DNA—in the second tumor and the healthy tissues of children. This specific mutational footprint contributes to our understanding of when the second cancer formed.

In short, one of the patients in the study developed leukemia (or blood cancer) four years after undergoing chemotherapy for the treatment of a first tumor (sarcoma) in one leg. The mutational patterns found revealed that leukemia developed subsequently to this treatment.

"Although we know that the chemotherapy received years earlier is related to the development of the second cancer, we cannot determine whether this cancer has been caused by the mutagenic action of the chemotherapy or by other factors."

"Either way, these therapies increase the number of mutations in children's bodies beyond what would naturally accumulate over time, which makes us wonder how they could affect their health in the future," explains the first author of the study, Dr. Mónica Sánchez-Guixé, a postdoctoral researcher at IRB Barcelona.

Early mutations of independent events

Another key discovery made by the study is that, in the case of one patient, both tumors (the first and the second, which manifested 8 years later) developed from a single mutation that the child had acquired at an early stage of embryonic development, long before receiving any cancer treatment.

In two other cases, the researchers found that the two tumors had a completely independent origin. In these cases, the two mutations that led to the two pathologies probably also occurred during embryonic development but as two separate events that evolved independently.

The importance of sharing clinical data to propel research

Progress in medical research, especially in complex and critical fields such as cancer, largely depends on the availability and analysis of clinical data. Particularly in the case of rare diseases (developmental cancer being one of them), the lack of data is one of the major obstacles in their research, as it limits scientists' ability to identify patterns, test hypotheses, and develop effective therapies.

The decision of patients and families to share this very personal and sensitive information is an act of generosity that has the potential to transform research and save lives. "This study would not have been possible if the parents of the patients had not shown total commitment to research throughout their journey."

"First, by authorizing the use of their children's samples for further investigation. Second, their authorization of the study of autopsy samples in cases of death Is an extraordinary act of generosity that reflects their firm commitment to continue helping those affected in the future. This conviction has driven the creation of the Pediatric Cancer Center

Barcelona (PCCB)," adds Dr. Jaume Mora, the Scientific Director of said center at Sant Joan de Déu Hospital and coordinator of the Pediatric Cancer Programme at IRSJD.

"This study not only contributes significantly to our understanding of pediatric cancer but also emphasizes the importance of improving treatments, with patients´ futures in mind, ensuring not only their survival but also their long-term quality of life," says Dr. Núria López-Bigas, ICREA researcher at IRB Barcelona and co-lead of Cancer Grand Challenges team PROMINENT.

More information: Mònica Sánchez-Guixé et al, Origins of second tumors and mutational footprint of chemotherapy in normal tissues, *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-23-1186

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