Hôpital général juif
Jewish General Hospital

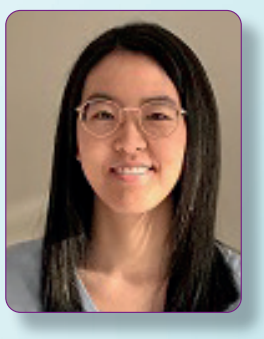
McGill

INSTITUT LADY DAVIS DE RECHERCHES MÉDICALES | LADY DAVIS INSTITUTE FOR MEDICAL RESEARCH

PAPER OF THE MONTH • MARCH 2023

Anne-Sophie Chong, MSc

PhD student, University of Barcelona, Spain



Anne-Laure Chong

Research Assistant, Foulkes Laboratory, Lady Davis Institute

William Foulkes, MBBS, PhD, FRCP

Head, Cancer Genetics Laboratory, Lady Davis Institute

Director, Program in Cancer Genetics, Jewish General Hospital

James McGill Professor, Oncology,
Medicine and Human Genetics, McGill

nature communications

Genomic characterization of DICER1-associated neoplasms uncovers molecular classes

Felix K. F. Kommoss, Anne-Sophie Chong, Anne-Laure Chong, Elke Pfaff, David T.W. Jones, Laura S. Hiemcke-Jiwa, Lennart A. Kester, Uta Flucke, Manfred Gessler, Daniel Schrimpf, Felix Sahm, Blaise A. Clarke, Colin J. R. Stewart, Yemin Wang, C. Blake Gilks, Friedrich Kommoss, David G. Huntsman, Ulrich Schüller, Christian Koelsche, W. Glenn McCluggage, Andreas von Deimling and William D. Foulkes.

DICER1 syndrome is a tumor predisposition syndrome that is associated with up to 30 different tumors, usually affecting children and adolescents.

Here we identify a group of mesenchymal tumors (i.e., soft tissue tumors, also known as connective tissue tumors) which is highly associated with DICER1 syndrome (i.e., mutations in the DICER1 gene increase the risk of certain types of tumors, including tumors of the kidney, thyroid, ovary, cervix, testicle, brain, eye, and lining of the lung), and which is molecularly distinct from other DICER1-associated tumors. This group of DICER1-associated mesenchymal tumors encompasses multiple well-established tumor entities and can be further divided into three clinically meaningful classes designated “low-grade mesenchymal tumor with DICER1 alteration” (LGMT DICER1), “sarcoma with DICER1 alteration” (SARC DICER1), and primary intracranial sarcoma with DICER1 alteration (PIS DICER1).

The identification of these DICER1-associated tumor classes from various anatomical sites will enable meaningful clinical trial stratification (i.e., subgrouping) in the future and suggests that rational drug development addressing the differing molecular foundations of mesenchymal tumors with DICER1 alteration may be a plausible goal.

Our study not only provides a combined approach to classify DICER1-associated tumors for improved clinical management but also suggests a role for global hypomethylation (a hallmark of cancer) and other recurrent molecular events in progression to malignancy in mesenchymal tumors with DICER1 alteration. In our study, DNA methylation profiling was able to classify tumors of the female genital tract previously diagnosed as MAS, ERMS or MAS/ERMS (cases which could not be confidently diagnosed as either of these tumor types due to morphological overlap) into specific clusters of MAS or SARC DICER1, highlighting the potential for molecular markers to aid tumor classification.

Our results will facilitate future investigations into prognostication and therapeutic approaches for affected patients.

https://www.nature.com/articles/s41467-023-37092-w.