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MESOMICS project uncovers molecular variation in mesothelioma, paving the way for improved diagnosis and treatment

Lyon, France, 16 March 2023 – Malignant pleural mesothelioma (MPM), a deadly cancer with no cure, has confounded doctors for decades. MPM is associated with asbestos exposure and remains a major public health concern, with many countries still using asbestos despite its classification as a carcinogen by the International Agency for Research on Cancer (IARC) more than 50 years ago. The Rare Cancers Genomics Team at IARC has used sequencing data to uncover sources of molecular variation in MPM, paving the way for a revised classification system that could change the manner in which the disease is diagnosed and treated.

The MESOMICS project represents the most comprehensive molecular characterization of MPM to date, using the largest whole-genome sequencing dataset yet reported. The researchers demonstrated that the current World Health Organization classification system for MPM only accounts for up to 10% of molecular differences between patients. Four factors were identified by which to categorize MPM: (i) the number of chromosomes in the cancer cells; (ii) the morphological appearance of the cancer cells; (iii) the patient's immune-system response to the cancer; and (iv) how certain parts of the cancer genes are turned on or off by epigenetic marks. These four factors capture major inter-patient molecular differences and could be used to develop a new, more comprehensive classification system for MPM.

The study, published in the journal *Nature Genetics*,[1] is the largest of its kind, using whole-genome sequencing data from more than 120 patients with MPM. "Our findings unearth the interplay between MPM functional biology and its genomic history and provide insights into the variations observed in the clinical behavior of MPM patients", the researchers said in the article. "The four molecular factors we identified are complementary, capture major inter-patient molecular differences, and are delimited by extreme phenotypes that reflect tumor specialization. Our work paves the way for a future revised classification of MPM that takes these molecular variations into account and could improve the diagnosis and treatment of this deadly disease."

These findings represent a major step forward in the battle against MPM, in line with the global goal of the Rare Cancers Genomics initiative (https://rarecancersgenomics.com), which aims to shed light on the molecular

[1] Mangiante L, Alcala N, Sexton-Oates A, Di Genova A, Gonzalez-Perez A, Khandekar A, et al. (2023). Multiomic analysis of malignant pleural mesothelioma identifies molecular axes and specialized tumor profiles driving intertumor heterogeneity. *Nat Genet,* Published online 16 March 2023; https://doi.org/10.1038/s41588-023-01321-1

characteristics of rare cancers to ultimately improve the clinical management and prognosis of patients with these frequently neglected and forgotten diseases.

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