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SPATIAL MULTIOMICS PROFILING REVEALS IMMUNE AND PROLIFERATIVE MARKERS OF MOYAMOYA DISEASE

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Background and aims: Moyamoya disease (MMD) is a rare cerebrovascular disorder characterized by progressive intracranial arterial stenosis and fragile collateral vessel formation. Excessive proliferation of vascular smooth muscle cells (VSMCs) with contractile-to-synthetic phenotypic switching is a central pathological feature, yet the molecular mechanisms driving these changes remain incompletely understood.

Methods: We studied 12 patients with well-documented MMD, including one post-mortem autopsy case, using a multi-omics approach integrating whole-exome sequencing and plasma proteomics. To obtain spatially resolved molecular insights, we performed in-depth spatial proteomics on an occluded intracranial artery retrieved post-mortem from one idiopathic MMD patient, combining targeted antibody-based imaging with laser capture microdissection and mass spectrometry.

Results: Genetic predispositions were identified in 8 of 12 patients (67%), including variants in the major susceptibility gene RNF213 and other pathogenic conditions such as trisomy 21 and variants in ACTA2, SAMHD1, and NFIA. Spatial proteomics revealed VSMC phenotypic switching, with loss of contractile markers, gain of synthetic markers, and infiltration of VSMCs into the intima. Notably, increased expression of cellular fibronectin in the occluded artery correlated with elevated plasma levels, suggesting its potential as a tissue leakage biomarker. In addition, infiltration of macrophages and antigen-presenting cells indicated an inflammatory contribution to disease progression. In ongoing work, we are extending these analyses with spatial and single cell transcriptomics data.

Conclusions: This study provides an unprecedented spatial molecular view of an occluded moyamoya artery, identifying synthetic VSMC infiltration, immune activation, and cellular

fibronectin as key features, with implications for future biomarker development and mechanistic studies.

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