Establishing a Foundation for Next-Generation Preventive Medicine Targeting Clonal Hematopoiesis in Older Adults

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This study aims to elucidate the impact of clonal hematopoiesis (CH) on COVID-19 severity and a broad range of disease risks, as well as the underlying pathophysiological mechanisms. Using Japan's largest COVID-19 cohort comprising 4,731 individuals, we performed integrated genomic, transcriptomic, and proteomic analyses. CH-positive individuals exhibited an increased risk of severe COVID-19, with mutations other than DNMT3A and TET2 (non-DT mutations) showing a particularly strong association. RNA-seq analyses revealed activation of inflammatory pathways in individuals with non-DT mutations, suggesting that inflammatory responses are already heightened prior to infection. In addition, analysis of approximately 55,000 participants from Biobank Japan identified CH in about 20% of individuals and led to the discovery of both known and novel CH driver genes. Moving forward, we plan to integrate comprehensive clinical data and multi-omics datasets from Biobank Japan to further characterize CH-associated pathophysiology. These findings provide an important foundation for developing CH-based disease risk prediction models and preventive strategies for severe outcomes in future pandemics.