“SIMPLE MENDELIAN DISEASE” IS SIMPLISTIC: THE CASE OF SICKLE CELL DISEASE

Although sickle cell disease (SCD) results from a single mutation in the HBB gene, its clinical expression is highly variable. In a recent commentary[1], A. Starlard-Davenport uses SCD as a case study to challenge the notion that monogenic disorders are inherently simple.

Genetic modifiers such as BCL11A, HBS1L-MYB, and HBG2, which influence fetal hemoglobin (HbF) levels, along with epigenetic mechanisms and environmental factors, contribute to the disease’s complexity.

Social determinants, healthcare disparities, and limited access to advanced therapies further exacerbate outcomes, particularly in underserved populations.

SCD highlights the inadequacy of labeling monogenic conditions as “simple” and underscores the need for personalized, multidisciplinary care.

1. https://www.cell.com/ajhg/abstract/S0002-9297(25)00189-2?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929725001892%3Fshowall%3Dtrue