Pharmacogenomics of Sickle Cell Disease Therapeutics

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Sickle cell disease (SCD) is the first disease whose genetic etiology was defined, and is one of the most common severe monogenic diseases in humans. SCD refers to a group of recessively inherited blood disorders characterized by the predominance of sickle hemoglobin (HbS), the result of a single nucleotide change in the structural gene for the beta unit of hemoglobin, causing sickling of red blood cells (RBCs) under hypoxic conditions, vaso-occlusion and adherence to other cells and endothelium, and downstream cellular and organ damage, ultimately resulting in higher morbidity and mortality relative to healthy people.

Data are emerging with pharmacogenomics (PGx) associations for therapeutics for patients with sickle cell disease, specifically with regard to hydroxyurea. Although early data suggest PGx associations with hydroxyurea, these have not yet resulted in clinical guidelines for use in guided therapy. Aside from disease-modifying therapy, patients with SCD receive many drugs for supportive care to manage symptoms such as pain, anticoagulation and iron chelation. Mental health issues are also very common, with the prevalence of depression estimated to be between 25% and 40%. The nature of SCD as a chronic disease results in high healthcare utilization and exposure to multiple drugs and drug classes over a patient's lifespan.

Furthermore, metabolic profiling differentiated SCD from healthy controls and patients with various genotypes. Associations with hemolysis, vaso-occlusive events, nephropathy, pulmonary hypertension, and mortality were identified, thus making metabolomics the most promising "omics" related to the SCD. Although several studies reported metabolic effects of hydroxyurea, transfusion therapy, and mitapivat, other therapies such as L-glutamine, crizanlizumab, and other curative treatments or drugs remain underexplored. Therapy adherence complicates the interpretation of treatment effects on the metabolome. This issue is specifically relevant for hydroxyurea, in which poor adherence is a well-known phenomenon. Metabolomics-based assessment of hydroxyurea exposure, as already done for mitapivat, could reduce confounding factors, improve treatment predictions, and optimize disease management in SCD. While most studies compared metabolic profiles between treated and untreated patients, future research should also focus on understanding individual treatment responses to support personalizing treatment strategies. It seems that in SCD significant effort has gone into attempting to define a composite measure of sickle cell severity, which can be used to compare changes in either individual or panels of biomarkers.

As there has been no consensus in the field on a composite definition of sickle severity, it is likely that each clinical manifestation will have its own set of non-overlapping biomarkers, in addition to those that are in common. The former will be of greater interest for predicting severity and guiding appropriate therapeutic approaches or precision medicine.