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342 - GENOME-WIDE ASSOCIATION STUDY OF REDOX-RELATED MARKERS: AN INTEGRATIVE APPROACH TO INFORM POTENTIAL COLOCALIZATION STUDIES

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Resumen

Background/Objectives: Oxidative stress and inflammation are tightly interconnected processes involved in the development of multiple chronic diseases. Although redox imbalance has been proposed as a common underlying mechanism across a wide range of health conditions, genome-wide association studies (GWAS) of oxidative stress biomarkers remain scarce. Our aim was to explore the genetic architecture of key redox biomarkers and explore regulatory mechanisms that may link genetic variation to complex diseases.

Methods: High-quality GWAS summary statistics (TOPMED imputed SNPs from Illumina GSA), for three oxidative stress biomarkers: 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG), malondialdehyde (MDA), and the ratio of oxidized to reduced glutathione (GSSG/GSH); were obtained following metaGWASmanager pipeline in the Hortega Study population (N = 1,429). Downstream analyses included quality control filtering, linkage disequilibrium clumping, SNP annotation, functional enrichment, protein-protein interaction network, hubs identification, and integration of expression quantitative trait locus (eQTL) data to identify potential regulatory signals and colocalization hotspots.

Results: The analyses revealed a predominantly trait-specific genetic architecture, with limited overlap of associated SNPs across biomarkers in the overall population. Functional annotation highlighted genes with potential relevance to redox biology, including POLR1C, WWOX and STX8 for 8-oxo-dG; EGFR, NCK2 and ESRRG for MDA; and CCDC102B and CDCA7L for GSSG/GSH. Enrichment analyses consistently pointed to signalling-related pathways and mitochondrial-associated processes, as well as genes previously implicated in nervous system and cardiovascular diseases. Integration of eQTL data identified tissue-specific regulatory associations for a limited subset of statistically significant SNPs, particularly for MDA, highlighting candidate loci of interest for subsequent colocalization and mendelian randomization studies.

Conclusions/Recommendations: This integrative post-GWAS analysis framework points to potentially novel molecular mechanisms underlying redox-related traits and regulatory loci that may contribute to redox imbalance across biological systems. Although findings are exploratory, the results support the use of integrated GWAS-eQTL approaches and suggest that genetic signals may inform future colocalization studies aimed at refining causal links between oxidative stress and complex diseases beyond cancer and cardiovascular conditions.

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