Gac Sanit. 2025;39(S2):229

Gaceta Sanitaria

https://www.gacetasanitaria.org

915 - GENOME-WIDE ASSOCIATION STUDY AND METANALYSIS OF ESSENTIAL ELEMENTS: PRELIMINARY RESULTS FROM THE METAL-GWAS INITIATIVE SPANISH COHORTS

L. Sánchez-Rodríguez, R. González-Martín, Z. Rodríguez-Hernández, P. Fernández-Navarro, M. Grau-Pérez, J.C. Martín-Escudero, B. Moreno, K. Kahe, M. Téllez-Plaza

Department of Chronic Diseases Epidemiology, CNE-ISCIII; Institute of Genetic Epidemiology, UCF Freiburg; Department of Statistics and Operational Research, UV; HURT; IIS Aragon, HUMS; Department of Environmental Health Sciences, New York; IDIBELL; Department of Genetics, TBI, TX.

Resumen

Background/Objectives: Genetic variation has been linked to essential elements overload or deficiency, which has major health implications. However, previous genome-wide association studies (GWAS) of essential trace elements have been modest in sample size. We propose a multi-cohort meta-analysis approach aimed at identifying genetic regions consistently associated with biomarkers of essential element concentrations.

Methods: Six international cohorts are currently participating in the metal-GWAS initiative: AWHS, Hortega and MCC (Spain), and MESA, REGARDS and SHS (US). For this pilot analysis, we used data from AWHS (n = 1,852) and Hortega (n = 1,421) participants with measured concentrations of essential metals in plasma or urine, along with TOPMed-imputed SNPs. GWAS were conducted separately in each cohort using REGENIE, and results were meta-analyzed using METAL, following the metalGWAS pipeline.

Results: We identified genome-wide significant SNPs ($p < 5\times10?8$) associated with plasma levels of cobalt (5 SNPs, including rs12001012 [$p = 1.82 \times 10^{-8}$, ? = 0.51], located in ZNF782, a gene known to be involved in DNA binding), copper (SNP rs6979036 [$p = 1.09 \times 10^{-8}$, ? = -0.20] located in ADAP1, a gene involved in intracellular signaling) as well as with urinary molybdenum (4 SNPs, including rs72965589 [$p = 3.60 \times 10^{-8}$, ? = -0.56], located in TMEM135, a gene involved in mitochondrial dynamics). Plasma zinc showed the highest number of associations, including rs185659820 ($p = 1.10 \times 10^{-11}$, ? = -0.51) and rs945992692 ($p = 3 \times 10^{-12}$, ? = 0.55), located in FYB1 and RPTOR, respectively. These genes encode proteins involved in immune cell signalling and nutrient-sensitive pathways regulating cell growth.

Conclusions/Recommendations: This pilot meta-analysis identified genomic regions associated with essential metal concentrations. Expanding the sample with additional cohorts will strengthen the Metal-GWAS initiative and enable more robust and reproducible assessment of potential metal-related health effects and gene-environment interactions. Other epidemiologic studies with available metal biomarkers and genomic data are welcome to join this collaborative effort.

Funding: AESI PI20CIII/0029, AEI PID2019-108973RB-C21 and PID2023-147163OB-C22.