Large-scale pharmacogenomics analysis of cancer patients in UK Biobank: Integrating WGS and medical records to inform clinical practice.

Anoop Joseph[1], Rodney Lea[1], Euan Walpole[2], Shivashankar Nagaraj[1]

[1]CGPH, School of Biomedical Sciences, QUT; [2]Cancer Alliance Queensland, Australia.

Background: Cancer medications are frequently associated with severe adverse effects, affecting nearly half of all patients and often resulting in suboptimal treatment. A large proportion of these medication-related toxicities arise from inherited genetic variations in genes that regulate drug metabolism or action - an area studied through pharmacogenomics (PGx). By identifying patients who carry PGx variants, treatment can be personalised to reduce toxicity and improve therapeutic outcomes.

Methods: Germline whole-genome sequencing (WGS) data from 99,548 UK Biobank participants were analysed to identify pharmacogenetic variants in five key PGx genes - DPYD, CYP2D6, NUDT15, TPMT, and MTHFR – each associated with toxicity induced by commonly used cancer medications (Fluorouracil (5-FU), Capecitabine, Tamoxifen, Mercaptopurine, and Methotrexate). Genomic data were integrated with drug prescription records and hospital medical records (ICD-10) to perform a phenome-wide association study (PheWAS), to identify whether adverse drug reaction (ADR)-related phenotypes were enriched among drug-exposed individuals carrying relevant PGx variants. Subgroup analyses were performed by cancer type and ancestry. The PyPGx tool was used to assign star-allele diplotypes and metaboliser categories for each gene, and CPIC guideline-based pharmacogenomic treatment recommendations were generated for the full cohort. In a focused analysis of 2,105 female breast cancer patients, CYP2D6 variants were evaluated for associations with Tamoxifen-related ADRs.

Results: We identified 246 Level 1A-evidence PGx variants across the five genes, as catalogued in ClinPGx, representing all reported star-allele defining variants. Of these, 122 variants were present in the UK Biobank cancer cohort. PheWAS analysis showed significant associations between ADR-related phenotypes and no-function or decreased-function variants in DPYD, NUDT15, and MTHFR. Treatment recommendations derived from metaboliser categories indicated potential dose reduction or alternative therapy for 50.2% of cancer patients if treated with Mercaptopurine (TPMT/NUDT15), 39.8% for Tamoxifen (CYP2D6), and 5.1% for 5-FU/Capecitabine (DPYD). In the breast cancer subgroup, CYP2D6 PGx variants showed significant associations with Tamoxifen-related toxicity phenotypes.

Conclusions: Integrating PGx variants from germline WGS with medical records can provide clinically actionable insights. Identifying high-risk patients based on their PGx profile enables more informed prescribing decisions and can help reduce the likelihood of ADRs.