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Genetically Informed Precision Drug Repurposing for Rheumatoid Arthritis

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Abstract : Background: Rheumatoid arthritis (RA) is a chronic, systematic, inflammatory, autoimmune disease that involves damages to joints and erosions to the associated bones and cartilage, resulting in reduced physical function and disability. RA is a multifactorial disorder influenced by heterogenous genetic and environmental factors. Whilst different medications have proven successful in reducing inflammation associated with RA, they often come with significant side effects and limited efficacy. To address this, the novel pharmagenic enrichment score (PES) algorithm was tested in self-reported RA patients from the UK Biobank (UKBB), which is a cohort of predominantly European ancestry, and identified individuals with a high genetic risk in clinically actionable biological pathways to identify novel opportunities for precision interventions and drug repurposing to treat RA. Methods and materials: Genetic association data for rheumatoid arthritis was derived from publicly available genome-wide association studies (GWAS) summary statistics (N=97173). The PES framework exploits competitive gene set enrichment to identify pathways that are associated with RA to explore novel treatment opportunities. This data is then integrated into WebGestalt, Drug Interaction database (DGIdb) and DrugBank databases to identify existing compounds with existing use or potential for repurposed use. The PES for each of these candidates was then profiled in individuals with RA in the UKBB (Ncases = 3,719, Ncontrols = 333,160). Results A total of 209 pathways with known drug targets after multiple testing correction were identified. Several pathways, including interferon gamma signaling and TID pathway (which relates to a chaperone that modulates interferon signaling), were significantly associated with self-reported RA in the UKBB when adjusting for age, sex, assessment centre month and location, RA polygenic risk and 10 principal components. These pathways have a major role in RA pathogenesis, including autoimmune attacks against certain citrullinated proteins, synovial inflammation, and bone loss. Encouragingly, many also relate to the mechanism of action of existing RA medications. The analyses also revealed statistically significant association between RA polygenic scores and self-reported RA with individual PES scorings, highlighting the potential utility of the PES algorithm in uncovering additional genetic insights that could aid in the identification of individuals at risk for RA and provide opportunities for more targeted interventions. Conclusions In this study, pharmacologically annotated genetic risk was explored through the PES framework to overcome inter-individual heterogeneity and enable precision drug repurposing in RA. The results showed a statistically significant association between RA polygenic scores and self-reported RA and individual PES scorings for 3,719 RA patients. Interestingly, several enriched PES pathways were targeted by already approved RA drugs. In addition, the analysis revealed genetically supported drug repurposing opportunities for future treatment of RA with a relatively safe profile.

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