Local Genetic Correlation and Pleiotropy Between Serum Urate and Gout

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Introduction

Gout is a common form of arthritis caused by the deposition of monosodium urate (MSU) crystals, typically arising in the setting of hyperuricemia. Although elevated serum urate is a primary risk factor for gout, most individuals with hyperuricemia remain asymptomatic throughout their lives. This clinical divergence indicates that factors beyond urate regulation drive the transition from hyperuricemia to symptomatic gout. Recent genome-wide association studies (GWAS) have demonstrated that while serum urate and gout share substantial polygenic architecture, a significant portion of gout risk is mediated through loci independent of urate level regulation.

However, conventional global genetic correlation analyses cannot capture regional heterogeneity, leaving it unclear whether shared associations at specific loci reflect identical underlying genetic signals, distinct localized mechanisms, or gout-specific effects. To resolve these regional dynamics, local genetic correlation methods provide a powerful framework to disentangle shared pleiotropy from independent disease pathways.

Methods

Materials

Traits	Source	Ancestry	Sex	N (Cases/Controls)
Gout	GCST90428601 Major et al., 2024	European	Male	302,431 (22,784/279.647)
Serum Urate	GCST90319906 Cho et al., 2024	European	Both	677,373

- GWAS summary statistics were obtained from **GWAS Catalog harmonized files**.
- Gene regions were defined using **GRCh38** annotations.

Study Design

LDSC Analysis

- Genome-wide SNP-based heritability (h^2_{SNP})
- Global genetic correlation (r_g) and cross-trait intercept to estimate sample overlap.

LAVA Uni&Bivariate Analysis

- Extend each gene by 50 kb to form an LD block and use the UKB 10,000 genome as a reference panel.
- Univariate test: estimate local heritability of one trait.
- Bivariate test: for loci significant ($p < 0.05$) in both traits, estimate local genetic correlation (ρ) between two traits.

Gene Classification

	Gout P_{univar}	Urate P_{univar}	Bivariate P_{bivar} (H_0: $\rho = 1$)
H1: Gout-specific	≤ 0.05	> 0.05 (or NA)	-
H2: Urate-specific	> 0.05 (or NA)	≤ 0.05	-
H3: Shared Pleiotropic	≤ 0.05	≤ 0.05	> 0.05 (or NA)
H4: Independent Pathway	≤ 0.05	≤ 0.05	≤ 0.05

GO BP Enrichment

- Over-representation analysis (ORA) for Biological Process (BP) genes, applying Benjamini-Hochberg false discovery rate (FDR) correction (p−adjust < 0.05, $q < 0.2$).

Results

Table 1. Overall Genetic Heritability and Correlation for Serum Urate and Gout

	Estimate	SE
Urate SNP-h^2	8.18%	0.007
Gout SNP-h^2	11.35%	0.007
Genome-wide genetic correlation	87.06%	0.172

Fig 1. H1 (Gout-Specific): Top Loci Local Heritability
Top 5 loci ordered by Gout h² size

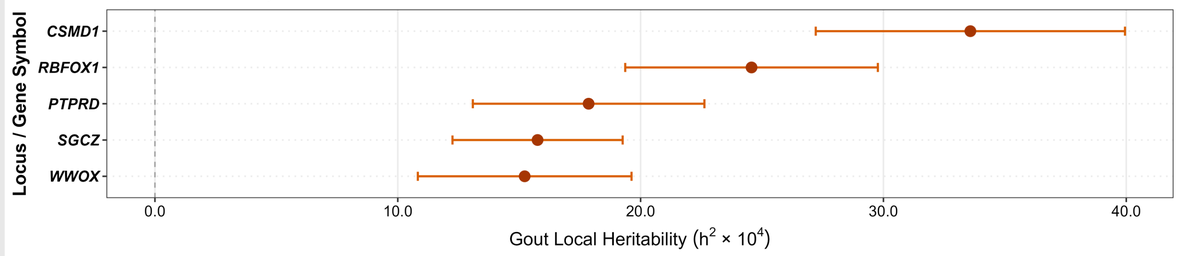
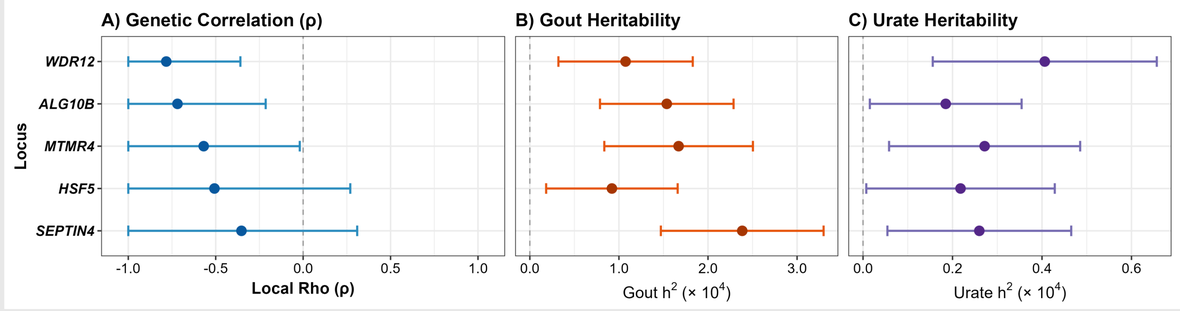
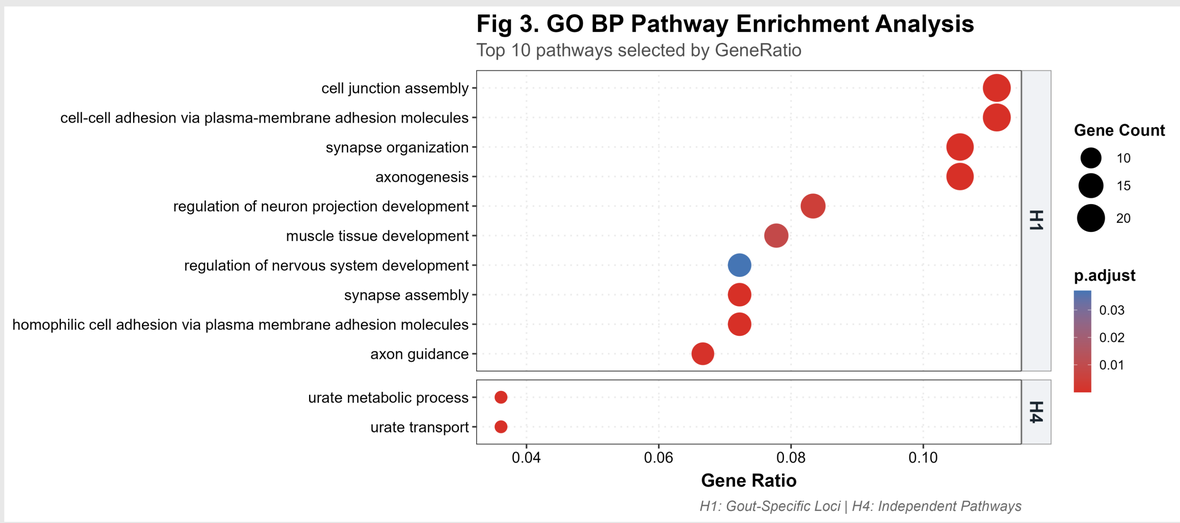


Fig 2. H4 (Independent Pathways): Bivariate LAVA Profile
Top discordant loci ordered by local genetic correlation (ρ)



A total of 5,077 and 194 loci were identified in the H1 and H4 categories, respectively. For GO enrichment analysis, the top 200 loci with the highest heritability (h^2) from the H1 category were selected.

Fig 3. GO BP Pathway Enrichment Analysis
Top 10 pathways selected by GeneRatio



Dichotomy of the Local Genetic Architecture

- **H4 Category (Independent Pathway):** Representing 194 loci characterized by discordant or independent local signal profiles, H4 is strictly and specifically enriched in fundamental physiological processes—namely, **urate metabolic process** and **urate transport** (Figure 3). These loci encapsulate the classic renal and intestinal transport genes (e.g., *SLC2A9*, *ABCG2*, *SLC22A12*) governing systemic serum urate homeostasis.
- **H1 Category (Gout-Specific):** Comprising 5,077 loci displaying prominent gout-specific local heritability (h^2), the top prioritized H1 loci were enriched in **cell junction assembly**, **cell-cell adhesion**, and **neurodevelopmental/synaptic organization** (e.g., axonogenesis, axon guidance, synapse organization). This highlights that local susceptibility to gout extends beyond serum urate supersaturation, heavily involving structural tissue integrity, tissue barrier permeability, and neuro-inflammatory sensing within the joint microenvironment.