Mendelian randomization using biological foundation models improves discovery power over additive QTLs and prioritizes cell-type specific therapeutic targets

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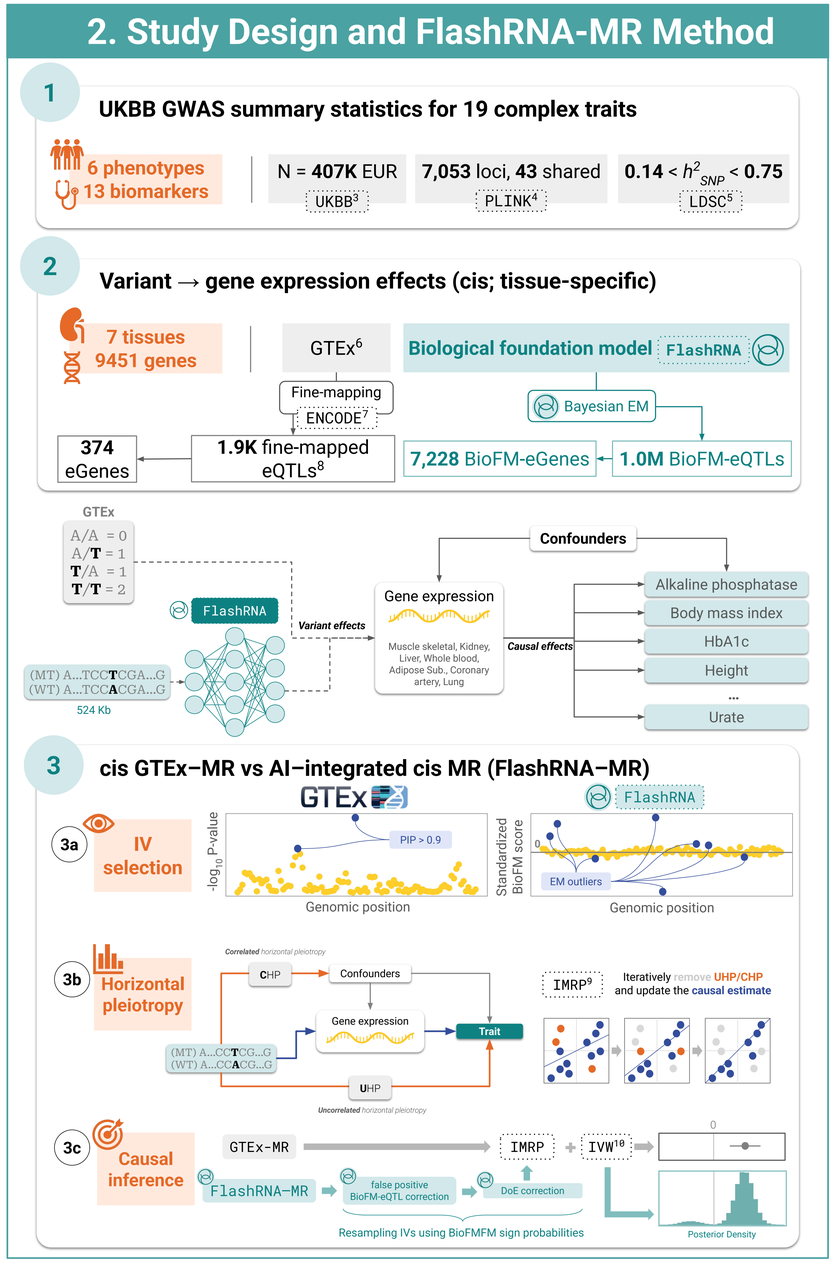
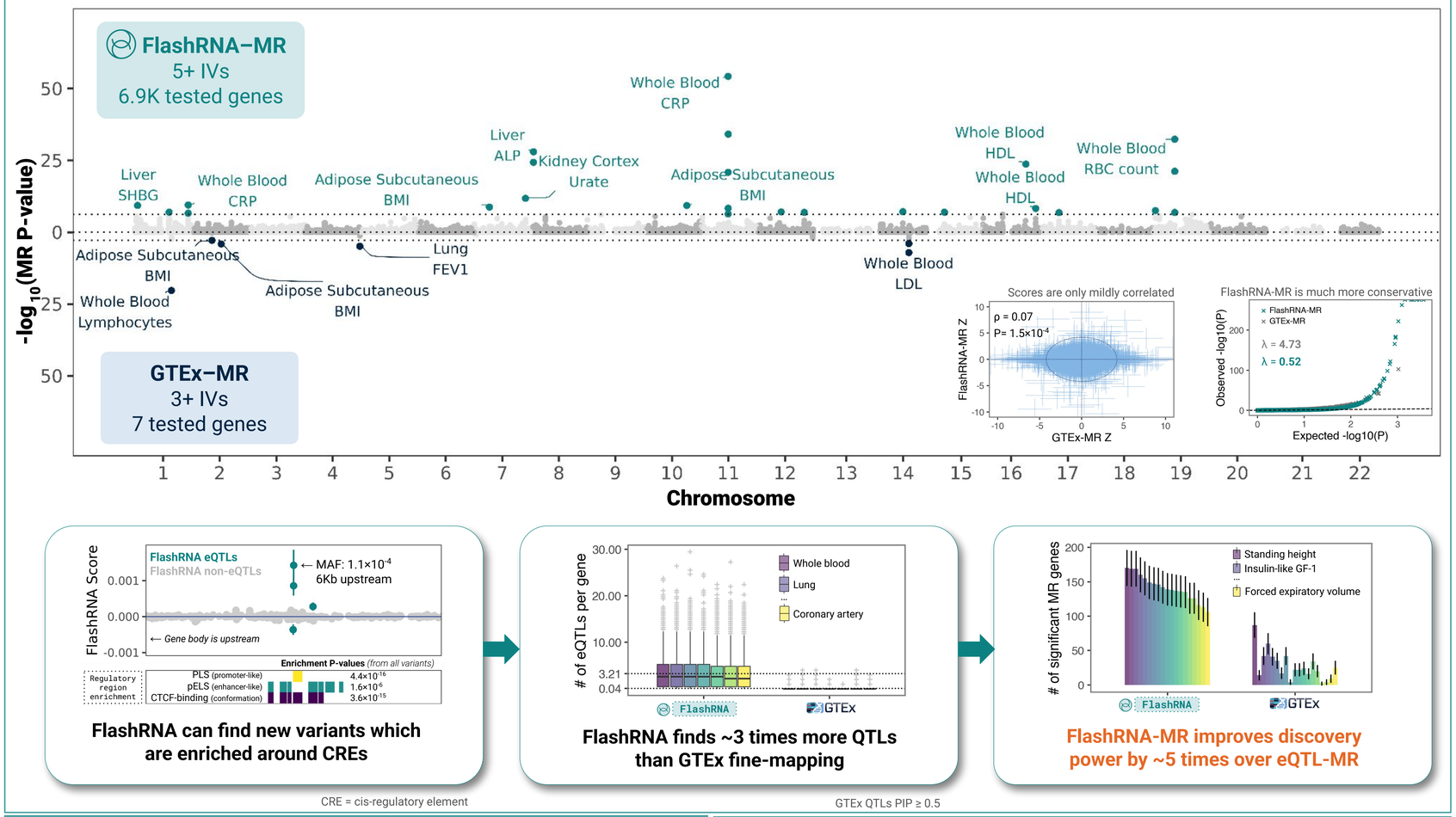
1. Background and Objectives

- **Biological foundation models** (BioFMs) such as FlashRNA[1] and AlphaGenome[2] can predict the regulatory effects of genetic variants across biological contexts, but frameworks for translating these predictions into **therapeutic target discoveries remain limited**.
- Mendelian Randomization (MR) is an established causal inference framework for target discovery that uses **genetically predicted molecular perturbations** to estimate a gene's effects on disease and other traits **using genetic variants as instrumental variables (IVs)**.
- **Quantitative trait loci (QTLs)** are genetic variants associated with variation in **molecular phenotypes**, such as gene expression (eQTLs).
- **Conventional MR** relies on experimentally measured QTLs, which may provide **few strong genetic instruments** due to low statistical power to detect them.
- We developed **AI-integrated Mendelian Randomization** (AIMR) to combine BioFM-predicted xQTLs with MR, enabling higher-powered, context-specific causal inference of **molecular mechanisms and therapeutic targets**.

2. Study Design and FlashRNA-MR Method



3. FlashRNA-MR finds 5x more genome-wide significant associations than eQTL-MR (n=141 vs 27)



FlashRNA can find new variants which are enriched around CREs

FlashRNA finds ~3 times more QTLs than GTEx fine-mapping

FlashRNA-MR improves discovery power by ~5 times over eQTL-MR

CRE = cis-regulatory element

GTEx QTLs PIP ≥ 0.5

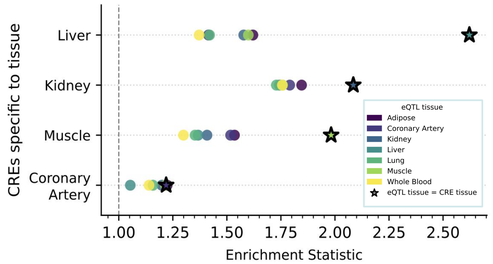
4. Next steps and future directions

Application

1. **Population-rare, high-impact variants may be better captured by the BioFM** than GTEx.
2. **Structural variants** characterized by the BioFM may have large functional effects and reveal key regulatory mechanisms.
3. **Cell type-specific BioFM predictions** from fine-tuned models may uncover novel cell & disease-specific therapeutic targets.

Methodological

1. Higher enrichment of **cis BioFM-eQTLs in tissue-specific CREs** suggests that active non-coding genomic regions could provide a **useful prior for BioFM-eQTL inference** across variant–gene pairs.
2. BioFM cis-variant effect estimates show **statistical correlation across genes and tissues**, highlighting an opportunity to further **improve inference by jointly modeling** or selecting among **correlated gene–tissue combinations**.



BioFM QTLs from FlashRNA are ~1.5x more enriched in CREs of their matched tissues than unmatched tissues

5. Study Conclusions

1. Here we introduce a method for **inferring QTLs** from BioFM models, finding at least one causal variant for **19x more genes** than cis-eQTLs from GTEx v8.
2. We show that these FlashRNA-QTLs can be used for discovery using **Mendelian Randomization (MR)** **increasing power by 5x** while remaining conservative.

This study demonstrates that BioFMs represent an important advance in causal target discovery when considered in robust analytical frameworks.

6. References

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