

Whole-genome and small RNA sequencing-based microRNA-eQTL mapping in Japanese elucidates variant-microRNA-disease links

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Conflict of Interest (COI) Disclosure

The author has no financial conflicts of interest to disclose.

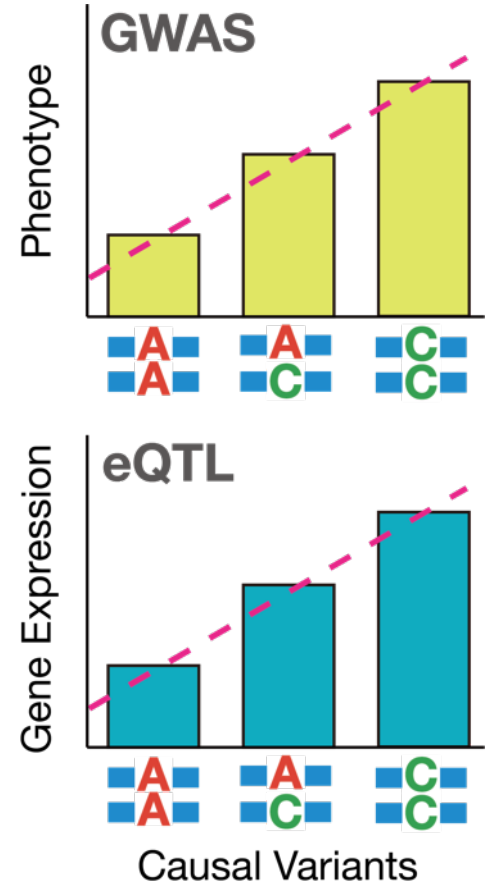
Interpretation of GWAS findings is a challenging problem.

> 50,000 of trait-associated genetic loci have been reported.
Most of them are situated in the *non-coding region*.



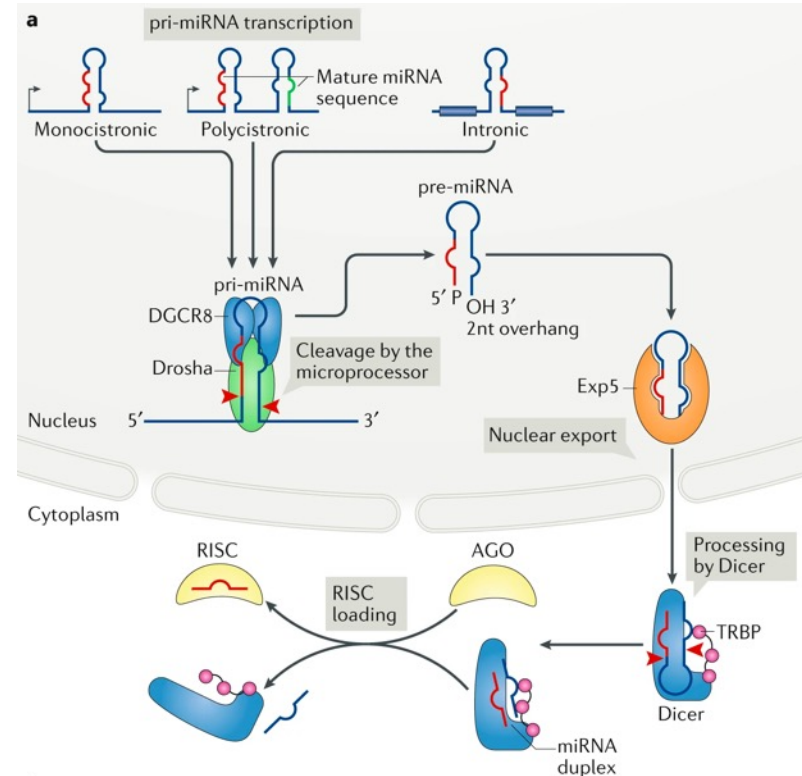
eQTL analysis links GWAS findings to gene expression

- Expression quantitative trait loci (eQTL) are genetic variants regulating gene expression.
- GWAS-identified variants significantly overlap with eQTL.
- While eQTL of protein-coding genes have been exhaustively investigated, eQTL studies on **non-coding genes** are limited.
- Non-coding RNA eQTL analysis will identify disease-associated non-coding RNAs.



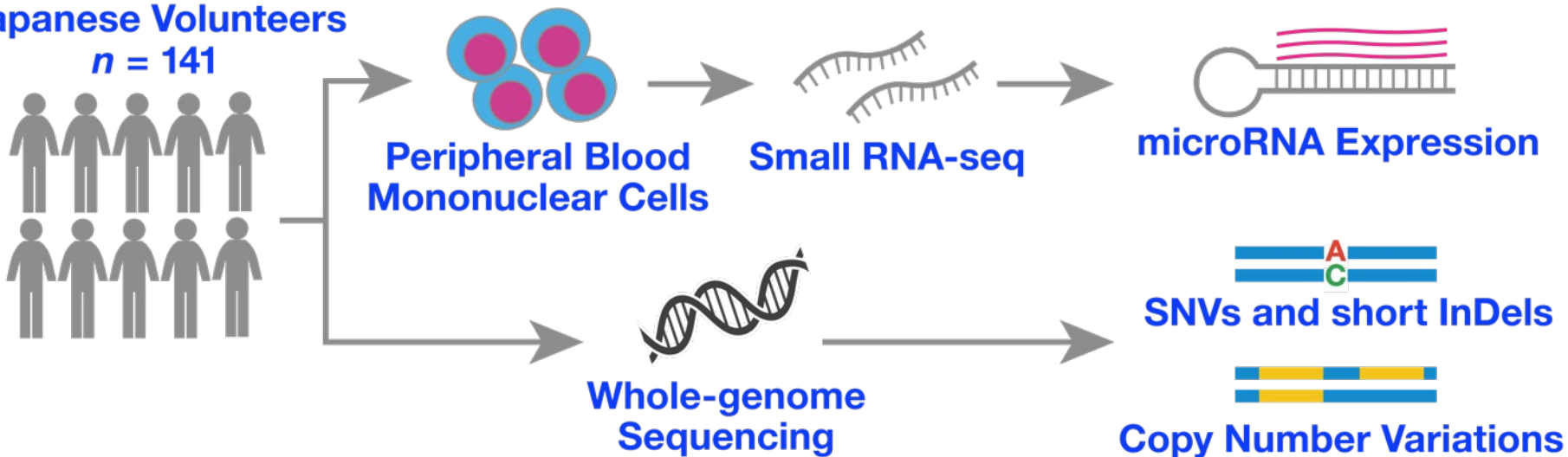
microRNA: a key post-transcriptional gene regulator

- Small non-coding RNA of 21–25 nt.
- miRNA plays a vital role in post-transcriptional gene regulation.
- miRNA is involved in diverse diseases.
- Despite its biological importance, **miRNA-eQTL have never been studied in the Asian populations.**



Study design

Japanese Volunteers
 $n = 141$

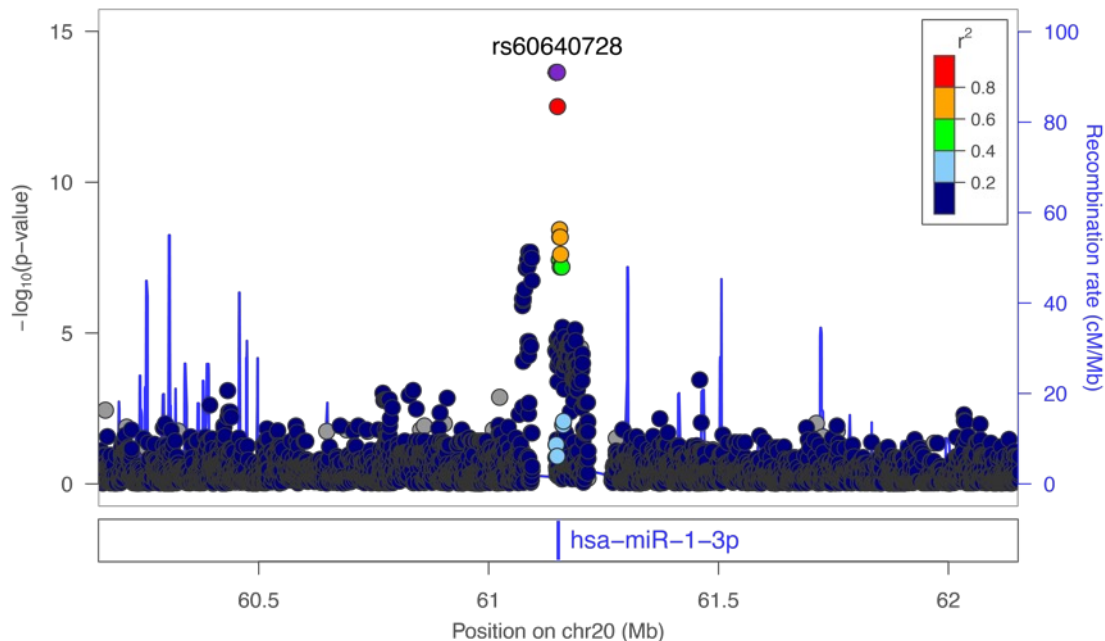
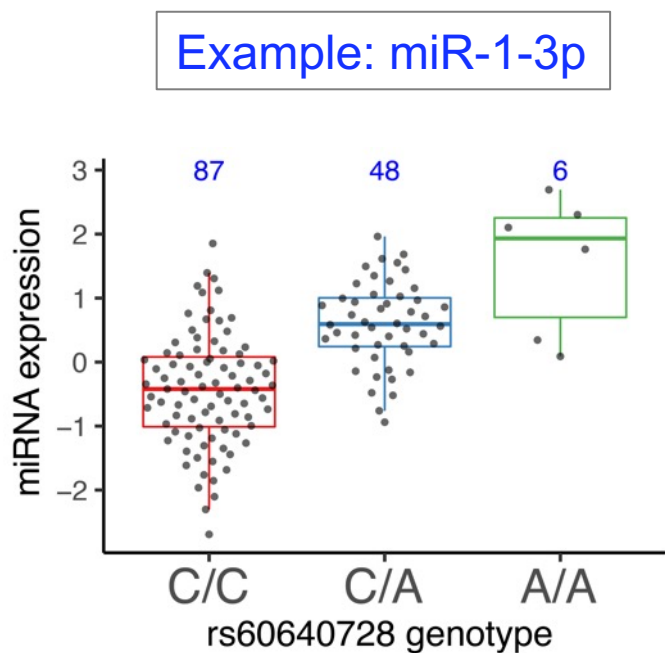


We performed

1. genome-wide miRNA-eQTL mapping of SNVs, short InDels, and CNVs
2. miRNA-editing detection
3. a miRNA transcriptome-wide association study (TWAS) to identify disease-associated miRNAs

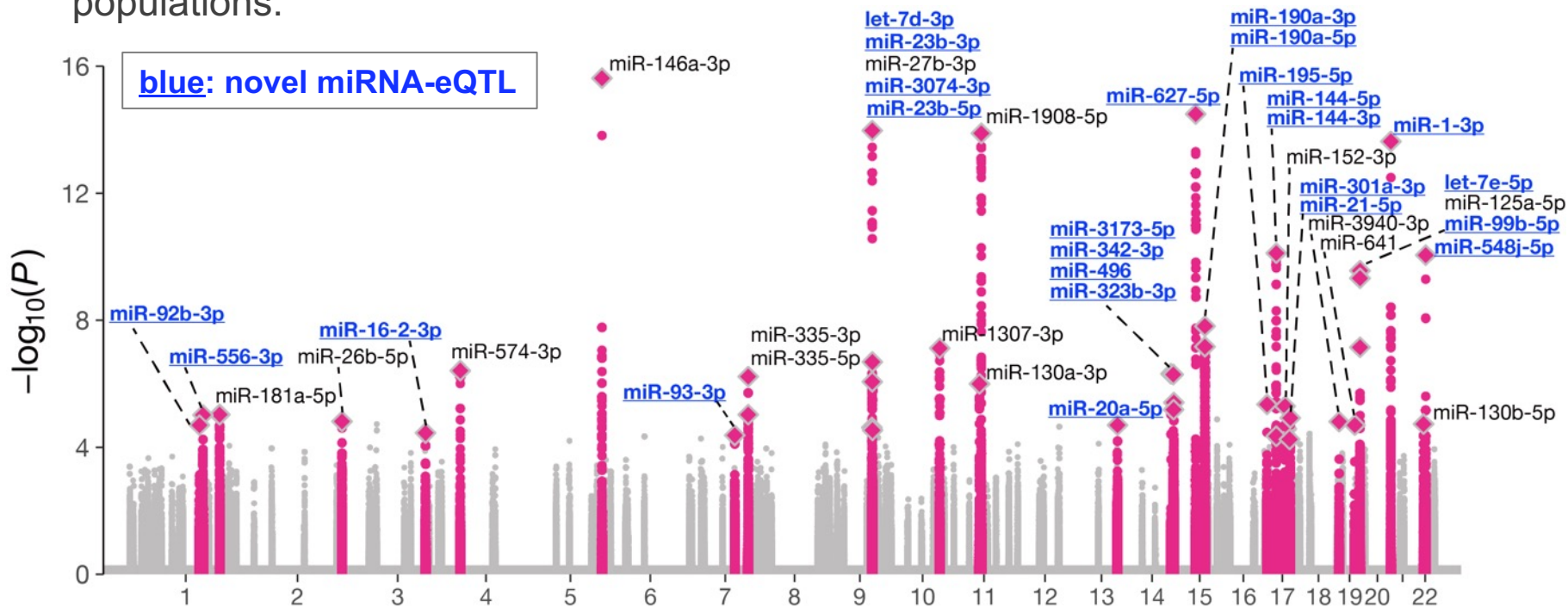
miRNA-eQTL analysis

- We correlated a total of 343 miRNA expression with adjacent genetic variants.



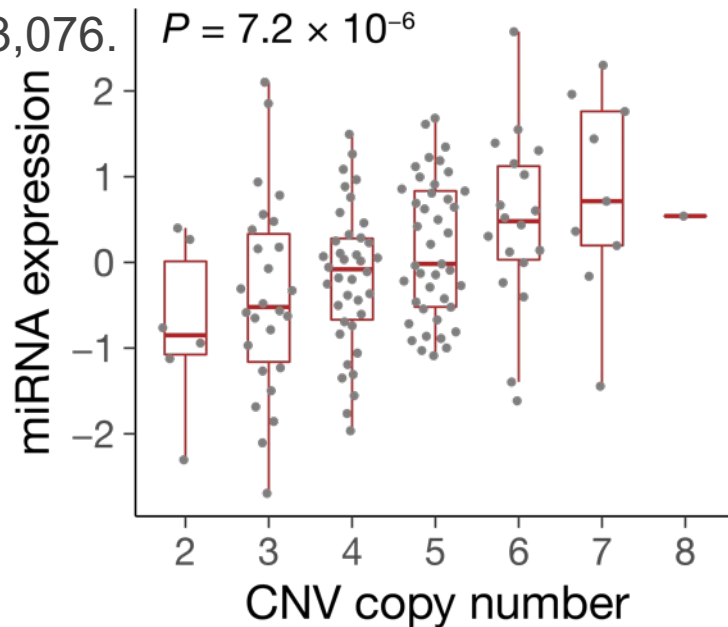
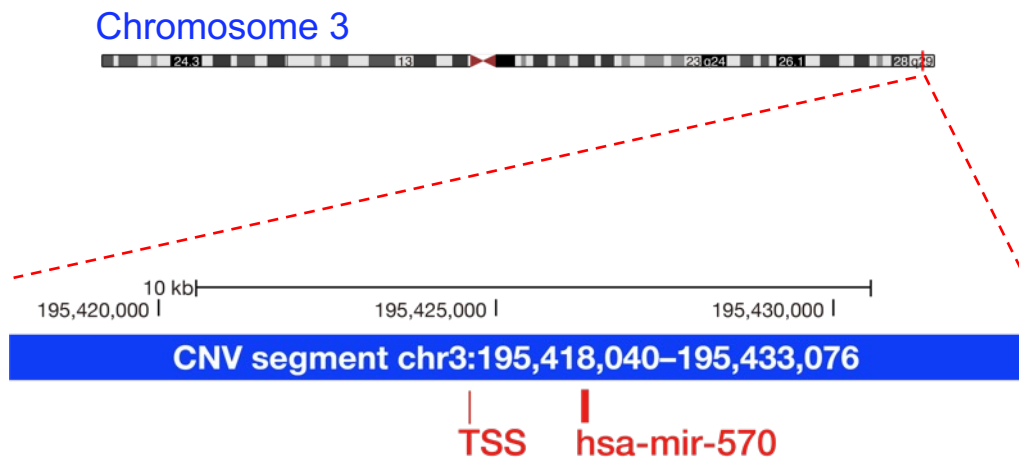
miRNA-eQTL analysis

- We identified **40 miRNAs having a significant eQTL**.
- Of these, **25 were unreported** in the previous miRNA-eQTL studies in the European populations.



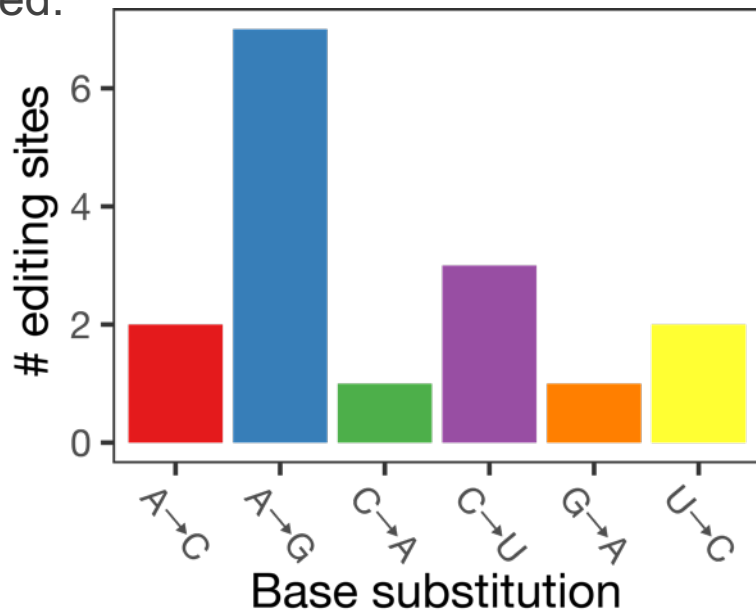
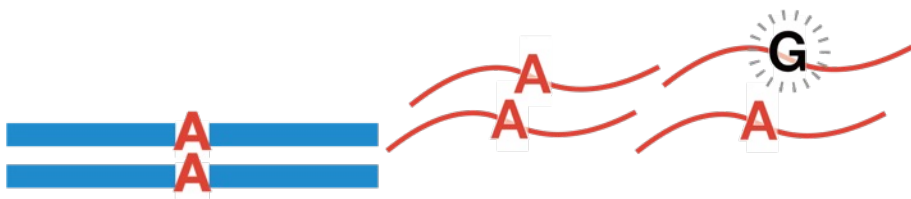
CNV influences miRNA expression

- We correlated **genomic copy number variations (CNVs)** with miRNA expression.
- We identified a significant association between miR-570 and a CNV chr3:195,418,040–195,433,076.



miRNA-editing detection

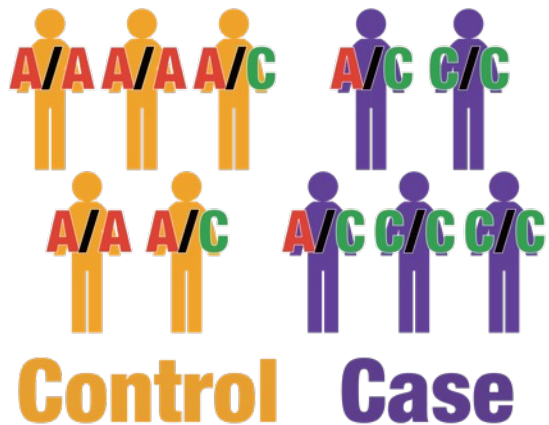
- To investigate a post-transcriptional modification in miRNA, we performed miRNA-editing calling.
- We detected **16 miRNA-editing sites**, among which the canonical RNA-editing of A-to-G substitution was most over-represented.



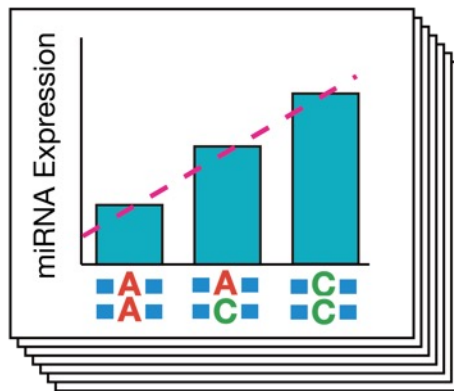
miRNA transcriptome-wide association study (TWAS) links disease risk to miRNA

- We trained a machine learning model **predicting miRNA expression based on multiple genetic variants**.
- Using this prediction model, we **correlated miRNA expression with disease risk**.

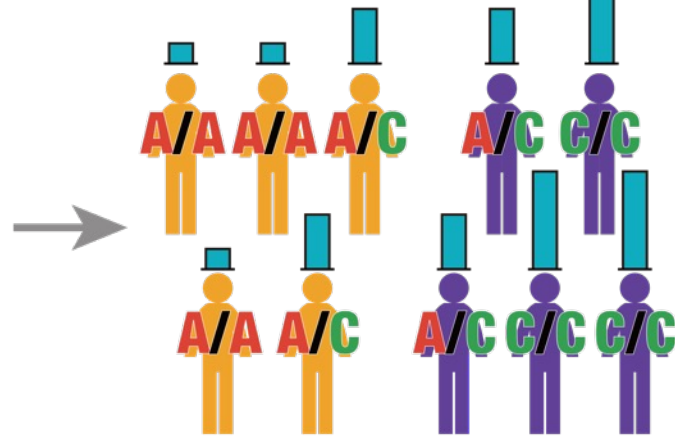
Genotype–Phenotype association (GWAS)



Genotype-based Expression prediction



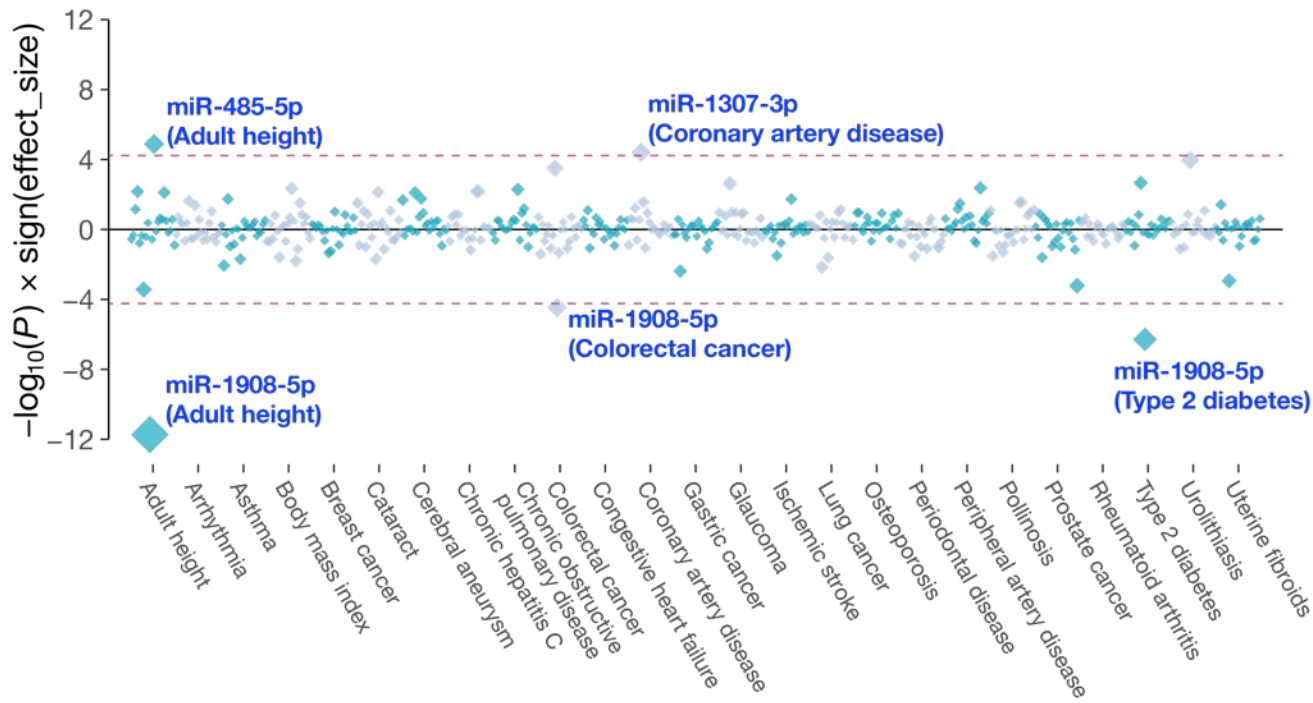
Expression–Phenotype association (TWAS)



miRNA TWAS identified

5 significant miRNA–phenotype associations

- Using large-scale Japanese GWASs of 25 complex traits (23 diseases, BMI, and adult height; mean $n > 190,000$), we performed a miRNA TWAS.



Conclusions

- We performed **the first miRNA-eQTL mapping in the Asian populations**.
- We identified **40 miRNAs** having a significant eQTL, including **25 novel ones**.
- We demonstrate that **genomic CNV influences miRNA expression**.
- We created **a catalog of miRNA-editing sites** in the Asian population.
- miRNA TWAS identified **5 significant miRNA–trait associations**.
- Our miRNA-eQTL resource should facilitate **interpretation of disease-associated genetic loci found in Asian populations**.
(***We will release the miRNA-eQTL data for public use!***)

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