



# Transcriptome-Wide Association Identifies KLC1 as a Regulator of Mitophagy in Non-Syndromic Cleft Lip with or without Palate

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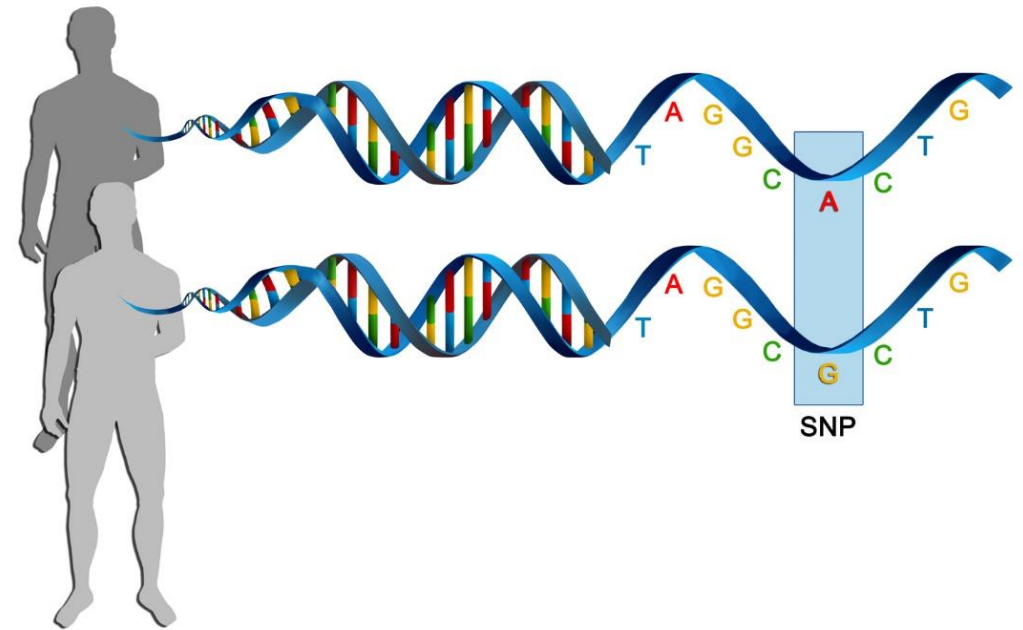
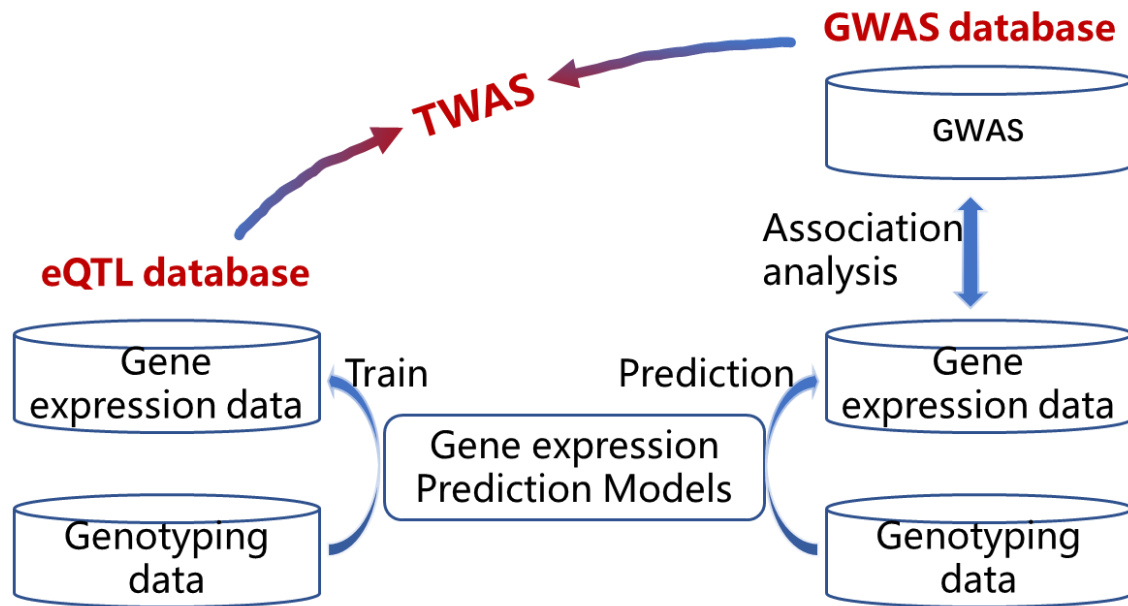
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# Introduction

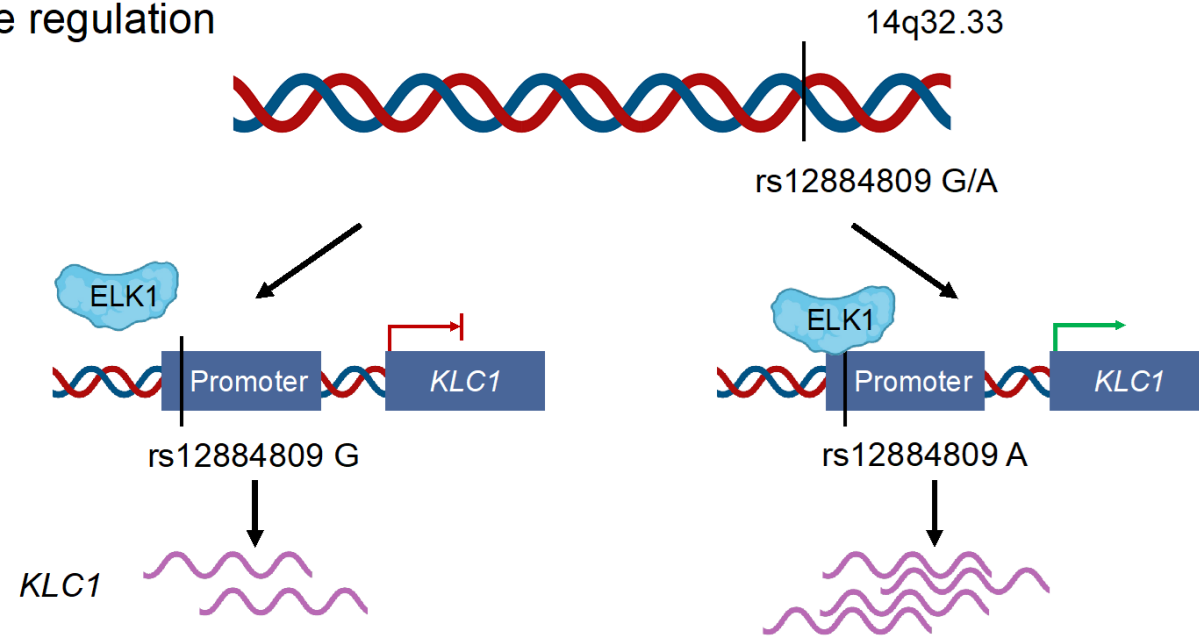


- ❑ Non-syndromic cleft lip with or without cleft palate (NSCL/P) is one of the most prevalent congenital craniofacial anomalies, affecting approximately one in 700 live births worldwide.
- ❑ It is crucial to integrate additional approaches with genome-wide association studies (GWAS) to gain a more comprehensive understanding of the biological underpinnings of disease risk.
- ❑ The present study systematically applies the transcriptome-wide association studies (TWAS) method to prioritize potential pathogenic genes involved in NSCL/P.

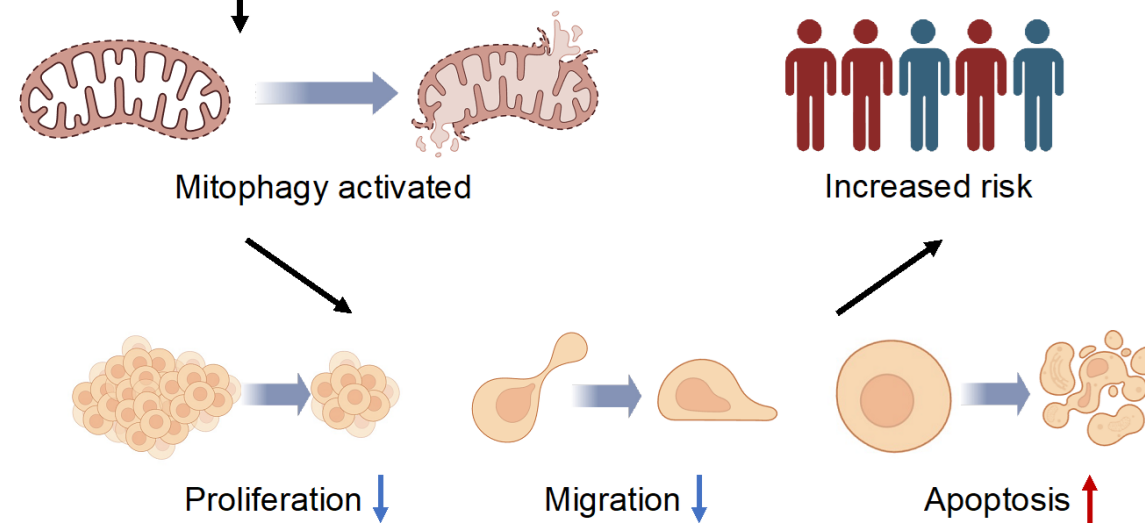


# Graphical abstract

## Gene regulation

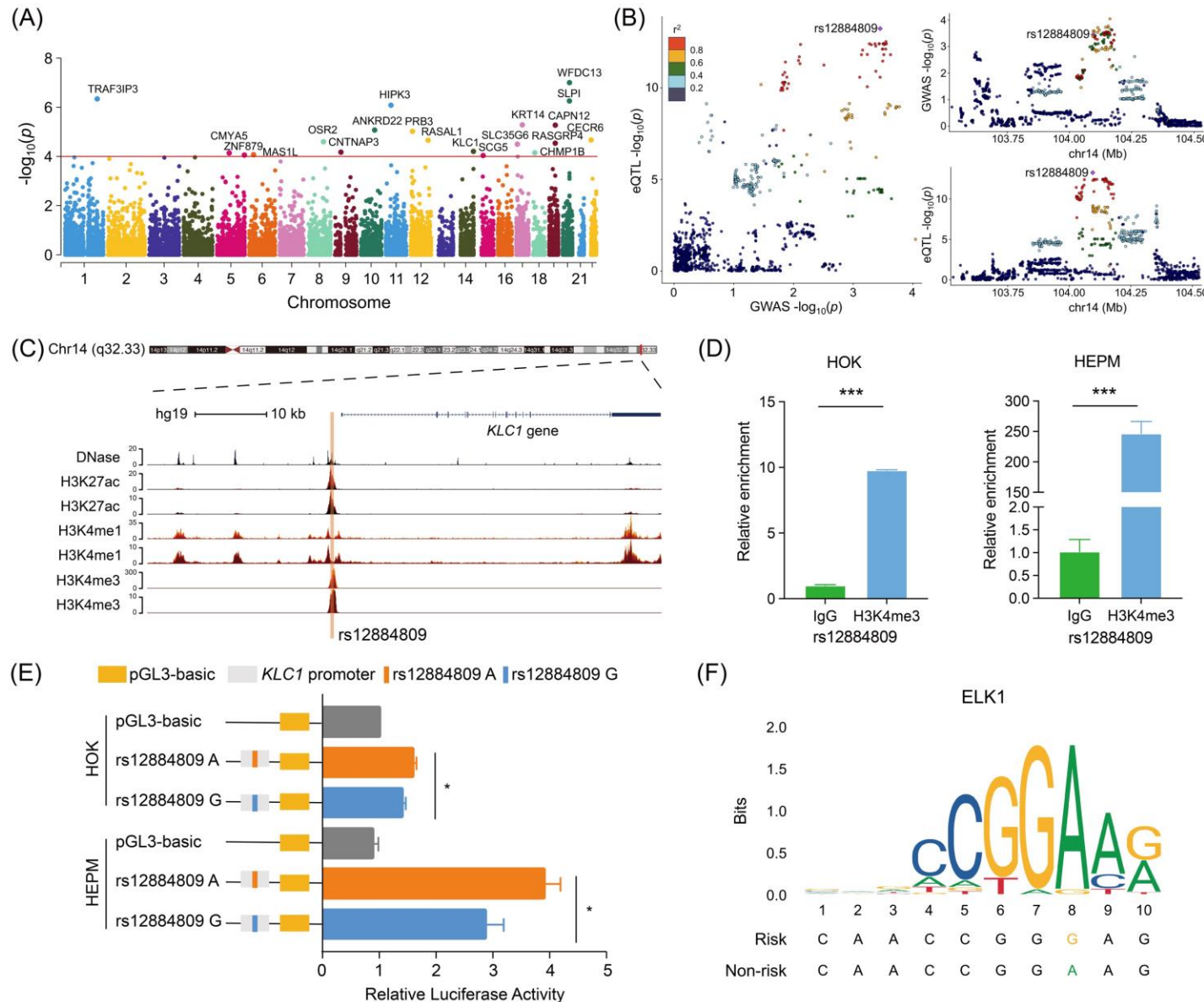


## Biological function





# Results and discussion



□ TWAS analysis identified *KLC1* as a novel gene significantly associated with NSCL/P across multiple tissues.

□ SNP rs12884809 G>A enhances ELK1 binding to the *KLC1* promoter, increasing *KLC1* expression.

Figure 1. Genetic associations by both GWAS and TWAS and allele-specific effect of rs12884809.



# Results and discussion

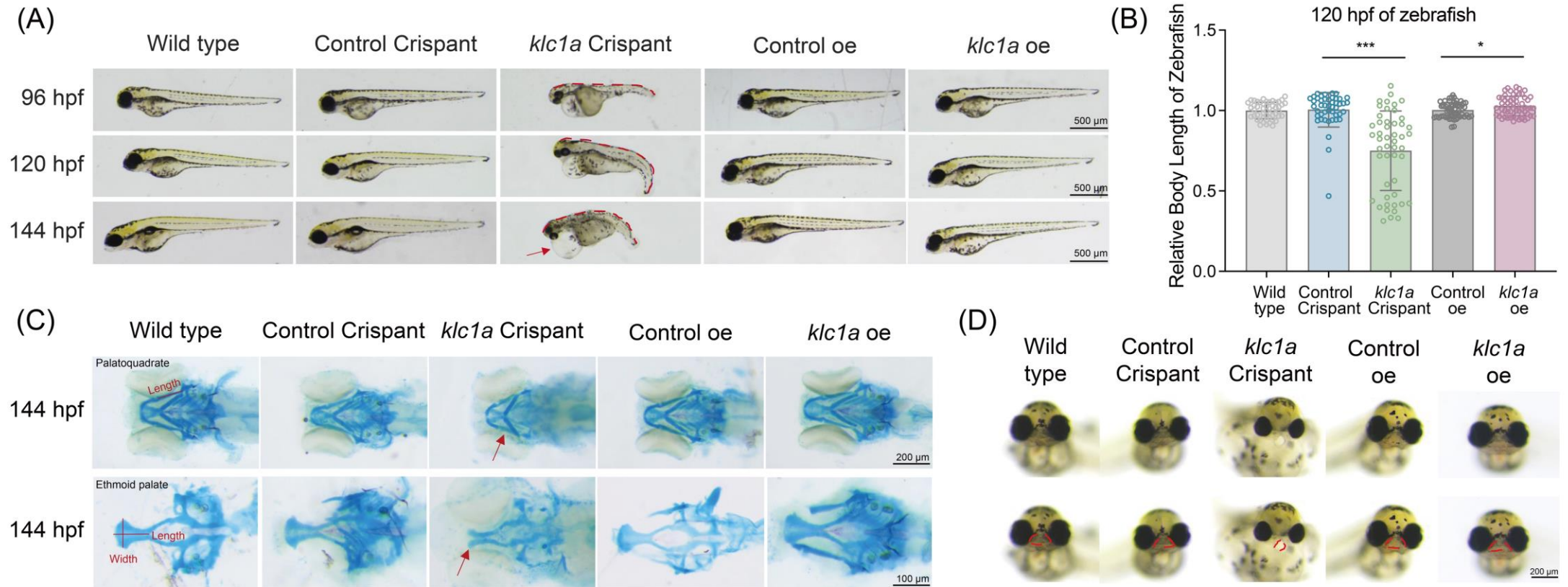
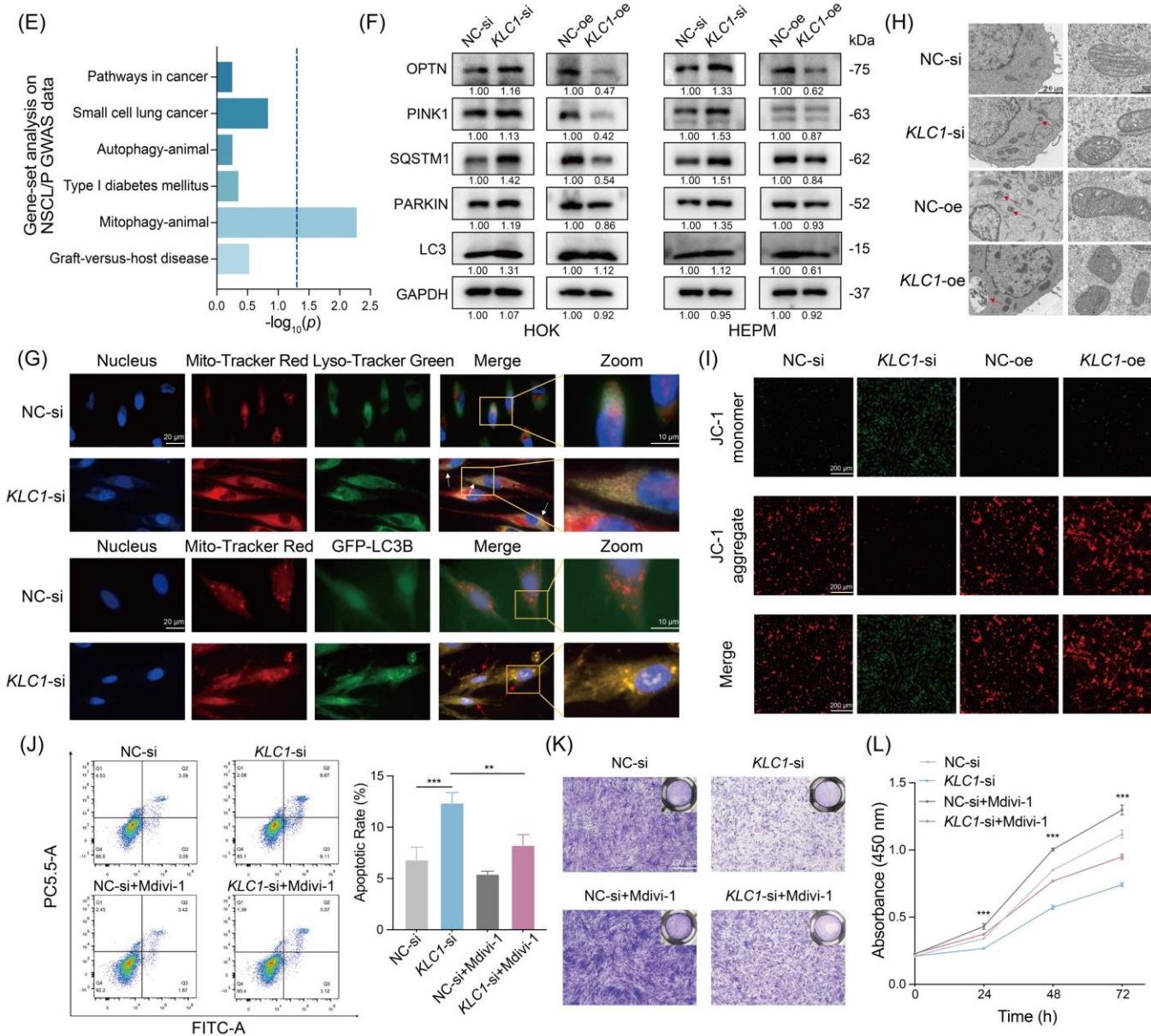


Figure 2. *In vivo* and *in vitro* role of *KLC1* and its regulation of mitophagy.



# Results and discussion



Knockdown of *klc1a* in zebrafish leads to craniofacial abnormalities and reduced survival rates.

*KLC1* knockdown enhanced mitophagy, inhibiting cell proliferation and migration while promoting apoptosis.

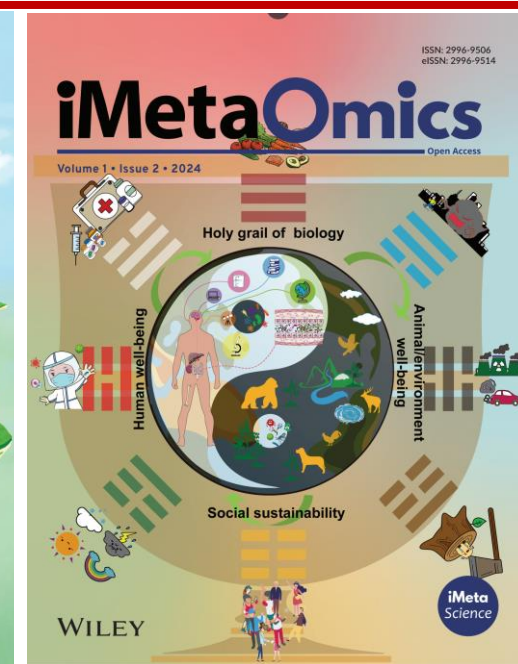
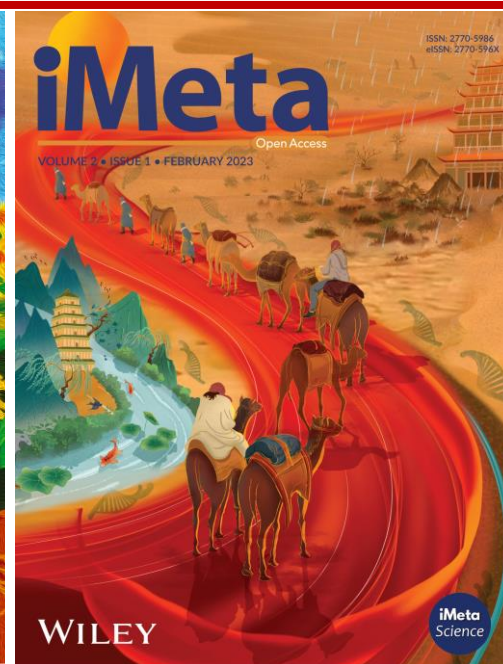
Figure 2. *In vivo* and *in vitro* role of *KLC1* and its regulation of mitophagy.



# Summary



- ❑ In this study, utilized the TWAS approach to integrate eQTL data with NSCL/P GWAS data, identifying key loci and genes involved in NSCL/P development.
- ❑ Rs12884809 G>A enhanced the binding of the transcription factor ELK1 to the *KLC1* promoter region, which increased *KLC1* expression.
- ❑ Reduced *KLC1* expression promoted mitophagy, which could lead to decreased cell proliferation and migration, increased apoptosis, and consequently a higher risk of NSCL/P.

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