News Release

Zero-Shot Reconstruction of Mutant Spatial Transcriptomes: A New Machine-Learning Method Predicts Spatial Gene Expression in Mutants and Diseases Without Requiring Mutant-Specific Spatial Data

Key Points

- Researchers have developed ZENomix, a novel machine-learning method that predicts spatial transcriptomes of mutant samples from single-cell measurements without requiring any mutant-specific training data.
- ZENomix accurately predicts mutant spatial transcriptomes, as validated using simulated and real datasets.
- A spatially variable gene screen powered by ZENomix identified novel genes regulated by Nodal signaling.
- By applying ZENomix to the large body of existing single-cell datasets from mutants and disease models, the method is expected to have broad applications across biology and medical research.

Summary

Understanding where and how genes function in the body is essential to unraveling the mechanisms of life and disease. A technology known as spatial transcriptomics has recently made it possible to visualize, as a comprehensive map, where genes are active within a tissue. These datasets, called spatial transcriptomes, are increasingly used in biological and biomedical research. However, the technology remains costly and technically demanding, and its use is still limited to a small number of laboratories.

A research group led by Assistant Professor Yasushi Okochi and Professor Naoki Honda at the Graduate School of Medicine, Nagoya University, Associate Professor Takaaki Matsui at the Graduate School of Science and Technology, Nara Institute of Science and Technology (NAIST), and Team Leader Takefumi Kondo at the RIKEN Center for Biosystems Dynamics Research has developed ZENomix, a new machine-learning method that predicts spatial transcriptomes from single-cell RNA sequencing (scRNA-seq) data without requiring teaching mutant spatial data.

ZENomix was shown to accurately predict the spatial transcriptome of Maternal-zygotic oep (*MZoep*) mutant zebrafish embryos in early development.

Using ZENomix's predictions, the team also succeeded in identifying eight previously unknown genes whose expression is suppressed by Nodal signaling. The predicted spatial expression patterns of the identified genes were consistent with experimental measurements obtained by *in situ* hybridization.

The advantage of ZENomix is that, given only spatial data from healthy (wild-type) tissue, it can predict the spatial gene expression patterns of diseased or mutant tissue. No disease- or mutant-specific spatial transcriptome dataset needs to be newly acquired. ZENomix thus makes it possible to add a spatial perspective to the vast amount of scRNA-seq data accumulated worldwide, and is expected to substantially accelerate both disease mechanism research and developmental biology. The study was published in the international journal Patterns on June 12, 2026.

Research Background

Understanding where and how genes function in the body is essential for elucidating the mechanisms underlying life and disease. To investigate gene function, researchers obtain gene expression data. A recent measurement technology, spatial transcriptomics, makes it possible to comprehensively visualize where in a tissue each gene is expressed, producing a spatial map of gene activity. The resulting dataset, called a spatial transcriptome, is increasingly used in biological and disease research. However, because the technology is expensive and technically demanding, its use remains confined to a limited number of research settings.

Meanwhile, single-cell RNA sequencing (scRNA-seq) enables comprehensive profiling of gene expression at single-cell resolution. scRNA-seq is now widely available across laboratories, but the measurement process requires dissociating tissue into individual cells, which means information about where each cell was originally located in the tissue is lost. Various methods have been proposed to reconstruct a spatial transcriptome from scRNA-seq data by reassembling the cells like a jigsaw puzzle. However, when applied to mutants or diseased tissues, these methods have required spatial gene expression data from the corresponding mutant or diseased tissue to serve as the "puzzle picture", which is a major limitation.

Research Results

In the present study, the research group developed ZENomix, a method that

uses wild-type (healthy) spatial expression data as an auxiliary reference to reconstruct mutant scRNA-seq data without a mutant-specific "puzzle picture," thereby predicting the mutant spatial transcriptome (**Figure 1**).

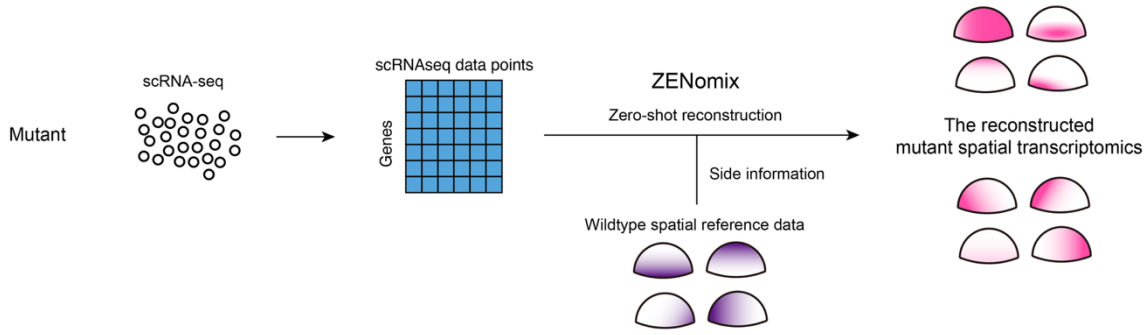

Figure 1:Scheme of ZENomix

ZENomix is based on a simple idea: wild-type and mutant gene expression data must share some common spatial information. Building on this idea, differences between wild-type and mutant gene expression data are calibrated by machine learning, transferring the spatial information contained in the wild-type data to the mutant data and thereby reconstructing the mutant spatial transcriptome. The research group named this machine learning method ZENomix (**Figure 2**).

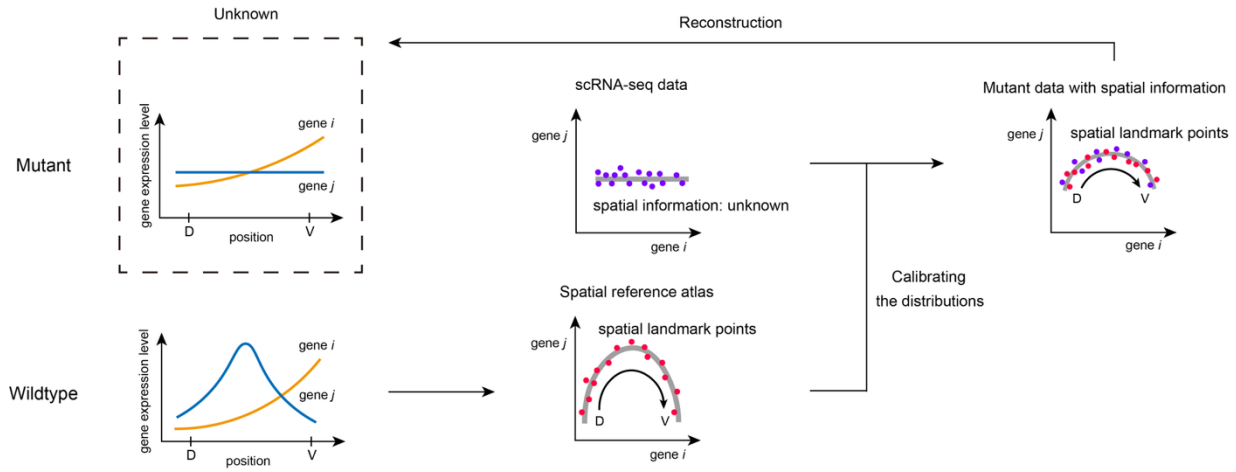

Figure 2:Mechanism of zero-shot reconstruction

The team first used data from a mouse olfactory bulb model of Alzheimer's disease to generate simulated datasets and verified that ZENomix could accurately predict mutant-type spatial transcriptomes. They also applied the method to human cerebral cortex data, confirming that ZENomix is applicable to a wide range of spatial datasets.

Next, the team examined whether ZENomix could predict a mutant spatial transcriptome from actual scRNA-seq data, using early-stage zebrafish embryos carrying the Maternal-zygotic oep (*MZoep*) mutation (**Figure 3A**). The predictions generated by ZENomix faithfully reproduced the gene expression changes that had been experimentally established in previous studies.

MZoep mutants are known to lack Nodal signaling. Taking advantage of this, the team used ZENomix's predictions to screen for genes whose expression is suppressed by Nodal signaling. This screen identified 11 previously unreported candidate genes as potentially being suppressed by Nodal. Experimental validation using *in situ* hybridization showed that the spatial expression patterns of 8 of the 11 genes matched the predictions precisely (**Figure 3B**). These results demonstrate that ZENomix can discover novel genes relevant to mutants and disease.

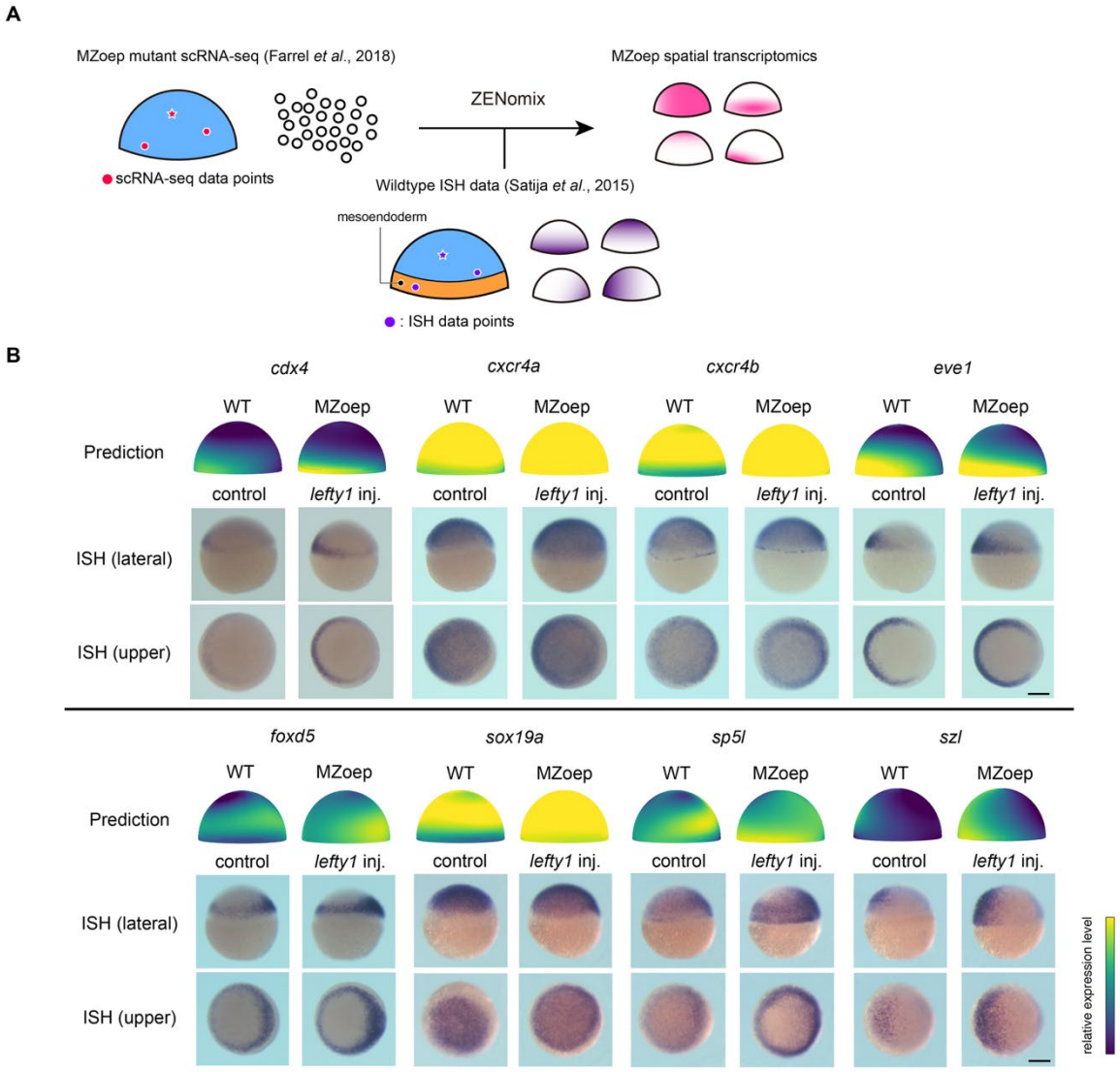

Figure 3：Application of ZENomix to *MZoep* zebrafish embryo

A. Schematic of the experiment. Using scRNA-seq data from MZoep mutants together with wild-type spatial gene expression data as input, ZENomix predicts the spatial transcriptome of the MZoep mutant.
B. Eight Nodal-downregulated genes identified by ZENomix. For each gene, validation by in situ hybridization is shown below the corresponding prediction.

Research Summary and Future Perspective

ZENomix, the analytical method developed in this study, can predict the spatial gene expression patterns of mutant or diseased tissues from spatial data for healthy (wild-type) tissues alone. There is no need to newly acquire dedicated spatial transcriptome data for each disease or mutant. By using ZENomix, it becomes possible to add a spatial perspective to the enormous amount of scRNA-seq data already accumulated around the world. The method is therefore expected to serve as a technology that substantially accelerates research on disease mechanisms and developmental biology.

Publication

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