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From beginner to expert



1. Kellis lab at Broad Institute of MIT and Harvard



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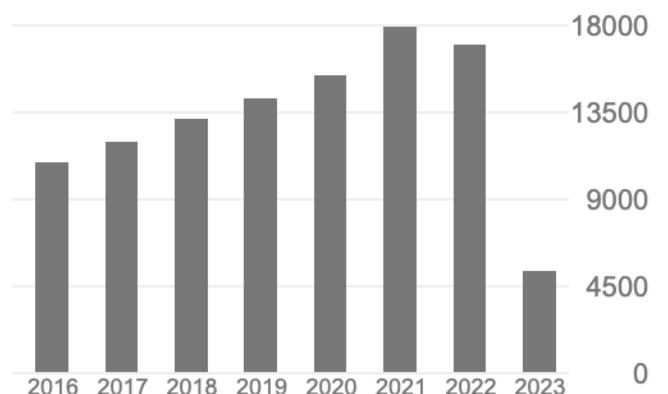
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Kellis Lab at MIT Computer Science and Broad Institute

We seek to understand the mechanistic basis of human disease, using a combination of computational and experimental techniques. This involves developing methods for:

- the systematic discovery and characterization of functional elements in the human genome
- the discovery and validation of the gene-regulatory circuitry controlling these elements
- the use of epigenomic information for annotating regulatory regions and their activity across different cell types
- the use of comparative genomics for recognizing coding and non-coding regions of functional importance for evolutionary fitness.

We work in a highly interdisciplinary environment at the interface of computer science and biology. Members of the group come from a primarily computational background and share a strong passion for understanding biological systems. We are engaged in several collaborative research partnerships with biological and experimental collaborators, at the Broad Institute, the ENCODE, modENCODE, GTEx, and Epigenomics Roadmap consortia, the Harvard Medical School, and other universities.



人员构成：

Admin: 6

Postdoc: 16

PhD students: 6

Undergraduate: 27

Visiting scholar: 6

近五年文章：

CNS: 5

大子刊：4

小子刊：12

其他：4

研究方向一：单细胞基因组学 (single cell genomics)

Article

Single-cell dissection of the human brain vasculature

<https://doi.org/10.1038/s41586-022-04521-7>

Received: 6 April 2021

Accepted: 4 February 2022

Published online: 14 February 2022

 Check for updates

Francisco J. Garcia^{1,2,3,10}, Na Sun^{3,4,5,10}, Hyeseung Lee^{2,3}, Brianna Godlewski^{6,7}, Hansruedi Mathys^{2,3,8}, Kyriaki Galan^{3,4,5}, Blake Zhou^{2,3}, Xueqiao Jiang^{2,3}, Ayesha P. Ng^{2,3}, Julio Mantero^{3,4,5}, Li-Huei Tsai^{1,2,3}, David A. Bennett⁹, Mustafa Sahin^{6,7}, Manolis Kellis^{3,4,5,23} & Myriam Heiman^{1,2,3,23}

Despite the importance of the cerebrovasculature in maintaining normal brain physiology and in understanding neurodegeneration and drug delivery to the central nervous system¹, human cerebrovascular cells remain poorly characterized owing to their sparsity and dispersion. Here we perform single-cell characterization of the human cerebrovasculature using both ex vivo fresh tissue experimental enrichment and post mortem *in silico* sorting of human cortical tissue samples. We capture 16,681 cerebrovascular nuclei across 11 subtypes, including endothelial cells, mural cells and three distinct subtypes of perivascular fibroblast along the vasculature. We uncover human-specific expression patterns along the arteriovenous axis and determine previously uncharacterized cell-type-specific markers. We use these human-specific signatures to study changes in 3,945 cerebrovascular cells from patients with Huntington's disease, which reveal activation of innate immune signalling in vascular and glial cell types and a concomitant reduction in the levels of proteins critical for maintenance of blood–brain barrier integrity. Finally, our study provides a comprehensive molecular atlas of the human cerebrovasculature to guide future biological and therapeutic studies.

Article

APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes

<https://doi.org/10.1038/s41586-022-05439-w>

Received: 27 September 2021

Accepted: 12 October 2022

Published online: 16 November 2022

 Check for updates

Joel W. Blanchard^{1,2,11,14}, Leyla Anne Akay^{1,2,3,14}, Jose Davila-Velderrain^{3,12,14}, Djuna von Maydell^{1,2,3,14}, Hansruedi Mathys^{1,2,13}, Shaw M. Davidson⁴, Audrey Effenberger^{1,2}, Chih-Yu Chen⁵, Kristal Maner-Smith⁵, Ihab Hajjar⁶, Eric A. Ortlund^{5,7}, Michael Bula^{1,2}, Emre Agbas^{1,2}, Ayesha Ng^{1,2}, Xueqiao Jiang^{1,2}, Martin Kahn^{1,2}, Cristina Blanco-Duque^{1,2}, Nicolas Lavoie^{1,2}, Liwang Liu^{1,2}, Ricardo Reyes⁸, Yuan-Ta Lin^{1,2}, Tak Ko¹, Lea R'Bilo⁸, William T. Ralvenius^{1,2}, David A. Bennett⁹, Hugh P. Cam^{1,2}, Manolis Kellis^{3,10,23} & Li-Huei Tsai^{1,2,10,23}

APOE4 is the strongest genetic risk factor for Alzheimer's disease^{1–3}. However, the effects of APOE4 on the human brain are not fully understood, limiting opportunities to develop targeted therapeutics for individuals carrying *APOE4* and other risk factors for Alzheimer's disease^{4–8}. Here, to gain more comprehensive insights into the impact of *APOE4* on the human brain, we performed single-cell transcriptomics profiling of post-mortem human brains from *APOE4* carriers compared with non-carriers. This revealed that *APOE4* is associated with widespread gene expression changes across all cell types of the human brain. Consistent with the biological function of APOE^{2–6}, APOE4 significantly altered signalling pathways associated with cholesterol homeostasis and transport. Confirming these findings with histological and lipidomic analysis of the post-mortem human brain, induced pluripotent stem-cell-derived cells and targeted-replacement mice, we show that cholesterol is aberrantly deposited in oligodendrocytes—myelinating cells that are responsible for insulating and promoting the electrical activity of neurons. We show that altered cholesterol localization in the *APOE4* brain coincides with reduced myelination. Pharmacologically facilitating cholesterol transport increases axonal myelination and improves learning and memory in *APOE4* mice. We provide a single-cell atlas describing the transcriptional effects of APOE4 on the aging human brain and establish a functional link between APOE4, cholesterol, myelination and memory, offering therapeutic opportunities for Alzheimer's disease.

ARTICLE

<https://doi.org/10.1038/s41467-020-18416-6>

OPEN

A multiresolution framework to characterize single-cell state landscapes

Shahin Mohammadi^{1,2,3✉}, Jose Davila-Velderrain^{1,2,3✉} & Manolis Kellis^{1,2✉}

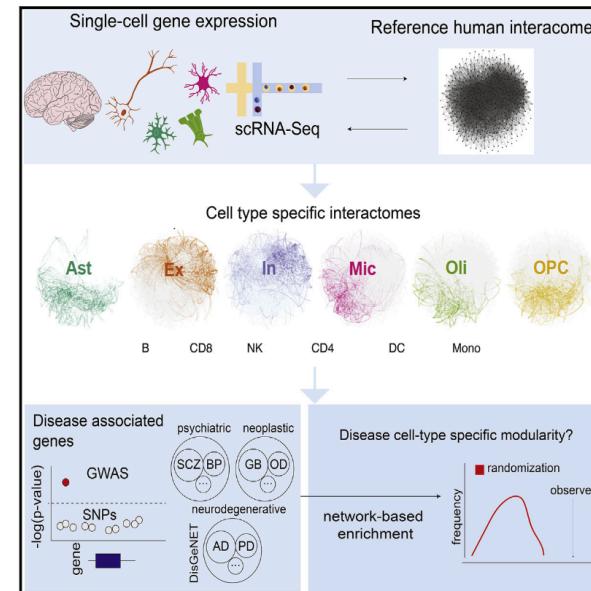
Dissecting the cellular heterogeneity embedded in single-cell transcriptomic data is challenging. Although many methods and approaches exist, identifying cell states and their underlying topology is still a major challenge. Here, we introduce the concept of multi-resolution cell-state decomposition as a practical approach to simultaneously capture both fine- and coarse-grain patterns of variability. We implement this concept in ACTIONNet, a comprehensive framework that combines archetypal analysis and manifold learning to provide a ready-to-use analytical approach for multiresolution single-cell state characterization. ACTIONNet provides a robust, reproducible, and highly interpretable single-cell analysis platform that couples dominant pattern discovery with a corresponding structural representation of the cell state landscape. Using multiple synthetic and real data sets, we demonstrate ACTIONNet's superior performance relative to existing alternatives. We use ACTIONNet to integrate and annotate cells across three human cortex data sets. Through integrative comparative analysis, we define a consensus vocabulary and a consistent set of gene signatures discriminating against the transcriptomic cell types and subtypes of the human prefrontal cortex.

Article

Cell Systems

Reconstruction of Cell-type-Specific Interactomes at Single-Cell Resolution

Graphical Abstract



Authors

Shahin Mohammadi,
Jose Davila-Velderrain, Manolis Kellis

Correspondence

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In Brief

Mohammadi et al. introduce a computational framework to infer the context specificity of gene interactions based on single-cell transcriptomic data and a reference global interactome.

研究方向二：突变和疾病关系（Variation and disease）

Article

Regulatory genomic circuitry of human disease loci by integrative epigenomics

<https://doi.org/10.1038/s41586-020-03145-z>

Received: 30 October 2019

Accepted: 18 December 2020

Published online: 3 February 2021

Open access

 Check for updates

Carles A. Boix^{1,2,3}, Benjamin T. James^{1,2}, Yongjin P. Park^{1,2,4}, Wouter Meuleman⁵ & Manolis Kellis^{1,2}✉

Annotating the molecular basis of human disease remains an unsolved challenge, as 93% of disease loci are non-coding and gene-regulatory annotations are highly incomplete^{1–3}. Here we present EpiMap, a compendium comprising 10,000 epigenomic maps across 800 samples, which we used to define chromatin states, high-resolution enhancers, enhancer modules, upstream regulators and downstream target genes. We used this resource to annotate 30,000 genetic loci that were associated with 540 traits⁴, predicting trait-relevant tissues, putative causal nucleotide variants in enriched tissue enhancers and candidate tissue-specific target genes for each. We partitioned multifactorial traits into tissue-specific contributing factors with distinct functional enrichments and disease comorbidity patterns, and revealed both single-factor monotropic and multifactor pleiotropic loci. Top-scoring loci frequently had multiple predicted driver variants, converging through multiple enhancers with a common target gene, multiple genes in common tissues, or multiple genes and multiple tissues, indicating extensive pleiotropy. Our results demonstrate the importance of dense, rich, high-resolution epigenomic annotations for the investigation of complex traits.

Leading several large genomic consortia:

ENCODE,

modENCODE,

GTEX,

Epigenomics Roadmap

研究方向三：代谢，肥胖，糖尿病 (Metabolism, obesity, Diabetes)



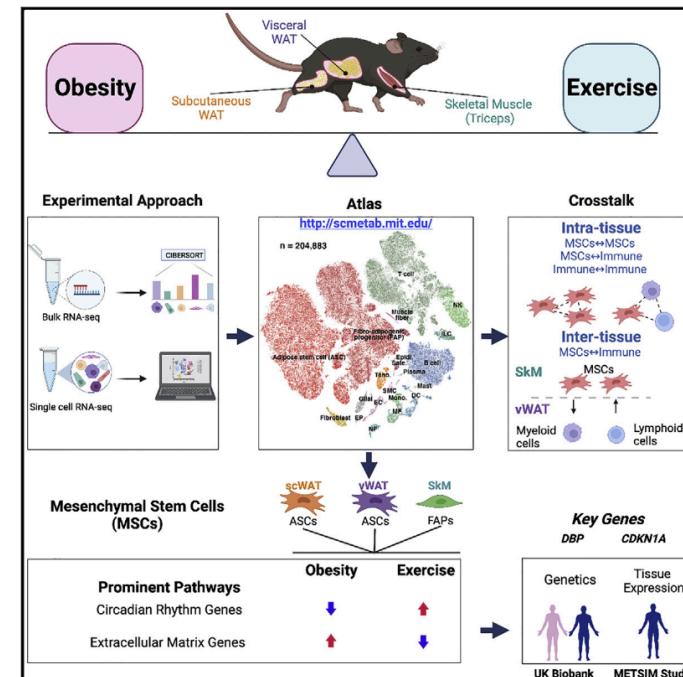
FTO Obesity Variant Circuitry and Adipocyte Browning in Humans

Melina Claussnitzer, Ph.D., Simon N. Dankel, Ph.D., Kyoung-Han Kim, Ph.D., Gerald Quon, Ph.D., Wouter Meuleman, Ph.D., Christine Haugen, M.Sc., Viktoria Glunk, M.Sc., Isabel S. Sousa, M.Sc., Jacqueline L. Beaudry, Ph.D., Vijitha Puvilandran, B.Sc., Nezar A. Abdennur, M.Sc., Jannel Liu, B.Sc., Per-Arne Svensson, Ph.D., Yi-Hsiang Hsu, Ph.D., Daniel J. Drucker, M.D., Gunnar Mellgren, M.D., Ph.D., Chi-Chung Hui, Ph.D., Hans Hauner, M.D., and Manolis Kellis, Ph.D.

Cell Metabolism

Single-cell dissection of the obesity-exercise axis in adipose-muscle tissues implies a critical role for mesenchymal stem cells

Graphical abstract



Resource

Authors

Jiekun Yang, Maria Vamvini, Pasquale Nigro, ..., Kevin Grove, Laurie J. Goodyear, Manolis Kellis

Correspondence

laurie.goodyear@joslin.harvard.edu (L.J.G.), manoli@mit.edu (M.K.)

In brief

In this paper, Yang et al. provide a high-quality single-cell atlas of obesity-exercise interactions in subcutaneous and visceral white adipose tissue and skeletal muscle in mice. It uncovers a previously underappreciated role of mesenchymal stem cells in the response to obesity and exercise training in these three tissues.

研究方向四：癌症基因组学 (Cancer Genomics)

SCIENCE ADVANCES | RESEARCH ARTICLE

DISEASES AND DISORDERS

Plasma-derived extracellular vesicle analysis and deconvolution enable prediction and tracking of melanoma checkpoint blockade outcome

Alvin Shi^{1,2}, Gyulnara G. Kasumova³, William A. Michaud³, Jessica Cintolo-Gonzalez³, Marta Díaz-Martínez³, Jacqueline Ohmura³, Arnav Mehta⁴, Isabel Chien¹, Dennie T. Frederick³, Sonia Cohen³, Deborah Plana^{4*}, Douglas Johnson⁵, Keith T. Flaherty⁴, Ryan J. Sullivan⁴, Manolis Kellis^{1,2†‡}, Genevieve M. Boland^{2,3†‡}

Immune checkpoint inhibitors (ICIs) show promise, but most patients do not respond. We identify and validate biomarkers from extracellular vesicles (EVs), allowing non-invasive monitoring of tumor- intrinsic and host immune status, as well as a prediction of ICI response. We undertook transcriptomic profiling of plasma-derived EVs and tumors from 50 patients with metastatic melanoma receiving ICI, and validated with an independent EV-only cohort of 30 patients. Plasma-derived EV and tumor transcriptomes correlate. EV profiles reveal drivers of ICI resistance and melanoma progression, exhibit differentially expressed genes/pathways, and correlate with clinical response to ICI. We created a Bayesian probabilistic deconvolution model to estimate contributions from tumor and non-tumor sources, enabling interpretation of differentially expressed genes/pathways. EV RNA-seq mutations also segregated ICI response. EVs serve as a non-invasive biomarker to jointly probe tumor-intrinsic and immune changes to ICI, function as predictive markers of ICI responsiveness, and monitor tumor persistence and immune activation.

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研究方向五：RNA 生物学 (RNA biology)

nature

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Published: 15 December 2013

Genome-wide probing of RNA structure reveals active unfolding of mRNA structures *in vivo*

Silvi Rouskin, Meghan Zubradt, Stefan Washietl, Manolis Kellis & Jonathan S. Weissman 

[Nature](#) 505, 701–705 (2014) | [Cite this article](#)

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TECHNIQUES AND RESOURCES | 28 MARCH 2019

A gene expression atlas of embryonic neurogenesis in *Drosophila* reveals complex spatiotemporal regulation of lncRNAs

In collection: Neural development

Alexandra L. McCorkindale  , Philipp Wahle, Sascha Werner, Irwin Jungreis, Peter Menzel, Chinmay J. Shukla, Rúben Lopes Pereira Abreu, Rafael A. Irizarry, Irmtraud M. Meyer, Manolis Kellis, Robert P. Zinzen  

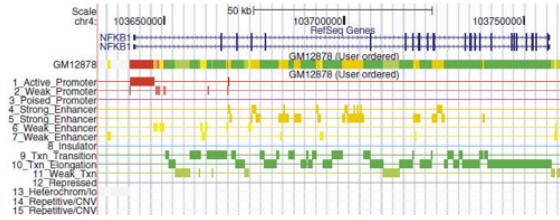
+ Author and article information

Development (2019) 146 (6): dev175265.

<https://doi.org/10.1242/dev.175265> Article history 

Algorithmic papers in Computational Biology

While most of our papers have been in biological journals and in collaboration with experimental investigators, we have also written a small number of computational papers, for computational biology conferences or computational journals. These have frequently introduced new algorithms that we have independently or in parallel applied to biological datasets, and other times provided more details on the methods underlying some of our genomics results. These papers will be of particular interest to computational scientists seeking to gain a deeper understanding of the computational challenges associated with the genomics problems we are working on. The algorithms presented in these papers include methods for ortholog and paralog determination, gene identification from their evolutionary signatures, motif discovery and clustering, network motif discovery using symmetry breaking conditions, and network inference methods.



67. ChromHMM: automating chromatin-state discovery and characterization ([pdf](#)) ([scholar](#))

Ernst, Kellis

Chromatin-state annotation using combinations of chromatin modification patterns has emerged as a powerful approach for discovering regulatory regions and their cell type-specific activity patterns and for interpreting disease-association studies. However, the computational challenge of learning chromatin-state models from large numbers of chromatin modification datasets in multiple cell types still requires extensive bioinformatics expertise. To address this challenge, we developed ChromHMM, an automated computational system for learning chromatin states, characterizing their biological functions and correlations with large-scale functional datasets and visualizing the resulting genome-wide maps of chromatin-state annotations.

[Nature Methods 9:215-6, Feb 28, 2012.](#)