BIOGRAPHICAL SKETCH

NAME: Rhie, Suhn Kyong

eRA COMMONS USER NAME (credential, e.g., agency login): SUHNRHIE

POSITION TITLE: Assistant Professor of Research, Biochemistry and Molecular Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of California, Los Angeles	B.S.	06/2007	Biochemistry
University of Southern California	Ph.D.	05/2013	Genetic, Molecular and Cellular biology
University of Southern California	Postdoc	08/2018	Bioinformatics, Genomics, Molecular biology

A. Personal Statement

As a girl who enjoyed asking questions with enormous curiosity, I dreamed to become a scientist. To develop my career, I completed a Bachelor of Science, *magna cum laude* in biochemistry at the University of California, Los Angeles, investigating signaling pathways and cell biology in Dr. Rachelle Crosbie-Waston's lab. For most of the past decade, I have been studying epigenetic regulation of gene expression focusing on cancer, first as a graduate student in Dr. Gerhard Coetzee's lab, as a postdoctoral scholar in Dr. Peter Laird's lab, as a senior research associate in Dr. Peggy Farnham's lab at USC, and as an assistant professor in Dept. Biochemistry and Molecular Medicine at USC. I have acquired expertise and training in both wet (performing experiments using molecular biology techniques) and dry lab (bioinformatics) from experts in Los Angeles and published more than 25 scientific papers, which include top journals such as *Nature Genetics* and *Cell*. I have participated in many cancer genome-wide association studies (GWAS) and Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium, unraveling the mechanism of risk genetic variants in transcription factor binding with functional assays and data analysis. I characterized heterogeneous tumor tissues as a leader of DNA methylation analysis for The Cancer Genome Atlas (TCGA) Consortium and discovered how genetic alterations such as somatic mutations, fusions, copy number variations are associated with epigenetic changes in cancer. I have also led epigenomic data analysis to investigate how transcription factors act at regulatory elements in a 3D nucleome structure in cancer and psychiatric diseases as part of the ENCODE and PsychENCODE Consortia. My current research interests are to characterize key transcription factor and understand roles of regulatory elements activated in different types of cancers and neurodevelopmental diseases. My long-term goal is to use both molecular biology and bioinformatics to address how genes are regulated in 3D nucleome structure, discovering new molecular mechanisms of human diseases that can aid in the development of therapeutics to enhance quality of life for patients.

Selected Publications

1. **Rhie SK** Yao L Witt H Schreiner S Luo Z Farnham PJ (2018). ZFX acts as a transcription activator in multiple types of human tumors by binding downstream of transcription start sites at the majority of CpG island promoters. *Genome Research* 28:310-320.
2. **Rhie SK** Schreiner S Witt H Armoskus C Lay F Camarena A Spitsyna VN Berman B Evgrafov OV Knowles JA Farnham PJ Using 3D epigenomic maps of primary olfactory neuronal cells from living individuals to understand gene regulation. *Under review in Science Translational Medicine*
3. Cancer Genome Atlas Research Network (**Rhie SK**) (2015). The Molecular Taxonomy of Primary Prostate Cancer. *Cell* 163(4):1011-25. ***Rhie led DNA methylation analysis. TCGA PRAD analysis working group is a first-author as a group.***
4. Guo Y Perez A Hazelett DJ Coetzee GA **Rhie SK**[#] Farnham PJ[#] (2018). CRISPR-mediated deletion of prostate cancer risk-associated CTCF loop anchors identifies repressive chromatin loops. *Genome Biology In Press.* [#]***Rhie is a co-corresponding author.***

B. Positions and Honors

Positions and Employment

2005-2008	Undergraduate research/Research Assistant, UCLA (Dr. Rachelle Crosbie-Watson's lab)
2008-2013	Ph.D. student/Research Assistant, Dept. Urology, USC (Dr. Gerhard Coetzee's lab)
2013-2015	Postdoctoral Scholar, Epigenome Center, USC (Dr. Peter Laird's lab)
2015-2018	Sr. Research Associate, Dept. Biochemistry and Mol Medicine, USC (Dr. Peggy Farnham's lab)
2018-present	Assistant Professor of Research, Dept. Biochem and Mol Medicine, Keck School of Medicine, USC

Honors, Awards, and Professional Memberships

2003	Outstanding Academic Excellence, President Education Academic Program
2003	Bank of America Achievement Award in the field of Science
2003-2005	Dean's Honors, Pasadena City College
2005	Superior Achievement in Physics in the Natural Sciences Division, Pasadena City College
2006-2007	President, Disabled Student Union, UCLA
2007	Departmental Honors, Dept. Biochemistry, UCLA
2007	Magna Cum Laude, Dept. Biochemistry, UCLA
2007	Ethel Terry McCoy Award for Excellence in Chemistry and Biochemistry, Dept. Biochemistry, UCLA
2007	Women for Change 2007 Student Leadership Award, The Deans of Students' Office in collaboration with UCLA Alumni Association
2011-2013	Member, GAME-ON (Genetic Associations and Mechanisms in Oncology)
2011-2015	Member, Genetic Epidemiology Seminar and Working Group, USC
2013-2017	Leader of DNA methylation analysis, TCGA (The Cancer Genome Atlas) Prostate adenocarcinoma (PRAD) analysis working group
2013-2017	Leader of DNA methylation analysis, TCGA (The Cancer Genome Atlas) Breast invasive carcinoma (BRCA) analysis working group
2013-2017	Member, TCGA (The Cancer Genome Atlas) Epigenetics working group
2014-2017	Leader of DNA methylation analysis, TCGA (The Cancer Genome Atlas) Cholangiocarcinoma (CHOL) analysis working group
2013-Present	Member, AACR (the American Association for Cancer Research)
2013-Present	Member, AAAS (the American Association for the Advancement of Science)
2015-Present	Member, ENCODE (Encyclopedia of DNA Element) 3D Nucleosome and GWAS working group
2015-Present	Member, PsychENCODE Data analysis working group
2016	Poster award, Dept. Biochemistry and Molecular Medicine, USC
2016-Present	Leader of epignomics data analysis, PsychENCODE CNON (Cultured Neuronal Cells Derived from Olfactory Neuroepithelium) and Capstone projects
2016-Present	Member, ASHG (American Society of Human Genetics)
2016-Present	Member, SfN (Society for Neuroscience)
2018	NCI (National Cancer Institute) Career Development Award

C. Contributions to Science

1. Unraveling transcription factor and regulatory element networks in cancer. Although technological advances now allow increased tumor profiling, a detailed understanding of the mechanisms leading to the development of different cancers remains elusive. My approach toward understanding the molecular events that lead to cancer is to characterize changes in transcriptional regulatory networks between normal and tumor tissue. Two types of DNA elements involved in gene activation include promoters and enhancers. Promoters are defined as genomic regions near transcription start sites and active promoters display a region of open chromatin spanning the TSS that is flanked on either side by a nucleosome containing histone H3 trimethylated on lysine 4. Enhancers have a smaller region of open chromatin flanked on either side by one or more nucleosomes containing histone H3 acetylated on lysine 27 and/or histone H3 monomethylated on lysine 4. By using techniques such as FAIRE, ChIP, and NOMe-seq, I have investigated regulatory elements and

transcription factors that bind to these elements. For example, I found that ZFX, which is correlated with proliferation, tumorigenesis, and patient survival in multiple types of tumors, acts as a transcriptional activator by binding downstream of transcription start sites at the majority of CpG island promoters. To facilitate understanding of enhancer networks deregulated in tumors, I have developed a bioinformatics tool called Tracing Enhancer Networks using Epigenetic Traits (TENET), which identifies enhancer and gene expression relationships (links) genome-wide. Using TENET, with epigenomic and RNA expression data from breast, prostate, and kidney tumor and normal tissue samples, I found more than 25,000 differentially activated enhancers, ~800,000 enhancer:gene links, and key transcription factors involved in tumor-specific enhancer networks. Using cutting-edge techniques such as Hi-C and CRISPR/Cas9, I am currently studying transcription factors and enhancer-target gene chromatin interactions.

a. **Rhie SK** Yao L Witt H Schreiner S Luo Z Farnham PJ (2018). ZFX acts as a transcription activator in multiple types of human tumors by binding downstream of transcription start sites at the majority of CpG island promoters. *Genome Research* 28:310-320.
b. **Rhie SK** Guo Y Tak YG Yao L Shen H Coetzee GA Laird PW Farnham PJ (2016). Identification of Activated Enhancers and Linked Transcription Factors in Breast, Prostate, and Kidney Tumors by Tracing Enhancer Networks using Epigenetic Traits (TENET). *Epigenetics Chromatin* 9:50.
c. **Rhie SK** Hazelett DJ Coetzee SG Yan C Noushmehr H Coetzee GA (2014). Nucleosome Positioning and Histone Modifications Define Relationships between Regulatory Elements and Nearby Gene Expression in Breast Epithelial Cells. *BMC Genomics* 15:331.
d. **Rhie SK** Perez AA Lay F Schreiner S Farnham PJ Mapping high-resolution genome-wide looping interactions in prostate cancer cells using in situ Hi-C *In preparation*

2. Identification of risk variants and their functions in non-coding regions. Apart from a few examples of genetic mutations with high penetrance, genome wide association studies (GWASs) identify multiple low penetrance genetic risk loci. To date, several hundred cancer risk loci have been identified. In contrast to Mendelian disorders, where most disease-causing mutations result in absent or non-functional proteins, many complex disease-associated variants, such as those for breast and prostate cancers, are mainly found in non-coding regions of the genome. Since >90% of the genome is non-coding and risk mechanisms of complex diseases are likely due to subtle regulation of gene expression, risk-SNPs are more often found in non-coding regions. In recent years, advances in next-generation sequencing and technology have allowed the production of epigenomic maps in different cell types. By working together with epidemiologists and molecular biologists, I fine-mapped and annotated risk loci to identify underlying mechanisms that explain how SNPs affect disease risk. For example, I performed ChIP and FAIRE assays to scan risk loci, allele-specific enhancer assays and expression quantitative trait loci analyses to reveal and confirm the function of breast cancer risk variants. I also co-developed a method called FunciSNP (PMID: 22684628), an R/bioconductor tool that integrates functional non-coding data sets with genetic association studies to identify candidate regulatory SNPs. I believe that the analysis results on risk variants will inform preventive and clinical benefits to individuals at risk. I have published more than 10 papers to characterize risk loci of various cancer types (breast, prostate, ovarian, lung), phenotype (body mass index) and psychiatric diseases (schizophrenia). Selected publications are shown below.

a. Garcia-Closas M Couch FJ Lindstrom S Michailidou K Schmidt MK Orr N **Rhie SK** Riboli E Feigelson HS Marchand LL et al. (2013). Genome-wide Association Studies Identify Four ER-negative Specific Breast Cancer Risk Loci. *Nature Genetics* 45(4):392–8.
b. Hazelett DJ **Rhie SK** Gaddis M Yan C Lakeland DL Coetzee SG Henderson BE Noushmehr H Cozen W Kote-Jarai Z Eeles RA Easton DF Haiman CA Lu W Farnham PJ Coetzee GA (2014). Comprehensive Functional Annotation of Seventy-seven Prostate Cancer Risk Loci *Plos Genetics* 10 (1) e1004102.
c. **Rhie SK** Coetzee SG Noushmehr H Yan C Kim JM Haiman CA Coetzee GA (2013). Comprehensive Functional Annotation of Seventy-One Breast Cancer Risk Loci. *Plos One* 8(5): e64925 ***Selected as the top 25% most cited articles***
d. Feng Y^ **Rhie SK^** Huo D Ruiz-Narvaez EA Haddad S Ambrosome AB et al (2017). Characterizing Genetic Susceptibility to Breast Cancer in Women of African Ancestry. *Cancer Epidemiol Biomarkers Prev* 26(7):1**–**11. ***^Rhie is a co-first author.***

3. Comprehensive molecular characterization of primary tumor tissues. There is substantial heterogeneity even among the same tissue-type tumors, evident in the spectrum of molecular abnormalities and variable clinical courses. Therefore, understanding the molecular taxonomy of cancer and characterizing cancer subtype

is in great demand. As part of The Cancer Genome Atlas (TCGA), I led the DNA methylation analysis of more than a thousand prostate, breast, and bile duct tumor tissues, and revealed subtypes of tumors that have distinct epigenetic profiles. For example, I found that prostate tumors with IDH1 mutation had notably elevated levels of genome-wide DNA hyper-methylation; this work was published in *Cell*, and it was the first study that reported an IDH1 mutant subset with a methylator phenotype in prostate cancer. I also revealed the subgroup of ERG fusion-positive tumors, which contained twice the number of hyper-methylated loci, compared to the rest of ERG fusion-positive tumors. Moreover, I revealed epigenetically silenced genes found in most prostate tumors and ones in a subgroup of prostate tumors. For example, I found that SPOP and FOXA1 mutant tumors have the highest levels of AR-induced transcripts, along with subtype-specific DNA methylation and gene expression profiles. Besides prostate cancer, I contributed characterizing breast tumors, including invasive lobular, ductal and mixed. I identified that mutations targeting PTEN, TBX3, and FOXA1, and E-cadherin loss are enriched in invasive lobular carcinoma. Interestingly, FOXA1 mutations in breast tumors correlate with increased FOXA1 expression and activity. I showed that FOXA1 mutations are anti-correlated with DNA methylation at FOXA1 binding sites, indicating more FOXA1 binding consistent with increased FOXA1 activity. I also characterized cholangiocarcinoma and highlighted distinct IDH mutant DNA methylation profiles in bile duct tumors.

a. Cancer Genome Atlas Research Network (**Rhie SK**) (2015). The Molecular Taxonomy of Primary Prostate Cancer. *Cell* 163(4):1011-25. ***Rhie led DNA methylation analysis. TCGA PRAD analysis working group is a first-author as a group.***
b. Huo D Hu H **Rhie SK** Gamazon ER Cherniack AD Liu J Yoshimatsu TF Pitt JJ Hoadley KA Troester M et al. (2017). Comparison of Breast Cancer Molecular Features and Survival by African and European Ancestry in The Cancer Genome Atlas. *JAMA Oncology* 2017 Dec 1;3(12):1654-1662. ***Rhie led DNA methylation analysis.***
c. Ciriello G Gatza ML Beck AH Wilkerson MD **Rhie SK** Pastore A Zhang H McLellan M Yau C et al. (2015). Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. *Cell* 163(2):506-19. PMID: 26451490 ***Rhie led DNA methylation analysis.***
d. Farshidfar Zheng Gingrans Newton Shih Robertson Hinoue Hoadley Gibb Roszik Covington Wu Shinbrot Stransky Hegde Yang Reznik Sadeghi Pedamallu Ojesna Hess Auman **Rhie SK** Bowlby Borad et al. (2017). Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles. *Cell Rep* 18(11):2780-94. ***Rhie co-led DNA methylation analysis.***

4. Deciphering molecular and epigenomic processes dysregulated in psychiatric diseases. The brain is responsible for the cognitive and behavioral repertoire of humans, and it is also the most complex biological tissue with a myriad of molecularly, morphologically and functionally distinct regions and cell types. Many molecular and cellular processes, transpiring over a prolonged course of development, enable this complexity. However, the precise genetic regulation underlying this protracted development, as well as the regulation of processes and functions in adulthood, is not yet well-characterized. So far, very few studies attempted integrative multi-dimensional genomic analyses at the levels of brain regions and cell types, and fewer studies had large sample sizes studying human brains and neuronal cells or comparing healthy and diseased individuals. In 2015, PsychENCODE Consortium was established with the goals of generating an enhanced framework of functional genomic elements, cataloging regulatory elements and epigenetic modifications, quantifying coding and noncoding RNA and protein expression, identifying epigenetic variation, and functionally characterizing population-level and disease-associated genetic and epigenetic variants in tissue and single-cell samples from healthy (neurotypical) control and disease-affected post-mortem human brains. As part of the PsychENCODE, I have participated profiling the developing and adult human brain in both healthy and disease states. Moreover, as a leader of data analysis for the USC PsychENCODE project, I developed a 3-dimensional epigenomic map of primary Cultured Neuronal cells derived from Olfactory Neuroepithelium (CNON). I mapped topological associating domains and high-resolution chromatin interactions using Hi-C and identified regulatory elements using chromatin immunoprecipitation and nucleosome-positioning assays. Using epigenomic datasets from biopsies of 63 living individuals, I found that epigenetic marks at distal regulatory elements are more variable than marks at proximal regulatory elements. By integrating genotype and metadata, I identified enhancers having activity changes linked to genetic variation, gender, smoking, and schizophrenia. Motif searches revealed that many CNON enhancers are bound by neuronal-related transcription factors. Finally, I combined 3D epigenomic maps and gene expression profiles to predict enhancer-target gene interactions on a genome-wide scale. Future studies that validate enhancer and target gene interactions and that characterize the function of genes whose expression is linked to regulatory elements shown to be associated with

schizophrenia will provide new insights into neurodevelopmental diseases and possibly provide new targets for therapeutic intervention.

a. **Rhie SK** Schreiner S Witt H Armoskus C Lay F Camarena A Spitsyna VN Berman B Evgrafov OV Knowles JA Farnham PJ Using 3D epigenomic maps of primary olfactory neuronal cells from living individuals to understand gene regulation. *Under review in Science Translational Medicine*
b. Wang Liu Warrell Won Shi Navarro Clarke Gu Emani Xu Yang Park **Rhie SK** Manakongtreecheep Zhou Nathan Zhang Peters Mattei Fitzgerald Brunetti Moore PsychENCODE Consortium Sestan Jaffe White Weng Geschwind Knowles Gerstein Comprehensive functional genomic resource and integrative model for the adult brain *Under review in Science*
c. Amiri A Coppola G Scuden S Wu F Roychowdhury T Liu F Pochareddy S Shin Y The PsychENCODE Consortium (**Rhie SK**) Gerstein M Sestan N Abyzov A Vaccarino FM Integrative multi-omics analyses of iPSC-derived brain organoids identify early determinants of human cortical development *Under review in Science*
d. **Rhie SK** Schreiner S Farnham PJ (2018). Defining Regulatory Elements in the Human Genome Using Nucleosome Occupancy and Methylome Sequencing (NOMe-seq). *Methods in Molecular Biology* 1766:209-229.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/43769025/

D. Research Support

Active

K01 CA229995 Rhie (PI) 09/01/18-08/31/21
NIH / NCI
Transcription Factor Isoforms Linked to Breast and Prostate Cancer Subgroups
The goal of this study is to identify and clinically validate key transcription factor isoforms linked to breast and prostate cancer subgroups using epigenetic traits
Rhie Role: PI

R01 CA136924 Farnham, Coetzee, Lu (Multi-PIs) 03/09/15-01/31/20
NIH / NCI
Prostate cancer Risk Enhancers
The goal of this study is to systematically identify target genes of all the newly identified PCa risk enhancers using eQTL, CRISPR, and 4C.
Rhie Role: Responsible for data analysis, manuscript preparation, and student training