Qun Li

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Education

2020.09 – 2023.07	**Ph.D.,** Advised by Prof. Lei Wang **Institutes of Biomedical Sciences, Fudan University, China** Major: Biochemistry and Molecular Biology
2018.09 - 2020.06	**M.S.,** Advised by Prof. Mingzhi Liao **College of Life Sciences, Northwest A & F University, China** Major: Bioinformatics
2014.09 - 2018.07	**B.S.,** Advised by Prof. Mingzhi Liao **College of Innovation and Experiment, Northwest A & F University, China** Major: Biotechnology

Skills

Dry: RNA-seq (Bulk/Single Cell), ATAC-seq, Chip-seq, WES/WGS

For bulk RNA-seq, I performed differential expression (sex-associated splicing or spermatogenesis), co-expression analysis to find hub genes (*Molecular Omics, 2020*; *J Clin Invest, 2023*). For single cell, I identified several subsets during female fetal germ cells (*Genome Biol, 2023*). For ATAC-seq or Chip-seq, I identified several key factors in porcine induced pluripotent stem cells (*FASEB J, 2021*).

Wet: Plasmid construction and *in vitro* transcription

Programming: Python, R

I identified *de novo* variants from nearly 480 trio using in-house Python scripts and these scripts were uploaded to GitHub (https://github.com/QunATCG). Usually, I show the results using a graph drawn by R or do some statistics with R.

Research Experience

2020.09 – 2022.12 **Project: *De novo* mutations in female infertility**
(Principal)

Oocyte maturation arrest and early embryonic arrest are important reproductive phenotypes resulting in female infertility and cause recurrent failure of assisted reproductive technology (ART). However, the genetic etiologies of these female infertility-related phenotypes are poorly understood. Previous studies have mainly focused on inherited mutations based on large pedigrees or consanguineous patients. However, role of *de novo* mutations (DNMs) in these phenotypes remain to be elucidated.

To decipher the role of DNMs in ART failure and female infertility with oocyte and embryo defects, we explore the landscape of DNMs in 473 infertile parent-child trios and identify a set of 481 confident DNMs distributed in 474 genes. Gene ontology analysis reveals that the identified genes with DNMs are enriched in signaling pathways associated with female reproductive processes such as meiosis, embryonic development and reproductive structure development. We perform functional assays on the effects of DNMs in a representative gene Tubulin Alpha 4a (*TUBA4A*), which shows the most significant enrichment of DNMs in the infertile parent-child trios. DNMs in *TUBA4A* disrupt the normal assembly of the microtubule network in HeLa cells, and microinjection of DNM *TUBA4A* cRNAs cause abnormalities in mouse oocyte maturation or embryo development, suggesting the pathogenic role of these DNMs in *TUBA4A*.

Our findings suggest novel genetic insights that DNMs contribute to female infertility with oocyte and embryo defects. This study also provides potential genetic markers and facilitates the genetic diagnosis of recurrent ART failure and female infertility.

—Fudan University, China. Supervisor: Prof. Lei Wang and Asst. Prof. Qing Sang

2021.09 – 2022.01 **Project: Loss of function mutations in female infertility**
(Principal)

The genetic causes of oocyte maturation arrest leading to female infertility are largely unknown, and no population based genetic analysis has been applied in cohorts of infertile patients. We aimed to identify novel pathogenic genes causing oocyte maturation arrest by using gene-based burden test.

Through comparison of whole exome sequencing data from 716 infertile females characterized with oocyte maturation arrest and 3539 controls, we performed a gene-based burden test and identified a novel pathogenic gene LIM homeobox 8 (*LHX8*). Splicing event was evaluated with minigene assay, expression of *LHX8* proteins was assessed in HeLa cells, and nuclear subcellular localization were detected in both HeLa cells and mouse oocytes. Five heterozygous loss-of-function *LHX8* variants were identified from six independent families. All the identified variants in *LHX8* produced truncated LHX8 proteins

and resulted in loss of LHX8 nuclear localization in both HeLa cells and mouse oocytes.

By combining genetic evidence and functional evaluations, we identified a novel pathogenic gene *LHX8*, and established the causative relationship between LHX8 haploinsufficiency and female infertility characterized by oocyte maturation arrest.

—Fudan University, China. Supervisor: Prof. Lei Wang and Asst. Prof. Qing Sang

2018.11 - 2019.12
(Principal)

Project: Study on sex-associated alternative splicing based on RNA-seq

The biological differences between the sexes have long been recognized at the physiological and pathological levels. The reasons for these differences are mostly related to the differences in the activity and function of genes between the sexes. Alternative splicing is an important mechanism for generating protein diversity and participating in the regulation of gene expression. As we known, alternative splicing plays a significant role in development, disease and aging. Although variants of alternative splicing are produced in most cell types, the cells will lead to different alternative splicing events subjected to external interference and their development requirements. The number of alternative splicing in testis is much higher than other tissues.

However, there is no systematic research on the sexual dimorphism from the perspective of alternative splicing. We have analyzed the sex biased alternative splicing events and gene expression of different mammals based on RNA-seq. At the same time, we constructed the alternative splicing related to sexes' differences database. In addition, we focused on the dynamic of alternative splicing during spermatogenesis. Using non-human mammals to assess the conservation of sex-biased gene expression and alternative splicing across multiple species and tissues will help researchers understand sex-related phenotypic differences.

—Northwest A & F University, China. Supervisor: Prof. Mingzhi Liao

2018.11 - 2021.01
(Participant)

Project: Epigenetic pluripotency network of porcine induced pluripotent stem cells

The pluripotency gene regulatory network of porcine induced pluripotent stem cells(piPSCs), especially in epigenetics, remains elusive. To determine the biological function of epigenetics, we cultured piPSCs in different culture conditions. We found that activation of pluripotent gene- and pluripotency-related pathways requires the erasure of H3K9 methylation modification which was further influenced by mouse embryonic fibroblast (MEF) served feeder. By dissecting the dynamic change of H3K9 methylation during loss of pluripotency, we demonstrated that the H3K9 demethylases KDM3A and KDM3B regulated global H3K9me2/me3 level and that their co-depletion led to the collapse of the pluripotency gene regulatory network. Immunoprecipitation-mass spectrometry (IP-MS) provided evidence that KDM3A and KDM3B formed a complex to perform H3K9 demethylation. The genome-wide regulation analysis revealed that OCT4 (O) and SOX2 (S), the core pluripotency transcriptional activators, maintained the pluripotent state of piPSCs depending on the H3K9

hypomethylation. Further investigation revealed that O/S cooperating with histone demethylase complex containing KDM3A and KDM3B promoted pluripotency genes expression to maintain the pluripotent state of piPSCs. Together, these data offer a unique insight into the epigenetic pluripotency network of piPSCs.

—Northwest A & F University, China. Supervisor: Prof. Mingzhi Liao and Prof. Jinlian Hua

2020.11 - 2022.10
(Participant)

Project: Bi-allelic pathogenic variants in *PABPC1L* cause oocyte maturation arrest

Oocyte maturation arrest is one of the important causes of female infertility, but the genetic factors remain largely unknown. PABPC1L, a predominant poly(A)-binding protein in *Xenopus*, mouse, and human oocytes and early embryos prior to zygotic genome activation, plays a key role in translational activation of maternal mRNAs. Here, we identified compound heterozygous and homozygous variants in *PABPC1L* that are responsible for female infertility mainly characterized by oocyte maturation arrest in five individuals. *In vitro* studies demonstrated that these variants resulted in truncated proteins, reduced protein abundance, altered cytoplasmic localization, and reduced mRNA translational activation by affecting the binding of PABPC1L to mRNA. *In vivo*, three strains of *Pabpc1l* knock-in (KI) female mice were infertile. RNA sequencing analysis showed abnormal activation of the Mos-MAPK pathway in the zygotes of KI mice. Finally, we activated this pathway in mouse zygotes by injecting human *MOS* mRNA, and this mimicked the phenotype of KI mice. Our findings reveal the important roles of PABPC1L in human oocyte maturation and add a genetic potential candidate gene to be screened for causes of infertility.

—Fudan University, China. Supervisor: Prof. Lei Wang and Asst. Prof. Qing Sang

2020.11 - 2022.03
(Participant)

Project: Karyopherin α deficiency contributes to human preimplantation embryo arrest

Preimplantation embryo arrest (PREMBA) is a common cause of female infertility and recurrent failure of assisted reproductive technology. However, the genetic basis of PREMBA is largely unrevealed. Here, using whole-exome sequencing data from 606 women experiencing PREMBA compared with 2,813 controls, we performed a population and gene-based burden test and identified a candidate gene, karyopherin subunit α7 (*KPNA7*). In vitro studies showed that identified sequence variants reduced KPNA7 protein levels, impaired KPNA7 capacity for binding to its substrate ribosomal L1 domain-containing protein 1 (RSL1D1), and affected KPNA7 nuclear transport activity. Comparison between humans and mice suggested that mouse KPNA2, rather than mouse KPNA7, acts as an essential karyopherin in embryonic development. *Kpna2*-/- female mice showed embryo arrest due to zygotic genome activation defects, recapitulating the phenotype of human PREMBA. In addition, female mice with an oocyte-specific knockout of *Rsl1d1* recapitulated the phenotype of *Kpna2*-/- mice, demonstrating the vital role of substrate RSL1D1. Finally, complementary RNA (cRNA) microinjection of human *KPNA7*, but not mouse Kpna7, was able to rescue the

embryo arrest phenotype in *Kpna2*-/- mice, suggesting mouse KPNA2 might be a homologue of human *KPNA7*. Our findings uncovered a mechanistic understanding for the pathogenesis of PREMBA, which acts by impairing nuclear protein transport, and provide a diagnostic marker for PREMBA patients.

—Fudan University, China. Supervisor: Prof. Lei Wang and Asst. Prof. Qing Sang

Research Interests

Human Genetics | Gene Mutation | Genetic heterogeneity | Expression Regulation

My work focused on exploring associations between rare germline variants and female infertility. Through *integrating gene expression profiles, whole-exome sequencing data from large population, epigenetic modification data and public datasets,* I try to identified candidate pathogenic genes contributed to female infertility. With the help of collaborators, we validated candidate genes' role in female infertility by functional assays.

The overall interest of mine is to *understand genetic and epigenetic mechanisms related to disease processes using omics methods.*

Publications

Co-first authors

- **Li Q**, Zhao L, Zeng Y, Kuang Y, Guan Y, Chen B, Xu S, Tang B, Wu L, Mao X, et al: Large-scale analysis of *de novo* mutations identifies risk genes for female infertility characterized by oocyte and early embryo defects. Genome Biol 2023, 24:68.
- Wang W, Guo J, Shi J, **Li Q**, Chen B, Pan Z, Qu R, Fu J, Shi R, Xue X, et al: Bi-allelic pathogenic variants in *PABPC1L* cause oocyte maturation arrest and female infertility. EMBO Mol Med 2023: e17177.
- Zhao L, **Li Q**, Kuang Y, Xu P, Sun X, Meng Q, Wang W, Zeng Y, Chen B, Fu J, et al: Heterozygous loss-of-function variants in *LHX8* cause female infertility characterized by oocyte maturation arrest. Genet Med 2022, 24:2274-2284.
- Zhu Z, Wu X, **Li Q**, Zhang J, Yu S, Shen Q, Zhou Z, Pan Q, Yue W, Qin D, et al: Histone demethylase complexes KDM3A and KDM3B cooperate with OCT4/SOX2 to define a pluripotency gene regulatory network. Faseb j 2021, 35: e21664.
- **Li Q**, Li T, Xiao X, Ahmad DW, Zhang N, Li H, Chen Z, Hou J, Liao M: Specific expression and alternative splicing of mouse genes during spermatogenesis. Molecular Omics 2020, 16:258-267.

Other publications

- Qu R, Zhang Z, Wu L, **Li Q**, Mu J, Zhao L, Yan Z, Wang W, Zeng Y, Liu R, et al: *ADGB* variants cause asthenozoospermia and male infertility. Hum Genet 2023.
- Wang W, Miyamoto Y, Chen B, Shi J, Diao F, Zheng W, **Li Q**, Yu L, Li L, Xu Y, et al: Karyopherin α deficiency contributes to human preimplantation embryo arrest. J Clin Invest 2023, 133.

• Li T, **Li Q**, Li H, Xiao X, Ahmad Warraich D, Zhang N, Chen Z, Hou J, Liu T, Weng X, et al: Pig-specific RNA editing during early embryo development revealed by genome-wide comparisons. FEBS Open Bio 2020, 10:1389-1402.

• Sun C, Zhang N, Yu P, Wu X, **Li Q**, Li T, Li H, Xiao X, Shalmani A, Li L, et al: Enhancer recognition and prediction during spermatogenesis based on deep convolutional neural networks. Mol Omics 2020, 16:455-464.

• Wang X, Wu X, Zhu Z, Li H, Li T, **Li Q**, Zhang P, Li L, Che D, Xiao X, et al: Landscape of RNA editing reveals new insights into the dynamic gene regulation of spermatogenesis. Cell Cycle 2019, 18:3351-3364.

• Wang X, Zhang P, Li L, Che D, Li T, Li H, **Li Q**, Jia H, Tao S, Hua J, et al: miRNA editing landscape reveals miR-34c regulated spermatogenesis through structure and target change in pig and mouse. Biochem Biophys Res Commun 2018, 502:486-492.

Referrer

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