My training has been unique in that I have experience in conducting research in genetics, epigenetics and computational biology to answer important clinical questions. I plan to leverage my unique background to understand the function of non-coding variants and epigenetic effects across different diseases using a combination of computational approaches and laboratory work. When trio studies and population-based GWAS and sequencing studies identify missense and nonsense variants, the path to determine function is relatively straightforward. However, as we are all aware, the large majority of genetic variants identified in these studies are non-coding. My goal is to develop a research program that uses both computational and experimental approaches to understand 1) if there is good evidence that specific identified variants are indeed pathogenic for the disease studied and 2) how these variants produce their pathogenic effects through regulatory mechanisms. My expertise lies in the intersection of genetics and epigenetics, so I intend to use my skills and build a laboratory to understand how both genetic variation and epigenetic variation work in non-coding regions to produce disease. I envision building the following pipeline to assess the functionality of identified genetic variants and epigenetic effects using ….

One area that I’m particularly interested in investigating is the role of epigenetics in modifying the effects of known PGx variants. Much of the variation in drug response is not explained by known genetic variants. My hypothesis is that epigenetic effects at these genes also contribute to the drug response and potentially interact with the previously described genetic variants. So, one of the first studies that I would like to conduct would look at the pharmaco-epigenetics at important PGx genes. I envision a pilot study where my lab will…

The sample sets that I would have access to at UW-Madison would be ideal to conduct these types of studies because…

I am extremely interested in this position at UW-Madison, where I believe my Ph.D and Postdoctoral training in human genetics, clinical epigenetics and bioinformatics will allow me to meet the challenge of precision medicine in which genetics, epigenetics and computatio-nal biology are combined to address important clinical problems. I view this position as an opportunity to apply my computational and wet-lab skills to develop a multi-faceted research program in precision medicine, investigating the interactions between genetic and epigenetic factors that underlie complex diseases.

On one side, current I was involved in several collaborations between MCRI and UW-Madison. For example, we have an ICTR proposal which is under review to investigate the cell-free DNA methylation signal and fragmentation size in oral cancer and another collaboration with Steven Schrodi and Judy Smith on the genetic study to ankylosing spondylitis.

On the another side, I will make full use of UW-Madison resource such as SickKids project, TSB-biobank at Carbone Cancer Center

Take Sickkids project as example, as we know, we will identify 100-1000 potential disease or risk associated genetic variations for the specific family or trios. How to determine the real causal variation and how to functional evaluate these genetic variants are great challenge. If the variants identified in the Sickkids project are similar to those identified by GWAS, more than 80% of the significant hits are not protein-coding variations. In order to provide better understanding to these diseases associated variations, we need focus our attention to these non-coding variation or regulatory variations. However, the current functional evaluation are seriously lack of regulatory annotation to genetic variants. As I have expertise in DNA methylation, current I am exactly working on the regulatory genetic variants mediated by epigenetic modifications. For example, for human, DNA methylation almost only occurred in CpG dinucleotide, any genetic variations break or create CpG dinucleotide will change the ability of DNA methylation or not and then will influence the gene expression or splicing. Another example in genetic variations located in seed region of microRNA or Piwi-RNA will change the miRNA-binding target and then change the gene expression network. Finally, genetic variations occurred in transcript-factor binding site will also change the chromatin status and further gene expression. Only when we recruited all these variations into the association model or prediction model, we can provide better interpretation with genetic variants to phenotypes. Meanwhile, when we enrolled all these functional variants, we can have better gene based association model, such as recessive model, compound heterozygote model and further high level models such as pathway based analysis model. With these features, we can have better prediction ability to mapping the variants to potential tissues or organ systems. Current, working with Dr. Steven Schrodi, I almost finished an updated compound heterozygote analysis pipeline, which was created in my previous blood paper, in which eQTL and loss-of-function were integrated to increase the power of the association study. After I completed the functional CpG-SNP, functional miRNA-seq and functional TFBS-Seq, I can integrate all these feature in my analysis pipeline and apply it in SickKids project to identify novel functional disease variants. Finally, I will also introduce the novel approach such as WGBS, ATAC-seq, histone ChIP-seq to extend the evaluation pipeline to regulatory SNPs.

Meanwhile, I always investigate epigenetics with genetic concepts. It has been shown with my previous research, such as I proposed methylation haplotype to reflect methylation level and methylation diversity at the same time. I also want to extent this kind of research strategy in UW-Madison. For example, I will start a pilot study in pharmaco-epigenomics research together with current running pharmacogenomics research. My hypothesis is pharcogenetic will provide baseline prediction potential for the drugs while pharmaco-epigenomics could provide recent prediction ability. It will be have higher prediction ability combined these together. I know several scientist such as Dr. [Arash Bashirullah](https://apps.pharmacy.wisc.edu/sopdir/arash_bashirullah/index.php) are working on pharcogenetic research to leukemia, I can proposal an integrative proposal and try to submit the proposal to Pharmacology Study Section.