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Dr. Guo joined Dr. Schrodi’s lab at Marshfield Clinic Research Institute on 11/27/2017. In the past two years, Dr. Guo worked with Dr. Schrodi and other collaborators resulting in 10 published scientific papers. As the first and co-first author, Dr Guo published two papers in *Blood* (2019) and *Scientific Reports* (2019). As the co-corresponding author, Dr. Guo published two papers on *Cell Death & Diseases* (2018) and *Frontiers in Genetics* (2019). In addition, he is the co-author on another 6 publications. Dr. Guo gave five presentations at the Marshfield Clinic Scientific Seminar and MCRI Scientist meeting, gave an invited presentation at the Shanghai Academy of Chinese Medical Sciences and has an accepted presentation at the American Society of Human Genetics 2019 Conference. Additionally, Dr. Guo has been offered a CIBM postdoctoral fellowship to study epigenetic/genetic interactions across diseases in PMRP. All the research conducted by Dr. Guo has been focused on human health issues including the identification of novel diseases genes and the development of novel cancer diagnosis using prognostic/diagnostic biomarker panels.

**Presentations**:

UK Biobank Whole-Exome Sequence Binary Phenome Analysis with Robust Region-Based Rare-Variant Test, Marshfield Clinic Research Institute, Marshfield, WI, 01/19/2020

Deep learning prediction of chemotherapy response using multi-omics features. 2019 Am Soc Hum Genet Conference, October, 2019

Using Computational Biology, Genetics and Epigenetics to Understand Disease Etiologies and Improve Precision Medicine, Scientific Seminar, 05/15/2019.

Identification and Validation of Cell-free DNA Methylation Biomarkers for Human Cancers. Marshfield Clinic Research Institute, Scientist meeting, 04/18/2019.

Mapping Hemochromatosis Genes using a Novel Recessive Diplotype Approach in the Marshfield Clinic Personalized Medicine Research Project (PMRP), Scientific Seminar, 3/13/2019.

Latest Progress of Epigenetic Research in Rheumatoid Arthritis. Shanghai Academy of Chinese Medical Sciences, August 2018.

**Publications**: (1-5)

Chen C, Zhang K, Dong P, Fanning Gregory, Tao C, Zhang H, **Guo S**, Wang Z, Hong Y, Yang X, Lai S, Ding H, Zhao H, Zeng C, Protzer Ulrike, Zhang D. Noninvasive chimeric DNA profiling identifies tumor-originated HBV integrants contributing to viral antigen expression in liver cancer. Hepatology International, 2020 (accepted).

**Guo S**\*, Liu J, Jiang T, Lee D, Wang R, Zhou X, Jin Y, Shen Y, Wang Y, Bai F, Ding Q, Wang G, Zhang Y, Zhou X, Schrodi SJ, He D. (5R)-5-Hydroxytriptolide (LLDT-8) induces substantial epigenetic mediated immune response network changes in fibroblast-like synoviocytes from rheumatoid arthritis patients. Scientific Reports 2019.

Chen S, Pu W, **Guo S**, Jin L, He D, Wang J. Genome-wide DNA methylation profiles reveal common epigenetic patterns of interferon-related genes in multiple autoimmune diseases. Front Genet 2019;10:223.

**Guo S**, Jiang S, Epperla N, Ma Y, Maadooliat M, Ye Z, Olson B, Wang M, Kitchner T, Joyce J, An P, Wang F, Strenn R, Mazza JJ, Meece JK, Wu W, Jin L, Smith JA, Wang J, Schrodi SJ. A gene-based recessive diplotype exome scan discovers fgf6, a novel hepcidin-regulating iron-metabolism gene. Blood 2019;133:1888-98.

Jiang D, He Z, Wang C, Zhou Y, Li F, Pu W, Zhang X, Feng X, Zhang M, Yecheng X, Xu Y, Jin L, **Guo S**, Wang J, Wang M. Epigenetic silencing of znf132 mediated by methylation-sensitive sp1 binding promotes cancer progression in esophageal squamous cell carcinoma. Cell Death Dis 2018;10:1.

Wang C, Pu W, Zhao D, Zhou Y, Lu T, Chen S, He Z, Feng X, Wang Y, Li C, Li S, Jin L, **Guo S#**, Wang J**#**, Wang M**#**. Identification of hyper-methylated tumor suppressor genes-based diagnostic panel for esophageal squamous cell carcinoma (escc) in a chinese han population. Front Genet 2018;9:356.

Feng W, Guo X, Huang H, Xu C, Li Y, **Guo S**, Zhao Z, Li Q, Lu D, Jin L, Wang J, Jiang G, Wu J. Polymorphism rs3819102 in thymidylate synthase and environmental factors: Effects on lung cancer in chinese population. Curr Probl Cancer 2019;43:66-74.

Pu W, Wang C, Chen S, Zhao D, Zhou Y, Ma Y, Wang Y, Li C, Huang Z, Jin L, **Guo S#**, Wang J**#**, Wang M**#**. Targeted bisulfite sequencing identified a panel of DNA methylation-based biomarkers for esophageal squamous cell carcinoma (ESCC). Clin Epigenetics 2017; 9:129-140.

He D, Liu J, Hai Y, Zhu Q, Shen Y, **Guo S**, Zhang W, Zhou X. Increased DOTL1 in synovial biopsies of patients with OA and RA. Clin Rheumatol 37(5):1327-1332.

**Originality, Uniqueness and Significance of the Research**

1. **Guo S**\*, Jiang S\*, Epperla N, Ma Y, Maadooliat M, Ye Z, Olson B, Wang M, Kitchner T, Joyce J, An P, Wang F, Strenn R, Mazza JJ, Meece JK, Wu W, Jin L, Smith JA, Wang J, Schrodi SJ. A gene-based recessive diplotype exome scan discovers FGF6, a novel hepcidin-regulating iron-metabolism gene. Blood 2019;133:1888-98.

Frequently, disease gene mapping experiments rely on genome-wide association studies. While these studies are effective at identifying additive disease-susceptibility effects at single nucleotide polymorphisms (SNPs), this approach ignores more complex effects. By specifically looking at disruptive variants on both copies of a gene, the researchers were able to discover novel diseases genes. Dr. Guo speculate that the large number of very rare genetic variants found in humans may produce these effects across a wide array of diseases as individuals without one copy of a normally functioning gene may be predisposed to pathologies. In this original manuscript, Dr. Guo conduct an exome-wide, gene-based scan for single site recessive effects and compound heterozygous effects underlying iron overload susceptibility. Dr. Guo have identified *FGF6*, encoding for the fibroblast growth factor 6, as being experiment-wide significant in his study and demonstrate that FGF-6 induces transcriptional regulation of hepcidin—a central hormone central in the maintenance of iron homeostasis and decreases ferrous absorption in hepatocytes. Moreover, specific *FGF6* variants identified in his study are shown to carry functional effects, reducing FGF-6 activity compared to wildtype alleles. These findings reveal a novel iron metabolism mechanism and will motivate subsequent studies in this field. Additionally, his approach uses exome genotype data to interrogate a mode of inheritance—recessive diplotypes—that standard GWAS statistical methods are poorly powered to uncover. Hence, not only does his study discover a novel protein involved in iron metabolism, but they foresee the genetic approach enjoying wide applicability across all complex diseases using existing genetic datasets.

Genome-wide association studies have difficulty finding these genes, but the new recessive diplotype scan is a powerful method to discover these disease genes. Once these disease genes are found, they can serve as targets for new treatments. In the study, he not only show that the FGF-6 protein regulates a key hormone in iron metabolism, hepcidin (encoded by *HAMP*), but that the loss-of-function variants in FGF-6, strongly attenuate the signaling in this important iron pathway. Dr. Guo also show that FGF-6 changes the uptake of iron into cells. Further, he demonstrate the involvement of FGF-6 in the iron overload condition observed in cancers and systemic sclerosis. He provide evidence that the disruption of iron metabolism by the *FGF6* variants are driven by dysfunctional binding to heparin and the FGF receptor (FGFR). As such, the study provides a new understanding of the mechanisms underlying iron homeostasis and may aid the development of therapeutic interventions for patients with hemochrom-atosis and possibly anemia. Dr. Guo developed a new method to identify novel disease genes with compound heterozygous effects and he identified a novel susceptibility genes or therapeutic target for hemochrom-atosis and possibly anemia.

1. Jiang D, He Z, Wang C, Zhou Y, Li F, Pu W, Zhang X, Feng X, Zhang M, Yecheng X, Xu Y, Jin L, **Guo S**#, Wang J#, Wang M#. Epigenetic silencing of *ZNF132* mediated by methylation-sensitive SP1 binding promotes cancer progression in esophageal squamous cell carcinoma. Cell Death Dis 2018;10:1.

Esophageal cancer (ESCC) ranks 8th in most common cancers and 6th in cancer-related mortality worldwide. For the past decades, the incidence of and estimated deaths due to esophageal cancers have been increasing continuously. Considering the characteristics of highly invasive, metastatic, and poor prognosis, there is an urgent need for identifying early diagnostic biomarkers for ESCC so that the physicians will have enough time to investigate the best therapy approach for the cancer patients. DNA methylation has been demenstrated to be the most promising early biomarkers for cancer diagnosis, especially the circulating cell-free DNA. In this study, Dr. Guo scanned the genome-wide DNA methylation dataset from TCGA project and identified a strongly signficant ESCC hypermethylated gene: *ZNF132*.

To validate the diagnostic biomarker performance of ZNF132 and determine the role of ZNF132 in ESCC, he applied targeted methylation sequencing and profiled DNA methylation status of promoter region of ZNF132 in ESCC cell lines and ESCC biopsy specimens. He found ZNF132 are hypermethylated in ESCC cell line and ESCC biospy samples. Dr. Guo also dementrated hypermethylation in ZNF132 promoter region caused down-regulated of ZNF132 while he demenstrated ZNF132 expression could be rescured with 5-Azacytidine (de-methylation agents) treatment. In addtion, Dr. Guo scanned transcriptor binding sites from 161 transcript factors within promoter region of ZNF132 and a 6-base-pair (GGGCGG) Sp1-binding motif located in the CpG island of *ZNF132* promoter region and its binding region was supported by ENCODE Transcription Factor ChIP-seq data. Dr. Guo speculate SP1 binding might be affected by DNA methylation status and then he validated his hypothesis with methylation luciferase reporter assay. Finally, Dr. Guo also investigate the function of *ZNF132*  as the tumor suppressor genes with in vivo xenograft mouse model. He found ZNF132 over-expressed nude mice have significant decrease of tumor size. Overall, in his study, Dr. Guo demenstrate that epigenetic silencing of *ZNF132* mediated by methylation-sensitive SP1 binding promote cancer progression in esophageal squamous cell carcinoma. Overall, Dr. Guo identified a novel ESCC tumor suppressor factors and ZNF132 maybe a promising drug target for cancer diagnosis and therapy.