THE OHIO STATE UNIVERSITY
BIOMEDICAL SCIENCES
GRADUATE PROGRAM
SPRING 2015

THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

Madelyn M. Gerber
PhD Candidate

“The Identification of Colorectal Cancer Susceptibility Genes Using a Cross-Species, Systems Genetics Approach”

Tuesday, April 7, 2015
105 Biomedical Research Tower
9:00AM-10:00AM
VITA

August 6, 1988 . . . . . . . . . . . . . . . . . . . . . Born – Maplewood, MN

2010 . . . . . . . . . . . . . . . . . . . . . . . . . B.A. Biology and Psychology
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2010-present . . . . . . . . . . . . . . . . . . . . . . . . PhD candidate in
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COMMITTEE MEMBERS

Amanda Ewart Toland, PhD, Advisor

Joanna Groden, PhD

Jeffrey Parvin, MD, PhD

Wolfgang Sadee, Dr.rer.nat.
ABSTRACT

Colorectal cancer (CRC) is the third most commonly diagnosed and third leading cause of cancer-related death in the United States. As much as 35% of risk for developing this disease is due to genetic risk factors. Genome-wide association studies (GWAS) have identified ~40 independent common risk variants that contribute to genetic predisposition. However, these variants fail to explain the majority of the genetic component for risk. Identification of additional susceptibility alleles for CRC is critical for developing genetic screening tools capable of predicting individuals at heightened genetic risk. My dissertation research was aimed at uncovering CRC susceptibility genes using a cross-species systems genetics approach.

We first assessed single nucleotide polymorphisms (SNPs) at loci that were linked to CRC risk by GWAS for allele-specific somatic copy number gains or losses in human colorectal tumor genomes. We hypothesized that GWAS-identified SNPs exhibit allele-specific copy number changes (termed ‘allele-specific imbalance,’ or ASI) in the tumor genome of patient specimens in much the same fashion as oncogenes are amplified and tumor suppressors are lost. We tested this hypothesis using quantitative genotyping to detect relative gains or losses of GWAS-identified SNP alleles in a cohort of human paired colorectal tumor/normal DNA samples. Testing of 17 SNPs revealed statistically significant allele-specific copy number changes at one SNP, rs6983267 at 8q24, which suggests that ASI occurs at CRC risk loci but perhaps at low frequency.

Having established that ASI can occur at CRC susceptibility loci, we next conducted a large ASI screen of SNPs tagging for candidate genes at the human orthologs of three murine CRC susceptibility quantitative trait loci (QTL). We prioritized genes for inclusion in this study based on RNA-seq data generated from the normal colons of the CRC-resistant and CRC-susceptible mouse parental strains that were used to linkage-map these QTLs. Because no protein-damaging coding SNPs were identified by RNA-seq, we focused largely on genes showing differential
expression between the strains and/or genes with a documented role in cancer-relevant pathways or processes. Two SNPs in \textit{SNX10} emerged from our screen as showing statistically significant ASI in human colorectal tumors. These SNPs and the linkage disequilibrium blocks in which they reside warrant further investigation for functionality.

In the last phase of my dissertation research, we conducted preliminary functional investigations of the hypoxia-inducible factor Epas1, whose gene maps to the \textit{Scc4} susceptibility QTL. This gene is differentially expressed in the colons of the CRC-resistant and CRC-susceptible mouse strains used to map \textit{Scc4}. Furthermore, five tagging SNPs within \textit{EPAS1} show suggestive evidence of ASI in human colorectal tumor/normal DNA pairs, but were not statistically significant after correction for multiple comparisons. These data prompted us to investigate \textit{EPAS1}/\textit{Epas1} for functional effects in human and mouse colon cell lines. We tested this gene for effects on β-catenin/TCF-mediated transcriptional activity under conditions of normoxia and hypoxia in SW480 and HCT116 human colon adenocarcinoma cell lines. Under hypoxic culture conditions, we observed activation of our TOPflash β-catenin/TCF reporter construct when \textit{Epas1} expression was enforced, suggesting a plausible role for \textit{EPAS1} in modifying CRC susceptibility by converging on the aberrantly activity Wnt/β-catenin signaling axis. Collectively, our data validate our cross-species approach as an innovative strategy for uncovering novel candidate CRC susceptibility genes.
RECENT ABSTRACTS AND PRESENTATION


RECENT PUBLICATIONS


AWARDS AND HONORS

Alumni Grants for Graduate Research and Scholarship (2015)
Council of Graduate Students Career Development Grant (2014)
Council of Graduate Students Ray Travel Award (2014)
OSUWMC Trainee Research Day Scientific Travel Award (2014)
Council of Graduate Students Ray Travel Award (2013)
Pelotonia Graduate Fellowship (2013)
Sigma Xi Grant-in-Aid of Research (2012)
College of Medicine Systems and Integrated Biology Training Program
Training Grant (2011-2012, 2012-2013)
Ohio State Graduate School University Fellowship (2011)

FUTURE PLANS

I will be pursuing a postdoctoral fellowship position upon graduation. I wish to continue my studies of human genetics and perhaps pursue a career in pediatric clinical genetics.