Human Genetics

RESEARCH AND TRAINING DETAILS

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CLINICAL ACTIVITIES AND TRAINING

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Research Highlights

Elizabeth Schorry, MD
As a member of the Neurofibromatosis Clinical Trials consortium, Dr. Schorry and her team have completed a clinical trial of the mTOR inhibitor, sirolimus, for plexiform neurofibromas in patients with neurofibromatosis type 1 (NF1). They demonstrated that use of sirolimus prolonged the time to progression of plexiform neurofibromas by about 30%, indicating that this agent is capable of slowing growth of these challenging tumors. They also completed a trial of lovastatin for learning disabilities in NF1, and demonstrated that lovastatin was not effective in improving attention or working memory in children with NF1.

Ying Sun, PhD
Dr. Sun and her team developed the protocol and conducted preclinical studies in evaluating new small pharmaceutical compound (produced by Genzyme) for substrate reduction therapy (SRT) to treat neuronopathic Gaucher disease. The results demonstrated that the new, and central nervous system (CNS) accessible, SRT reduced the level of lipid substrate accumulation and CNS inflammation in Gaucher disease mouse model and leads to delayed neurodegeneration and improved survival. This study supports the clinical efficacy of this first SRT in attenuating neuronopathic Gaucher disease.

In addition, Dr. Sun’s lab has performed the extensive ribonucleic acid (RNA) analyses of neuronopathic Gaucher disease mice brain by RNASeq technology. The results of these analyses revealed dynamic alterations of miRNAs and mRNA in the brain of animal model. The identified miRNAs and target mRNAs are involved in the biological pathways that have not been explored in Gaucher disease. These data provide the molecular basis for further investigation of biological pathways underlying the disease and develop new therapeutic targets. The manuscript is in revision in Human Molecular Genetics.

Ge Zhang, MD, PhD
Dr. Zhang has conducted multiple genome-wide quantitative genetic analyses of human complex traits and diseases. He has helped in identifying genetic loci associated with diisocyanate-induced occupational asthma. He developed a novel Mendelian randomization approach using non-transmitted maternal haplotype as a genetic instrument to infer causal relationship between parental phenotype and outcomes in offspring. Using this method, he and his collaborators defined the causal relationship for the strong association of maternal height with fetal growth measures (i.e. birth length and birth weight) and gestational age.

Taosheng Huang, MD, PhD
Dr. Huang, with collaborators Robert Hufnagel, MD, PhD, and Elizabeth Schorry, MD, studied two sisters with an unusual syndrome of optic atrophy, cerebellar degeneration, and axonal peripheral neuropathy. Through whole exome sequencing, they identified mutations in SLC25A46, which codes for a protein located in the outer mitochondrial membrane. Phylogenetic and structural analyses suggest that SLC25A46 interacts with proteins associated with OPA1 and MFN2 and acts as a carrier inside mitochondria. However, the function of SLC25A46 and its carried substrate are yet to be identified, discovery of which may lead to important clues linking mitochondrial fission and fusion to a common pathway of disease pathogenesis. In their funded CpG project, they plan to create two mouse models to study pathogenesis of SLC25A46 mutations. The goal is to identify additional patients with SLC25A46-associated optic atrophy plus syndrome in order to better study the role of SLC25A46 in mitochondrial dynamics and human disease.

Derek Neilson, MD
Dr. Neilson received a grant from the Center for Pediatric Genomics (CPG) to study the hypermobile type of Ehlers Danlos syndrome. This connective tissue disorder, served by the Connective Tissue Clinic which sees 600 new patients per year, predisposes to multiple problems including chronic pain, fatigue and gastrointestinal disorders. The CPG funds will be used to identify genes and biological markers that could lead to new treatments and prevention of these disabling
complications.

**Significant Publications**


This paper reports a novel human craniofacial malformation syndrome caused by mutations in a gene that was not previously known to be associated with human disease. Remarkably, three of the four unrelated individuals described have the same de novo missense mutation. In vitro and in vivo studies demonstrated that the Tyr129Phe mutation results in complex, context-specific effects on the ligand specificity and downstream signaling of the endothelin receptor type A. These effects may underlie the common phenotype shared by individuals with MFDA.


We identified glucosylceramide mediated complement activation and the generation of C5a as one of the main drivers of upregulation of the co-stimulatory molecules, increased production of pro inflammatory cytokines and chemokines and tissue damage in Gaucher disease. This finding uncovers the C5a/C5aR axis as a novel therapeutic target in Gaucher disease, which can potentially be used as an innovative adjunctive therapeutic approach for lung and brain defects, for which no appropriate treatment options exist.


Previously, we identified and captured in separate mouse lines two chromosomal regions carrying opposite-effect genes linked to differential susceptibilities to high-dose oxygen. This report extends those findings to demonstrate that sensitivity directly depends on the sex of mice and a 4-week age period in early adulthood, thereby establishing our unique mouse lines as valuable tools to delineate the complex biological mechanisms defining these susceptibility differences.


Here we identify the first mutations in human FZD2 and show they are associated with omodyplasia, a disease affecting the skeleton. This represents a successful application of human next-generation sequencing and subsequent biological analysis from a recently formed Cincinnati Children's collaborative network.


The study provides the first electrophysiological characterization of Gaucher disease neurons that will expedite dissecting the pathological mechanisms of neuronopathic Gaucher disease. The electrophysiological properties of Gaucher disease iPSC-derived neurons could represent a novel area for therapeutic target screening.
Division Publications


24. Ha S, Stottmann RW, Furley AJ, Beier DR. A forward genetic screen in mice identifies mutants with abnormal


39. Neilson D, Martin VT. **Joint hypermobility and headache: understanding the glue that binds the two together--part 1.** *Headache*. 2014; 54:1393-402.


45. Prows CA, Tran G, Blosser B. **Whole exome or genome sequencing: nurses need to prepare families for the possibilities.** *J Adv Nurs*. 2014; 70:2736-45.


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**Faculty, Staff, and Trainees**

**Faculty Members**

**Nancy Doan Leslie, MD**, Professor  
**Leadership** Co-Director, Division of Human Genetics; Director, Biochemical Genetics Laboratory; Director, Medical Biochemical Genetics Fellowship; Program Director, Laboratory Fellowships  
**Research Interests** Inborn errors of metabolism, with an emphasis on long term outcome in PKU and in the molecular biology of galactosemia.

**William Nichols, PhD**, Professor  
**Leadership** Co-Director, Division of Human Genetics; Associate Director of Research; Director, National Biological Sample and Data Repository for PAH
Research Interests The identification of genetic variants contributing to disease susceptibility with an emphasis on pulmonary arterial hypertension and Parkinson disease.

Carrie Atzinger, MS, Assistant Professor
Leadership Assistant Director, The Genetic Counseling Graduate Program

T. Andrew Burrow, MD, Assistant Professor
Research Interests Lysosomal storage diseases, particularly Gaucher disease; Inborn errors of metabolism, and neurogenetics.

Hatice Duzkale, MD, MPH, PhD, Assistant Professor
Leadership Assistant Director, Molecular Genetics Laboratory
Research Interests Liquid biopsy approaches to monitor disease course in pediatric solid tumors; discovery of novel treatment targets for metastatic Ewing sarcoma; novel causative gene discovery in MODY through exome analysis.

Lisa Dyer, PhD, Instructor
Leadership Assistant Director, Clinical Cytogenetics Laboratory
Research Interests Identification and characterization of translocation positive pediatric renal cell carcinoma.

Min-Xin Guan, PhD, Adjunct
Research Interests Mechanisms of mitochondrial disorders, with a focus on maternally transmitted hearing loss and vision loss.

Robert Hopkin, MD, Associate Professor
Leadership Director, Genetic Residency Programs
Research Interests Fabry disease; Robin sequence; 22q11 deletion; neurofibromatosis; craniofacial genetics; chromosomal anomalies.

Taosheng Huang, MD, PhD, Professor
Leadership Director, Program of Mitochondrial Medicine; Associate Director, Molecular Diagnostic Laboratory
Research Interests Disease-causing gene discovery with next generation sequencing and iPS cell therapy.

Ronghua Li, PhD, Instructor
Research Interests Cell-specific models of mitochondrial diseases and mitochondrial epigenetics.

Xia Li, PhD, Assistant Professor
Leadership Associate Director, Clinical Cytogenetics Laboratory
Research Interests The role of molecular markers in hematological disorders for prediction, treatment, and monitoring.

Lisa Martin, PhD, Professor
Leadership Director, Cincinnati Genomic Control Cohort; Co-Team Leader for United Way
Research Interests Improving the understanding of human genetic variation through the integration of statistical genetics with biology and epidemiology especially how it relates to pediatric heart conditions, allergic disorders and obesity.

Melanie Myers, PhD, MS, LGC, Associate Professor
Leadership Director, The Genetic Counseling Graduate Program
Research Interests Clinical utility of family health history and other genomic tools in health promotion.

Derek Neilson, MD, Assistant Professor
Research Interests Genetic and pathogenesis of Ehlers Danlos as well as genetics of neurologic disorders.

Manoj Pandey, PhD, Instructor
Research Interests Immunobiology of the lysosomal storage disease.

Carlos Prada, MD, Assistant Professor
Research Interests Inborn errors of metabolism with emphasis in newborn screening technologies and implementation; biomarkers of disease progression of lysosomal storage disorders and neurofibromatosis.

Daniel R Prows, PhD, Associate Professor
Research Interests Mouse models of complex human diseases, with specific interest in mouse models of acute lung injury; use of quantitative trait locus analysis to identify regions linked to complex traits.

Howard Saal, MD, Professor
Leadership Director, Clinical Genetics; Medical Director, Cytogenetics Laboratory; Director, Cincinnati Children’s Craniofacial Center
Research Interests The natural history of genetic disorders, especially as they relate to craniofacial disorders; developing treatment and management protocols for craniofacial disorders, and treatment of tongue based airway disorders.

Iris Sageser, RDH, MS, Associate Professor
Research Interests Multidisciplinary management of individuals affected by craniofacial abnormalities.

Elizabeth K Schorry, MD, Professor
Leadership Director, Neurofibromatosis Clinic
Research Interests Psychosocial and orthopedic aspects of neurofibromatosis; clinical drug trials for NF1, and Ehlers Danlos syndrome.

Teresa A Smolarek, PhD, Associate Professor
Leadership Director, Clinical Cytogenetics Laboratory; Director, Clinical Cytogenetics Fellowship Program
Research Interests Application of SNP microarrays to determine constitutional and acquired DNA copy number changes; the genetic basis of pulmonary lymphangioleiomyomatosis.

Rolf W Stottmann, PhD, Assistant Professor
Leadership Director, Student Admissions for the MDB program
Research Interests Genetic analysis of congenital malformations affecting the brain and face.

Ying Sun, PhD, Associate Professor
Research Interests The pathological mechanisms of lysosomal storage diseases.

C. Alexander Valencia, PhD, Assistant Professor
Leadership Assistant Director, Molecular Genetics Laboratory
Research Interests Clinical genomics and proteomics: a systems biology view in human genetics.

Stephanie Ware, MD, PhD, Adjunct
Research Interests Genetic disorders of cardiac structure and function.

K. Nicole Weaver, MD, Instructor
Research Interests Cardiovascular genetics; Costello syndrome; craniofacial genetics; Robin sequence.

Ge Zhang, MD, PhD, Associate Professor
Research Interests Genome-wide association studies and mathematical modeling of human genetic variations.

Kejian Zhang, MD, MBA, Associate Professor
Leadership Director, Molecular Genetics Laboratory
Research Interests Molecular defects and molecular diagnosis of primary immunodeficiency diseases; genetic aspects of predictive personalized medicine, e.g., pharmacogenetics.

Joint Appointment Faculty Members

Artem Barski, PhD, Assistant Professor (Allergy & Immunology)
Research Interests Chromatin biology; epigenomic and transcriptional regulation of immune response; use of epigenomic data to augment genome –wide association studies.
John Greinwald, MD, Associate Professor (Otolaryngology)
   Research Interests Genetics of hearing loss.

Kenneth Kaufman, PhD, Professor (Center for Autoimmune Genomics and Etiology)
   Research Interests Genetics of complex diseases such as systemic lupus erythematosus.

Kakajan Komurov, PhD, Assistant Professor (Exp. Hem. & Cancer Bio.)
   Research Interests Interested in identifying global molecular network models of cancer progression.

Clinical Staff Members
- Laurie Bailey, MS, LGC, Coordinator, Clinical Research Program ;Coordinator, Cincinnati STAR Center for Lysosomal Diseases
- Michelle Baric, MS, LGC
- Janet Basil, MS, LGC
- Patricia Bender, RN, MSN
- Lisa Berry, MS, LGC
- Chinmayee Bhimarao Nagaraj, MS, LGC
- Ashley Brazil, MS, LGC
- Anne Burroughs, RN
- Kathleen Collins, MS, LGC
- Jennifer Glass, MS, LGC
- Carol Hetteburg, RN, MSN
- Hopper Jennifer, MS, LGC
- Sandy Kaiser, LPN
- Betty Leech, MS, LGC
- Anne Lovell, RN, MSN, APN
- Abigail Masunga, MS, LGC
- Kimberly Page, RD
- Emily Partack, MS, LGC
- Cynthia Prows, MSN, APRN, FAAN
- Cecilia Rajakaruna, MS, LGC
- Jodie Rueger-Johnson, MS, LGC
- Megan Shearouse, MS
- Rebecca Sisson, MS, LGC
- Christine Spaeth, MS, LGC
Grants, Contracts, and Industry Agreements

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### Genotype-Phenotype Associations in Pediatric Cardiomyopathy

National Institutes of Health (Wayne State University)

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### Zhang, G

**Genetic Susceptibility for Occupational Asthma**

National Institutes of Health (University of Cincinnati)

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#### Current Year Direct

$2,976,611

### Industry Contracts

#### Burrow, T

- Genzyme Corporation: $94,122
- Synageva BioPharma Corp: $14,939
- Shire Human Genetic Therapies: $16,575
- Hyperion Therapeutics: $11,900

#### Hopkin, R

- Genzyme Corporation: $114,117
- Sanofi Pasteur Biologics LLC: $16,071
- Health Research Associates, Inc.: $1,300

#### Leslie, N

- Shire Human Genetic Therapies: $14,039
- Genzyme Corporation: $52,282

#### Prows, D

- Terapio Corporation: $20,054

#### Saal, H

- Alexion Pharmaceuticals, Inc: $114,520

#### Sun, Y

- Genzyme Corporation: $74,926
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A Cincinnati geneticist’s exploration of rare cranioskeletal malformations and abnormal limbs in three patients worldwide has led to the discovery of a dysfunctional gene as the culprit and a name for the syndrome — acrofacial dysostosis, Cincinnati Type.

K. Nicole Weaver, MD, a geneticist with the Division of Human Genetics, said the severity of a Cincinnati patient’s craniofacial abnormalities and discovery of a suspicious gene led her on a worldwide search for answers for the child’s family. A German colleague scoured a large database of patients with undiagnosed craniofacial anomalies and identified two additional patients with a defective copy of the same gene, POLR1A, which is involved in ribosome biogenesis. Ribosomes play an essential role in the process of synthesizing proteins. A Missouri genetics colleague studied zebrafish with absent POLR1A expression, and the fish developed skull, facial, jaw and limb abnormalities similar to those in the children.

Discovering similar cranioskeletal abnormalities in zebrafish lacking expression of POLR1A provided “pretty strong evidence that dysfunction of this gene could cause these problems in a human,” says Weaver, whose findings were published online April 23, 2015, in the American Journal of Human Genetics.

The defective POLR1A gene, the team found, resulted in a deficiency of neural-crest-derived skeletal precursor cells that led to the craniofacial anomalies.

“It’s unclear why the dysfunction of this ribosome gene affects only certain parts of the body,” she says. Follow-up research will try to reproduce the anomalies in mice as a way to learn more about the role of ribosome malfunction in human development.

“For this patient, it was really important to be able to tell the family why this abnormality happened, that it wasn’t inherited and that it likely would not happen again in another child,” Weaver says. “And the patient is doing really, really well.”
“It was really important to be able to tell the family why this abnormality happened, that it wasn’t inherited and that it likely would not happen again in another child.”

Individuals with acrofacial dysostosis, Cincinnati type, each have a heterozygous mutation in POLR1A, which encodes a core component of RNA polymerase 1. These images of an affected newborn show: (A) extensive craniofacial malformations at birth; (B and C) images taken at age 18 months after multiple reconstructive surgeries; (D) severe maxillary and zygomatic hypoplasia (black open-dashed arrow) and severe micrognathia and retrognathia (white block arrow); (E) severe microtia with absent pinnae (white arrows), external auditory atresia (white open-dashed arrows), and severe middle-ear hypoplasia and ossicular dysplasia (black open arrows); and (F) bilateral hip dysplasia and anterior bowing deformity of the femurs.