Human Genetics

Division Details

RESEARCH AND TRAINING DETAILS

<table>
<thead>
<tr>
<th>Faculty</th>
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<tr>
<td>Joint Appointment Faculty</td>
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<tr>
<td>Research Fellows and Post Docs</td>
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<tr>
<td>Research Graduate Students</td>
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<tr>
<td>Total Annual Grant Award Dollars</td>
<td>$4,536,233</td>
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<tr>
<td>Total Annual Industry Award Dollars</td>
<td>$430,694</td>
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<td>Total Publications</td>
<td>103</td>
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CLINICAL ACTIVITIES AND TRAINING

<table>
<thead>
<tr>
<th>Clinical Fellows</th>
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<tr>
<td>Inpatient Encounters</td>
<td>680</td>
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<tr>
<td>Outpatient Encounters</td>
<td>6,224</td>
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Research Highlights

Derek Neilson, MD

Dr. Derek Neilson, MD, implemented an adult learning session about Ehlers Danlos Syndrome in order to provide education to adult patients, families and medical providers.

Dr. Neilson worked with a multidisciplinary team to establish that echocardiograms in children with Ehlers Danlos hypermobility are flawed in their methodology, leading to false positive results. It reveals that we do not need to monitor echocardiograms on a yearly basis, which is a significant cost savings.

Howard M. Saal, MD, FACMG

Dr. Howard Saal participated in the pivotal trial of asfotase alfa for perinatal and infantile hypophosphatasia, a life threatening bone disease. This trial successfully demonstrated that this drug can transform the lives of treated infants and children, improving bone mineralization and prolonging life. It also demonstrated that survivors with severe disease may develop significant tracheobronchomalacia, which will impact future airway management.

Elizabeth Schorry, MD

Through an important collaboration between the Divisions of Human Genetics, Oncology, and Experimental Hematology and Cancer Biology, along with members of the national Neurofibromatosis (NF) Consortium, we have completed a clinical trial of the MEK inhibitor Selumetinib for children with NF1 and large plexiform neurofibromas. This is the first study to show shrinkage of plexiform neurofibroma tumor volume by targeted therapy in NF1.
An additional important accomplishment is the study of MRI screen in children with NF1. This study showed that visual outcome may improve in children who have baseline MRI imaging in early childhood, compared to those who are screened only with ophthalmology exam.

**Melanie Myers, PhD, MS, LGC**

Dr. Stephanie Myers is developing tools used across the organization as a growing number of specialties incorporate genomics into their clinical practices and programs of research. To promote patient/family shared decision making, Dr. Myers led an interdisciplinary team which included parent representatives to develop a decision aid to help patients and families make informed decisions about learning or not learning secondary findings when offering whole exome sequencing for clinical purposes. Dr. Myers and her team received funding from the Center for Pediatric Genomics to develop a decision aid and complimentary just-in-time instruction resources to enable researchers to facilitate shared decision making when offering participants the option to learn genomic research results.

**Ying Sun, PhD**

The Sun lab received funding from Genzyme studying CNS-accessible inhibitor of glucosylceramide synthase for substrate reduction therapy (SRT) on genetic Gaucher disease mouse model. Our study demonstrated significant CNS efficacy of SRT Genz-682452 in ameliorating Gaucher disease that holds promise as a potential therapeutic approach for patients with CNS type Gaucher disease. Genz-682452 is in the Phase II clinical trial for type-3 Gaucher disease patients.

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**Significant Publications**


This paper elucidates the molecular mechanism of disease in a Cincinnati Children's family and three additional families studied by other investigators afflicted with both optic atrophy and peripheral neuropathy. The gene identified encodes a transporter linked to mitochondrial dynamics. Further study of this gene in a mouse model is ongoing at Cincinnati Children's.


In this paper, a family with a craniofacial malformation in mother and daughter showed to have a chromosome deletion that included the SIX2 gene. While mouse models had previously shown a relationship between this malformation and the SIX2 gene, this was the first human family identified. This paper expands the number of genes associated with this specific craniofacial malformation. Translation of this knowledge should improve the diagnostic yield of molecular genetic panels.


This study showed that induced pluripotent stem cells (iPSCs), particularly those isolated from older individuals, could have mutations in mitochondrial DNA that impact the function of mitochondria in cells with higher mutation load. Since iPSCs are of interest for therapeutic purposes, this paper suggests screening these cell lines for mitochondrial mutations before therapeutic use.


Children with neurofibromatosis type 1 (NF1) are at risk for optic pathway tumors. There has not been a consensus as to how often MRIs need done to ascertain risk for these tumors, and whether these patients are at risk for vision loss. This paper describes MRI findings in the very large NF1 cohort followed at Cincinnati Children's over 20 years and helps to define the age for new risk of tumor
development as well as MRI features that predict health consequences. This data will help refine protocols for tumor surveillance in young children with NF1.


This paper reports the analysis of family cohorts and the impact of genetics as opposed to the fetal environment on fetal growth and gestational age. Researchers have long known that taller mothers have bigger babies, and the assumption has been that this effect is mainly a function of “room to grow”. This paper shows that fetal growth is an outcome of fetal growth genes. This information will inform future work on optimizing fetal growth and prevention of prematurity.

**Division Publications**


Functiona l Character i zation of Bs t (+/−) Mouse Ret i na.

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7. 0

6. 9

6. 8

6. 7

6. 6

6. 5

6. 4

6. 3

6. 1

6. 0

5. 9

5. 8

5. 7

5. 6

5. 5

5. 4

5. 3

5. 2

5. 1

5. 0

4. 9

4. 8

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4. 2

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## Grants, Contracts, and Industry Agreements

### Annual Grant Award Dollars

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<tr>
<th>Investigator</th>
<th>Title</th>
<th>Sponsor</th>
<th>ID</th>
<th>Dates</th>
<th>Amount</th>
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<tr>
<td>Taosheng Huang, MD-PH.D</td>
<td>SLC25A46 Mutations Cause Optic Atrophy, Axonal Neuropathy, and Cerebellar Neurodegeneration</td>
<td>National Institutes of Health</td>
<td>R01 EY026609</td>
<td>5/1/2016 - 4/30/2021</td>
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<td>Lisa Martin, PHD</td>
<td>Genetic Underpinnings of Isolated Hypoplastic Left Heart</td>
<td>Children's Heart Foundation</td>
<td>Children's Heart Fdn</td>
<td>1/1/2015 - 12/31/2016</td>
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<td>William C Nichols, PHD</td>
<td>National Biological Sample and Data Repository for Pulmonary Arterial Hypertension</td>
<td>National Institutes of Health</td>
<td>R24 HL105333</td>
<td>3/1/2016 - 2/28/2017</td>
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<td>Dao Pan, PHD</td>
<td>Gaucher Disease: Treatment of Neurodegenerative Disease</td>
<td>National Institutes of Health</td>
<td>R01 NS086134</td>
<td>6/1/2016 - 5/31/2018</td>
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<td>Daniel Prows, PHD</td>
<td>Mutigene-environment Interactions Lead to Dilated Cardiomyopathy and Death</td>
<td>National Institutes of Health (University of Cincinnati)</td>
<td>Prows CEG UC</td>
<td>4/1/2015 - 3/31/2016</td>
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<td>Howard Saal, MD</td>
<td>Cincinnati Regional Genetics Center</td>
<td>Ohio Department of Health</td>
<td>03130011GS0613</td>
<td>7/1/2012 - 6/30/2016</td>
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<td>Elizabeth K Schorry, MD</td>
<td>A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis 1 (NF1)</td>
<td>Department of Defense Army (University of Utah)</td>
<td>W81XWH1210487</td>
<td>9/15/2012 - 9/14/2016</td>
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<td>Rolf Walter Stottmann, PHD</td>
<td>A Genetic Approach to Defining the Ttc21b Interactome in Mammalian Ciliopathies</td>
<td>National Institutes of Health</td>
<td>R01 GM112744</td>
<td>2/1/2015 - 1/31/2019</td>
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<td>Ying Sun, PHD</td>
<td>Nanovesicle-based Intravenous Protein/enzyme Therapy for CNS Disorders</td>
<td>National Institutes of Health (University of Cincinnati)</td>
<td>R21 NS095047</td>
<td>8/31/2015 - 8/31/2017</td>
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<td>Ying Sun, PHD</td>
<td>Non-invasive iPSC-based Therapies for Treatment of Neurodegenerative Diseases</td>
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<td>Ying Sun, PHD</td>
<td>The Development of Small Molecule Inhibitors for Gaucher Disease Type 3</td>
<td>National Institutes of Health (University of Michigan)</td>
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<td>8/1/2015 - 7/31/2020</td>
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Ge Zhang, MD  Genetic Susceptibility for Occupational Asthma  National Institutes of Health (University of Cincinnati)  Zhang  Subcontract UC  11/15/2014  - 3/31/2016  $11,305

Total Annual Grant Award Dollars  $4,536,233

**Annual Industry Award Dollars**

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<td>Thomas Burrow, MD</td>
<td>Synageva BioPharma</td>
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<td>Robert J Hopkin, MD</td>
<td>Genzyme Corporation</td>
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<td>Carlos Enrique Prada, MD</td>
<td>BioMarin Pharmaceutical Inc.</td>
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<td>Ying Sun, PHD</td>
<td>Lysosomal Therapeutics, Inc.</td>
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Total Annual Industry Award Dollars  $430,694