Human Genetics

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**28**
Joint Appointment Faculty	**5**
Research Fellows and Post Docs	**5**
Research Graduate Students	**5**
Total Annual Grant Award Dollars	**$4,536,233**
Total Annual Industry Award Dollars	**$430,694**
Total Publications	**103**

CLINICAL ACTIVITIES AND TRAINING	
Clinical Fellows	**5**
Inpatient Encounters	**680**
Outpatient Encounters	**6,224**

Row 1: L Dyer, K Zhang, L Walters-Sen, N Leslie, N Weaver, Y Sun, C Atzinger

Row 2: T Smolarek, M Myers, R Hopkin, C Prows, M Pandey, H Duzkale

Row 3: I Sageser, H Saal, B Nichols, R Stottmann, D Prows, B Dawson, X Sun

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.

Significant Publications

Abrams AJ, **Hufnagel RB**, Rebelo A, Zanna C, Patel N, Gonzalez MA, Campeanu IJ, Griffin LB, Groenewald S, Strickland AV, Tao F, Speziani F, Abreu L, Schule R, Caporali L, La Morgia C, Maresca A, Liguori R, Lodi R, Ahmed ZM, Sund KL, Wang X, Krueger LA, Peng Y, **Prada CE**, **Prows CA**, **Schorry EK**, Antonellis A, Zimmerman HH, Abdul-Rahman OA, Yang Y, Downes SM, Prince, J, Fontanesi F, Barrientos A, Nemeth AH, Carelli V, **Huang T**, Zuchner S, Dallman JE. **Mutations in SLC25A46, encoding a UGO1-like protein, cause an optic atrophy spectrum disorder**. *Nat Genet*. 2015 Aug;47(8):926-32.

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.

Hufnagel RB, Zimmerman SL, Krueger LA, Bender PL, Ahmed ZM, **Saal HM**. **A new frontonasal dysplasia syndrome associated with deletion of the SIX2 gene**. *Am J Med Genet A*. 2016 Feb;170A(2):487-91.

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.

Kang E, Wang X, Tippner-Hedges R, Ma H, Folmes CD, Gutierrez NM, Lee Y, Van Dyken C, Ahmed R, Li Y, Koski A, Hayama T, Luo S, Harding CO, Amato P, Jensen J, Battaglia D, Lee D, Wu D, Terzic A, Wolf DP, **Huang T**, Mitalipov S. **Age-Related Accumulation of Somatic Mitochondrial DNA Mutations in Adult-Derived Human iPSCs**. *Cell Stem Cell*. 2016 May;18(5):625-36.

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.

Prada CE, **Hufnagel RB**, Hummel TR, Lovell AM, **Hopkin RJ**, **Saal HM**, **Schorry EK**. **The Use of Magnetic Resonance Imaging Screening for Optic Pathway Gliomas in Children with Neurofibromatosis Type 1**. *J Pediatr*. 2015 Oct;167(4):851-856.

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.

Zhang G, Bacelis J, Lengyel C, Teramo K, Hallman M, Helgeland O, Johansson S, Myhre R, Sengpiel V, Njolstad PR, Jacobsson B, Muglia L. **Assessing the Causal Relationship of Maternal Height on Birth Size and Gestational Age at Birth: A Mendelian Randomization Analysis**. *PLoS Med*. 2015 Aug 18;12(8):e1001865.

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

1. Abdalgani M, Filipovich A, Choo S, Zhang K, Gifford C, Villanueva J, Bleesing J, Marsh R. **Accuracy of Flow Cytometric Perforin Screening for Detecting Patients with Fhl Due to Prf1 Mutations.** *Blood*. 2015; 126:1858-59.
2. Abrams AJ, Hufnagel RB, Rebelo A, Zanna C, Patel N, Gonzalez MA, Campeanu IJ, Griffin LB, Groenewald S, Strickland AV, Tao F, Speziani F, Abreu L, Schule R, Caporali L, La Morgia C, Maresca A, Liguori R, Lodi R, Ahmed ZM, et al. **Mutations in Slc25a46, Encoding a Ugo1-Like Protein, Cause an Optic Atrophy Spectrum Disorder.** *Nat Genet*. 2015; 47:926-32.
3. Aisner DL, Berry A, Dawson DB, Hayden RT, Joseph L, Hill CE. **A Suggested Molecular Pathology Curriculum for Residents: A Report of the Association for Molecular Pathology.** *J Mol Diagn*. 2016; 18:153-62.
4. Alcalay RN, Levy OA, Waters CC, Fahn S, Ford B, Kuo SH, Mazzoni P, Pauciulo MW, Nichols WC, Gan-Or Z, Rouleau GA, Chung WK, Wolf P, Oliva P, Keutzer J, Marder K, Zhang X. **Glucocerebrosidase Activity in Parkinson's Disease with and without Gba Mutations.** *Brain*. 2015; 138:2648-58.
5. Allsbrook K, Atzinger C, He H, Engelhard C, Yager G, Wusik K. **The Relationship between the Supervision Role and Compassion Fatigue and Burnout in Genetic Counseling.** *J Genet Couns*. 2016.
6. Alvarado Socarras JL, Laverde Amaya DC, Prada C, Garcia Carrillo J. **[Polydactyly, Holoprosencephaly, Cleft Lip and Cleft Palate Are Not Always What They Seem: Case Report].** *Arch Argent Pediatr*. 2015; 113:e290-3.
7. Aypar U, Hoppman N, Thorland E, Dawson D. **Patients with Mosaic Methylation Patterns of the Prader-Willi/Angelman Syndrome Critical Region Exhibit as-Like Phenotypes with Some Pws Features.** *Mol Cytogenet*. 2016; 9.
8. Balwani M, Burrow TA, Charrow J, Goker-Alpan O, Kaplan P, Kishnani PS, Mistry P, Ruskin J, Weinreb N. **Recommendations for the Use of Eliglustat in the Treatment of Adults with Gaucher Disease Type 1 in the United States.** *Mol Genet Metab*. 2016; 117:95-103.
9. Barber JC, Rosenfeld JA, Graham JM, Kramer N, Lachlan KL, Bateman MS, Collinson MN, Stadheim BF, Turner CL, Gauthier JN, Reimschisel TE, Qureshi AM, Dabir TA, Humphreys MW, Marble M, Huang T, Beal SJ, Massiah J, Taylor EJ, Wynn SL. **Inside the 8p23.1 Duplication Syndrome; Eight Microduplications of Likely or Uncertain Clinical Significance.** *Am J Med Genet A*. 2015; 167A:2052-64.
10. Basil JS, Santoro SL, Martin LJ, Healy KW, Chini BA, Saal HM. **Retrospective Study of Obesity in Children with Down Syndrome.** *J Pediatr*. 2016; 173:143-8.
11. Benson DW, Martin LJ, Lo CW. **Genetics of Hypoplastic Left Heart Syndrome.** *J Pediatr*. 2016; 173:25-31.
12. Berry SA, Leslie ND, Edick MJ, Hiner S, Justice K, Cameron C. **Inborn Errors of Metabolism Collaborative: Large-Scale Collection of Data on Long-Term Follow-up for Newborn-Screened Conditions.** *Genet Med*. 2016.

13. Botkin JR, Belmont JW, Berg JS, Berkman BE, Bombard Y, Holm IA, Levy HP, Ormond KE, Saal HM, Spinner NB, Wilfond BS, McInerney JD. **Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents.** *Am J Hum Genet*. 2015; 97:6-21.

14. Boutin M, Sun Y, Shacka J, Auray-Blais C. **Tandem Mass Spectrometry Multiplex Analysis of Glucosylceramide and Galactosylceramide Isoforms in Brain Tissues at Different Stages of Parkinson Disease.** *Anal Chem*. 2016; 88:1856-63.

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16. Bronicki LM, Stevenson RE, Spranger JW. **Beyond Osteogenesis Imperfecta: Causes of Fractures During Infancy and Childhood.** *Am J Med Genet C Semin Med Genet*. 2015; 169:314-27.

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18. Chen J, Riazifar H, Guan M-X, Huang T. **Modeling Autosomal Dominant Optic Atrophy Using Induced Pluripotent Stem Cells and Identifying Potential Therapeutic Targets.** *Stem Cell Res Ther*. 2016; 7.

19. Chidambaran V, Venkatasubramanian R, Zhang X, Martin LJ, Niu J, Mizuno T, Fukuda T, Meller J, Vinks AA, Sadhasivam S. **Abcc3 Genetic Variants Are Associated with Postoperative Morphine-Induced Respiratory Depression and Morphine Pharmacokinetics in Children.** *Pharmacogenomics J*. 2016.

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23. Dasgupta N, Xu YH, Li R, Peng Y, Pandey MK, Tinch SL, Liou B, Inskeep V, Zhang W, Setchell KD, Keddache M, Grabowski GA, Sun Y. **Neuronopathic Gaucher Disease: Dysregulated Mrnas and Mirnas in Brain Pathogenesis and Effects of Pharmacologic Chaperone Treatment in a Mouse Model.** *Hum Mol Genet*. 2015; 24:7031-48.

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Characterization in 13 Individuals with Chromosome Xp11.22 Duplications. *Am J Med Genet A*. 2016; 170A:967-77.

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Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Taosheng Huang, MD-PHD	SLC25A46 Mutations Cause Optic Atrophy, Axonal Neuropathy, and Cerebellar Neurodegeneration	National Institutes of Health	R01 EY026609	5/1/2016 - 4/30/2021	$390,000
Lisa Martin, PHD	Genetic Underpinnings of Isolated Hypoplastic Left Heart	Children's Heart Foundation	Children's Heart Fdn	1/1/2015 - 12/31/2016	$99,768
William C Nichols, PHD	National Biological Sample and Data Repository for Pulmonary Arterial Hypertension	National Institutes of Health	R24 HL105333	3/1/2016 - 2/28/2017	$2,039,947
Dao Pan, PHD	Gaucher Disease: Treatment of Neurodegenerative Disease	National Institutes of Health	R01 NS086134	6/1/2016 - 5/31/2018	$414,457
Daniel Prows, PHD	Mutigene-environment Interactions Lead to Dilated Cardiomyopathy and Death	National Institutes of Health (University of Cincinnati)	Prows CEG UC	4/1/2015 - 3/31/2016	$15,000
Howard Saal, MD	Cincinnati Regional Genetics Center	Ohio Department of Health	03130011GS0613	7/1/2012 - 6/30/2016	$331,550
Elizabeth K Schorry, MD	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)	Department of Defense Army (University of Utah)	W81XWH1210487	9/15/2012 - 9/14/2016	$49,331
Rolf Walter Stottmann, PHD	A Genetic Approach to Defining the Ttc21b Interactome in Mammalian Ciliopathies	National Institutes of Health	R01 GM112744	2/1/2015 - 1/31/2019	$300,300
Rolf Walter Stottmann, PHD	Forward Genetic Analysis of Congenital Defects in Cortical Circuits and Structure	National Institutes of Health	R01 NS085023	5/15/2014 - 4/30/2019	$484,374
Ying Sun, PHD	Nanovesicle-based Intravenous Protein/enzyme Therapy for CNS Disorders	National Institutes of Health (University of Cincinnati)	R21 NS095047	8/31/2015 - 8/31/2017	$81,900
Ying Sun, PHD	Non-invasive iPSC-based Therapies for Treatment of Neurodegenerative Diseases	The Local Initiative for Excellence Fdtn	Sun LIFE	7/1/2015 - 6/30/2017	$50,000
Ying Sun, PHD	The Development of Small Molecule Inhibitors for Gaucher Disease Type 3	National Institutes of Health (University of Michigan)	UH2NS092981	8/1/2015 - 7/31/2020	$268,301

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

Investigator	Industry Sponsor	Amount
Thomas Burrow, MD	Synageva BioPharma	$102,827
Robert J Hopkin, MD	Genzyme Corporation	$28,921
Carlos Enrique Prada, MD	BioMarin Pharmaceutical Inc.	$98,946
Ying Sun, PHD	Lysosomal Therapeutics, Inc.	$200,000
Total Annual Industry Award Dollars		**$430,694**