Human Genetics

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**30**
Joint Appointment Faculty	**5**
Research Fellows and Post Docs	**9**
Research Graduate Students	**17**
Total Annual Grant Award Dollars	**$3,138,499**
Total Annual Industry Award Dollars	**$696,070**

CLINICAL ACTIVITIES AND TRAINING	
Clinical Fellows	**5**
Inpatient Encounters	**723**
Outpatient Encounters	**5,645**

Row 1: Q Guan, M Sun, N Leslie, L Muglia, R Hopkin, L Dyer, T Smolarek, W Zhang

Row 2: N Weaver, L Walters-Sen, W Nichols, T Huang, H Saal, L Martin

Row 3: K Zhang, I Sageser, C Atzinger, M Pandey, R Stottmann, C Prada, X Sun, G Zhang

Row 4: M Myers, L Bailey, B Schorry, S Bhattacharyya, B Dawson

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Division Highlights

D. Brian Dawson, PhD

Dr. D. Brian Dawson, PhD, began integration of clinical cytogenetics and molecular genetics laboratories within the Division of Human Genetics. In order to achieve integration, initiated multiple activities included: A Pulse survey of clinical lab directors by clinical technologists, consolidation of Cytogenetic and Molecular Genetic DNA extractions, a visit to Mayo medical labs with key lab members to help inform opportunities for automation/process improvement, formation of teams for communications, recognition and remote reporting in response to Pulse Survey, started LGG management monthly meetings, started working with Cincinnati Children's Human Resources to develop a comprehensive plan for clinical laboratory director development, and started planning for renovations to improve workflows/integration and LIS replacement with Cerner Epic.

Lisa J. Martin, PhD

In a groundbreaking study, researchers from Cincinnati Children's and Medical College of Wisconsin joined forces with investigators from the University of Pittsburgh School of Medicine to combine genomic studies in humans and mice. Using a novel statistical approach, developed by Dr. Lisa Martin, PhD, the researchers were able to demonstrate that there is significant overlap between the genes identified in mice and humans. This study, published online May 22, 2017, in *Nature Genetics*, is the first to demonstrate a shared complex genetic etiology between human and mouse. This work is an essential step towards moving beyond the current surgical interventions to alternative strategies that may improve long term outcomes.

Carlos Prada, MD

In August 2016, we began the Rasopathy Clinic in the Division of Human Genetics at Cincinnati Children's. As of June 2017, the division evaluated over 150 patients in our clinical program. There has been expansion to the current molecular panel for RASopathies in the institution from 12 to over 20 disease-associated genes, expanding the ability to confirm a diagnosis in our program. However, 30% of patients remained without an identifiable causative gene, while many others have variants of uncertain significance in known genes.

This year, we received a Center for Pediatrics Genomics grant to further study novel approaches to diagnose and follow-up our patients with RASopathies. There are some candidate genes for novel RASopathies that will receive validation with animal models in collaboration with our team of basic scientists, Drs. Nancy Ratner, PhD, and Steve Wu, MD (tumors); Dr. Ronald Waclaw, MS, PhD (brain); Dr. Joshua Waxman, PhD (heart): and Dr. Robert Hufnagel, MD, PhD (eye).

Ying Sun, PhD

In collaboration with Dr. Chuanju Liu, PhD, a professor at NYU, our study identified progranulin as a biomarker and new therapeutic target for Gaucher disease. The recombinant progranulin reversed most effects of Gaucher disease in mouse and human cells and mouse tissues. Our results provide a new treatment option for inherited Gaucher disease. The published study is in *EBioMedicine*, and reported in *Science Daily*. Our NIH R01 grant application of determining the precise mechanism by which progranulin diminish Gaucher disease received Impact Score 25 and 10th percentile in NINDS TAG study section.

Partnering with two corporations, Sanofi Genzyme and Lysosomal Therapeutics, we developed new blood brain barrier penetrant small molecules for neuronopathic Gaucher and Parkinson's disease. These are the first treatments which address neuronopathic components of these diseases. Both drugs are currently in Phase I (Lysosomal Therapeutics), and Phase II (Sanofi Genzyme) human trials.

Division Publications

1. Dombi E; Baldwin A; Marcus LJ; Fisher MJ; Weiss B; Kim A; Whitcomb P; Martin S; Aschbacher-Smith LE; Rizvi TA. **Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas.** *The New England journal of medicine*. 2016; 375:2550-2560.

2. Pandey MK; Burrow TA; Rani R; Martin LJ; Witte D; Setchell KD; Mckay MA; Magnusen AF; Zhang W; Liou B. **Complement drives glucosylceramide accumulation and tissue inflammation in Gaucher disease.** *Nature*. 2017; 543:108-112.

3. Kang E; Wu J; Gutierrez NM; Koski A; Tippner-Hedges R; Agaronyan K; Platero-Luengo A; Martinez-Redondo P; Ma H; Lee Y. **Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations.** *Nature*. 2016; 540:270-275.

4. Arendt D; Musser JM; Baker CVH; Bergman A; Cepko C; Erwin DH; Pavlicev M; Schlosser G; Widder S; Laubichler MD. **The origin and evolution of cell types.** *Nature Reviews: Genetics*. 2016; 17:744-757.

5. Redin C; Brand H; Collins RL; Kammin T; Mitchell E; Hodge JC; Hanscom C; Pillalamarri V; Seabra CM; Abbott MA. **The genomic landscape of balanced cytogenetic abnormalities associated with human congenital anomalies.** *Nature Genetics*. 2017; 49:36-45.

6. Newman JH; Rich S; Abman SH; Alexander JH; Barnard J; Beck GJ; Benza RL; Bull TM; Chan SY; Chun HJ. **Enhancing Insights into Pulmonary Vascular Disease through a Precision Medicine Approach A Joint NHLBI-Cardiovascular Medical Research and Education Fund Workshop Report.** *American journal of respiratory and critical care medicine*. 2017; 195:1661-1670.

7. Morris DW; Stucke EM; Martin LJ; Abonia JP; Mukkada VA; Putnam PE; Rothenberg ME; Fulkerson PC. **Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis.** *Journal of Allergy and Clinical Immunology*. 2016; 138:915-918.e5.

8. Rubin TS; Zhang K; Gifford C; Lane A; Choo S; Bleesing JJ; Marsh RA. **Perforin and CD107a testing is superior to NK cell function testing for screening patients for genetic HLH.** *Blood*. 2017; 129:2993-2999.

9. Pavlicev M; Wagner GP; Chavan AR; Owens K; Maziarz J; Dunn-Fletcher C; Kallapur SG; Muglia L; Jones H. **Single-cell transcriptomics of the human placenta: inferring the cell communication network of the maternal-fetal interface.** *Genome research*. 2017; 27:349-361.

10. Sanderson SC; Brothers KB; Mercaldo ND; Clayton EW; Antommaria AHM; Aufox SA; Brilliant MH; Campos D; Carrell DS; Connolly J. **Public Attitudes toward Consent and Data Sharing in Biobank Research: A Large Multi-site Experimental Survey in the US.** *The American Journal of Human Genetics*. 2017; 100:414-427.

11. Glauser TA; Holland K; O'Brien VP; Keddache M; Martin LJ; Clark PO; Cnaan A; Dlugos D; Hirtz DG; Shinnar S. **Pharmacogenetics of Antiepileptic Drug Efficacy in Childhood Absence Epilepsy.** *Annals of Neurology*. 2017; 81:444-453.

12. Breugem CC; Evans KN; Poets CF; Suri S; Picard A; Filip C; Paes EC; Mehendale FV; Saal HM; Basart H. **Best Practices for the Diagnosis and Evaluation of Infants With Robin Sequence A Clinical Consensus Report.** *JAMA Pediatrics*. 2016; 170:894-902.

13. Mitteroecker P; Huttegger SM; Fischer B; Pavlicev M. **Cliff- edge model of obstetric selection in humans.** *Proceedings of the National Academy of Sciences of the United States of America*. 2016; 113:14680-14685.

14. Wang M; Peng Y; Zheng J; Zheng B; Jin X; Liu H; Wang Y; Tang X; Huang T; Jiang P. **A deafness-associated tRNA(Asp) mutation alters the m(1)G37 modification, aminoacylation and stability of tRNA(Asp) and mitochondrial function.** *Nucleic Acids Research*. 2016; 44:10974-10985.

15. He JR; Liu Y; Xia XY; Ma WJ; Lin HL; Kan HD; Lu JH; Feng Q; Mo WJ; Wang P. **Ambient Temperature and the Risk of Preterm Birth in Guangzhou, China (2001-2011).** *Environmental health perspectives*. 2016; 124:1100- 1106.

16. Chen JR; Tang ZH; Zheng J; Shi HS; Ding J; Qian XD; Zhang C; Chen JL; Wang CC; Li L. **Effects of genetic correction on the differentiation of hair cell-like cells from iPSCs with MYO15A mutation.** *Cell Death and Differentiation*. 2016; 23:1347-1357.

17. Payne JM; Barton B; Ullrich NJ; Cantor A; Hearps SJC; Cutter G; Rosser T; Walsh KS; Gioia GA; Wolters PL. **Randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1.** *Neurology*. 2016; 87:2575-2584.

18. Wolters PL; Martin S; Merker VL; Tonsgard JH; Solomon SE; Baldwin A; Bergner AL; Walsh K; Thompson HL; Gardner KL. **Patient-reported outcomes of pain and physical functioning in neurofibromatosis clinical trials.** *Neurology*. 2016; 87:S4-S12.

19. 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.** *Genetics in Medicine*. 2016; 18:1276-1281.

20. Brubaker D; Liu Y; Wang J; Tan H; Zhang G; Jacobsson B; Muglia L; Mesiano S; Chance MR. **Finding lost genes in GWAS via integrative-omics analysis reveals novel sub-networks associated with preterm birth.** *Human Molecular Genetics*. 2016; 25:ddw325.

21. Liou B; Peng Y; Li R; Inskeep V; Zhang W; Quinn B; Dasgupta N; Blackwood R; Setchell KDR; Fleming S. **Modulating ryanodine receptors with dantrolene attenuates neuronopathic phenotype in Gaucher disease mice.** *Human Molecular Genetics*. 2016; 25:ddw322.

22. Jiang P; Liang M; Zhang C; Zhao X; He Q; Cui L; Liu X; Sun YH; Fu Q; Ji Y. **Biochemical evidence for a mitochondrial genetic modifier in the phenotypic manifestation of Leber's hereditary optic neuropathy-associated mitochondrial DNA mutation.** *Human Molecular Genetics*. 2016; 25:3613-3625.

23. Cowan JR; Tariq M; Shaw C; Rao M; Belmont JW; Lalani SR; Smolarek TA; Ware SM. **Copy number variation as a genetic basis for heterotaxy and heterotaxy-spectrum congenital heart defects.** *Philosophical Transactions of the Royal Society of London: Biological Sciences*. 2016; 371:20150406.

24. Yang J; Baer RJ; Berghella V; Chambers C; Chung P; Coker T; Currier RJ; Druzin ML; Kuppermann M; Muglia LJ. **Recurrence of Preterm Birth and Early Term Birth.** *Obstetrics and Gynecology*. 2016; 128:364-372.

25. Ortiz A; Abiose A; Bichet DG; Cabrera G; Charrow J; Germain DP; Hopkin RJ; Jovanovic A; Linhart A; Maruti SS. **Time to treatment benefit for adult patients with Fabry disease receiving agalsidase beta: data from the Fabry Registry.** *Journal of medical genetics*. 2016; 53:495-502.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Rolf Walter Stottmann, PhD	Forward Genetic Analysis of Congenital Defects in Cortical Circuits and Structure	National Institutes of Health	R01 NS085023	05/15/2014 - 04/30/2019	$435,934
Elizabeth K Schorry, MD	NF Consortium Infrastructure and Trial#1: Open-label, Phase 2 Study of Bevacizumab in Children and Young Adults with Neurofibromatosis 2 and Progressive Vestibular Schwannomas that are Poor Candidates for Standard Treatment with Surgery or Radiation	Department of Defense (University of Alabama-Birmingham)	W81XWH120155	05/15/2012 - 05/14/2018	$39,817
Rolf Walter Stottmann, PhD	A Genetic Approach to Defining the Ttc21b Interactome in Mammalian Ciliopathies	National Institutes of Health	R01 GM112744	02/01/2015 - 01/31/2019	$300,300
Stephanie Ware	Genotype-Phenotype Associations in Pediatric Cardiomyopathy	National Institutes of Health (Wayne State University)	R01 HL111459	08/10/2014 - 03/31/2018	$148,200
Ying Sun, PhD	The Development of Small Molecule Inhibitors for Gaucher Disease Type 3	National Institutes of Health (University of Michigan)	UH2 NS092981	08/01/2015 - 07/31/2020	$318,262
Ying Sun, PhD	Nanovesicle-based Intravenous Protein/Enzyme Therapy for CNS Disorders	National Institutes of Health (University of Cincinnati)	R21 NS095047	08/31/2015 - 08/31/2017	$68,250
Ying Sun, PhD	Non-invasive iPSC-based Therapies for Treatment of Neurodegenerative Diseases	The Local Initiative for Excellence Fdtn	Sun LIFE	07/01/2015 - 06/30/2017	$50,000
Taosheng Huang, MD, PhD	SLC25A46 Mutations Cause Optic Atrophy, Axonal Neuropathy, and CerebellaNeurodegeneration	National Institutes of Health	R01 EY026609	05/01/2016 - 04/30/2018	$390,000
Ge Zhang, MD, PhD	Integrated GWAS and EWAS of Cardopmetabolic Traits in and Island Population	National Institutes of Health (University of Cincinnati)	R56 HL128493	09/19/2016 - 08/31/2020	$23,324
William C Nichols, PhD	Clinical and Mechanistic Role of HDGF in Pulmonary Hypertension	National Institutes of Health (Johns Hopkins	R01 HL135114	01/01/2017 -	$98,609

		School of Medicine)		12/31/2020	
Danil Prows, PhD Nives Zimmermann	A Novel Mouse Model of Eosinophilic Vasculitis with Cardiac Complications	National Institutes of Health	R21 HL135507	01/12/2017 - 12/31/2019	$117,000
Nancy Doan Leslie, MD	Cincinnati Regional Medical Center: Genetics Services	Ohio Department of Health	Leslie ODH 03130011G	07/01/2016 - 06/30/2018	$309,906
Louis Muglia	Harnessing “omics”: A Systems Biology Approach to Discovery of Biological Pathways in Placental Development and Parturition	National Institutes of Health	R01 HD091527	03/10/2017 - 02/28/2022	$668,125
Ying Sun, PhD	Non-invasive iPSC-based cell and Gene Therapies for Treatment of Parkinson’s Disease.	The Michael J Fox Fdn for Parkinson's Research	13558	04/04/2017 - 04/03/2019	$125,000
Elizabeth K Schorry, MD	A Study of INFUSE Bone Graft in the treatment of Tibial Pseudarthrosis in NF1	Department of Defense (University of Alabama-Birmingham)	W8IXWH-12-I-0155	05/15/2016 - 05/14/2018	$28,000
Elizabeth K Schorry, MD	A Study of INFUSE Bone Graft in the Treatment of Tibial Pseudarthrosis in NF1	Department of Defense (University of Alabama-Birmingham)	W81XWH-12-I-0155	05/15/2016 - 05/14/2018	$17,772
Total Annual Grant Award Dollars					**$3,138,499**

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Howard Saal, MD	BioMarin Pharmaceutical Inc.	$206,996
Laurie A Bailey	Genzyme Corporation	$75,000
Nancy Doan Leslie, MD	Alexion Pharmaceuticals, Inc.	$161,922
Robert J Hopkin, MD	Protein Sciences Corporation	$123,902
Ying Sun, PhD	Shire Human Genetic Therapies	$128,250
Total Annual Industry Award Dollars		**$696,070**