Cincinnati Children's
change the outcome

Human Genetics

Division Photo

First Row: G. Grabowski, N. Leslie, T. Smolarek

Second Row: S. Zimmerman, K. Zhang, H. Du, Y. Sun, L. Martin, M. Pandey, R. Hopkin, M. Myers, D. Neilson, A. Burrow

Third Row: M. Guan, Y. Xu, C. Prows, L. Bao, E. Schorry, I. Sageser, B. Nichols, S. Ware, D. Prows, B. Tinkle, S. Theru Arumugam

Division Data Summary

Research and Training Details	
Number of Faculty	25
Number of Joint Appointment Faculty	3
Number of Support Personnel	108
Direct Annual Grant Support	$2,805,206
Direct Annual Industry Support	$1,103,795
Peer Reviewed Publications	71
Clinical Activities and Training	
Number of Clinical Staff	22
Number of Clinical Fellows	8
Number of Clinical Students	23
Number of Other Students	10
Inpatient Encounters	385
Outpatient Encounters	6,055

Significant Publications

D.J. Bowen, J. Harris, C.M. Jorgensen, M.F. Myers, A. Kuniyuki, Socioeconomic influences on the effects of a genetic testing direct-to-consumer marketing campaign, Public Health Genomics 13 (2009) 131-142.

First study to directly correlate socioeconomic status and direct to consumer marketing of genetic testing and their use.

M. Ednick, B.T. Tinkle, J. Phromchairak, J. Egelhoff, R. Amin, N. Simakajornboon, Sleep-related respiratory abnormalities and arousal pattern inachondroplasia during early infancy, J Pediatr 155 (2009) 510-515.

Demonstrates the high incidence of early sleep-disordered breathing that predisposes these infants to sudden death.

F. Elefteriou, M. Kolanczyk, A. Schindeler, D.H. Viskochil, J.M. Hock, E.K. Schorry, A.H. Crawford, J.M. Friedman, D. Little, J. Peltonen, J.C. Carey, D. Feldman, X. Yu, L. Armstrong, P. Birch, D.L. Kendler, S. Mundlos, F.C. Yang, G. Agiostratidou, K. Hunter-Schaedle, D.A. Stevenson, Skeletal abnormalities in neurofibromatosis type 1: approaches to therapeutic options, Am J Med Genet A 149A (2009) 2327-2338.

Redirects focus of clinical and research efforts in NF1 to the frequent skeletal involvement and toward improved clinical care.

D.E. Neilson, M.D. Adams, C.M. Orr, D.K. Schelling, R.M. Eiben, D.S. Kerr, J. Anderson, A.G. Bassuk, A.M. Bye, A.M. Childs, A. Clarke, Y.J. Crow, M. Di Rocco, C. Dohna-Schwake, G. Dueckers, A.E. Fasano, A.D. Gika, D. Gionnis, M.P. Gorman, P.J. Grattan-Smith, A. Hackenberg, A. Kuster, M.G. Lentschig, E. Lopez-Laso, E.J. Marco, S. Mastroyianni, J. Perrier, T. Schmitt-Mechelke, S. Servidei, A. Skardoutsou, P. Uldall, M.S. van der Knaap, K.C. Goglin, D.L. Tefft, C. Aubin, P. de Jager, D. Hafler, M.L. Warman, Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2, Am J Hum Genet 84 (2009) 44-51.

Demonstration of genetics basis of ANC and the regional susceptibility of the brain to specific viral insults.

Y. Sun, B. Liou, H. Ran, M.R. Skelton, M.T. Williams, C.V. Vorhees, K. Kitatani, Y.A. Hannun, D.P. Witte, Y.H. Xu, G.A. Grabowski, Neuronopathic Gaucher disease in the mouse: viable combined selective saposin C deficiency and mutant glucocerebrosidase (V394L) mice with glucosylsphingosine and glucosylceramide accumulation and progressive neurological deficits, Hum Mol Genet 19 (2010) 1088-1097.

Development of the only viable animal model for studying the pathogenesis and intervention approaches to neuronopathic lysosomal diseases.

Division Highlights

Xiaoyang Qi, Ph.D.

A new saposin C (SapC) coupled dioleoylphosphatidylserine (DOPS) nanovesicle is under development and has the potential to offer a targeted, potent, broad, and safe therapeutic agent for patients with a wide variety of cancers. SapC-DOPS nanovesicles preferentially induce apoptotic cell death in cancerous cells via a ceramide- and caspase-mediated pathway. In preclinical studies, these nanovesicles have shown tumor-specific targeting activity and cancer-selective killing efficacy with significant inhibition of tumor growth in various animal models in the absence of toxicities and significant side effects.

Sarah Zimmerman, Ph.D., Teresa Smolarek, Ph.D.

Illumina's Certified Service Provider Program (CSPro) was established as a partnership between service provider laboratories and Illumina. CCHMC Cytogenetics Laboratory has obtained CSPro certification in order to expand our microarray capabilities and services by providing wet lab technical expertise to smaller facilities and hospitals that are unable to generate microarray data and thereby facilitating them to generate personal analyses and interpretations. This CSPro certification, is for an elite group of international providers whom are recognized for excellence. The CSPro also enables us with a competitive advantage in the market place and expanding microarray research capabilities.

Faculty Members

Gregory Grabowski, MD, Professor ; *The A. Graeme Mitchell Chair in Human Genetics; Director, Division of Human Genetics; Professor of Pediatrics and Molecular Genetics, Biochemistry and Microbiology*

Research Interests: Molecular pathogenesis and therapy of human genetic disease

Liming Bao, MD, PhD, Associate Professor Clinical ; *Associate Director, Clinical Cytogenetics Laboratory*

Research Interests: Genetic biomarkers of hematological diseases and their underlying pathogenesis and clinical relevance

T. Andrew Burrow, MD, Assistant Professor Clinical

Research Interests: Lysosomal storage diseases, particularly Gaucher disease; Inborn errors of metabolism, particularly focusing on development of evidence based medicine

Hong Du, PhD, Research Associate Professor

Research Interests: Understanding the molecular mechanisms of genetic disorders of lipid metabolism and the development of therapeutic treatments for these disorders

Min-Xin Guan, PhD, Associate Professor

Research Interests: Mechanisms of mitochondrial disorders, with a focus on maternally transmitted hearing loss and vision loss

Robert Hopkin, MD, Associate Professor Clinical ; *Director, Genetic Residency Programs*

Research Interests: Fabry Disease; Robin Sequence; 22q11 deletion; Neurofibromatosis; craniofacial genetics; chromosomal anomalies

Mehdi Keddache, MS, Research Instructor ; *Leader, Genomics Core*
Research Interests: DNA Sequencing / Genotyping Core

Nancy Doan Leslie, MD, Professor Clinical ; *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

Derek Neilson, MD, Assistant Professor
Research Interests: The genetic contribution to acute necrotizing encephalopathy, a disorder in which children are predisposed to devastating neurologic injury following common infections

William Nichols, PhD, Associate Professor ; *Chairman, DHG Research Review Committee*
Research Interests: The identification of genetic variants contributing to disease susceptibility

Cindy Prows, MSN, CNS, RN, FAAN, Adjunct Associate Professor
Research Interests: Developing and testing education models to teach nurses about genetics; family responses to genetic information, technology and services

Daniel R Prows, PhD, Assistant 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

Xiaoyang Qi, PhD, Research Associate Professor
Research Interests: Translational research focused on the role of saposin C in multivesicular body bioformation and neuropathogenesis and the development of saposin C-containing nanovesicles as a novel anticancer agent

Howard Saal, MD, Professor Clinical ; *Director, Clincal 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

Iris Sageser, RDH, MS, Field Service Assistant Professor ; *Craniofacial Center*
Research Interests: Multidisciplinary management of individuals affected by craniofacial abnormalities

Elizabeth K Schorry, MD, Associate Professor Clinical
Research Interests: Psychosocial and orthopedic aspects of neurofribromatosis; Clinical drug trials for NF1

Teresa A Smolarek, PhD, Associate Professor Clinical ; *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 lymphagioleiomyomatosis

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

Bradley T Tinkle, MD, Assistant Professor Clinical ; *Clinical Geneticist; Assistant Director, Molecular Genetics Laboratory; Director, Skeletal Dysplasia Center; Co-Director, Marfan/Ehlers-Danlos Syndromes Clinic*
Research Interests: Natural history of connective tissue disorders and outcome studies of various clinical interventions

Nancy Warren, MS, Adjunct Associate Professor ; *Program Director, Genetic Counseling Graduate Program*
Research Interests: Genetic counseling education, professional development and cultural competence

You-hai Xu, MD, PhD, Research Assistant Professor
Research Interests: Molecular and pathophysiological mechanisms of Gaucher Disease, particularly of neuronopathic Gaucher Disease

Kejian Zhang, MD, Assistant Professor Clinical ; *Director, Molecular Genetics Laboratory*
Research Interests: Molecular defects and molecular diagnosis of primary immunodeficiency diseases; Genetic aspects of predictive personalized medicine, eg., Pharmacogenetics; Fanconi Anemia SeqChip development

Sarah Zimmerman, PhD, Assistant Professor Clinical ; *Assistant Director, Clinical Cytogenetics Laboratory*
Research Interests: Genome-wide analysis for chromosome aberrations in congenital disorders and cancer using molecular cytogenetic techniques

Joint Appointment Faculty Members

John Greinwald, MD, Associate Professor
Otolaryngology

Genetics of Hearing Loss

Lisa Martin, PhD, Research Associate Professor
Biostatistics and Epidemiology
Focus on common complex diseases including obesity and heart malformations

Melanie Myers, PhD, MS, CGC, Adjunct Assistant Professor
Genetics Counseling Program, College of Medicine
Clinical utility of family health history and other genomic tools in health promotion

Stephanie Ware, MD, PhD, Assistant Professor
Molecular Cardiovascular Biology
Genetic disorders of cardiac structure and function

Clinical Staff Members

- **Erin Acra, MS**
- **Carrie Atzinger, MS**
- **Laurie Bailey, MS**
- **Angela Bedard, MS**
- **Judy Belli, RN**
- **Patricia Bender, RN, MSN**
- **Lisa Berry, MS**
- **Kathleen Collins, MS**
- **Kimberly Edge, MS**
- **Carol Hetteburg, RN, MSN**
- **Judy Johnson, MS**
- **Sandy Kaiser, LPN**
- **Sara Knapke, MS**
- **Anne Lovell, RN, MSN, APN**
- **Erin Miller, MS**
- **Elizabeth Peach, MS**
- **Jodie Rueger, MS**
- **Jennifer Ruschman, SCM**
- **Kerry Shooner, MS**
- **Christine Spaeth, MS**
- **Martha Walker, MS**
- **Connie Wehmeyer, RN**
- **Katie Wusik, MS**

Trainees

- **Jaya George-Abraham, MD,** PGY4, Medical Genetics Fellowship
- **Stephanie Peters Santoro, MD,** PGY1, Pediatrics/Genetics Combined Residency
- **Carlos Prada, MD,** PGY3, Pediatrics/Genetics Combined Residency
- **Elizabeth Sellars, MD,** PGY1, Pediatrics/Genetics Combined Residency
- **Dipesh Tamakuwala, PhD,** Clinical Cytogenetics Fellowship
- **K. Nicole Weaver, MD,** PGY1, Pediatrics/Genetics Combined Residency
- **Wenying Zhang, MD, PhD,** Clinical Molecular Genetics Fellowship

Significant Accomplishments

STAR Lysosomal Disease Center

The STAR Lysosomal Disease Center, founded in 1998, provides services, treatments, advocacy are research for more than 350 families affected by these conditions. In particular, we have provided life-changing enzyme therapy for individuals with Gaucher, Fabry, and Pompe diseases and mucopolysaccharidoses I, II, and VI. During the past year, the STAR Center played a leading international role in managing care for Gaucher and Fabry disease patients during a

manufacturer-related enzyme shortage. Major research progress also has been made toward the next generation of therapies for these diseases using substrate synthesis inhibitors, in situ molecular engineering, and gene therapy approaches.

New enzyme treatments for rare diseases

Gregory Grabowski, MD, and Hong Du, PhD, have developed a new enzyme treatment for two rare devastating diseases -- Wolman Disease and Cholesteryl Ester Storage Disease -- that are expected to move into clinical trials in the next year. Components of this work were funded through the Lysosomal Disease Network, an NIH-funded program for rare diseases. Longer term, this enzyme may have impacts beyond these rare diseases. In mice, this enzyme was shown to reverse atheromatous plaques and the inflammatory fatty liver disease that accompanies obesity.

Progress in craniofacial disorders

The Velocardiofacial Syndrome Center, led by Howard Saal, MD, FACMG, was established as a multidisciplinary effort to enhance medical care and research for VCF and craniofacial disorders. In October 2009, Cincinnati Children's hosted the Tri-State Craniofacial Conference to share research and clinical information. We also have developed a collection of online information and education videos for families who have children with orofacial clefts: http://www.cincinnatichildrens.org/svc/alpha/c/craniofacial/links.htm

Division Publications

1. :

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct / Project Period Direct
Du, H		
Pathophysiology of PPARgamma in the Lung National Institutes of Health R01 HL 087001	06/09/08 - 05/31/13	$259,000 / $1,250,000
Grabowski, G		
Cincinnati Regional Genetics Center Ohio Department of Health (Health Resources & Services Administration) 31-3-001-1GS0310	07/01/09 - 06/30/10	$383,500 / $2,392,387
Studies of Gaucher Disease: A Prototype Lipidosis National Institutes of Health R01 DK 036729	09/27/07 - 08/31/12	$339,832 / $1,537,712
Studies of Gaucher Disease: A Prototype Lipidosis National Institute of Diabetes and Digestive and Kidney Diseases R01 DK 036729	04/01/10 - 03/31/11	$66,667 / $66,667
Lysosomal Disease Network: Epidemiology and Natural History of Wolman Disease and Cholesteryl Ester Storage Disease University of Minnesota (National Institutes of Health) U54 NS 065768	09/30/09 - 08/31/10	$40,000 / $200,000
Therapy of Gaucher Disease: In Vivo Enhancement National Institutes of Health R21 NS 064352	05/15/09 - 04/30/11	$148,117 / $275,000
Therapy of Neuronopathic Gaucher Disease National Institutes of Health R21 HD 059823	01/01/09 - 12/31/10	$173,250 / $273,250
Therapy of Neuronopathic Gaucher Disease National Institutes of Health R21 HD 059823	05/01/10 - 09/30/10	$4,200 / $4,200
Digestive Health Center: Bench to Bedside in Pediatric Digestive Disease National Institutes of Health P30 DK 078392	08/01/07 - 05/31/12	$21,421 / $21,421
Guan, M		
Nuclear Modifier Genes for Maternally Inherited Deafness National Institutes of Health		

R01 DC 007696 07/01/07 - 06/30/11 $209,738 / $678,821

Nuclear Modifier Genes for Maternally Inherited Deafness
National Institutes of Health
R01 DC 007696 06/01/09 - 10/31/10 $10,000 / $10,000

Knapke, S

Hereditary Breast & Ovarian Cancer Syndrome: Life After a BRCA Mutation
Komen Breast Cancer Foundation
04/01/10 - 03/31/11 $38,016 / $38,016

Leslie, N

Implementing Newborn Screening for Duchenne Muscular Dystrophy in the Community
The Research Institute at Nationwide Hospital
5 R18 DD 000344-02 09/30/07 - 09/29/10 $12,466 / $62,073

Neilson, D

Genetic Mechanisms of Acute Necrotizing Encephalopathy
National Institutes of Health
K08 NS 050331 09/01/08 - 06/30/10 $157,525 / $250,954

Nichols, W

Genetic Analysis of Murine Chronic Hypoxia-Induced Pulmonary Hypertension
National Institutes of Health
R01 HL 102107 04/01/10 - 03/31/14 $442,498 / $1,922,929

Prows, D

Genetic Analysis of Hyperoxia Induced Acute lung Injury
National Institutes of Health
R01 AI 075562 05/01/09 - 04/30/13 $260,139 / $1,102,662

Schorry, E

Spinal Abnormalities in Neurofibromatosis Type 1
University of Utah (National Institutes of Health)
R01 NS 050509 07/01/06 - 03/31/11 $42,934 / $333,163

Neurofibromatosis Consortium Development Operation
University of Alabama-Birmingham (Department of Defense Army)
W81XWH0510615 07/01/07 - 03/31/12 $25,806 / $155,702

Neurofibromatosis Consortium Development Operation PK Center STOPN
University of Alabama-Birmingham (Department of Defense Army)
W81XWH0510615 07/01/08 - 06/30/11 $65,070 / $271,690

Neurofibromatosis Consortium mTOR STOPN Laboratory
University of Alabama-Birmingham (Department of Defense Army)
W81XWH0510615 07/01/08 - 06/30/11 $98,199 / $265,132

A Randomized Placebo-Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1
University of Alabama-Birmingham (Department of Defense Army)
W81XWH0510615 03/01/09 - 04/30/10 $29,108 / $103,502

Current Year Direct **$2,805,206**

Industry Contracts

Grabowski, G

Genzyme Corporation $ 127,500

Shire Human Genetic Therapies $ 655,071

Hopkin, R

Genzyme Corporation $ 26,637

Leslie, N

Amicus Therapeutics, Inc.	$ 40,501
Genzyme Corporation	$ 210,787
Qi, X	
Bexion Pharmaceticals	$ 43,299
Current Year Direct Receipts	**$1,103,795**
Total	**$3,909,001**