Human Genetics

Division Photo

First Row: *G. Grabowski;* ***Second Row:*** *N. Leslie, M.X. Guan, B. Tinkle. R. Hopkin;* ***Third Row:*** *H. Du, E. Schorry, L. Martin, C. Prows;* ***Fourth Row:*** *I. Sageser, L. Bao, D. Neilson, K. Zhang, H. Saal, T. Smolarek, W. Nichols;* ***Fifth Row:*** *Y. Sun, Y.H. Xu, X. Qi, D. Prows*

Division Data Summary

Research and Training Details

Number of Faculty	20
Number of Joint Appointment Faculty	7
Number of Research Fellows	1
Number of Support Personnel	123
Direct Annual Grant Support	$2,335,160
Direct Annual Industry Support	$688,906
Peer Reviewed Publications	62

Clinical Activities and Training

Number of Clinical Staff	17
Number of Clinical Fellows	8
Number of Clinical Students	9
Number of Other Students	7
Inpatient Encounters	364
Outpatient Encounters	4,996

Faculty Members

Greg 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: Studies of genetic biomarkers of hematological diseases and their underline pathogenesis and clincal relevance

Hong Du, PhD, Research Associate Professor
Research Interests: Research to understand molecular mechanisms of genetic disorders of lipid metabolism and development of therapeutic treatments for these disorders

Min-Xin Guan, PhD, Associate Professor
Research Interests: To investigate the mechanism of mitochondrial disorders, focused on maternally transmitted hearing loss and vision loss

Robert Hopkin, MD, Assistant Professor Clinical ; *Director, Genetic Residency Programs*
Research Interests: Fabry Disease; Robin Sequence; 22q11 deletion; Neurofibromatosis; craniofacial genetics; chromosomal anomalies

Mehdi Keddache, MS, Research Instructor
Research Interests: DNA Sequencing / Genotyping Core

Nancy Doan Leslie, MD, Professor Clinical ; *Director, Biochemical Genetics Laboratory*
Research Interests: Focus on 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: Studies the genetic contribution to the disorders acute necrotizing encephalopathy, in which children are predisposed to devastating neurologic injury following common infections

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

Cindy Prows, MSN, CNS, RN, 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: Use of quantitative trait locus analysis to establish mouse models of complex human diseases, with specific interest in models of acute lung injury

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

Howard Saal, MD, Professor ; *Director, Clincal Genetics; Medical Director, Cytogenetics Laboratory; Director, Cincinnati Children's Craniofacial Center*
Research Interests: Interested in the natural history of genetic disorders, especially as they relate to craniofacial disorders; also developing treatment and management protocols for craniofacial disorders

Elizabeth K Schorry, MD, Associate Professor Clinical
Research Interests: Psychosocial and orthopedic aspects of neurofribromatosis

Teresa A Smolarek, PhD, Assistant Professor Clinical ; *Director of Clinical Cytogenetics Laboratory; Director, Clinical Cytogenetics Fellowship Program*
Research Interests: Application of SNP microarrays to determine constitutional and acquired DNA copy number changes; Study of the genetic basis of pulmonary lymphagioleiomyomatosis

Ying Sun, PhD, Research Assistant Professor
Research Interests: Investigate 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 Field Services Assistant ; *Program Director, Genetic Counseling Graduate Program; Professor*
Research Interests: Genetic counseling education, professional development and cultural competence

You-hai Xu, 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

Joint Appointment Faculty Members

John Greinwald, MD, Associate Professor
Otolaryngology

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

Melanie Myers, PhD, MS, CGC, Adjunct Assistant Professor
College of Applied Health Sciences
Clinical Utility of Genomic Tools in Health Promotion

Todd Nick, PhD, Professor
Biostatistics and Epidemiology

Iris Sageser, RDH, MS, Field Service Associate Professor
Craniofacial Center
Multidisciplinary management of indivduals affected by craniofacial abnormalities

Ning Wang, PhD, Research Assistant Professor
Allergy and Immunology

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**
- **Sara Knapke, MS**
- **Anne Lovell, RN, MSN, APN**
- **Erin Miller, MS**
- **Elizabeth Peach, MS**
- **Jennifer Ruschman, SCM**
- **Kerry Shooner, MS**
- **Christine Spaeth, MS**
- **Martha Walker, MS**
- **Connie Wehmeyer, RN**
- **Katie Wusik, MS**

Trainees

- **Jillene Kogan, MD, PhD,** PL-6, University of Illinois College of Medicine
- **Cong Liu, PhD,** PL-5, University of Cincinnati
- **Sarah Zimmerman, PhD,** PL-5, University of Dayton
- **Margaret Reiley, MD,** PL-4, Tufts University School of Medicine
- **Andrew Burrow, MD,** PGY5, Pediatrics/Genetics Combined Residency
- **Yuri Zarate, MD,** PGY4, Pediatrics/Genetics Combined Residency
- **Carlos Prada, MD,** PGY3, Pediatrics/Genetics Combined Residency
- **Elizabeth Sellars, ,** PGY1, Pediatrics/Genetics Combined Residency

Significant Accomplishments in FY08

Basic, Translational, and Clinical Research at the CCHMC STAR Lysosomal Disease Center

Improving the outcome for patients devastated by lysosomal storage diseases began at CCHMC. In 1967 Drs. William F. Schubert and George Hug first showed that enzymes could be given to patients with Pompe disease, a lysosomal storage disease, and potentially improve their lives. Over the subsequent four decades, this pioneering work paved the way for revolutionary treatments to alleviate patients' suffering and demise. During this period, Dr. Grabowski has led a quest to effectively treat these diseases. His establishment of the CCHMC STAR Lysosomal Disease Center has begun to fulfill this quest to transform basic research, into clinical trials, and into effective/life-saving treatments for affected children and adults.

The lysosomal storage diseases affect 1/7000 newborns and result from the defective or deficient activity of specific enzymes that are present in the subcellular organelles, lysosomes – a major recycling station in all cells of the body. Dr. Grabowski's team of scientists and clinicians have made major advancements in the understanding of the molecular genetics and the pathobiology, in preclinical studies by creating unique disease models in mice, by conducting clinical trials (currently 12 trials) needed for FDA approval, toward developing innovative clinical treatment studies (currently 21), and by the formation of multidisciplinary/integrated medical teams at CCHMC and UC to treat affected patients and families. As an international leader, CCHMC's STAR Lysosomal Disease Center now provides life-changing therapy to >240 (at CCHMC) and >1,000 (international) children and adults affected by lysosomal storage diseases. These include transformative therapies for Gaucher, Fabry and Niemann-Pick diseases, the Mucopolysaccharidoses I (MPS I, Hurler syndrome), II (Hunter disease), VI (Maroteaux-Lamy disease), and, of course, Pompe disease -- a long road from Drs. Schubert's and Hug's visionary experiments.

But, the quest continues since enzyme treatment, albeit highly effective for visceral disease, does not alter brain involvement. Basic and clinical research by Dr. Grabowski's team continues to explore innovative research to improve the disease outcomes: 1) With the transplantation team, hematopoietic stem cells, that produce therapeutic enzymes, are being used in MPS I clinical studies to evaluate the utility in combination with enzyme therapy. 2) The enzyme crystal structures elucidated at CCHMC are being harnessed to engineer selected lysosomal enzymes to enhance efficacy through increasing their stability, delivery to specific cells, and catalytic activities. 3) Innovative metabolic pathway manipulations of the lysosomal diseases are being systematically evaluated to treat the CNS lysosomal diseases by either slowing the natural synthesis of the toxic biochemicals or by using small molecules, termed pharmacologic chaperones, to refold the mutant enzymes in situ to improve function. Testing in mouse disease models provides the platform for evaluating superior effectiveness of novel therapies. Such studies have potential application for treatment of common degenerative brain diseases. Clinical trials are already underway with novel treatments for selected lysosomal diseases in the CCHMC STAR Center. This Center provides a unique, integrated environment that blends basic science, pathobiology, and clinical science directed to improving the lives of families afflicted by these devastating inherited diseases, the lysosomal storage diseases.

Quantitative Trait Identification in Pulmonary Disease

Mapping genes that contribute to the susceptibility to environmental toxins cannot be done by direct experimentation in humans. However, mice can be used by being exposed to various noxious agents and then mapping the genes for either susceptibility or resistance to specific agents. Use of oxygen for treatment of various disorders is commonplace, in specific circumstances this useful agent can be toxic to the lungs and/or eyes. To map the genes that relate to the susceptibility to oxygen toxicity, various strains of mice and their congenetic derivatives were used in Dr. Daniel Prows' laboratory. High level oxygen exposure (>95%) was used to induce hyperoxic adult lung inflammation (ALI). Eighteen inbred strains were tested to identify a mouse model of acute respiratory distress syndrome for genetic assessment. Quantitative trait locus (QTL) analyses of nearly 1800 recombinant mice detected 5 regions (QTLs) significantly linked to ALI survival time, and an additional locus with significant interaction with a major locus. Detailed analyses of recombinant populations from all possible mating schemes revealed that overall survival time in hyperoxia involved decreased pretrance, and significant sex, cross and parent-of-origin effects. Such studies promise to provide insights into potential genes that are targets for therapy in humans with hyperoxic exposure.

Significant Publications in FY08

Xu YH, Reboulet R, Quinn B, Huelsken J, Witte D, Grabowski GA. Dependence of reversibility and progression of mouse neuronopathic Gaucher Disease on acid beta-glucosidase residual activity levels. Mol Genet Metab. 2008 Jun;94(2):190-203.

This study developed mouse models of Gaucher Disease by genomic and chemical approaches to study the pathogenesis of CNS disease. These models indicate a threshold level of activity is necessary for the prevention of progression of CNS involvement. The study also demonstrated that the CNS lesions, once established, are not

reversible to any significant degree even by reconstitution of enzyme levels in all brain cells to wild-type levels.

Nichols WC, Elsaesser VE, Pankratz N, Pauciulo MW, Marek DK, Halter CA, et al. LRRK2 mutation analysis in Parkinson Disease families with evidence of linkage to PARK8. Neurology. 2007 Oct 30;69(18):1737-1744.

A comprehensive study was performed of all 51 exons of the LRRK2 gene in one PD patient from each of 88 multiplex families who had the highest family-specific multipoint lod score at the LRRK2 locus from a cohort of 430 PD families without the G2019S mutation. Five novel variants were identified in LRRK2, with two of these in the N-terminal region of LRRK2, where no pathogenic substitutions have been previously reported. These mutations broaden the potential mechanisms whereby mutations in LRRK2 result in Parkinson Disease.

Sun Y, Jia L, Williams MT, Zamzow M, Ran H, Quinn B, Aronow BJ, Vorhees CV, Witte DP, Grabowski GA. Temporal gene expression profiling reveals CEBPD as a candidate regulator of brain disease in prosaposin deficient mice. BMC Neurosci. 2008;9:76.

The first comprehensive report of brain regional transcriptome analyses in a lysosomal disease. This study identified a single gene, CEBPD, that is involved in pathogenesis of glycosphingolipid diseases in the brain and other organs.

Prows DR, Hafertepen AP, Winterberg AV, Gibbons WJ, Jr., Liu C, Nick TG. Genetic analysis of hyperoxic acute lung injury survival in reciprocal intercross mice. Physiological genomics. 2007 Aug 20;30(3):271-281.

This project seeks to identify the critical susceptibility genes for hyperoxia so that therapeutic agents can be designed that will ultimately permit higher doses of oxygen to be given for longer periods of time and allow critical patients to overcome their injuries.

Division Highlights

Kejian Zhang, MD

This study identifies a novel biomarker for the clinical diagnosis of MAS in patients with Systemic Juvenile Idiopathic Arthritis and provides future directions of molecular studies in the macrophage activation syndrome (MAS).

Hong Du, PhD

The major accomplishment in the last year is that we secured NIH R01 research funding for PPARy project, which is to test the physiological role of PPARy mediating lung injury and remodeling phenotypes in the lysosomal acid lipase deficiency mouse model. The proposed studies will use a doxycycline induced cell specific bitransgenic mouse model to over express dominant negative forms of PPARy in pulmonary type II epithelia cells or macrophages.

Bradley Tinkle, MD, PhD

We have conducted a natural history study of patients with Ehlers-Danlos syndrome using clinically-validated standard surveys. Patients with EDS have significant pain (brief pain inventory), sleep disturbance (Pittsburgh Sleep Quality Index), fatigue (brief fatigue inventory), and reduced quality of life (SF-36). Although theses observations are essentially known to those in the field of EDS, few have ever studied this population with these validated instruments. We hope to garner appreciation that these patients indeed have a chronic pain syndrome that to date has been little appreciated by primary care physicians and specialists.

William Nichols, PhD

The major finding was that mutations in the glucocerebrosidase gene are associated with familial Parkinson Disease susceptibility and age of onset. We performed a comprehensive screen of all GBA exons in one PD patient from each of 96 PD families, selected based on the family specific LOD scores at the GBA locus. Identified GBA variants were subsequently screened in all 1325 PD cases from 566 multiplex PD families and 359 controls. This study suggests that GBA is a susceptibility gene for familial PD and patients with GBA variants have an earlier age of onset than those PD patients without GBA variants.

Xiaoyang Qi, PhD

This translational research focuses on innovative SapC-DOPS technologies with potential for cancer treatment and drug delivery. SapC-DOPS, as a novel anticancer agent, preferentially induces apoptic cell death in cancerous cells via a ceramide-caspase-mediated pathway. In preclinical mouse studies, SapC-DOPS nanovesicles have potent killing activity toward cancer cells and have shown inhibition of tumor growth in various mouse xenografts.

Nancy Leslie, MD

Complete characterization of individuals with disorders of long chain fatty acid metabolism, particularly those indentified by newborn screening, has been difficult. Direct measurement of enzymatic activity for Very Long Chain Acyl Co A

dehydrogenase (VCLAD) activity is available in Europe, but not the US. We developed the capability to directly measure VCLAD activity in cultured fibroblasts, in addition to molecular characterization, in vitro functional studies, and analysis of metabolites. This provides the infrastructure for a planned trial of PPAR agonists in patients with VCLAD deficiency.

Division Collaboration

Collaboration with Pulmonary Biology; Allergy and Immunology; Experimental Hematology and Cancer Biology

Collaborating Faculty: Timothy LeCras, PhD; John Shannon, PhD; Ann Akeson, PhD; Gurjit Hershey, MD, PhD; Punam Malik, MD

Mouse Studies: Exposing their mice to chronic hypoxia and/or performing right heart catheterizations to measure right ventricular systolic pressures. (Shared transgenic mice with Ann Akeson in Pulmonary Biology).

Collaboration with Hematology/Oncology

Collaborating Faculty: Alexandra Filipovich, MD

Diagnostic center for Heritable Immunodeficiencies: a partnership that is now internationally recognized as a clinical diagnostic center.

Collaboration with Pediatric Otolaryngology

Collaborating Faculty: John Greinwald, MD

Genetic testing for hearing loss

Collaboration with Neurology; Clinical Pharmacology

Collaborating Faculty: Tracy Glauser, MD; Alexander Vinks, PhD

Provide genetic testing to assess drug metabolism

Collaboration with Cincinnati Children's Research Foundation

Collaborating Faculty: Arnold Strauss, MD

Inborn error/metabolic disorders services

Collaboration with Hematology/Oncology

Collaborating Faculty: Stella Davies, PhD; Jacob Bleesing, MD, PhD

Developed molecular testing for bone marrow engraftment monitoring; Introduced sub-cell-type BME assay which allow physicians to look at the cell engraftment at different cell populations

Collaboration with Hematology/Oncology

Collaborating Faculty: Ralph Gruppo, MD

Molecular testing for thrombosis

Collaboration with Developmental and Behaviorial Pediatrics

Collaborating Faculty: Patty Manning, MD

Genetic testing for children with mental retardation and developmental delay - hoping to develop novel molecular diagnosis for patients

Collaboration with Gastroenterology, Hepatology and Nutrition

Collaborating Faculty: Jorge Bezerra, MD

Diagnostic Center for Heritable Liver Diseases: introducing "The Jaundice Chip," a microarray based molecular test for children and adults with heritable liver diseases

Collaboration with Hematology/Oncology

Collaborating Faculty: Parinda Mehta, MD

Retrospective chromosome analysis in the bone marrow of patients with Fanconi Anemia

Collaboration with Cardiology

Collaborating Faculty: Bing Hinton, MD

Characterization of a translocation breakpoint in a family with cardiac defects

Collaboration with Developmental and Behavioral Pediatrics

Collaborating Faculty: Patty Manning, MD; Jennifer Ruschman, SCM, CGC

Retrospective Chart Review of patients with autism and microarray studies (led by Jennifer Ruschman - Division of

Human Genetics)

Collaboration with Pulmonary Biology

Collaborating Faculty: Steve Glasser, PhD; Tim Weaver, PhD; Jeffrey Whitsett, MD; Machiko Ikigami, PhD

Project 2: Modifier genes of SP-C induced interstitial lung disease - project seeks to indentify modifier genes affecting the severity of interstitial lung disease in a mouse model of surfactant protein-C deficiency

Collaboration with Biomedical Informatics

Collaborating Faculty: Bruce Aronow, PhD

Seeking to identify the major genes controlling hyperoxia induced acute lung injury susceptibility; Dr. Aronow provides the microarray, statistical, and *in silico* analyses support to help identify and critically characterize candidate and postional candidate genes for HALI susceptibility

Mentions in Consumer Media

- CCF Awards 2008 Research Grants Childrens Cardiomyopathy Foundation Heart to Heart , Web Site

Division Publications

1. Abu-Baker S, Qi X, Lorigan GA. Investigating the interaction of saposin C with POPS and POPC phospholipids: a solid-state NMR spectroscopic study. *Biophys J.* 2007; 93: 3480-90.
2. Bailey L. An overview of enzyme replacement therapy for lysosomal storage diseases. *Online J Issues Nurs.* 2008; 13:
3. Bedard AC, Huether CA, Shooner K, Buncher CR, Warren NS. Career research interests and training of genetic counseling students. *J Genet Couns.* 2007; 16: 645-53.
4. Bleesing J, Johnson J, Zhang K. (2007) Autoimmune lymphoproliferative syndrome. GeneReviews. Seattle, University of Washington. 2008:
5. Bowling BV, Acra EE, Wang L, Myers MF, Dean GE, Markle GC, Moskalik CL, Huether CA. Development and evaluation of a genetics literacy assessment instrument for undergraduates. *Genetics.* 2008; 178: 15-22.
6. Burrow TA, Hopkin RJ, Leslie ND, Tinkle BT, Grabowski GA. Enzyme reconstitution/replacement therapy for lysosomal storage diseases. *Curr Opin Pediatr.* 2007; 19: 628-35.
7. Cao H, Alston L, Ruschman J, Hegele RA. Heterozygous CAV1 frameshift mutations (MIM 601047) in patients with atypical partial lipodystrophy and hypertriglyceridemia. *Lipids Health Dis.* 2008; 7: 3.
8. Chen B, Sun D, Yang L, Zhang C, Yang A, Zhu Y, Zhao J, Chen Y, Guan M, Wang X, Li R, Tang X, Wang J, Tao Z, Lu J, Guan MX. Mitochondrial ND5 T12338C, tRNA(Cys) T5802C, and tRNA(Thr) G15927A variants may have a modifying role in the phenotypic manifestation of deafness-associated 12S rRNA A1555G mutation in three Han Chinese pedigrees. *Am J Med Genet A.* 2008; 146A: 1248-58.
9. Chen J, Yang L, Yang A, Zhu Y, Zhao J, Sun D, Tao Z, Tang X, Wang J, Wang X, Tsushima A, Lan J, Li W, Wu F, Yuan Q, Ji J, Feng J, Wu C, Liao Z, Li Z, Greinwald JH, Lu J, Guan MX. Maternally inherited aminoglycoside-induced and nonsyndromic hearing loss is associated with the 12S rRNA C1494T mutation in three Han Chinese pedigrees. *Gene.* 2007; 401: 4-11.
10. Cordell HJ, de Andrade M, Babron MC, Bartlett CW, Beyene J, Bickeboller H, Culverhouse R, Cupples LA, Daw EW, Dupuis J, Falk CT, Ghosh S, Goddard KA, Goode EL, Hauser ER, Martin LJ, Martinez M, North KE, Saccone NL, Schmidt S, Tapper W, Thomas D, Tritchler D, Vieland VJ, Wijsman EM, Wilcox MA, Witte JS, Yang Q, Ziegler A, Almasy L, Maccluer JW. Genetic Analysis Workshop 15: gene expression analysis and approaches to detecting multiple functional loci. *BMC Proc.* 2007; 1 Suppl 1: S1.
11. Cox TM, Aerts JM, Belmatoug N, Cappellini MD, vom Dahl S, Goldblatt J, Grabowski GA, Hollak CE, Hwu P, Maas M, Martins AM, Mistry PK, Pastores GM, Tylki-Szymanska A, Yee J, Weinreb N. Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring. *J Inherit Metab Dis.* 2008; 31: 319-36.
12. Crimmins NA, Martin LJ. Polymorphisms in adiponectin receptor genes ADIPOR1 and ADIPOR2 and insulin resistance. *Obes Rev.* 2007; 8: 419-423.
13. Crimmins NA, Woo JG, Kaushal RD, Deka R, Dolan LM, Martin LJ. Adiponectin receptor 1 variants associated with lower insulin resistance in African Americans. *Obesity (Silver Spring).* 2007; 15: 1903-7.
14. Friedlander SL, Dooms KT, Seroogy CM, Voss CY, Agger WA, Zhang K, Bleesing J, Filipovich AH. Adolescent presentation of x-linked lymphoproliferative disease. *Ann Allergy Asthma Immunol.* 2008; 100: 398-400.
15. Grabowski GA. Treatment perspectives for the lysosomal storage diseases. *Expert Opin Emerg Drugs.* 2008; 13:

197-211.

16. Grabowski GA, Hopkin R. **"Lysosomal storage diseases."** In: AS Fauci, E Braunwald, DL Kasperet al, eds. *Harrison's principles of internal medicine.* New York: McGraw-Hill; 2008: 2452-2456.
17. Halperin J, Devi SY, Elizur S, Stocco C, Shehu A, Rebourcet D, Unterman TG, Leslie ND, Le J, Binart N, Gibori G. **Prolactin signaling through the short form of its receptor represses forkhead transcription factor FOXO3 and its target gene galt causing a severe ovarian defect**. *Mol Endocrinol.* 2008; 22: 513-22.
18. Harvey EK, Stanton S, Garrett J, Neils-Strunjas J, Warren NS. **A case for genetics education: collaborating with speech-language pathologists and audiologists**. *Am J Med Genet A.* 2007; 143A: 1554-9.
19. Haugarvoll K, Rademakers R, Kachergus JM, Nuytemans K, Ross OA, Gibson JM, Tan EK, Gaig C, Tolosa E, Goldwurm S, Guidi M, Riboldazzi G, Brown L, Walter U, Benecke R, Berg D, Gasser T, Theuns J, Pals P, Cras P, De Deyn PP, Engelborghs S, Pickut B, Uitti RJ, Foroud T, Nichols WC, Hagenah J, Klein C, Samii A, Zabetian CP, Bonifati V, Van Broeckhoven C, Farrer MJ, Wszolek ZK. **Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson disease**. *Neurology.* 2008; 70: 1456-60.
20. Hinton RB, Jr., Martin LJ, Tabangin ME, Mazwi ML, Cripe LH, Benson DW. **Hypoplastic left heart syndrome is heritable**. *J Am Coll Cardiol.* 2007; 50: 1590-5.
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23. Kogan JM, Egelhoff JC, Saal HM. **Interstitial deletion of 13q associated with polymicrogyria**. *Am J Med Genet A.* 2008; 146: 910-6.
24. Kotsopoulos J, Lubinski J, Lynch HT, Klijn J, Ghadirian P, Neuhausen SL, Kim-Sing C, Foulkes WD, Moller P, Isaacs C, Domchek S, Randall S, Offit K, Tung N, Ainsworth P, Gershoni-Baruch R, Eisen A, Daly M, Karlan B, Saal HM, Couch F, Pasini B, Wagner T, Friedman E, Rennert G, Eng C, Weitzel J, Sun P, Narod SA, Garber J, Osborne M, Fishman D, McLennan J, McKinnon W, Merajver S, Olsson H, Provencher D, Pasche B, Evans G, Meschino WS, Lemire E, Chudley A, Rayson D, Bellati C. **Age at first birth and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers**. *Breast Cancer Res Treat.* 2007; 105: 221-8.
25. Li Y, Du H, Qin Y, Roberts J, Cummings OW, Yan C. **Activation of the signal transducers and activators of the transcription 3 pathway in alveolar epithelial cells induces inflammation and adenocarcinomas in mouse lung**. *Cancer Res.* 2007; 67: 8494-503.
26. Li Y, Qin Y, Li H, Wu R, Yan C, Du H. **Lysosomal acid lipase over-expression disrupts lamellar body genesis and alveolar structure in the lung**. *Int J Exp Pathol.* 2007; 88: 427-36.
27. Li Z, Liu Y, Yang L, Wang S, Guan MX. **Maternally inherited hypertension is associated with the mitochondrial tRNA(Ile) A4295G mutation in a Chinese family**. *Biochem Biophys Res Commun.* 2008; 367: 906-11.
28. Liao Z, Zhao J, Zhu Y, Yang L, Yang A, Sun D, Zhao Z, Wang X, Tao Z, Tang X, Wang J, Guan M, Chen J, Li Z, Lu J, Guan MX. **The ND4 G11696A mutation may influence the phenotypic manifestation of the deafness-associated 12S rRNA A1555G mutation in a four-generation Chinese family**. *Biochem Biophys Res Commun.* 2007; 362: 670-6.
29. Liu A, Qi X. **Molecular dynamics simulation of saposin c-membrane binding.** *Open Struct Biol J.* 2008; 2: 21-30.
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31. Lv L, Kerzic P, Lin G, Schnatter AR, Bao L, Yang Y, Zou H, Fu H, Ye X, Gross SA, Armstrong TW, Irons RD. **The TNF-alpha 238A polymorphism is associated with susceptibility to persistent bone marrow dysplasia following chronic exposure to benzene**. *Leuk Res.* 2007; 31: 1479-85.
32. Lv L, Lin GW, Wang XQ, Bao LM, Zou HJ. **[A case-control study of risk factors for myelodysplastic syndromes]**. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi.* 2007; 25: 705-9.
33. Maas M, Hangartner T, Mariani G, McHugh K, Moore S, Grabowski GA, Kaplan P, Vellodi A, Yee J, Steinbach L. **Recommendations for the assessment and monitoring of skeletal manifestations in children with Gaucher disease**. *Skeletal Radiol.* 2008; 37: 185-8.
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35. Martin LJ, Woo JG, Avery CL, Chen HS, North KE, Au K, Broet P, Dalmasso C, Guedj M, Holmans P, Huang B, Kuo PH, Lam AC, Li H, Manning A, Nikolov I, Sinha R, Shi J, Song K, Tabangin M, Tang R, Yamada R. **Multiple testing**

in the genomics era: findings from Genetic Analysis Workshop 15, Group 15. *Genet Epidemiol.* 2007; 31 Suppl 1: S124-31.

36. McEachern KA, Fung J, Komarnitsky S, Siegel CS, Chuang WL, Hutto E, Shayman JA, Grabowski GA, Aerts JM, Cheng SH, Copeland DP, Marshall J. A specific and potent inhibitor of glucosylceramide synthase for substrate inhibition therapy of Gaucher disease. *Mol Genet Metab.* 2007; 91: 259-67.
37. Nichols WC, Elsaesser VE, Pankratz N, Pauciulo MW, Marek DK, Halter CA, Rudolph A, Shults CW, Foroud T. LRRK2 mutation analysis in Parkinson disease families with evidence of linkage to PARK8. *Neurology.* 2007; 69: 1737-44.
38. Nieh MP, Katsaras J, Qi X. Controlled release mechanisms of spontaneously forming unilamellar vesicles. *Biochim Biophys Acta.* 2008; 1778: 1467-71.
39. Noll RB, Reiter-Purtill J, Moore BD, Schorry EK, Lovell AM, Vannatta K, Gerhardt CA. Social, emotional, and behavioral functioning of children with NF1. *Am J Med Genet A.* 2007; 143A: 2261-73.
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41. Prows CA, Beery TA. Pharmacogenetics in critical care: a trial fibrillation as an exemplar. *Crit Care Nurs Clin North Am.* 2008; 20: 223-31, vi-vii.
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Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct / Project Period Direct
Bao, L		
Studies of Benzene Toxicity American Petroleum Institute (University of Colorado Health Science Center)	11/01/01 - 06/30/08	$26,032 / $290,332
Burrow, T		
Genzyme/ACMGF Clinical Genetics Fellowship in Biochemical Genetics American College of Medical Genetics Foundation	07/01/07 - 06/30/08	$69,445 / $69,445
Du, H		
PPARgamma in the Lung National Institutes of Health R01 HL 087001	06/09/08 - 05/31/13	$250,000 / $1,250,000
Grabowski, G		
Cincinnati Regional Genetics Center Ohio Department of Health 31-3-001-1AU-08	07/01/07 - 06/30/08	$383,500 / $1,534,000
Nucleic Acid Therapy for Alpha1-Antitrypsin Disease: Reinventing the Ribozyme Alpha One Foundation	07/01/06 - 06/30/08	$64,792 / $129,702
Studies of Gaucher Disease National Institutes of Health R01 DK 036729	09/27/07 - 08/31/12	$275,687 / $1,449,180
Guan, M		
Nuclear Modifier Genes for Maternally Inherited Deafness National Institutes of Health R01 DC 007696	07/01/07 - 06/30/11	$212,500 / $850,000

Keddache, M

Digestive Health Center - Bench to Bedside Research in Pediatric Digestive Disease - Sequencing Core
National Institutes of Health
P30 DK 078391 | 08/01/07 - 05/31/12 | $21,243 / $52,397

Knapke, S

Hereditary Cancer Community and Family Education Initiative
Komen Breast Cancer Foundation
04/01/08 - 03/31/09 | $76,716 / $76,716

Leslie, N

Implementing Newborn Screening for Duchenne Muscular Dystrophy to the Community
Centers for Disease Control and Prevention (The Research Institute at Nationwide Children's Hospital)
R18 DD 000344 | 09/30/07 - 09/29/10 | $19,723 / $62,072

Nichols, W

Project II: Genetic Modifiers of Murine Pulmonary Hypertension
National Institutes of Health (Vanderbilt University)
P01 HL 072058 | 08/01/03 - 07/31/09 | $251,973 / $1,259,865

Parkinson Disease Collaborative Study
National Institutes of Health (Indiana University-Purdue University at Indianapolis)
R01 NS 037167 | 02/01/04 - 01/31/09 | $228,063 / $1,239,388

Prows, D.

Genetic Analysis Of Hyperoxia-Induced Acute Lung Injury
National Institutes of Health
R56 HL075562 | 12/15/03 - 04/30/09 | $252,073 / $1,246,198

Regulation of Respiratory Epithelial Cell Homeostasis
National Institutes of Heath
P01 HL061646 | 07/01/00 - 06/30/09 | $169,307 / $1,320,627

Qi, X

A Novel Biotherapeutic Treatment for Prostate Cancer
National Institutes of Health (Bexion Pharmaceuticals)
R43 CA 130228 | 09/01/07 - 08/31/08 | $30,000 / $30,000

Ruschman, J

Puberty and Cancer Initiation: Environment, Diet and Obesity
National Institutes of Health (University of Cincinnati)
U01 ES 012770 | 09/29/03 - 07/31/10 | $4,106 / $22,240

Current Year Direct **2,335,160**

Industry Contracts

Grabowski, G

Amicus Therapeutics, Ind	$ 219,893
Genzyme Corporation	$ 26,500
Shire Human Genetics Therapies	$ 254,378

Hopkin, R

Genzyme Corporation	$ 86,590

Leslie, N

Amicus Therapeutics, Inc	$ 21,408
Genzyme Corporation	$ 15,593
Transkaryotic Therapies	$ 62,388

Tinkle, B

Novartis Pharmaceuticals	$ 2,156
Current Year Direct Receipts	**$688,906**
Total	**$3,024,066**