Cincinnati Children's

2015 Research Annual Report

Human Genetics

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	**27**
Joint Appointment Faculty	**5**
Research Fellows	**4**
Research Students	**3**
Support Personnel	**135**
Direct Annual Grant Support	**$2,976,611**
Direct Annual Industry Support	**$544,845**
Peer Reviewed Publications	**72**

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	**29**
Clinical Fellows	**4**
Clinical Students	**24**
Other Students	**4**
Inpatient Encounters	**563**
Outpatient Encounters	**6,165**

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Research Highlights

Elizabeth Schorry, MD

As a member of the Neurofibromatosis Clinical Trials consortium, Dr. Schorry and her team have completed a clinical trial of the mTOR inhibitor, sirolimus, for plexiform neurofibromas in patients with neurofibromatosis type 1 (NF1). They demonstrated that use of sirolimus prolonged the time to progression of plexiform neurofibromas by about 30%, indicating that this agent is capable of slowing growth of these challenging tumors. They also completed a trial of lovastatin for learning disabilities in NF1, and demonstrated that lovastatin was not effective in improving attention or working memory in children with NF1.

Ying Sun, PhD

Dr. Sun and her team developed the protocol and conducted preclinical studies in evaluating new small pharmaceutical compound (produced by Genzyme) for substrate reduction therapy (SRT) to treat neuronopathic Gaucher disease. The results demonstrated that the new, and central nervous system (CNS) accessible, SRT reduced the level of lipid substrate accumulation and CNS inflammation in Gaucher disease mouse model and leads to delayed neurodegeneration and improved survival. This study supports the clinical efficacy of this first SRT in attenuating neuronopathic Gaucher disease.

In addition, Dr. Sun's lab has performed the extensive ribonucleic acid (RNA) analyses of neuronopathic Gaucher disease mice brain by RNASeq technology. The results of these analyses revealed dynamic alterations of miRNAs and mRNA in the brain of animal model. The identified miRNAs and target mRNAs are involved in the biological pathways that have not been explored in Gaucher disease. These data provide the molecular basis for further investigation of biological pathways underlying the disease and develop new therapeutic targets. The manuscript is in revision in *Human Molecular Genetics*.

Ge Zhang, MD, PhD

Dr. Zhang has conducted multiple genome-wide quantitative genetic analyses of human complex traits and diseases. He has helped in identifying genetic loci associated with diisocyanate-induced occupational asthma. He developed a novel Mendelian randomization approach using non-transmitted maternal haplotype as a genetic instrument to infer causal relationship between parental phenotype and outcomes in offspring. Using this method, he and his collaborators defined the causal relationship for the strong association of maternal height with fetal growth measures (i.e. birth length and birth weight) and gestational age.

Taosheng Huang, MD, PhD

Dr. Huang, with collaborators Robert Hufnagel, MD, PhD, and Elizabeth Schorry, MD, studied two sisters with an unusual syndrome of optic atrophy, cerebellar degeneration, and axonal peripheral neuropathy. Through whole exome sequencing, they identified mutations in SLC25A46, which codes for a protein located in the outer mitochondrial membrane. Phylogenetic and structural analyses suggest that SLC25A46 interacts with proteins associated with OPA1 and MFN2 and acts as a carrier inside mitochondria. However, the function of SLC25A46 and its carried substrate are yet to be identified, discovery of which may lead to important clues linking mitochondrial fission and fusion to a common pathway of disease pathogenesis. In their funded CpG project, they plan to create two mouse models to study pathogenesis of SLC25A46 mutations. The goal is to identify additional patients with SLC25A46-associated optic atrophy plus syndrome in order to better study the role of SLC25A46 in mitochondrial dynamics and human disease.

Derek Neilson, MD

Dr. Neilson received a grant from the Center for Pediatric Genomics (CPG) to study the hypermobile type of Ehlers Danlos syndrome. This connective tissue disorder, served by the Connective Tissue Clinic which sees 600 new patients per year, predisposes to multiple problems including chronic pain, fatigue and gastrointestinal disorders. The CPG funds will be used to identify genes and biological markers that could lead to new treatments and prevention of these disabling

complications.

Significant Publications

Gordon CT, Weaver KN, Zechi-Ceide RM, Madsen EC, Tavares AL, Oufadem M, Kurihara Y, Adameyko I, Picard A, Breton S, Pierrot S, Biosse-Duplan M, Voisin N, Masson C, Bole-Feysot C, Nitschke P, Delrue MA, Lacombe D, Guion-Almeida ML, Moura PP, Garib DG, Munnich A, Ernfors P, Hufnagel RB, **Hopkin RJ**, Kurihara H, **Saal HM**, Weaver DD, Katsanis N, Lyonnet S, Golzio C, Clouthier DE, Amiel J. Mutations in the endothelin receptor type A cause mandibulofacial dysostosis with alopecia. *Am J Hum Genet.* 2015;96(4):519-31.

This paper reports a novel human craniofacial malformation syndrome caused by mutations in a gene that was not previously known to be associated with human disease. Remarkably, three of the four unrelated individuals described have the same de novo missense mutation. In vitro and in vivo studies demonstrated that theTyr129Phe mutation results in complex, context-specific effects on the ligand specificity and downstream signaling of the endothelin receptor type A. These effects may underlie the common phenotype shared by individuals with MFDA.

Pandey M, Tinch S, Inskeep V, Zhang W, Setchell K, Köhl J, Grabowski G. **Glucosylceramide induced complement activation triggers inflammation in Gaucher disease (CCR5P.212).** *J Immunol*. 2015;194(1 Supplement):186.14.

We identified glucosylceramide mediated complement activation and the generation of C5a as one of the main drivers of upregulation of the co-stimulatory molecules, increased production of pro inflammatory cytokines and chemokines and tissue damage in Gaucher disease. This finding uncovers the C5a/C5aR axis as a novel therapeutic target in Gaucher disease, which can potentially be used as an innovative adjunctive therapeutic approach for lung and brain defects, for which no appropriate treatment options exist.

Prows DR, Gibbons WJ, Smith JJ, Pilipenko V, **Martin LJ**. Age and Sex of Mice Markedly Affect Survival Times Associated with Hyperoxic Acute Lung Injury. *PLoS One.* 2015 Jun 23;10(6):e0130936.

Previously, we identified and captured in separate mouse lines two chromosomal regions carrying opposite-effect genes linked to differential susceptibilities to high-dose oxygen. This report extends those findings to demonstrate that sensitivity directly depends on the sex of mice and a 4-week age period in early adulthood, thereby establishing our unique mouse lines as valuable tools to delineate the complex biological mechanisms defining these susceptibility differences.

Saal HM, **Prows CA**, Guerreiro I, Donlin M, Knudson L, Sund KL, Chang CF, Brugmann SA, **Stottmann RW**. A mutation in FRIZZLED2 impairs Wnt signaling and causes autosomal dominant omodysplasia. *Hum Mol Genet.* 2015 Jun 15;24(12):3399-409.

Here we identify the first mutations in human FZD2 and show they are associated with omodysplasia, a disease affecting the skeleton. This represents a successful application of human next-generation sequencing and subsequent biological analysis from a recently formed Cincinnati Children's collaborative network.

Sun Y, Florer J, Mayhew CN, Jia Z, Zhao Z, Xu K, Ran H, Liou B, Zhang W, Setchell KD, Gu J, Grabowski GA. Properties of neurons derived from induced pluripotent stem cells of Gaucher disease type 2 patient fibroblasts: potential role in neuropathology. *PLoS One.* 2015 May;10(3):e0118771.

The study provides the first electrophysiological characterization of Gaucher disease neurons that will expedite dissecting the pathological mechanisms of neuronopathic Gaucher disease. The electrophysiological properties of Gaucher disease iPSC-derived neurons could represent a novel area for therapeutic target screening.

Division Publications

1. Akil O, Sun Y, Vijayakumar S, Zhang W, Ku T, Lee CK, Jones S, Grabowski GA, Lustig LR. **Spiral ganglion degeneration and hearing loss as a consequence of satellite cell death in saposin B-deficient mice**. *J Neurosci*. 2015; 35:3263-75.

2. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, Mukkada VA, Succop PA, Abonia JP, Foote H, Eby MD, Grotjan TM, Greenler AJ, Dellon ES, Demain JG, Furuta GT, Gurian LE, Harley JB, Hopp RJ, Kagalwalla A, Kaul A, Nadeau KC, Noel RJ, Putnam PE, von Tiehl KF, Rothenberg ME. **Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis**. *J Allergy Clin Immunol*. 2014; 134:1084-1092 e1.

3. Anand G, Visagan R, Chandratre S, Segal S, Nemeth AH, Squier W, Sheerin F, Neilson D, Jayawant S. **H1N1 triggered recurrent acute necrotizing encephalopathy in a family with a T653I mutation in the RANBP2 gene**. *Pediatr Infect Dis J*. 2015; 34:318-20.

4. Ankala A, Tamhankar PM, Valencia CA, Rayam KK, Kumar MM, Hegde MR. **Clinical applications and implications of common and founder mutations in Indian subpopulations**. *Hum Mutat*. 2015; 36:1-10.

5. Atzinger CL, Lewis K, Martin LJ, Yager G, Ramstetter C, Wusik K. **The impact of supervision training on genetic counselor supervisory identity development**. *J Genet Couns*. 2014; 23:1056-65.

6. Barnes S, Xu YH, Zhang W, Liou B, Setchell KD, Bao L, Grabowski GA, Sun Y. **Ubiquitous transgene expression of the glucosylceramide-synthesizing enzyme accelerates glucosylceramide accumulation and storage cells in a Gaucher disease mouse model**. *PLoS One*. 2014; 9:e116023.

7. Baughn LB, Biegel JA, South ST, Smolarek TA, Volkert S, Carroll AJ, Heerema NA, Rabin KR, Zweidler-McKay PA, Loh M, Hirsch B. **Integration of cytogenomic data for furthering the characterization of pediatric B-cell acute lymphoblastic leukemia: a multi-institution, multi-platform microarray study**. *Cancer Genet*. 2015; 208:1-18.

8. Biagini Myers JM, Martin LJ, Kovacic MB, Mersha TB, He H, Pilipenko V, Lindsey MA, Ericksen MB, Bernstein DI, LeMasters GK, Lockey JE, Khurana Hershey GK. **Epistasis between serine protease inhibitor Kazal-type 5 (SPINK5) and thymic stromal lymphopoietin (TSLP) genes contributes to childhood asthma**. *J Allergy Clin Immunol*. 2014; 134:891-899 e3.

9. Biagini Myers JM, Simmons JM, Kercsmar CM, Martin LJ, Pilipenko VV, Austin SR, Lindsey MA, Amalfitano KM, Guilbert TW, McCoy KS, Forbis SG, McBride JT, Ross KR, Vauthy PA, Khurana Hershey GK. **Heterogeneity in asthma care in a statewide collaborative: the Ohio Pediatric Asthma Repository**. *Pediatrics*. 2015; 135:271-9.

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11. Brazil A, Stanford K, Smolarek T, Hopkin R. **Delineating the phenotype of 1p36 deletion in adolescents and adults**. *Am J Med Genet A*. 2014; 164A:2496-503.

12. Burrow TA, Sun Y, Prada CE, Bailey L, Zhang W, Brewer A, Wu SW, Setchell KD, Witte D, Cohen MB, Grabowski GA. **CNS, lung, and lymph node involvement in Gaucher disease type 3 after 11 years of therapy: clinical, histopathologic, and biochemical findings**. *Mol Genet Metab*. 2015; 114:233-41.

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panoramic radiographs in children with cleft lip and palate. *Cleft Palate Craniofac J*. 2014; 51:e88-93.

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Faculty, Staff, and Trainees

Faculty Members

Nancy Doan Leslie, MD, Professor

Leadership Co-Director, Division of Human Genetics; 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.

William Nichols, PhD, Professor

Leadership Co-Director, Division of Human Genetics; Associate Director of Research; Director, National Biological Sample and Data Repository for PAH

Research Interests The identification of genetic variants contributing to disease susceptibility with an emphasis on pulmonary arterial hypertension and Parkinson disease.

Carrie Atzinger, MS, Assistant Professor

Leadership Assistant Director, The Genetic Counseling Graduate Program

T. Andrew Burrow, MD, Assistant Professor

Research Interests Lysosomal storage diseases, particularly Gaucher disease; Inborn errors of metabolism, and neurogenetics.

Hatice Duzkale, MD, MPH, PhD, Assistant Professor

Leadership Assistant Director, Molecular Genetics Laboratory

Research Interests Liquid biopsy approaches to monitor disease course in pediatric solid tumors; discovery of novel treatment targets for metastatic Ewing sarcoma; novel causative gene discovery in MODY through exome analysis.

Lisa Dyer, PhD, Instructor

Leadership Assistant Director, Clinical Cytogenetics Laboratory

Research Interests Identification and characterization of translocation positive pediatric renal cell carcinoma.

Min-Xin Guan, PhD, Adjunct

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

Robert Hopkin, MD, Associate Professor

Leadership Director, Genetic Residency Programs

Research Interests Fabry disease; Robin sequence; 22q11 deletion; neurofibromatosis; craniofacial genetics; chromosomal anomalies.

Taosheng Huang, MD, PhD, Professor

Leadership Director, Program of Mitochondrial Medicine; Associate Director, Molecular Diagnostic Laboratory

Research Interests Disease-causing gene discovery with next generation sequencing and iPS cell therapy.

Ronghua Li, PhD, Instructor

Research Interests Cell-specific models of mitochondrial diseases and mitochondrial epigenetics.

Xia Li, PhD, Assistant Professor

Leadership Associate Director, Clinical Cytogenetics Laboratory

Research Interests The role of molecular markers in hematological disorders for prediction, treatment, and monitoring.

Lisa Martin, PhD, Professor

Leadership Director, Cincinnati Genomic Control Cohort; Co-Team Leader for United Way

Research Interests Improving the understanding of human genetic variation through the integration of statistical genetics with biology and epidemiology especially how it relates to pediatric heart conditions, allergic disorders and obesity.

Melanie Myers, PhD, MS, LGC, Associate Professor

Leadership Director, The Genetic Counseling Graduate Program

Research Interests Clinical utility of family health history and other genomic tools in health promotion.

Derek Neilson, MD, Assistant Professor

Research Interests Genetic and pathogenesis of Ehlers Danlos as well as genetics of neurologic disorders.

Manoj Pandey, PhD, Instructor

Research Interests Immunobiology of the lysosomal storage disease.

Carlos Prada, MD, Assistant Professor

Research Interests Inborn errors of metabolism with emphasis in newborn screening technologies and implementation; biomarkers of disease progression of lysosomal storage disorders and neurofibromatosis.

Daniel R Prows, PhD, Associate 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.

Howard Saal, MD, Professor

Leadership Director, Clinical 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, and treatment of tongue based airway disorders.

Iris Sageser, RDH, MS, Associate Professor

Research Interests Multidisciplinary management of individuals affected by craniofacial abnormalities.

Elizabeth K Schorry, MD, Professor

Leadership Director, Neurofibromatosis Clinic

Research Interests Psychosocial and orthopedic aspects of neurofibromatosis; clinical drug trials for NF1, and Ehlers Danlos syndrome.

Teresa A Smolarek, PhD, Associate Professor

Leadership 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 lymphangioleiomyomatosis.

Rolf W Stottmann, PhD, Assistant Professor

Leadership Director, Student Admissions for the MDB program

Research Interests Genetic analysis of congenital malformations affecting the brain and face.

Ying Sun, PhD, Associate Professor

Research Interests The pathological mechanisms of lysosomal storage diseases.

C. Alexander Valencia, PhD, Assistant Professor

Leadership Assistant Director, Molecular Genetics Laboratory

Research Interests Clinical genomics and proteomics: a systems biology view in human genetics.

Stephanie Ware, MD, PhD, Adjunct

Research Interests Genetic disorders of cardiac structure and function.

K. Nicole Weaver, MD, Instructor

Research Interests Cardiovascular genetics; Costello syndrome; craniofacial genetics; Robin sequence.

Ge Zhang, MD, PhD, Associate Professor

Research Interests Genome-wide association studies and mathematical modeling of human genetic variations.

Kejian Zhang, MD, MBA, Associate Professor

Leadership Director, Molecular Genetics Laboratory

Research Interests Molecular defects and molecular diagnosis of primary immunodeficiency diseases; genetic aspects of predictive personalized medicine, e.g., pharmacogenetics.

Joint Appointment Faculty Members

Artem Barski, PhD, Assistant Professor (Allergy & Immunology)

Research Interests Chromatin biology; epigenomic and transcriptional regulation of immune response; use of epigenomic data to augment genome –wide association studies.

John Greinwald, MD, Associate Professor (Otolaryngology)
Research Interests Genetics of hearing loss.

Kenneth Kaufman, PhD, Professor (Center for Autoimmune Genomics and Etiology)
Research Interests Genetics of complex diseases such as systemic lupus erythematosus.

Kakajan Komurov, PhD, Assistant Professor (Exp. Hem. & Cancer Bio.)
Research Interests Interested in identifying global molecular network models of cancer progression.

Clinical Staff Members

- **Laurie Bailey, MS, LGC**, Coordinator, Clinical Research Program ;Coordinator, Cincinnati STAR Center for Lysosomal Diseases
- **Michelle Baric, MS, LGC**
- **Janet Basil, MS, LGC**
- **Patricia Bender, RN, MSN**
- **Lisa Berry, MS, LGC**
- **Chinmayee Bhimarao Nagaraj, MS, LGC**
- **Ashley Brazil, MS, LGC**
- **Anne Burroughs, RN**
- **Kathleen Collins, MS, LGC**
- **Jennifer Glass, MS, LGC**
- **Carol Hetteburg, RN, MSN**
- **Hopper Jennifer, MS, LGC**
- **Sandy Kaiser, LPN**
- **Betty Leech, MS, LGC**
- **Anne Lovell, RN, MSN, APN**
- **Abigail Masunga, MS, LGC**
- **Kimberly Page, RD**
- **Emily Partack, MS, LGC**
- **Cynthia Prows, MSN, APRN, FAAN**
- **Cecilia Rajakaruna, MS, LGC**
- **Jodie Rueger-Johnson, MS, LGC**
- **Megan Shearouse, MS**
- **Rebecca Sisson, MS, LGC**
- **Christine Spaeth, MS, LGC**

- **Elizabeth Ulm, MS, LGC**
- **Emily Wakefield, MS**
- **Martha Walker, MS, LGC**
- **Connie Wehmeyer, RN**
- **Katie Wusik, MS, LGC**

Trainees

- **Sophia Hufnagel, MD**, PGY5, Pediatrics/Genetics Combined Residency
- **Rob Hufnagel, MD, PhD**, PGY4, Pediatrics/Genetics Combined Residency
- **Harry Lesmana, MD**, PGY3, Pediatrics/Genetics Combined Residency
- **Rachel Lombardo, MD**, PGY2, Pediatrics/Genetics Combined Residency
- **Bianca Russell, MD**, PGY2, Pediatrics/Genetics Combined Residency
- **Danielle Monteil, MD**, PGY6, Medical Genetics Fellowship
- **Stephanie Balow, PhD**, PGY6, Clinical Cytogenetics Fellowship
- **K. Nicole Weaver, MD**, PGY6, Clinical Biochemical Genetics Fellowship
- **Fanngeng Zou, PhD**, PGY7, Clinical Fellow Molecular Genetics
- **Lijun Wang, PhD**, PGY6, Clinical Molecular Genetics Fellowship

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct

Berry, L

Genetic Counseling Fellowship in Lysosomal Storage Disorders

Genzyme Corporation

	6/15/2015-6/14/2016	$74,987

Leslie, N

Defining the Natural History of Inborn Errors of Metabolism

National Institutes of Health (Michigan Public Health Institute)

R01 HD069039	4/15/2011-2/28/2016	$24,076

Martin, L

Genetic Underpinnings of Isolated Hypoplastic Left Heart

Children's Heart Foundation

	1/1/2015-12/31/2016	$99,769

Epithelial Genes in Allergic Inflammation

National Institutes of Health

U19 AI070235	9/1/2011-8/31/2016	$87,789

Nichols, W

National Biological Sample and Data Repository for PAH

National Institutes of Health

R24 HL105333	3/3/2012-2/28/2017	$1,401,835

Saal, H

Cincinnati Regional Genetics Center

Ohio Department of Health

03130011GS0815	7/1/2012-3/31/2016	$331,551

Schorry, E

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	$87,039

NF Consortium Infrastructure and Trial#1

Department of Defense(University of Alabama Birmingham)

W81XWH-12-1-0155	5/15/2012-5/14/2016	$133,731

Stottmann, R

A Genetic Approach to Defining the Ttc21b Interactome in Mammalian Ciliopathies

National Institutes of Health

R01 GM112744	2/1/2015-1/31/2019	$192,500

Forward Genetic Analysis of Congenital Defects in Cortical Circuits and Structure

National Institutes of Health

R01 NS085023	5/15/2014-4/30/2019	$310,496

Ware, S

Genotype-Phenotype Associations in Pediatric Cardiomyopathy

National Institutes of Health(Wayne State University)

WSU15021	8/10/2014-3/31/2017	$223,316

Zhang, G

Genetic Susceptibility for Occupational Asthma

National Institutes of Health(University of Cincinnati)

	11/15/2014-8/31/2017	$9,522

Current Year Direct	**$2,976,611**

Industry Contracts

Burrow, T

Genzyme Corporation	$94,122
Synageva BioPharma Corp	$14,939
Shire Human Genetic Therapies	$16,575
Hyperion Therapeutics	$11,900

Hopkin, R

Genzyme Corporation	$114,117
Sanofi Pasteur Biologics LLC	$16,071
Health Research Associates, Inc.	$1,300

Leslie, N

Shire Human Genetic Therapies	$14,039
Genzyme Corporation	$52,282

Prows, D

Terapio Corporation	$20,054

Saal, H

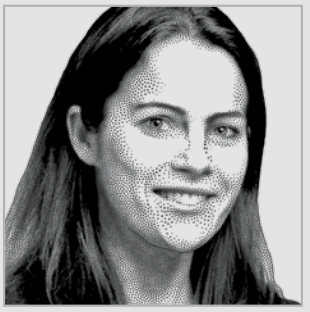
Alexion Pharmaceuticals, Inc	$114,520

Sun, Y

Genzyme Corporation	$74,926

Current Year Direct Receipts	**$544,845**
Total	**$3,521,456**

Dysfunctional Ribosome Gene Linked to Rare Craniofacial and Limb Abnormalities



K. Nicole Weaver, MD

RESEARCH AND TRAINING DETAILS

Faculty	27
Joint Appointment Faculty	5
Research Fellows	4
Research Students	3
Support Personnel	135
Direct Annual Grant Support	$2.9M
Direct Annual Industry Support	$544,845
Peer Reviewed Publications	72

Weaver KN, Watt KE, Hufnagel RB, Navajas Acedo J, Linscott LL, Sund KL, Bender PL, Konig R, Lourenco CM, Hehr U, Hopkin RJ, Lohmann DR, Trainor PA, Wieczorek D, Saal HM. Acrofacial Dysostosis, Cincinnati Type, a Mandibulofacial Dysostosis Syndrome with Limb Anomalies, Is Caused by POLR1A Dysfunction. *Am J Hum Genet.* 2015;96(5):765-774.

PUBLISHED APRIL 23, 2015
American Journal of Human Genetics

A Cincinnati geneticist's exploration of rare cranioskeletal malformations and abnormal limbs in three patients worldwide has led to the discovery of a dysfunctional gene as the culprit and a name for the syndrome — acrofacial dysostosis, Cincinnati Type.

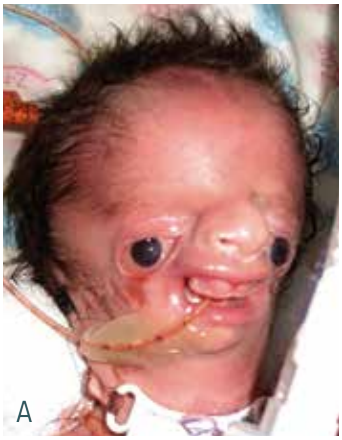
K. Nicole Weaver, MD, a geneticist with the Division of Human Genetics, said the severity of a Cincinnati patient's craniofacial abnormalities and discovery of a suspicious gene led her on a worldwide search for answers for the child's family. A German colleague scoured a large database of patients with undiagnosed craniofacial anomalies and identified two additional patients with a defective copy of the same gene, POLR1A, which is involved in ribosome biogenesis. Ribosomes play an essential role in the process of synthesizing proteins. A Missouri genetics colleague studied zebrafish with absent POLR1A expression, and the fish developed skull, facial, jaw and limb abnormalities similar to those in the children.

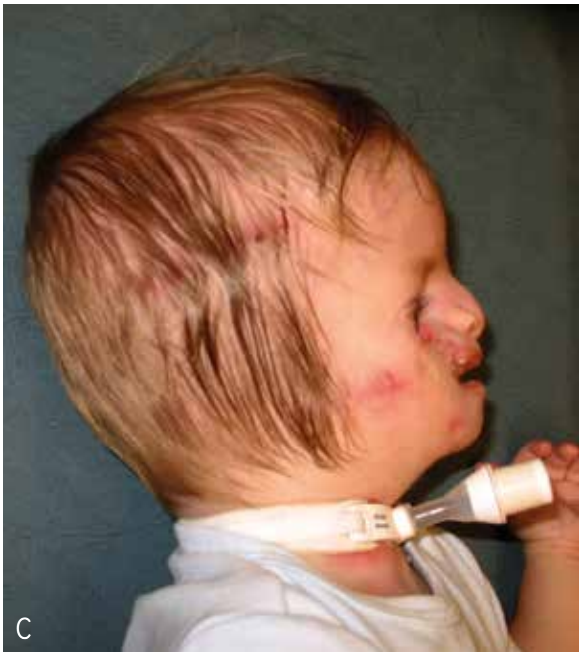
Discovering similar cranioskeletal abnormalities in zebrafish lacking expression of POLR1A provided "pretty strong evidence that dysfunction of this gene could cause these problems in a human," says Weaver, whose findings were published online April 23, 2015, in the *American Journal of Human Genetics*.

The defective POLR1A gene, the team found, resulted in a deficiency of neural-crest-derived skeletal precursor cells that led to the craniofacial anomalies.

"It's unclear why the dysfunction of this ribosome gene gene affects only certain parts of the body," she says. Follow-up research will try to reproduce the anomalies in mice as a way to learn more about the role of ribosome malfunction in human development.

"For this patient, it was really important to be able to tell the family why this abnormality happened, that it wasn't inherited and that it likely would not happen again in another child," Weaver says. "And the patient is doing really, really well."





Individuals with acrofacial dysostosis, Cincinnati type, each have a heterozygous mutation in POLR1A, which encodes a core component of RNA polymerase 1. These images of an affected newborn show: (A) extensive craniofacial malformations at birth; (B and C) images taken at age 18 months after multiple reconstructive surgeries; (D) severe maxillary and zygomatic hypoplasia (black open-dashed arrow) and severe micrognathia and retrognathia (white block arrow); (E) severe microtia with absent pinnae (white arrows), external auditory atresia (white open-dashed arrows), and severe middle-ear hypoplasia and ossicular dysplasia (black open arrows); and (F) bilateral hip dysplasia and anterior bowing deformity of the femurs.

"It was really important to be able to tell the family why this abnormality happened, that it wasn't inherited and that it likely would not happen again in another child."