Cincinnati Children's

2015 Research Annual Report

Endocrinology

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	17
Joint Appointment Faculty	3
Support Personnel	27
Direct Annual Grant Support	$1,488,844
Direct Annual Industry Support	$113,816
Peer Reviewed Publications	37

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	47
Clinical Fellows	12
Inpatient Encounters	4,010
Outpatient Encounters	14,450

Download Report in PDF Format Visit Endocrinology

Research Highlights

Andrew Dauber, MD, MMSc

Dr. Dauber's research focuses on genetic causes of extreme short stature. Dr. Dauber's work has resulted in the identification of a number of new etiologies of severe growth disorders including a new paradigm in the growth hormone-

IGF-1 axis (factors affecting the bioavailability of IGF-1) resulting in short stature. For his work, Dr. Dauber has received numerous awards including the Early Investigator Award from the Endocrine Society, the Young Physician-Scientist Award from the American Society of Clinical Investigation, and the Young Investigator Award from the European Society of Pediatric Endocrinology. Dr. Dauber leads the Cincinnati Center for Growth Disorders, a research program spanning clinical, translational and basic research into growth disorders with a strong reliance on cutting edge genomic techniques.

Amy Sanghavi Shah, MD, MS

Dr. Shah's research focuses on the development of premature cardiovascular disease in high-risk youth with an emphasis on the role of lipids and lipoproteins. Dr. Shah's work combines vascular non-invasive imaging techniques with molecular laboratory studies to study the mechanisms by which high density lipoprotein subfractions contribute to the development and progression of early cardiovascular disease in youth with type 2 diabetes. Dr. Shah's work is currently funded by a K23 career development award from the National Institutes of Health (NIH). For this work, Dr. Shah received the following honors: Young Investigator Award from the National Lipid Association and the Young Investigator Award for the International Society for Pediatric and Adolescent Diabetes (ISPAD).

Significant Publications

Elder DA, Hornung LN, Herbers PM, Prigeon R, Woo JG, D'Alessio DA. Rapid deterioration of insulin secretion in obese adolescents preceding the onset of type 2 diabetes. *J Pediatr.* 2015 Mar;166(3):672-8.

Adults develop type 2 diabetes due to a progressive loss of insulin production over many years. The development of T2DM in adults is a progressive process that manifests over years and perhaps decades. While it is clear that adolescents who develop T2DM are obese, insulin resistant, and have abnormalities in beta-cell function, the pathophysiology behind the transition from prediabetes to diabetes is not well understood. Our goal was to identify the key changes involved in the transition from normal glucose tolerance to diabetes, and our results support a rapid decline in beta-cell function as the key feature in this progression.

Backeljauw PF, Miller BS, Dutailly P, Houchard A, Lawson E, Hale DE, Reiner B, Sperling MA, MS16 Study Group. Recombinant human growth hormone plus recombinant human insulin-like growth factor-1 co-administration therapy in short children with low insulin-like growth factor-I and growth hormone sufficiency: results from a randomized, multicenter, open-label, parallel-group, active treatment-controlled trial. *Horm Res Paediatr.* 2015;83(4):268-79.

This three year randomized, multi-center, open-labelled study of the efficacy and safety of combined growth hormone and IGF-1 therapy in growth hormone sufficient children with short stature and low IGF-I concentration demonstrated that the therapy was safe. Over the three years of the study the combination therapy accelerated linear growth and sustained improvements in height standard deviation score compared to growth hormone monotherapy. These results provide a basis for further study of combined growth hormone and IGF-1 therapy to improve adult height in growth hormone sufficient subjects with (idiopathic) short stature.

Lawson SA, Urbina EM, Gutmark-Little I, **Khoury PR**, Gao Z, **Backeljauw PF**. Vasculopathy in the young Turner syndrome population. *J Clin Endocrinol Metab.* 2014 Oct;99(10):E2039-45.

Adults with Turner syndrome are at increased risk for premature cardiovascular disease including hypertension, vasculopathy, and aortic dilation and dissection. This study demonstrates for the first time the presence of vasculopathy (increased arterial thickness and stiffness) in young individuals with Turner syndrome. The presence of vasculopathy in youth with Turner syndrome suggests that studies of the natural history of vasculopathy may provide avenues for intervention to prevent or limit premature cardiovascular disease in individuals with Turner syndrome.

Division Publications

1. Alman AC, Talton JW, Wadwa RP, Urbina EM, Dolan LM, Daniels SR, Hamman RF, D'Agostino RB, Marcovina SM, Mayer-Davis EJ, Dabelea DM. **Cardiovascular health in adolescents with type 1 diabetes: the SEARCH CVD study**. *Pediatr Diabetes*. 2014; 15:502-10.

2. Backeljauw P, Cohen P, Dattani M, Rosenfeld R. **Disorders of Growth Hormone/Insulin-Like Growth Factor Secretion and Action**. In: MA Sperling, ed. *Sperling Textbook of Pediatric Endocrinology*. Philadelphia, PA: Elsevier Saunders; 2014:292 -404.

3. Backeljauw PF, Miller BS, Dutailly P, Houchard A, Lawson E, Hale DE, Reiner B, Sperling MA. **Recombinant human growth hormone plus recombinant human insulin-like growth factor-1 coadministration therapy in short children with low insulin-like growth factor-1 and growth hormone sufficiency: results from a randomized, multicenter, open-label, parallel-group, active treatment-controlled trial**. *Horm Res Paediatr*. 2015; 83:268-79.

4. Brunner HI, Silva CA, Reiff A, Higgins GC, Imundo L, Williams CB, Wallace CA, Aikawa NE, Nelson S, Klein-Gitelman MS, Rose SR. **Randomized, double-blind, dose-escalation trial of triptorelin for ovary protection in childhood-onset systemic lupus erythematosus**. *Arthritis Rheumatol*. 2015; 67:1377-85.

5. Dauber A, Rosenfeld RG, Hirschhorn JN. **Genetic evaluation of short stature**. *J Clin Endocrinol Metab*. 2014; 99:3080-92.

6. de Bruin C, Mericq V, Andrew SF, van Duyvenvoorde HA, Verkaik NS, Losekoot M, Porollo A, Garcia H, Kuang Y, Hanson D, Clayton P, van Gent DC, Wit JM, Hwa V, Dauber A. **An XRCC4 splice mutation associated with severe short stature, gonadal failure, and early-onset metabolic syndrome**. *J Clin Endocrinol Metab*. 2015; 100:E789-98.

7. Elder DA, Hornung LN, Herbers PM, Prigeon R, Woo JG, D'Alessio DA. **Rapid deterioration of insulin secretion in obese adolescents preceding the onset of type 2 diabetes**. *J Pediatr*. 2015; 166:672-8.

8. Fu JF, Liang JF, Zhou XL, Prasad HC, Jin JH, Dong GP, Rose SR. **Impact of BMI on gonadorelin-stimulated LH peak in premenarcheal girls with idiopathic central precocious puberty**. *Obesity (Silver Spring)*. 2015; 23:637-43.

9. Gass D, Dewire M, Chow L, Rose SR, Lawson S, Stevenson C, Pai AL, Jones B, Sutton M, Lane A, Pruitt D, Fouladi M, Hummel TR. **Pediatric tectal plate gliomas: a review of clinical outcomes, endocrinopathies, and neuropsychological sequelae**. *J Neurooncol*. 2015; 122:169-77.

10. Giri N, Hollenberg T, Lodish M, Petryk A, Rose S, Rutter M, Kanakatti Shankar R, Stratakis C. **Endorince Disorders**. In: D Frohnmayer, LF JD, E Guinan, T Kennedy, K Larsen, eds. *Fanconi Anemia: Guidelines for Diagnosis and Management*. Eugene, OR: Fanconi Anemia Research Fund, Inc.; 2014:144-178.

11. Gordon SM, Li H, Zhu X, Shah AS, Lu LJ, Davidson WS. **A comparison of the mouse and human lipoproteome: suitability of the mouse model for studies of human lipoproteins**. *J Proteome Res*. 2015; 14:2686-95.

12. Gutmark-Little I, Shah KN. **Obesity and the metabolic syndrome in pediatric psoriasis**. *Clin Dermatol*. 2015; 33:305-15.

13. Howell JC, Joshi SA, Hornung L, Khoury J, Harris RE, Rose SR. **Growth hormone improves short stature in children with Diamond-Blackfan anemia**. *Pediatr Blood Cancer*. 2015; 62:402-8.

14. Kanakatti Shankar R, Inge TH, Gutmark-Little I, Backeljauw PF. **Oophorectomy versus salpingo-oophorectomy in Turner syndrome patients with Y-chromosome material: clinical experience and current practice patterns**

assessment. *J Pediatr Surg*. 2014; 49:1585-8.

15. Kerns SL, Guevara-Aguirre J, Andrew S, Geng J, Guevara C, Guevara-Aguirre M, Guo M, Oddoux C, Shen Y, Zurita A, Rosenfeld RG, Ostrer H, Hwa V, Dauber A. **A novel variant in CDKN1C is associated with intrauterine growth restriction, short stature, and early-adulthood-onset diabetes**. *J Clin Endocrinol Metab*. 2014; 99:E2117-22.

16. Kessler CA, Stanek JW, Stringer KF, Handwerger S. **ETS1 induces human trophoblast differentiation**. *Endocrinology*. 2015; 156:1851-9.

17. Law JR, Stafford JM, D'Agostino RB, Jr., Badaru A, Crume TL, Dabelea D, Dolan LM, Lawrence JM, Pettitt DJ, Mayer-Davis EJ. **Association of parental history of diabetes with cardiovascular disease risk factors in children with type 2 diabetes**. *J Diabetes Complications*. 2015; 29:534-9.

18. Lawson SA, Urbina EM, Gutmark-Little I, Khoury PR, Gao Z, Backeljauw PF. **Vasculopathy in the young Turner syndrome population**. *J Clin Endocrinol Metab*. 2014; 99:E2039-45.

19. Maahs DM, Daniels SR, de Ferranti SD, Dichek HL, Flynn J, Goldstein BI, Kelly AS, Nadeau KJ, Martyn-Nemeth P, Osganian SK, Quinn L, Shah AS, Urbina E, American Heart Association Atherosclerosis H, Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young CoCCCoC, Stroke Nursing CfHBPR, Council on L, Cardiometabolic H. **Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association**. *Circulation*. 2014; 130:1532-58.

20. Myer GD, Faigenbaum AD, Foss KB, Xu Y, Khoury J, Dolan LM, McCambridge TM, Hewett TE. **Injury initiates unfavourable weight gain and obesity markers in youth**. *Br J Sports Med*. 2014; 48:1477-81.

21. Nakamura T. **[Role of double-stranded RNA pathways in immune-metabolic regulation]**. *BIO Clinica: Chronic Inflamm Endocrinol Metab*. 2015; 4:104-108.

22. Nakamura T, Kunz RC, Zhang C, Kimura T, Yuan CL, Baccaro B, Namiki Y, Gygi SP, Hotamisligil GS. **A critical role for PKR complexes with TRBP in Immunometabolic regulation and eIF2alpha phosphorylation in obesity**. *Cell Rep*. 2015; 11:295-307.

23. Nilsson O, Guo MH, Dunbar N, Popovic J, Flynn D, Jacobsen C, Lui JC, Hirschhorn JN, Baron J, Dauber A. **Short stature, accelerated bone maturation, and early growth cessation due to heterozygous aggrecan mutations**. *J Clin Endocrinol Metab*. 2014; 99:E1510-8.

24. Petryk A, Kanakatti Shankar R, Giri N, Hollenberg AN, Rutter MM, Nathan B, Lodish M, Alter BP, Stratakis CA, Rose SR. **Endocrine disorders in Fanconi anemia: recommendations for screening and treatment**. *J Clin Endocrinol Metab*. 2015; 100:803-11.

25. Shah AS, Black S, Wadwa RP, Schmiege SJ, Fino NF, Talton JW, D'Agostino R, Jr., Hamman RF, Urbina EM, Dolan LM, Daniels SR, Marcovina SM, Dabelea D. **Insulin sensitivity and arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study**. *J Diabetes Complications*. 2015; 29:512-6.

26. Shah AS, Dabelea D, Talton JW, Urbina EM, D. Agostino RB J, Wadwa RP, Marcovina S, Hamman RF, Daniels SR, Dolan LM. **Smoking and arterial stiffness in youth with type 1 diabetes: the SEARCH Cardiovascular Disease Study**. *J Pediatr*. 2014; 165:110-6.

27. Shah AS, Dolan LM, Dabelea D, Stafford JM, D'Agostino RB, Jr., Mayer-Davis EJ, Marcovina S, Imperatore G, Wadwa RP, Daniels SR, Reynolds K, Hamman RF, Bowlby DA, Maahs DM, Study SfDiY. **Change in adiposity minimally affects the lipid profile in youth with recent onset type 1 diabetes**. *Pediatr Diabetes*. 2015; 16:280-6.

28. Sheridan R, Belludi C, Khoury J, Stanek J, Handwerger S. **FOXO1 expression in villous trophoblast of preeclampsia and fetal growth restriction placentas**. *Histol Histopathol*. 2015; 30:213-22.

29. Swartz JM, Akinci A, Andrew SF, Sigirci A, Hirschhorn JN, Rosenfeld RG, Dauber A, Hwa V. **A novel ERCC6 splicing variant associated with a mild Cockayne syndrome phenotype**. *Horm Res Paediatr*. 2014; 82:344-52.

30. Tomer Y, Dolan LM, Kahaly G, Divers J, D'Agostino RB, Jr., Imperatore G, Dabelea D, Marcovina S, Black MH, Pihoker C, Hasham A, Hammerstad SS, Greenberg DA, Lotay V, Zhang W, Monti MC, Matheis N, Study SfDiY. **Genome wide identification of new genes and pathways in patients with both autoimmune thyroiditis and type 1 diabetes**. *J Autoimmun*. 2015; 60:32-9.

31. Totaro S, Khoury PR, Kimball TR, Dolan LM, Urbina EM. **Arterial stiffness is increased in young normotensive subjects with high central blood pressure**. *J Am Soc Hypertens*. 2015; 9:285-92.

32. Urbina EM, Khoury PR, McCoy CE, Daniels SR, Dolan LM, Kimball TR. **Comparison of mercury sphygmomanometry blood pressure readings with oscillometric and central blood pressure in predicting target organ damage in youth**. *Blood Press Monit*. 2015; 20:150-6.

33. Valenzuela JM, Smith LB, Stafford JM, D'Agostino RB, Jr., Lawrence JM, Yi-Frazier JP, Seid M, Dolan LM. **Shared decision-making among caregivers and health care providers of youth with type 1 diabetes**. *J Clin Psychol Med Settings*. 2014; 21:234-43.

34. Wang SR, Jacobsen CM, Carmichael H, Edmund AB, Robinson JW, Olney RC, Miller TC, Moon JE, Mericq V, Potter LR, Warman ML, Hirschhorn JN, Dauber A. **Heterozygous mutations in natriuretic peptide receptor-B (NPR2) gene as a cause of short stature**. *Hum Mutat*. 2015; 36:474-81.

35. Watson CL, Mahe MM, Munera J, Howell JC, Sundaram N, Poling HM, Schweitzer JI, Vallance JE, Mayhew CN, Sun Y, Grabowski G, Finkbeiner SR, Spence JR, Shroyer NF, Wells JM, Helmrath MA. **An in vivo model of human small intestine using pluripotent stem cells**. *Nat Med*. 2014; 20:1310-4.

36. Xanthakos SA, Crimmins NA, Chernausek SD. **Abnormalities in the growth hormone axis and risk of nonalcoholic steatohepatitis: active player or innocent bystander?**. *J Pediatr*. 2014; 165:12-4.

37. Youssef OA, Safran SA, Nakamura T, Nix DA, Hotamisligil GS, Bass BL. **Potential role for snoRNAs in PKR activation during metabolic stress**. *Proc Natl Acad Sci U S A*. 2015; 112:5023-8.

Faculty, Staff, and Trainees

Faculty Members

Lawrence M Dolan, MD, Professor

Leadership Division Director, Robert and Mary Shoemaker Professor of Pediatrics

Research Interests Diabetes mellitus; non-insulin dependent diabetes; sexual development disorders; growth disorders; disorders of the thyroid; goiters; hypoglycemia

Philippe Backeljauw, MD, Professor

Leadership Director, Cincinnati Turner Syndrome Center

Research Interests Growth disorders; disorders of bone and calcium metabolism; Turner syndrome.

Sarah Corathers, MD, Assistant Professor

Research Interests Transition to adult care; type 1 diabetes in adolescents and adults; quality improvement.

Nancy Crimmins, MD, MS, Associate Professor

Leadership Residency Elective Coordinator

Research Interests Diabetes; obesity.

Andrew Dauber, MD, MMSc, Assistant Professor

Leadership Program Director and Director of Translational Research, Cincinnati Center for Growth Disorders

Research Interests Genetic basis of growth disorders. His research group uses cutting edge genomic techniques to discover novel genetic etiologies of short stature as well as precocious puberty.

Deborah Elder, MD, Assistant Professor

Research Interests Diabetes; growth disorders; precocious puberty; calcium disorders.

Iris Gutmark-Little, MD, Assistant Professor

Research Interests Airway and great vessel disorders in Turner syndrome.

Stuart Handwerger, MD, Professor

Leadership Professor of Cancer and Cell Biology

Research Interests Growth and thyroid disorders; perinatal endocrinology.

Jonathan Howell, MD, PhD, Assistant Professor

Research Interests Using human stem cell derived intestinal tissue to understand human gut hormone development and function in order to facilitate new therapeutic options for diabetes.

Vivian Hwa, PhD, Associate Professor

Leadership Director of Basic Research, The Cincinnati Center for Growth Disorders

Research Interests Understanding the mechanism(s) of human growth failure resulting from mutations along, and beyond, the GH-IGF-I axis. Genes currently under investigation include STAT5B, GHR, IGF1R, CDKN1C, PAPPA2.

Sarah Lawson, MD, Assistant Professor

Research Interests Turner syndrome; septo-optic dysplasia; endocrine abnormalities related to oncology and its treatments.

Takahisa Nakamura, PhD, Assistant Professor

Research Interests Focus on endogenous dsRNA pathways to address questions concerning why and how inflammatory responses are initiated and thus involved in the pathogenesis of obesity.

Susan Rose, MD, Professor

Research Interests Hypothalamic pituitary function; thyroid disorders; disorders of growth or puberty; endocrine function in cancer survivors; endocrine function after head injury.

Meilan Rutter, MD, Assistant Professor

Research Interests Calcium disorders; endocrine function in childhood cancer survivors; endocrine function in muscular dystrophy.

Amy Shah, MD, MS, Assistant Professor

Research Interests Type 2 diabetes; pre-diabetes; insulin resistance; obesity; lipid disorders.

Peggy Stenger, DO, Assistant Professor

Research Interests Disorders of bone and calcium metabolism; growth disorders; disorders of sexual development; pubertal disorders; disorders of the thyroid; goiter.

Nana-Hawa Yayah Jones, MD, Assistant Professor

Research Interests Adherence/compliancein type 1 diabetes.

Joint Appointment Faculty Members

Jonathan Katz, PhD, Professor (Immunobiology)

Research Interests The immunology of type 1 diabetes mellitus.

Jane Khoury, PhD, Associate Professor (Biostatistics & Epidemiology)
Research Interests Diabetes in pregnancy and effect on offspring; stroke.

James Wells, PhD, Professor (Developmental Biology)
Research Interests Vertebrate gut development, stem cells, mammal.

Trainees

- **Cassandra Brady, MD**, PL-6, Vanderbilt University
- **Christiaan de Bruin, MD, PhD**, PL-5, University Medical Center, St. Radboud, Nijmegen
- **Marjorie Golekoh, MD**, PL-6, Cincinnati Children's Hospital Medical Center
- **Vincent Horne, MD**, PL-4, University of Missouri - Columbia
- **Chijioke Ikomi, MD**, PL-4, Metropolitan Hospital Centre, New York
- **Pranati Jha, MBBS**, PL-6, Albany Medical Center
- **Jose Jimenez-Vega, MD**, PL-5, University of Minnesota Medical School
- **Christel Keefe, MD**, PL-6, Cincinnati Children's Hospital Medical Center
- **Arti Shah, MBBS**, PL-6, University at Buffalo Program
- **Nicole Sheanon, MD**, PL-8, University of Massachusetts
- **Allison Smego, MD**, PL-5, Vanderbilt University
- **Halley Wasserman, MD**, PL-6, Cincinnati Children's Hospital Medical Center

Grants, Contracts, and Industry Agreements

Endocrinology

Grant and Contract Awards		Annual Direct

Dauber, A

Rare Genetic Variants as Novel Causes of Idopathic or Syndromic Short Stature

National Institutes of Health

K23 HD073351	2/15/2015-5/31/2017	$252,533

Dolan, L

SEARCH for Diabetes in Youth, Phase 3: Registry Study - Ohio Center

Ctr for Disease Control and Prevention

U18 DP002709	9/30/2010-9/29/2015	$421,894

Air Pollution, Subclinical CVD and Inflammatory Markers in the SEARCH Cohort

National Institutes of Health(University of Maryland)

R01 ES019168	9/27/2011-6/30/2015	$15,516

Handwerger, S

Transcriptional Control of Human Placental Differentiation

National Institutes of Health

R01 HD065339	2/1/2011-1/31/2016	$210,948

Hwa, V

Roles of STAT5b in IGF-1 Production and Human Growth

National Institutes of Health

R01 HD078592	9/1/2014-6/30/2019	$207,500

Nakamura,T

Role of TRBP and its Phosphorylation in Obesity-induced Insulin Resistance and Type 2 Diabetes

Diabetes Action Research & Education Fdn

	1/15/2015-1/14/2016	$13,636

Analysis of Pathogenic Double-Stranded RNA in Chronic Inflammatory Disease

Japan Science and Technology Corporation

	2/11/2013-3/31/2016	$119,398

Shah, A

Understanding the Role of HDL Subspecies in Adolescents with Type 2 Diabetes

National Institutes of Health

K23 HL118132	4/15/2014-3/31/2019	$145,360

Sheanon, N

Training Program - Molecular Epidemiology in Children's Environmental Health (MECEH)

National Institutes of Health(University of Cincinnati)

T32 ES010957	7/30/2014-7/29/2015	$50,963

Wasserman, H

Training Program - Molecular Epidemiology in Children's Environmental Health (MECEH)

National Institutes of Health(University of Cincinnati)

T32 ES010957	7/1/2014-6/30/2015	$51,096
	Current Year Direct	**$1,488,844**

Industry Contracts

Backeljauw, P

Eli Lilly and Company	$2,426
Novo Nordisk Pharmaceuticals	$10,600
Tercica, Inc	$693
Versartis, Inc	$9,625

Dolan, L

Jaeb Center for Health Res Fdn. Inc.	$21,503

Elder, D

Novo Nordisk Pharmaceuticals	$16,958

Rose, S

Debiopharm SA	$6,627
Prolor Biotech	$13,668

Crimmins, N

TrialNet	$31,716
Current Year Direct Receipts	**$113,816**
Total	**$1,602,660**

Whole Exome Sequencing Uncovers Defective Gene Linked to Severe Growth and Metabolic Disorder

Andrew Dauber, MD, MSc

RESEARCH AND TRAINING DETAILS

Faculty	17
Joint Appointment Faculty	3
Support Personnel	27
Direct Annual Grant Support	$1.4M
Direct Annual Industry Support	$113,816
Peer Reviewed Publications	37

de Bruin C, Mericq V, Andrew SF, van Duyvenvoorde HA, Verkaik NS, Losekoot M, Porollo A, Garcia H, Kuang Y, Hanson D, Clayton P, van Gent DC, Wit JM, Hwa V, Dauber A. An XRCC4 splice mutation associated with severe short stature, gonadal failure, and early-onset metabolic syndrome. *J Clin Endocrinol Metab.* 2015;100(5):E789-798.

PUBLISHED MARCH 5, 2015
The Journal of Clinical Endocrinology & Metabolism

An emerging technology called whole exome sequencing — which enables researchers to sequence all 20,000 of the body's genes at once rather than one gene at a time — has helped identify a defective gene that causes a rare condition marked by a spectrum of growth and metabolic disorders in children.

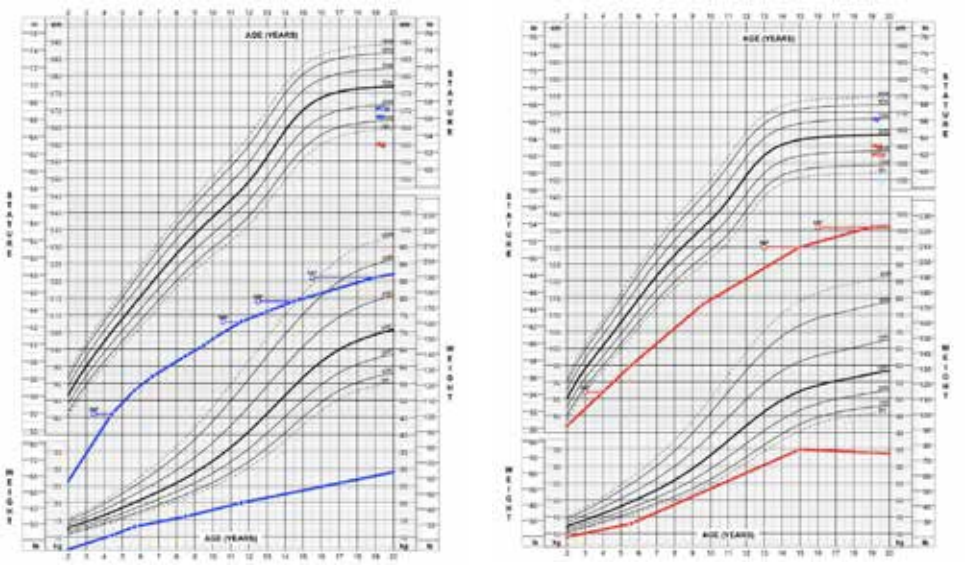
The defective XRCC4 gene, identified by Andrew Dauber, MD, MMSc, co-leader of the newly formed Cincinnati Center for Growth Disorders, includes a splice mutation that deletes 23 amino acids from the gene, interfering with the body's ability to repair DNA damage.

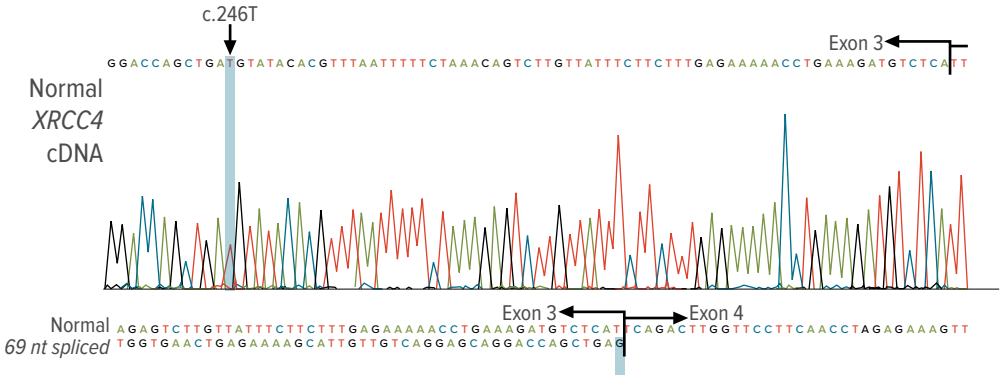
XRCC4 was discovered by examining DNA from a Chilean brother and sister, both of whom were diagnosed with severe short statue, gonadal failure and early-onset metabolic syndromes that resulted in a gastrointestinal tumor in the sister, diabetes and other multi-system complications. The 39-year-old brother is still alive; the sister died at 36. Findings based on their tissues were published online March 5, 2015, in *The Journal of Clinical Endocrinology & Metabolism*.

"The body is constantly repairing damage that occurs to DNA, and this gene is part of the DNA damage repair process," says Dauber. "We were able to show in skin cells from one of the patients that the cells were not able to execute the DNA damage repair process correctly."

The finding creates deeper understanding of a spectrum of complications associated with the defective gene, and creates direct links among patient genome sequencing, translational biology in the lab, patient diagnosis and genetic counseling, he says.

"Our patients are among the oldest in the world to be identified, and because of this new understanding, the hope is that we'll be better able to counsel them and their families about a variety of other issues that they might face, including predisposition to tumors, insulin resistance and other complications."





Growth charts (top) of two siblings from a rural family in Chile exhibit a novel syndrome consisting of severe short stature, microcephaly, hypergonadotropic hypogonadism, early-onset metabolic syndrome, and possible increased tumor susceptibility. Combined microarray analysis and whole exome sequencing detected an underlying XRCC4 mutation, a gene involved in the DNA damage repair process. The next figure shows Sanger sequencing of XRCC4 cDNA with the nucleotide c.246T highlighted demonstrating that the mutation results in a novel splice site causing deletion of 69 nucleotides.

"The body is constantly repairing damage that occurs to DNA, and this gene is part of the DNA damage repair process."