BIOGRAPHICAL SKETCH

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NAME: Reue, Karen

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POSITION TITLE: Professor, Human Genetics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Arizona, Tucson	B.S.	05/1981	Microbiology
University of California, Los Angeles	Ph.D.	09/1985	Microbiology
Rockefeller University, New York City	Postdoctoral	06/1988	Molecular Genetics

A. Personal Statement

Our primary research goal is to identify genes and pathways that are required for metabolic homeostasis, and determine how these become dysregulated in obesity, lipodystrophy, diabetes and atherosclerosis. By positional cloning of naturally occurring mutations, we identified the lipin gene family (*Lpin1*, *Lpin2*, *Lpin3)*, which has roles in lipid synthesis and energy metabolism, and the *Diet1* gene, a determinant of plasma cholesterol levels and atherosclerosis. We are also investigating the mechanisms underlying sex differences in obesity and cardiovascular disease using mouse models. We have identified X chromosome copy number as a determinant of sex differences in obesity and lipid metabolism, and have identified specific X chromosome genes that escape X-inactivation as key drivers. Importantly, these genes regulate chromatin architecture and gene expression throughout the genome. Our ongoing studies investigate the role of sex chromosomes and gonadal sex in the regulation of white and brown adipose tissue biology, postprandial lipid metabolism, and response to statin drugs.

Current grant funding relevant to sex differences and metabolism:

U54 DK120342 (Reue, PI) 10/01/18–09/30/23
NIDDK/ORWH
Specialized Centers of Research Excellence (SCORE) on Sex Differences: "*Sex Differences in the Metabolic Syndrome*"
Goal: To elucidate risk factors and treatments for components of the Metabolic Syndrome such as obesity, insulin resistance, dyslipidemia, and mitochondrial dysfunction in mouse models and human tissues.
Role: U54 Program Director; Leader, Project 1: "Sex chromosome effects on metabolic syndrome risk and treatment" investigates the role of X chromosome gene dosage on obesity and insulin resistance; Leader, Administrative Core: This core oversees operation of the entire SCORE program, including scientific projects, scientific cores, and career enhancement core.

R01 DK128898 (Reue, PI) 07/01/22–06/30/27
NIDDK Sex Differences in Postprandial Lipid Metabolism
Goal: To identify the genetic and hormonal mechanisms that account for differential processing of dietary lipids in male and female mice. Role: PI

Leducq Foundation Transatlantic Network Award (Civelek, den Ruijter, MPI)
Leducq Foundation for Cardiovascular Research 01/01/23–12/30/27
Title: AtheroGEN
Goal: To elucidate mechanisms that explain sex differences in atherosclerosis using human and mouse pathology, genomic, and transcriptomic analyses. Role: investigator

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021–pres.	Associate Director, UCLA/Caltech Medical Scientist (MD-PhD)Training Program
2016–pres.	Vice Chair, Department of Human Genetics, UCLA
2014–2016	Interim Chair, Department of Human Genetics, UCLA
2006–2011	Associate Editor, *Diabetes*
2004–pres.	Editorial Board, *Journal of Lipid Research*
2002–pres.	Professor, Departments of Human Genetics and Medicine, UCLA
1997–2002	Associate Professor, Department of Medicine, UCLA
1997	Visiting Faculty, Department of Cell and Molecular Biology, Lund University, Sweden
1992–1997	Assistant Professor, Department of Medicine, UCLA
1988–1992	Research Cardiologist, Department of Medicine, UCLA

Honors and Professional Activities

2019	Rubenstein Lecture, Canadian Vascular & Lipid Summit
2019	Greenblatt Lecture in Physiology, Medical College of Georgia
2019	Keynote address, Wayne Lipid Symposium, Detroit, Michigan
2018–2022	NHLBI Institutional Training Mechanism Study Section
2017	Russell Ross Memorial Lecture, American Heart Association
2015	Avanti Award in Lipids, American Society of Biochemistry and Molecular Biology
2015	Featured in “Women in Metabolism” series for *Cell Metabolism* 10th Anniversary
2015	Brasza Lecture in Diabetes, Wayne State University, Detroit, Michigan
2015	Goldberg Lecture in Signal Transduction and Metabolism, University of Minnesota
2014	*Biochimica Biophysica Acta* Award Lecture, Federation of Am. Societies for Exptl. Biol.
2013	Program Co-chair, Cold Spring Harbor Asia Conference on Metabolism and Obesity
2011–2016	NHLBI Program Project Grant Parent Committee study section
2010–2015	American Heart Association Page Award Committee (Chair 2012–2014)
2010	Program Chair, FASEB Conference on Lipid Droplets
2009	J*ournal of Lipid Research* 50th Anniversary Lectureship
2008–2014	Deuel Conference on Lipids Board (Program Chair 2008)
2006–2011	Kern Lipid Conference Board (Program Chair 2011)
2004–2010	External Advisor, NIH-NIDDK Mouse Metabolic Phenotypic Centers
2000–2004	NIH NHLBI Metabolism Study Section member
1992–1997	Established Investigator of the American Heart Association
1986–1988	Fellow of the American Heart Association, New York Affiliate
1983–1985	Public Health Service Pre-doctoral Fellowship
1981	B.S. *summa cum laude*; Phi Beta Kappa; Phi Kappa Phi

C. Contributions to Science

1. Discovery and characterization of the lipin gene family. After graduate training in mouse genetics and postdoctoral training in molecular genetics, I set out to identify novel genes that participate in lipid homeostasis in conditions such as obesity and diabetes. My approach was to select naturally occurring mutant mouse strains with impaired lipid metabolism and identify the affected gene by positional cloning. Using a mutant mouse strain with lipodystrophy and insulin resistance, we positionally cloned a novel gene, *Lpin1*, and identified two family members (*Lpin2* and *Lpin3*). (*Nature Genetics* 2001). We went on to demonstrate that all three mammalian lipins function as phosphatidate phosphatase enzymes. We showed that modulating lipin 1 levels can confer two extremes of adiposity—lipodystrophy or obesity—and affects insulin sensitivity in mice and humans. Through studies of lipin-deficient mouse models, we uncovered roles for lipin family members in lipid homeostasis in the aging brain, in intestinal lipoprotein synthesis, in autophagy, and in the maintenance of mitochondrial function in skeletal muscle. Our work on lipin 1 in autophagy and muscle homeostasis helped explain the severe, life-threatening rhabdomyolysis in children with lipin 1 deficiency. Our recent studies have helped establish lipin protein structure and uncovered a novel role for lipin 1 in nutrient-responsive regulation of mRNA splicing.

a. Phan J, **Reue K**. (2005) Lipin, a lipodystrophy and obesity gene. *Cell Metab* 1:73–83. [Featured in *Cell Metabolism* and *Nature Reviews Genetics* commentaries]

b. Zhang P, Verity MA, **Reue K** (2014) Lipin-1 regulates autophagy clearance and intersects with statin drug effects in skeletal muscle. *Cell Metab* 20:267–279. [PMC4170588]

c. Zhang P, Csaki LS, Ronquillo E, Baufeld LJ, Lin JY, Gutierrez A, Dwyer JR, Brindley DN, Fong LG, Tontonoz P, Young SG, and **Reue K**. (2019) Lipin 2/3 phosphatidic acid phosphatases maintain phospholipid homeostasis and regulate chylomicron synthesis. *J Clin Invest* 129:281–295. [PMC6307960]

d. Wang H, Chan TW, Vashisht AA, Drew BG, Calkin AC, Harris TE, Wohlschlegel JA, Xiao X, **Reue K**. (2021) Lipin 1 modulates mRNA splicing during fasting adaptation in liver. *JCI Insight* 6:e150114. [PMC8492312]

2. Identification of Diet1 and its role in bile acid homeostasis. Plasma cholesterol levels are a well-established risk factor for cardiovascular disease. Using a mouse strain that is resistant to hypercholesterolemia and atherosclerosis, we identified the *Diet1* gene via positional cloning. We determined that *Diet1*-deficient mice are protected from hypercholesterolemia because of continual conversion of excess cholesterol to bile acids. *Diet1* is expressed exclusively in intestinal enterocytes and kidney proximal tubule cells. One role of *Diet1* in enterocytes is to regulate fibroblast growth factor 15 (FGF15) secretion into the enterohepatic circulation. FGF15 normally signals in liver to repress bile acid synthesis, and *Diet1*-deficient mice have reduced FGF15 secretion and higher rates of bile acid synthesis. The significance of *Diet1* in physiology and its potential as a therapeutic target have been recognized in commentaries on our work in *Cell Metabolism* and in F1000 Prime (by two independent Faculty of 1000 members). We subsequently identified genetic polymorphisms in human *DIET1* that are associated with altered bile acid levels.

a. Phan J, Pesaran T, Davis RC, **Reue K** (2002) The *Diet1* locus confers protection against hypercholesterolemia through enhanced bile acid metabolism. *J Biol Chem* 277:469–464.

b. Vergnes L, Phan J, Strauss M, Tafuri S, **Reue K** (2003) Cholesterol and cholate components of an atherogenic diet induce distinct stages of hepatic inflammatory gene expression. *J Biol Chem* 278:42774–42784.

c. Vergnes L, Lee JM, Chin RG, Auwerx J, **Reue K** (2013) Diet1 functions in the FGF15/19 enterohepatic signaling axis to modulate bile acid and lipid levels. *Cell Metab* 17:916–928. [PMC3956443] [Featured in *Cell Metabolism* commentary and Faculty of 1000]

d. Lee JM, Ong JR, Vergnes L, de Aguiar Vallim TQ, Nolan J, Cantor RM, Walters JRF, **Reue K.** (2018) Diet1, bile acid diarrhea, and FGF15/19: mouse model and human genetic variants. *J Lipid Res* 59:429–438. [PMC5832924]

3. Sex chromosomes and obesity. Biological sex profoundly affects lipid metabolism and storage. Our research seeks to understand sex differences by breaking the sex variable into its component parts—hormones and sex chromosomes—so we can assess their respective contributions to sex differences in metabolism. Most studies of sex differences in obesity focus on effects of estrogens and androgens. By contrast, we varied the sex chromosomes, keeping the hormones constant, enabling us to discern sex chromosome effects from hormonal effects. We showed that a mouse with two X chromosomes stores much more fat than a mouse with one X chromosome, when other factors are kept equal. These findings are rigorous; the X chromosome dosage effect occurs in multiple mouse models with different bases for altered sex chromosome type and number. The effect of X chromosome number on obesity is as large as the effect of sex hormones under specific conditions relevant to humans, particularly consumption of a high-fat diet. Furthermore, we identified X-chromosome genes whose expression levels differ in males and females and contribute to the sex differences in fat storage. Our studies have potential therapeutic applications in metabolic diseases, as the findings help us both to understand the fundamental genetic differences between males and females and to explain the magnitude of sex differences.

a. Chen X, McClusky R, Chen J, Beaven SW, Tontonoz P, Arnold AP, **Reue K** (2012) The number of X chromosomes causes sex differences in adiposity in mice. *PLoS Genet* 8:e1002709. [PMC3349739]

b. Link JC, Chen X, Prien C, Borja MS, Hammerson B, Oda MN, Arnold AP, **Reue K** (2015) The presence of XX versus XY sex chromosomes is associated with increased HDL cholesterol levels in the mouse. *Arterioscler Thromb Vasc Biol* 35:1778–1786 [PMC4668127]

c. Link JC, Wiese CB, Chen X, Avetisyan R, Ronquillo E, Ma F, Guo X, Yao J, Allison M, Chen Y-DI Rotter JI, El-Sayed Moustafa JS, Small KS, Iwase S, Pellegrini M, Vergnes L, Arnold AP, **Reue K**. (2020) X chromosome dosage of histone demethylase KDM5C determines sex differences in adiposity. *J Clin Invest* 130:5688–5702. [PMC7598065]

d. Salisbury DA, Casero D, Zhang Z, Wang D, Kim J, Wu X, Vergnes L, Mirza AH, Leon-Mimilla P, Williams KJ, Huertas-Vazquez A, Jaffrey SR, **Reue K**, Chen J, Sallam T. (2021) Transcriptional regulation of N(6)-methyladenosine orchestrates sex-dimorphic metabolic traits. *Nat Metab* 3:940–953. [PMC8422857]

4. Cellular energetics, disease, and aging. A major challenge in biology is to understand how mitochondria influence aging and age-related diseases. We became interested in mitochondrial function during our studies of lipin 1 in muscle (described under point 1 above). In collaboration with many investigators, we applied this

expertise to analyze energy metabolism in other diseases and in aging. Our studies have deepened our understanding of how mitochondrial dysfunction influences aging, the immune response, insulin resistance, and neurological degeneration.

a. Rajbhandari P, Thomas BJ, Feng AC, Hong C, Wang J, Vergnes L, Sallam T, Wang B, Sandhu J, Seldin MM, Lusis JA, Fong LG, Lee R, Young SG, **Reue K**, Smale ST, Tontonoz P. (2018) IL10 signaling remodels adipose chromatin architecture to limit thermogenesis and energy expenditure. *Cell* 172:218–233. [PMC5766418]

b. Vergnes L, Lin JY, Davies GR, Church CD, **Reue K**. (2020) Induction of UCP1 and thermogenesis by a small molecule via AKAP1/PKA modulation. *J Biol Chem* 295:15054–15069. [PMC7606676]

c. Rahbani JF, Roesler A, Hussain MF, Samborska B, Dykstra CB, Tsai L, Jedrychowski MP, Vergnes L, **Reue K,** Spiegelman BM, Kazak L. (2021) Creatine kinase B controls futile creatine cycling in thermogenic fat. *Nature* 590:480–485. [PMC8647628]

d. Qian K, Tol MJ, Wu J, Uchiyama LF, Xiao X, Cui L, Bedard AH, Weston TA, Rajendren PS, Vergnes L, Shimanaka Y, Yin Y, Jami-Alahmade Y, Cohn W, Bajar BT, Lin CH, Jin B, DeNardo LA, Black DL, Whitelegge JP, Wohlschlegel JA, **Reue K**, Shivkumar K, Chen FJ, Young SG, Li P, Tontonoz P. (2023) CLSTN3β enforces adipocyte multilocularity to facilitate lipid utilization. *Nature* 613:160–168.

Complete List of Published Work in MyBibliography (total > 200):

http://www.ncbi.nlm.nih.gov/sites/myncbi/1BQ8oy5_sb0A-/bibliography/47980982/public/?sort=date&direction=descending