

Initial genome-wide testing of common variants for association with CF-related diabetes

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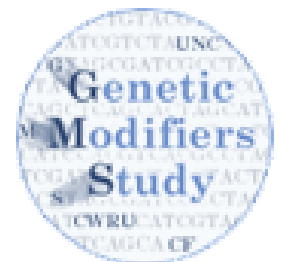


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MEDICINE



CF Twin and Sib Study

"Investigating the factors that modulate the severity of Cystic Fibrosis by studying affected twins and sibling pairs..."



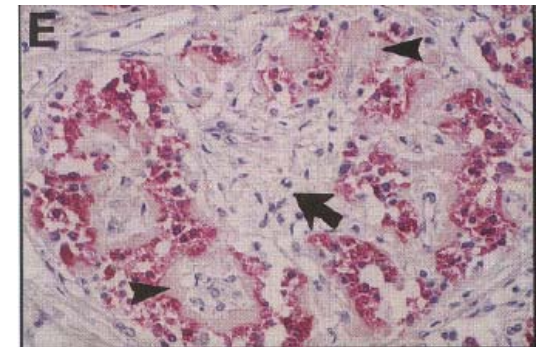
Scott M. Blackman and all co-authors have no relevant financial disclosures.

Diabetes in Cystic Fibrosis

- ... develops over time in PI CF patients:
 - 25% age 10-19, 40% age >30
 - Females at greater risk in most studies
- ... worsens lung function and nutritional status, and insulin treatment improves it.
- ... is caused mainly by genes other than CFTR*
- ... is a bit like type 1 diabetes:
 - not much insulin resistance; patients are thin.
- ... is a bit like type 2 diabetes:
 - A slow decline in insulin production over years.
 - Family history of T2DM is a risk factor for CFRD.**
 - TCF7L2 is a modifier gene for CFRD and a susceptibility gene for T2DM.**



CF lung disease

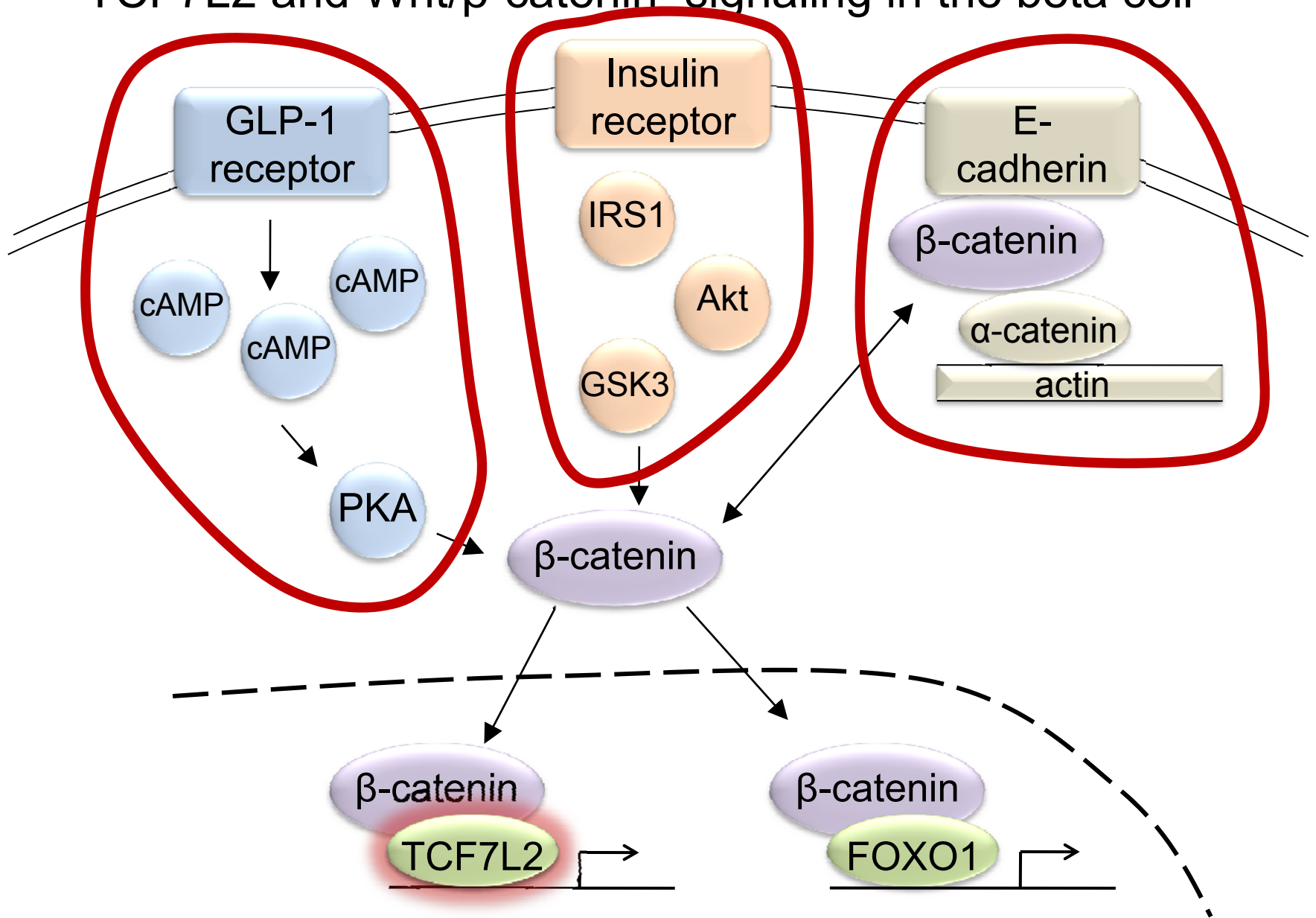


CF diabetic pancreatic islet

*Blackman et al., 2009 J.Clin.Endocrinol.Metab.

**Blackman et al., 2009 Diabetologia 52:1858

TCF7L2 and Wnt/ β -catenin signaling in the beta cell



Primary Study sample: CF Twin and Sibling Study

- 113 CF centers (mostly U.S.); recruitment ongoing

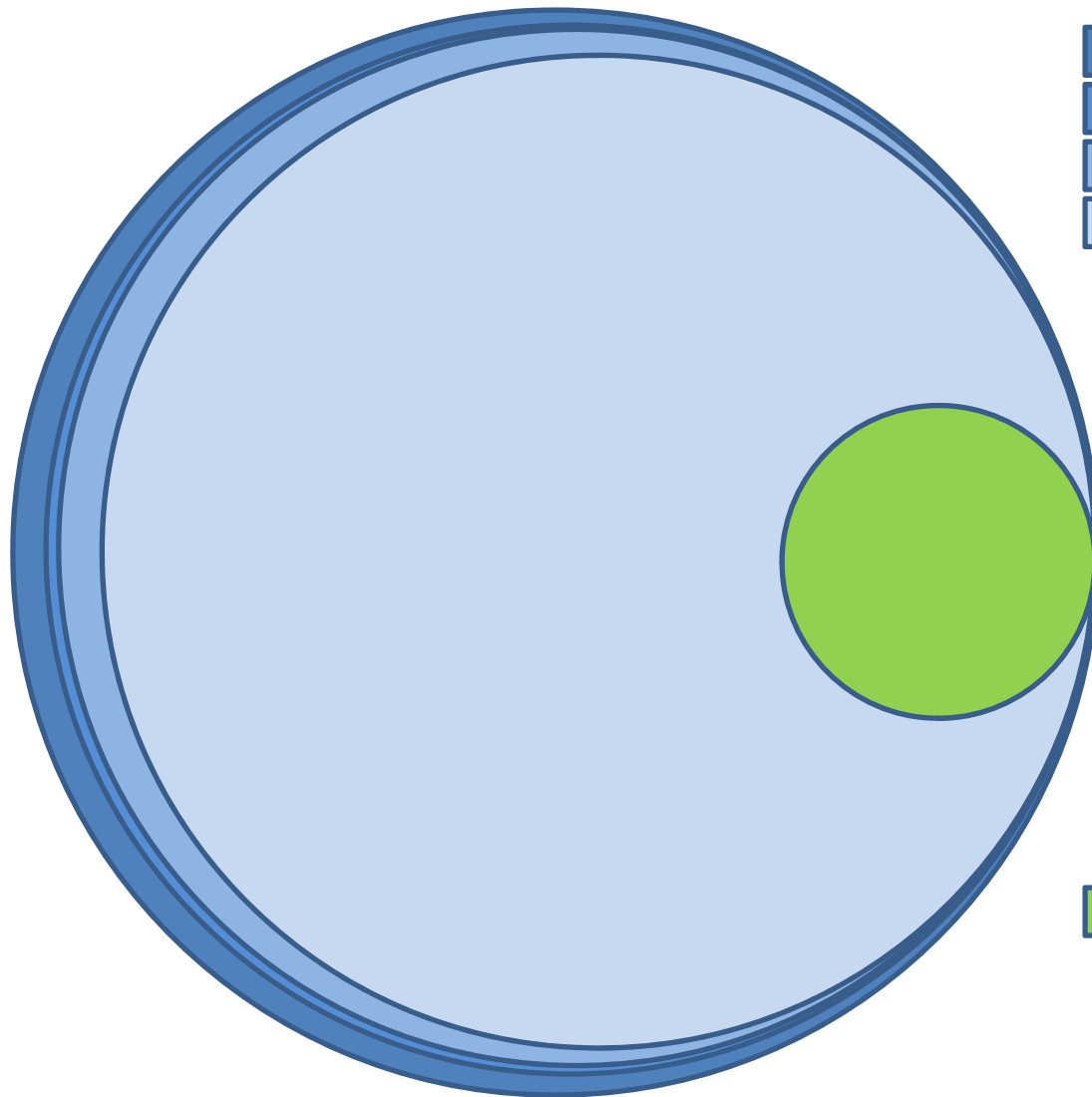
■ 1360 patients with CF



CFRD

- 580 families up to 5 per family
- DNA, family history, longitudinal clinical information collected
- Patients identified with CFRD and normal glucose status:
 - Clinician diagnosed CFRD, >1 yr insulin or oral medication use
 - Confirmed by test results (OGTT, A1c, glucose data) in 45%
 - Excluded
 - Inadequate screening
 - Pancreatic sufficient CF
 - Type 1 DM
 - High glucose only during exacerbation, normal A1c, no treatment
 - 137 of 1220 phenotyped have CFRD (11%)

Selection of single nucleotide polymorphisms (SNPs) for analysis



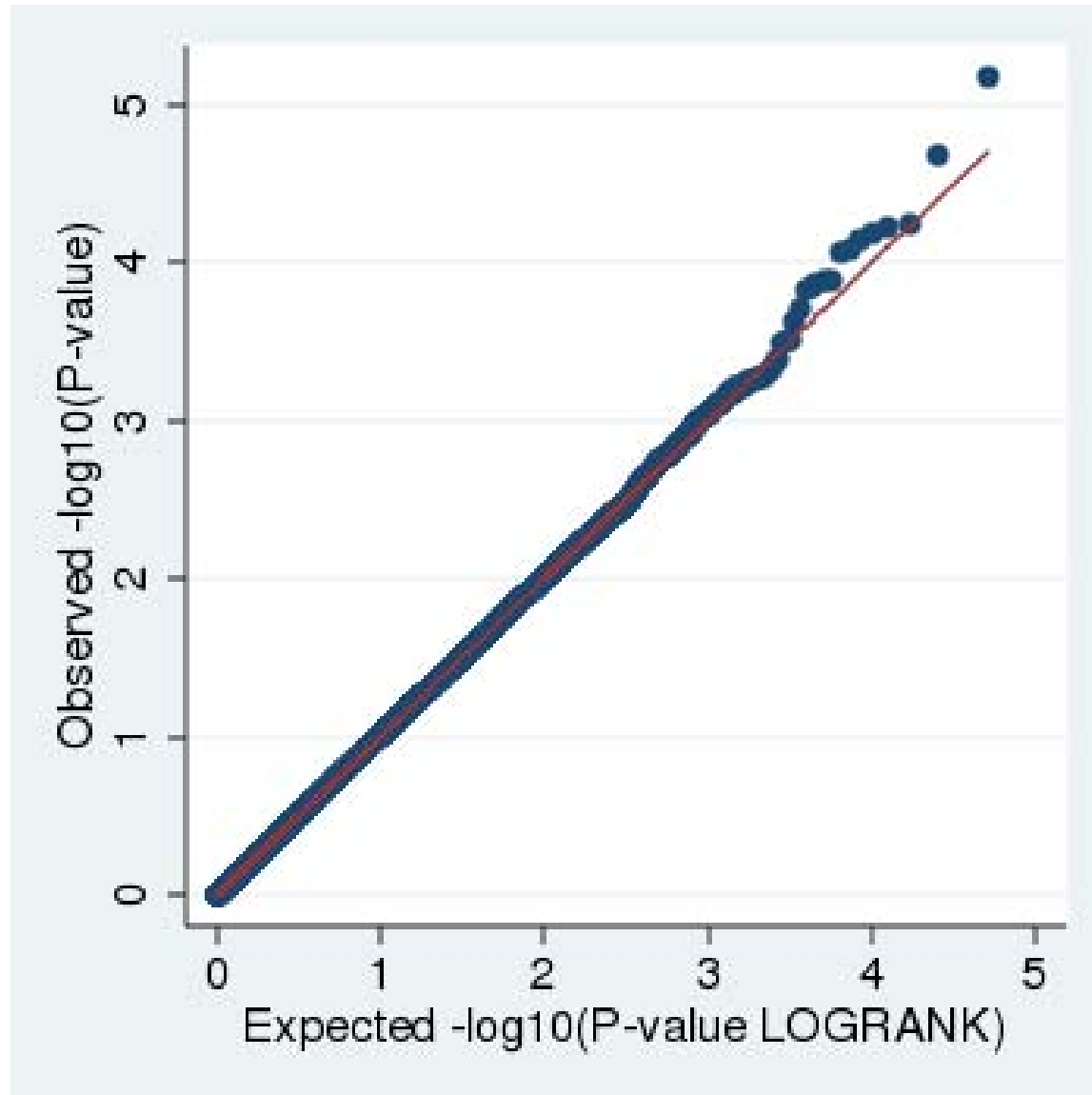
- 610,000 on chip
- 570,725 (96.5%) met QC
- 556,445 on chromosomes 1-22
- 511,443 minor allele frequency >5%

Plan to analyze with family-based association test using log rank statistic implemented in PBAT.

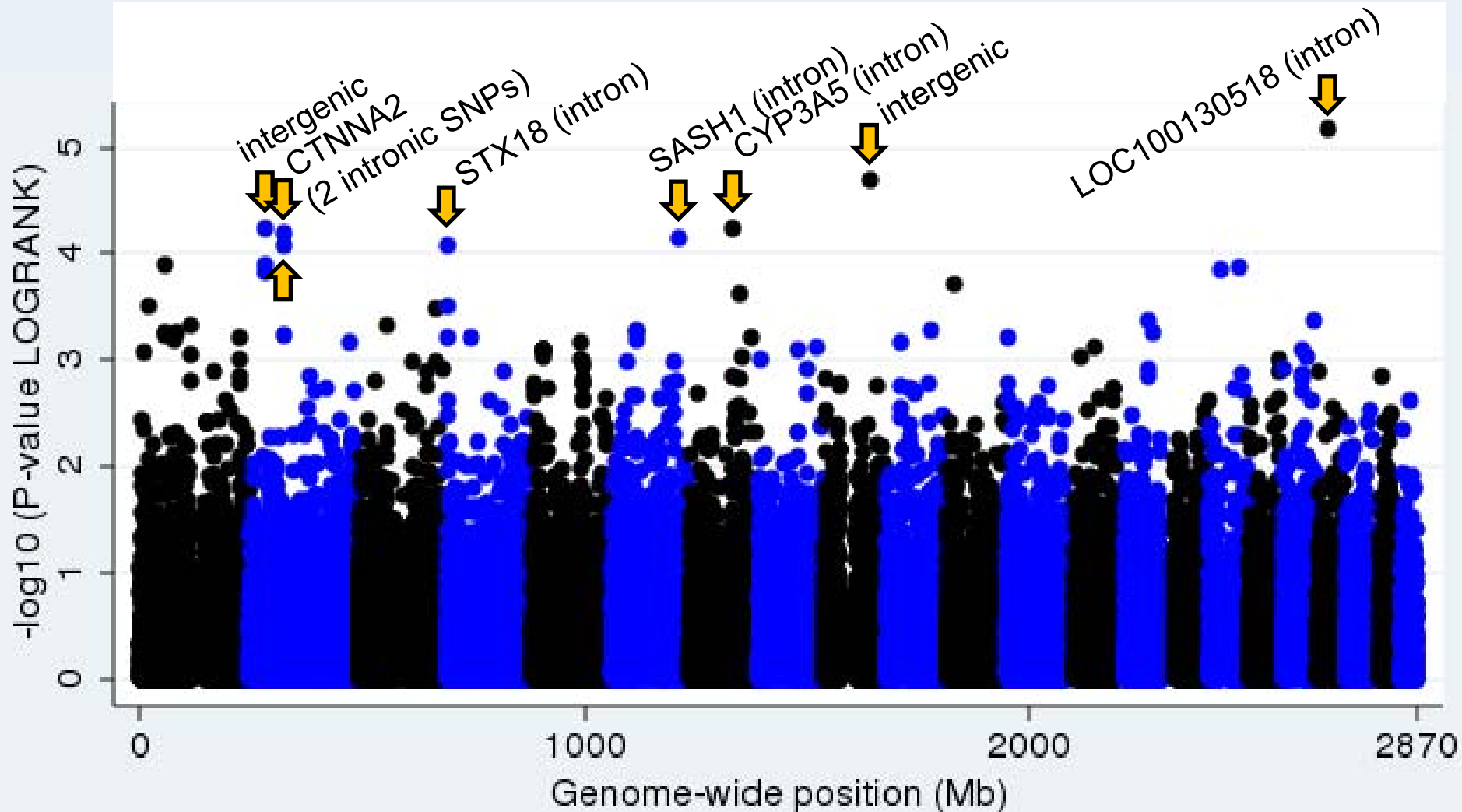
Conditional power is calculated prior to analysis by parents genotypes and children's phenotypes. Allows to select markers based on pre-test power (Van Steen et al 2005 Nat Genet 37:683)

- 51,144 (10%) with highest pre-test power selected for association testing.

P-values distribute as expected (Quantile-Quantile plot)
(Top 51,144 markers by power)



Genome-wide P-values for association with diabetes diagnosis age (Top 51,144 markers by power)



Follow-up study (Gene Modifiers Study)

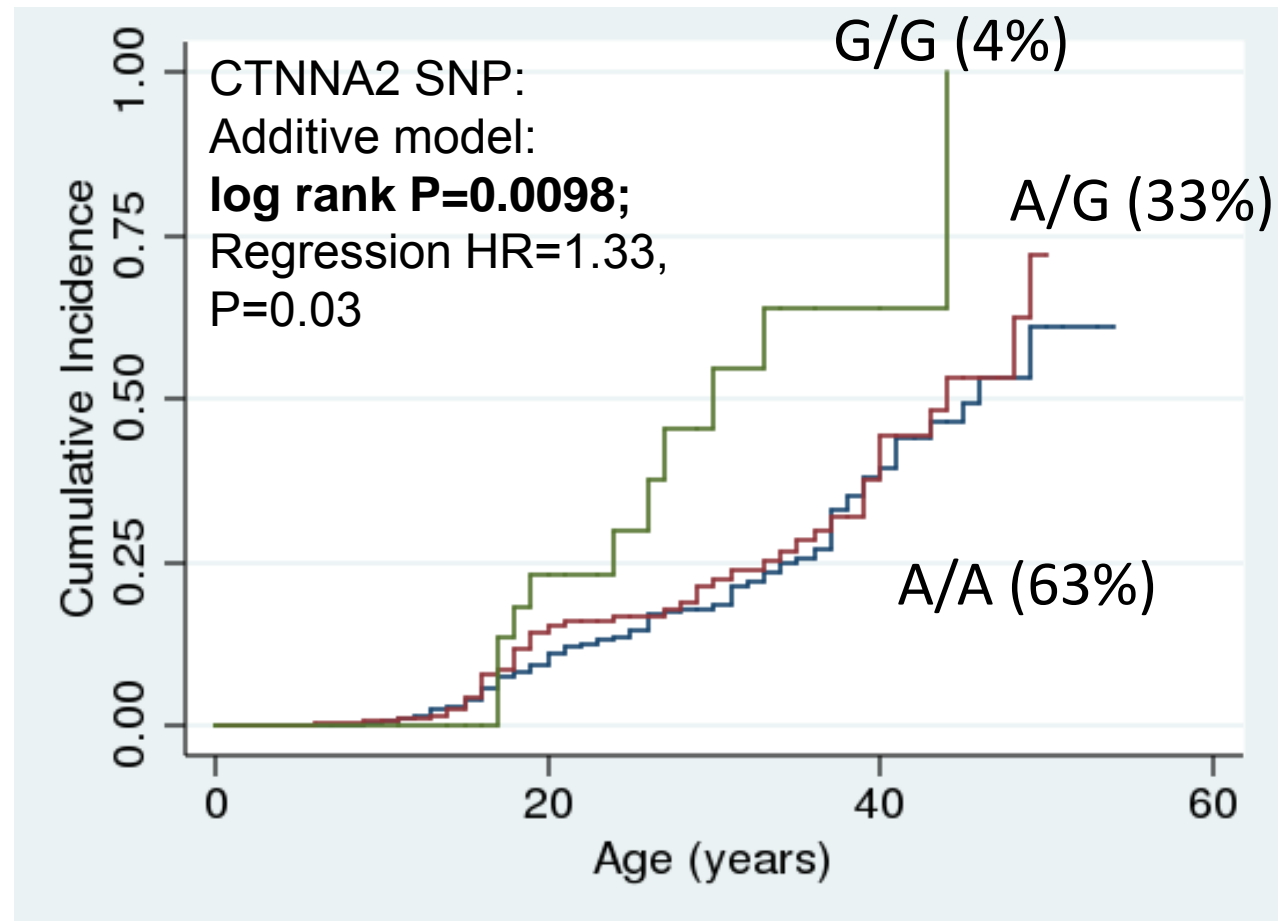
n=763 (160 diabetes, 603 PI CF control)

8 loci tested for replication

1 locus showed evidence of association with the same allele

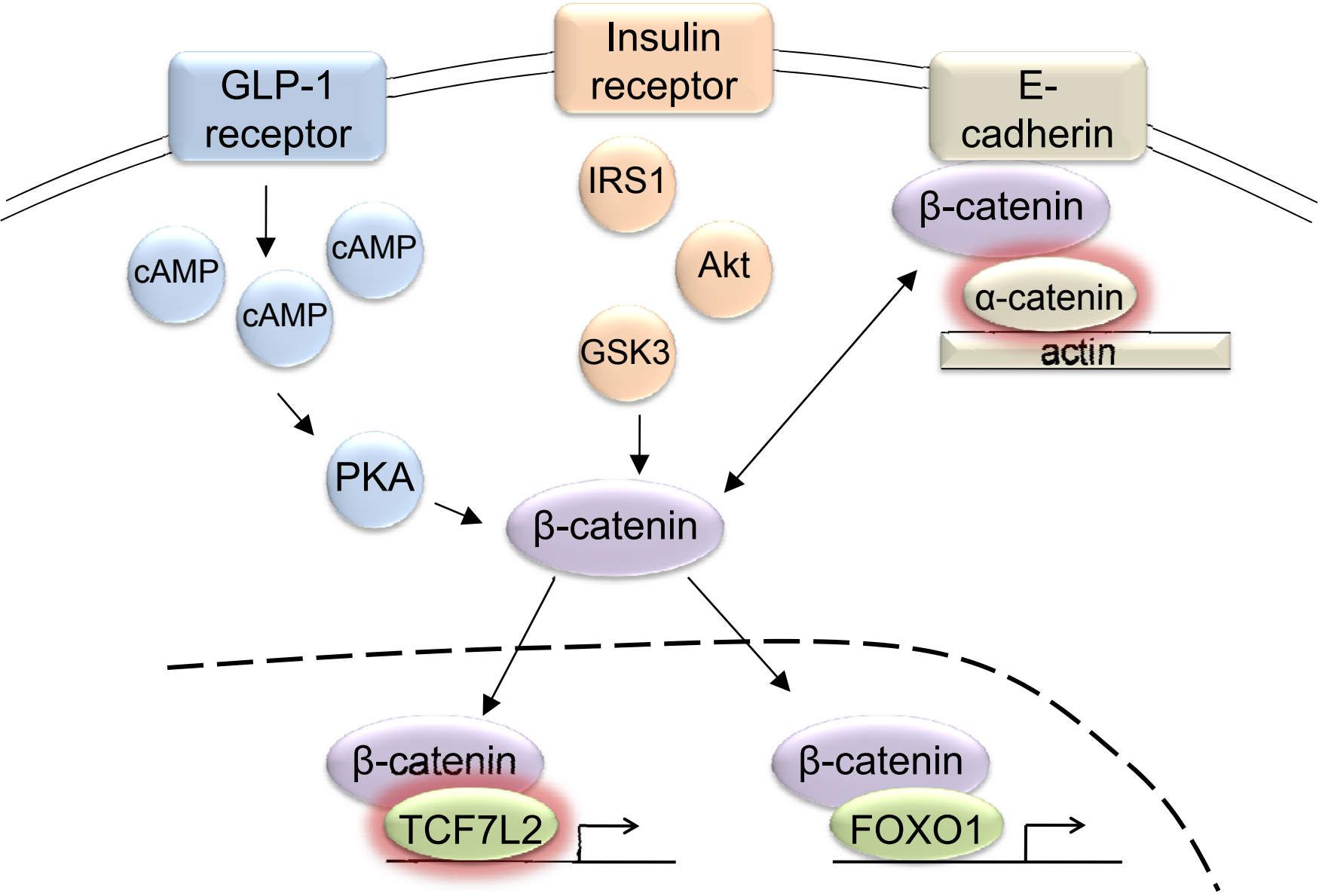
(CTNNA2 SNP, recessive model: log rank P=0.005; HR=2.17, P=0.01)

Study-wide combined P-value = 3×10^{-6} (51,152 tests), Suggestive for association



The same “G” allele of the CTNNA2 SNP associates with decreased age of diabetes diagnosis in the follow-up study.

Cross-talk between Wnt and important β -cell-signaling pathways



Adapted from Welters (2008) Trends Endocrinol Metab 19:349

Conclusions

- Diabetes in CF is largely due to genetic modifiers, that is, variants in genes other than CFTR.
- Involvement of TCF7L2 and CTNNA2 implicate Wnt/ β -catenin signaling in CFRD.
 - Cell/tissue(s) of action are unknown
- CTNNA2 and other CFRD modifier genes may play a role in type 2 diabetes.
- Identification of at-risk CF patients may allow individualizing therapy such as earlier screening and prevention of diabetes-related complications in CF.

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■ JHU Institute of Genetic Medicine

- **Garry Cutting**
- Kathleen Naughton
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- Mike Collaco
- Lindsay B. Henderson
- Vishal Doshi
- Lori Vanscoy
- Patrick Sosnay
- Deanna Green
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- David Cutler

■ U of NC / CWRU

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- Fred Wright
- Mitchell Drumm
- Aaron Webel
- Rhonda Pace

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- Julian Zielenski
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- Ruslan Dorfman
- Lisa Strug

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CF Twin and Sib Study

"Investigating the factors that modulate the severity of Cystic Fibrosis by studying affected twins and sibling pairs..."

Albany Medical College Albany, NY
All Children's Hospital St. Petersburg, FL
Asthma & Allergy Specialists, PA Charlotte, NC
Baylor College, Houston TX
Children's Asthma Respiratory & Exercise Specialists, Chicago
Children's Health Care of Atlanta, GA
Children's Hospital and Clinics
Children's Hospital of Akron, OH
Children's Hospital of Boston, MA
Children's Hospital of Buffalo, NY
Children's Hospital of Denver, CO
Children's Hospital of Los Angeles, CA
Children's Hospital and Medical Center of Cincinnati
Children's Hospital and Medical Center of Dallas
Children's Hospital and Regional Medical Center Seattle WA
Children's Hospital of Oakland Oakland CA
Children's Hospital of Orange County Orange, CA
Children's Hospital of Philadelphia Philadelphia, PA
Children's Hospital of Pittsburgh Pittsburgh, PA
Children's Hospital of Milwaukee Milwaukee, WI
Children's Memorial Medical Center Chicago, IL
Children's Mercy Hospital Kansas City, MO
Columbia University
Connecticut Children's Medical Center Hartford, CT
Cook Children's Medical Center Forth Worth, TX
Dartmouth Hitchcock Medical Center Lebanon, NH
Eastern Maine Medical Center Bangor ME
Emory University CF Center Atlanta, GA
Fletcher Allen Health Care Burlington, VT
Great Falls Clinic Great Falls MT

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Arlene Stecenko, MD Carrie Cutchins
Thomas Lahiri, MD Jackie Swartz
Jerrold Eichner, MD Laura Hodges



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Hasbro Children's Hospital Providence, RI
Hershey Medical Center Hershey, PA
Hospital of the University of Pennsylvania Philadelphia, PA
Joe DiMaggio Pulmonary Center Hollywood, FL
Johns Hopkins Hospital Baltimore, MD
Kaiser Permanente Medical Center Oakland, CA
Kaiser Permanente Portland, OR
Kaiser Permanente Panorama City, CA
Long Island College Hospital Brooklyn, NY
Lutheran General Hospital Park Ridge, IL
Lutheran Hospital Fort Wayne, IN
Marshfield Clinics Marshfield, WI
Massachusetts General Hospital Boston, MA
Medical College of Georgia Augusta, GA
Medical University of South Carolina Charleston, SC
Memphis Lung Physicians South Haven, MS
Methodist Children's Hospital San Antonio, TX
Miami Children's Hospital, Miami FL
Michigan State University Lansing, MI
Monmouth Medical Center Long Branch, NJ
Morristown Memorial Hospital Morristown, NJ
Mountain State CF Center Morgantown, WV
National Naval Medical Center Bethesda, MD
Nationwide Children's Hospital Columbus, OH
Naval Medical Center San Diego, CA

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Kathryn Moffett, MD Linda Baer
Joel Schmidt, MD Monica Leupold
Karen McCoy, MD Terri Johnson
Henry Wojtczak, MD



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New York Medical College Valhalla, NY
Oklahoma Health Science Center Oklahoma City, OK
Pediatric Diagnostic Center Ventura, CA
Pediatric Pulmonary Associates Columbia, SC
Phoenix Children's Hospital Phoenix, AZ
Portsmouth Naval Medical Center Portsmouth, VA
The Prince Charles Hospital Brisbane, Australia
Providence Medical Center Anchorage, AK
Providence Medical Center Spokane WA
Rainbow Babies and Children's Hospital Cleveland OH
Riley Children's Hospital Indianapolis IN
Royal Hospital for Sick Children Yorkhill, Scotland
Rush Presbyterian/St. Luke's Medical Center Chicago, IL
Saint Alexius Heart and Lung Center Bismarck, ND
Saint Christopher's Hospital for Children Philadelphia, PA
Saint Luke's CF Clinic Boise, ID
Saint Mary's Medical Center West Palm Beach, FL
Saint Vincent's Hospital Green Bay, WI
Saint Vincent's Hospital and Medical Center, New York, NY
Schneider Children's Hospital New Hyde Park, NY
Sparks Regional Medical Center Fort Smith, AR
St. Louis Children's Hospital and the Barnes Jewish Hospital
St. Louis, MO
Stanford University Medical Center Palo Alto, CA
SUNY Pediatric Pulmonary and CF Center Syracuse, NY
Sutter Medical Center Sacramento, CA
T.C. Thompson Children's Hospital Chattanooga, TN

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Joan DeCelie-Germana, MD Susan Galvin
Louay Nassri, MD Janet Austin
Thomas Ferkol, MD Daniel Rosenbluth, MD Mary Boyle

Richard Moss, MD Colleen Dunne
Ran Anbar, MD Donna Lindner
Bradley Chipps, MD Kasey Pearson
Joel Ledbetter, MD Karen Saronosky



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Texas Children's Hospital Houston, TX
Toledo Children's Hospital Toledo, OH
Tufts New England Medical Center
Tulsa CF Center Tulsa, OK
University of Alabama CF Center Birmingham, AL
University of Arizona Tucson AZ
University of California at San Francisco CA
University of Chicago Chicago, IL
University of Florida Pediatric CF Center Gainesville, FL
University of Kansas Medical Center Kansas City, KS
University of Iowa Hospitals and Clinics Iowa City, IA
University of Kentucky Lexington, KY
University of Massachusetts Medical Center Worcester, MA
University of Michigan Ann Arbor, MI
University of Minnesota Minneapolis, MN
University of Mississippi Medical Center Jackson, MS
University of Nebraska Omaha, NE
University of New Mexico Health Sciences Center Albuquerque, NM
University of North Carolina at Chapel Hill Chapel Hill, NC
University of Oklahoma Oklahoma City, OK
University of Rochester Strong Memorial Hospital Rochester, NY
University of Tennessee Le Bonheur Childrens Hospital Memphis, TN
University of Texas Health Center Tyler ,TX
University of Utah Salt Lake City UT
University of Virginia Health System Charlottesville, VA
University of Wisconsin Hospital Madison, WI
Vanderbilt University Medical Center, Nashville, TN

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Pierre Vauthy, MD Jeffrey Lewis, MD Mary Vauthy
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John Kramer, MD Sue Hensel
Hector Guitierrez, MD JP Clancy, MD Valerie Tarn
Wayne Morgan, MD Joanne Douthit
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Gaylin Perry, MD Adrienne Liebergen
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Via Christi Health Center Wichita, KS

Wake Forest University, Baptist Medical Center Winston-Salem, NC

Western Carolina CF Center, Charlotte, NC

Wilford Hall Medical Center Lackland AFB San Antonio, TX

Yale University New Haven, CT

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Janet Messamore

Bruce Rubin, MD

Hugh Black, MD William Ashe, MD

Andrew Lipton, MD

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