

# CF-related diabetes and type 2 diabetes: Different on the outside, similar on the inside?

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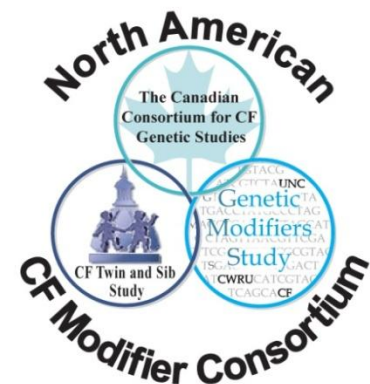


JOHNS HOPKINS  
M E D I C I N E



CF Twin and Sib Study

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



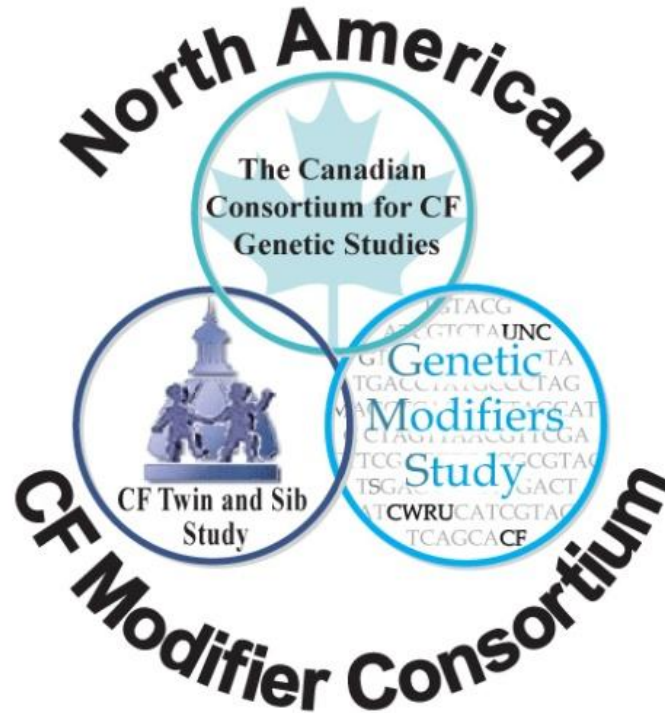
Scott M. Blackman has no relevant  
financial disclosures

# North American CF Modifier Consortium: (CFRD-centric list)

## Twin-Sibling Study (JHU)

Garry Cutting  
Kathleen Naughton  
Chris Watson  
Mike Collaco  
Vishal Doshi  
Lindsay B. Henderson  
Stephanie Hsu  
Sarah Ritter  
Lori Vanscoy  
Bridget Stuart  
Deanna Green  
  
David Cutler

Funding: NIH, CFF, LWPES



## Genetic Modifiers Study (UNC/CWRU)

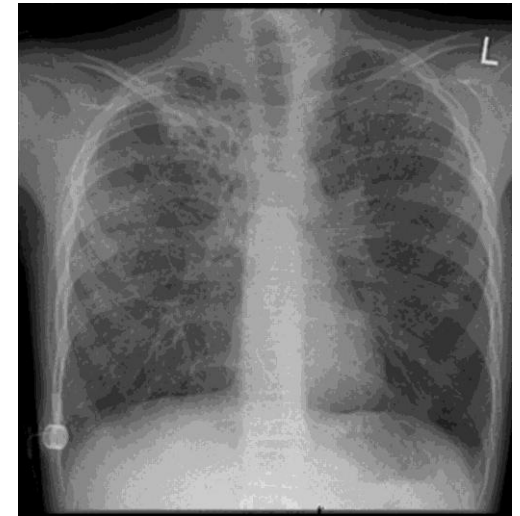
Michael Knowles  
Clayton Commander  
Aaron Webel  
Sarah Norris  
Rhonda Pace  
Fred Wright  
Mitchell Drumm

## Canadian CF Consortium

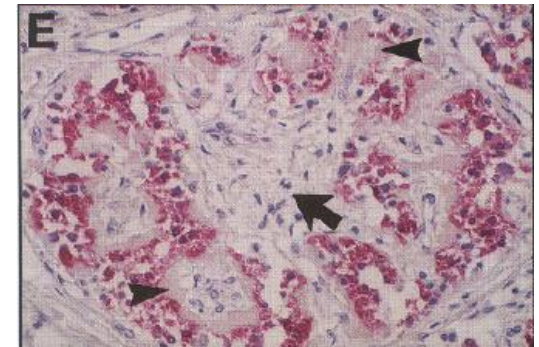
Peter Durie  
Lisa Strug  
Johanna Rommens  
Chelsea Taylor  
Julian Zielenski  
Mary Corey  
Ruslan Dorfman

# Diabetes in Cystic Fibrosis

- Diabetes (a.k.a. CFRD) develops over time:
  - Most common co-morbidity of CF
  - 26% age 10-19, 43% age >30
- Diabetes is correlated with worse lung function, nutritional status, and mortality. Treatment of diabetes improves these.
- CF is caused by mutations in CFTR, but CFRD is caused mainly by variation in genes other than CFTR.
  - Twin and sibling study:  
heritability  $\sim 1.0$  (95% CI, 0.4-1)\*
- One or more genes for Type 2 diabetes may play a role
  - Family history of type 2 diabetes increases risk of CFRD (OR = 3.39, P=0.0004)

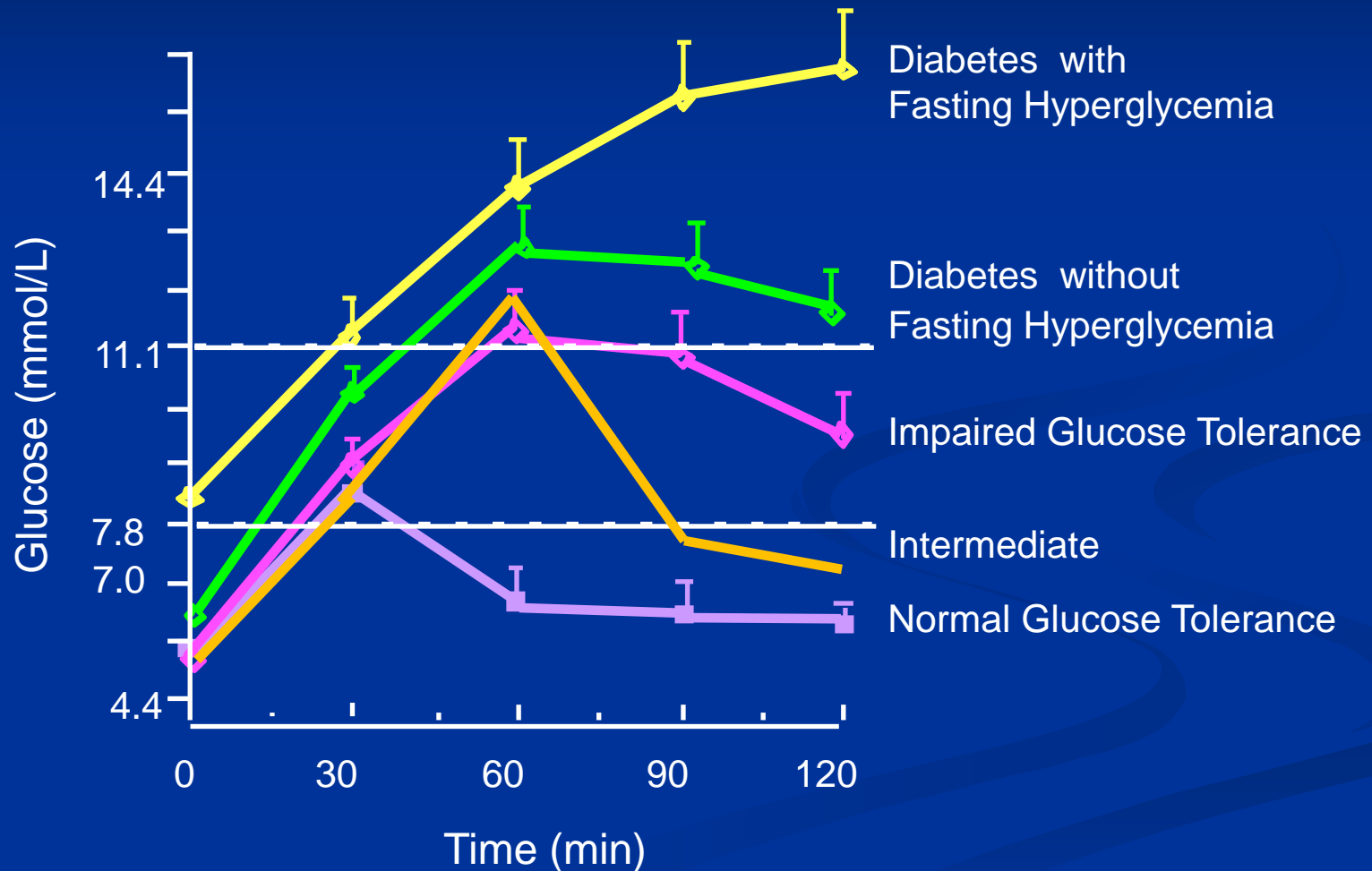


CF lung disease



CF diabetic pancreatic islet

# Glucose Tolerance in CF



# Continuum of CF glycemia



Normal glucose

Elevated  
1hr glucose  
("pre-IGT")

Impaired  
glucose  
tolerance

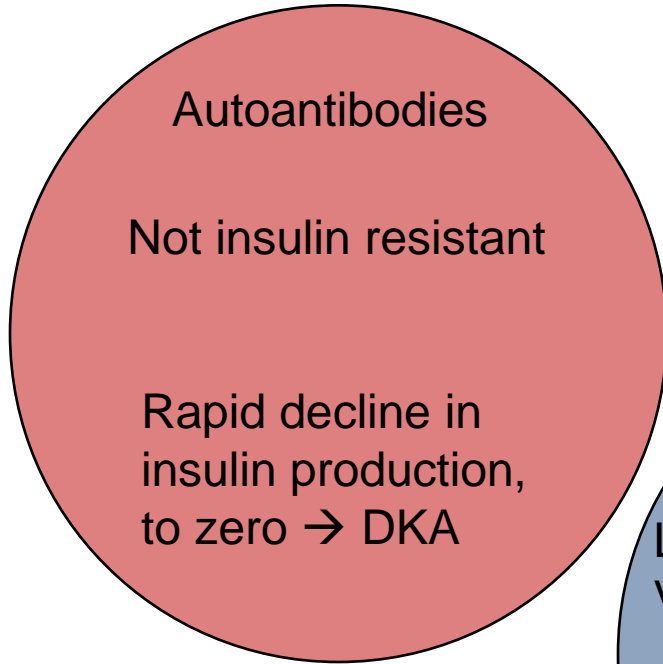
Normal fasting,  
elevated  
postprandial  
CFRD (-) FH

Chronic  
insulin  
deficiency  
CFRD (+) FH

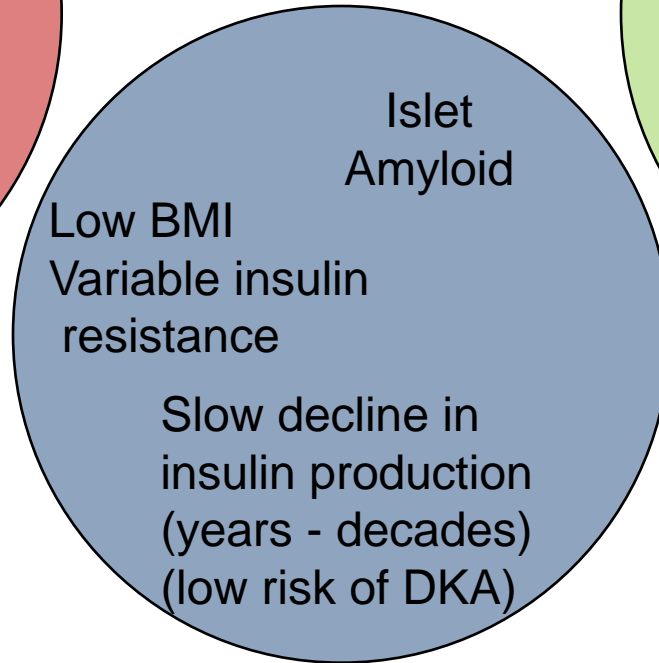
# Risk factors for CFRD

- exocrine pancreatic insufficiency or severe CFTR mutation class
- increasing age
- female sex
- CF-related liver disease
- poorer lung function, more CF exacerbations
- height < 25% (thought to reflect chronic undernutrition)
- P.aeruginosa infection; B.cepacia infection
- allergic bronchopulmonary aspergillosis (ABPA)
- Oral or implanted contraceptives

## Type 1A Diabetes

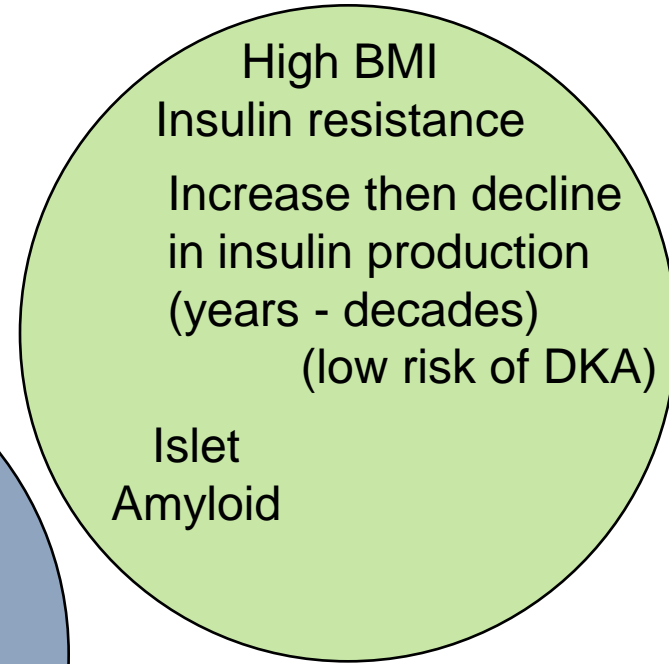


## Complications

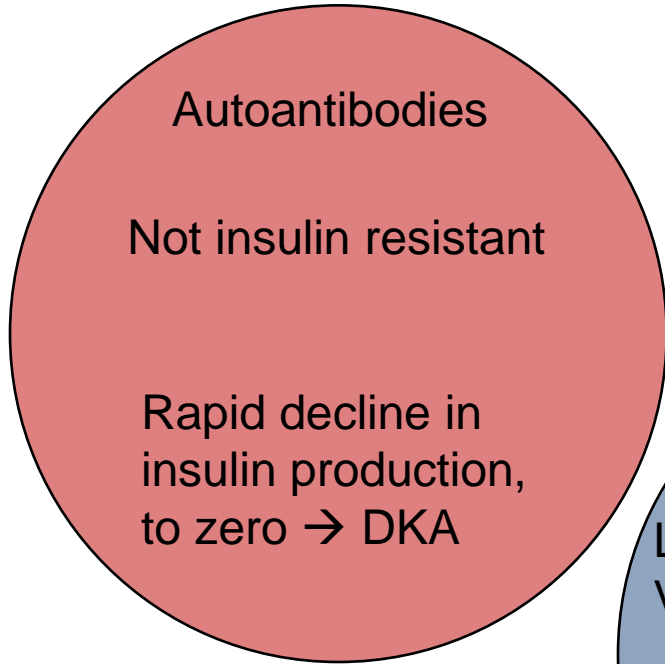


## CF-related Diabetes

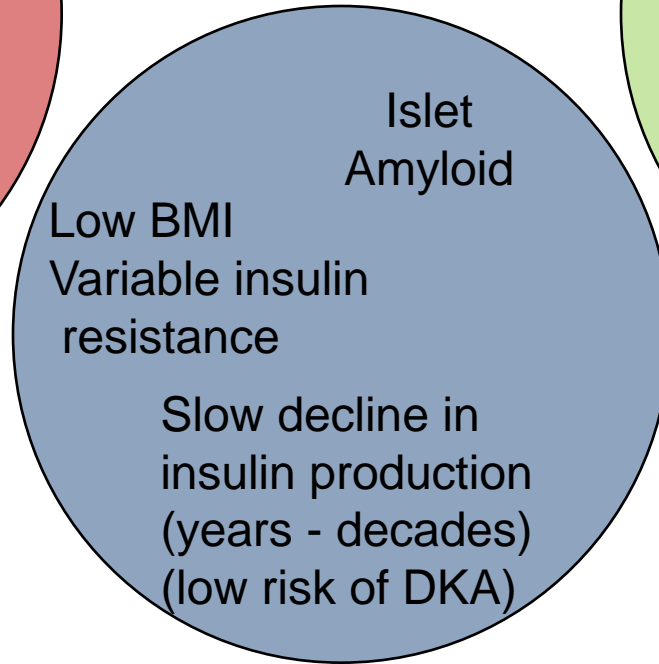
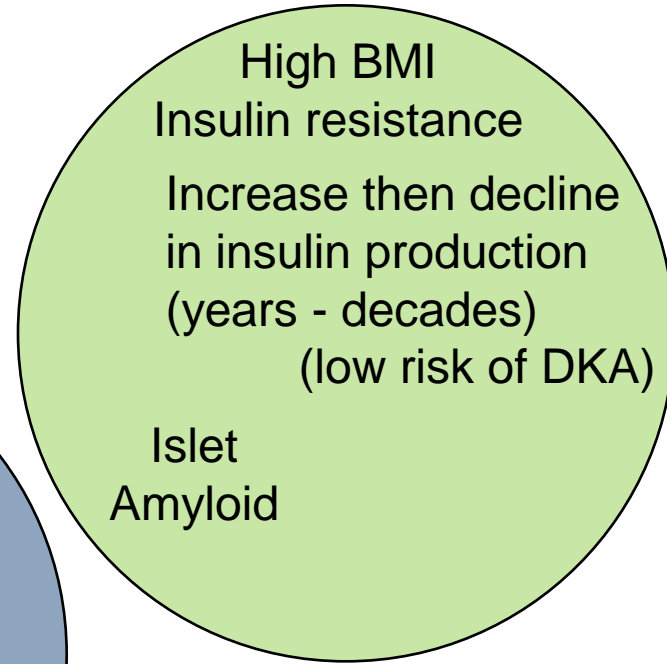
## Type 2 Diabetes



## Type 1A Diabetes

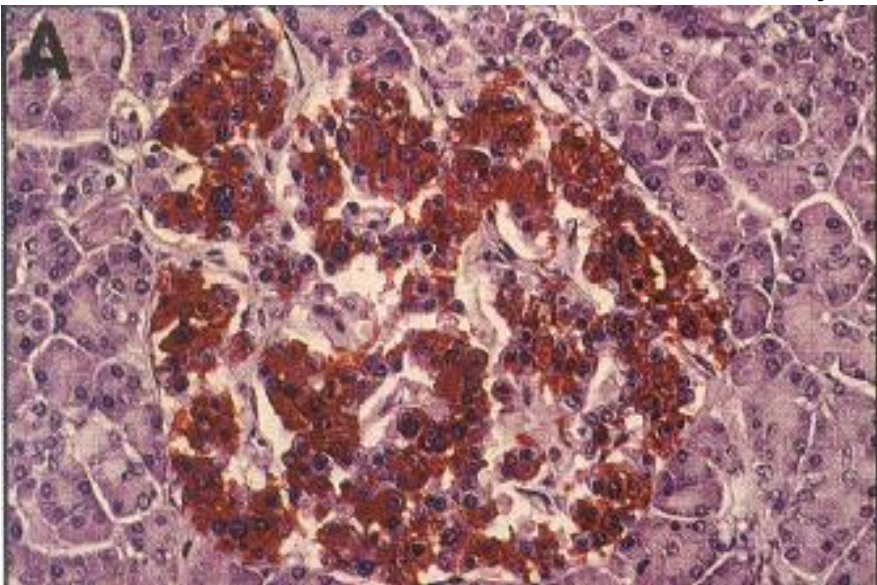


## Type 2 Diabetes

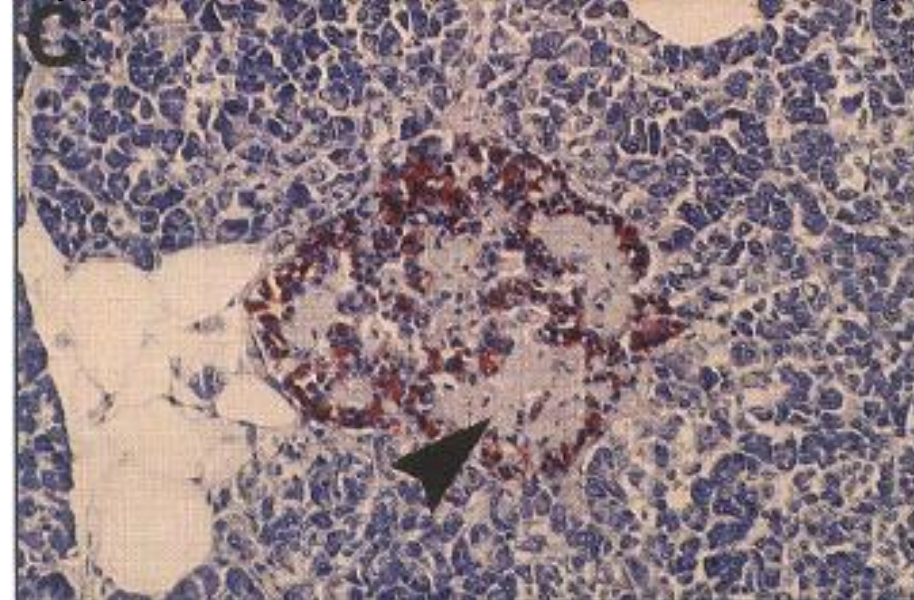


## CF-related Diabetes

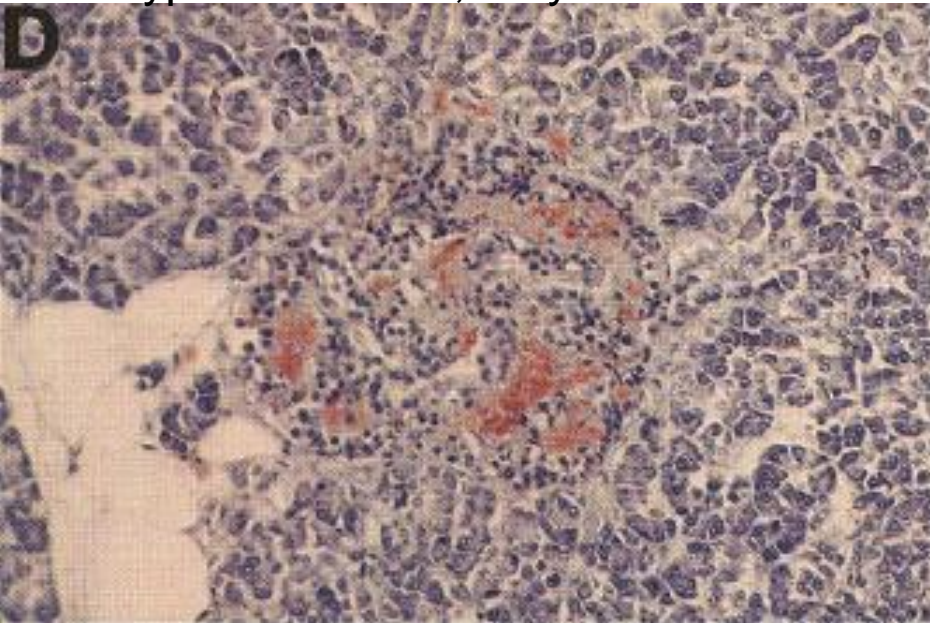
Normal islet, insulin immunoreactivity



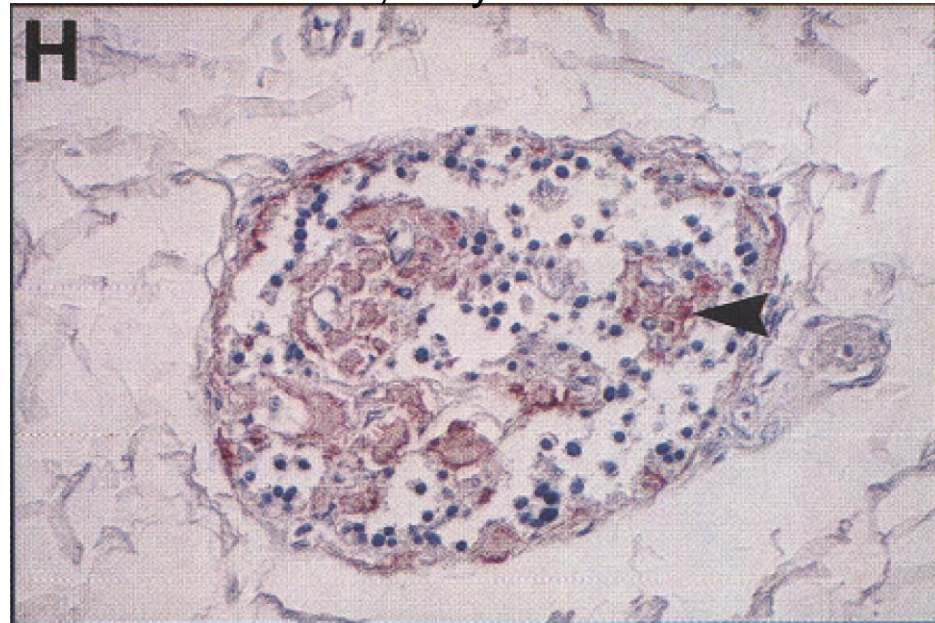
Type 2 diabetes, insulin immunoreactivity



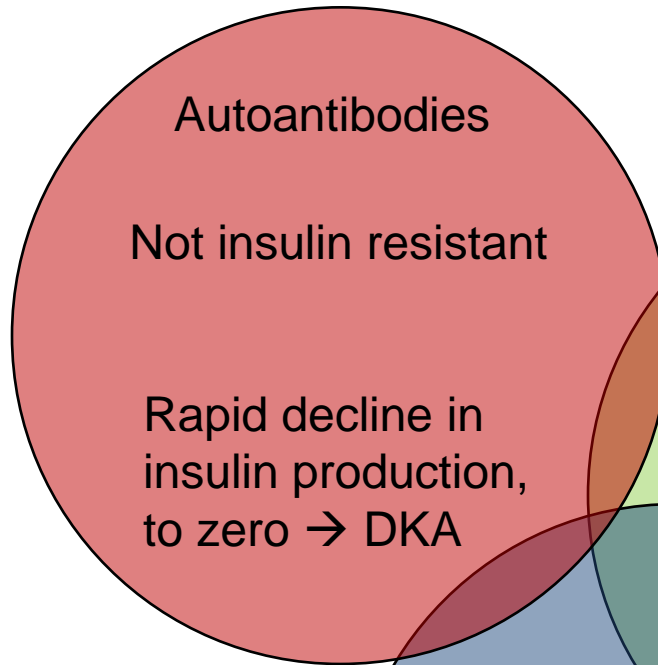
Type 2 diabetes, amyloid stain



Diabetes in CF, amyloid immunostain



## Type 1A Diabetes



## Type 2 Diabetes

High BMI

Insulin resistance

Increase then decline in insulin production (years - decades) (low risk of DKA)

Islet Amyloid

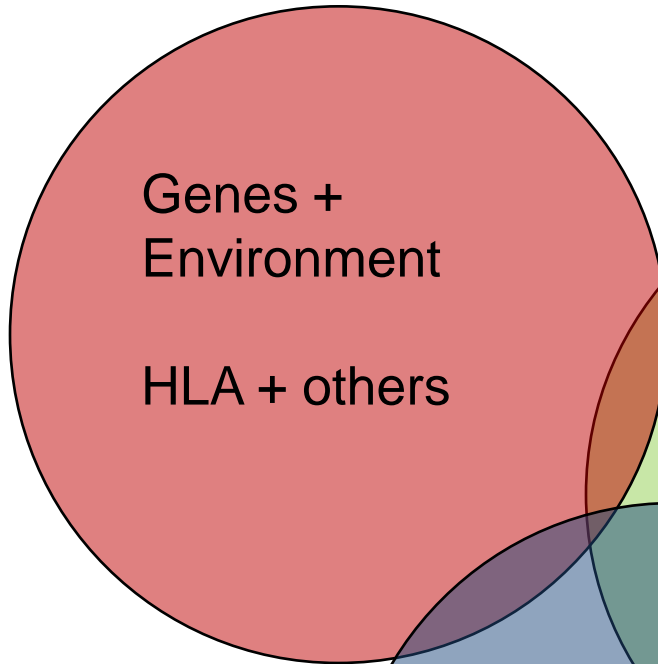
Low BMI

Variable insulin resistance

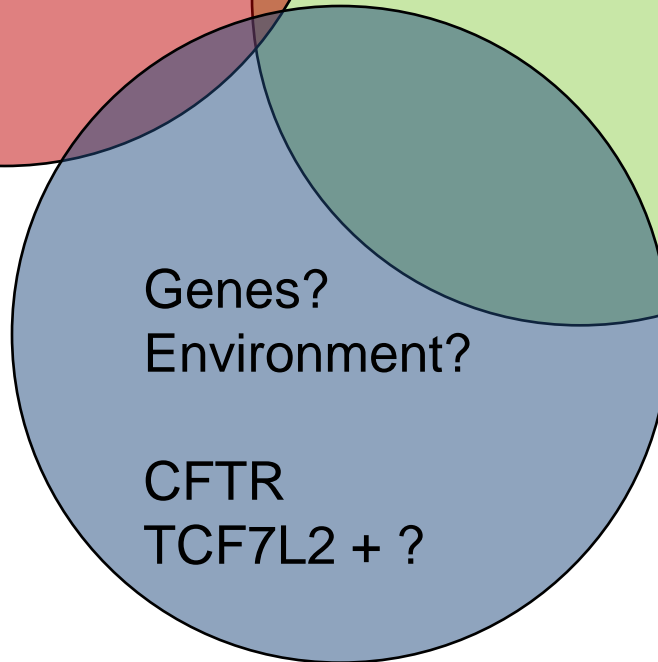
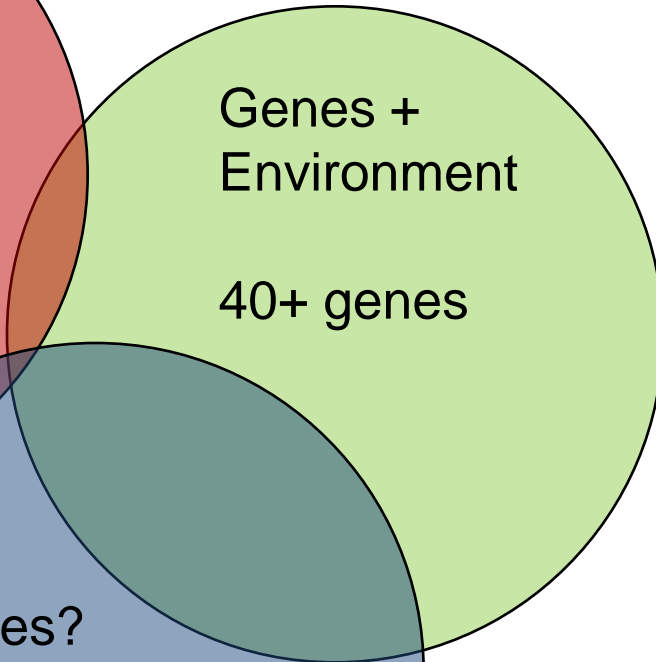
Slow decline in insulin production (years - decades) (low risk of DKA)

## CF-related Diabetes

Type 1A Diabetes



Type 2 Diabetes



CF-related Diabetes

# Family Study sample: CF Twin and Sibling Study

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

Euglycemic



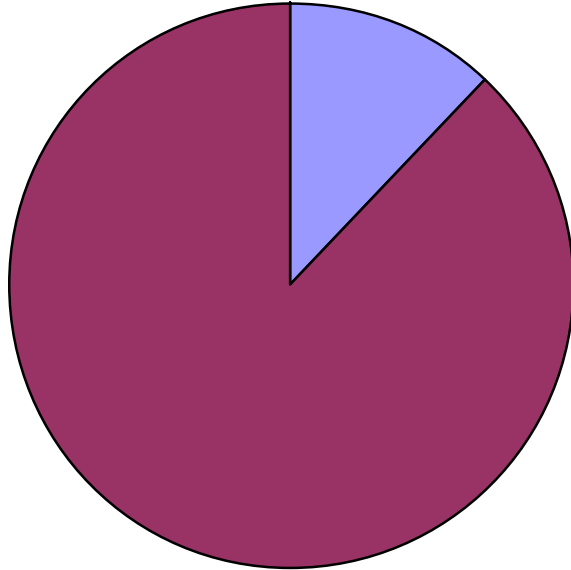
CFRD

- 580 families up to 5 per family
- DNA + detailed, longitudinal clinical information (multiple phenotypes)
- 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%)

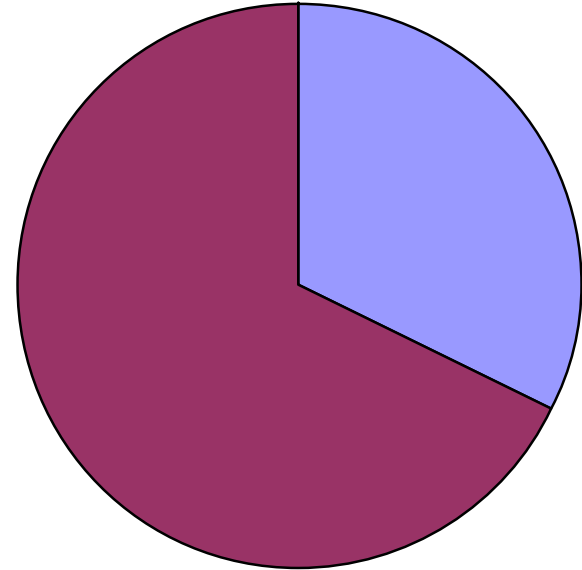
# Family history of T2D in 1 first or 2 second-degree relatives

## One or more T2D-susceptibility genes may play a role in CF

(emphasizes shared genes > environment)



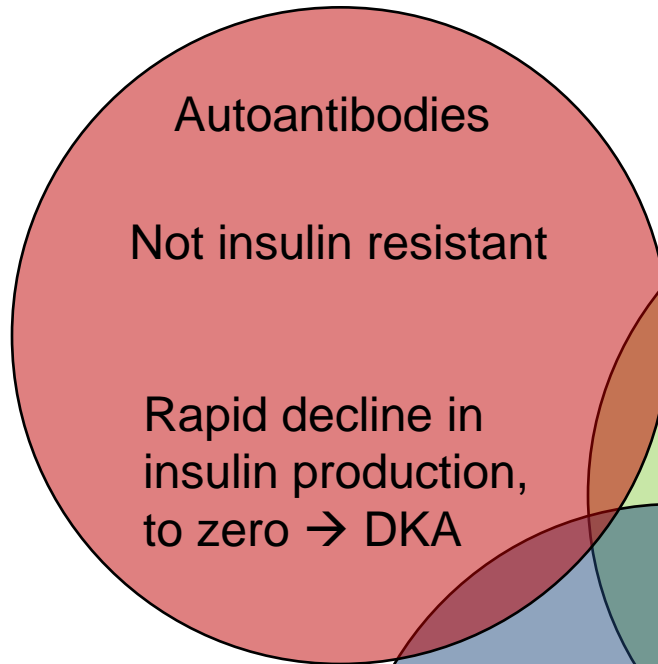
No diabetes family history  
12% (31 of 252) patients have  
CFRD



Positive diabetes family history  
32% (20 of 62) patients have  
CFRD

OR = 3.39, P=0.0004

## Type 1A Diabetes



## Type 2 Diabetes

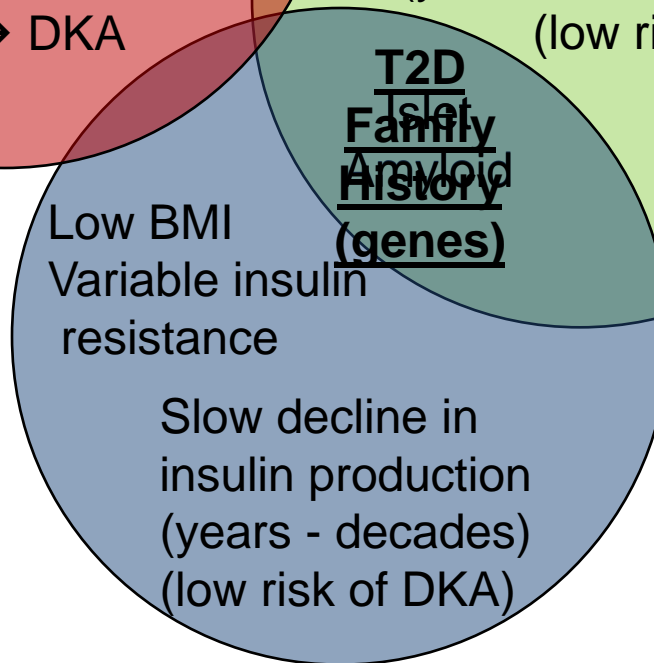
High BMI

Insulin resistance

Increase then decline in insulin production (years - decades)

(low risk of DKA)

A green circle representing the characteristics of Type 2 Diabetes.



T2D  
ISlet  
Family  
Amyloid  
History  
(genes)

Text describing genetic and clinical features associated with the overlap of Type 2 Diabetes and CF-related Diabetes.

## CF-related Diabetes

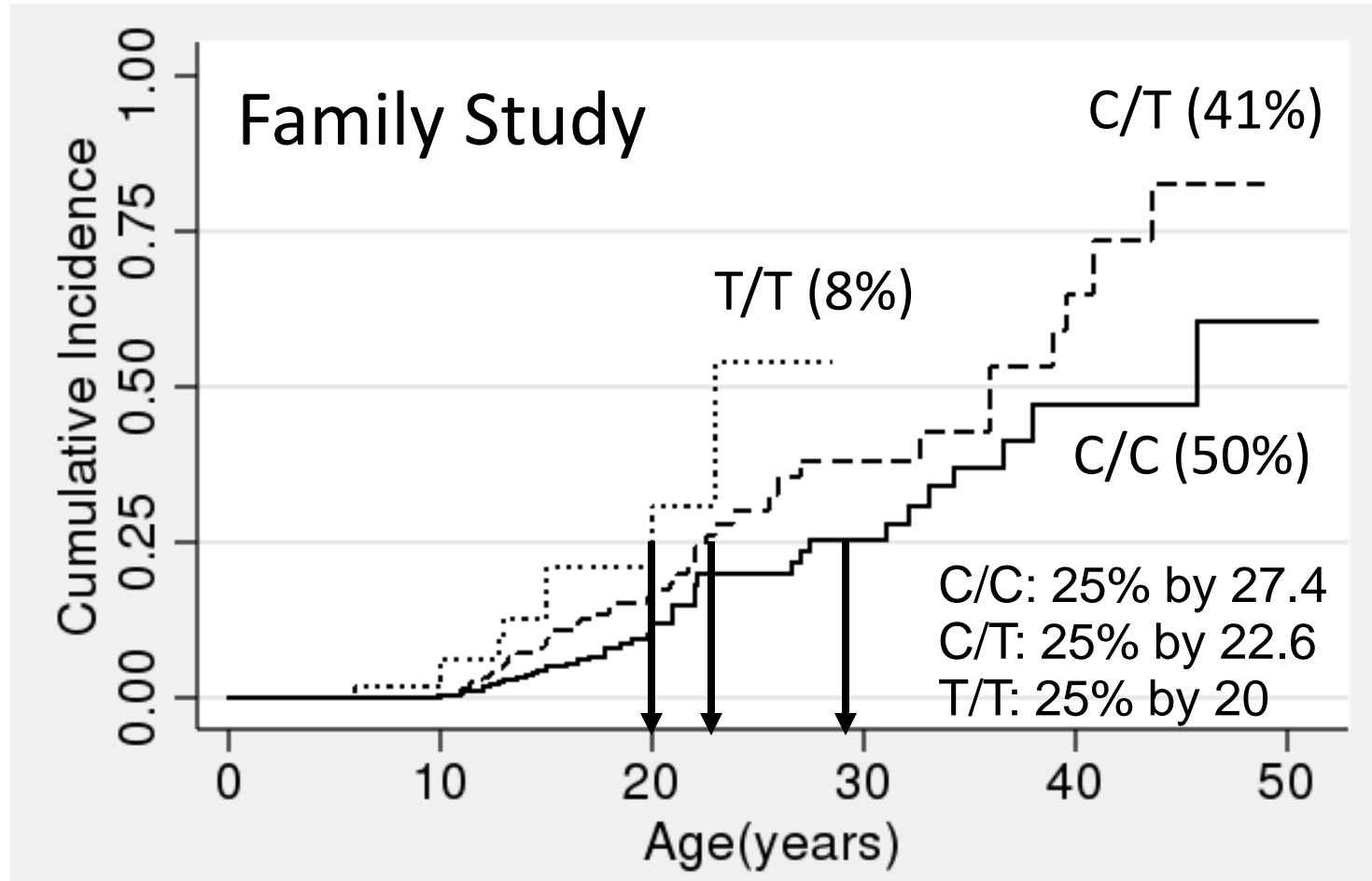
# Type 2 diabetes

## 19 susceptibility genes for type 2 diabetes

■ **TCF7L2** (one “T” allele, OR = 1.4; two “T” alleles, OR = 2)

- PPARG (1.19)
- KCNJ11 (1.14)
- CDKN2A/B (1.2)
- FTO (1.17)
- HHEX-IDE (1.13)
- SLC30A8 (1.12)
- CDKAL1 (1.12)
- IGF2BP2 (1.14)
- HNF1A/TCF1 (1.17)
- WFS1 (1.15)
- THADA (1.15)
- HNF1B/TCF2 (1.12)
- NOTCH2 (1.13)
- JAZF1 (1.1)
- CDC123-CAMK1D (1.11)
- TSPAN8-LGR5 (1.09)
- ADAMTS9 (1.09)
- HNF4A
- CAPN10
- ENPP1

# TCF7L2 “T” alleles decrease the age of diabetes diagnosis



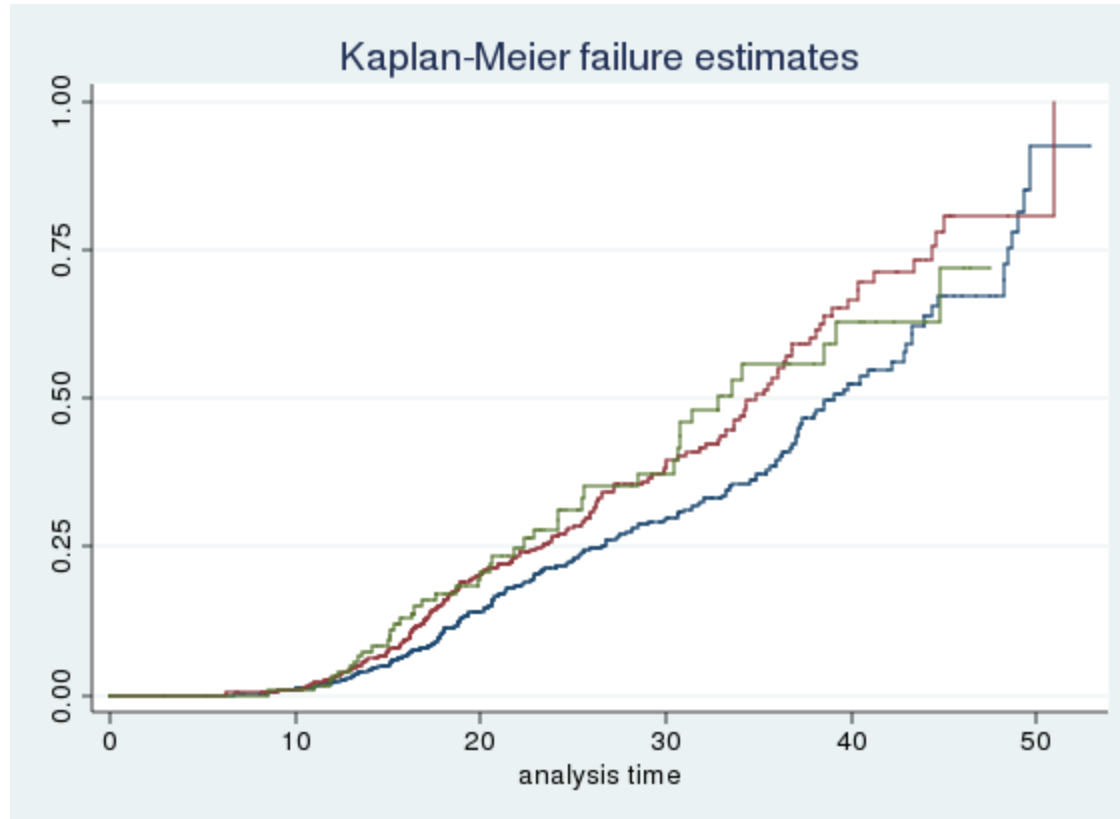
943 patients, log rank,  $P=0.004$ , allele  $HR=1.75$ ,  $P=0.0006$

## rs7903146 (TCF7L2) SNP

UNC, new phenotypes, GWAS genotypes

64 JHU (13 diabetic) dropped leaving n=1278 (376 diabetic) with known onset age

CC = blue  
CT = red  
TT = green



Dominant model: HR=1.40 [1.1-1.7], p=0.0009, log rank p=0.0009

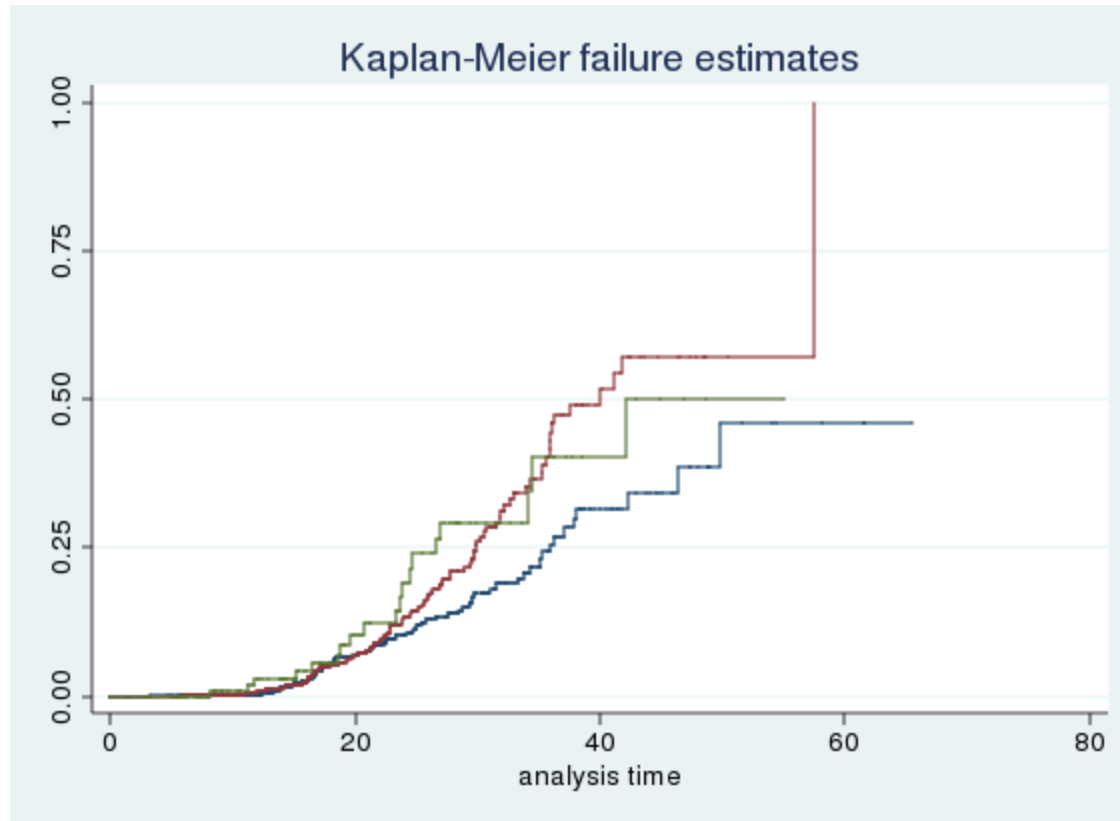
Additive model: HR=1.25 per allele [1.08-1.45], p=0.002, log rank p=0.004

Recessive model: HR= 1.22 [0.9-1.7], p=0.22, log rank p=0.22

## rs7903146 (TCF7L2) SNP

GC, 11/9/2009 phenotypes, GWAS genotypes  
N=2262 (205 diabetic) with known onset age

CC = blue  
CT = red  
TT = green



Dominant model: HR=1.58 [1.17-2.14], p=0.003, log rank p=0.003

Additive model: HR=1.38 per allele [1.1-1.7], p=0.004, log rank p=0.01

Recessive model: HR=1.34 [0.8-2.2], p=0.22, log rank p=0.22

# 3-center combined analysis (TCF7L2)

- JHU: HR=1.75 per allele (95% CI 1.3-2.4; p=0.0006); log rank p=0.001
- NC: HR=1.25 per allele [1.08-1.45], p=0.002, log rank p=0.004
- GC: HR=1.38 per allele [1.1-1.7], p=0.004, log rank p=0.01
  
- Meta-analysis: HR = 1.34 per allele [1.2-1.5], p=4.35×10<sup>-7</sup>\*

\*3-center fixed-effects; van Houelingen et al. 2002

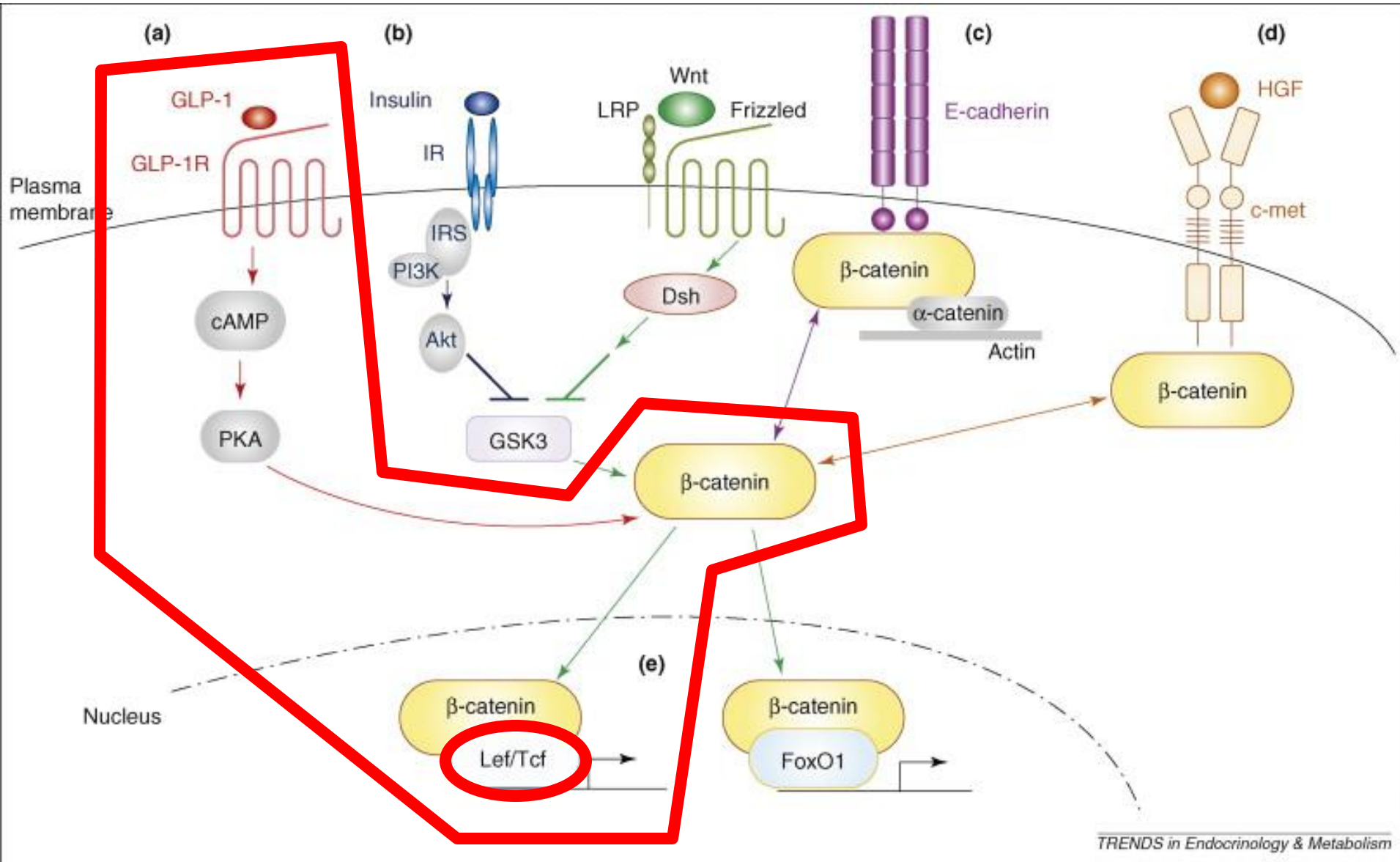
# Summary (TCF7L2)

- TCF7L2 is a susceptibility gene for diabetes in CF.
  - Accrual of new patients and replication in a 3<sup>rd</sup> independent cohort have strengthened evidence for TCF7L2 in CFRD

# What is TCF7L2 and what does it do?

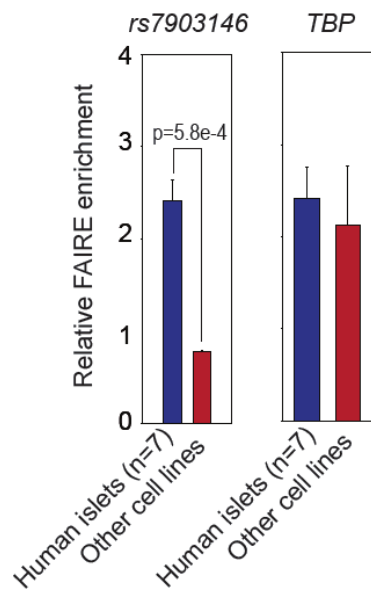
- Transcription factor involved in Wnt-dependent signaling
- Wnt signaling is involved in multiple tissues, often active during development / differentiation.
  - Adipocyte differentiation
  - Exocrine pancreatic development
  - Pancreatic  $\beta$ -cell

# Cross-talk between Wnt and important $\beta$ -cell-signaling pathways

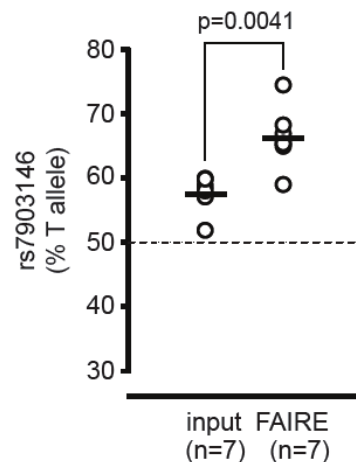


# A map of open chromatin in human pancreatic islets

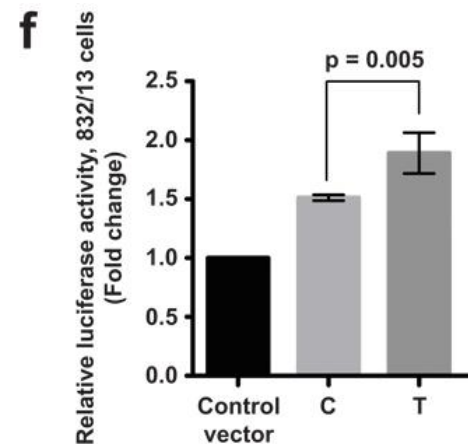
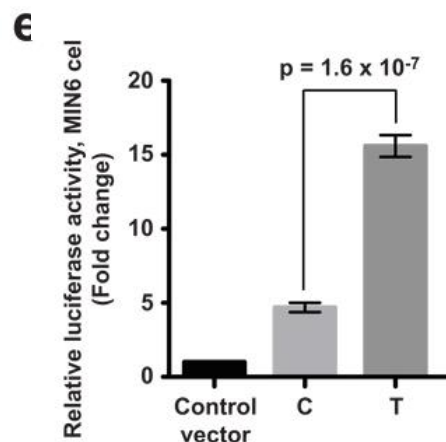
Kyle J Gaulton<sup>1,11</sup>, Takao Nammo<sup>2,3,11</sup>, Lorenzo Pasquali<sup>2,3,11</sup>, Jeremy M Simon<sup>1,4</sup>, Paul G Giresi<sup>4</sup>, Marie P Fogarty<sup>1</sup>, Tami M Panhuis<sup>1</sup>, Piotr Mieczkowski<sup>1</sup>, Antonio Secchi<sup>5</sup>, Domenico Bosco<sup>6</sup>, Thierry Berney<sup>6</sup>, Eduard Montanya<sup>3,7</sup>, Karen L Mohlke<sup>1,8,9</sup>, Jason D Lieb<sup>4,8,9</sup> & Jorge Ferrer<sup>2,3,10</sup>



The TCF7L2 locus is in a region of open chromatin (transcriptional activity) specific to islets

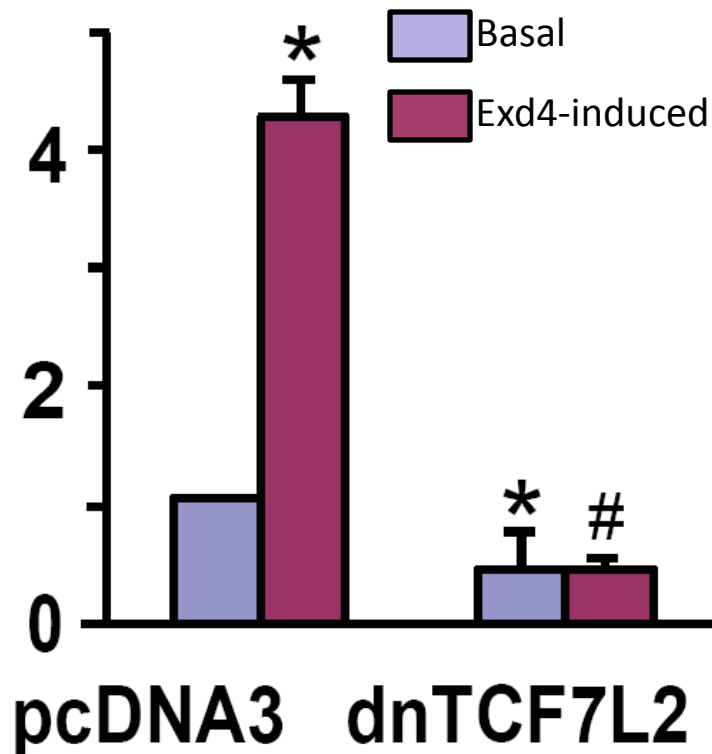


The variant conferring increased risk of diabetes (T allele) associated with increased *cis*-acting enhancer activity.



# Dominant negative TCF7L2 decreases basal and GLP-1 induced Wnt signaling

- Glucagon-like peptide-1 activation of TCF7L2-dependent Wnt signaling enhances pancreatic beta cell proliferation. Liu et al. J Biol Chem. 2008 Mar 28;283(13):8723-35. Epub 2008 Jan 23. PMID: 18216022



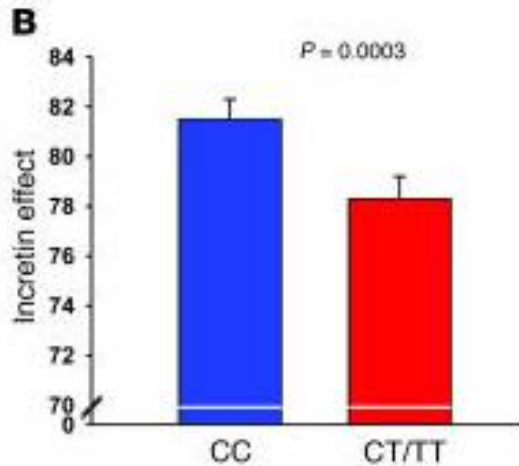
TCF7L2 is in the incretin pathway (which promotes insulin secretion after oral glucose).

Depletion of TCF7L2 by siRNA decreases insulin secretion,  $\beta$ -cell proliferation and promotes apoptosis (Shu et al. Diabetes. 2008).

Overexpression of TCF7L2 may promote insulin secretion, and protects against toxic cytokine and glucose levels (Shu et al. Diabetes. 2008).

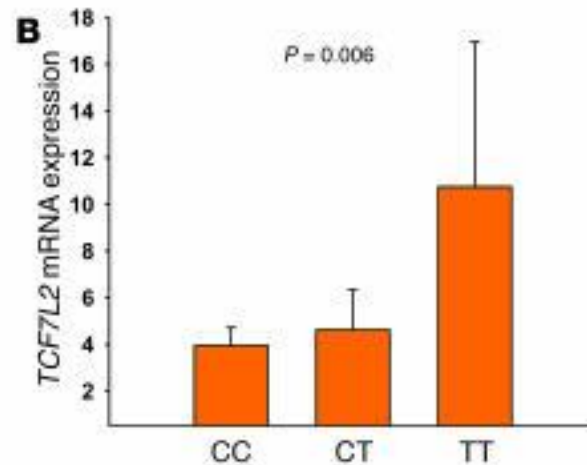
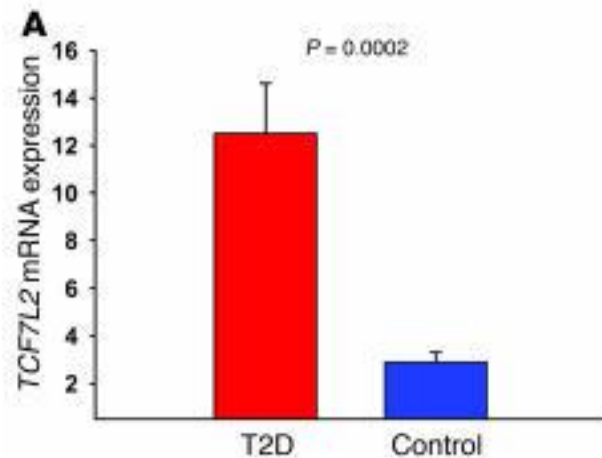
# Effect of TCF7L2 polymorphisms

- **Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes.** Lyssenko et al. J Clin Invest. 2007 Aug;117(8):2155-63. PMID: 17671651



Insulin response to oral vs. iv glucose (incretin effect) is decreased in carriers of TCF7L2 high-risk alleles.

$100\% \times (\text{AUCinsOGTT} - \text{AUCinsIVGTT}) / \text{AUCinsOGTT}$  in hyperglycemic subjects (fasting plasma glucose > 5.4 mmol/l)



TCF7L2 expression is increased in T2D, and in carriers of high-risk TCF7L2 alleles.

# Other T2DM candidates

- Hypothesis: One or more T2DM susceptibility genes play a role in CFRD. How to select?
  - Reported odds ratio (varies across populations and studies)
  - Power/size of reporting study compared to this study
  - Population(s) in which association was observed
  - Physiology

# Type 2 diabetes

## ■ TCF7L2 (one “T” allele, OR = 1.4; two “T” alleles, OR = 2)

- PPARG (1.19)
  - KCNJ11 (1.14)
  - CDKN2A/B (1.2)
  - FTO (1.17)
  - HHEX-IDE (1.13)
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  - TSPAN8-LGR5 (1.09)
  - ADAMTS9 (1.09)
  - HNF4A
  - CAPN10
  - ENPP1
  - IRS1
  - KCNQ1
- Others reported
- KLF14
  - PKN2
  - ABCC8
  - MTNR1B
  - DCD

# Type 2 diabetes

8 loci found in the first (similar-sized) studies

- **TCF7L2** (one “T” allele, OR = 1.4; two “T” alleles, OR = 2)
- PPARG (1.19)
- KCNJ11 (1.14)
- CDKN2A/B (1.2)
  
- HHEX-IDE (1.13)
- SLC30A8 (1.12)
- CDKAL1 (1.12)
- IGF2BP2 (1.14)

# Diabetes candidate SNPs tested

Locus	SNP	T2D risk allele	GMS (n=1278)		CGS (n=1580)		Joint analysis		
			Risk Allele	P-value	Risk Allele	P-value	Risk Allele	P-value	One-sided P-value
KCNJ11									
CDKAL1									
HHEX / KIF-1 / IDE									
SLC30A8									
CDKN2A/B									
IGF2BP2									

† Allele associates with increased risk of both T2D and CFRD

\*Study-wide P<0.001; \*\*Study-wide P<0.05

# Diabetes candidate SNPs tested

Locus	SNP	T2D risk allele	GMS (n=1278)		CGS (n=1580)		Joint analysis		
			Risk Allele	P-value	Risk Allele	P-value	Risk Allele	P-value	One-sided P-value
KCNJ11	rs5219	T	C	0.565	C	0.561	C	0.423	0.789
	rs5215	G	A	0.482	A	0.568	A	0.367	0.816
CDKAL1									
HHEX / KIF-1 / IDE									
SLC30A8									
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	rs5215	G	A	0.482	A	0.568	A	0.367	0.816
CDKAL1	rs7754840	C	C†	1.33×10 <sup>-3</sup> *	C†	0.051	C†	1.76×10 <sup>-4</sup> *	8.80×10 <sup>-5</sup> *
	rs7756992	C	C†	1.18×10 <sup>-4</sup> *	C†	0.058	C†	2.43×10 <sup>-5</sup> *	1.21×10 <sup>-5</sup> *
HHEX / KIF-1 / IDE									
SLC30A8									
CDKN2A/B									
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	rs7756992	C	C†	1.18×10 <sup>-4</sup> *	C†	0.058	C†	2.43×10 <sup>-5</sup> *	1.21×10 <sup>-5</sup> *
HHEX / KIF-1 / IDE	rs1111875	G	G†	0.815	A	0.112	A	0.498	0.751
	rs5015480	C	T	0.875	T	0.055	T	0.236	0.882
	rs7923837	G	G†	0.610	A	0.106	A	0.639	0.680
SLC30A8									
CDKN2A/B									
IGF2BP2									

† Allele associates with increased risk of both T2D and CFRD

\*Study-wide P<0.001; \*\*Study-wide P<0.05

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			GMS (n=1278)		CGS (n=1580)		Joint analysis		
Locus	SNP	T2D risk allele	Risk Allele	P-value	Risk Allele	P-value	Risk Allele	P-value	One-sided P-value
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	rs5015480	C	T	0.875	T	0.055	T	0.236	0.882
	rs7923837	G	G†	0.610	A	0.106	A	0.639	0.680
SLC30A8	rs13266634	C	C†	0.220	C†	0.755	C†	0.233	0.117
CDKN2A/B									
IGF2BP2									

† Allele associates with increased risk of both T2D and CFRD

\*Study-wide P<0.001; \*\*Study-wide P<0.05

# Diabetes candidate SNPs tested

			GMS (n=1278)		CGS (n=1580)		Joint analysis		
Locus	SNP	T2D risk allele	Risk Allele	P-value	Risk Allele	P-value	Risk Allele	P-value	One-sided P-value
KCNJ11	rs5219	T	C	0.565	C	0.561	C	0.423	0.789
	rs5215	G	A	0.482	A	0.568	A	0.367	0.816
CDKAL1	rs7754840	C	C†	1.33×10 <sup>-3</sup> *	C†	0.051	C†	1.76×10 <sup>-4</sup> *	8.80×10 <sup>-5</sup> *
	rs7756992	C	C†	1.18×10 <sup>-4</sup> *	C†	0.058	C†	2.43×10 <sup>-5</sup> *	1.21×10 <sup>-5</sup> *
HHEX / KIF-1 / IDE	rs1111875	G	G†	0.815	A	0.112	A	0.498	0.751
	rs5015480	C	T	0.875	T	0.055	T	0.236	0.882
	rs7923837	G	G†	0.610	A	0.106	A	0.639	0.680
SLC30A8	rs13266634	C	C†	0.220	C†	0.755	C†	0.233	0.117
CDKN2A/B	rs1412829	T	T†	1.13×10 <sup>-4</sup> *	T†	0.031	T†	1.03×10 <sup>-5</sup> *	5.14×10 <sup>-6</sup> *
IGF2BP2									

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# Diabetes candidate SNPs tested

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	rs5215	G	A	0.482	A	0.568	A	0.367	0.816
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HHEX / KIF-1 / IDE	rs1111875	G	G†	0.815	A	0.112	A	0.498	0.751
	rs5015480	C	T	0.875	T	0.055	T	0.236	0.882
	rs7923837	G	G†	0.610	A	0.106	A	0.639	0.680
SLC30A8	rs13266634	C	C†	0.220	C†	0.755	C†	0.233	0.117
CDKN2A/B	rs1412829	T	T†	1.13×10 <sup>-4</sup> *	T†	0.031	T†	1.03×10 <sup>-5</sup> *	5.14×10 <sup>-6</sup> *
IGF2BP2	rs4402960	A	A†	0.142	A†	0.134	A†	0.039	0.020
	rs1470579	G	G†	0.041	G†	0.095	G†	8.56×10 <sup>-3</sup>	4.28×10 <sup>-3</sup> **

† Allele associates with increased risk of both T2D and CFRD

\*Study-wide P<0.001; \*\*Study-wide P<0.05

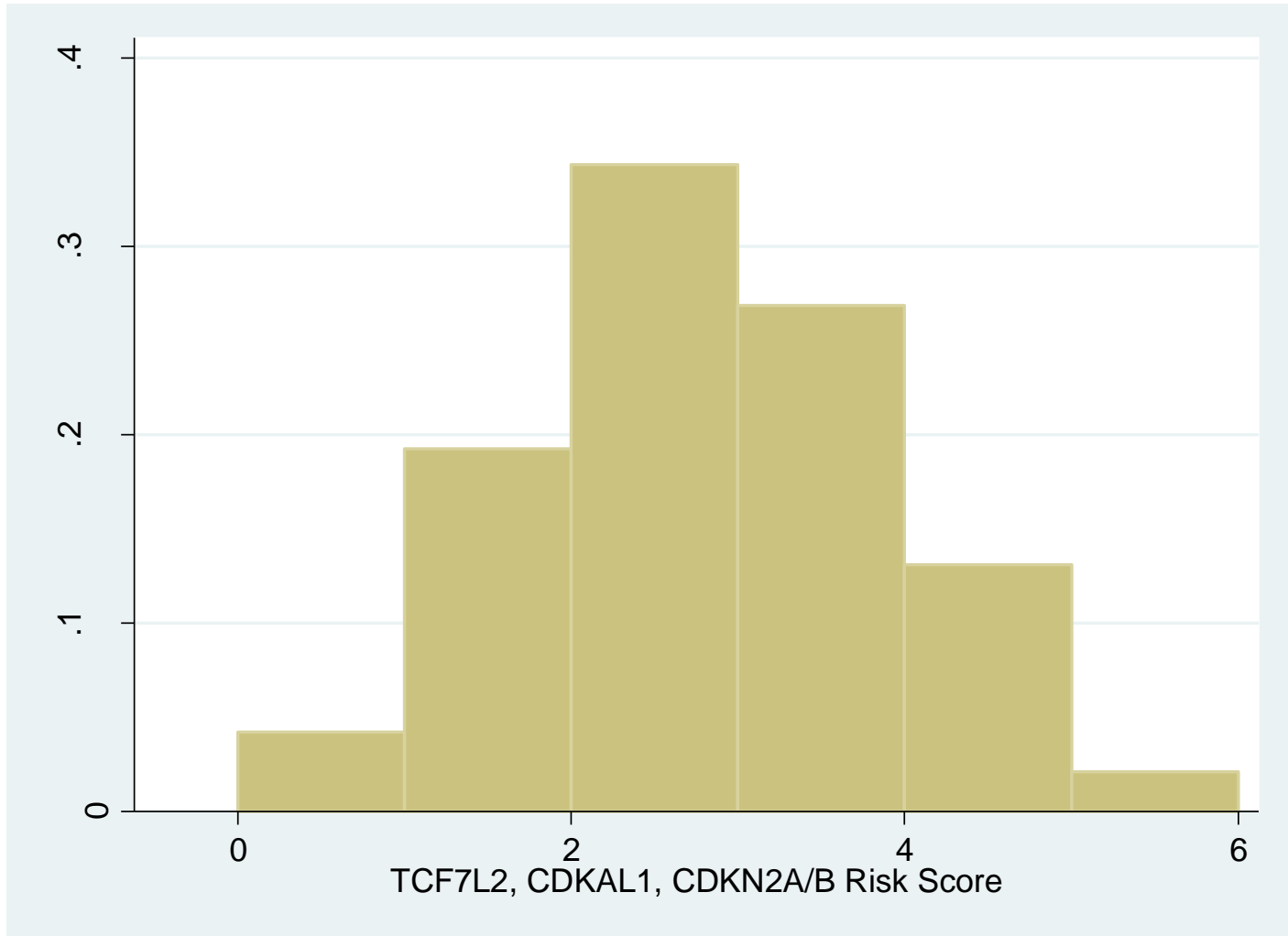
# Summary

- Study-wide significant association is seen for SNPs in CDKAL1 and CDKN2A/B loci (same risk allele as for T2DM)
- 1 of 2 SNPs in IGF2BP2 associated with CFRD
  - Study-wide significant one-sided P-value
- In all cases the same allele confers risk for T2DM and CFRD

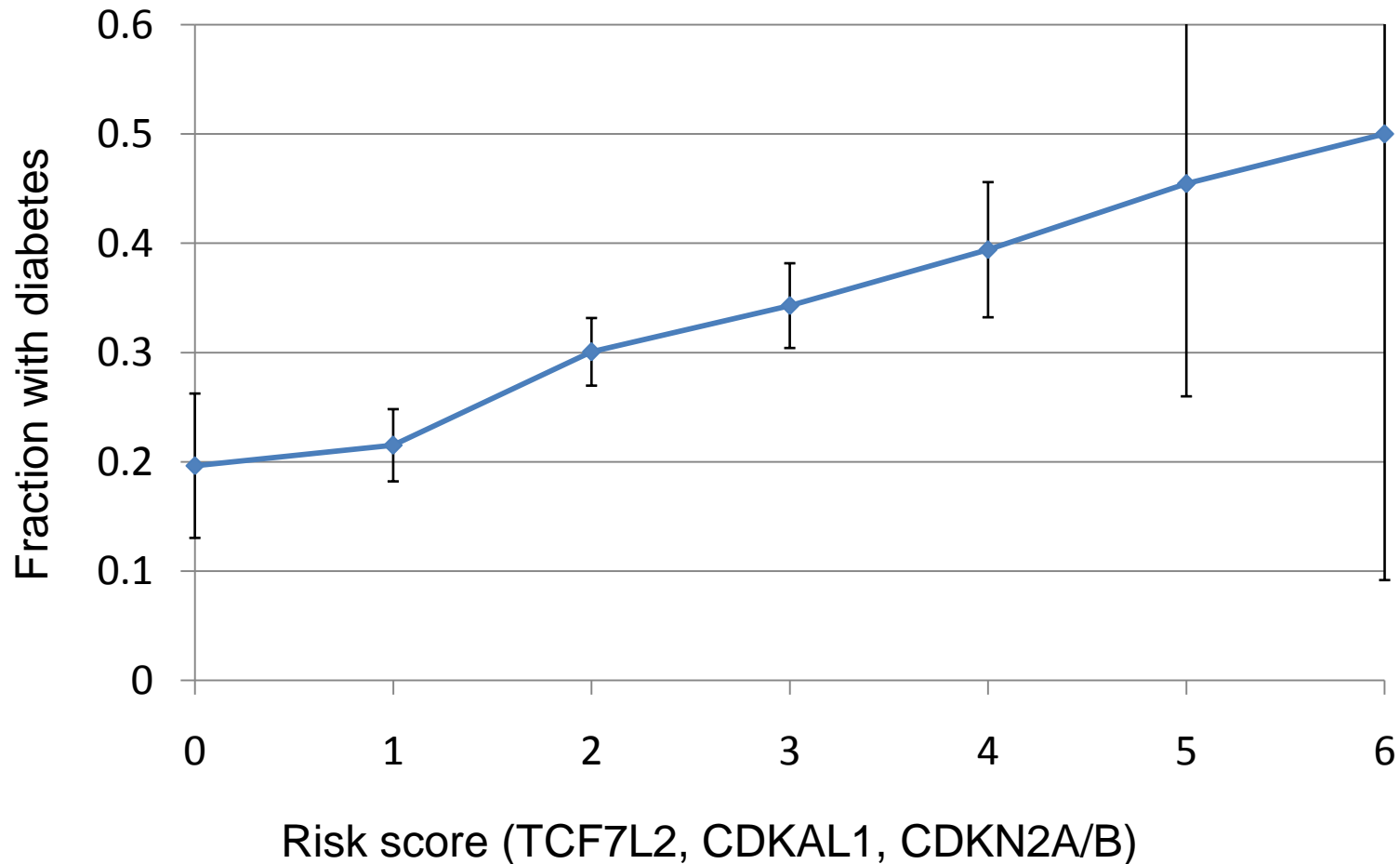
# Summary

- Mechanism of action of these susceptibility genes is not well-defined for T2D
- These T2DM/CFRD susceptibility genes may represent parts of pathways common to the disease mechanisms of T2D and CFRD
  - These SNPs may affect beta cell function (dysfunctional in both forms of diabetes) rather than insulin resistance (only in T2D)

# Risk score (# high-risk alleles)



# Prevalence of diabetes vs. 3-locus risk score



# Conclusions

- Diabetes in CF arises from gene variants beyond the CFTR gene
- Identification of at-risk CF patients raises the potential for individualized therapy such as earlier screening, treatment and prevention of diabetes.
- Gene variants conferring risk for both CFRD and T2D indicate that some disease mechanisms are shared between T2D and CFRD.

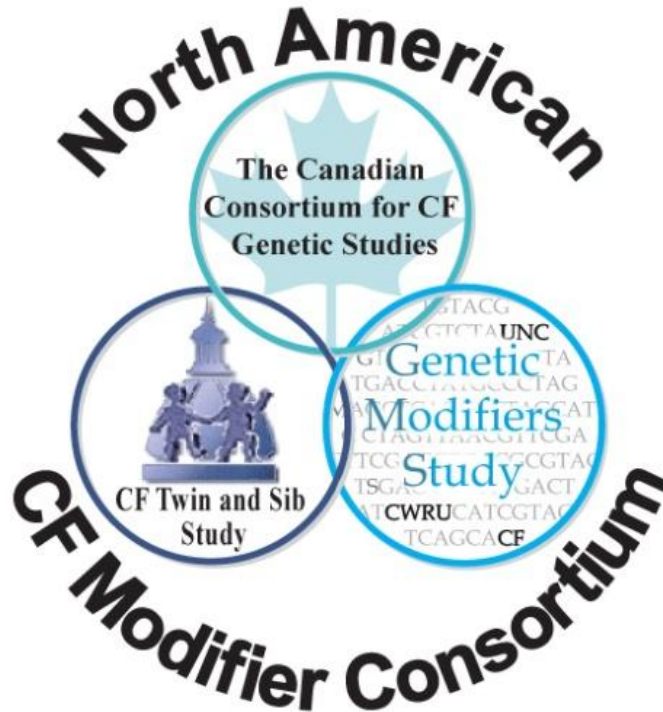
# Classes of gene associations

- CFRD and T2DM
  - Shared pathophysiology CFRD/T2DM
- T2DM only
  - Diabetes pathway unique to T2DM, e.g. insulin sensitivity, obesity, some insulin secretory
- CFRD only
  - Modifiers of CFTR function (specific to certain tissues or CFTR activity level)
- CFRD + other CF co-morbidities
  - Modifiers of CFTR function (globally)

# Many thanks to CF patient and family participants, CF center directors, and study coordinators

## Twin-Sibling Study (JHU)

Garry Cutting  
Scott Blackman  
Kathleen Naughton  
Chris Watson  
Mike Collaco  
Vishal Doshi  
Lindsay B. Henderson  
Stephanie Hsu  
Sarah Ritter  
Lori Vanscoy  
  
David Cutler



## Genetic Modifiers Study (UNC/CWRU)

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Fred Wright  
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## Canadian CF Consortium

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

Hadassah University, Israel  
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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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  
Royal Children's Hospital, Brisbane, Australia  
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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Ran Anbar, MD Donna Lindner  
Bradley Chipps, MD Kasey Pearson  
Joel Ledbetter, MD Karen Saronosky



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

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  
Univeristy of Pennsylvania Adult CF Center  
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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## CF Twin and Sib Study

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

---

Via Christi Health Center Wichita, KS

Virginia Commonwealth University

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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Andrew Lipton, MD

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