Genetics of Kidneys in Diabetes Study

DNA collection available for identifying genetic susceptibility factors for diabetic nephropathy in type 1 diabetes mellitus

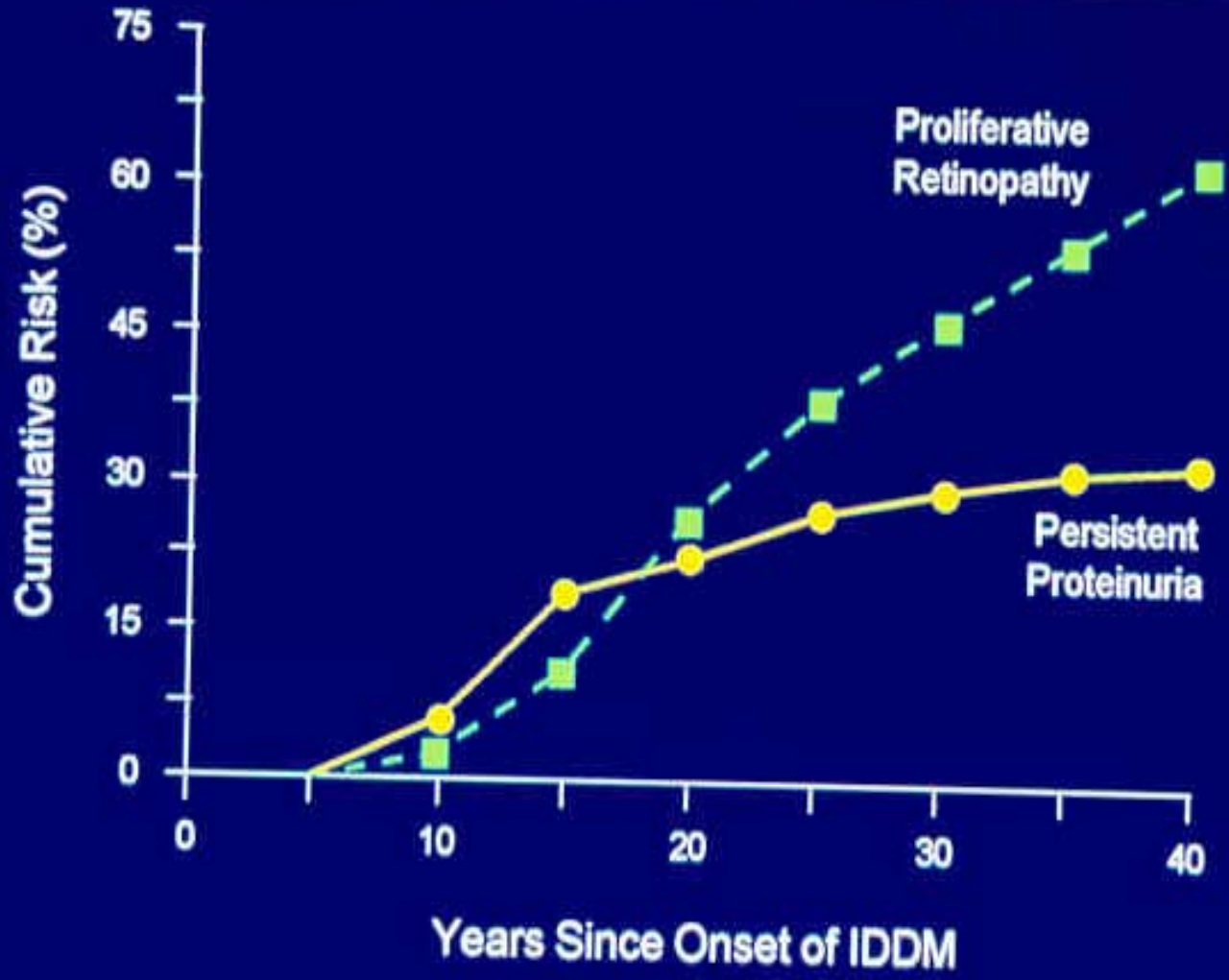
Diabetic Nephropathy

- Elevated urinary excretion of serum albumin and larger proteins as disease progresses (proteinuria)
- Progressive loss of renal function
- End-Stage Renal Disease which requires replacement therapy (dialysis or kidney transplant)

What is the evidence for genetic influence on the occurrence of nephropathy in type 1 diabetes?

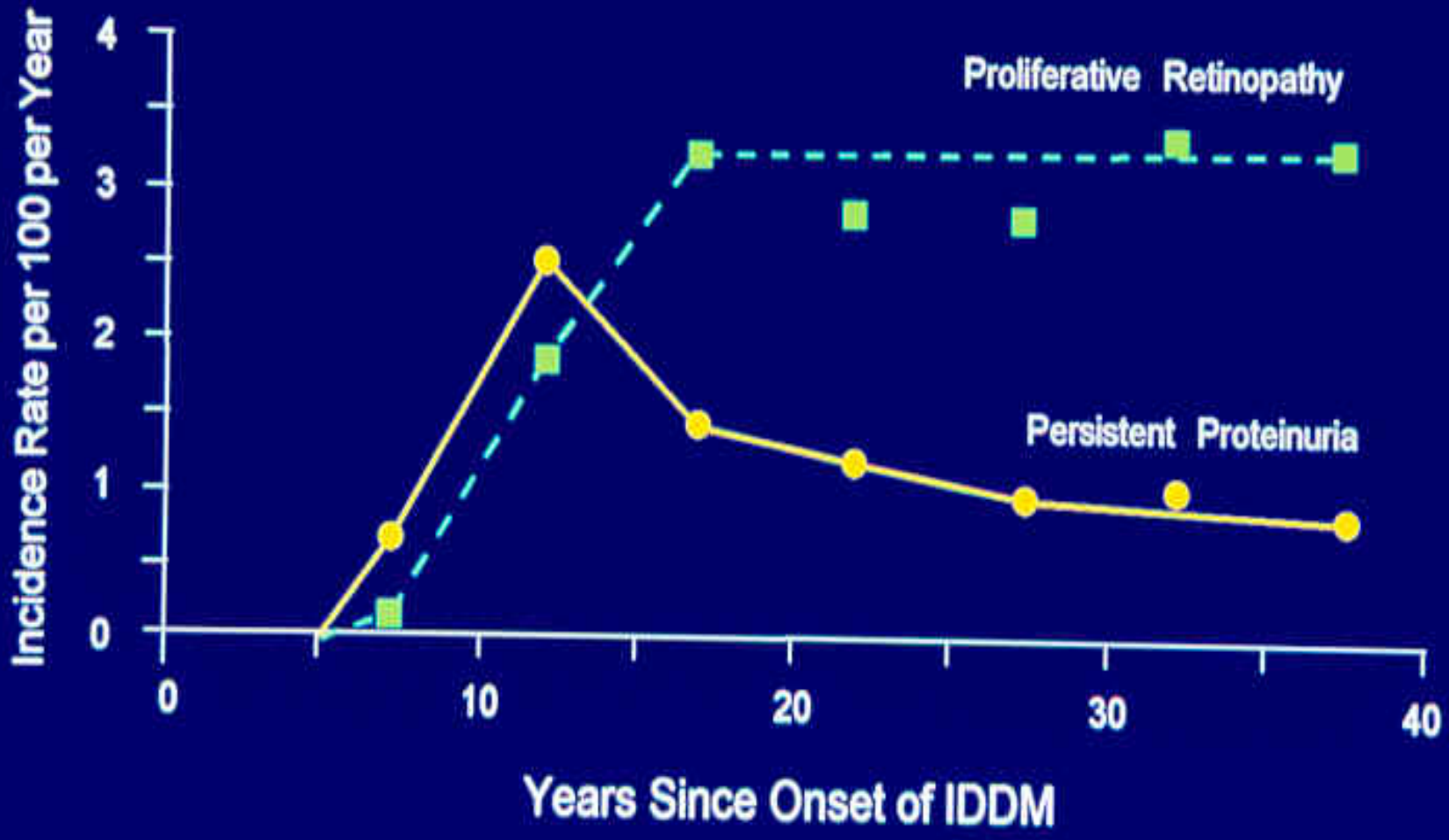
- Epidemiology
- Family Studies

Risk of Complications



(Krolewski et al. 1986)

Incidence of Complications

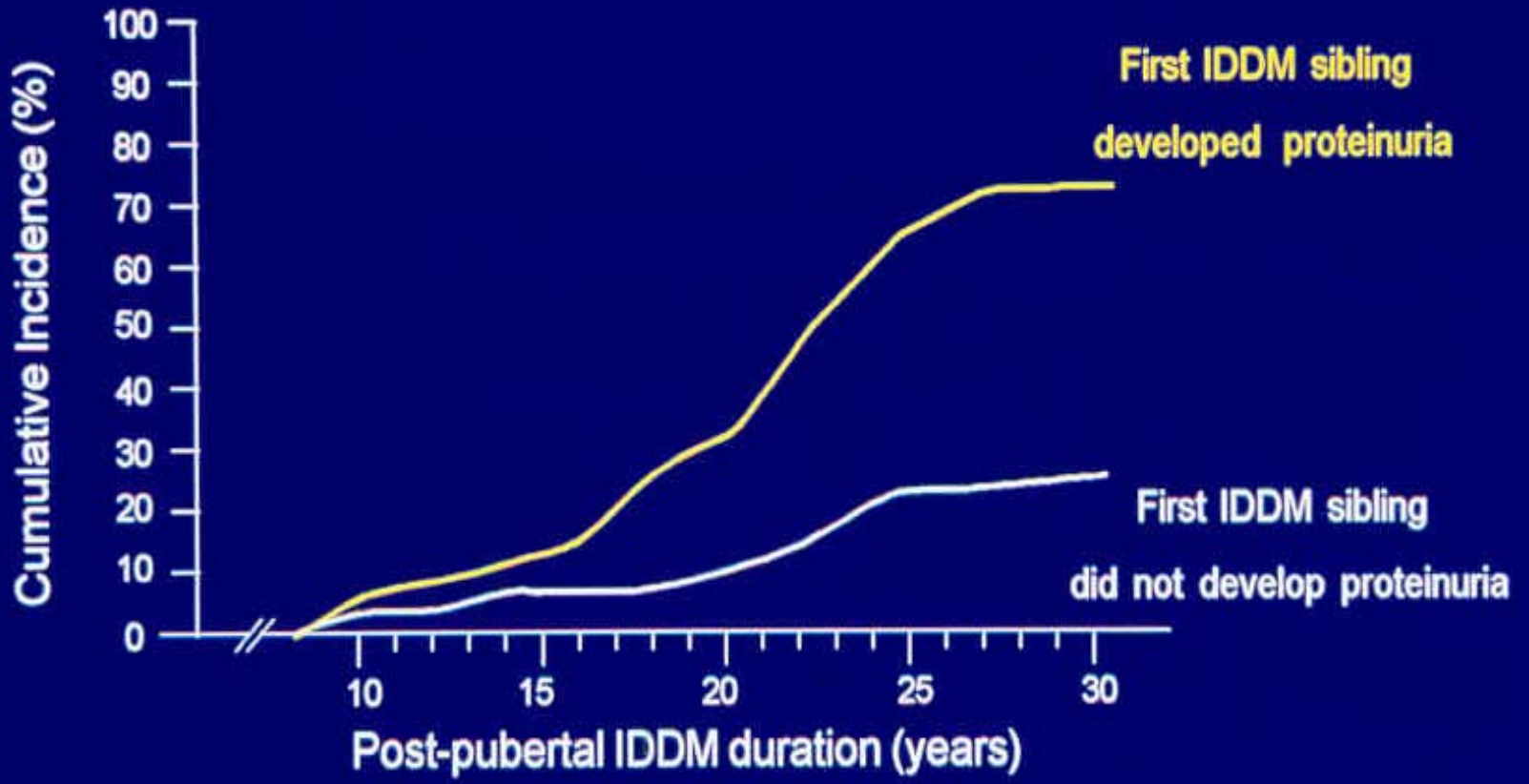


(Krolewski et al. 1986)

Diabetic Nephropathy (DN) Clusters in Families with T1DM

1) Seaquist et al. N Engl J Med 1989
2) Borch-Johnsen et al. Kidney Int 1992
3) Quinn et al. Diabetologia 1996
4) DCCT, Diabetes 1997
5) Harjutsalo et al. Diabetes 2004

Risk of Diabetic Nephropathy in the Second Sibling with IDDM in Families



The large differences between families can be explained by a major gene effect

(Quinn et al. Diabetologia 1996)

Conclusions

- The ratio (λ_s = 72% / 35% = 2.1) of the risk of DN in siblings of probands with proteinuria over the risk of DN in unrelated IDDM patients indicates the influence of genetic factors.

- A difference of nearly 50% in the DN risk to IDDM siblings, depending upon the proband's renal status, suggests that susceptibility to DN is determined by a MAJOR GENE.

- At present it is impossible to distinguish between two models ;

  a) Major gene + Hyperglycemia → DN

  b) Several oligo genes + Hyperglycemia → DN

Organization of GoKinD

- Coordinating center
  - Joslin Diabetes Center
  - GWU Biostatistical Center
- Central Biochemical Laboratory
  - University of Minnesota
- Specimen Repository
  - Centers for Disease Control and Prevention

Design of Collection

- **Cases**
  - Trios if both parents available
  - Singletons if a parent was unavailable
- **Controls**
  - Trios if both parents available
  - Singletons if a parent was unavailable

Eligibility Criteria for Cases

- Type 1 diabetes mellitus diagnosed before age 31 years
- Age 18-59 years
- Diabetes duration ≥ 10 years
- ESRD (chronic dialysis or transplant)

  or
- Proteinuria (ACR ≥ 300 µg/mg in 2 of last 3 urines)

Eligibility Criteria for Controls

- Type 1 diabetes mellitus diagnosed before age 31 years
- Age 18-59 years
- Diabetes duration ≥ 15 years
- No history of ACE-I or ARB use
- Normoalbuminuria (ACR < 20 µg/mg in 2 of last 3 urines)

Source of Cases

- Renal Unit of the Joslin Diabetes Center in New England and a network of medical centers and transplant centers elsewhere
- Data collected at examination and from medical records
- Proteinuria confirmed by the Central Biochemical Laboratory

Source of Controls

- Internal medicine clinic of the Joslin Diabetes Center in New England and a network of medical centers elsewhere
- Data collected at examination and from medical records
- Normal urinary albumin level confirmed by the Central Biochemical Laboratory

Recruitment

- Recruitment: **April 2001 - March 2005**
- Numbers enrolled:
  - Case Total: **944**
    - Trios **271**
    - Singletons **673**
  - Control Total: **945**
    - Trios **324**
    - Singletons **621**

Renal Characteristics of Study Groups

Characteristic	Cases		Controls
	ESRD	PROT	NORM
Kidney Transplant	90%	NA	NA
Duration at ESRD	24 ± 7	NA	NA
ESRD Duration	9 ± 6	NA	NA
ACR median mg/g	NA	1061	6
GFR <60 ml/min	100%	62%	3%

Demographic Characteristics

Characteristic	Cases	Controls
Caucasian	90%	97%
Female	50%	59%
Age (years)	42 ± 7	38 ± 9
BMI (kg/m^2)	26 ± 5	26 ± 4
Living Parents	50%	63%

Diabetes History

Characteristic	Case	Control
Age at Diagnosis	11 ± 7	11 ± 7
Diabetes Duration	30 ± 8	25 ± 8
Pancreas Transplant	25%	0%
HbA1c (%)	8.4 ± 1.6	7.5 ± 1.2
Insulin Pump	23%	40%

Related Characteristics

Characteristic	Cases	Controls
Hypertension	84%	6%
Retinopathy	85%	17%
CVD	87%	11%
Neuropathy	66%	12%

Quality Control

- Duplicate samples prepared for 5% of patients as quality control set
  - CBL measures: Coefficient of reliability 95%-99% except for ACR (91%)
- Sample mix-ups:
  - 3/1294 singletons
  - 10/595 trios
- Sample contamination: none detectable

GoKinD Collection Should Be a Valuable Resource for the Search for Genes for Diabetic Nephropathy in Type 1 DM

- Large number of cases with short diabetes duration enriched for genetic determinants
- Large number of controls with very long diabetes duration (>24 yrs) and most likely depleted of genetic determinants

Authorized Data Uses

- Susceptibility genes for diabetes and its complications
- Presently unknown ways that information from DNA can help the identification of these genes