



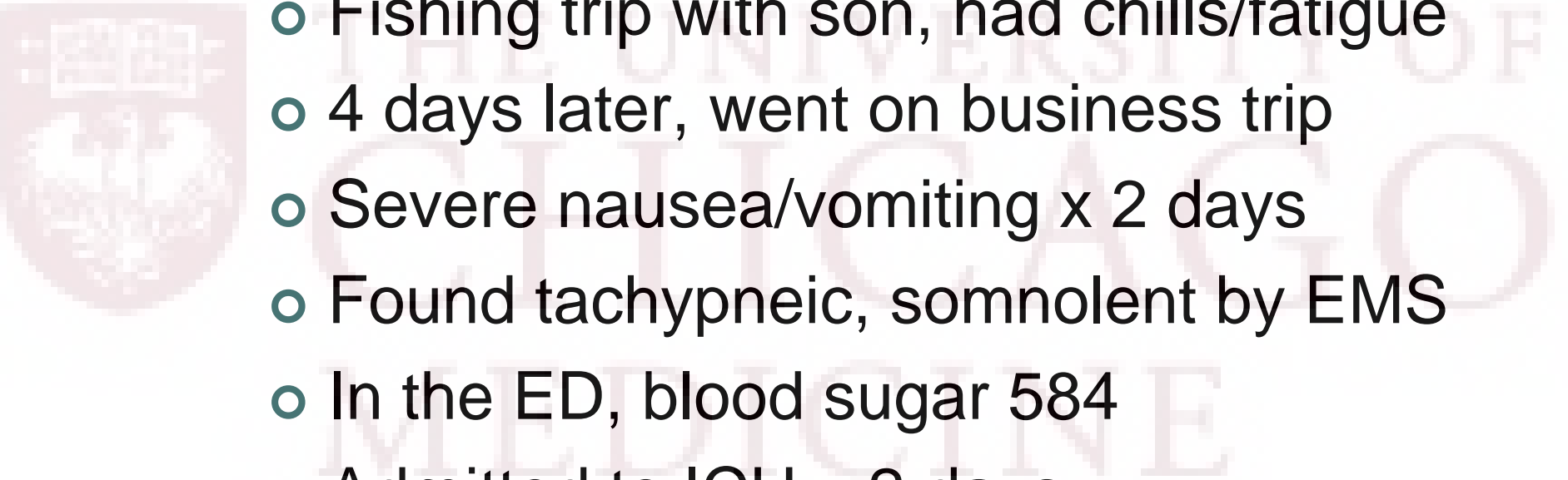
67 year-old Male with Flu-like Symptoms

Jess Hwang

12/6/12

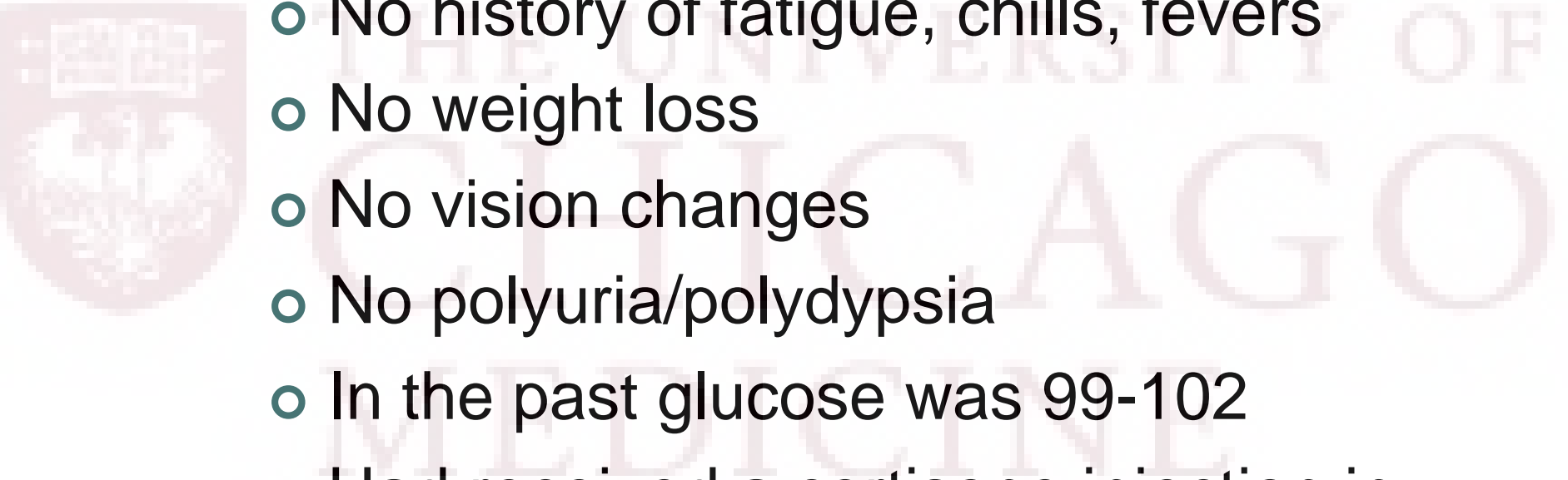


HPI

- 
- Fishing trip with son, had chills/fatigue
 - 4 days later, went on business trip
 - Severe nausea/vomiting x 2 days
 - Found tachypneic, somnolent by EMS
 - In the ED, blood sugar 584
 - Admitted to ICU x 2 days



Prior to fishing trip/hospitalization

- 
- No history of fatigue, chills, fevers
 - No weight loss
 - No vision changes
 - No polyuria/polydypsia
 - In the past glucose was 99-102
 - Had received a cortisone injection in his neck for bad DJD 1 week prior



More history

Past Medical History

Hypertension

DJD

Type 1 Diabetes

Family History

Mother- HTN, kidney stones

Diabetes only in maternal cousins and maternal uncle

Medications

Enalapril 20 mg

HCTZ 25 mg

Lantus 30U

Humalog 10U TID
w/meals

Social History

Tobacco: quit 7 years ago

EtOH: rare

Home: lives with wife

Employment: sells hardware

Initial Labs HD #1

130	102	29	461
4.5	7	1.6	

AG = 21, mod ketones

14	290
10.7	

6.3	3.3
1.4	62
27	27

UA: 3+ ketones

Lipase 102 (RR 11-52)

Amylase 125 (RR 29-100)

pH/CO₂ = 7.11/16.8

HbA1c 5.7

Anti-GAD < 5 (RR <5)



CT abdomen w/contrast

- No pancreatic hypoenhancing or hyperenhancing mass. Homogeneous enhancing pancreas.

THE UNIVERSITY OF
CHICAGO
MEDICINE



Physical Exam in Clinic

Vitals: 145/84, 75, 16, BMI 26

Gen: no distress, healthy-appearing

Neck: no thyromegaly or nodules

CV: RRR, no murmurs

Pulm: clear to auscultation, breathing comfortably

GI: soft, non-tender/non-distended

Neuro: A&O x 3

Skin: no rash



Labs from Clinic

128	93	15	201
4.1	28	0.8	

C-peptide <0.03 pmol/ml

HbA1c 6.0%

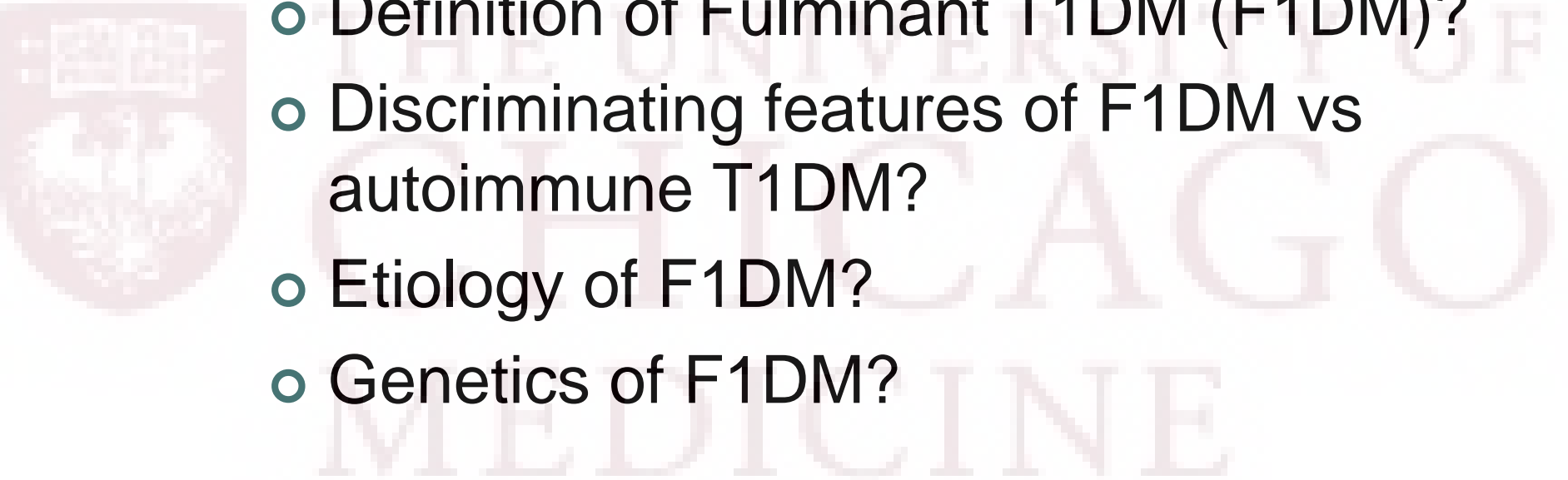
Anti-GAD 0.05 (RR <0.02)

Anti-insulin Ab neg

Anti-islet antigen (IA2) neg

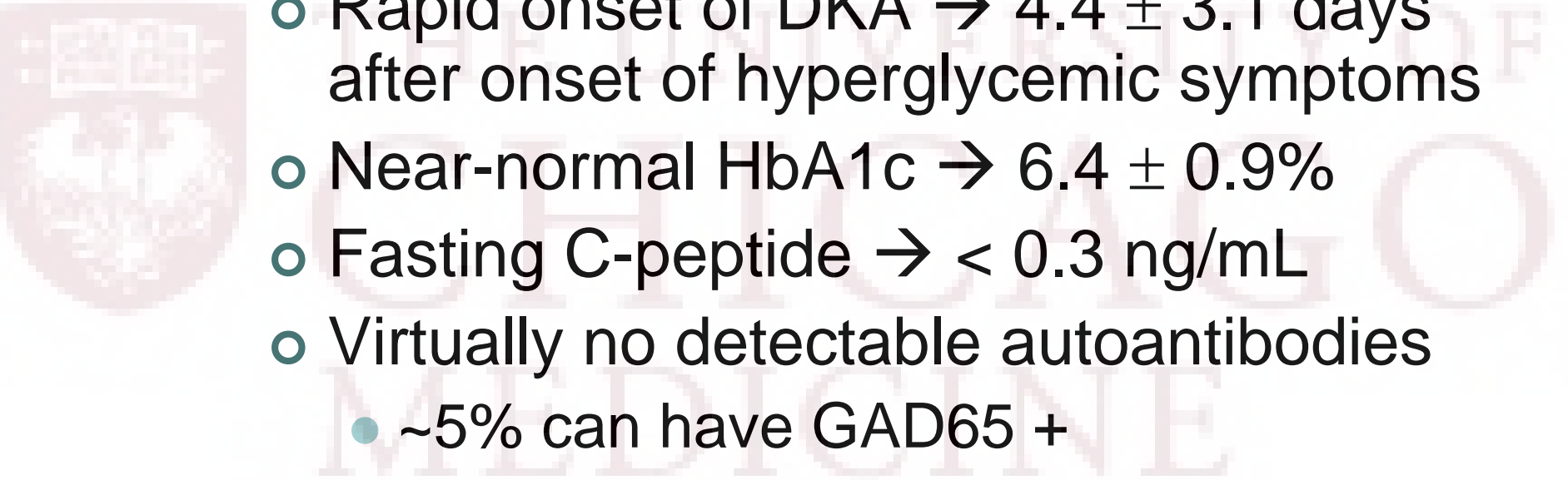


Clinical Questions

- 
- Definition of Fulminant T1DM (F1DM)?
 - Discriminating features of F1DM vs autoimmune T1DM?
 - Etiology of F1DM?
 - Genetics of F1DM?

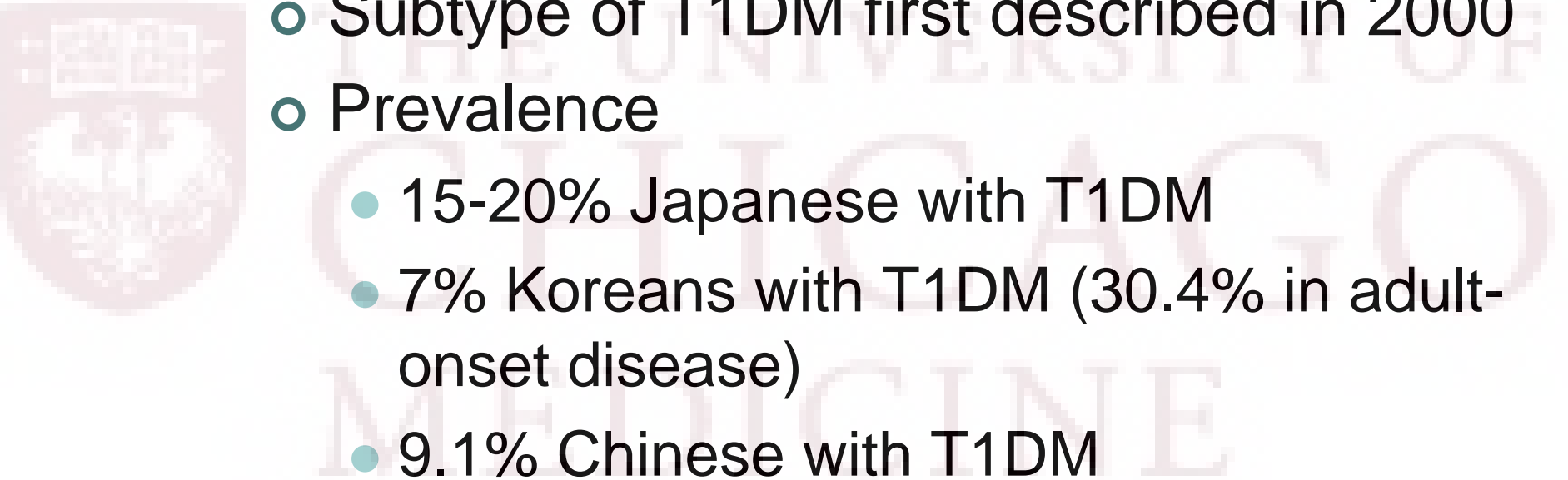


Fulminant Type 1 Diabetes

- 
- Rapid onset of DKA → 4.4 ± 3.1 days after onset of hyperglycemic symptoms
 - Near-normal HbA1c → $6.4 \pm 0.9\%$
 - Fasting C-peptide → < 0.3 ng/mL
 - Virtually no detectable autoantibodies
 - ~5% can have GAD65 +
 - Associated symptoms/labs/age



Fulminant Type 1 Diabetes

- 
- Subtype of T1DM first described in 2000
 - Prevalence
 - 15-20% Japanese with T1DM
 - 7% Koreans with T1DM (30.4% in adult-onset disease)
 - 9.1% Chinese with T1DM
 - First 3 Caucasian cases were described in 2008

Fulminant vs Typical T1DM

Characteristic	Fulminant type 1 DM	Autoimmune type 1A DM	<i>P</i> value
Duration of the disease (days)	4.4±3.1	36.4±25.1	NA
Symptoms			
Thirst	93.7	93.3	NS
Body weight loss (kg)	3.5±2.7	5.5±3.7	<0.0001
Flu-like symptoms (total)	71.7	26.9	<0.0001
Fever	60.0	ND	NA
Sore throat	25.2	ND	NA
Cough	12.0	ND	NA
Headache	11.5	ND	NA
Abdominal symptoms (total)	72.5	7.5	<0.0001
Nausea or vomiting	65.4	ND	NA
Upper abdominal pain	39.2	ND	NA
Lower abdominal pain	11.0	ND	NA
Disturbance of consciousness	45.2	5.3	<0.0001
Association with pregnancy ^a	21.0	1.5	0.0003

Fulminant vs Typical T1DM

Characteristic	Fulminant type 1 DM	Autoimmune type 1A DM	P value
Duration of the disease (days)	4.4±3.1	36.4±25.1	NA
Symptoms			
Thirst	93.7	93.3	NS
Body weight loss (kg)	3.5±2.7	5.5±3.7	<0.0001
Flu-like symptoms (total)	71.7	26.9	<0.0001
Fever	60.0	ND	NA
Sore throat	25.2	ND	NA
Cough	12.0	ND	NA
Headache	11.5	ND	NA
Abdominal symptoms (total)	72.5	7.5	<0.0001
Nausea or vomiting	65.4	ND	NA
Upper abdominal pain	39.2	ND	NA
Lower abdominal pain	11.0	ND	NA
Disturbance of consciousness	45.2	5.3	<0.0001
Association with pregnancy ^a	21.0	1.5	0.0003



Causes

- **Viral illness**: CMV/EBV, coxsackie virus B3, HHV-6, HSV, HAV, enterovirus
- **Drug hypersensitivity**: carbamazepine, mexilietine, allopurinol
- **Pregnancy**
- **Autoimmunity**: islet-specific?

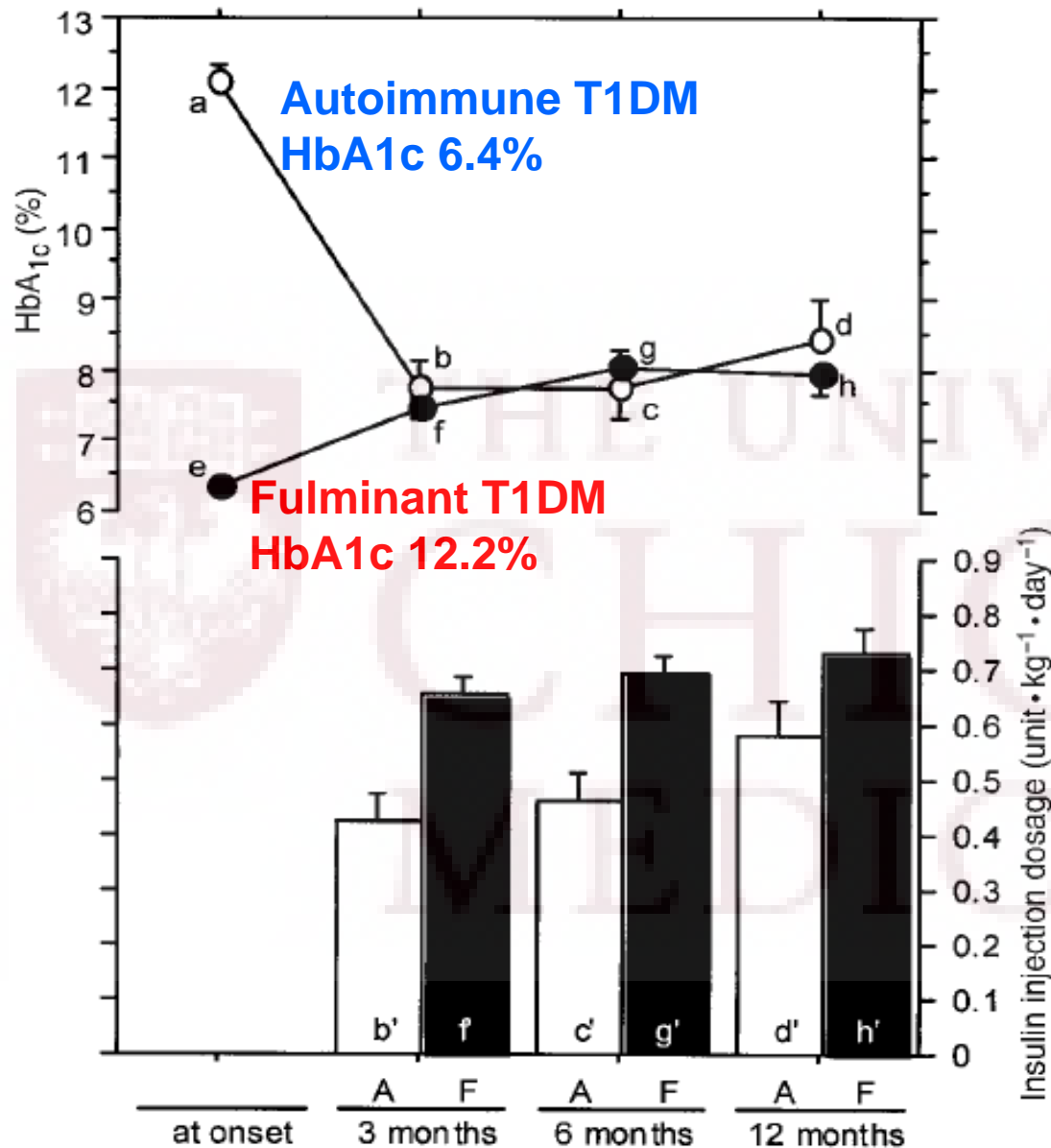
Discriminating Criteria

Discriminating criterion*	Sensitivity	Specificity
Σ C-peptide ≤ 0.540 nmol/l	96.0 (79.7–99.9)	94.0 (87.4–97.8)
Fasting serum C-peptide ≤ 0.033 nmol/l	96.0 (79.7–99.9)	94.0 (87.4–97.8)
Age at onset > 20 years	100.0 (86.2–100.0)	20.0 (12.7–29.2)
BMI > 19.1 kg/m ²	76.0 (54.9–90.6)	64.0 (53.8–73.4)
Duration ≤ 8.0 days	96.0 (79.7–99.9)	88.0 (80.0–93.6)
Glucose > 33.6 mmol/l	76.0 (54.9–90.6)	81.0 (71.9–88.2)
HbA _{1c} $\leq 8.0\%$	96.0 (79.7–99.9)	89.0 (81.2–94.4)
Arterial pH ≤ 7.21	84.0 (63.9–95.4)	74.0 (64.3–82.3)
Amylase > 345 IU/l	68.0 (46.5–85.1)	92.0 (84.8–96.5)
Lipase > 173 U/l	64.0 (42.5–82.0)	92.0 (84.8–96.5)

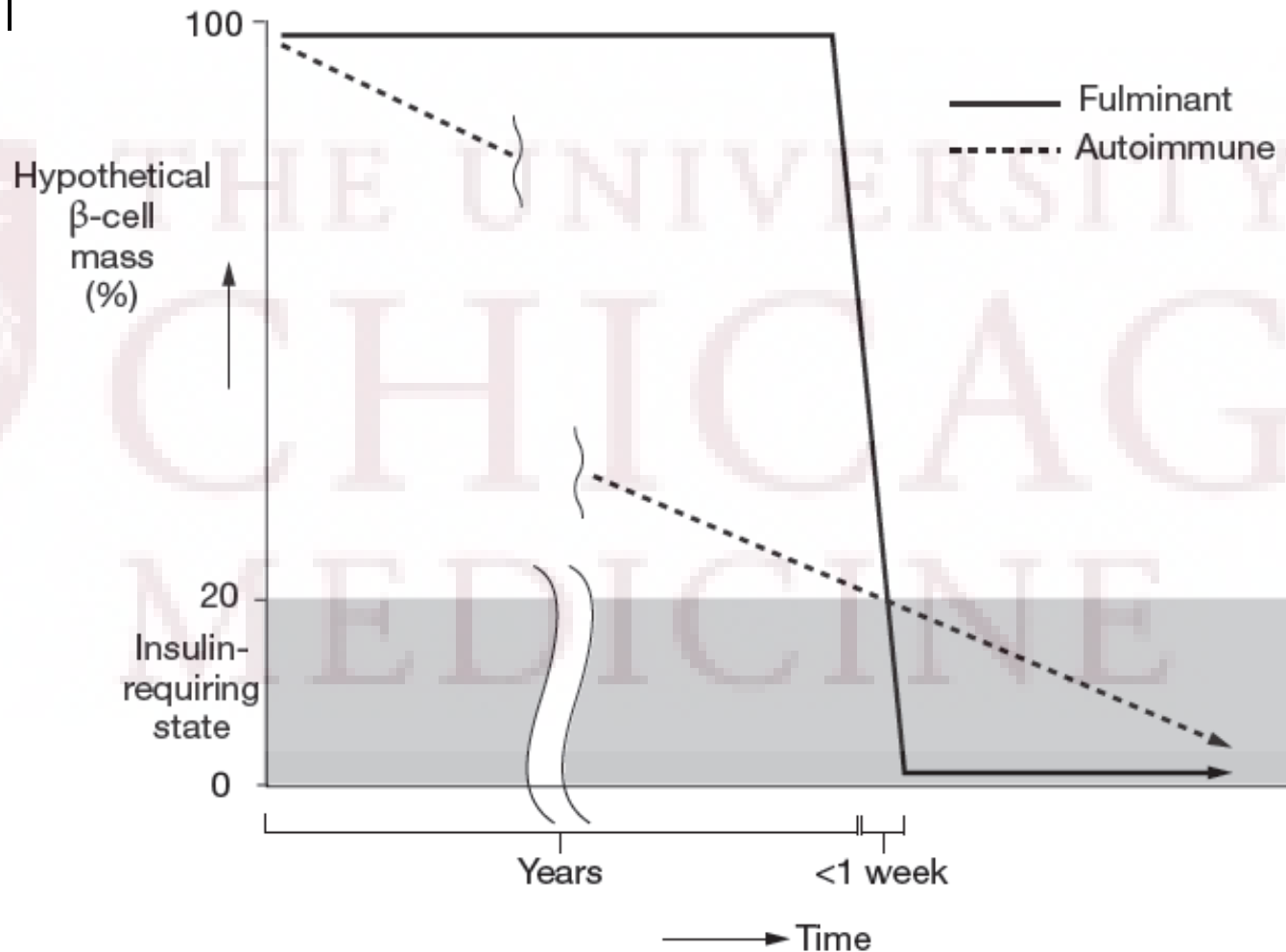
Discriminating Criteria

Discriminating criterion*	Sensitivity	Specificity
Σ C-peptide ≤ 0.540 nmol/l	96.0 (79.7–99.9)	94.0 (87.4–97.8)
Fasting serum C-peptide ≤ 0.033 nmol/l	96.0 (79.7–99.9)	94.0 (87.4–97.8)
Age at onset > 20 years	100.0 (86.2–100.0)	20.0 (12.7–29.2)
BMI > 19.1 kg/m ²	76.0 (54.9–90.6)	64.0 (53.8–73.4)
Duration ≤ 8.0 days	96.0 (79.7–99.9)	88.0 (80.0–93.6)
Glucose > 33.6 mmol/l	76.0 (54.9–90.6)	81.0 (71.9–88.2)
HbA _{1c} $\leq 8.0\%$	96.0 (79.7–99.9)	89.0 (81.2–94.4)
Arterial pH ≤ 7.21	84.0 (63.9–95.4)	74.0 (64.3–82.3)
Amylase > 345 IU/l	68.0 (46.5–85.1)	92.0 (84.8–96.5)
Lipase > 173 U/l	64.0 (42.5–82.0)	92.0 (84.8–96.5)
Our patient		

HbA1c & Insulin Dose



Beta cell destruction





HLA typing

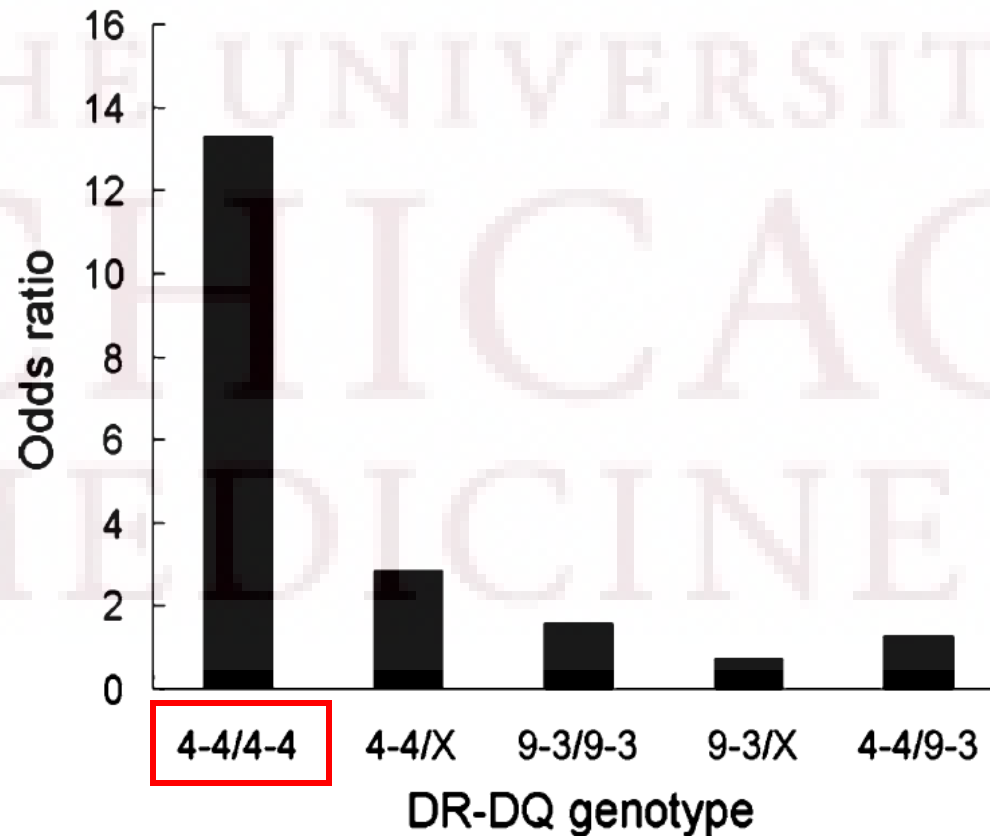
- 
- Class II HLA loci on chromosome 6q21.3 are most strongly associated with T1DM risk
 - HLA haplotypes in Chinese are different than in Japanese with F1DM
 - In pregnancy homozygotes for DR9-DQ3 is strongly associated with susceptibility to F1DM (OR 10.0)

HLA Genotypes in T1DM

<i>DRB1-DQB1</i>	Control (<i>n</i> =396)		Acute (<i>n</i> =338)		Fulminant (<i>n</i> =80)		SP (<i>n</i> =127)		A vs C		F vs C		SP vs C	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>p</i> _c value	OR	<i>p</i> _c value	OR	<i>p</i> _c value	OR
<i>DR4/4</i>	5	1.3	28	8.3	10	12.5	9	7.1	4.3×10^{-5}	7.1	1.4×10^{-6}	11.2	0.014	6.0
<i>DR9/9</i>	12	3.0	53	15.7	6	7.5	10	7.9	9.8×10^{-9}	6.0	NS	2.6	NS	2.7
<i>DR4/9</i>	15	3.8	46	13.6	11	13.8	12	9.4	1.4×10^{-5}	4.0	0.013	4.1	NS	2.7
<i>DR4/8</i>	1	0.3	33	9.8	1	1.3	5	3.9	5.6×10^{-10}	42.7	NS	5.0	0.034	16.2
<i>DR8/9</i>	3	0.8	9	2.7	1	1.3	1	0.8	NS	3.6	NS	1.7	NS	1.0
<i>DR4/X</i>	70	17.7	70	20.7	19	23.8	30	23.6	NS	1.2	NS	1.5	NS	1.4
<i>DR9/X</i>	75	18.9	48	14.2	14	17.5	29	22.8	NS	0.71	NS	0.91	NS	1.3
<i>DR8/X</i>	10	2.5	6	1.8	1	1.3	7	5.5	NS	0.70	NS	0.49	NS	2.3
<i>DRX/X</i>	205	51.8	45	13.3	17	21.3	24	18.9	1.9×10^{-28}	0.14	5.4×10^{-6}	0.25	2.2×10^{-10}	0.2

Kawabata Y et al. Diabetologia 2009;52:2513-2521.

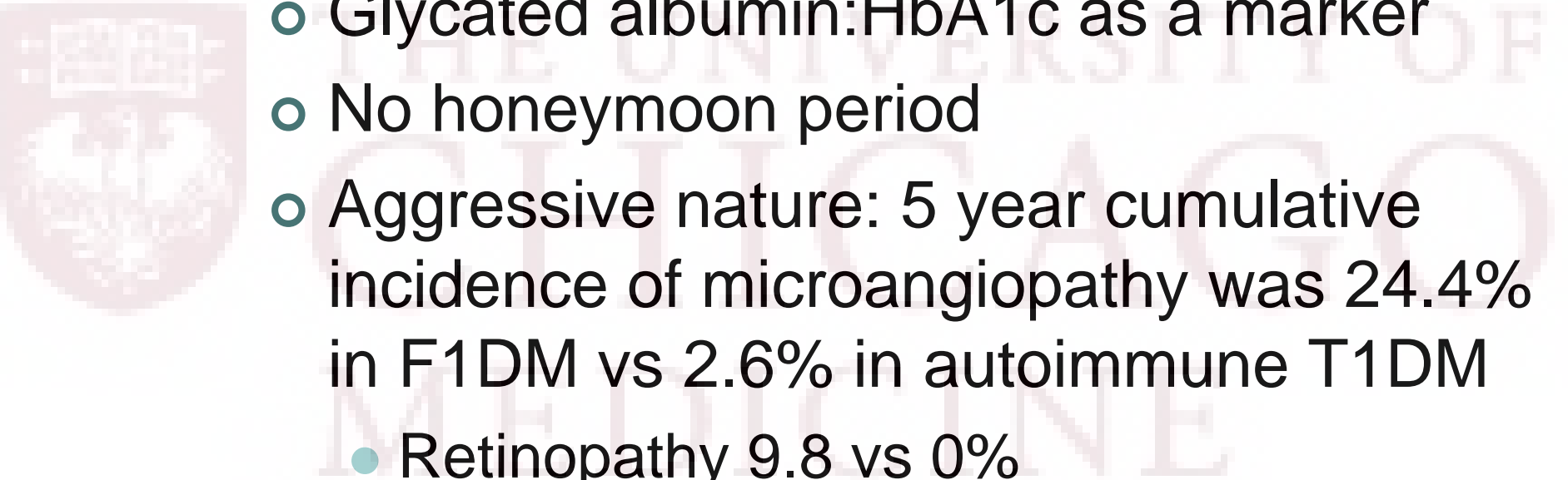
HLA subtypes and F1DM



Kawasaki E et al. Genetics of F1DM. Ann NY Acad Sci 2006;1079:24-30.

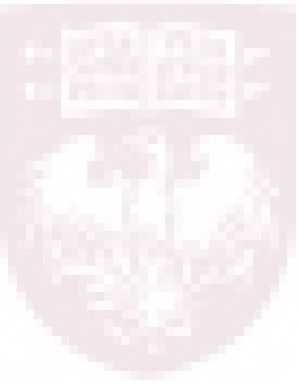


Management Points

- 
- Glycated albumin:HbA1c as a marker
 - No honeymoon period
 - Aggressive nature: 5 year cumulative incidence of microangiopathy was 24.4% in F1DM vs 2.6% in autoimmune T1DM
 - Retinopathy 9.8 vs 0%
 - Nephropathy 12.2 vs 2.6%
 - Neuropathy 12.2 vs 2.6%.

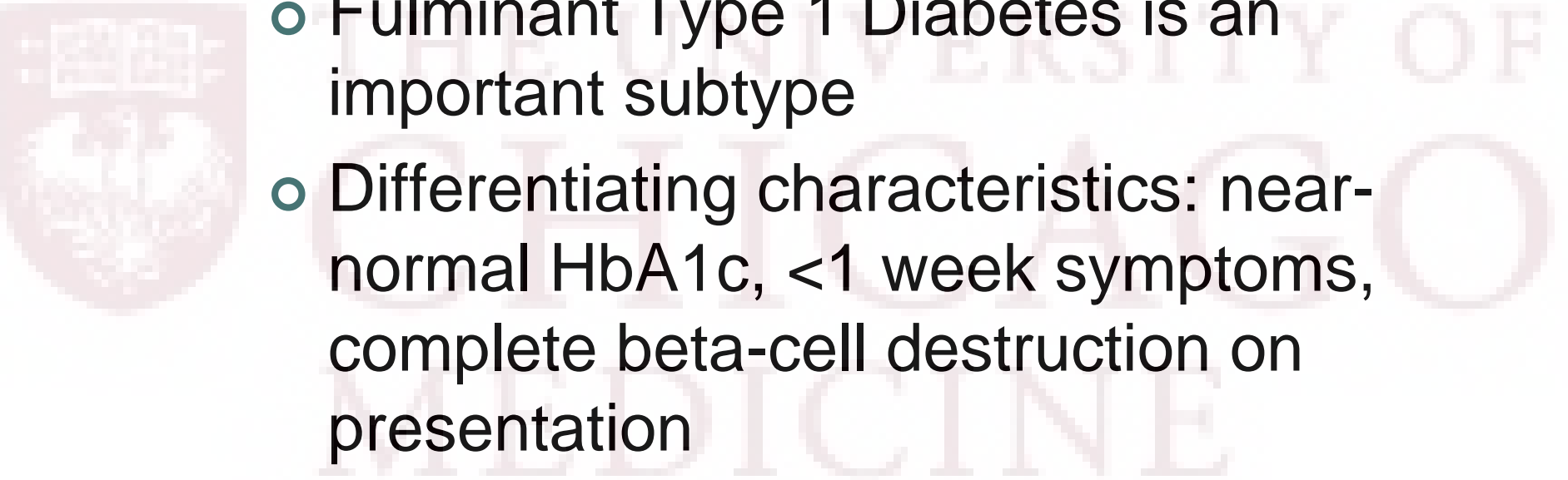


HLA testing for our patient

- 
- In Caucasians, susceptibility to T1DM is strongly associated with HLA DR3/DR4
 - Through the monogenic diabetes registry, testing showed he did not have HLA DR high risk genes



Take Home Points

- 
- Fulminant Type 1 Diabetes is an important subtype
 - Differentiating characteristics: near-normal HbA1c, <1 week symptoms, complete beta-cell destruction on presentation
 - Etiology is unclear, possible underlying genetic predisposition



References

- Zheng C et al. F1DM Exhibits Distinct Clinical and Autoimmunity Features From Classical T1DM in Chinese. Diab/Metab Research and Reviews. 2011;27:70-78.
- Murase-Mishiba Y et al. Fulminant T1DM as a Model of Nature to Explore the Role of C-peptide. Exp Db Research 2008;2 pgs.
- Imagawa A et al. F1DM. Diab Care 2003;26(8):2345-2352.
- Sue M. Characteristics of F1DM. Med Sci Monitor 2008;14(10):CS97-101.
- Hanafusa T et al. F1DM: a Novel Clinical Entity Req Special Attn by All Med Practitioners. Nature 2007;3(1):36-45.
- Tanaka S et al. Distinct Diagnostic Criteria of F1DM Based on Serum C-peptide Response and HbA1c levels at Onset. Diab Care 2004;27(8):1936-1941.
- Kawabata Y et al. Differential Assoc of HLA w/3 Subtypes of T1DM: F1DM, SP T1DM, Acute-Onset T1DM. Diabetologia 2009;52:2513-2521.
- Kawasaki E et al. Genetics of F1DM. Ann NY Acad Sci 2006;1079:24-30.
- Onuma H et al. High Freq HLA B62 in F1DM w/drug-induced Hypersensitivity Syndrome.