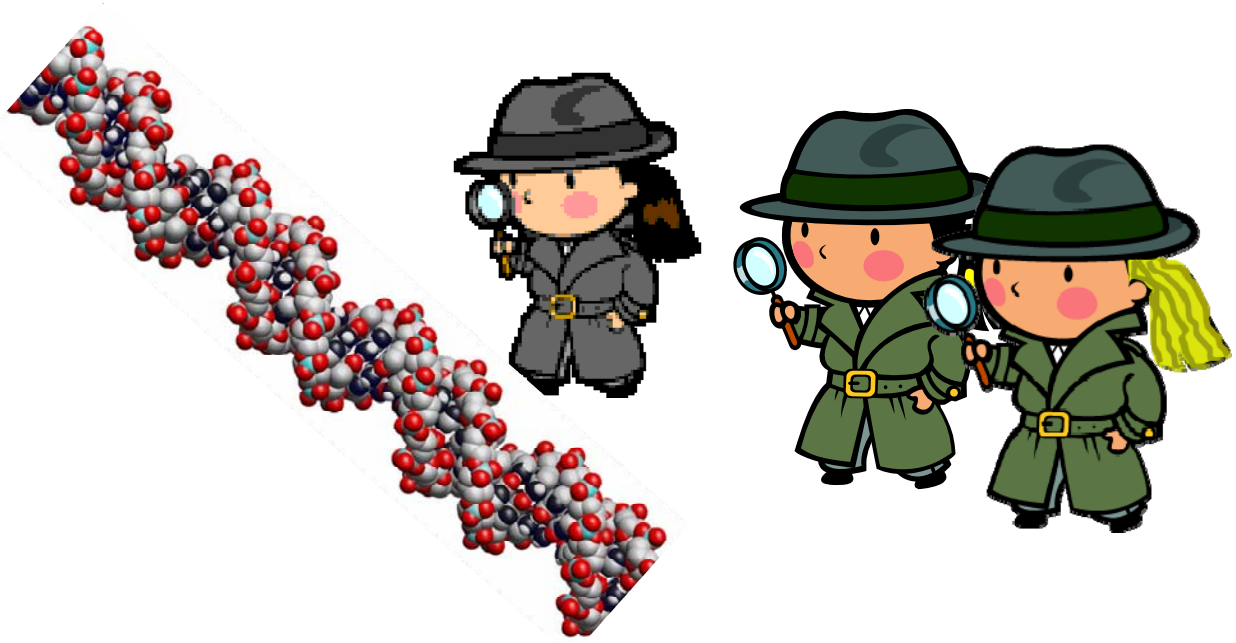
GENETIC STUDIES OF AUTOIMMUNE DISEASES

Benedicte Alexandre Lie
Institute of Immunology
Rikshospitalet
University Hospital



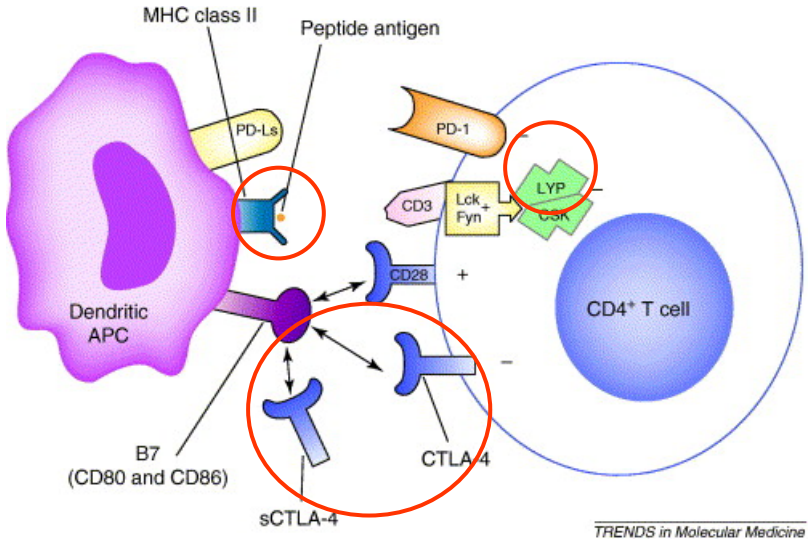
RIKSHOSPITALET

Autoimmune diseases

- Affects approximately 5 % of the population
- Results from an immune response against self tissue and organs
- Affects different organs; rheumatoid arthritis (joints), type 1 diabetes (pancreas), primary sclerosing cholangitis (liver)
- Mainly complex diseases with several underlying genetic and environmental risk factors
- Genetic heterogeneity – multiple combinations of risk alleles could cause the same disease

Shared genetic risk factors

- Several identified genetic risk factors are shared by several autoimmune diseases
- The common autoimmune risk factors are often genes of an immunological nature.
- Autoimmune diseases tend to accumulate in some families
- Different autoimmune diseases affect the same individual more often than expected
- Overlap between chromosomal regions showing linkage or association with different autoimmune diseases



Pearce and Marriman, Trends Mol Med, 2006

Diseases and networks

- **Type 1 diabetes** [Dag Undlien, Kjersti Skjold Rønningen, Knut Dahl-Jørgensen, Geir Joner]
- **Rheumatoid arthritis** [Tore Kvien, Øystein Førre, Knut Helgetveit]
- Primary sclerosing cholangitis [Tom Karlsen, Kirsten Boberg, Erik Schrumpf]
- Multiple sclerosis [Hanne Harbo, Elisabeth Celius]
- Myastenia gravis [Chantal Tallaksen, Hanne Harbo]
- Juvenile idiopathic arthritis [Berit Flatø, Anne Marit Selvaag, Øystein Førre]
- Inflammatory bowel disease [Morten Vatn]
- Celiac disease [Silja Amundsen, Ludvig Sollid]
- Systemic lupus erythematosis [Vibke Lilleby, Inge Margrete Gilboe, Øystein Førre]

Immunogenetics environment at IMMI

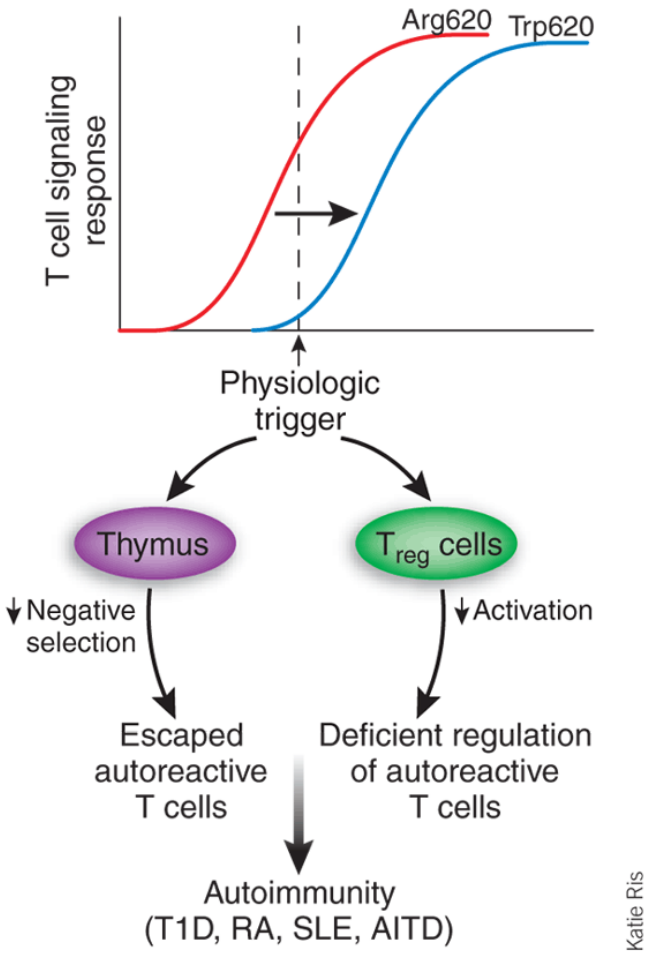
Immunogenetics group

Anne Blomhoff
Morten C. Eike
Siri T. Flåm
Linda Haugse
Johannes Hov
Tom H. Karlsen
Åslaug R. Lorentzen
Angelina Maniaol
Espen Melum
Inger-Lise Mero
Gry B. N. Nordang
Hege D. Sollid
Erik Thorsby
Marte K. Viken
Benedicte A. Lie

International collaborators

T1D genetic consortium
Marita Olsson
Tim Becker
Keith Humphreys
Anne Cambon-Thomsen
Flemming Pociot
Jørn Nerup
Ingrid Kockum

PTPN22 1858T is associated with a number of autoimmune diseases



- Identified as a risk factor for type 1 diabetes when studied as a candidate SNP based on function

Bottini et al, Nat Genet, 2004

- Simulaneously identified as a risk factor for rheumatoid arthrits through a screen

Begovich et al, Am J Hum Genet, 2004

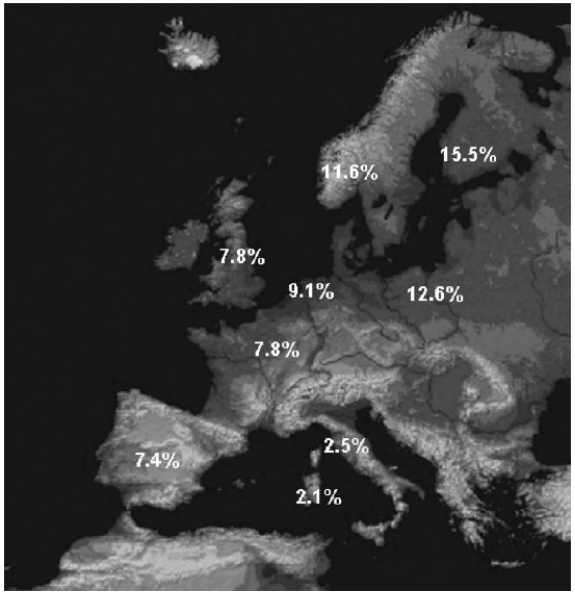
PTPN22 1858T is associated with a number of autoimmune diseases

	Celiac Disease	Primary sclerosing cholangitis	Systemic lupus erythematosus	Controls
	(N = 316)	*(N = 219)*	*(N = 162)*	*(N = 555)*
Carriers of T-allele, % (*n*)	26.9 (85)	20.6 (45)	20.4 (33)	21.4 (119)
Non-T-allele, % (*n*)	73.1 (231)	79.4 (173)	79.6 (129)	78.6 (436)
Odds ratio T-carriers *vs* non-T-carriers	1.35	0.95	0.94	
95% confidence interval for the OR	0.97–1.88	0.64–1.43	0.59–1.47	
Fisher's exact test, two-tailed *P*-value	0.08	0.8	0.8	

Viken et al, Genes Immunol, 2005

Diseases associated	**Not associated**
Type 1 diabetes	Inflammatory bowel disease
Rheumatoid arthritis	Psoriasis
Systemic lupus erythematosis	Multiple sclerosis
Juvenile idiopathic arthritis	Celiac disease
Grave's disease	Primary sclerosis cholangitis

PTPN22 1858T population differences

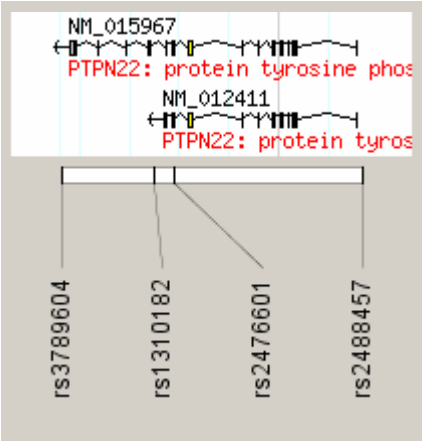


Gregersen et al, Semin Immunol, 2006

Asia < 1%

→ Is PTPN22 only a predisposing gene for autoimmune diseases in some populations?

→ Is the 1858T allele the causal and the only risk variant?



Other proposed variants:

rs1310182 and rs3789604 in RA

Carlton et al, Am J Hum Genet, 2005

rs2488457 (-1123G>C) in T1D in Asia

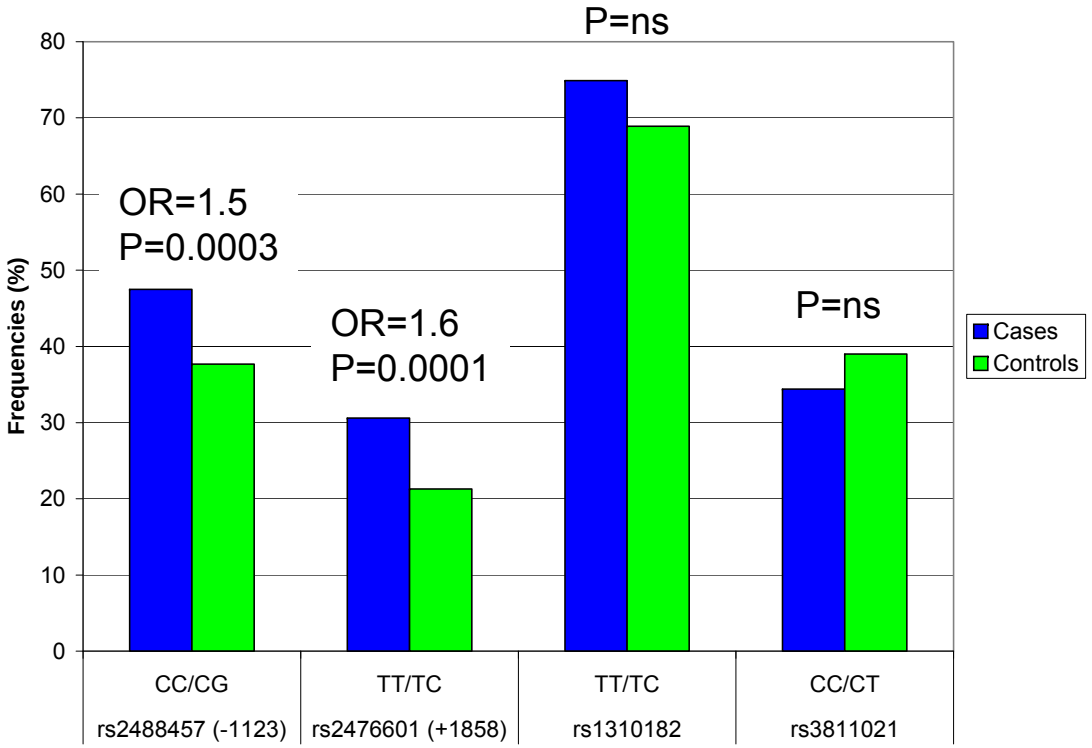
Kawasaki et al, Am J Med Genet, 2006

K750N (rare variant) in T1D

Onengut-Gumuscu et al, Diabetes, 2006

-1123C cannot be distinguished from 1858T in a Norwegian RA data set

The -1123C allele shows an association of similar magnitude as the 1858T allele

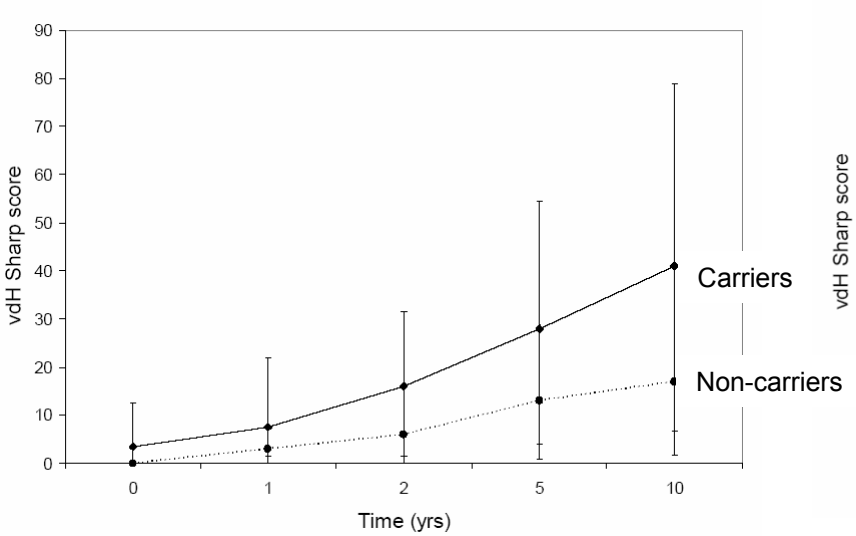


Either -1123C or 1858T can explain the association observed

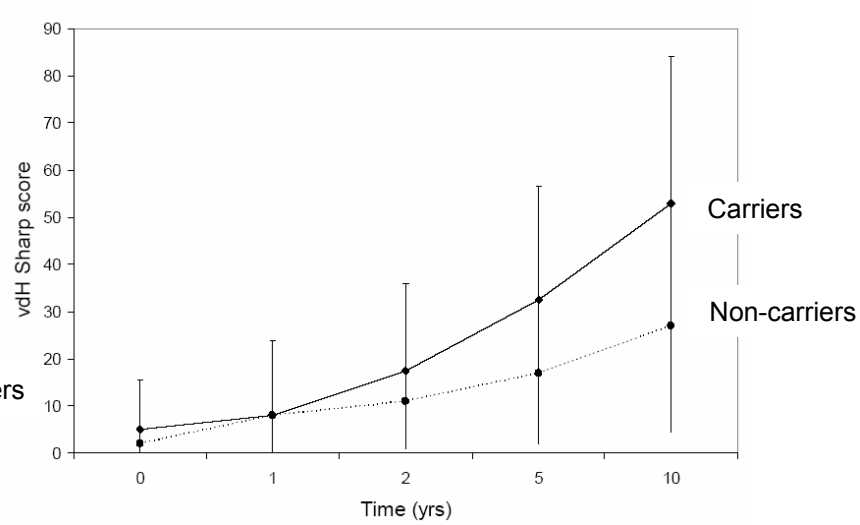
Viken et al, Tissue Antigens, 2007

PTPN22 1858T is associated with increased joint destruction in RA patients

All patients (P=0.01)



SE+ patients (P=0.02)



The radiographic progression was somewhat higher among patients carrying the PTPN22 1858T risk variant and this difference increased over time

Lie et al, Ann Rheum Dis, 2007

No association between joint destruction and the -1123C allele

Wellcome Trust Case Control Consortium

- The Wellcome Trust Case Control Consortium (WTCCC) is a collaboration of 24 human geneticists in the UK to identify genetic risk variants for 13 condition (http://www.wtccc.org.uk/).
- GWAS in 2000 type 1 diabetes, 2000 rheumatoid arthritis, 2000 type 2 diabetes and 3000 controls
- Affymetrix 500K


Vol 447|7 June 2007|doi:10.1038/nature05911 nature

ARTICLES

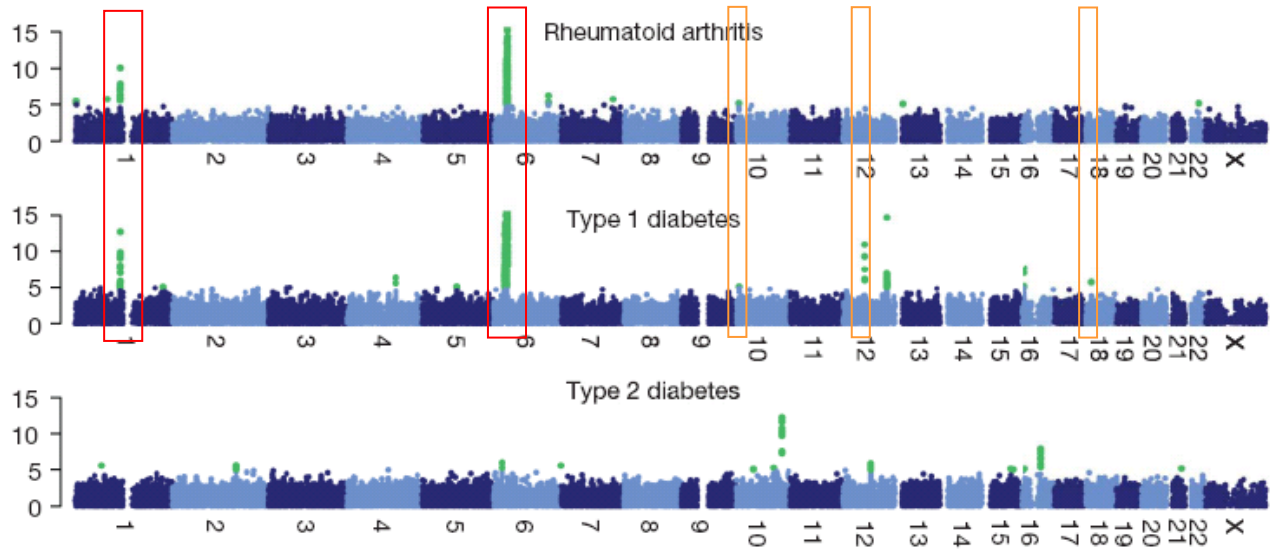
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

WTCCC, Nature, 2007

Risk factors in common

P<10-5 in green



- Five regions overlap between type 1 diabetes and rheumatoid arthritis (two previously known)
- No detected overlap between type 1 diabetes and type 2 diabetes

WTCCC, Nature, 2007

False negatives and positives

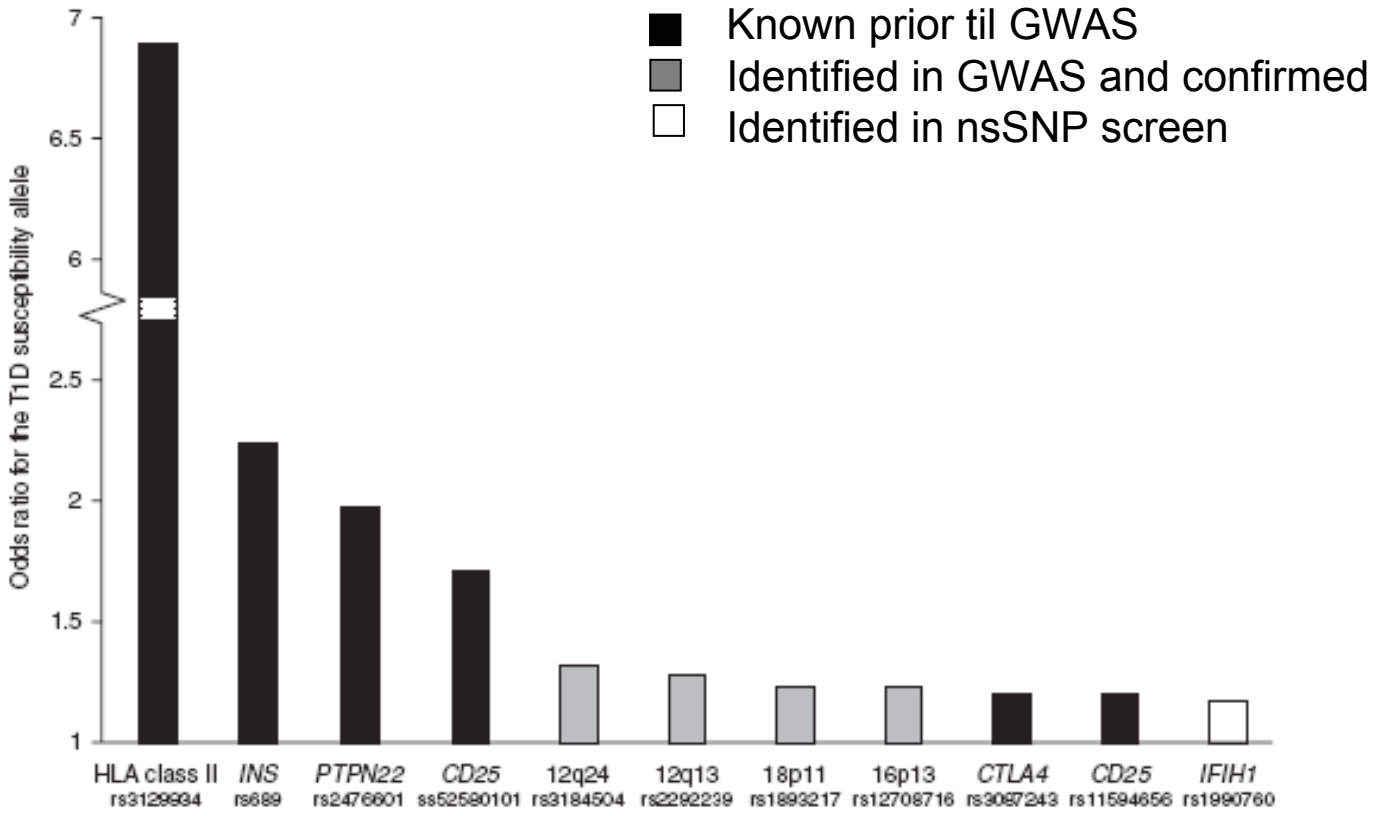
- Detected 13 of 15 variants with strong prior evidence of association
- Two lost due to poor tagging and failure of essential SNP
- Unability to detect association ($P<5 \times 10^{-7}$) does not exclude any given gene (rare variants, low effect size)

WTCCC, Nature, 2007

- 4000 patients – 5000 controls and 2997 trio families
- Attempted to validate six novel regions with $P<5 \times 10^{-7}$, and four was confirmed ($P<1.35 \times 10^{-9}$)
- Six other top findings ($P<1.64 \times 10^{-5}$) was tested, but not convincingly confirmed ($3 \times P \sim 10^{-3}$ or 10^{-4}) or false positives

Todd et al, Nat Genet, 2007

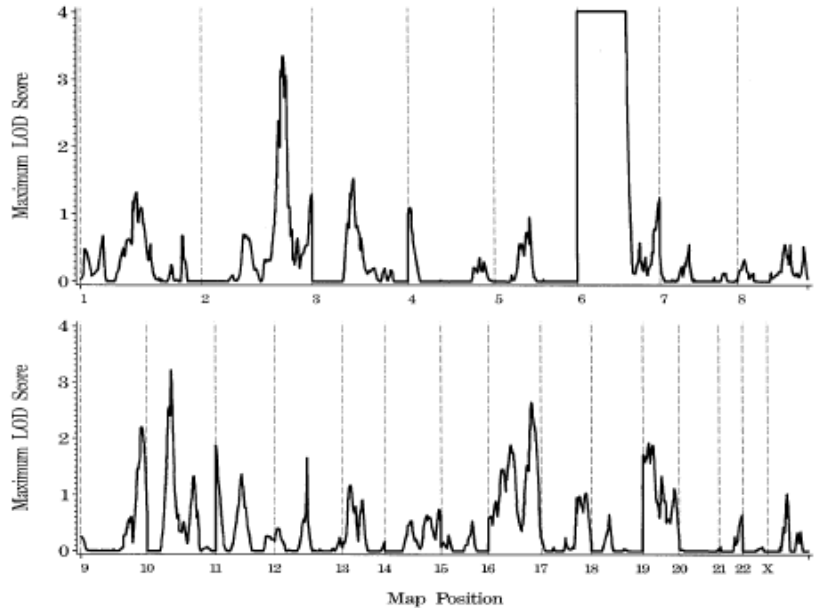
Susceptibility alleles in type 1 diabetes



Todd et al, Nat Genet, 2007

MHC is the main genetic determinant

- Linkage scans in 1435 multiplex families
- Ten regions showed evidence of linkage (nominal $P<0.01$), including MHC (nominal $P<2x10^{-52}$)
- Only MHC reached genome-wide significance
- About 40% of the familial aggregation of type 1 diabetes can be attributed to variants in the MHC



Concannon et al, Diabetes, 2005

Type 1 diabetes genetic consortium

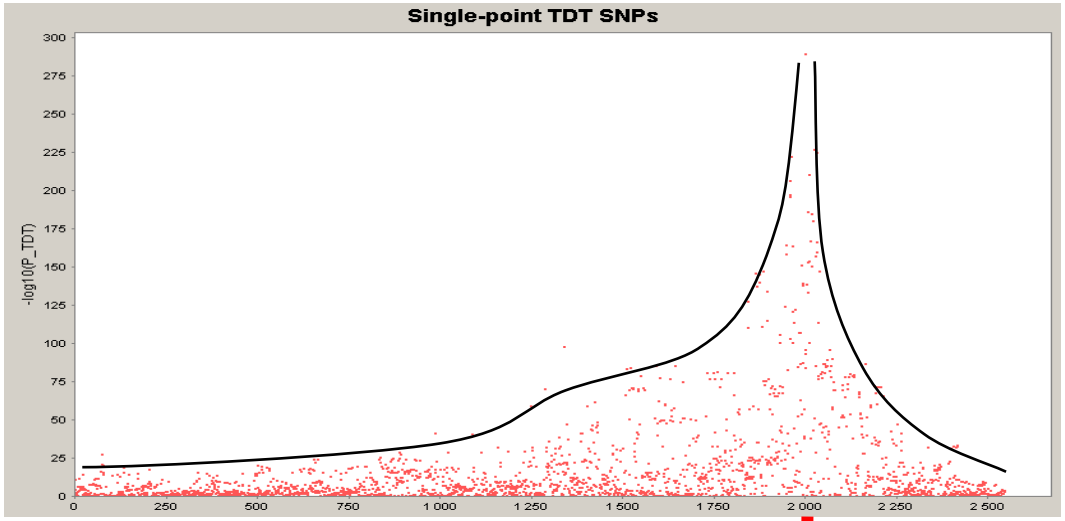
- International effort to identify genes that affect the risk of type 1 diabetes
- Cross-sectional collection of genetic material and phenotypic data from 2400 affected sib-pair families (~10000 individuals)
- Create a repository of DNA, biological samples and data for use by scientific community

Type 1 Diabetes Genetics Consortium (T1DGC)

www.t1dgc.org

Type 1 diabetes and the HLA association

- Three loci in the MHC known to carry risk alleles:
  DRB1, DQA1 and DQB1
- More risk variants are hiding in this chromosomal region
- The T1DGC-MHC project:
  - 2321 T1D families of multiple (mostly Caucasian) ethnicities
  - 2957 SNPs; 66 microsatellites; 8 HLA-loci

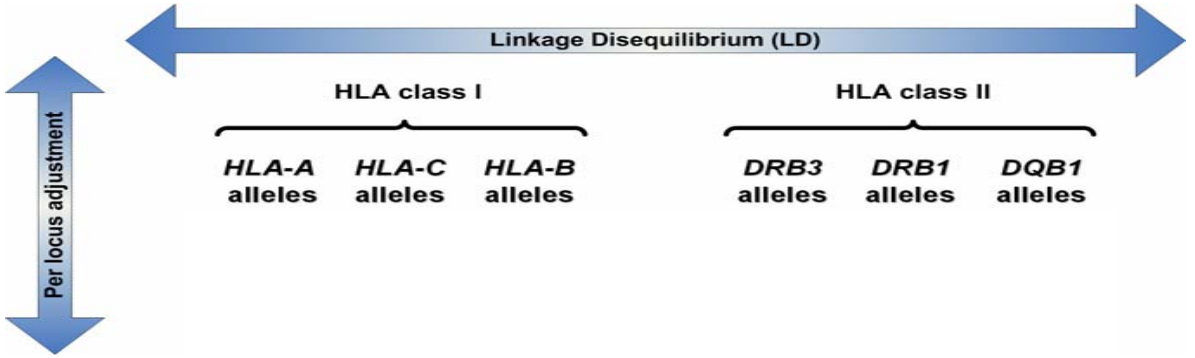


DRB1-DQA1-DQB1

Eike et al, unpublished

Challenges for mapping disease involved loci in the MHC

- Highly polymorphic; Alleles at a locus are not independent
- Strong linkage disequilibrium; Alleles at neighboring loci are not independent
- Multiple risk factors

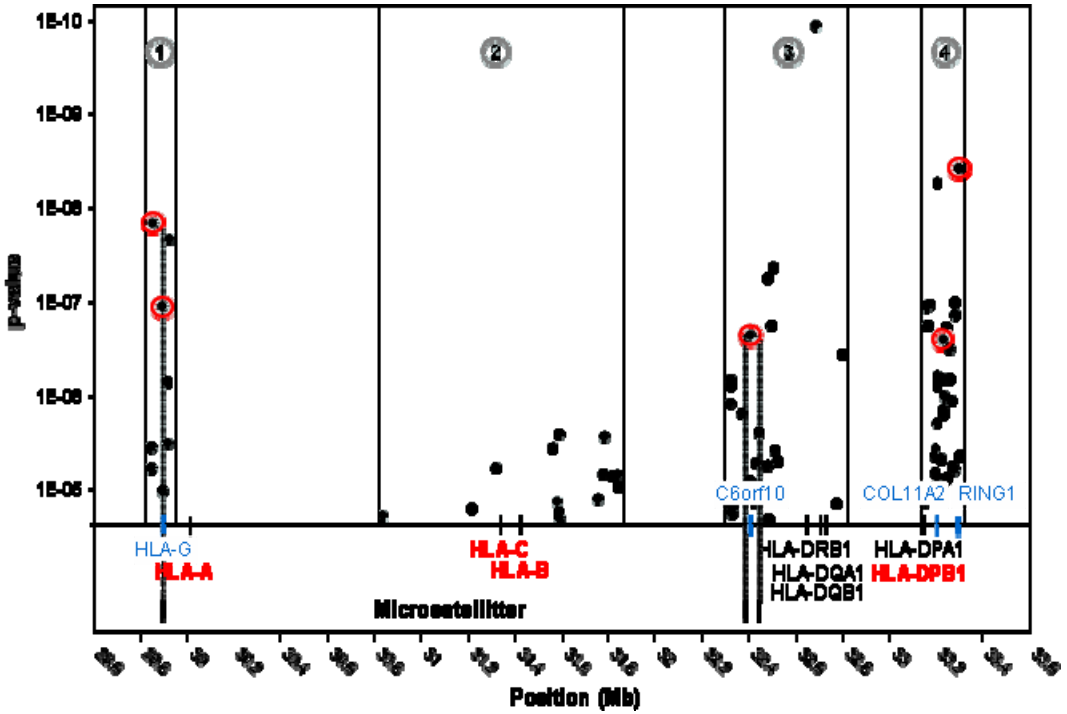


- Logistic regression (conditional and stepwise model fit)
- Map the association on particular HLA haplotypes

Four regions harbor additional T1D risk factor

- The presence of more risk factors, confined within 4 regions
- The associated regions were independent of each other
- A subset of polymorphisms that could explain the association within each region was identified
- No pronounced differences between the Caucasian populations

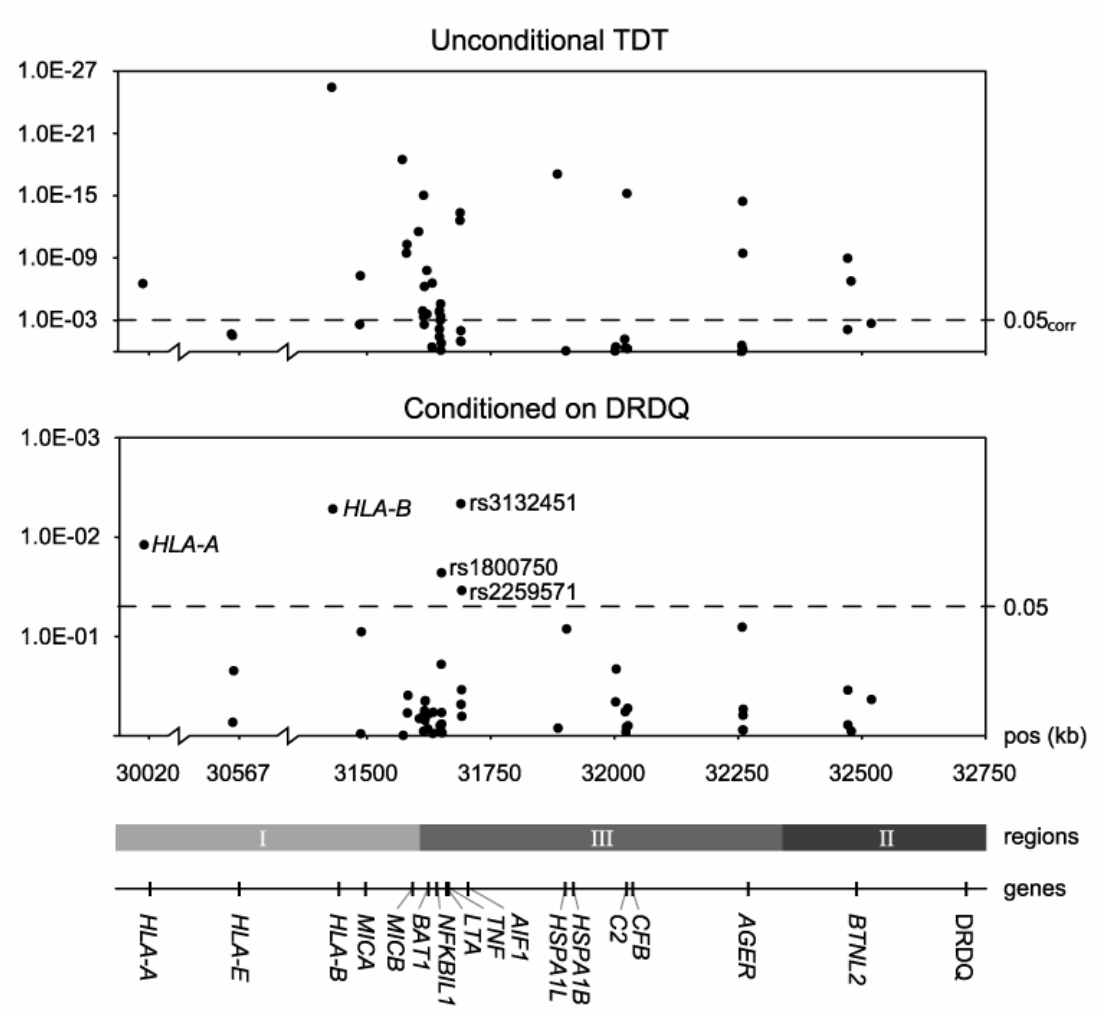
1. Two SNPs in the vicinity of *HLA-G*
2. *HLA-B* (*18 and *39)
3. A SNP in the *C6orf10* gene
4. *HLA-DPB1* and two SNPs close to the *COL11A2* and *RING1* genes



Eike et al, Genes Immun, in press

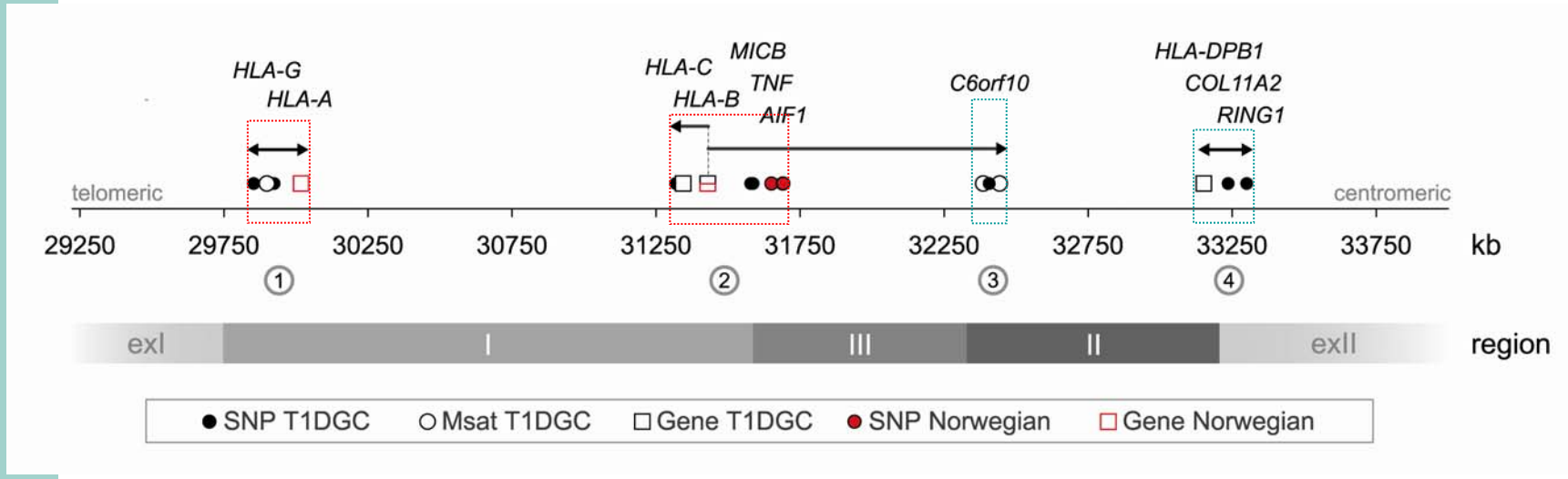
Candidate SNP screen of the MHC in the Norwegian population

- Polymorphisms previously suggested to be associated with type 1 diabetes or other autoimmune diseases were investigated
- Genotyped in 434 Norwegian T1D families
- HLA-A, -B and SNPs in AIF1 represent independent associations



Eike et al, Genes Immunity, in press

MHC harbors multiple risk loci for type 1 diabetes



Eike, unpublished

Genetics of autoimmune diseases

- Mainly complex diseases with several underlying genetic factors, mostly with OR<2
- The main genetic determinant is the MHC on chr 6p21
- Multiple disease risk loci are present in the MHC
- Several overlapping genetic risk factors elsewhere in the genome