Advances in Disease Associations Using NGS-based HLA Typing

Presenters: Marcello Scala, VP Sales, EMEA & Asia
Efi Melista, Head of Product

Guest Speakers: Professor Mehdi Tafti, University of Lausanne, Switzerland
Dr. Mohamed Jahromi, Dasman Institute of Diabetes, Kuwait

May, 2019

Agenda

- Corporate Overview
- Introduction to Holotype HLA
- Guest Speakers
- Omixon Product Updates
- Q&A

Corporate Statement

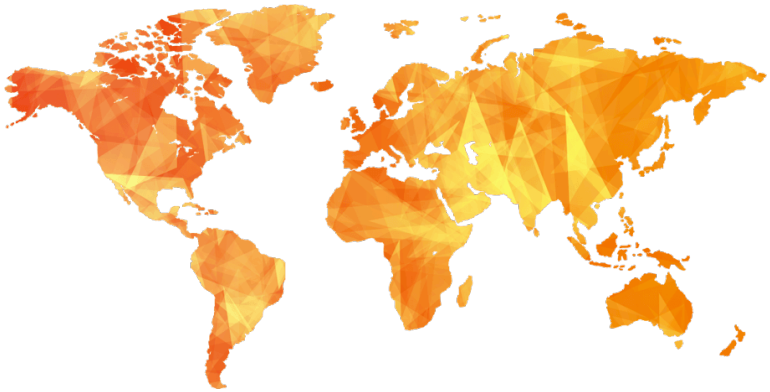
- Global Molecular Diagnostics Company
  - Budapest, Headquarters, Software R&D
  - Cambridge, MA, Operations and Manufacturing
- World leader in HLA Typing by NGS
  - Best in class Assay
  - Best in class Software
- Existing Products
  - Holotype HLA (Pre-Transplant Assay + Software)
  - Monotype HLA (Disease associations)
  - ABO (Blood groups)
  - MICA
  - HLA Twin (Software for clinicians)
  - HLA Explore (Software for researchers)

Innovation Award Winners!

Global coverage & operation

150+ HLA labs trained onsite worldwide, 50+ HLA labs in clinical routine worldwide, 11 ASHI accredited labs, 6 EFI accredited labs, product shipped to 26+ countries, 20+ distributors, 2 warehouses

- 54+ people from 7 countries
  - 43 people in Hungary
  - 5 people in Europe (non-Hungary)
  - 6 people in USA



- Contracted manufacturing: USA
- Key partners: Philadelphia, Iowa, Germany, Hungary

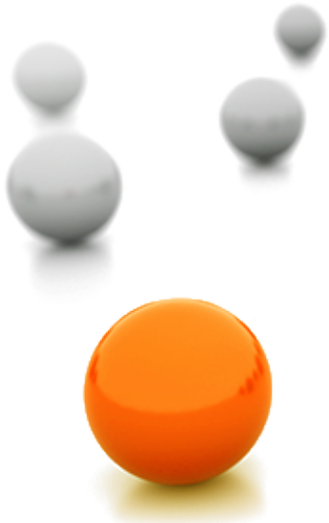
Omixon & Distributors

Omixon
Phoenix, Houston, Baltimore, Boston, Barcelona, Prague, Budapest, The Netherlands

Distributors (45+Territories, 20+ Distributors)
Albania, Algeria, Armenia, Australia, Belarus, Bosnia, Bulgaria, Brazil, China, Czech Republic, Egypt, Estonia, France, Georgia, Greece, Hong-Kong, India, Iraq, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lithuania, Macedonia, Malaysia, Morocco, Oman, Portugal, Qatar, Romania, Russia, Saudi-Arabia, Serbia, Singapore, South-Korea, Spain, Sub-Sahara & Africa, Taiwan, Thailand, Tunis, Turkey, U.A.E., Uzbekistan, Vietnam

High Throughput Labs/Contracts

- High Throughput Labs/Contracts:
  - EFS – 30K+ samples/year
  - Kazan Federal University – 10-20K samples/year
  - PBMDR – 10-15K samples/year
  - Romanian SCR – 10-15K samples/year
  - DCI – 10K samples/year
  - King Faisal Hospital – 5-6000 samples/year
  - UCSF – 7200 samples/year

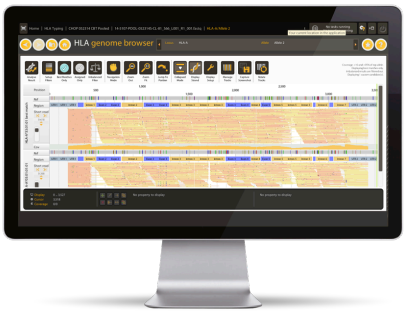


Introduction to Holotype HLA™

Holotype HLA is a combination Assay, Software, and fully automated genotype product for the comprehensive gene amplification of multiple HLA loci, and sequencing on Illumina platforms.

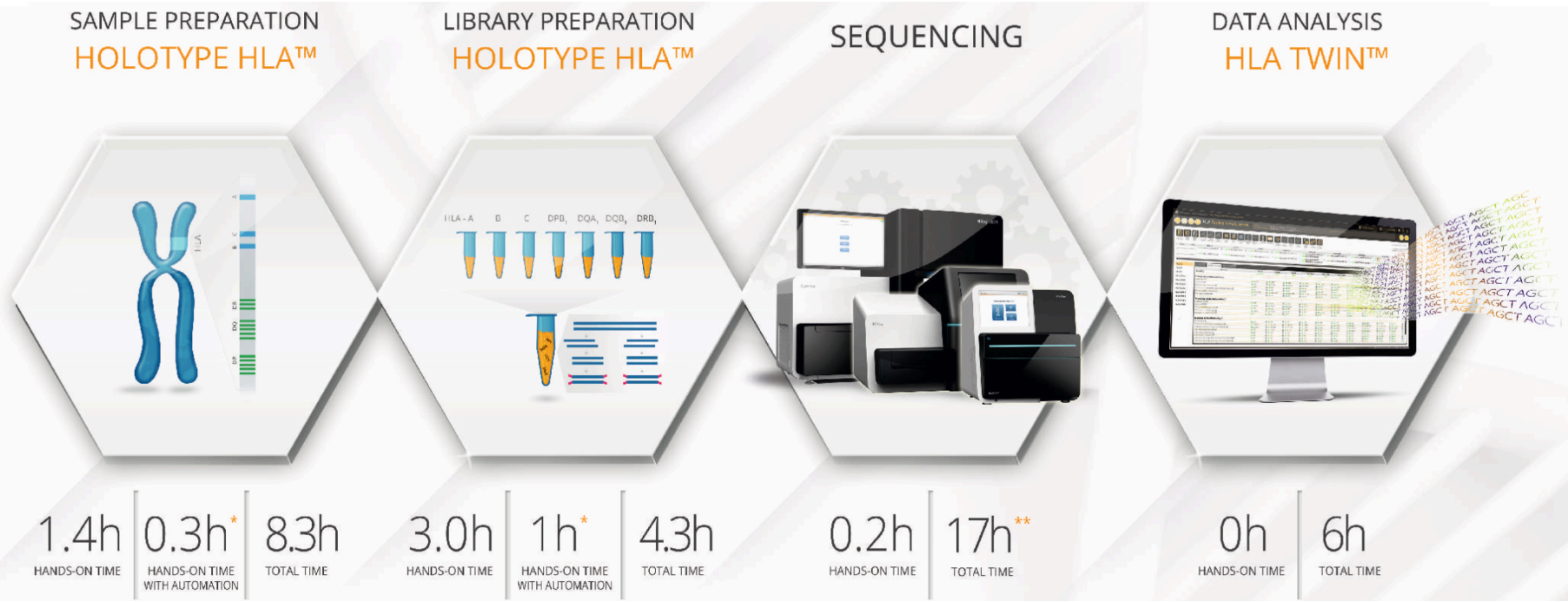
NGS Assay + NGS Software + Automation

Most Reliable, Accurate Genotyping Available



Steps in Holotype HLA

4.4 hours hands-on time
1.3 hours automated hands-on time
DNA sample to answer in <48 hours total time



Guest Speakers

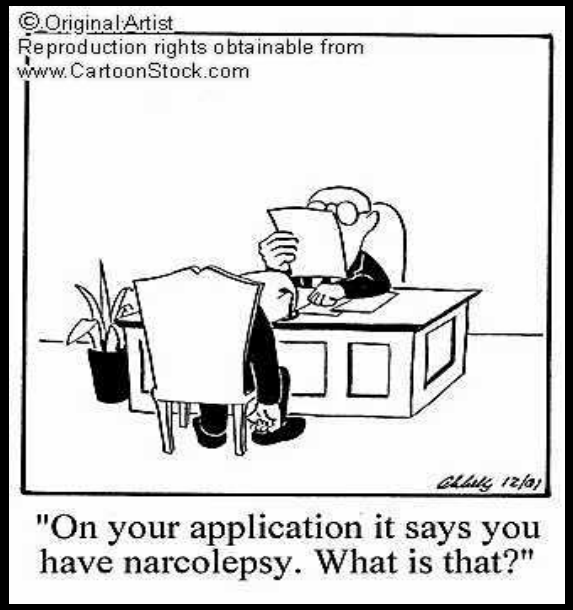
Professor Mehdi Tafti - University of Lausanne, Switzerland

UNIL | Université de Lausanne

Dr. Mohamed Jahromi - Dasman Institute of Diabetes, Kuwait

معهد دسمان للسكري
Dasman Diabetes Institute

Case-control and genome-wide HLA associations in narcolepsy



Mehdi Tafti
Department of Physiology
University of Lausanne
Switzerland

Strongest HLA association ever

1982: Honda et al., HLA B35…
1983: Honda et al., Sleep Res. 100% HLA-DR2

1984: Seignalet and Billiard: 100% HLA-B7
1984: Langdon et al., 100% HLA-DR2, B7, Cw7
Autoimmune hypothesis!
1986: Mueller-Eckardt et al., 98.3% HLA-DR2-DQw1, B7 but not B35

HLA ANTIGENS IN JAPANESE PATIENTS WITH NARCOLEPSY

Antigen	Narcolepsy (n=92)	Normal controls (n=244)	χ^2
A2	50 (54%)	99 (40·6%)	5·14
B35	34 (34%)	40 (16·4%)	12·00
Bw52	9 (10%)	56 (23·0%)	−7·42
Bw67	10 (11%)	5 (2·0%)	12·19
DR2	92 (100%)	82 (33·6%)	117·95
DRw52	24 (26%)	148 (60·7%)	−31·95
DRw53	36 (39%)	150 (61·5%)	−13·50
DQw1	92 (100%)	173 (70·9%)	33·94
DQw3	32 (35%)	130 (53·3%)	−8·71

	Frequency in:		
Antigen	*Narcoleptics*	*Controls*	P_c
A3	33%	26%	NS
Cw7	74%	48%	NS
B7	66%	21%	<0·0001
DR2	100%	22%	<0·00001
DQw1	100%	"unknown"	. .

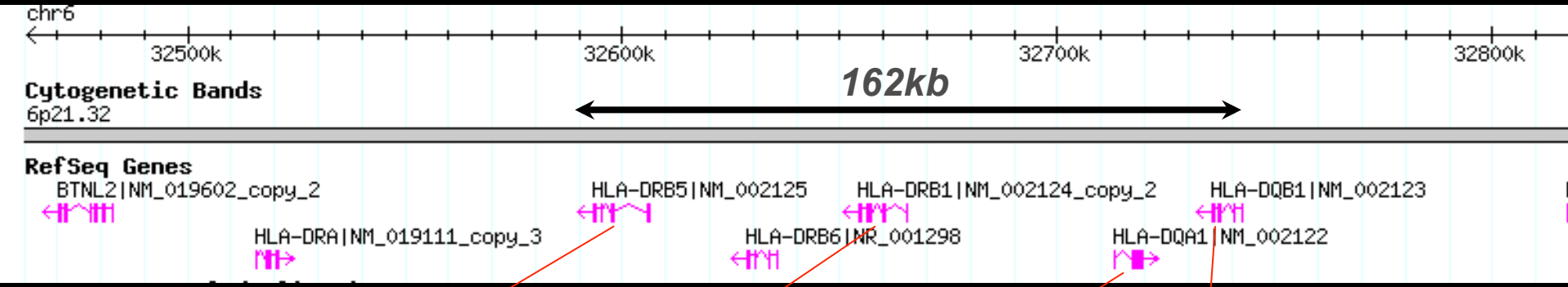
1974: Dausset et al., HLA association in MS
1974: Cudworth & Woodrow HLA association in Type 1 diabetes

[Association of HL-A1 and HL-A8 with childhood celiac disease]
Ludwig H et al., Z. Immunitatsforsch Exp Klin Immunol., 1973

HLA Class II association

HLA:

DR2, DRB15, DRB1*15:01, DQB1*06:02



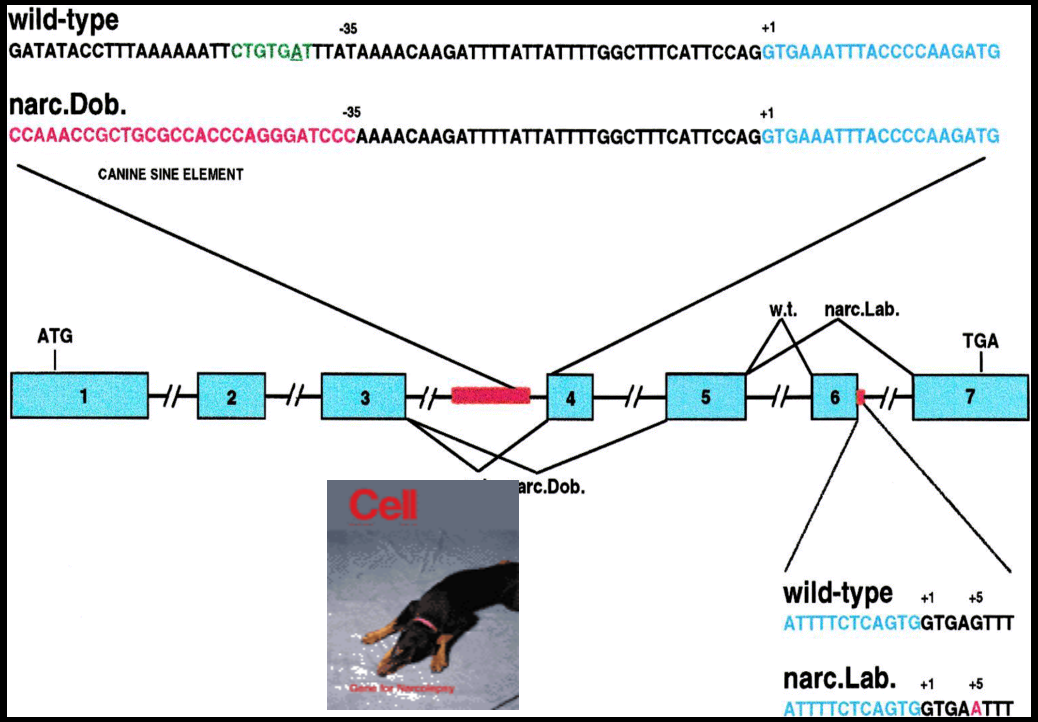
DRB5*01:01 DRB1*15:01 DQA1*01:02 DQB1*06:02 Caucasians

DRB5*01:01 DRB1*15:03 DQA1*01:02 DQB1*06:02 Blacks

DRB5*01:01 DRB1*15:01 DQA1*01:02 DQB1*06:02 Asians

Class I association is due to linkage disequilibrium with Class II

Hypocretin receptor 2 mutations cause Canine narcolepsy



Lin L. et al., 1999, Cell, 98: 365-76.

Hypocretin gene defect causes narcolepsy in mice

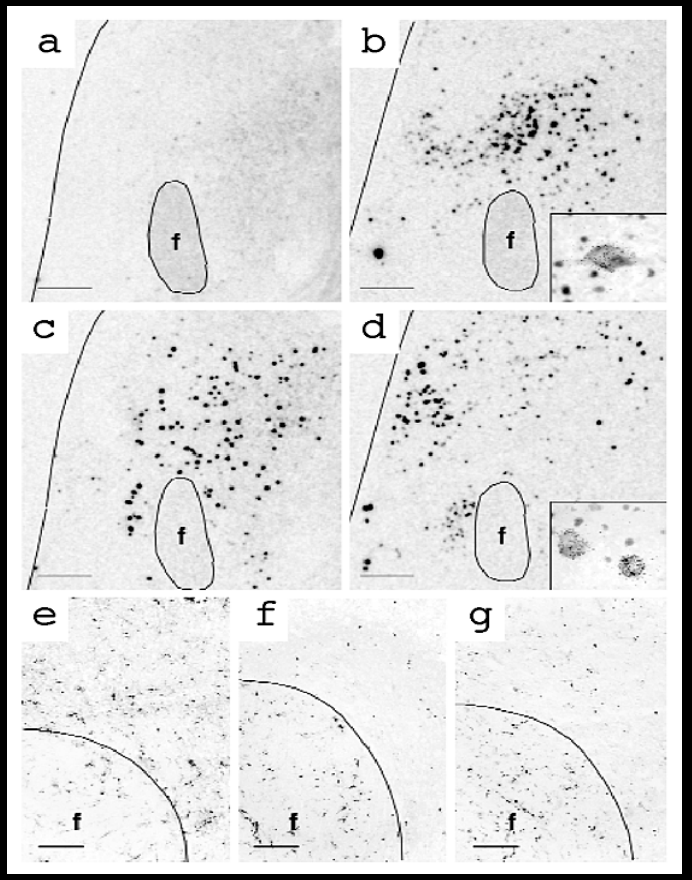
Chemelli RM et al., 1999, Cell, 98: 437-51.

Human narcolepsy is caused by hypocretin deficiency

A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains

NATURE MEDICINE • VOLUME 6 • NUMBER 9 • SEPTEMBER 2000

Christelle Peyron[1], Juliette Faraco[1], William Rogers[1], Beth Ripley[1], Sebastiaan Overeem[1,2], Yves Charnay[3], Sona Nevsimalova[4], Michael Aldrich[5], David Reynolds[6], Roger Albin[5], Robin Li[1], Marcel Hungs[1], Mario Pedrazzoli[1], Muralidhara Padigaru[6], Melanie Kucherlapati[6], Jun Fan[7], Richard Maki[7], Gert Jan Lammers[2], Constantin Bouras[3], Raju Kucherlapati[6], Seiji Nishino[1], & Emmanuel Mignot[1]

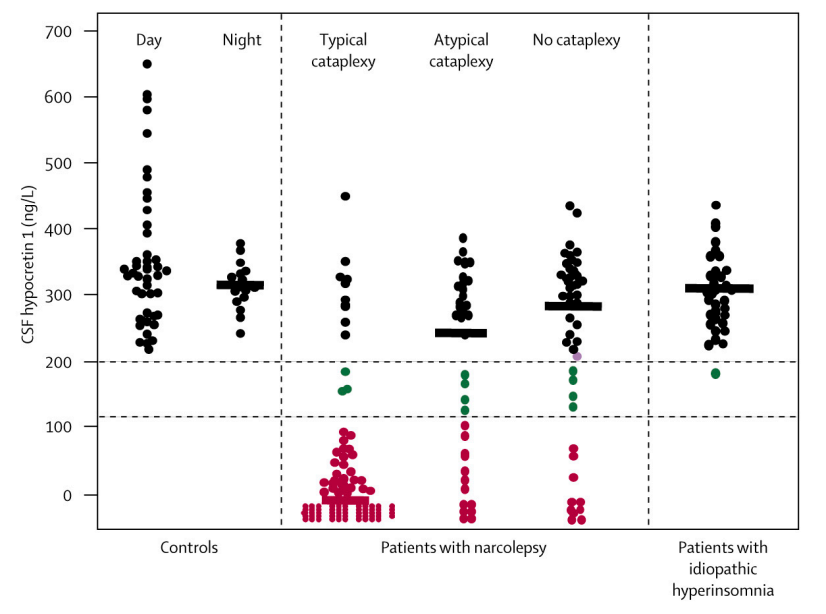


Human narcolepsy is not caused by hypocretin genes defect

Hypocretin (orexin) deficiency in human narcolepsy

THE LANCET • Vol 355 • January 1, 2000

Seiji Nishino, Beth Ripley, Sebastiaan Overeem, Gert Jan Lammers, Emmanuel Mignot



BRAIN
A JOURNAL OF NEUROLOGY

Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France

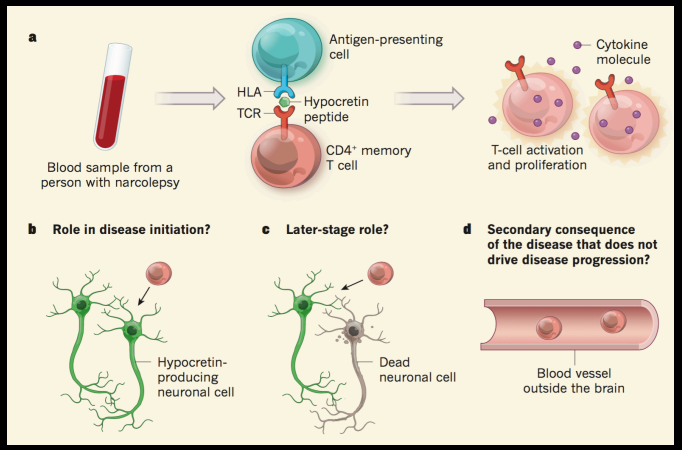
Yves Dauvilliers,[1,2] Isabelle Arnulf,[2,3] Michel Lecendreux,[2,4] Christelle Monaca Charley,[5] Patricia Franco,[2,6] Xavier Drouot,[7] Marie-Pia d'Ortho,[8] Sandrine Launois,[9] Séverine Lignot,[10] Patrice Bourgin,[11] Béatrice Nogues,[12] Marc Rey,[13] Sophie Bayard,[1,2] Sabine Scholz,[1,2] Sophie Lavault,[2,3] Pascale Tubert-Bitter,[14] Cristel Saussier[15] and Antoine Pariente[10] on behalf of the Narcoflu-VF study group

ARTICLE

nature

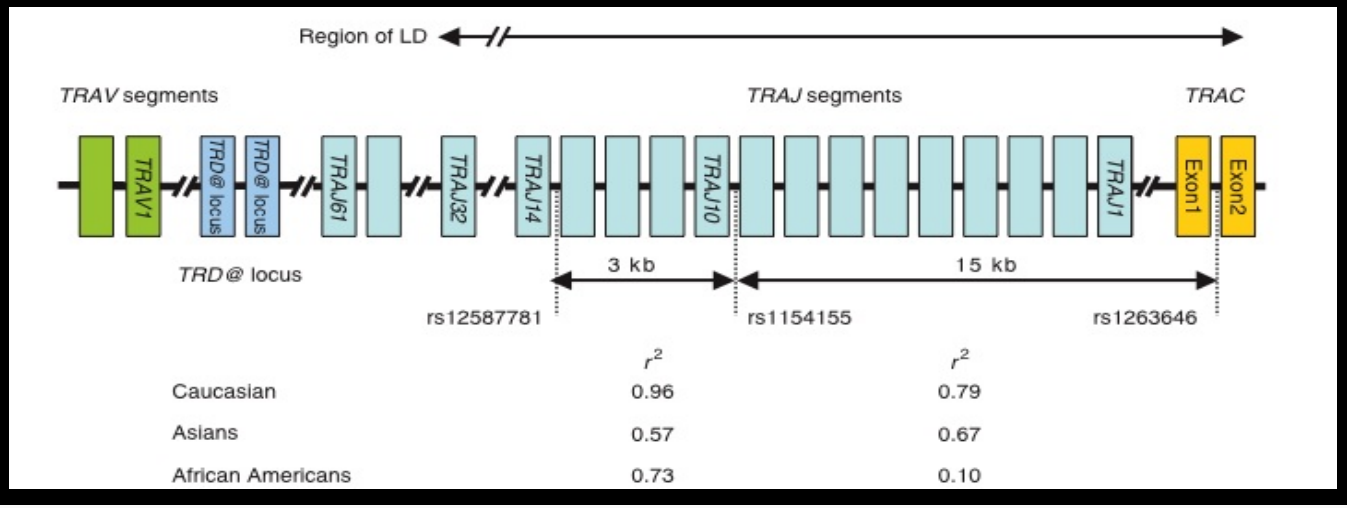
T cells in patients with narcolepsy target self-antigens of hypocretin neurons

Daniela Latorre[1,2,10], Ulf Kallweit[3,4,10], Eric Armentani[1], Mathilde Foglierini[1,5], Federico Mele[1], Antonino Cassotta[1,2], Sandra Jovic[1], David Jarrossay[1], Johannes Mathis[3], Francesco Zellini[6], Burkhard Becher[7], Antonio Lanzavecchia[1], Ramin Khatami[8], Mauro Manconi[3,6], Mehdi Tafti[9], Claudio L. Bassetti[3]* & Federica Sallusto[1,2]*



First Caucasian GWAS

807 Narcolepsy & 1074 Controls



Narcolepsy is strongly associated with the T-cell receptor alpha locus.
Nature Genetics 41, 708-711 (2009)

OR=1.79 in Caucasians, 1.4 in Japanese

Why narcolepsy is associated with HLA?

	Narcolepsy	Control	OR
DQB1*06:02	***99%***	***30%***	***231***
	95%	***20%***	***70***
	95%	***30%***	***44***
TCRA	***22%***	***14%***	***1.8***

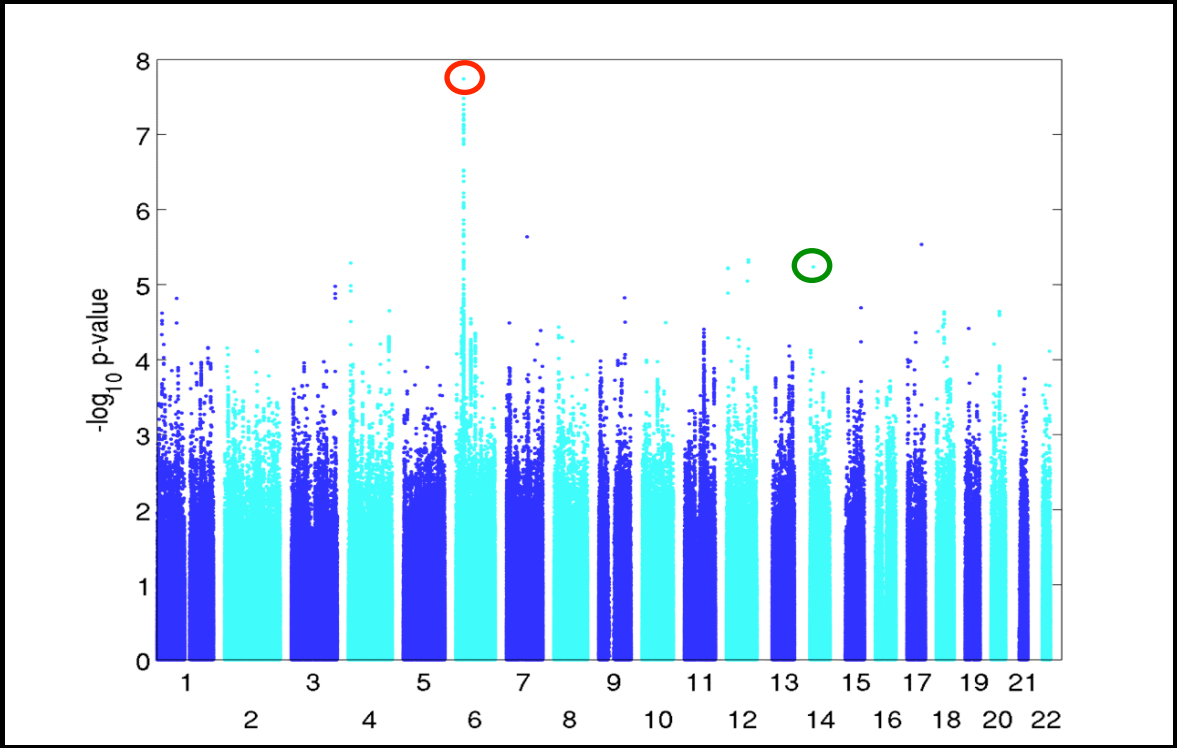
First European GWAS

GWAS: ***562 cases – 702 controls***
Replication: ***370 cases - 495 controls***

Origin: ***France*** ***Spain***
Netherlands ***Italy***
Denmark ***Switzerland***
Germany

Cases: ***Narcolepsy with cataplexy***

Cases + controls: ***all DQB1*06:02 positive***



TCRA Association

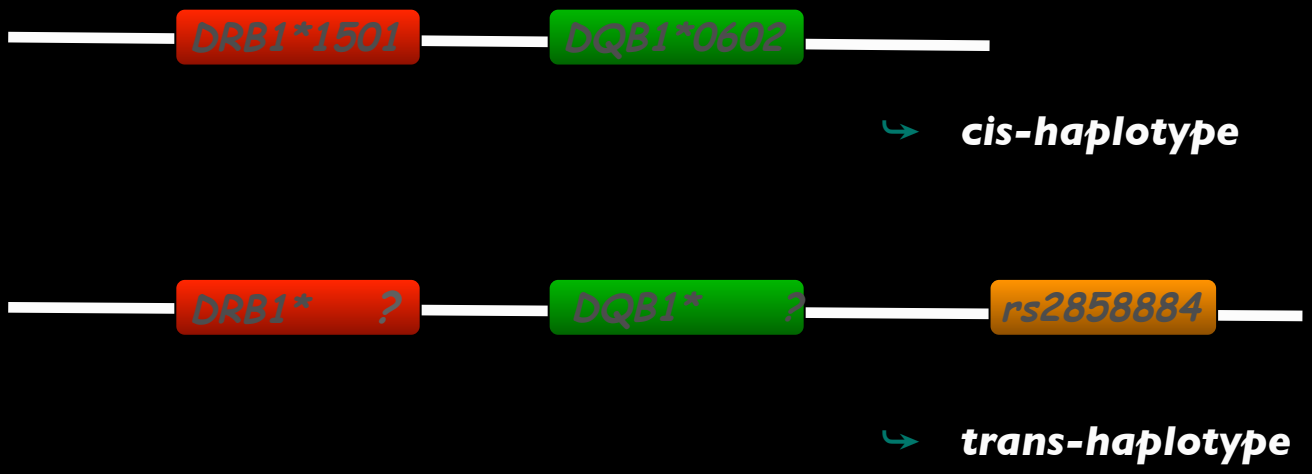
rs1154155: P < 2 x 10^{-4} (OR = 1.54)

HLA rs2858884: P = 5 x 10^{-8} (OR = 2.09)

Hor H et al. Nat. Genet. 2010, 42: 686-9.

A common HLA variant is protective

Trans HLA Haplotype



2nd EU-NN GWAS

1261 cases – 1422 HLA-Matched controls

Origin:

France	***Spain***
Netherlands	***Slovakia***
Switzerland	***Poland***
Germany	***Italy***

30 single nucleotide polymorphisms (SNPs) with $P<10^{-4}$ mapping to DHSs

TCA, P2RY11, CTSH, TNFSF4, HLA (rs2858884)

EU-NN Latest meta-analysis

1261 cases – 1422 HLA-Matched controls

rs#	p1	n1	p2	n2	pMeta	nMeta	Gene
rs2858884	4.65E-08	1264	6.40E-04	1353	**1.03E-09**	2617	**HLA**
rs1154155	1.92E-04	1264	2.12E-05	1365	**1.56E-08**	2629	**TCRA**
rs9291642	1.03E-05	1264	3.92E-01	1368	3.63E-04	2632	**P2RY11**
rs2305795	1.31E-01	1264	4.70E-03	1362	1.35E-03	2626	**CTSH**

Tafti M et al. Sleep 2014

Table 2. DQB1*0602 association in European countries

Country (case, control)	Case-DQB1+ N (%)	Control-DQB1+ N (%)	OR	*P*
DE (232,296)	227 (97.84)	72 (24.3.2)	141.24	9.71E-26
CH (66,473)	65 (98.48)	102 (21.56)	236.42	7.01E-8
NL (323, 469)	318 (98.45)	114 (24.31)	198.05	3.62E-30
PL (63,197)	63 (100)	44 (22.33)	438.08	2.65E-09
SP (127,1174)	126 (99.21)	170 (14.48)	744.14	5.25E-11
FR (341, 499)	335 (98.24)	94 (18.84)	240.56	1.18R-37
IT (66,433)	64 (96.97)	30 (6.93)	429.87	3.21E-16
Mantel-Haenszel (meta-analysis)	1198(98.36)	626 (17.68)	**251.12**	**1.04E-120**

DE: Germany, CH: Switzerland, NL: Netherlands, PL: Poland, SP: Spain, FR: France, IT: Italy, OR: odds ratio.

Tafti M et al. Sleep 2014

Why narcolepsy is associated with HLA?

	Narcolepsy	Control	OR
DQB1*06:02	99%	18%	251

Prevalence of narcolepsy: 0.02%

Most control subjects are protected

Protective HLA alleles are Dominant

*DQB1*06:02 dominantly protects against Diabetes Type 1*

Table 4. Mantel-Haenzel odds ratios for *trans DQB1* alleles between DQB1*06:02 heterozygous cases and controls in European countries.

DQB1	DE	CH	NL	PL	SP	FR	IT	MH OR	MH *P*	HM OR	MH P
								univariate		multivariate	
2	1.37	0.97	0.65	0.44	1.45	1.08	0.74	**0.95**	5.96E-01	0.76	**3.51E-03**
03:01	1.29	0.96	1.63	2.07	1.71	1.75	0.96	1.5	8.19E-06	1.06	9.39E-01
03:02	0.59	1.39	1.47	1.96	0.6	0.89	1.94	1.03	8.35E-01	0.74	3.33E-02
03:03	0.51	0.49	1.89	0.66	0.52	0.49	4.59	0.81	3.24E-01	0.63	3.59E-02
03:04	0.88	NA	1.71	0.45	4.01	3.26	NA	1.45	5.99E-01	NA	NA
04:02	2.59	2.79	2.41	11.7	0.56	1.26	0.14	1.63	1.40E-02	1.17	4.39E-01
05:01	0.8	0.66	0.49	0.44	0.7	0.7	0.19	**0.61**	2.21E-04	0.56	**1.43E-05**
05:02	1.44	2.5	1.61	7.13	1.91	1.25	15.03	1.98	3.85E-04	1.60	1.71E-02
05:03	1.53	0.89	0.92	1.53	1.35	0.68	0.21	0.96	8.51E-01	0.71	1.19E-01
06:01	0.29	0.35	8.59	2.29	1.33	0.22	0.44	0.61	3.99E-01	0.44	1.70E-01
06:03	0.12	0.89	0.12	0.27	0.06	0.23	1.12	**0.19**	4.29E-11	0.19	**4.29E-11**
06:04	1.12	2.79	1.79	1.14	1.91	1.5	0.55	1.54	1.51E-02	1.07	7.31E-01
06:09	0.53	0.35	0.21	NA	0.26	0.1	4.59	**0.24**	6.98E-03	0.21	**2.95E-03**

*P<0.05; **P<0.01; ***P<1E-3; ****P<1E-6, (multivariate) P-values in bold survive Bonferroni correction. MH: Mantel-Haenzel. OR: Odds ratio. NA: not applicable. Multivariate ORs and P-values were calculated in a stepwise fashion, where carriers of the most significant haplotypes are removed in each iteration (Han et al. Tissue Antigens. 2012 Oct;80(4):328-35).

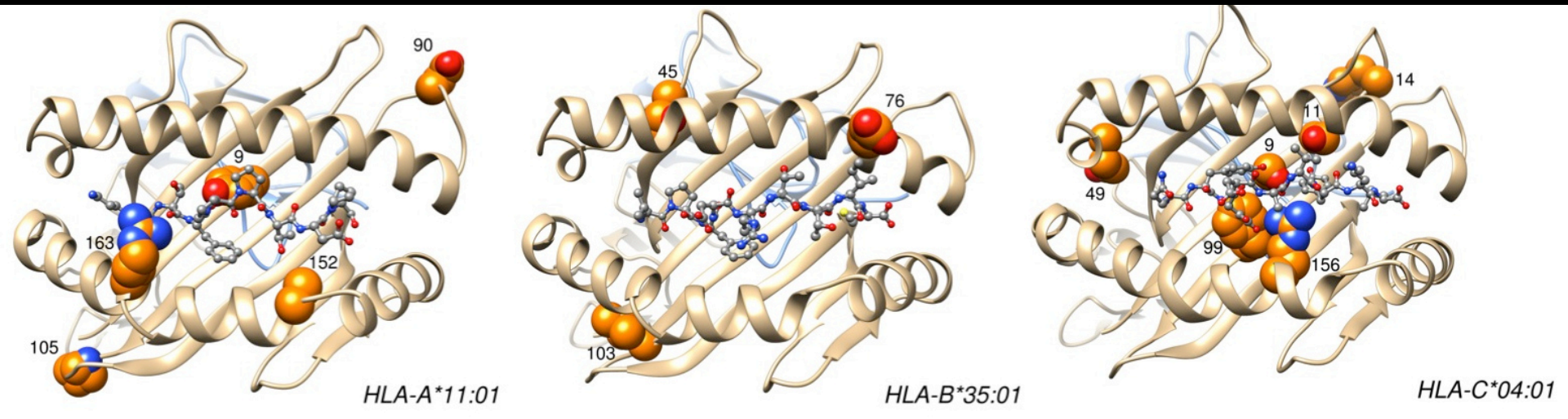
ARTICLE

HLA-DPB1 and HLA Class I Confer Risk of and Protection from Narcolepsy

Hanna M. Ollila,[1,24] Jean-Marie Ravel,[1,24] Fang Han,[2] Juliette Faraco,[1] Ling Lin,[1] Xiuwen Zheng,[3] Giuseppe Plazzi,[4,5] Yves Dauvilliers,[6] Fabio Pizza,[4,5] Seung-Chul Hong,[7] Poul Jennum,[8] Stine Knudsen,[9] Birgitte R. Kornum,[8,10] Xiao Song Dong,[2] Han Yan,[2] Heeseung Hong,[1] Cristin Coquillard,[11] Joshua Mahlios,[1] Otto Jolanki,[1] Mali Einen,[1] Sophie Lavault,[12] Birgit Högl,[13] Birgit Frauscher,[13] Catherine Crowe,[14] Markku Partinen,[15,16] Yu Shu Huang,[17] Patrice Bourgin,[18] Outi Vaarala,[19] Alex Désautels,[20] Jacques Montplaisir,[21] Steven J. Mack,[22] Michael Mindrinos,[23] Marcelo Fernandez-Vina,[11] and Emmanuel Mignot[1,*]

The American Journal of Human Genetics *96*, 136–146, January 8, 2015

	NL	FR	DE	CH	PL	CMH OR	P
	334:2158	258:583	223:559	67:570	62:173	(95% CI)	
*A*11:01*	1.25	1.96	1.25	2	1.65	1.49 (1.18-1.88)	**7.00E-04**
*C*04:01*	1.33	1.39	1.13	1.7	1.23	1.34 (1.10-1.63)	**3.23E-03**
*B*35:01*	1.47	1.67	1.21	1.41	1.41	1.46 (1.13-1.89)	**3.64E-03**



Tafti M et al. Sleep 2016

Future Perspectives

- *HLA contribution is causal to narcolepsy:*
  - *Large HLA-matched analysis*

NGS-based HLA typing

Sample	Allele	HLA-A	HLA-B	HLA-C	HLA-DPB1	HLA-DQA1	HLA-DQB1	HLA-DRB1
LP077-Lei-16082018S-	ALLELE_1	HLA-A*26:01:01	HLA-B*52:01:01	HLA-C*12:02:02	HLA-DPB1*02:01:02	HLA-DQA1*01:02:01	HLA-DQB1*06:09:01	HLA-DRB1*13:02:01
	ALLELE_2	HLA-A*11:01:01	HLA-B*07:02:01	HLA-C*07:02:01	HLA-DPB1*04:01:01	HLA-DQA1*01:02:01	HLA-DQB1*06:02:01	HLA-DRB1*15:01:01
LP078-Lei-16082018S-	ALLELE_1	HLA-A*02:01:01	HLA-B*07:02:01	HLA-C*03:04:01	HLA-DPB1*04:01:01	HLA-DQA1*04:01:01	HLA-DQB1*04:02:01	HLA-DRB1*08:01:01
	ALLELE_2	HLA-A*24:02:01	HLA-B*40:01:02	HLA-C*07:02:01	HLA-DPB1*04:01:01	HLA-DQA1*01:02:01	HLA-DQB1*06:02:01	HLA-DRB1*15:01:01
LP085-Lei-16082018S-	ALLELE_1	HLA-A*03:01:01	HLA-B*07:02:01	HLA-C*07:02:01	HLA-DPB1*04:01:01	HLA-DQA1*01:02:01	HLA-DQB1*05:02:01	HLA-DRB1*16:01:01
	ALLELE_2	HLA-A*03:01:01	HLA-B*67:01:02	HLA-C*12:03:01	HLA-DPB1*23:01:01	HLA-DQA1*01:02:02	HLA-DQB1*06:02:01	HLA-DRB1*15:01:01
NC4-Juil-05-16082018S-	ALLELE_1	HLA-A*24:02:01	HLA-B*08:01:01	HLA-C*07:01:01	HLA-DPB1*01:01:01	HLA-DQA1*05:01:01	HLA-DQB1*02:01:01	HLA-DRB1*03:01:01
	ALLELE_2	HLA-A*11:01:01	HLA-B*07:02:01	HLA-C*07:02:01	HLA-DPB1*23:01:01	HLA-DQA1*01:02:01	HLA-DQB1*06:02:01	HLA-DRB1*15:01:01

HLA class II association (not expressed by neurons): CD4+, So far no evidence
HLA class I association (expressed by neurons): CD8+, most likely

- *Hyun Hor*
- *Gianina Luca*
- *Brice Petit*
- *Corinne Pfister*
- *Angélique Vaucher*
- *Keith Harshman*
- *Sylvain Pradervand*

- *Zoltan Kutalik*
- *Gert Jan Lamnmers*
- *Geert Mayer*
- *Claudio Bassetti*
- *Rosa Peraita Adrados*
- *Michel Lecendreux*
- *Yves Dauvilliers (Montpellier)*

EU-NN

FNSNF
FONDS NATIONAL SUISSE DE LA RECHERCHE SCIENTIFIQUE

NOVARTIS

fondation Pierre Mercier pour la science

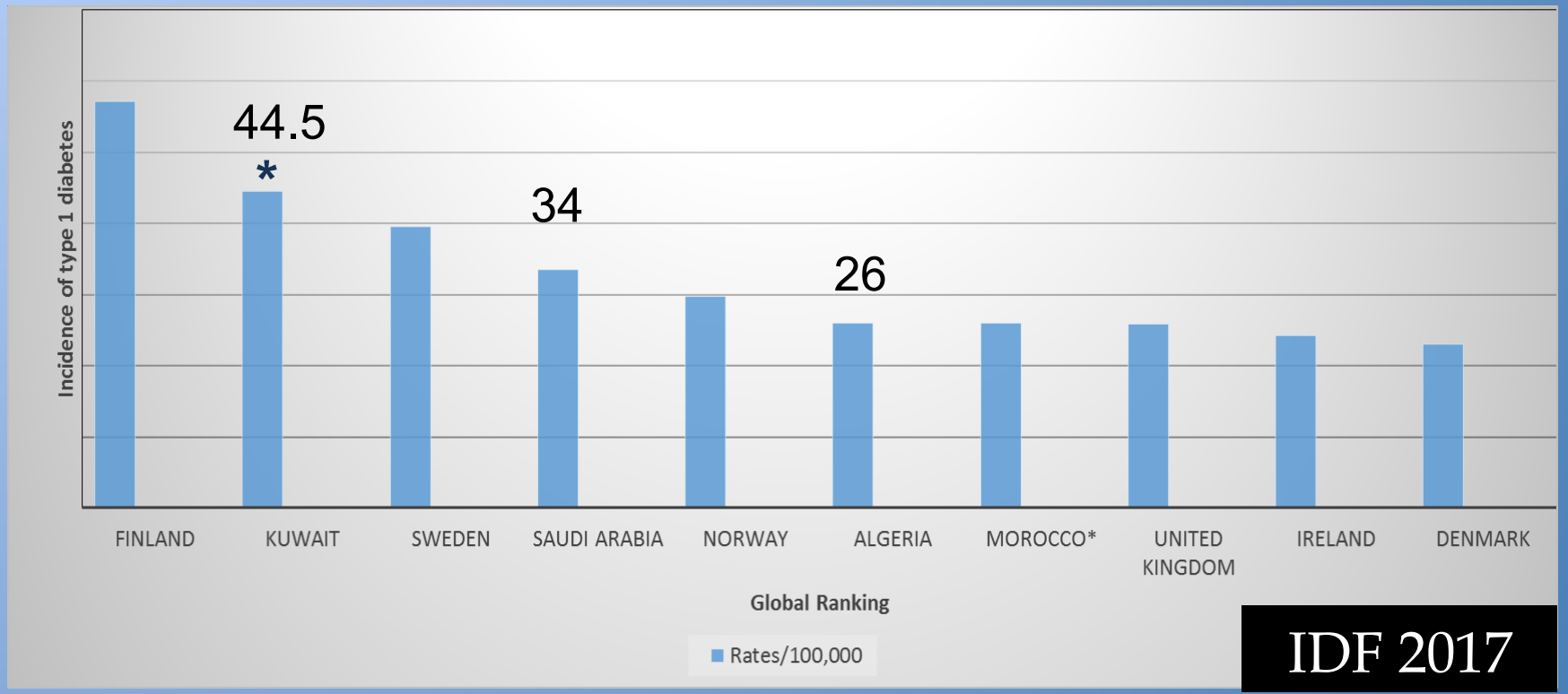
EUMODIC

Characterization of type 1 diabetes in Kuwaiti population using NGS-based HLA typing

Mohamed M. Jahromi (PhD)
Dasman Diabetes Institute, Kuwait

معهد دسمان للسكري
Dasman Diabetes Institute

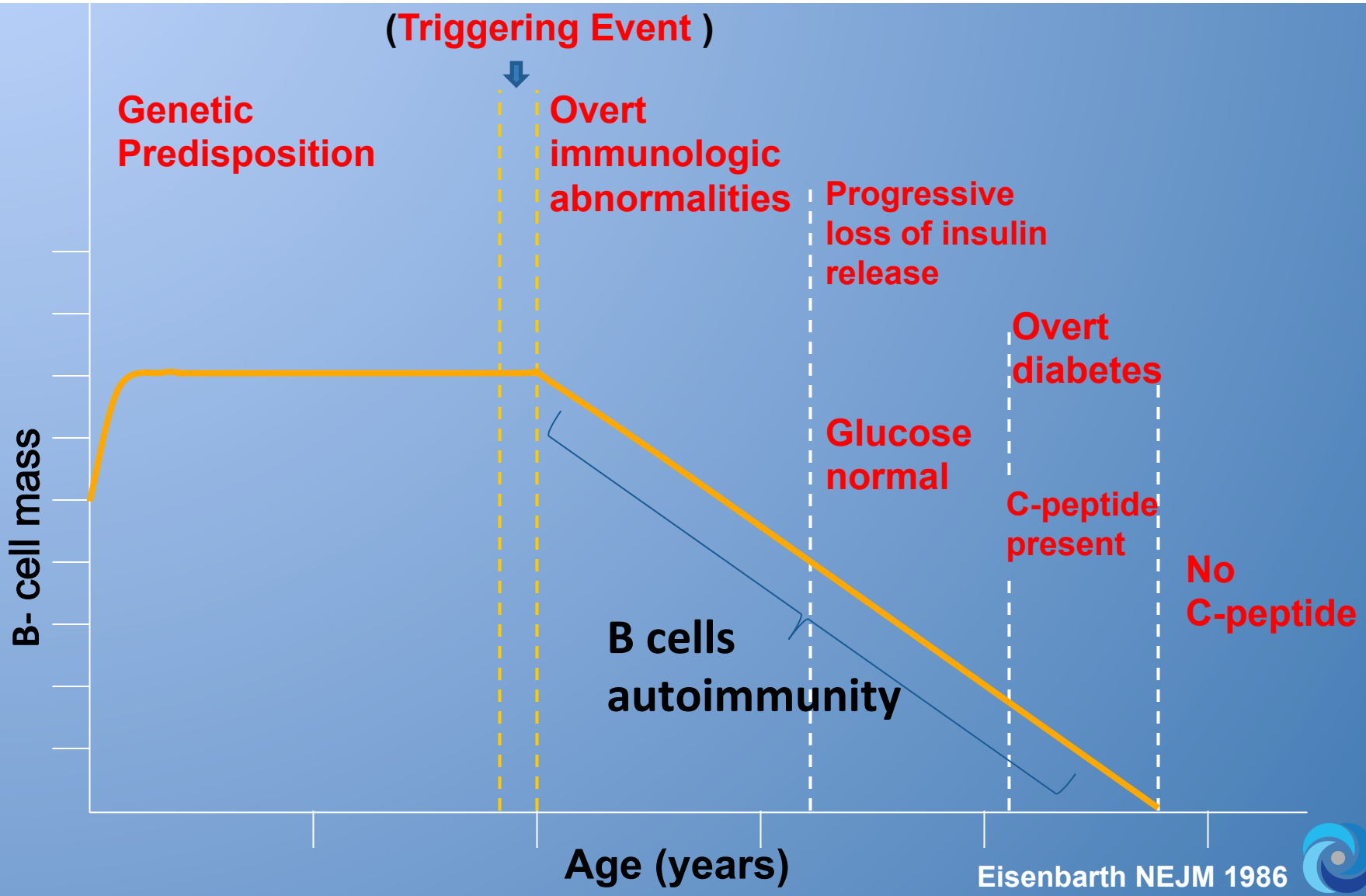
Top 10 countries/ territories for the incidence rates (100,000 children/ year) with Type 1 Diabetes (T1D)



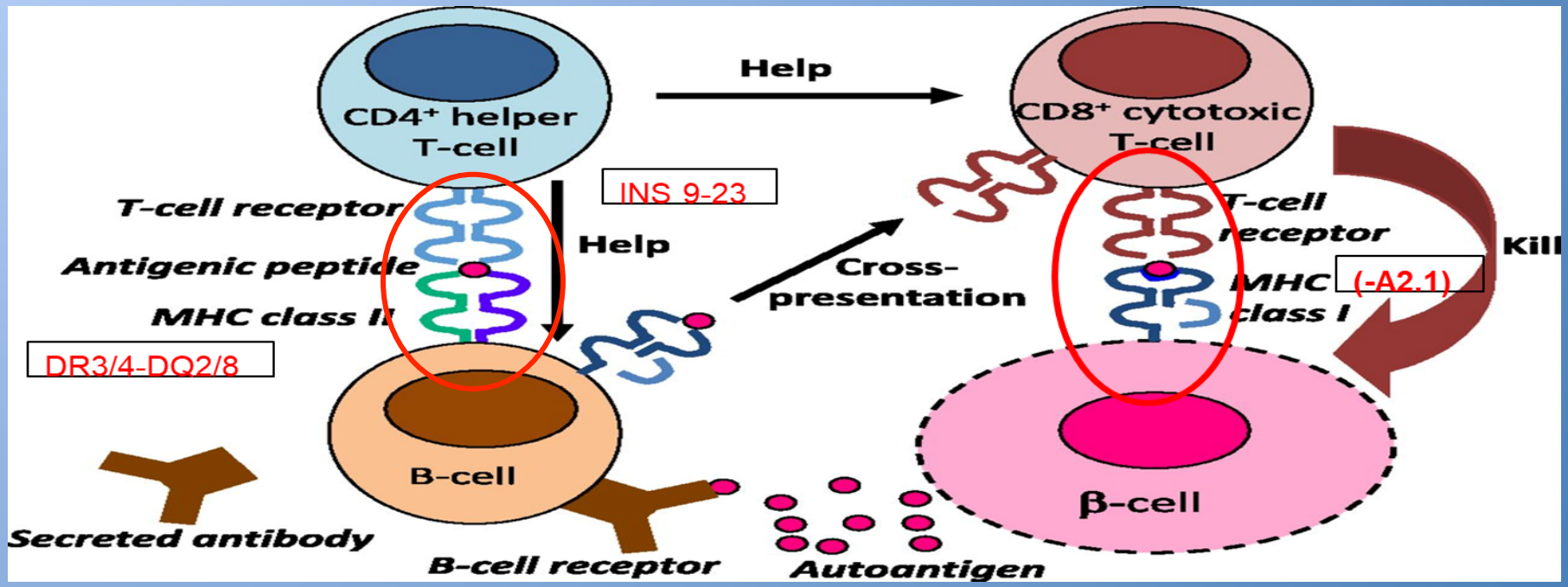
Although the Arab population counts for only 5.4 % of the total world population, it carries a significant portion of the burden!

معهد دسمان للسكري
Dasman Diabetes Institute

T1D Natural History



Tri-molecular complex of T1D pathogenesis



Michael R. Christie Diabetes 2016;65:1146-1148, with alterations

American Diabetes Association.

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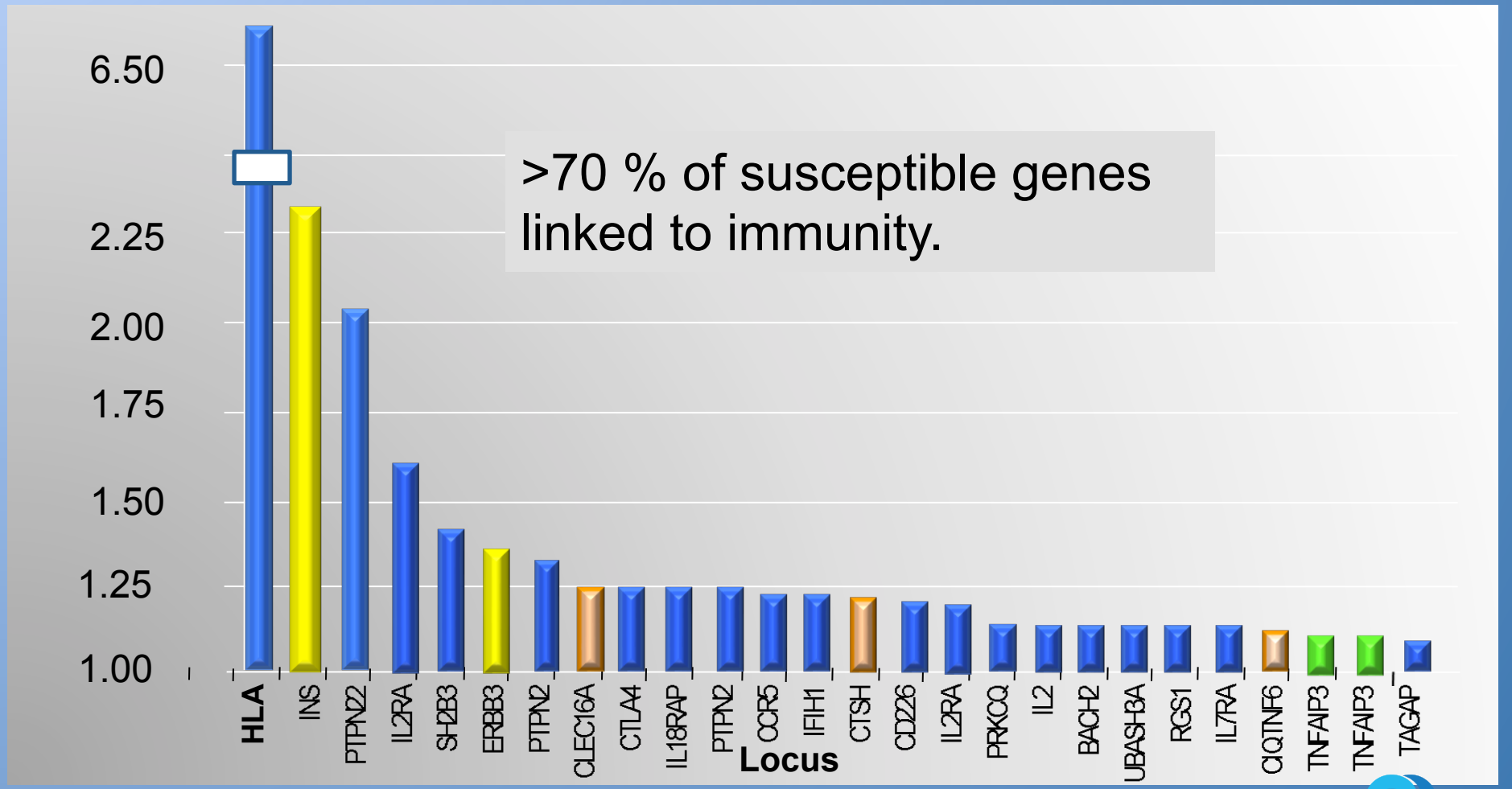
Genome-wide associations in T1D



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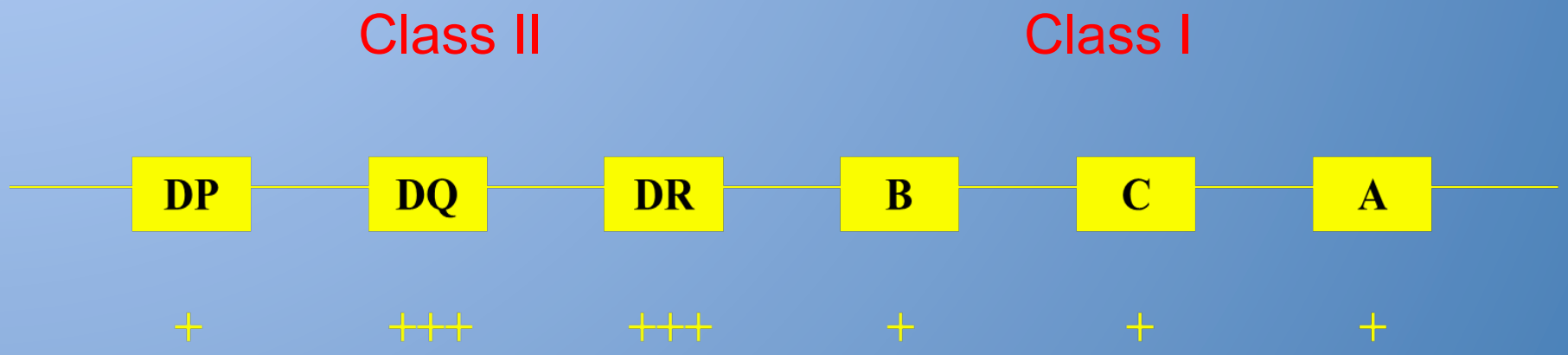
Which HLA loci are mostly involved?



HLA Associations With T1D

More than 80% of young patients carry HLA-high risk haplotypes.

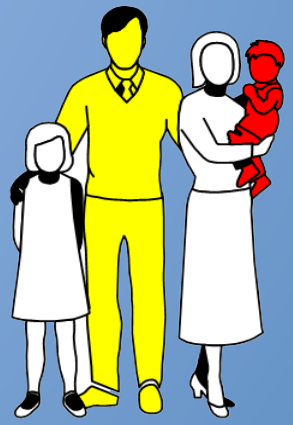
HLA-A, -B, -C and HLA-DRB1, -DQB1, -DPB1 genes (40% of familial aggregation).

Most HLA associations are based on low resolution typing techniques

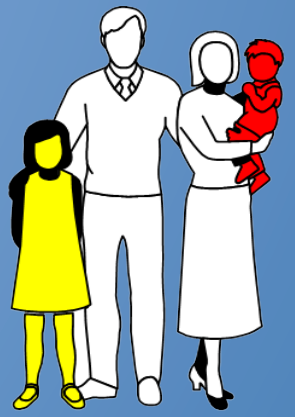
Kuwaiti Autoimmune Diabetes Study (KADS)

Newborn Cohort (NEC)
General population cohort

(SOC)
Sibling/Offspring Cohort



offspring



siblings

Identify : high risk
moderate risk
average-low risk

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Determination of Kuwaiti T1D HLA haplotype pattern

Type HLA-A, -B, -C, -DPA1, -DPB1, -DQA1, -DQB1, -DRB1, -DRB3, -DRB4 and DRB5 in Type 1 Diabetes patients and healthy controls using Holotype HLA NGS (Omixon).

Estimate allele and haplotype frequencies in patients and control subjects.

High rate of consanguinity adds value to Kuwaiti data to disclose certain facts about this nasty disease

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HLA alleles associated with T1D
(Caucasian population)

High Risk
DR3: DQB1*0201, DQA1*0501, DRB1*0301
DR4: DQA1*0301, DQB1*0302, DRB1*0401

Protective
DR2: DQB1*0602, DQA1*0102,, DRB1*1501

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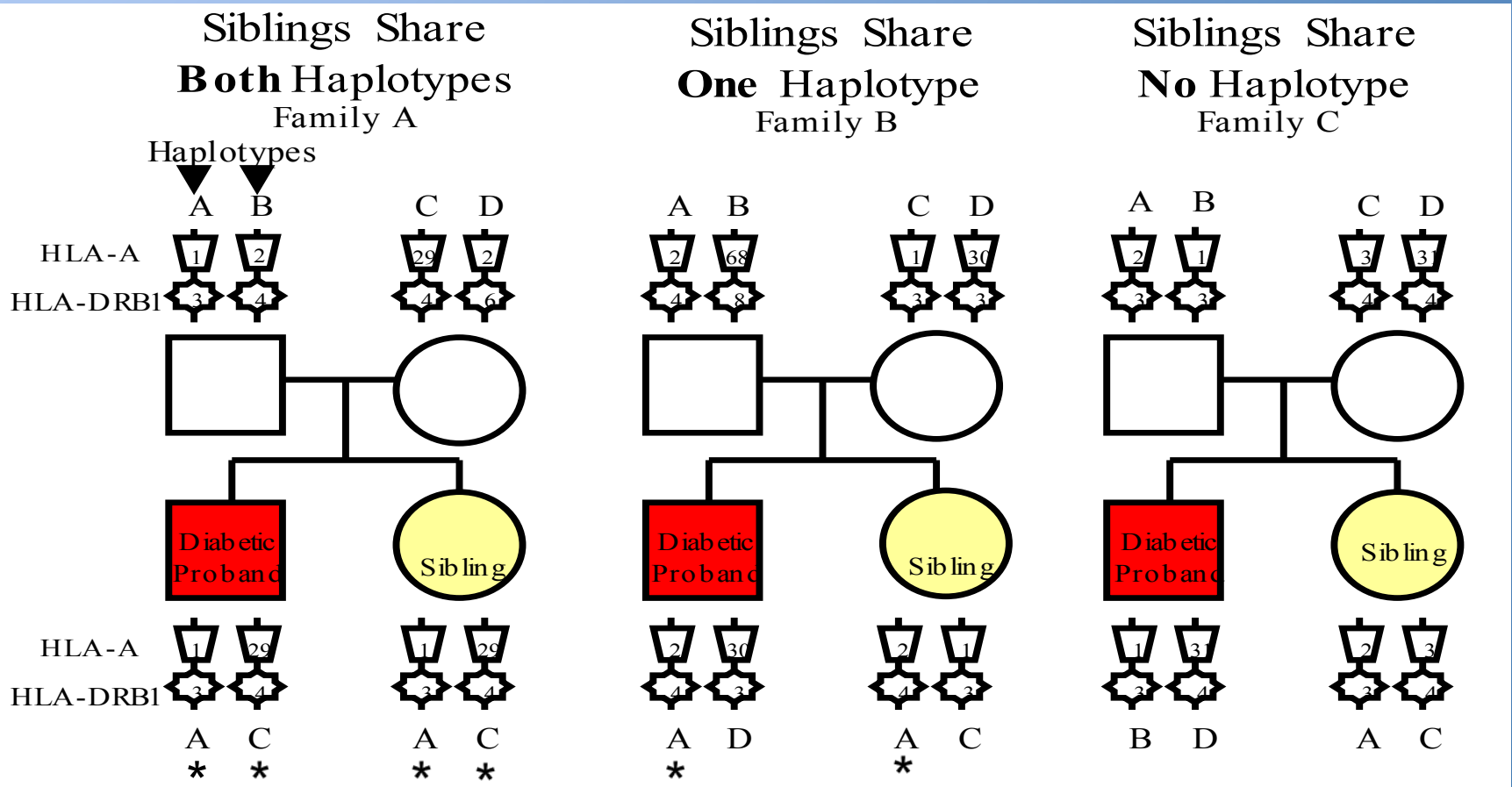
Affected Familial Base Control (AFBAC)



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Affected Familial Base Control (AFBAC)

Participants ID	Allele	HLA-A	HLA-B	HLA-C	HLA-DPA1	HLA-DPB1	HLA-DQA1	HLA-DQB1	HLA-DRB1	HLA-DRB3	HLA-DRB4	HLA-DRB5
KADS008p1pb	ALLELE_1	HLA-A*33:03:01	HLA-B*58:01:01	HLA-C*03:02:02	HLA-DPA1*01:03:01	HLA-DPB1*04:01:01	HLA-DQA1*05:01:01	HLA-DQB1*02:01:01	HLA-DRB1*03:147	HLA-DRB3*02:02:01		
									HLA-DRB1*03:01:01			
	ALLELE_2	HLA-A*33:03:01	HLA-B*58:01:01	HLA-C*03:02:02	HLA-DPA1*01:03:01	HLA-DPB1*04:01:01	HLA-DQA1*05:01:01	HLA-DQB1*02:01:01	HLA-DRB1*03:147	HLA-DRB3*02:02:01		
									HLA-DRB1*03:01:01			
KADS008p2m	ALLELE_1	HLA-A*02:01:01L	HLA-B*07:02:01	HLA-C*03:02:02	HLA-DPA1*01:03:01	HLA-DPB1*04:01:01	HLA-DQA1*05:01:01	HLA-DQB1*02:01:01	HLA-DRB1*03:147	HLA-DRB3*02:02:01		
		HLA-A*02:01:01							HLA-DRB1*03:01:01			
	ALLELE_2	HLA-A*33:03:01	HLA-B*58:01:01	HLA-C*07:02:01	HLA-DPA1*02:01:01	HLA-DPB1*14:01:05	HLA-DQA1*05:01:01	HLA-DQB1*02:01:01	HLA-DRB1*03:147	HLA-DRB3*02:02:01		
									HLA-DRB1*03:01:01			
KADS008p3f	ALLELE_1	HLA-A*31:01:02	HLA-B*51:01:01	HLA-C*03:02:02	HLA-DPA1*01:03:01	HLA-DPB1*04:01:01	HLA-DQA1*01:03:01	HLA-DQB1*02:01:01	HLA-DRB1*03:01:01	HLA-DRB3*01:01:02		
									HLA-DRB1*03:147			
	ALLELE_2	HLA-A*33:03:01	HLA-B*58:01:01	HLA-C*15:02:01	HLA-DPA1*01:03:01	HLA-DPB1*04:01:01	HLA-DQA1*05:01:01	HLA-DQB1*06:03:01	HLA-DRB1*13:01:19	HLA-DRB3*02:02:01		
									HLA-DRB1*13:01:01			
KADS008p4	ALLELE_1	HLA-A*02:01:01L	HLA-B*07:02:01	HLA-C*03:02:16	HLA-DPA1*01:03:01	HLA-DPB1*04:01:01	HLA-DQA1*05:01:01	HLA-DQB1*02:01:01	HLA-DRB1*03:147	HLA-DRB3*02:02:01		
		HLA-A*02:01:01							HLA-DRB1*03:01:01			
	ALLELE_2	HLA-A*33:03:01	HLA-B*58:01:01	HLA-C*07:02:01	HLA-DPA1*02:01:01	HLA-DPB1*14:01:05	HLA-DQA1*05:01:01	HLA-DQB1*02:01:01	HLA-DRB1*03:147	HLA-DRB3*02:02:01		
									HLA-DRB1*03:01:01			

KEY:

proband or affected child

inherited alleles to the affected child

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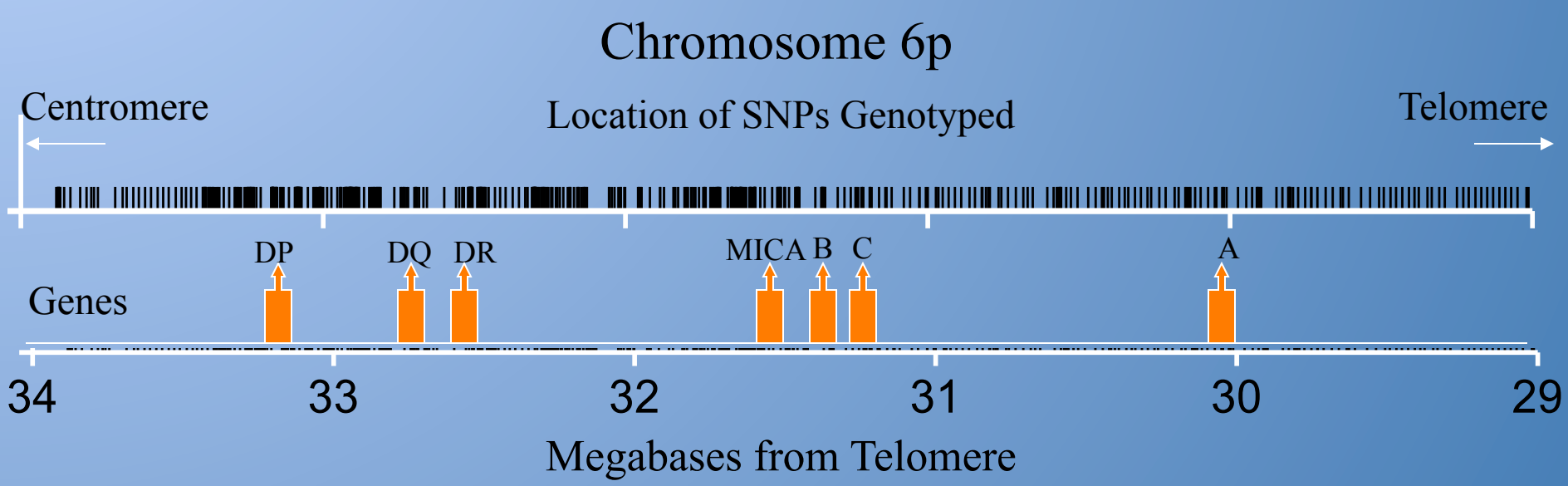
HLA Region



Future goals

Determination of high, intermediate and low HLA-risk pattern in Kuwaiti T1D

Run screening methods based on HLA haplotype sharing as prerequisite all neoepitopes to delay or halt β-cell autoimmunity or any future intervention for T1D

Data from this part of the world is extremely valuable and might contribute to a better understanding of the occurrence of T1D.

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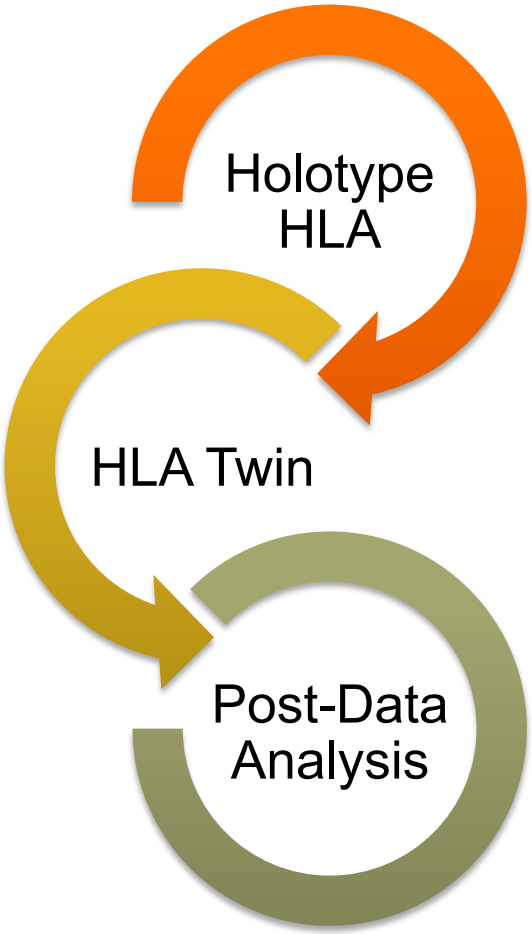
Omixon Product Updates

Efi Melista, Head of Product

Our Difference: Streamlined Workflows



- Holotype HLA
  - Simple, straight-forward assay protocol
  - NGS Workbook for traceability and minimize user error
  - Liquid Handlers for pre and post-PCR steps
- HLA Twin
  - Automated data analysis post-sequencing
  - QC metrics for simple result interpretation
- Post-Data Analysis
  - Epitope analysis via PIRCHE
  - Custom file export for LIMS handling

New Holotype HLA Developments

Holotype HLA v3.1

- RUO in Q4 2019
- *SinglePlex* product
- Extended HLA gene coverage & Fast PCR protocol
- DNA to library in about 8 hours

HLA Twin v4.0

- RUO in June 2019, CE-IVD in Sept 2019
- Significant performance improvements
- Updated screen layout
- Epitope Analysis via PIRCHE

Holotype HLA v4.0

- EAP in Q4 2019
- *MultiPlex* product
- Fast PCR protocol
- DNA to library in about 6 hours

Post-Analysis Data Management

- PIRCHE in HLA Twin
  - 1st NGS software to include epitope analysis
  - Direct integration with HLA Twin
  - Significant usability for solid organ labs

PIRCHE

- LIMS Data Management Support
  - Direct or indirect via custom file export
  - mTilda
  - Histotrac
  - HPRIM

HLA DATA SYSTEMS

mTILDA

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Dr. Peter Meintjes
Chief Executive Officer
peter.meintjes@omixon.com

Marcello Scala
VP Sales, EMEA & Asia
marcello.scala@omixon.com

Dr. Attila Berces
Founder & Chairman
attila.berces@omixon.com

Efi Melista
Head of Product
efi.melista@omixon.com

Davide Resio
Sales Manager, EMEA
davide.resio@omixon.com

Nora Nagy
Head of Market Development and Marketing
nora.nagy@omixon.com

Dr. Libor Kolesar
S. Field Applications Scientist
libor.kolesar@omixon.com

Dr. Nina Lauterbach
S. Field Applications Scientist
nina.lauterbach@omixon.com

Vera Siffnerova
Field Applications Scientist
Vera.siffnerova@omixon.com

Dr. Gergely Tölgyesi
Head of Assay RnD
gergely.tolgyesi@omixon.com

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