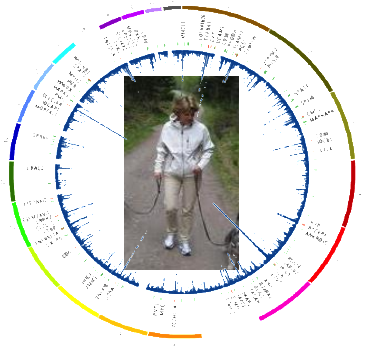
Multiple Sclerosis Research Group
Oslo University Hospital

Mapping of genetic risk factors in MS - and beyond



Hanne Flinstad Harbo, Professor (MD, PhD, MHA)
PI Multiple Sclerosis Research Group,
Department of Neurology, Oslo University Hospital /
Deputy Head, Institute of Clinical Medicine
University of Oslo

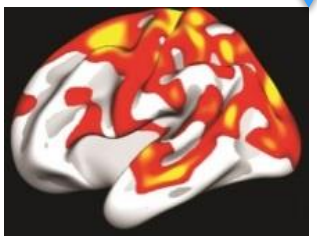
From clinic to genes and molecules – and back

Department of Neurology

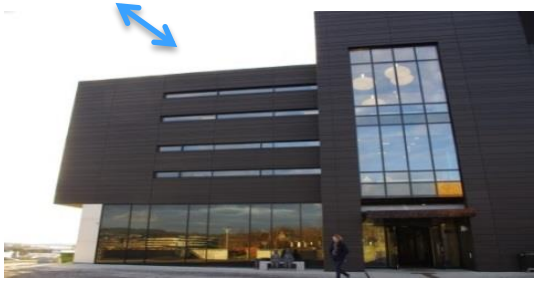
MS Research Group OUS/UiO

Oslo MS Registry and Biobank n= 2000
+ 3000 from Norwegian MS Reg and Biobank

MS clinic



MRI facility

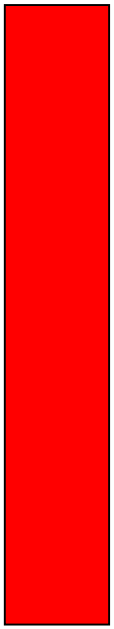


NevGene lab at Neuroscience Research Unit, Domus Medica 4

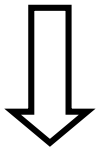
http://ous-research.no/harbo/

MS aetiology is complex

Monogenic disease

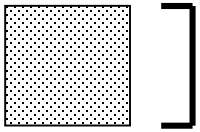


One (rare) genetic variant causes disease

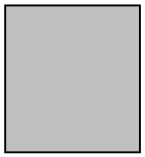


Huntingtons Chorea
50% risk of children
*(Gusella 1983:*Expanded CAG repeat at 4p16.3)

Polygenic, multifactorial disease



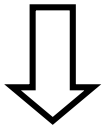
Stochastic factors



Environmental factors:
Smoking/ Vitamin D//
EBV/ BMI/ ?

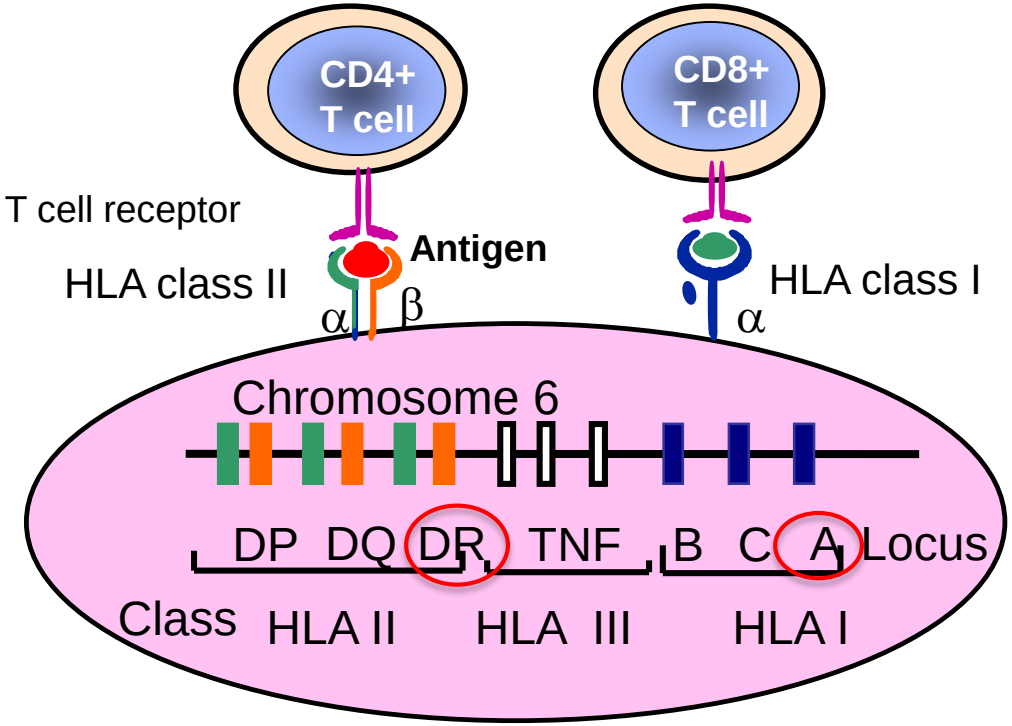
X
Y
z
HLA

Many common genetic *(and/ or some rare?)* variants



Multiple Sclerosis
Diabetes, RA, colitis

HLA genes are associated with MS risk



Allele	OR	p
DRB1*15:01	3.10	$p< 10^{-320}$
HLA-A*02:01	0.73	$p= 10^{-29}$
DRB1*03:01	1.26	$p= 10^{-10}$
DRB1*13:03	2.40	$p= 10^{-11}$
rs9277535_G	1.28	$p= 10^{-22}$

HLA DQ6- **DR2**-B7-A3 haplotype /**HLA-DRB1*1501:** 60% MS, 30% controls
Jersild et al 1972 - Sawcer and IMSGC, 2011

International MS Genetics Consortium

IMSGC

https://www.imsgc.org/

Nordic MS Genetics Network

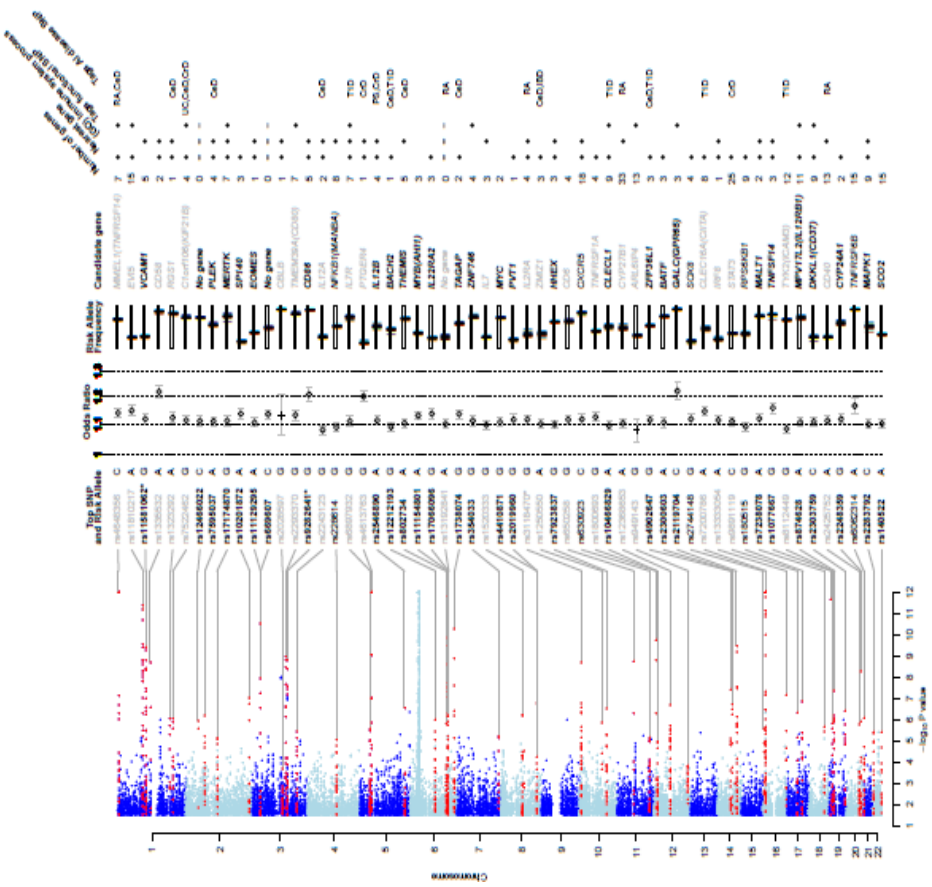
LETTER

IMSGC & WTCCC2 Nature (2011) 476; 214-9

doi:10.1038/nature10251

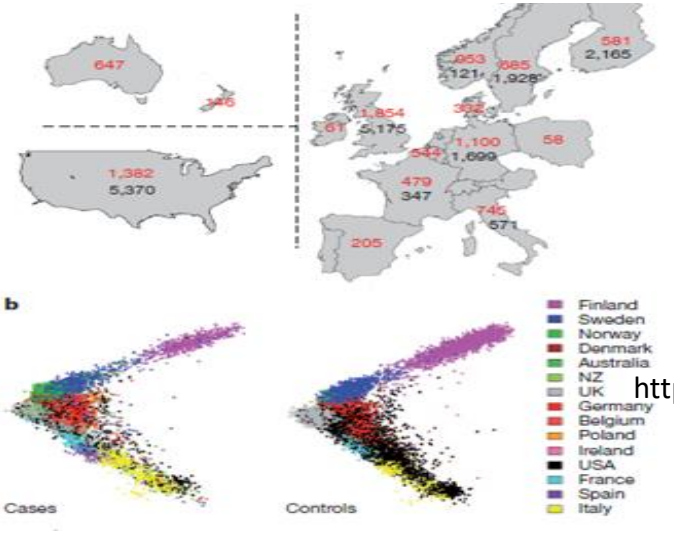
Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis

The International Multiple Sclerosis Genetics Consortium* & the Wellcome Trust Case Control Consortium 2*



- **>52 non-HLA MS risk loci identified**
- 9,772 MS cases
- 17,376 controls
- 475,806 SNPs

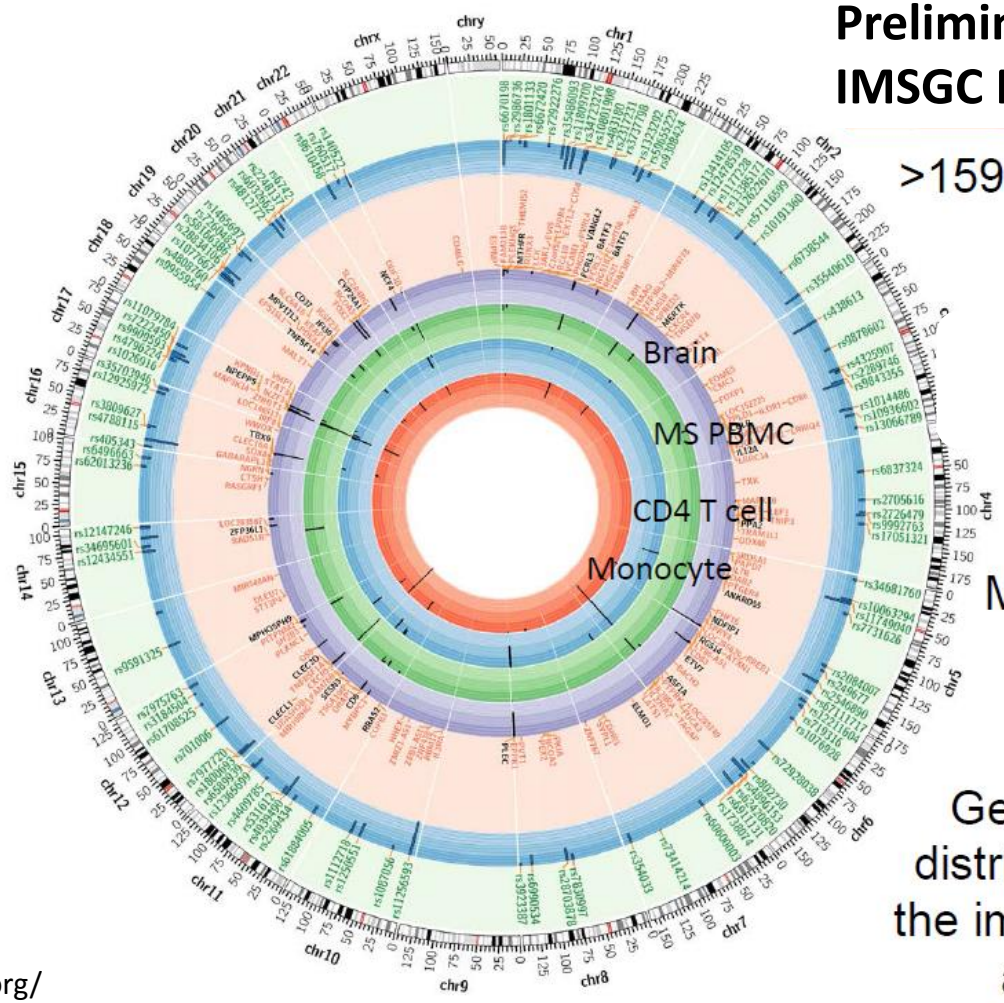
MS group OUS/UiO



IMSGC

https://www.imsgc.org/

Approx. 200 MS risk variants identified in 2016



Preliminary data
IMSGC MS chip project:

>159 MS susceptibility variants

35,314 MS
48,848 controls

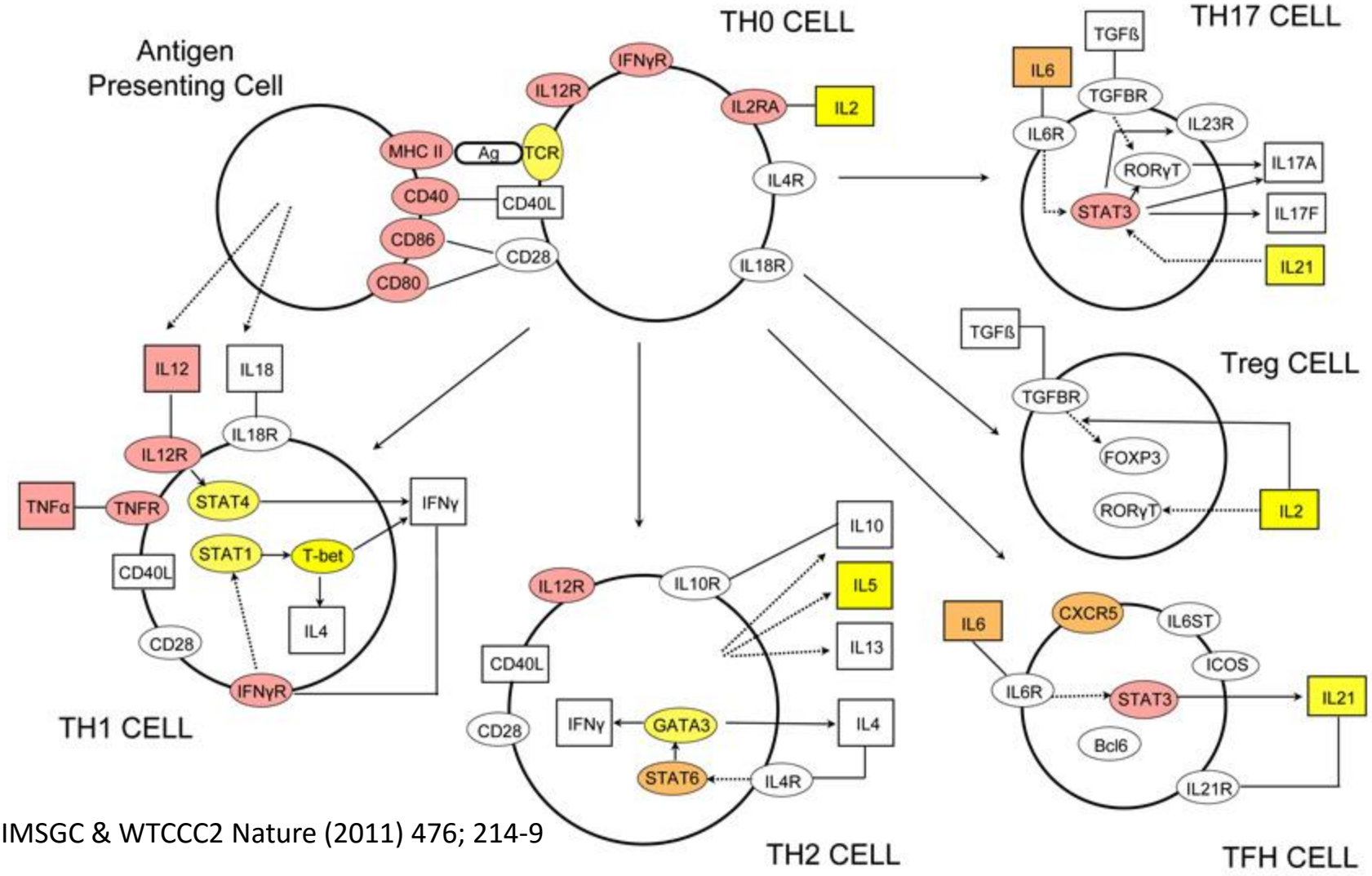
Multiple variants in a given locus

Genetic risk is distributed across the immune system and brain

IMSGC
https://www.imsgc.org/

IMSGC, in progress

Follow-up 1:
Identification of molcular pathways can be based on genetic screens



IMSGC & WTCCC2 Nature (2011) 476; 214-9

Follow-up 2: Genetics and clinical features

Summary MS genetic score is higher in MS with oligoclonal bands in CSF

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–9

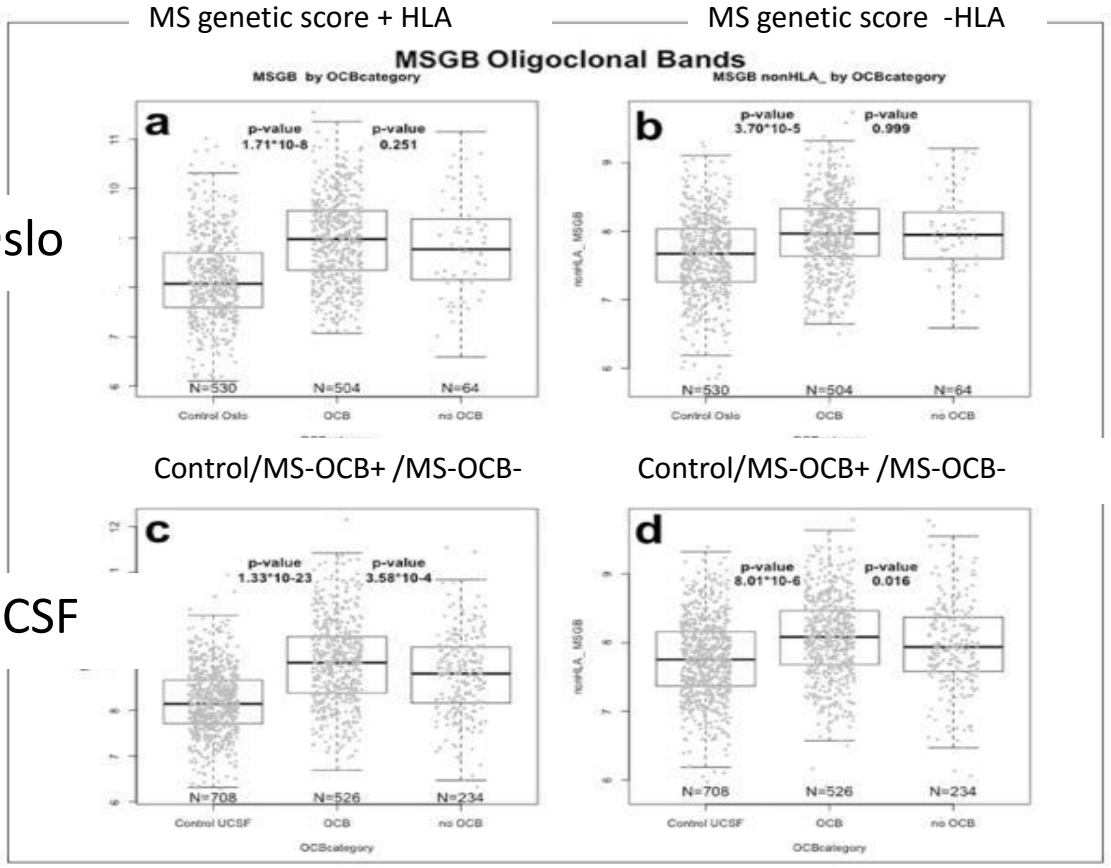
DOI: 10.1177/1352458513506503
msj.sagepub.com
SAGE

Oligoclonal bands and age at onset correlate with genetic risk score in multiple sclerosis

Hanne F Harbo[1,2], Noriko Isobe[3], Pål Berg-Hansen[1,2], Steffan D Bos[1,2], Stacy J Caillier[3], Marte W Gustavsen[1,2], Inger-Lise Mero[1], Elisabeth Gulowsen Celius[1], Stephen L Hauser[3], Jorge R Oksenberg[3] and Pierre-Antoine Gourraud[3]

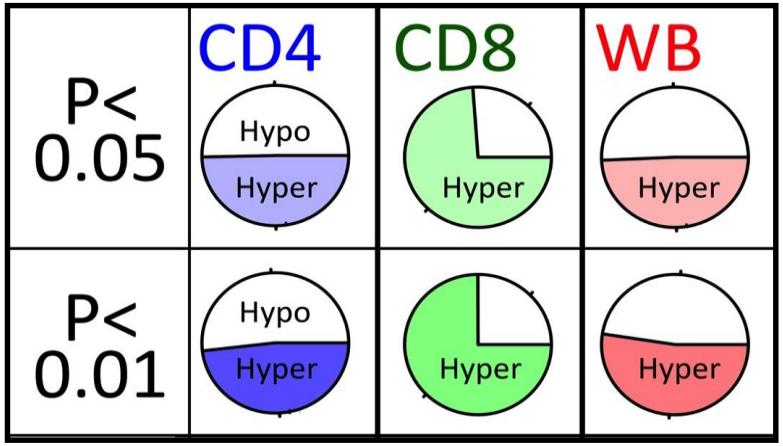






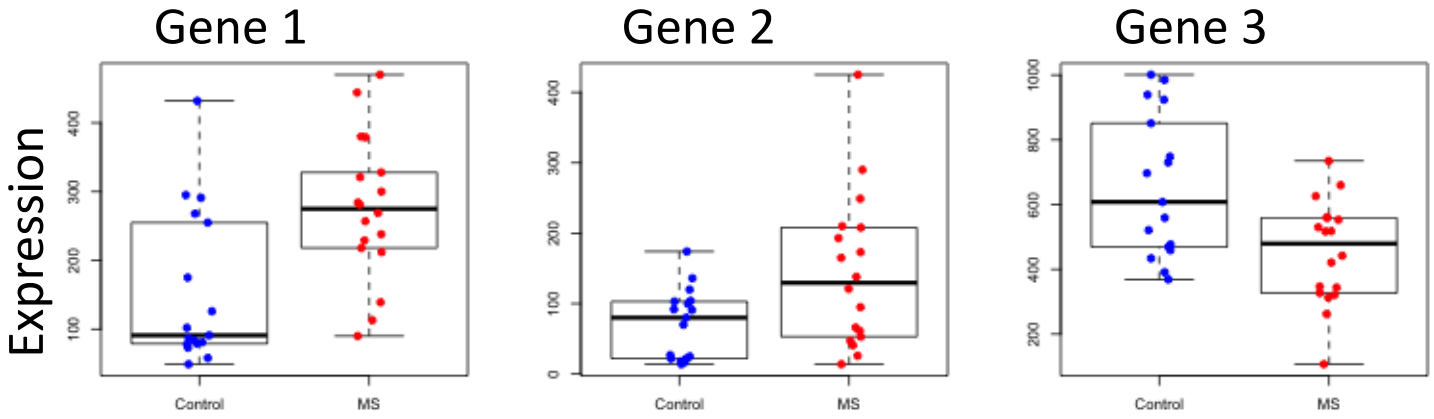
Folllow-up 3:

Methylation and gene expression patterns



DNA is hypermethylated in CD8+ T cells from untreated MS females

Bos, et al.I PlosOne 2015,
collaboration with UC Berkeley (L. Barcellos)



RNA sequencing of CD4+ T cells from MS females

Bos, et al. In progress

Folllow-up 4:

Integration of brain imaging and genetic data

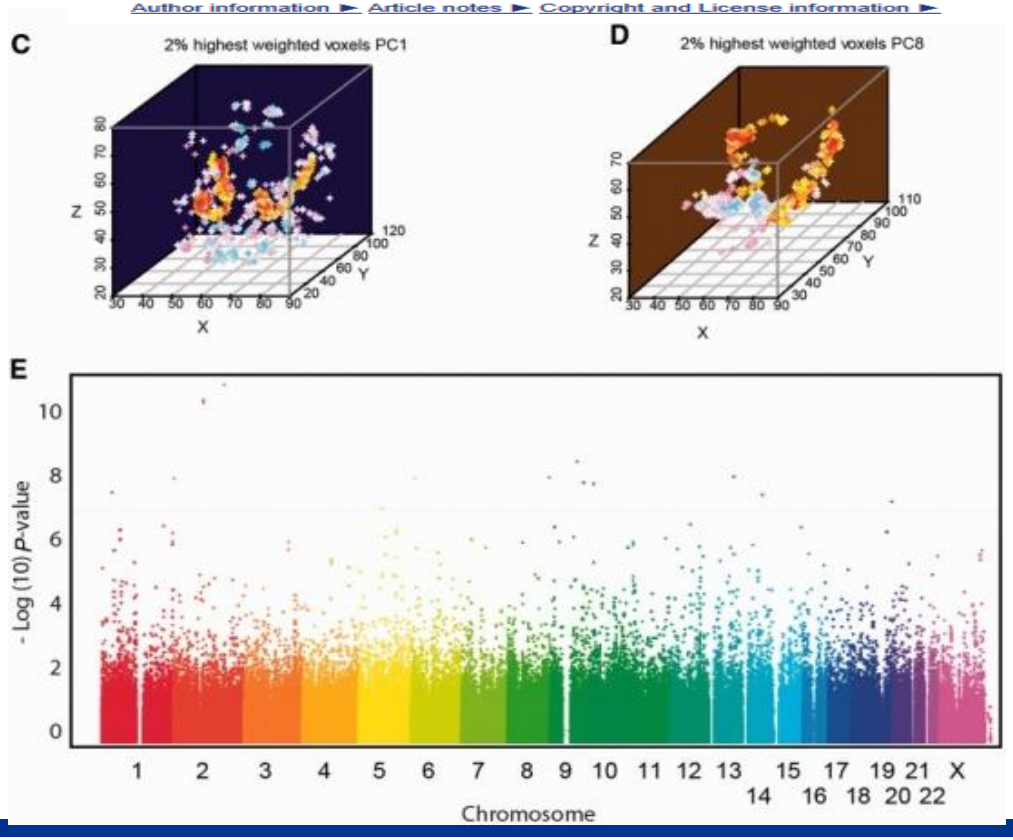
OXFORD JOURNALS Brain

Brain. Apr 2013; 136(4): 1012–1024.
Published online Feb 13, 2013. doi: 10.1093/brain/aws363
PMCID: PMC3613709

A genome-wide association study of brain lesion distribution in multiple sclerosis

Pierre-Antoine Gourraud,[1] Michael Sdika,[1] Pouya Khankhanian,[1] Roland G. Henry,[1] Azadeh Beheshtian,[1] Paul M. Matthews,[2,3] Stephen L. Hauser,[1] Jorge R. Oksenberg,[1] Daniel Pelletier,[1,4] and Sergio E. Baranzini[1]

Author information ► Article notes ► Copyright and License information ►



Distribution of MS lesions on MRI is associated with specific MS-associated genes in an American cohort of 350 MS

Large -scale international study in progress

Example of European research initiative: EU Horizon 2020 grant application 2016 Multiple MS

Proposal template
(technical annex)

Research and Innovation actions
Innovation actions

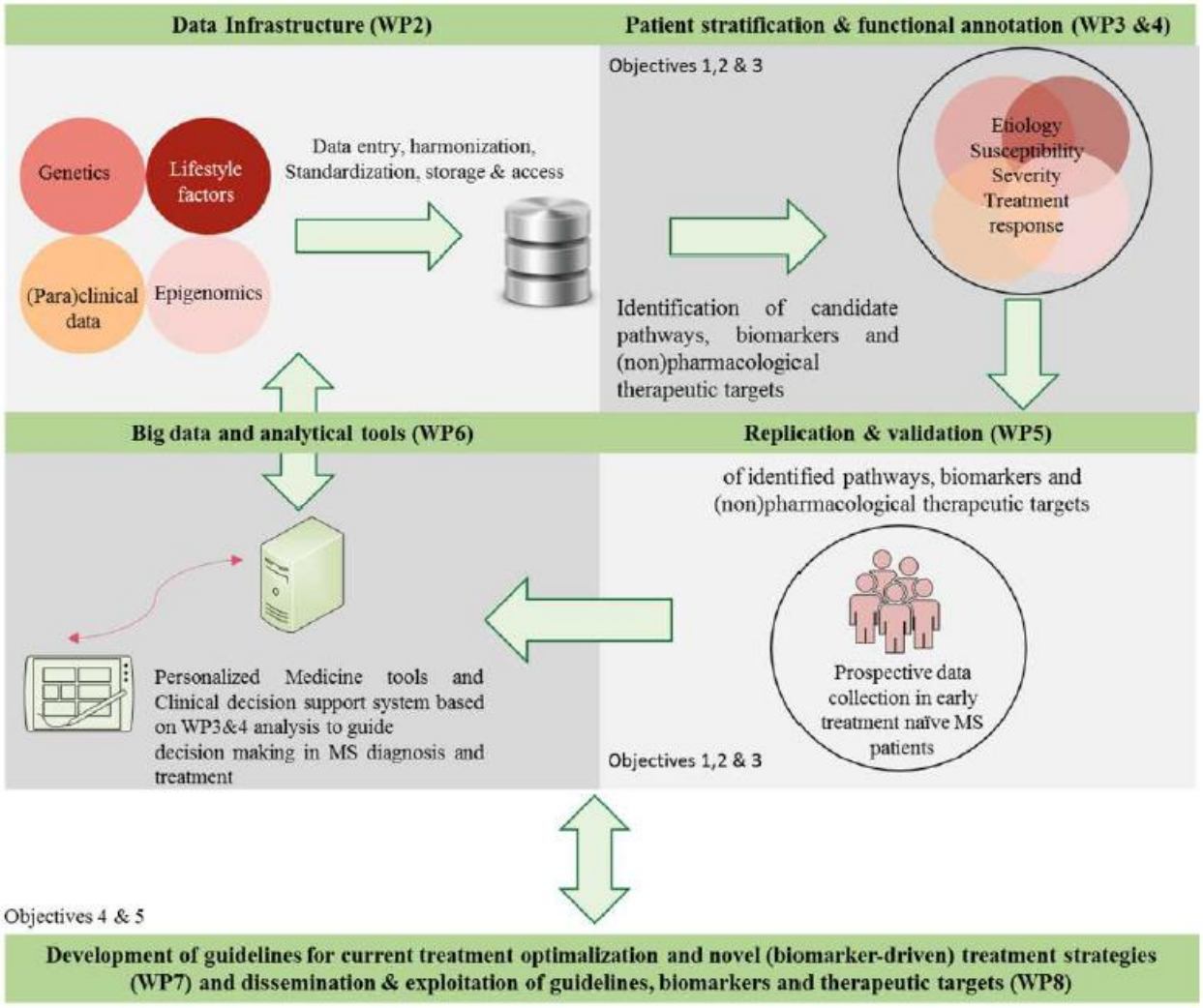
TITLE: ***Multiple*** **manifestations of genetic and non-genetic factors in** ***Multiple*** **Sclerosis disentangled with a** ***multi*****-omics approach to accelerate personalised medicine**

ACRONYM: ***MultipleMS***

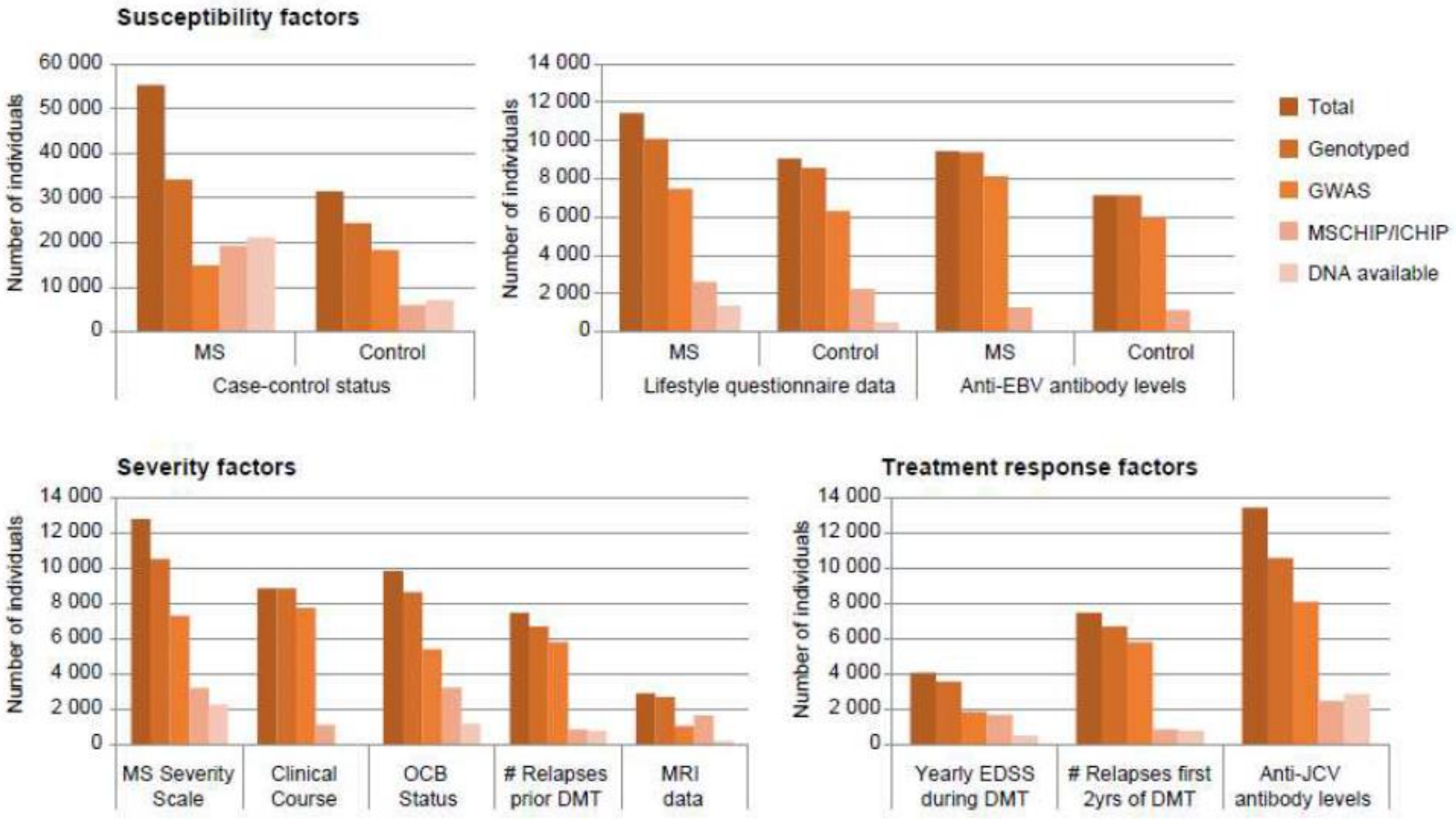
List of participants

Participant No *		Participant organisation name	Country
1	Ingrid Kockum	Department of Clinical Neuroscience, Centre for Molecular Medicine, Karolinska Institutet, Stockholm	SE
2	Staffan Pauli	Mabtech AB (Swedish biotech company), Stockholm	SE
3	Jesper Tegner	YouHealth AB (Swedish bioinformatics company), Stockholm	SE
4	Janna Saarela	Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki	FI
5	Timo Kanninnen	Biocomputing Platforms Oy, (Finnish bioinformatics company), Espoo	FI
6	Hanne Harbo	Department of Neurology, University of Oslo, Oslo	NO
7	Annette Bang Oturai	Department of Neurology, Danish Multiple Sclerosis Center, Rigshospitalet, Copenhagen	DK
8	Bernhard Hemmer	TUM School of Medicine, Technical University of Munich, Munich	DE
9	An Goris	Department of Neurosciences, KU Leuven, Leuven	BE
10	Stephan Beck	Department of Cancer Biology, University College London, London	UK
11	Clare Jones	MedImmune (AstraZeneca), Cambridge	UK
12	Stephen Sawcer	Department of Clinical Neurosciences, University of Cambridge, Cambridge	UK
13	Daniel Zerbino	European Molecular Biology Laboratory, European Bioinformatics Institute, Hinxton	UK
14	Mathurin Baquie	NEURIX (Swiss biotech company), Geneva	CH
15	Pablo Villoslada	Institut d'Investigacions Biomediques August Pi Sunye (IDIBAPS), Barcelona	ES
16	Filippo Martinelli Boneschi	Laboratory of Human Genetics of Neurological Disoders & Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute San Raffaele, Milan,	IT
17	Sandra D'Alfonso	Department of Health Sciences Università del Piemonte Orientale, Novara	IT
18	Sergio Baranzini	Department of Neurology, University of California and San Francisco, San Francisco,	USA
19	Chris Cotsapas	Department of Neurology, Yale School of Medicine, New Haven	USA
20	Wojtek Chacholski	Department of Mathematics, KTH Royal Institute of Technology, Stockholm	SE
21	Irina Antonijevic	Sanofi Genzyme, Early Development, MS Neurology & Ophthalmology, Cambridge	USA

MultipleMS project strategy



Available MS data for the *MultipleMS* project



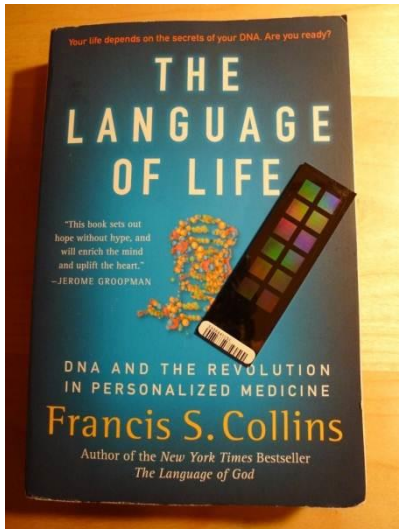
MultipleMS Stakeholder Forum

"..Stakeholders will be asked to provide *MultipleMS* with their knowledge and (in kind) contribution when needed. In addition, it will be discussed with these stakeholders how they can be involved in exploiting relevant Multiple MS output…."

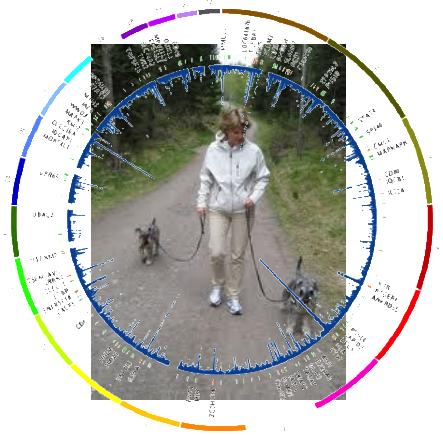
Table 3.2b *Current composition of the Stakeholder Forum (see letters of support attached to chapter 4 and 5)*

Name	Position	Expertise/reason
Anne Winslow	President European Multiple Sclerosis Platform (EMSP)	Umbrella organisation for national MS organisations in Europe, building alliances between MS advocates across Europe with the aim of improving treatment and care of MS patients
Mona Enstad	CEO MS Society of Norway	A "trade union" for MS patients providing a channel of communication with politicians, clinicians and researchers in the MS field
Annette Bang	Head of the Danisch Society for	DAREMUS is a society promoting research in MS. The society offers advisory and coordinating efforts in MS research in Denmark and Danish
Oturai	Research in Multiple Sclerosis (DAREMUS)	participation in international research projects via the company's board. The society encourages and organizes meetings, symposia, conferences, seminars and courses on MS
Klaus Hom	CEO Danish MS Society	The Danish MS society provides its members with updated information on MS research, new treatment methods and rehabilitation.
Joachim Burman	Chairman Swedish MS association	The Swedish MS association gathers healthcare personnel and researchers with interest of MS from the whole of Sweden. In addition, it develops recommendations and common protocols used in Swedish health care.

Summary and perspectives: MS genetics and beyond



«The future has already happened»
Francis Collins, NIH Director



- Genetic profiling - is available
  - Including genetic and molecular risk markers - research purpose
- Molecular subphenotyping - in progress
  - Better characterization of patients
- Pharmacogenomics and use of biomarkers- personalized therapy
  - Genetic variants, molecular mechamisms and MRI are biomarkers for treatment effect and can be used in personalized therapy

Thanks!

Collaborators:

- Our patients and controls
- MS research group at Department of Neurology, Oslo University Hospital (OUH) and University of Oslo (UiO)
- Institutes of Immunology, Medical Genetics, Basic Medical Sciences, Psychology, Biostatics, UiO
- Departments of Neurology, Neuroradiology, Ophthalmology, OUH
- Norwegian MS registry and biobank
- Nordic MS genetics Network
- University of Cambridge, UK
- University of San Francisco, USA
- International MS Genetic Consortium (IMSGC) and collaborating institutions

Our patients

MS Research Group OUH/UiO

IMSGC

https://www.imsgc.org/

Funding:

- Norwegian Research Council (NRC)
- NevroNor, NRC
- Oslo University Hospital
- University of Oslo
- Norwegian South East Health Authorities
- Wellcome Trust, UK through IMSGC grant
- Oslo , Bergen, Odda and Norwegian MS Society Norway (unrestricted grants)
- Odd Fellow MS society, Norway (unrestricted grants)
- Novartis, Biogen Idec, Aventis, Schering, Norway (unrestricted grants)