Mapping of genetic risk factors in MS - and beyond

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University of Oslo
From clinic to genes and molecules – and back

Department of Neurology

MS patients

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/ ?

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

Multiple Sclerosis
Diabetes, RA, colitis

Monogenic disease
Polygenic, multifactorial disease
HLA genes are associated with MS risk

- 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

Nordic MS Genetics Network

https://www.imsgc.org/
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

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

IMSGC
https://www.imsgc.org/

MS group OUS/UiO

https://www.ous.no/en/research/regions/neurology/neurology-research/immunology/
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, in progress

https://www.imsgc.org/
Follow-up 1: Identification of molecular 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.
Follow-up 3: Methylation and gene expression patterns

DNA is hypermethylated in CD8+ T cells from untreated MS females
Bos, et al. PlosOne 2015, collaboration with UC Berkeley (L. Barcellos)

RNA sequencing of CD4+ T cells from MS females
Bos, et al. In progress
Distribution of MS lesions on MRI is associated with specific MS-associated genes in an American cohort of 350 MS patients. 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 personalized medicine

ACRONYM: MultipleMS

List of participants:

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Participant organisation name</th>
<th>Country</th>
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<tbody>
<tr>
<td>1</td>
<td>Ingrid Kockum, Department of Clinical Neuroscience, Centre for Molecular Medicine, Karolinska Institutet, Stockholm</td>
<td>SE</td>
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<td>2</td>
<td>Stoffin Paul, Multitech AB (Swedish biotech company), Stockholm</td>
<td>SE</td>
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<tr>
<td>3</td>
<td>Jesper Tegner, YouthLife AB (Swedish biopharmaceutical company), Stockholm</td>
<td>SE</td>
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<td>4</td>
<td>Janna Saarala, Institute for Molecular Medicine Finland (FeMi), University of Helsinki, Helsinki</td>
<td>FI</td>
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<tr>
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<td>Taro Kanaan, Bioinformatics Platform Ov, (Finnish bioinformatics company), Espoo</td>
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<td>Hanna Herlo, Department of Neurology, University of Oslo, Oslo</td>
<td>NO</td>
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<tr>
<td>7</td>
<td>Annette Bang Otsou, Department of Neurology, Danish Multiple Sclerosis Center, Rigshospitalet, Copenhagen</td>
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<td>8</td>
<td>Bernhard Herense, TUM School of Medicine, Technical University of Munich, Munich</td>
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<td>10</td>
<td>Stephan Beck, Department of Cancer Biology, University College London, London</td>
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<td>Clare Jones, MedImmune (AstraZeneca), Cambridge</td>
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<td>12</td>
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<td>13</td>
<td>Daniel Zerboni, European Molecular Biology Laboratory, European Bioinformatics Institute, Hanover</td>
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<tr>
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<td>Mathias Boccia, NERI (Swiss biotech company), Geneva</td>
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<td>15</td>
<td>Pablo Villalba, Institute of Investigative Biomedicine August Pi i Sunyer (IDIBAPS), Barcelona</td>
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<td>16</td>
<td>Filippo Martuscelli Bonacchi, Laboratory of Human Genetics of Neurological Disorders &amp; Department of Neurology, Institute of Experimental Neurology, Scientific Institute San Raffaele, Milan</td>
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<td>17</td>
<td>Sandra D'Alessio, Department of Health Sciences, Università del Piemonte Orientale, Novara</td>
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<td>18</td>
<td>Sergio Baranzini, Department of Neurology, University of California and San Francisco, San Francisco</td>
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<td>19</td>
<td>Chris Cotzapas, Department of Neurology, Yale School of Medicine, New Haven</td>
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<td>Wojtek Chacholzki, Department of Mathematics, KTH Royal Institute of Technology, Stockholm</td>
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<tr>
<td>21</td>
<td>Irena Antonjevic, Sanofi Genzyme, Early Development, MS Neurology &amp; Ophthalmology, Cambridge</td>
<td>USA</td>
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MultipleMS project strategy

Data Infrastructure (WP2)
- Genetics
- Lifestyle factors
- (Para)clinical data
- Epigenomics
  - Data entry, harmonization, standardization, storage & access

Patient stratification & functional annotation (WP3 & 4)
- Objectives 1, 2 & 3
- Etiology
- Susceptibility
- Severity
- Treatment response
- Identification of candidate pathways, biomarkers and (non)pharmaceutical therapeutic targets

Replication & validation (WP5)
- Objectives 1, 2 & 3
- Prospective data collection in early treatment naive MS patients
- Development of guidelines for current treatment optimization and novel (biomarker-driven) treatment strategies (WP7) and dissemination & exploitation of guidelines, biomarkers and therapeutic targets (WP8)

Big data and analytical tools (WP6)
- Personalized Medicine tools and Clinical decision support system based on WP3&4 analysis to guide decision making in MS diagnosis and treatment

Development of guidelines for current treatment optimization and novel (biomarker-driven) treatment strategies (WP7) and dissemination & exploitation of guidelines, biomarkers and therapeutic targets (WP8)

Oslo universitetssykehus
Multiple Sclerosis Research Group
Oslo University Hospital
UiO Universitet i Oslo
Available MS data for the *MultipleMS* project
“..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)

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Expertise/reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anne Winslow</td>
<td>President European Multiple Sclerosis Platform (EMSP)</td>
<td>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</td>
</tr>
<tr>
<td>Mona Enstad</td>
<td>CEO MS Society of Norway</td>
<td>A “trade union” for MS patients providing a channel of communication with politicians, clinicians and researchers in the MS field</td>
</tr>
<tr>
<td>Annette Bang</td>
<td>Head of the Danish Society for</td>
<td>DAREMUS is a society promoting research in MS. The society offers advisory and coordinating efforts in MS research in Denmark and Danish</td>
</tr>
<tr>
<td>Oturai</td>
<td>Research in Multiple Sclerosis (DAREMUS)</td>
<td>participation in international research projects via the company’s board. The society encourages and organizes meetings, symposia, conferences, seminars and courses on MS</td>
</tr>
<tr>
<td>Klaus Hom</td>
<td>CEO Danish MS Society</td>
<td>The Danish MS society provides its members with updated information on MS research, new treatment methods and rehabilitation.</td>
</tr>
<tr>
<td>Joachim Burman</td>
<td>Chairman Swedish MS association</td>
<td>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</td>
</tr>
</tbody>
</table>
Summary and perspectives: MS genetics and beyond

- 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 mechanisms and MRI are biomarkers for treatment effect and can be used in personalized therapy

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

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)

https://www.imsgc.org/