

Multiple Sclerosis (MS) Research Group – Annual report 2016



Group Leader

Hanne Flinstad Harbo, Professor and consultant of Neurology (MD, PhD, MHA), Department of Neurology. Oslo University Hospital (OUH)¹ and Institute of Clinical Medicine, University of Oslo (UiO)² (h.f.harbo@medisin.uio.no/uxhahb@ous-hf.no).

Group members

- Hanne Flinstad Harbo, MD/PhD/MHA, Professor, OUH¹/UiO²
- Elisabeth Gulowsen Celius, MD/PhD, Professor, OUH¹/UiO
- Tone Berge, MSc/PhD, researcher OUH¹, Ass. prof. Oslo and Akershus University College of Applied Sciences
- Steffan D. Bos-Haugen, MSc/PhD, researcher, UiO²
- Pål Berg-Hansen, MD/PhD, engagement ass. professor UiO² and consultant OUH¹
- Gro Owren Nygaard, MD/PhD, OUH¹
- Sigrid Aune de Rodez Benavent, MD/PhD fellow, Department of Ophthalmology, OUH/UiO²
- Piotr Sowa, MD/PhD fellow, Department of Radiology, OUH
- Christian Page, MSci/PhD fellow, UiO² (until dissertation November 2016)
- Ingvild Sørum Leikfoss, MSci/PhD, UiO² (maternity leave in 2016)
- Pankaj K. Keshari, MSci/PhD fellow, OUH¹
- Anna M. Eriksson, MSci/PhD fellow, UiO² (maternity leave most of 2016)
- Ina S. Brorson, MSci/PhD fellow, UiO²
- Einar August Høgestøl, MD/PhD fellow, UiO²
- Cecilia Smith Simonsen, MD/PhD fellow, Drammen Hospital/OUH¹
- Heidi Øyen Flemmen, MD/PhD fellow, Skien Hospital/OUH¹
- Fernanda Kropf Correia, BSc, Masterstudent, UiO (MatNat)
- Ingrid Mo, BSc, Masterstudent, UiO (MatNat)
- Åshild Skardhamar, MD /PhD-fellow (application in preparation), OUH

Associated Group Members

- Marte Wendel Gustavsen, MD/PhD, Skien Hospital
- Stine Marit Moen, MD/PhD, MS Rehabilitation Center, Hakadal

We have this year had 6 medical students connected to our group, writing student theses:
Harbo: Helga Bøe Kleiven (submitted 2016), Ellen Trap Eggen, Ingerid Maria Tutturen
Celius and Berg-Hansen: Inger Bjurstrøm, Victoria Løvstad and Hedda H. Gretland.





Research profile and aims

Multiple Sclerosis (MS) research group at the Department of Neurology, OUH and UiO, aims to identify characteristics and susceptibility factors of MS, and to contribute to a better understanding of the disease and development of better treatments. We perform genetic, immunological, clinical, epidemiological, environmental, MRI and translational studies of MS in collaboration with national and international research partners and networks.

Ongoing projects

- Gro Owren Nygaard, PhD fellow: A longitudinal cohort study of disability, cognition and MRI in early MS patients in Oslo (Health South East grant held by Harbo). Supervisor: Hanne F. Harbo, Co-supervisors: Elisabeth G. Celius and Kristine Beate Walhovd (dissertation January 2016).
- Christian Page, PhD fellow: Rare Variant Genotyping in Complex Diseases and Identification of Differentially methylated regions (UiO grant held by Harbo). Supervisor: Bettina K. Andreassen, Co-supervisors: Hanne F. Harbo and Benedicte A. Lie (dissertation October 2016)
- Sigrid Aune de Rodez Benavent, PhD fellow: A longitudinal cohort study of ophthalmologic biomarkers correlated with neurodegeneration in early MS. (OUH D-position Department of Ophthalmology) Supervisor: Elisabeth G. Celius, Co-supervisors: Emilia Kerty, Bruno Laeng and Liv Drosalum.
- Tone Berge, researcher: Vitamin D responsive and other MS susceptibility genes. (Health South East grant held by Harbo).
- Steffan Daniel Bos, researcher: Identification of molecular mechanisms and biomarkers of Multiple Sclerosis (MS-biomarkers) – RNA sequencing of CD4+ and CD8+ T cells as potential biomarkers of MS phenotypes. (NFR researcher project grant held by Harbo).
- Piotr Sowa, PhD fellow: MRI biomarkers of disease activity and progression in multiple sclerosis (Health South East grant held by Beyer). Supervisor: Mona Beyer, Co-supervisor: Hanne F. Harbo.
- Pankaj K. Keshari, PhD fellow: Immunogenetic loci characterization of multiple sclerosis. (South-Eastern Norway Regional Health Authority grant held by Harbo). Supervisor: Tone Berge, Co-supervisors: Hanne F. Harbo and Steffan Daniel Bos.
- Anna M. Eriksson, PhD fellow: Identification of molecular mechanisms and biomarkers of Multiple Sclerosis (MS-biomarkers) – molecular characterization of DEXI and other MS susceptibility genes (NFR researcher project grant held by Harbo). Supervisor: Tone Berge, Co-supervisors: Hanne F. Harbo and Steffan Bos.
- Ina S. Brorson, PhD fellow from 1.12.15 (UiO grant held by Harbo): Defining and characterizing molecular pathways in multiple sclerosis. Supervisor: Steffan Bos, Co-supervisors: Hanne F Harbo and Tone Berge.
- Einar August Høgestøl, PhD fellow from 1.12.15: MRI- and other biomarkers in multiple sclerosis. (NFR researcher project grant held by Harbo). Supervisor: Hanne F Harbo, Co supervisor: Lars T Westlye and Gro O Nygaard





- Cecilia Smith Simonsen, PhD fellow (OUH-Drammen grant): Predictors for disease susceptibility and disease progression in Multiple sclerosis, Supervisor: Elisabeth Gulowsen Celius, Co supervisors: Stine Marit Moen and Kari Anne Bjørnerå.
- Heidi Øyen Flemmen, PhD fellow (Skien grant): Socioeconomic factors as predictors for disease susceptibility and disease progression in Multiple sclerosis, Supervisor: Elisabeth Gulowsen Celius, Co supervisor: Pål Berg-Hansen. Åshild Skardhamar, MD, PhD fellow: Fatigue in Multiple Sclerosis. Supervisor: Elisabeth Gulowsen Celius
- Fernanda Kropf Correia (Master project): Molecular characterization of TAGAP- a GTPase-activating protein encoded by a multiple sclerosis susceptibility gene. Supervisor Tone Berge.
- Ingrid Mo (Master project): Identifying protein interaction partners for DEXI – encoded by the multiple sclerosis associated dexamethasone-induced gene, DEXI. Supervisor Tone Berge
- Tone Berge, collaboration with Professor Frode Bervem at the University of Bergen; Mass spectrometry analyses of immune cells in multiple sclerosis.
- Ingvild Sørnum Leikfoss (Senior engineer): CLEC16A and other candidate genes (parental leave most of 2016).
- Hanne F Harbo, Steffan Bos, Elisabeth G Celius. MS chip study, collaboration with IMSGC (Harbo Oslo PI).
- Hanne F Harbo, Steffan Bos, Elisabeth G Celius. Exome chip study, collaboration with IMSGC. (Harbo Oslo PI).
- Hanne F Harbo, Steffan Bos, Pål Berg-Hansen, Mona Beyer: BorrSci study, lead from Kristiansand (South-Eastern Norway Multi- Regional Health Authority grant).
- Hanne F Harbo, Steffan Bos, Pål Berg-Hansen, Tone Berge, Ingvild S Leifoss, Elisabeth G Celius Mona Beyer: Multiple MS - partner in EU Horizon 2020-prosjekt (Harbo Oslo PI).
- Hanne F Harbo, Einar A Høgestøl, Sigrid de Rodez Benavent, Steffan Bos, Tone Berge, Elisabeth G Celius, Mona Beyer: Sys4MS- Biotek 2021/NFR Project. (Harbo Oslo PI).
- Einar A Høgestøl, Steffan Bos, Hanne F Harbo: MYO Project. Wit Prof Pierre Gourraud, Nantes. NFR support for travel. NFR-Aurora travel grant (Harbo Oslo PI).
- Elisabeth G. Celius, Mona Beyer, Piotr Sowa, Tobias Granberg : Neuroprotective effects of alemtuzumab in patients with MS in a clinical setting.
- Cecilia Smith simonsen, Astrid Edland, Elisabeth G. Celius : Effekt av FAMPYRA® på gange, syn, kognisjon, fatigue og vannlating hos pasienter med multiple sklerose
- Elisabeth G. Celius and SINTEF : AutoActive :Tools and Methods for Autonomous Analysis of Human Activities from Wearable Device Sensor Data.
- E.G.Celius, P. Berg-Hansen, Kamila Rasova, Prague, Czech republic, Sunnaas, Hakadal MS center, Kysthospitalet Stavern, HiOA :Physiotherapy in the Czech Republic and Norway. Project funded by EU.





MS research group OUS-UiO photo summer 2016 at OUS Ullevål:

From left: Elisabeth Gulowsen Celius (consultant of neurology and project leader, MD, PhD), Melanie Van Cauwenberghe (Erasmus Master Student), Ina Skaara Brorson (PhD student, MSc), Fernanda Kropf (Master student), Stine Marit Moen (consultant of neurology, MD, PhD), Pål Berg-Hansen (Ass.professor, PhD and consultant of neurology, MD,), Heidi Øyen Flemmen (consultant of neurology, PhD student, MD), Ingrid Mo (Master student), Marte Gustavsven (PhD, MD), Pankaj Kumar Keshari (PhD student, MSc), Piotr Sowa (PhD student, consultant of radiology, MD), Dan Rinker (visiting PhD student from UCLA, MSc), Steffan Daniel Bos (post doc, PhD, MSc), Sigrid A. de Rodez Benavent (consultant of opthalmology, PhD student, MD), Hanne F. Harbo (professor, consultant of neurology and group leader, MD, MHA, PhD), Einar August Høgestøl (PhD student, MD), Tone Berge (research coordinator and post doc, MSc, PhD).

Funding

- South-Eastern Norway Regional Health Authority
- The Research Council of Norway
- University of Oslo
- European Commission: EU Horizon 2020
- European Commission/The Reserach Council of Norway: Sys4MS - Biotek 2021
- Norwegian Extra Foundation for Health and Rehabilitation
- South-Eastern Norway Multi- Regional Health Authority grant
- Unrestricted research grants from Novartis, Biogen, Genzyme, Odd Fellow, Forsberg and Aulie, and Ingrid and Fritz Nilsen, UNIFOR



Most important national and international collaborators

National

- Mona Beyer, Dept. of Radiology, OUH
- Benedicte A. Lie, Dept. of Medical Genetics, OUH /UiO
- Kristine Walhovd and Anders Fjell, Dept. of Psychology, UiO
- Anne Spurkland, Institute of Basic Medical Sciences, UiO
- Bettina Kulle Andreassen, Cancer Registry, Norway
- Emilia Kerty, Dept. of Neurology, OUH/UiO
- Liv Drolsum, Dept. of Ophthalmology, OUH/UiO
- Ole A. Andreassen, Dept. of Psychiatry, OUH/UiO
- Camilla Stoltenberg, Norwegian Institute of Public Health
- Inger Johanne Bakken, Norwegian Institute of Public Health
- Odd Stokke Gabrielsen, Section for Biochemistry and Molecular Biology, UiO
- Greger Abrahamsen, Division of Anatomy, Molecular Immunology (MOLIMMUN), UiO
- Vibeke Sundvold Gjerstad, Division of Anatomy, Molecular Immunology (MOLIMMUN), UiO
- Trygve Holmøy, Dept. of Neurology, Akershus University Hospital
- Torbjørn Rognes, Section for Biomedical Informatics, Dept. of Informatics, UiO
- Nils Inge Landrø and Bruno Laeng, Dept. of Psychology, UiO
- Ole Landsverk, Dept of Pathology, KLM, OUH
- K.B Nilsen and L. Etholm, , Dept. of Neurophysiology, OUH
- Kjell-Morten Myhr and Jan Aarseth, Haukeland University Hospital
- Atle Bjørnerud, Dept. of Physics, Intervention Centre, UiO/OUH
- Frode Berven, Dept. of Biomedicine, University of Bergen
- Lars T. Westlye, Dept. of Psychiatry, OUH
- Rigmor Lundby, Dept. of Radiology, OUH

International

- Lisa Barcellos, University of California, Berkeley, US
- Jorge Oksenberg, University of California, San Francisco, US
- Sergio E. Baranzini, University of California, San Francisco, US
- Pablo Villoslada (Hospital Clinic of Barcelona, Spain)
- Steve Francis, University of California, San Francisco, US
- Anders Dahle, University of California San Diego, US
- Soheil Damangir and Gabriela Spulber, Karolinska Institute, Stockholm, Sweden
- Jan Damoiseaux, Dept. of Neurology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands
- Joost Smolders, Dept. of Neurology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands
- B. Wilhelm, Steinbeis Transfer-Centre for Biomedical Optics and Function Testing, Tübingen, Germany
- Nordic MS genetics consortium (Hillert, Olsson, Kockum, Oturai, Sørensen, Saareala)
- International MS Genetics Consortium (Adrian Ivinson, Stephen Sawcer, Stephen Hauser, An Goris)
- Helen Tremlett, Dept of Neurology, Vancouver, Canada
- Pierre Antoine Gourraud, Hôpital St-Jacques - CHU de Nantes
- Tobias Granberg, Karolinska, Stockholm
- Prof. Kamila Rasova, University of Prague,
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Peer reviewed original research articles: 16

Other publications (abstracts excluded):

Ingvild Sørum Leikfoss. September 2016: *Forståelsen av multippel sklerose-disponerende gener; fra genotype til fenotype*. BestPractice Psykiatri, nevrologi og geriatri.Nr.27/Sep.2016, 7. Årgang

Pål Berg-Hansen. Hvor vanlig er MS i Norge? BestPractice Psykiatri, nevrologi og geriatri.Nr.26/April 2016, 7. Årgang

Elisabeth Gulowsen Celius: Rebound ved seponering av MS behandling. BestPractice Psykiatri, nevrologi og geriatri.Nr.25/Januar 2016, 7. Årgang

Hanne F Harbo og Anne Hege Aamodt: Bruk hjernen! Blogg Forskningssykehuset, June 2016

Hanne F Harbo og Anne-Grethe Strøm-Erichsen: Norge må satse mer på hjernehelse. Kronikk Dagens Medisin, August 2016 og i Fædrelandsvennen, August 2016.

Invited lectures at international congresses:

Elisabeth G. Celius: Long term prognosis in multiple sclerosis – a 25 year follow-up.International MS Cognition Society, New York, June 2016.

Hanne F Harbo: Mapping of MS Genetic Risk Factors in MS. European association of MS societies (EMSP). May 18th 2016

Doctoral dissertations:

Gro Owren Nygaard 27. Jan. 2016: Cognition, disease activity and MRI changes in early multiple sclerosis. Main supervisor: Hanne Flinstad Harbo. Co-supervisors: Kristine Walhovd, Elisabeth G Celius.

Christian Page 21. Nov. 2016: DNA Methylation and Exome Chip Analysis in Complex Disease. Main supervisor: Bettina K. Andreassen. Co-supervisor: Hanne Flinstad Harbo





Three selected publications:

1. Berge T, Leikfoss IS, Brorson IS, Bos SD, Page CM, Gustavsen MW, et al. The multiple sclerosis susceptibility genes TAGAP and IL2RA are regulated by vitamin D in CD4+ T cells. *Genes Immun.* 2016;17(2):118-27.
2. Simonsen CS, Celius EG, Brunborg C, Tallaksen C, Eriksen EF, Holmoy T, et al. Bone mineral density in patients with multiple sclerosis, hereditary ataxia or hereditary spastic paraplegia after at least 10 years of disease - a case control study. *BMC Neurol.* 2016;16(1):252.
3. Keshari PK, Harbo HF, Myhr KM, Aarseth JH, Bos SD, Berge T. Allelic imbalance of multiple sclerosis susceptibility genes IKZF3 and IQGAP1 in human peripheral blood. *BMC Genet.* 2016;17:59

List of original research articles 2016

1. Berge T, Leikfoss IS, Brorson IS, Bos SD, Page CM, Gustavsen MW, et al. The multiple sclerosis susceptibility genes TAGAP and IL2RA are regulated by vitamin D in CD4+ T cells. *Genes Immun.* 2016;17(2):118-27.
2. Bos SD, Berge T, Celius EG, Harbo HF. From genetic associations to functional studies in multiple sclerosis. *Eur J Neurol.* 2016;23(5):847-53.
3. Keshari PK, Harbo HF, Myhr KM, Aarseth JH, Bos SD, Berge T. Allelic imbalance of multiple sclerosis susceptibility genes IKZF3 and IQGAP1 in human peripheral blood. *BMC Genet.* 2016;17:59.
4. International Multiple Sclerosis Genetics Consortium. Electronic address cbo. NR1H3 p.Arg415Gln Is Not Associated to Multiple Sclerosis Risk. *Neuron.* 2016;92(4):929.
5. a) Moen SM, Harbo HF, Sowa P, Celius EG, Nygaard GO, Beyer MK. [MRI in multiple sclerosis]. *Tidsskr Nor Laegeforen.* 2016;136(16):1373-6.
b) Moen SM, Harbo HF, Celius EG, Sowa P, Nygaard GO, Beyer MK. *Tidsskr Nor Laegeforen.* 2016;136(20):1702
c) Moen SM, Harbo HF, Celius EG, Sowa P, Nygaard GO, Beyer MK. *Tidsskr Nor Laegeforen.* 2016;136(19):1608.
6. Simonsen CS, Celius EG, Brunborg C, Tallaksen C, Eriksen EF, Holmoy T, et al. Bone mineral density in patients with multiple sclerosis, hereditary ataxia or hereditary spastic paraplegia after at least 10 years of disease - a case control study. *BMC Neurol.* 2016;16(1):252.
7. George MF, Briggs FB, Shao X, Gianfrancesco MA, Kockum I, Harbo HF, et al. Multiple sclerosis risk loci and disease severity in 7,125 individuals from 10 studies. *Neurol Genet.* 2016;2(4):e87.





8. Wang Y, Bos SD, Harbo HF, Thompson WK, Schork AJ, Bettella F, et al. Genetic overlap between multiple sclerosis and several cardiovascular disease risk factors. *Mult Scler.* 2016;22(14):1783-93
9. Bjørnevik K, Riise T, Benjaminsen E, Celius EG, Dahl OP, Kampman MT, Løken-Amsrud KI, Midgard R, Myhr KM, Torkildsen Ø, Vatne A, Grytten N (2016) Level of education and multiple sclerosis risk over a 50-year period: Registry-based sibling study *Mult Scler*, 23 (2), 213-219
10. Keshavan A, Paul F, Beyer MK, Zhu AH, Papinutto N, Shinohara RT, Stern W, Amann M, Bakshi R, Bischof A, Carriero A, Comabella M, Crane JC, D'Alfonso S, Demaerel P, Dubois B, Filippi M, Fleischer V, Fontaine B, Gaetano L, Goris A, Graetz C, Gröger A, Groppa S, Hafler DA, Harbo HF, Hemmer B, Jordan K, Kappos L, Kirkish G, Llufriu S, Magon S, Martinelli-Boneschi F, McCauley JL, Montalban X, Mühlau M, Pelletier D, Pattany PM, Pericak-Vance M, Cournu-Rebeix I, Rocca MA, Rovira A, Schlaeger R, Saiz A, Sprenger T, Stecco A, Uitdehaag BM, Villoslada P, Wattjes MP, Weiner H, Wuerfel J, Zimmer C, Zipp F; International Multiple Sclerosis Genetics Consortium, Hauser SL, Oksenberg JR, Henry RG. *Neuroimage.* 2016 Jul 1;134:281-94. "
11. Gustavsen, Marte Wendel; Celius, Elisabeth Gulowsen; Winsvold, Bendik K S; Moen, Stine Marit; Nygaard, Gro Owren; Berg-Hansen, Pål; Lie, Benedicte Alexandra; Zwart, John-Anker; Harbo, Hanne Flinstad. Migraine and frequent tension-type headache are not associated with multiple sclerosis in a Norwegian case-control study. *Multiple Sclerosis Journal, Experimental, Translational and Clinical* 2016; Volum 2. s. 1-4
12. Simonsen, Cecilia Smith; Edland, Astrid; Berg-Hansen, Pål; Celius, Elisabeth Gulowsen. High prevalence and increasing incidence of multiple sclerosis in the Norwegian county of Buskerud. *Acta Neurologica Scandinavica* 2016; 135(4 s.412-418
13. Celius EG, Rocca M, Andersen O. Preface. *Acta Neurol Scand.* 2016 Sep;134 Suppl 200:3. doi: 10.1111/ane.12653. No abstract available.
14. George MF, Briggs FB, Shao X, Gianfrancesco MA, Kockum I, Harbo HF, Celius EG, Bos SD, Hedström A, Shen L, Bernstein A, Alfredsson L, Hillert J, Olsson T, Patsopoulos NA, De Jager PL, Oturai AB, Søndergaard HB, Sellebjerg F, Sorensen PS, Gomez R, Caillier SJ, Cree BA, Oksenberg JR, Hauser SL, D'Alfonso S, Leone MA, Martinelli Boneschi F, Sorosina M, van der Mei I, Taylor BV, Zhou Y, Schaefer C, Barcellos LF. Multiple sclerosis risk loci and disease severity in 7,125 individuals from 10 studies. *Neurol Genet.* 2016 Aug 4;2(4):e87.
15. 17. Simonsen, C. S., Hansen, G., Piehl, F., & Edland, A. (2016). Chronic inflammatory demyelinating polyradiculoneuropathy occurring after autologous haematopoietic stem cell transplantation for multiple sclerosis. *Multiple Sclerosis Journal – Experimental, Translational and Clinical*, 2. doi:10.1177/2055217316658304
16. Cortese, M., Riise, T., Bjornevik, K., Bhan, A., Farbu, E., Grytten, N., Hogenesch, I., Midgard, R., Simonsen, CS., Telstad, W., Aschiero, A., Myhr, K. M. (2016). Pre-clinical disease activity in multiple sclerosis- a prospective study on cognitive performance prior to first symptom. *Ann Neurol.* doi:10.1002/ana.24769

