Poster

The road towards implementation of TMEM106B genetic testing in clinical practice in progranulin pathogenic variant carriers

Marijne Vandebergh (1), Jolien Perneel (1), Eliana Marisa Ramos (2), Daniel Geschwind (3), Saira Mirza (4), Mario Masellis (4,5), Ekaterina Rogaeva (6), Lucy Chisman-Russell (7), Jonathan Rohrer (7), Hilary W Heuer (8), Leah K Forsberg (9), Adam L Boxer (8), Howard J Rosen (8), Bradley F Boeve (10), Rosa Rademakers (1,11)

(1) VIB Center for Molecular Neurology, VIB, Antwerp, Belgium; Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium
(2) Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
(3) Institute for Precision Health, Departments of Neurology, Psychiatry and Human Genetics at David Geffen School of Medicine, UCLA, Los Angeles, CA, USA
(4) L. C. Campbell Cognitive Neurology Research Unit, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada.
(5) Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre and the University of Toronto, Toronto, ON, Canada.
(6) Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Krembil Discovery Tower, Toronto, ON, Canada
(7) Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK
(8) Department of Neurology, Memory and Aging Center, University of California, San Francisco Weill Institute for Neurosciences, San Francisco, CA, USA.
(9) Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA.
(10) Department of Neurology, Mayo Clinic, Rochester, MN, USA
(11) Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

Clinical genetic testing has been focused on autosomal dominant risk-increasing mutations rather than on genetic modifiers of disease. While TMEM106B has been shown to modify disease penetrance in GRN pathogenic variant carriers, genotyping of TMEM106B in GRN pathogenic variant carriers is currently not conducted in a clinical setting, not even in the event of a positive genetic test result for GRN in an asymptomatic individual.

Through characterization of the TMEM106B haplotype in large well-characterized cohorts of GRN pathogenic variant carriers, we aim to provide support for implementation of TMEM106B genetic testing in GRN pathogenic variant carriers in clinical testing.

Systematic genotype screens for TMEM106B haplotype in well-characterized cohorts are conducted.

Our preliminary data indicate a lower proportion of individuals homozygous for the protective TMEM106B haplotype in GRN carriers compared to individuals with a C9orf72 repeat expansion, MAPT pathogenic variant or non-mutation carriers. The majority of GRN carriers homozygous for the protective TMEM106B haplotype are asymptomatic. Importantly, some are still healthy despite relatively old age (> 70y). In those that are symptomatic, we have identified a case with a CSF1R mutation on top of the GRN mutation with a Parkinson-like phenotype. Whole genome sequencing is currently ongoing to further investigate other genetic causes of disease in symptomatic GRN carriers homozygous for the protective TMEM106B haplotype.

Through investigation of TMEM106B haplotypes in GRN carriers we show that individuals with a GRN variant and homozygous for the protective haplotype are still healthy despite relatively old age, and that the disease in those affected might be caused by other genetic factors. Screening for TMEM106B in a clinical setting has important implications for genetic counselling and clinical trial inclusion criteria for GRN carriers.