DANDRITE
Danish Research Institute of Translational Neuroscience
Nordic EMBL Partnership for Molecular Medicine

AARHUS UNIVERSITY

DANDRITE Topical Seminar

Thursday 3 May 2018
11.00 – 12.00

The Biomedicine Auditorium, building 1170, 3rd floor, room 347
Ole Worms Allé, 8000 Aarhus C

Henne Holstege, PhD

VUmc Alzheimer Center, Amsterdam, the Netherlands

- Alzheimer Center, Department of Neurology, VU University Medical Center, de Boelelaan 1118, 1081 HZ Amsterdam, Neuroscience Campus Amsterdam, The Netherlands;
- Department of Clinical Genetics, VU University Medical Center, de Boelelaan 1118, 1081 HZ Amsterdam, Neuroscience Campus Amsterdam, The Netherlands;
- Delft Bioinformatics Lab, Delft University of Technology, Mekelweg 4, 2628 CD Delft, The Netherlands;

SORL1… The fourth autosomal dominant Alzheimer gene?

Familial Alzheimer disease (AD) is an extremely rare early onset form of AD that is heritable from parent to child with an autosomal dominant inheritance pattern. In the 1990's, linkage studies identified specific mutations in presenilin 1 (PSEN1), preseniilin 2 (PSEN2) and the Amyloid precursor protein (APP) genes to be causative for disease in a subset of AD families. Now there is evidence that pathogenic mutations in the *SORL1* gene should be considered next to the pathogenic mutations in PSEN1, PSEN2 and APP, and that *SORL1* should be considered as "the fourth" autosomal dominant Alzheimer gene.

Like mutations in PSEN1, PSEN2 and APP, mutations in SORL1 are associated with an increased load of neurotoxic amyloid-β in the brain. Like mutations in PSEN1, PSEN2 and APP, a pathogenic mutation in the SORL1 protein gives rise to relatively early onset of AD: >80% of the carriers of predicted pathogenic SORL1 variants developed AD before the age of 65. However, whereas mutations in PSEN1, PSEN2 and APP, explain only a fraction of a percent of all AD cases, predicted pathogenic SORL1 variants were detected in 2% of all AD cases tested (and <0.2% of the controls). This suggests the impact of pathogenic SORL1 mutations on Alzheimer's disease may be more substantial than PSEN1, PSEN2 and APP collectively.

The discussion arises: should SORL1 mutation carriers be counseled in the clinic? If so, carriers of which mutation types should be eligible for counseling? Should one or more family members be affected? Does a counseling strategy similar to what is currently being applied to carriers of pathogenic PSEN1/PSEN2/APP variants also apply for SORL1 variant carriers? And what about patient treatment strategies: should carriers of pathogenic SORL1 variants be eligible for clinical trials such as DIAN?

Host: Associate Prof. Olav Andersen, Department of Biomedicine and DANDRITE Affiliated Researcher