QUANTITATIVE ANALYSIS OF VASCULAR NOTCH3 ACCUMULATION IN A NOVEL HUMAN NOTCH3 TRANSGENIC MOUSE MODEL; A PRE-CLINICAL BIOMARKER FOR CADASIL

Julie Rutten, Sjoerd van Duinen, Roselin Klever, Ingrid Hegeman, Sjef Verbeek, Arn van den Maagdenberg, Saskia Lesnik Oberstein
1 Department of Human Genetics, Leiden University Medical Center, Netherlands
2 Department of Pathology, Leiden University Medical Center, Netherlands
3 Department of Clinical Genetics, Leiden University Medical Center, Netherlands

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary small vessel disease caused by mutations in the NOTCH3 gene, which lead to toxic NOTCH3 protein accumulation in the small- to medium sized arteries. The NOTCH3 accumulation is systemic, but is most pronounced in the brain where it leads to clinical symptoms of recurrent stroke and dementia. Currently, there is no therapy for CADASIL. Some therapeutic strategies are in pre-clinical development, but this development is complicated by the lack of robust biomarkers. In this study, we aimed to develop a pre-clinical biomarker for CADASIL by studying the progression pattern of NOTCH3 accumulation in mice. We generated a novel CADASIL mouse model which is transgenic for the full length human NOTCH3 gene, with the archetypal c.544CT, p.Arg182Cys mutation. Four mutant strains were generated, with human NOTCH3 expression levels ranging from ~100% to ~350% relative to endogenous mouse Notch3 expression. NOTCH3 immunohistochemistry revealed characteristic cerebrovascular NOTCH3 accumulation in all four mutant transgenic mouse strains. The extent and progression of NOTCH3 accumulation correlated with the NOTCH3 expression level and with age. Using ImageJ software, we developed a quantitative approach to measure the load of NOTCH3 accumulation in the brain vasculature, which we showed to be a robust and sensitive method to assess the progression of NOTCH3 accumulation in the mice. Currently, we are testing this approach in skin biopsies of CADASIL patients, which will allow us to determine whether this pre-clinical NOTCH3 accumulation biomarker can also be used in humans.