CADASIL AND NOTCH3 MUTATIONS IN THE NETHERLANDS 1998-2015: 176 FAMILIES WITH 45 DISTINCT MUTATIONS.

Saskia Lesnik Oberstein¹, Pjotr Boere¹, Elles Boon¹, Julie Rutten¹²
¹Department of Clinical Genetics, Leiden University Medical Center, Netherlands
²Department of Human Genetics, Leiden University Medical Center, Netherlands

CADASIL is a monogenic vascular stroke and dementia syndrome caused by NOTCH3 mutations. In The Netherlands, the Leiden University Medical Center is the expertise centre for CADASIL patient care and research since 1998. Also, all NOTCH3 DNA-analysis is performed in this centre, giving a good overview of the Dutch CADASIL population. We have made an inventory of the Dutch CADASIL population, using our in house NOTCH3 mutation database as source. We looked at number of families and patients diagnosed between 1998 and 2015, as well as the distinct Dutch mutations. In a 17 year period, 383 patients from 176 families were diagnosed. These families originate from all Dutch provinces, most of Dutch origin, but also from the Dutch immigrant population, including Turkish, Surinamese and Moluccans. In 104 families (58%), only one family member is registered with a (molecular) diagnosis. There are 45 distinct Dutch NOTCH3 mutations so far, including some founder mutations as determined by haplotype analysis. The most frequent is the p.Arg578Cys mutation in exon 11 (16.3% of patients). Most other prevalent mutations are in exon 4 (p.Arg207Cys p.Arg141Cys, p.Arg153Cys, p.Arg182Cys, p.Cys162Trp). Based on our data, the calculated minimum prevalence of CADASIL in the Netherlands is 2.2/100,000. However, our data also suggest that CADASIL is more prevalent than reported so far, as in the Netherlands alone there are numerous distinct mutations, new Dutch CADASIL families are still being identified, and there is under-diagnosis illustrated by the fact that in most families only one patient has been diagnosed.