

CADASIL - Molecular and Cellular Mechanisms

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is caused by mutations in the *NOTCH3* gene and the most common monogenic cause of stroke and vascular dementia. CADASIL has evolved as a unique 'model' to study stroke mechanisms in small vessel disease and vascular dementia. Our research focuses on interventional and MR-imaging studies investigating the structural and functional correlates underlying vascular cognitive impairment. Another main focus is on the molecular and cellular mechanisms underlying CADASIL and includes work in animal models. This work involves strong collaborations with other research groups in Munich.

Projects

- Transgenic Mouse Models
- Aggregation properties of wt and mutant Notch3 Receptor (in vitro studies)
- Antiapoptotic effects of Notch3
- Genetic Modifiers in CADASIL
- Structural and Functional Correlates underlying Vascular Dementia (see Imaging)

Diagnostics

We offer molecular genetic testing by direct sequencing of the *NOTCH3*-gene. We further offer Ultrastructural examination of skin biopsy samples for vascular osmiophilic deposits which are specific for CADASIL and therefore diagnostic. Before sending (blood or biopsy) samples, please contact us for further details (sample processing etc.). The respective forms can be downloaded from this website ([Diagnostik](#)).

Background on CADASIL

NOTCH3 encodes a cell surface receptor, which has a role in arterial development and is expressed on vascular smooth muscle cells. The Notch3 receptor is a hetero-dimer composed of a large extracellular fragment and a smaller transmembrane intracellular fragment. Mutations are greatly stereotyped in that most if not all mutations change the number of cysteine residues within one of the extracellular epidermal-growth-factor-like repeat domains. There have been single reports on mutations not involving cysteine residues but the role of these sequence variants remains controversial. The mutational spectrum is broad. About 95% of the patients have missense mutations which cluster in exons 3 to 6. Preliminary evidence suggests that some mutations are associated with a slightly more aggressive phenotype. In general, however, the genotype seems to have no major influence on the phenotype. The mechanisms by which *NOTCH3* mutations become pathogenic are still poorly understood. Most mutations do not seem to interfere with Notch3 receptor signalling. However, studies in patients and transgenic mice have shown that the mutant Notch3 receptor accumulates in arteries and precapillaries. Electron microscopy shows granular osmiophilic deposits within the vascular basal lamina, which are specific for CADASIL, present throughout the arterial system and can therefore be used for diagnostic purposes. An important observation has been that the clinical course and MRI findings may vary from relatively benign to very severe. Recent evidence suggests that variations in disease severity are due to a modifying influence of genetic factors distinct from

the causative NOTCH3 mutation.

Team Members

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Recent Publications

Opherk C, Düring M, Peters N, Karpinska A, Rosner S, Schneider E, Bader B, Giese A, Dichgans M. CADASIL mutations enhance spontaneous multimerization of NOTCH3. Hum Mol Genet. 2009 Aug 1;18(15):2761-7

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Peters N, Freilinger T, Opherk C, Pfefferkorn T, Dichgans M. Enhanced L-arginine-induced vasoreactivity suggests endothelial dysfunction in CADASIL. J Neurol. 2008 Aug;255(8):1203-8

References (1998-2008)

Dichgans M, Mayer M, Uttner I, Bruning R, Müller-Höcker J, Rungger G, Ebke M, Klockgether T, Gasser T. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol. 1998;44:731-9. / Tatsch K, Koch W, Linke R, Poepperl G, Peters N, Holtmannspoetter M, Dichgans M. Cortical hypometabolism and crossed cerebellar diaschisis suggest subcortically induced disconnection in CADASIL: an 18F-FDG PET study. J Nucl Med. 2003;44:862-9. [a target="_blank" href="http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=pubmed&term=12791811"](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=pubmed&term=12791811) Pubmed/  width="10" height="10" border="0" alt="" src="http://neurogenetik.de/template/Symbole/externLink.png" /br / Dichgans M. Monogenic causes of stroke. Int Psychogeriatr. 2003;15 Suppl 1:15-22. [a target="_blank" href="http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=pubmed&term=16191212"](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=pubmed&term=16191212) >Pubmed



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Peters N, Herzog J, Opherk C, Dichgans M. A two-year clinical follow-up study in 80 CADASIL subjects: Progression patterns and implications for clinical trials. Stroke 2004;35:1603-08. [Pubmed](#)



Opherk C, Peters N, Herzog J, Luedtke R, Dichgans M. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. Brain 2004;127:2533-9. [Pubmed](#)



Peters N, Bergmann T, Castro M, Opherk C, Herzog J, Dichgans M. Spectrum of mutations in CADASIL. Arch of Neurology 2005; 62:1091-4. [Pubmed](#)