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Titel des Beitrags: Mutations in DNMT1 cause autosomal dominant cerebellar ataxia, deafness and narcolepsy.

Abstract: Autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN) is characterized by late onset (30-40 years old) cerebellar ataxia, sensory neuronal deafness, narcolepsy-cataplexy and dementia. We performed exome sequencing in five individuals from three ADCA-DN kindreds and identified DNMT1 as the only gene with mutations found in all five affected individuals. Sanger sequencing confirmed the de novo mutation p.Ala570Val in one family, and showed co-segregation of p.Val606Phe and p.Ala570Val, with the ADCA-DN phenotype, in two other kindreds. An additional ADCA-DN kindred with a p.GLY605Ala mutation was subsequently identified. Narcolepsy and deafness were the first symptoms to appear in all pedigrees, followed by ataxia. DNMT1 is a widely expressed DNA methyltransferase maintaining methylation patterns in development, and mediating transcriptional repression by direct binding to HDAC2. It is also highly expressed in immune cells and required for the differentiation of CD4+ into T regulatory cells. Mutations in exon 20 of this gene were recently reported to cause hereditary sensory neuropathy with dementia and hearing loss (HSAN1). Our mutations are all located in exon 21 and in very close spatial proximity, suggesting distinct
phenotypes depending on mutation location within this gene.