Abstracts

Articles appearing in the February 2018 issue

Biallelic *CHP1* mutation causes human autosomal recessive ataxia by impairing NHE1 function

Objective To ascertain the genetic and functional basis of complex autosomal recessive cerebellar ataxia (ARCA) presented by 2 siblings of a consanguineous family characterized by motor neuropathy, cerebellar atrophy, spastic paraparesis, intellectual disability, and slow ocular saccades.

Methods Combined whole-genome linkage analysis, whole-exome sequencing, and focused screening for identification of potential causative genes were performed. Assessment of the functional consequences of the mutation on protein function via subcellular fractionation, size-exclusion chromatography, and fluorescence microscopy were done. A zebrafish model, using Morpholinos, was generated to study the pathogenic effect of the mutation in vivo.

Results We identified a biallelic 3-bp deletion (p.K19del) in *CHP1* that cosegregates with the disease. Neither focused screening for *CHP1* variants in 2 cohorts (ARCA: n = 319 and NeurOmics: n = 657) nor interrogating GeneMatcher yielded additional variants, thus revealing the scarcity of *CHP1* mutations. We show that mutant *CHP1* fails to integrate into functional protein complexes and is prone to aggregation, thereby leading to diminished levels of soluble *CHP1* and reduced membrane targeting of NHE1, a major Na⁺/H⁺ exchanger implicated in syndromic ataxia-deafness. *Chp1* deficiency in zebrafish, resembling the affected individuals, led to movement defects, cerebellar hypoplasia, and motor axon abnormalities, which were ameliorated by coinjection with wild-type, but not mutant, human *CHP1* messenger RNA.

Conclusions Collectively, our results identified *CHP1* as a novel ataxia-causative gene in humans, further expanding the spectrum of ARCA-associated loci, and corroborated the crucial role of NHE1 within the pathogenesis of these disorders.

[NPG.org/NG/9020a](https://doi.org/10.1212/NXG.0000000000000920)

Alzheimer risk loci and associated neuropathology in a population-based study (Vantaa 85+)

Objective To test the association of distinct neuropathologic features of Alzheimer disease (AD) with risk loci identified in genome-wide association studies.

Methods Vantaa 85+ is a population-based study that includes 601 participants aged ≥85 years, of whom 256 were neuropathologically examined. We analyzed 29 AD risk loci in addition to *APOE* ε4, which was studied separately and used as a covariate. Genotyping was performed using a single nucleotide polymorphism (SNP) array (341 variants) and imputation (6,038 variants). Participants with Consortium to Establish a Registry for Alzheimer Disease (CERAD) (neuritic Aβ plaques) scores 0 (n = 65) vs score M + F (n = 171) and Braak (neurofibrillary tangle pathology) stages 0–II (n = 74) vs stages IV–VI (n = 119), and with capillary Aβ (CapAβ, n = 77) vs without (n = 179), were compared. Cerebral amyloid angiopathy (CAA) percentage was analyzed as a continuous variable.

Results Altogether, 24 of the 29 loci were associated (at *p* < 0.05) with one or more AD-related neuropathologic features in either SNP array or imputation data. Fifteen loci associated with CERAD score, smallest *p* = 0.0002122, odds ratio (OR) 2.67 (1.58–4.49), at *MEF2C* locus. Fifteen loci associated with Braak stage, smallest *p* = 0.004372, OR 0.31 (0.14–0.69), at *GAB2* locus. Twenty loci associated with CAA, smallest *p* = 7.17E–07, β 14.4 (8.88–20), at *CR1* locus. Fifteen loci associated with CapAβ, smallest *p* = 0.002594, OR 0.54 (0.37–0.81), at *HLA-DRB1* locus. Certain loci associated with specific neuropathologic features. *CASS4*, *CLU*, and *ZCWPW1* associated only with CAA, while *TREM2* and *HLA-DRB5* associated only with CapAβ.

Conclusions AD risk loci differ in their association with neuropathologic features, and we show for the first time distinct risk loci for CAA and CapAβ.

[NPG.org/NG/9020b](https://doi.org/10.1212/NXG.0000000000000920b)

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