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Abstracts

Articles appearing in the February 2018 issue

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 examined neuropathologically. 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's Disease (CERAD) (neuritic β-amyloid [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.

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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.

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