Abstracts

Articles appearing in the February 2018 issue

2017 Year in review and message from the editors to our reviewers

The February 2018 issue of *Neurology: Genetics* starts off with a review of articles that our editors found interesting in *Neurology: Genetics* and other journals over the course of 2017. It is a collection of articles from different walks of the genetics field, introduced with a brief commentary that should encourage readers to delve further into the details of the topic.

For example, in a review known as “The Helix,” Pulst et al. noted that

Next-generation sequencing is revolutionizing identification of novel disease genes and patient diagnosis. Ribonuclease H1 (RNASEH1) digests the RNA present in RNA:DNA hybrids and is present in the nucleus and mitochondria. Bugiardi et al. screened genomic DNA from 74 probands with multiple deletions/depletion in muscle mtDNA and mendelian progressive external ophthalmoplegia (PEO). They identified 3 pedigrees of Indian ancestry with homozygous or compound heterozygous mutations. In addition to PEO, half of the patients had cerebellar ataxia and dysphagia. In the authors' cohort, RNASEH1 mutations represented the 4th most common cause of adult-onset PEO with multiple mtDNA deletions after POLG, RRM2B, and TWN.

[NPub.org/NG/9018a](https://pub.org/NG/9018a)

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.

[NPub.org/NG/9018b](https://pub.org/NG/9018b)

Most-Read Articles

As of February 28, 2018

Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk

B. Rhead, M. Bäärnhielm, M. Gianfrancesco, et al. 2016;2:e97. doi: 10.1212/NXG.0000000000000097.

CHCHD10 variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease

M. Auranen, E. Ylikallio, M. Shcherbii, et al. 2015;1:e1. doi: 10.1212/NXG.0000000000000003.

A novel *DYNC1H1* mutation causing spinal muscular atrophy with lower extremity predominance

Q. Niu, X. Wang, M. Shi, and Q. Jin. 2015;1:e20. doi: 10.1212/NXG.0000000000000017.

The clinical outcome study for dysferlinopathy: An international multicenter study

E. Harris, C.L. Bladen, A. Mayhew, et al. 2016;2:e89. doi: 10.1212/NXG.0000000000000089.

Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to *AMPD2* loss

A.P.L. Marsh, V. Lukic, K. Pope, et al. 2015;1:e16. doi: 10.1212/NXG.0000000000000014.

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