The Helix

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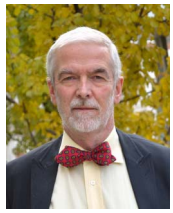
2017 Year in Review and Message from the Editors to Our Reviewers



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The February issue of *Neurology® Genetics* again 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 the reader to delve further into the details of the topic.

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. Bugiardini et al.[1] screened genomic DNAs 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.

Ahrens-Nicklas et al.[2] identified a mutation of the ATAD1 gene (p.E276X), encoding the AMPA receptor, as the etiology of a devastating neurologic disorder characterized by hypertonia, seizures, and death in a consanguineous family. This mutation was found to be associated with hyperactivity of the AMPA receptor. The authors designed used perampanel, an AMPA receptor antagonist, as a targeted therapeutic approach. They showed that perampanel therapy reversed the phenotype of ATAD1 knockout mice and improved hypertonicity and resolved seizures in patients. This is a good example of precision therapeutics applied to a human monogenic disorder.

As we are increasingly overwhelmed with DNA sequence data, computational solutions seem likely to be in the neurologist's future. This article explores 1 possibility to examine time-sensitive data, i.e., whole-genome DNA sequence (WGS) and RNA sequence from a glioblastoma patient's tumor.[3] The WGS results were also compared with a targeted cancer panel of known variants. For the WGS/RNA-sequence data, the authors compared human annotation by a team of bioinformatic cancer experts vs a supercomputer to identify actionable variants. Both the human and supercomputer found more actionable variants than the targeted panel, reflecting the higher sensitivity of WGS/RNA sequence. Comparing the results of the 2 WGS analyses, the authors state that the supercomputer and the human annotation had comparable results, although the human annotation found more changes. But while the human annotation took 150 hours, the supercomputer took 10 minutes. The future seems pretty clear.

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Editor Summary
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From the Department of Neurology (S.M.P., N.E.J.), University of Utah, Salt Lake City; Hôpital Erasme (M.P.), Université Libre de Bruxelles, Belgium; University of Chicago Medical Center (R.P.R.); and University of Miami (J.M.V.), Coral Gables, FL.

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The importance of the microbiome was recognized in several models of human disease. With the application of next-generation or massively parallel DNA and RNA sequencing techniques, we now know the vast complexity and diversity of the microbiome of the gut. The interaction between the GI and the brain appears to influence inflammatory responses such as in MS and may have direct involvement in the rise of neurodegenerative conditions. Sampson et al.[4] present evidence that the gut microbiome can directly affect the motor deficits, activation of microglia, and alpha-synuclein pathology in the brains of a Parkinson disease mouse model. They started with a PD mouse model that overexpresses alpha-synuclein, which had a "normal" mouse microbiome. This mouse model normally displays progressive motor deficits. Raising the same mouse strain in a germ-free environment, thus greatly decreasing their gut microbiome, reduced these deficits and pathologic changes in the mouse brain. Finally, adding back the microbiome of patients with Parkinson disease enhanced the motor deficits symptoms in the mice while the microbiome of non-PD patients had no appreciable effect. This interaction will become increasingly important in the care of neurologic patients as we move into the future.

Cerebral cavernous malformations (CCMs) are a cause of stroke and seizures with no effective medical therapy. CCMs arise from a loss of function in 3 genes that encode components of an adaptor complex that negatively regulates MEKK3–KLF2/4 signaling in brain endothelial cells. This article identified toll-like receptor 4 (TLR4) and the gut microbiome as critical stimulants of CCM formation.[5] TLR4 activation by Gram-negative bacteria accelerated CCM formation, and blockade of TLR4 signaling prevented CCM formation in mice. Germ-free mice were protected from CCM formation, and antibiotics permanently altered CCM susceptibility in mice. These studies identify unexpected roles of the microbiome and innate immune signaling in the pathogenesis of a cerebrovascular disease that is inherited, as well as strategies for its treatment.

Novel therapies made significant advances in 2017. Potter et al.[6] demonstrated significant advances in the treatment of dysferlinopathies using overlapping gene therapy vectors in a mouse model. In this study, they used dual vector dysferlin cassettes designed to capture either the 5′ or 3′ portion of the dysferlin cassette, with a 1-kb overlap for recombination. In a dysferlin knockout mouse model, the dual vectors were injected IV. Mice demonstrated improved myopathic features. The vectors were then shown to be safe in a rhesus macaque model. This study provides an important step in the development of gene therapies for muscular dystrophies, and we expect to see these promising therapies enter clinical trials shortly. More importantly, the study provides a proof of concept that dual vectors may be used when genes are too large for a single vector. This has important implications for gene therapy as a field.

Spinal muscular atrophy type 1 (SMA1) is a devastating disease resulting in death or the need for mechanical ventilation by 2 years of age. Affected infants never reach motor milestones like independent sitting. The disease is caused by insufficient levels of the survival motor neuron (SMN) protein because of deletions or other loss-of-function mutations in the SMN1 gene. Mendell et al.[7] delivered an adeno-associated virus (AAV) serotype 9 carrying SMN complementary DNA encoding the missing SMN protein by IV infusion to 15 infants with SMN1. All 15 patients were alive and event-free at 20 months of age as compared to a rate of survival of 8% in a historical cohort. AAV9-based gene therapy resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts. Side effects were minor, mostly limited to a transient increase in transaminases that was attenuated by prednisone. This is a landmark study demonstrating the potential of systemically administered gene therapy to revolutionize the treatment of neurogenetic diseases and radically change their prognosis.

Another approach to SMN treatment was pursued by Finkel et al.[8] The SMN2 gene also encodes an SMN protein; however, 90%–95% of the translated protein is truncated and nonfunctional as a result of aberrant splicing. Nusinersen is an antisense oligonucleotide (ASO) that corrects the aberrant splicing of SMN2 pre-mRNA, which results in more full-length SMN protein. This article reports the results of a phase 3 trial of repeated intrathecal doses of nusinersen in infants with SMA compared with a sham group with SMA. The trial was terminated early because an interim analysis showed significant efficacy of nusinersen vs sham with respect to improvements in motor function as well as survival without permanent assisted ventilation. The best results were seen in patients with the earliest treatment. This new treatment, which is not a cure, brings a number of new challenges to treating neurologists, including issues of costs, delivery, and uncertain efficacy of the treatment if given to older patients with SMA, prompting van der Ploeg to write *The New England Journal of Medicine* editorial "The dilemma of 2 innovative therapies for Spinal Muscular Atrophy."[9]

ASOs were also tested in preclinical models of other neurodegenerative disorders. Cognitive decline in Alzheimer disease and primary tauopathies is correlated with deposition of tau in the CNS. DeVos et al.[10] studied the effects of ASOs directed to human tau in a mouse model of tauopathy. They delivered an ASO via Alzet pumps to the lateral ventricle and showed that reducing total tau mRNA lessened tau pathology, prevented hippocampal volume loss, and reduced behavioral deficits. When injected into monkeys via lumbar puncture, ASOs showed wide CNS distribution and reduced the levels of tau protein. Reduction of tau in hippocampal tissue correlated with reduction in monkey CSF. These studies and several others in 2017 provide hope that ASO-based therapies may offer hope for changing the progression in patients with a number of neurodegenerative diseases.

We wish to acknowledge the individuals who have completed reviews for the journal over the course of 2017—your thoughtful comments are tremendously helpful and highly appreciated. We are also grateful for your cooperation in returning reviews in a timely manner. Please find the guidelines

for reviewing articles on the *Neurology: Genetics* website at http://ng.neurology.org/submit/peerreview. This page provides information on expectations of reviewers regarding confidentiality, timeliness, and reviewer conflicts of interest; it also provides instructions for formatting the comments to editors and authors to enable the most effective communication with authors.

Please email ngjournal@neurology.org if you are interested in completing more reviews for *Neurology: Genetics*, or if you have never reviewed for the journal but are interested in doing so. Include a description of your credentials and expertise in the areas in which you are qualified to review. We look forward to hearing from you!

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Dystrophy Foundation. M. Pandolfo has served on the scientific advisory boards of Apopharma and Voyager Therapeutics; has served on the editorial boards of *Acta Neurologica Belgica*, the *Orphanet Journal of Rare Diseases*, and as Associate Editor of *Neurology: Genetics*; holds patents and receives royalties for Direct molecular diagnosis of Friedreich ataxia; has consulted for Biomarin and UCB; and has received research support from Biomarin, Fonds National de la Recherche Scientifique, Offrez-moi-la-lune, Friedreich's Ataxia Research Alliance, and Association Belge contre les Maladies neuro-Musculaires. R.P. Roos serves on the editorial board of Virology and MedLink; conducts research supported by the NIH, the ALS Association, the Judith and Jean Pape Adams Charitable Foundation, the Ralph and Marian Falk Medical Research Trust Grant, and the Chicago Biomedical Consortium; and is a stockholder of Amgen, Merck, Ionis Pharmaceuticals, and Express Scripts. J. M. Vance has received funding for travel or speaker honoraria from the NETPR, Department of Defense, and NIH; serves on the editorial boards of the *American Journal of Neurodegenerative Diseases* and as Associate Editor of *Neurology: Genetics*; holds patents for method of detecting Charcot-Marie-Tooth disease type 2A, TRPC6 involved in glomerulonephritis, and methods for identifying an individual at increased risk of developing coronary artery disease; has received research support from the NIH/National Institute of Neurological Disorders and Stroke and the Hussman Foundation; and receives royalties from Duke University. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

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