

2016 in Review and Message from the Editors to our Reviewers

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For this Helix, the editors of *Neurology*[®] *Genetics* have chosen some of their favorite articles of the past year. It is an eclectic collection drawing on different journals including *Neurology: Genetics* and varied topics.

Two articles report major advances in the understanding of how the *C9orf72* GGGGCC repeat expansion exerts its pathogenic effect.^{1,2} This mutation is a major cause of familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) as well as the cause of 5%–10% of what appears to be sporadic ALS. Understanding the molecular and cellular mechanisms of its pathogenicity is an essential step toward finding therapies for these devastating diseases. The work reported in these articles is remarkable as it identifies effects of both toxic RNA and repeat associated non-AUG (RAN)-translation products generated by this repeat and links them to pathogenic mechanisms shared by other ALS/FTD-causing mutations.

A landmark publication this year describes the generation and characterization of a *C9orf72* bacterial artificial chromosome transgenic mouse.³ This mouse model will be important in helping to clarify the pathogenesis of ALS and FTD and can be used to explore the efficacy of potential treatments.

Two articles analyzed white matter changes in FTD due to *GRN* and *C9orf72* mutations and in primary familial brain calcifications due to a novel *PDGFB* mutation.^{4,5} The white matter changes preceded atrophy/calcifications and could be a pre-manifest marker in primary familial brain calcification. White matter changes could therefore exacerbate the pathogenic cascades in neurodegenerative diseases characterized by motor and cognitive signs. These changes may include oligodendroglial dysfunction, as suspected for the *GRN* haploinsufficiency. Extensive white matter changes are present also in mouse models of

neurodegeneration, and effects of altered oligodendrocyte function on disease progression are suspected.

Adams et al.⁶ provide an example of how “crowd-sourcing” data collection may provide enough power to detect genetic variants affecting normal variation as well as disease susceptibility. Combining data from many contributors allowed them to identify genetic variants affecting intracranial volume, strictly related to brain volume, which in turn affects the risk of cognitive impairment.

The use of gene therapy to treat peripheral neuropathies faces a number of challenges including ones related to delivery. A recent study describes rescue of an X-linked demyelinating form of Charcot-Marie-Tooth disease (CMT1X) in gap junction beta 1 gene (*GJB1*) null mice, which lack connexin32 (CX32) protein.⁷ One intrathecal injection of a lentiviral vector expressing *GJB1* gene under the control of the myelin protein zero (*MPZ*) promoter led to stable and cell-specific expression of CX32 in up to 50% of Schwann cells in multiple lumbar spinal roots and peripheral nerves. The treated mice had improved motor function and electrophysiologic indices, as well as less pathology. The virus vector presumably diffused from the spinal fluid in the subarachnoid space into the epineurium of the peripheral nerve, demonstrating that this delivery route could be used in the treatment of other peripheral neuropathies.

Phuah et al.⁸ extended the clinical phenotype of *APOE* ε4 carriers, long known as the major risk factor for Alzheimer disease. They found that *APOE* ε4 carriers had a significantly greater decline in serum total cholesterol and low-density lipoprotein in the 6 months preceding an intracerebral hemorrhage, relative to *APOE* ε2 carriers. *APOE* remains one of the most interesting genes in the CNS, and one of the most important. Despite being identified as a risk factor for Alzheimer disease in 1989, its function in that regard is still not fully understood. Mutations in the gene in humans and mice support its role in

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lipoprotein metabolism. It is fascinating to note that almost 30 years after its rise to clinical importance, we continue to identify its association with major neurologic events.

An impressive multinational effort characterized the variability of dysferlin mutations, including symptoms and rate of progression of their associated disease.⁹ Missense mutations were a frequent cause of the disease. The characterization of the mutation, which may cause a spectrum of disease syndromes, is increasingly important in neuromuscular disease as novel therapeutics may be broadly applicable across phenotypes. Indeed, it is likely that the mutation (e.g., missense, nonsense, etc.) is more likely to select the therapeutic trial population rather than the phenotype. Additional, similar, studies in other limb-girdle muscular dystrophies are now possible as the Jain Foundation, Muscular Dystrophy Association, and other patient advocacy foundations have subsidized genetic testing for limb-girdle muscular dystrophies. These resources will extend the knowledge of the genotype-phenotype variability and offer a more accurate understanding of the prevalence of these conditions.

Genome-wide association studies have identified many risk variants, most of them not changing the coding sequence of a gene, but potentially regulating gene expression. Several DNA variants upstream of the *SNCA* gene encoding α -synuclein have been identified, but their direct relationship to regulating *SNCA* expression was not known. Soldner et al.^{10(p1)} made use of a novel method to manipulate the genome, called CRISPR/Cas9, to delete or change specific sequences encompassing previously identified variants. They accomplished these genetic engineering feats in embryonic stem cells that they differentiated into neurons so that *SNCA* expression could be measured in the correct cell type. Indeed, the variant with the greatest associated risk for Parkinson disease increased *SNCA* expression in neurons.

The final selection does not directly relate to the nervous system, but is relevant in the context of neurogenetics, as it deals with the evaluation of DNA variants as causative for disease. The Kohane group examined variants that had previously been considered causal in hypertrophic cardiomyopathy.¹¹ Variants that were falsely classified as pathogenic occurred predominantly in African Americans. Simulations showed that the inclusion of even small numbers of African Americans in control cohorts probably would have prevented these misclassifications, highlighting the importance of diversity in variant databases. The problem of erroneously assigning mutation status to rare, sometimes population-dependent benign DNA variants is

widespread. It is of most actionable importance in the clinical arena, but as editors of *Neurology: Genetics*, we face similar challenges when deciding on acceptance of manuscripts reporting novel mutations in established disease-causing genes.

We wish to acknowledge the individuals who have completed reviews for the journal since its launch in April 2015. Your thoughtful comments are tremendously helpful and highly appreciated. We are also grateful for your cooperation in returning reviews in a timely manner. Please follow the guidelines for reviewing articles accessed by selecting the Information for Reviewers (IFR) link on the Neurology.org/ng website. The IFR 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 would like to do more reviews 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!

Our 2016 reviewers are listed at the end of this article.

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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. He is a stockholder of Amgen, Merck, Ionis Pharmaceuticals, and Express Scripts. J.M. Vance has received funding for travel or speaker honoraria from NETPR, Department of Defense, and NIH; serves on the editorial boards of *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 NIH/National Institute of Neurological Disorders and Stroke and Hussman Foundation; and receives royalties from Duke University. Go to Neurology.org/ng for full disclosure forms.

REFERENCES

- Freibaum BD, Lu Y, Lopez-Gonzalez R, et al. GGGGCC repeat expansion in *C9orf72* compromises nucleocytoplasmic transport. *Nature* 2015;525:129–133.
- Zhang K, Donnelly CJ, Haeusler AR, et al. The *C9orf72* repeat expansion disrupts nucleocytoplasmic transport. *Nature* 2015;525:56–61.
- Liu Y, Pattamatta A, Zu T, et al. *C9orf72* BAC mouse model with motor deficits and neurodegenerative features of ALS/FTD. *Neuron* 2016;90:521–534.
- Ameur F, Colliot O, Caroppo P, et al. White matter lesions in FTLD: distinct phenotypes characterize *GRN* and *C9ORF72* mutations. *Neurol Genet* 2016;1:e47. doi: 10.1212/NXG.0000000000000047.
- Biancheri R, Severino M, Robbiano A, et al. White matter involvement in a family with a novel *PDGFB* mutation. *Neurol Genet* 2016;2:e77. doi: 10.1212/NXG.0000000000000077.
- Adams HHH, Hibar DP, Chouraki V, et al. Novel genetic loci underlying human intracranial volume identified through genome-wide association. *Nat Neurosci* 2016;19:1569–1582.
- Kagiava A, Sargiannidou I, Theophilidis G, et al. Intrathecal gene therapy rescues a model of demyelinating peripheral neuropathy. *Proc Natl Acad Sci USA* 2016;113:E2421–E2429.
- Phuah CL, Raffeld MR, Ayres AM, et al. *APOE* polymorphisms influence longitudinal lipid trends preceding intracerebral hemorrhage. *Neurol Genet* 2016;2:e81. doi: 10.1212/NXG.0000000000000081.
- Harris E, Bladen CL, Mayhew A, et al. The Clinical Outcome Study for dysferlinopathy. *Neurol Genet* 2016;2:e89. doi: 10.1212/NXG.0000000000000089.
- Soldner F, Stelzer Y, Shivalila CS, et al. Parkinson-associated risk variant in distal enhancer of α -synuclein modulates target gene expression. *Nature* 2016;533:95–99.
- Manrai AK, Funke BH, Rehm HL, et al. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med* 2016;375:655–665.

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