2018: Year in Review and Message from the Editors to Our Reviewers

At the time of writing this Helix, the ranks of spinocerebellar ataxias (SCAs) have swelled to 48 genes or genetic loci mirroring a similar development in other categories of movement disorders such as dystonia or spastic paraplegia. Although SCAs have a worldwide distribution, some of the recently identified SCAs have shown regional aggregation. SCA42 is one such example. It is caused by mutation in CACNA1G and was initially described only in French and Japanese families. Now, Ngo et al. describe CACNA1G mutations in 3 pedigrees from Italy, Eastern Europe, and Yemen. Interestingly, all SCA42 families described so far share the same mutation suggesting that the mutation (hg19:chr17:48694921G>A, p.Arg1715His) is a mutational hot spot.

A recent publication in Neurology® Genetics deals with issues related to ascertainment of the incidence of familial amyotrophic lateral sclerosis (ALS) in Ireland. Ireland is an attractive country for this study since there is a reasonably stable population with relatively large family sizes. Using stringent criteria, the investigators identified 269 FALS cases from 197 unique families out of a total of 2,173 cases of ALS from 1994 to 2016. The annual age-standardized incidence of FALS grew from 3.2% in 1994 to 19.1% in 2016 for a number of reasons, including an increased recognition of genes known to cause FALS as well as increased awareness of patients with FALS from the second generation of known families with FALS. The authors note that bias can enter into this kind of study because of ascertainment methods (e.g., What constitutes a relative or family member of a patient with ALS?), how stringent a definition of FALS is used (e.g., Should one require upper as well as lower motor neuron signs for the diagnosis of FALS?), and the inclusion or exclusion of extended phenotypes or endophenotypes (e.g., Does the presence of frontotemporal dementia or psychosis in a relative of a patient with ALS indicate that these individuals have FALS?). The authors conclude that the population-based rate of FALS in Ireland is at least 20%, rising to 30% if one includes extended endophenotypes in the definition of FALS in family members. The study suggests that the incidence of FALS is presently underestimated and that this underestimate can have a significant effect on genetic counseling.

Congenital myopathies are a genetically heterogeneous group of disorders often manifesting with muscle weakness at birth and classified on the basis of specific histopathologic findings. Biallelic loss of function mutations in MYL1, which encodes the skeletal muscle fast-twitch-specific myosin essential light chain, was identified in a congenital myopathy. Patients presenting with hypotonia and respiratory insufficiency require ventilatory support at birth. They had no extraocular or cardiac muscle involvement. The myopathy was featured by...
selective involvement of type 2 fibers that pathologically were markedly reduced in number or size, a finding that is uncommon in congenital myopathies. Patient’s muscle had a marked reduction of MYL1 protein expression. Knock down of MYL1 in zebrafish demonstrated abnormal muscle structure and altered touch-evoked escape response, suggesting a crucial role of the protein in muscle fiber development.

Mendelian mutations can serve as a great starting point for understanding variation in phenotypes. The size of the repeat causing Huntington disease contributes to age at onset of HD, but does not explain all of the variance. For years, researchers have looked for DNA variation of environmental changes that explain the remaining 30% of unexplained variance, but without much success. Gardner et al.\(^5\) examined the bioenergetics of fibroblasts of patients with early vs late onset HD. They found that earlier-onset patients had significantly lower ATP concentrations than later-onset patients, suggesting that the metabolic environment that surrounds the CAG repeat could affect age at onset. In retrospect, this seems likely and suggests there may be targets in these bioenergetic pathways that could delay onset age in HD.

A new resource for large-scale epidemiologic and genetic studies is the UK Biobank representing a long-term effort to study volunteers in a prospective fashion. The genetic information consists of 96 million genetic variants obtained in 500,000 participants. This data set was publicly released in July 2017. Elliott et al.\(^6\) used this resource to conduct a genome-wide association study of a large number of single and complex multifactorial imaging phenotypes (in more than 8,000 individuals). They found that many of these imaging phenotypes were heritable. Their results have provided unique insights into the genetic architecture of brain morphology, which are relevant not only to development and normal aging but also to psychiatric and neurologic disorders. To highlight just one achievement, they identified 3 loci associated with dMRI tensor mode measures of anisotropy, which are known expression quantitative trait loci (eQTLs) of MAPT, TUBA1B, and TUBB3. These genes all belong to the class of microtubule-related genes, and MAPT, which encodes the TAU protein, is known to be associated with a number of neurodegenerative disorders.

Another example of application of novel technologies to large data sets is the assembly of deep genomes of 910 humans of African descent. The current sequence of the human reference genome derives from only a few individuals of non-Hispanic White (NHW) descent. Recently, many groups have worked to include all ethnic and racial groups into genomic research. Sherman et al.\(^7\) found that the pan-African genome contains \(~10\%\) more DNA in it than the current NHW reference genome used. This expands the variability of the human genome significantly.

Genetic variation in genomic DNA usually obtained from blood lymphocytes is often equated with identical presence of variants in somatic cells. We picked 2 publications that give different examples where this is not the case. One describes somatic genetic recombination, the other one loss of the 2nd allele of a gene in neurons.\(^8,9\)

Genetic recombination occurring in somatic cells can alter their genetic makeup creating new gene variants. This phenomenon may contribute to physiology, as in the immune system, where it generates diversity in antibodies. However, somatic gene recombination was not previously demonstrated in the brain, even though somatic mutations may randomly occur during brain development. The group of Jerold Chun recently described the recombination of the Alzheimer disease-related gene APP, encoding amyloid precursor protein, in human neurons.\(^8\) The phenomenon generated thousands of variant “genomic cDNAs” (gen-cDNAs) in different cells. gen-cDNAs lacked introns, resembling cDNA copies of expressed, brain-specific mRNAs. Some gen-cDNAs corresponded to full-length mRNA brain-specific splice variants, and many others contained intraexonic junctions, insertions, deletions, and/or single nucleotide variations. gen-cDNAs were distinct from the original loci and were only found in neurons. The authors provide evidence that gen-cDNAs were generated by “retroinsertion” of RNA, which increased with age. Expression of gen-cDNAs may have physiological as well as pathologic relevance. In healthy neurons, it may affect neuronal such as synaptic plasticity, learning, and memory. In neurons from individuals with sporadic Alzheimer disease (AD), the finding of increased diversity of APP gen-cDNAs, including 11 mutations known to be associated with familial AD that were absent from healthy neurons, suggests that their products may contribute to disease pathogenesis. Intriguingly, the authors notice that AD is rare in older individuals with HIV infection who have received prolonged, combined antiretroviral therapy (cART), which inhibits retrotranscription, while it is more common in individuals who suffered repeated brain traumatisms, known to favor DNA breaks, mechanisms that are both needed to generate gen-cDNAs. If confirmed, these findings may open new therapeutic perspectives for AD.

DEPDC5, a repressor of the recently recognized amino acid-sensing branch of the mTORC1 signaling pathway, is
recognized as the most frequently mutated gene in familial focal epilepsies. Germline loss-of-function mutations encompass a broad phenotypic spectrum, ranging from MRI-negative focal epilepsies to drug-resistant focal epilepsies with malformations of the cortical development such as focal cortical dysplasia. This wide phenotypic spectrum, as in other neurogenetic disorders, led Ribierre et al.\(^9\) to postulate the occurrence of Knudson’s 2-hit mechanism, as in cancer. This would cause a mosaic inactivation in addition to the germline mutation. In this original study, the authors proved for the first time that a biallelic 2-hit—brain somatic and germline—mutational mechanism in DEPDC5 causes the disease. They further discovered a mutation gradient with a higher mosaicism rate in the seizure-onset zone than in the surrounding epileptogenic zone from postoperative epileptic tissue. Subsequently, authors tested the impact of a somatic biallelic inactivation in the mouse brain combining in utero electroporation and CRISPR-Cas9 gene-editing to reproduce a focal mosaic knockout of DEPDC5. Mice with a low-level mosaic rate of crisprized neurons faithfully reproduced clinical and neuropathologic phenotypes of focal epilepsy. This work pointed out a so far unknown physiologic brain function of DEPDC5 in shaping dendrites and spines of excitatory neurons. Altogether this study emphasizes the fascinating and emerging concept that neurodevelopmental disorders are caused by mosaic mutations arising during brain development.

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is a common epilepsy syndrome, whose etiology remains elusive. Most cases are sporadic, but a few familial cases have been reported suggesting complex inheritance, as in most common genetic epilepsies. Wong et al.\(^10\) performed whole-exome sequencing (WES) in a small well-characterized cohort of Han Chinese patients from Hong Kong with MTLE-HS. These patients were clinically homogeneous as to seizure semiology, ictal/interictal EEG recordings, and high-definition brain MRI studies. They identified rare and de novo variants in a number of genes, including SEC24B, a gene involved in vesicle trafficking and development. Gene-set association analysis showed variant enrichment in the fragile X mental retardation protein (FMRP)-related group of genes, including the mammalian target of rapamycin (mTOR) pathway, which are associated with other forms of epilepsy and neurodevelopmental disorders, including autism spectrum disorders. In addition, analysis of trios revealed 21 de novo variants, many of which are also known to be associated with different neuropsychiatric disorders. Although no major hit emerged for MTLE-HS from this study, its results supported a complex genetic architecture for MTLE-HS and shared biology with other neuropsychiatric disorders. This study has to be commended for the accurate phenotyping of their cohort, but investigating a larger, equally well-characterized cohort, possibly with a larger number of trios, appears to be necessary to get more insights into the genetics of MTLE-HS.

The molecular diagnosis of a specific neuromuscular disease has become crucial as there are FDA approved treatments targeting specific genes or specific mutations. A recent study explored the diagnostic yield of whole exome sequencing (WES) in a cohort of patients affected by neuromuscular diseases of unknown etiology.\(^11\) The WES diagnostic yield in this cohort was 12.9%. The study compared the diagnostic yield of sequencing data analysis of genes linked to patient’s phenotype vs that of a broader set of genes (482 genes) causative of neuromuscular diseases. Analysis of a focused gene list and analysis of the larger neuromuscular disease gene list had similar diagnostic yield in patients with a clear myopathy or neuropathy phenotype. Broader genetic analysis was helpful in patients with a nonspecific neuromuscular phenotype not definitively suggestive of primary myopathy or neuropathy. The study also showed that only 62.5% of muscle biopsies or EMG studies suggested the correct type of neuromuscular disease later diagnosed by genetic test, suggesting early use of genetic analysis in the diagnostic process.

Two main directions at present in therapy and prevention of inherited neurodegenerative diseases in which the implicated genes are thought to have a gain in function causing toxicity involve the delivery of genes and antisense oligonucleotides to knockdown genes. On the horizon is gene editing, for example, by using CRISPR-Cas9. Gaj et al.\(^12\) apply this method to mutant SOD1 in neonatal G93A mutant SOD1-transgenic mice, which is a very aggressive mouse model of FALS. Compared with untreated G93A transgenic mice, the knockdown resulted in a ~2.5-fold decrease of SOD1 in the lumbar and thoracic spinal cord, ~50% more motor neurons at end stage, ~37% delay in disease onset, and ~25% increase in survival. Although there were a number of limitations to the study (e.g., a relatively small number of mice used in the experiments, a limited degree of knockdown that was conducted in neonates before clinical symptoms had begun), the publication provides a glimpse of the exciting future with respect to treatment of genetic diseases.

We wish to acknowledge the individuals who have completed reviews for the journal over the course of 2018—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 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.
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References