Paving the road for the study of epigenetics in neurodegenerative diseases

Oscar Harari^{1,2} · Carlos Cruchaga^{1,2}

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Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS), are among the most challenging health problems that still remain with no treatment. This becomes especially important in developed countries with an increasing population age. These diseases are characterized by progressive neuronal death, and aging is one of the most important risk factors. Currently, there are no effective treatments for any of these diseases, and the burden they cause, with incalculable economic and human costs, is growing inexorably as the population ages.

The identification of the genes causing the Mendelian forms of the diseases and the additional genetic studies have been instrumental to understand the biology of the diseases and to identify potential novel therapeutic targets. More specifically, genome-wide association studies (GWAS), aimed to identify common variants, have been very successful in identifying novel genetic regions associated with these complex traits. More than 20 loci have been reported to be associated with AD [8], 24 for PD [12] and fewer loci for FTLD [16]. However, only approximately half of the genetic heritability (the extent of the phenotypic variation in a population is due to genetic variation among individuals) of these diseases is explained by the GWAS hits or the Mendelian forms of the diseases. This

suggests that other types of genetic variation could explain the remaining heritability. Recent studies suggest that this missing heritability could be explained by low frequency and rare variants, structural and copy-number variants and also by epigenetic changes.

The epigenetics cluster in this issue of *Acta Neuropathologica* provides an overview of the role and findings related to epigenetics in Alzheimer's disease, Parkinson's disease, frontotemporal lobar degeneration and amyotrophic lateral sclerosis; it covers the latest findings, working hypotheses as well as future directions [1, 6, 7]. Epigenetic changes are well known to cause neuropsychiatric diseases including Prader–Willi syndrome and Angelman syndrome, and are also implicated in other complex traits, such as some forms of cancer and diabetes (see review from Robertson for a general overview of the role of epigenetics and human diseases [15]).

What is epigenetics?

As Belzil et al. [1] explain in their review on ALS and FTD, epigenetics is the study of heritable changes in gene expression that does not involve changes to the underlying DNA sequence. Epigenetic changes can be dynamic (changing by time and tissue), as opposed to the DNA sequences, which are the same for all of the cells for a given individual along time. Additionally, there are multiple epigenetic events that occur in human DNA. The most common epigenetic events studied in relation to human disease includes DNA and chromatin modification, as well as RNA-mediated epigenetic regulation [1].

DNA modification, specifically methylation, may be the most common epigenetic change studied in relation to its impact on neurodegenerative diseases. DNA methylation

✉ Carlos Cruchaga
ccruchaga@wustl.edu

¹ Department of Psychiatry, Washington University School of Medicine, 660 South Euclid Avenue B8134, St. Louis, MO 63110, USA

² Hope Center for Neurological Disorders, Washington University School of Medicine, 660 S. Euclid Ave. B8111, St. Louis, MO 63110, USA

is a crucial epigenetic modification of the genome that is involved in regulating many cellular processes. DNA methylation is a potent mechanism for silencing gene expression and maintaining genome stability in the face of a vast quantity of repetitive DNA, which can otherwise mediate illegitimate recombination events and cause transcriptional deregulation of nearby genes [15]. DNA methylation consists in the addition of a methyl group in a CpG group, and one of the reasons why it is widely studied in complex traits is because the latest advantages in technology enable to screen for methylation changes genome-wide for a large number of samples using commercial genomic arrays, similar to those used on GWA studies.

Epigenetics and DNA methylation in neurodegenerative diseases

DNA methylation studies are not common as GWAS, due to some intrinsic problems from a technical, analytical and also biological point of view. Genetic methylation increases with age [5], complicating the interpretation of the results in the context of age-dependent diseases such as AD, PD, FTLN or ALS. Additionally, different populations of cells are known to have different epigenetic modifications. This is particularly problematic when epigenetic studies are done in brain autopsies from AD or PD cases and controls that will contain multiple cell types, each with different methylation patterns [9]. Additionally, neuronal death due to the diseases would turn into different proportions of cell types assayed between cases and controls that would lead to different methylation profiles, which could be confounded with the original events associated with the diseases [9].

In any case, most of the studies have been so far performed on small datasets or have been focused to study the methylation states of the CpGs around target genes (Mendelian or GWAS hits). This is specially the case for FTLN, ALS and PD. The most common cause of FTLN and ALS is a hexanucleotide repeat in the first intron of the *C9ORF72* gene [3, 14]. Because the mutation is located on a non-coding region, it has been postulated that this mutation and any other change that affect *C9ORF72* gene expression could be also involved in disease [13]. As a result, multiple groups have interrogated the role of methylation in *C9ORF72* in expansion repeat carriers and not carriers, as explained by Belzil et al., in their review of FTLN and ALS epigenetics included in this cluster [1]. Similarly, there have been a lot of interest in studying the methylation state of CpGs around *SNCA*, involved in Parkinson disease, because of the known influence of α -synuclein expression levels in disease [7].

There are not large genome-wide methylation (eWAS) screens with replicable results for PD or FTLN-ALS. However, this is not the case for Alzheimer's disease: as discussed by Klein et al. [6] in this cluster of manuscripts, there are two relatively large eWAS for AD with replicable results [2, 9, 10]. CpG islands close to *ANKK1*, *RPL13*, *CDH23* and *RHBDF2* genes are differentially methylated in AD cases compared to controls. Additionally, these studies found differential methylation status for some of the genes identified by GWAS for AD [2, 9, 10].

An important finding from those studies, and covered in depth by Klein et al. [6], is that the epigenetic changes could explain a larger proportion of the heritability than regular SNPs, and therefore methylation studies would require smaller sample sizes compared to regular GWAS [6].

Other types of epigenetic changes

Although methylation is the most common epigenetic change so far studied in relation to complex traits, in part because current technologies enable their high-throughput assessments, there is also a lot of interest in RNA-mediated epigenetics. As explained by Labbe et al. [7], understanding and characterizing this type of epigenetic events can lead to clear therapeutic strategies. Gene expression can be downregulated or knocked down by using small interfering RNAs (siRNA) in a very specific manner. In fact, there are multiple clinical trials that are using this or similar approaches for neurodegenerative diseases, including ALS [4, 11].

Conclusions

Although epigenetic studies in neurodegenerative disease are in their earlier stages, recent advances in the technology allow analyzing systematically these events in larger datasets that should lead to novel and replicable findings. Similar to other genetic studies, the ultimate goal of understanding the epigenetic events implicated in neurodegeneration is to increase our knowledge of the biology of the disease and ultimately to identify novel therapeutic targets. Epigenetic studies include additional challenges not present in regular GWAS or sequencing studies due to the dynamic and cell-specific nature of these genomic events. However, successful studies and positive results obtained so far promise that these approaches will provide additional novel findings when all of these epigenetic modifications are ascertained systematically in larger cohorts, employing genome-wide approaches to interrogate a broader number of brain regions in cell type specific analyses.

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