REVIEW

The Neurodegenerative Disease Knowledge Portal

Propelling Discovery Through the Sharing of Neurodegenerative Disease Genomic Resources

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Abstract

Although large-scale genetic association studies have proven useful for the delineation of neurodegenerative disease processes, we still lack a full understanding of the pathologic mechanisms of these diseases, resulting in few appropriate treatment options and diagnostic challenges. To mitigate these gaps, the Neurodegenerative Disease Knowledge Portal (NDKP) was created as an open-science initiative with the aim to aggregate, enable analysis, and display all available genomic datasets of neurodegenerative disease, while protecting the integrity and confidentiality of the underlying datasets. The portal contains 218 genomic datasets, including genotyping and sequencing studies, of individuals across 10 different phenotypic groups, including neurologic conditions such as Alzheimer disease, amyotrophic lateral sclerosis, Lewy body dementia, and Parkinson disease. In addition to securely hosting large genomic datasets, the NDKP provides accessible workflows and tools to effectively use the datasets and assist in the facilitation of customized genomic analyses. Here, we summarize the genomic datasets currently included within the portal, the bioinformatics processing of the datasets, and the variety of phenotypes captured. We also present example use cases of the various user interfaces and integrated analytic tools to demonstrate their extensive utility in enabling the extraction of high-quality results at the source, for both genomics experts and those in other disciplines. Overall, the NDKP promotes open science and collaboration, maximizing the potential for discovery from the large-scale datasets researchers and consortia are expending immense resources to produce and resulting in reproducible conclusions to improve diagnostic and therapeutic care for patients with neurodegenerative disease.

Introduction

Neurodegenerative diseases are clinically heterogeneous and complex disorders. Given their relatively high estimates of heritability,[1-4] large-scale association studies are particularly useful for gaining a greater understanding of the pathologic mechanisms driving neurodegenerative disease processes, as demonstrated by their discoveries across neurodegenerative conditions including in Alzheimer disease, amyotrophic lateral sclerosis (ALS), and Parkinson disease.[5-12] Yet, there are still few appropriate treatment options across these diseases, and diagnoses remain a challenge, as a direct result of a lack of full understanding regarding their neuropathologic mechanisms.[13-16] To mitigate these gaps, greater effort must be made to combine resources in the pursuit of novel discovery in neurodegenerative disease genetics.

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Glossary

ALS = amyotrophic lateral sclerosis; **CMDGA** = Common Metabolic Diseases Genome Atlas; **GEM** = Genomic Region Miner; **GP2** = Global Parkinson's Genetics Program; **GWASs** = genome-wide association studies; **HuGE** = Human Genetic Evidence; **iChip** = ImmunoChip; **LDSC** = Linkage Disequilibrium Score Regression; **NDKP** = Neurodegenerative Disease Knowledge Portal; **NGS** = next-generation sequencing.

The application of open science and data-sharing principles in the pursuit of neurodegenerative disease research motivated the deployment of the Neurodegenerative Disease Knowledge Portal (NDKP),[17] consisting of 218 open-access genomic summary statistics and variant datasets of individuals across 10 different phenotypic groups, including neurologic conditions such as Alzheimer disease, ALS, Lewy body dementia, and Parkinson disease (all sample sizes were obtained in December 2023; annual updates to the NDKP are anticipated). In this study, we further describe the online, open-access resource including details of the available data and applications for genetic discovery and result replication in the study of neurodegenerative diseases.

Overview of the Neurodegenerative Disease Knowledge Portal

To maximize the potential for discovery from the many large, novel datasets being leveraged for various neurodegenerative disease genetic association studies and in taking inspiration from the successes of the previously deployed Type 2 Diabetes Knowledge Portal,[18] a centralized repository was assembled to securely store these datasets and make their summary results widely available to the research community. The portal was created and deployed by the developers at the Broad Institute of MIT and Harvard in collaboration with the Montreal Neurological Institute-Hospital, the Global Parkinson's Genetics Program (GP2), and NIH Intramural Center for Alzheimer's and Related Dementias into what is now known as the NDKP.

Overall, the aim of the NDKP is to aggregate, enable analysis, and display all available genomic datasets of neurodegenerative disease, while protecting the integrity and confidentiality of the underlying datasets. The NDKP is available to the broad scientific community studying neurodegeneration seeking to unveil novel genetic associations or validate primary findings from other approaches.

Available Datasets

Although the goal of the NDKP is to expand our genomic understanding of neurodegenerative diseases, the portal includes genomic datasets from cohorts spanning 10 phenotypic groups, including (1) cerebrovascular MRI traits, (2) COVID-19, (3) immunologic, (4) metabolite, (5) musculoskeletal, (6) neurologic, (7) psychiatric, (8) sleep and circadian, (9) stroke, and (10) cognitive. Across these groups, 239 subphenotypes are captured (eTable 1). It is important to note that this allows for the cross-analysis of neurodegenerative diseases with possible related and overlapping features. For example, given the known association between cerebrovascular disease features and neurodegeneration risk,[19-22] the NDKP can be used to identify genes or variants relevant in both a neurologic phenotype such as Alzheimer disease and a cerebrovascular MRI feature such as brain microbleeds, as will be discussed further. In total, 218 genomic datasets are currently captured within the NDKP (Figure 1), which can be subdivided into 2 data types: (1) genotyping studies and (2) sequencing studies (Figure 2).

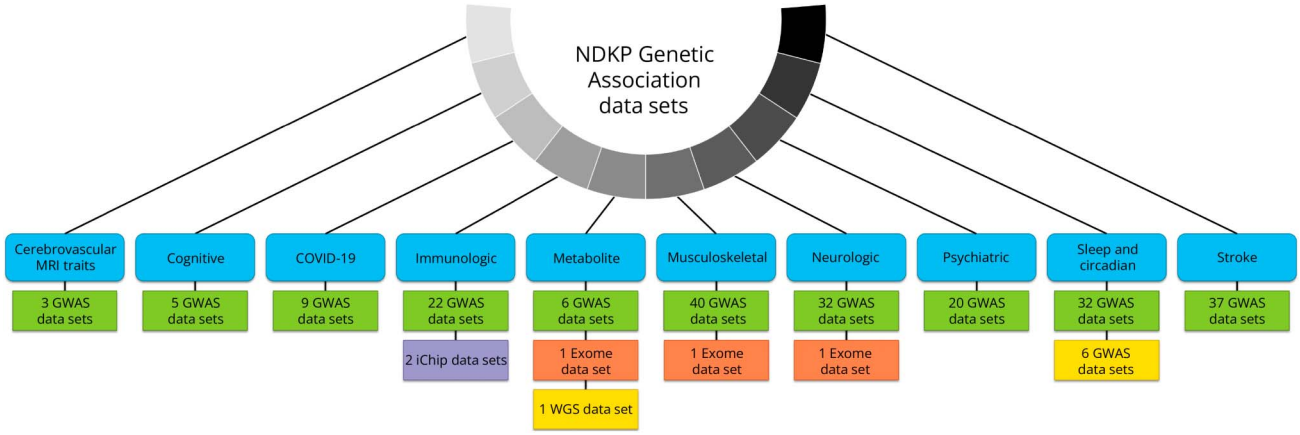
Genotyping Studies

The genotyping-based studies within the NDKP largely encompass genome-wide association studies (GWASs), which use genotyping microarray data and are aimed at identifying associations between variants and traits or disease states. GWASs require large sample pools of both individuals with a phenotype of interest and nonaffected controls and, depending on the type of quantitative trait, can generate an effect size per variant.[23] The NDKP includes datasets from 206 GWASs performed between 2010 and 2023, with the largest neurodegenerative disease dataset having been part of the 2023 GP2 GWAS that included 1,028,993 samples across multiple ancestries[24] (Figure 2). Summary statistics from many of the GWASs, which include the aforementioned effect sizes per statistically significant, phenotype-associated variant, are directly downloadable from the NDKP on the "Data Downloads" page.

In addition to the case-control variant calls and summary statistics, additional data types have been generated for the NDKP from the GWAS analyses. "Credible sets" include sets of variants near significant genetic association signals that are likely to include the causal variant for the signals and are generated through fine mapping of the GWAS results to further investigate genetic association signals. In addition, "effector gene lists" encompass lists of variant-adjacent genes potentially mediating the effects of the significantly phenotype-associated variants identified within the GWAS. Although the methods by which these genes are defined are study-dependent, their inclusion in the NDKP is important as stepping stones for experiments to further define the genes that may be truly causal for a particular phenotype.

Finally, the NDKP also has 2 datasets from the immunologic phenotype group that encompass ImmunoChip (iChip) data. The iChip is a custom-designed Illumina Infinium microarray

Figure 1 Genomic Association Datasets Captured by the Neurodegenerative Disease Knowledge Portal (NDKP) From Various Phenotypic Groups



The NDKP comprises genomic datasets from cohorts spanning 9 phenotypic groups, including cerebrovascular MRI traits, COVID-19, immunologic, metabolite, musculoskeletal, neurologic, psychiatric, sleep and circadian, and stroke. Datasets include genotyping data, such as genome-wide association studies (GWASs) and ImmunoChip (iChip), and sequencing studies, such as whole-genome sequencing (WGS) and exome sequencing.

that includes a specific set of single nucleotide variants and small insertion-deletions that were previously associated with autoimmune and inflammatory diseases through GWASs.[25] It provides the added benefit of being more cost-effective than typical exome-wide or genome-wide microarrays.

Sequencing Studies

Sequencing studies include the data from whole-genome, exome, or smaller panel-based next-generation sequencing (NGS) analyses. Typically, these studies include sequences from both affected (individuals with the phenotype of interest) and unaffected individuals because the data are used to perform variant-binned association analyses, such as rare variant burden association analysis. Generally, these approaches collapse rare variants into groups that can be dictated by a variety of factors, including, but not limited to, general genomic region, individual genes, pathways of interest, minor allele frequency, or functional consequence.[26] Various methods can be used to identify associations between the rare variant groups and the phenotype of interest, such as univariate or multivariate regression models. It is important to note that sequencing data allows for not only analysis of variant-level associations but also assessment of gene-level and region-level associations, using variants called from the complete sequencing of all loci within a given region of the genome.

Currently, the NDKP includes the data from 10 sequencing studies, including 7 whole-genome and 3 exome datasets (Figure 2). As NGS becomes more cost-effective, we expect larger and more ethnically diverse sequencing datasets to be made available and included in Knowledge Portal initiatives.

Neurologic Datasets

The NDKP includes 33 datasets within the neurologic phenotype subgroup, including 32 GWAS datasets and one exome sequencing dataset (Table 1). These neurologic phenotype datasets span 8 subphenotypes including Alzheimer disease (general and late-onset), ALS, Parkinson disease, epilepsy, and Lewy body dementia. While 26 of the datasets are of European ancestry, one dataset has individuals of African ancestry, another has individuals of Hispanic ancestry, and 5 datasets represent multiancestry analyses. In the coming years, it is a priority for the NDKP to continue expanding the ancestral diversity of the available datasets.

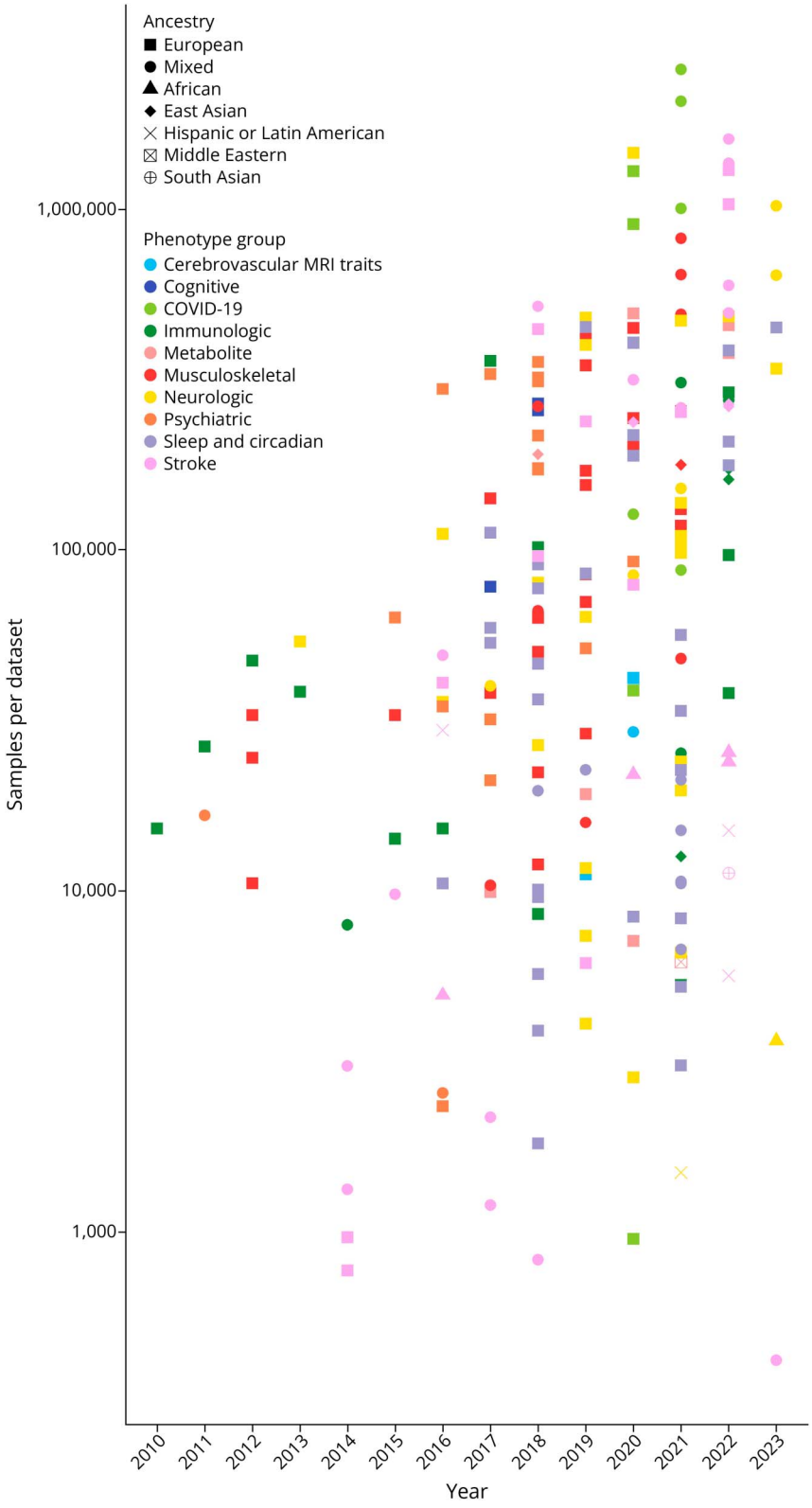
Multiomic Datasets

In addition to the genomic datasets available through the NDKP, multiomic data from the Common Metabolic Diseases Genome Atlas (CMDGA) are integrated through the various search pages and tools provided by the portal.[18] In brief, the CMDGA provides a compendium of epigenomic and other functional genomic data collated from the Accelerating Medicines Partnership Common Metabolic Disorders consortium, publicly available sources, and large resources such as ChIP-Atlas and the Encyclopedia of DNA Elements. In total, there are 6,890 multiomic datasets encompassed within the NDKP that were produced using a wide variety of methods including, but not limited to, ATAC-Seq, CaptureC, ChIP-Seq, HiC, and RNA-Seq. Of these, 378 datasets are derived from tissues relevant to the central nervous system. It is important to note that these datasets allow for the annotation of variants captured within the NDKP based on whether they are encompassed by regions considered accessible chromatin, binding sites, candidate regulatory elements, chromatin state, gene expression, histone modifications, or target variant predictions.

Bioinformatics Processing of the Data

On intake, genetic and genomic datasets are subjected to a suite of bioinformatic methods to glean additional insights from the processed and integrated results. Incoming genetic association datasets are first subjected to quality control and

Figure 2 Year of Publication and Sample Size of the 218 Genomic Association Datasets Captured by the Neurodegenerative Disease Knowledge Portal (NDKP) From Various Phenotypic Groups



Datasets include genotyping data, such as genome-wide association studies (GWASs) and ImmunoChip (iChip), and sequencing studies, such as whole-genome sequencing (WGS) and exome sequencing. For one study that provided prepublished data with no given date of publication, the year of publication 2023 was used. Samples per dataset are presented on a log10 scale.

harmonization, including ensuring that standardized column headings are used, inferring missing data for nonoptional columns (e.g., odds ratios can be used to infer effect sizes), and lifting over all datasets to GRCh37. We also ensure that all effect sizes are in reference to the alternate allele of GRCh37, remove variants with incompatible summary statistics for the

Table 1 Neurologic Datasets Included in the Neurodegenerative Disease Knowledge Portal (NDKP)

Dataset	Publication year	Cases (n)	Controls (n)	Ancestry	Data type
Alzheimer disease GWAS	2019	71,880	383,378	European	GWAS
Alzheimer disease GWAS	2021	75,024	397,844	European	GWAS
Alzheimer disease GWAS	2022	85,934	401,577	European	GWAS
Alzheimer disease GWAS	2023	101,061	543,127	Multi	GWAS
Alzheimer disease family history GWAS	2018	314,278	N/A[a]	European	GWAS
Amyotrophic lateral sclerosis exome case-control	2019	3,864	7,839	European	Exome
Amyotrophic lateral sclerosis GWAS	2016	12,577	23,475	European	GWAS
Amyotrophic lateral sclerosis GWAS	2017	13,811	26,325	Multi	GWAS
Amyotrophic lateral sclerosis GWAS	2018	20,806	59,804	European	GWAS
Amyotrophic lateral sclerosis GWAS	2020	22,040	62,654	Multi	GWAS
Amyotrophic lateral sclerosis GWAS	2021	29,612	122,656	Multi	GWAS
Amyotrophic lateral sclerosis GWAS	2021	27,205	110,881	European	GWAS
Carpal tunnel syndrome GWAS	2019	12,312	389,334	European	GWAS
Cognitive function GWAS	2016	112,067	N/A	European	GWAS
FinnGen r8 complex disease GWAS (Alzheimer disease)	2023	7,129	760,059	European	GWAS
Global Parkinson's Genetics Program GWAS	2023	62,976	966,017	Multi	GWAS
GR@CE Alzheimer's GWAS	2019	4,120	3,289	European	GWAS
Handedness GWAS	2020	1,470,460	N/A	European	GWAS
International League Against Epilepsy GWAS	2018	225	24,218	European	GWAS
IPDGC Parkinson's Disease GWAS (female)	2021	7,384	12,389	European	GWAS
IPDGC Parkinson's Disease GWAS (male)	2021	12,054	11,999	European	GWAS
IPDGC-UK Biobank Parkinson's disease and proxy cases GWAS (female)	2021	13,420	90,662	European	GWAS
IPDGC-UK Biobank Parkinson's disease and proxy cases GWAS (male)	2021	20,956	89,660	European	GWAS
IPDGC-UK Biobank Parkinson's disease GWAS (female)	2021	7,947	90,662	European	GWAS
IPDGC-UK Biobank Parkinson's disease GWAS (male)	2021	13,020	89,660	European	GWAS
LARGE-PD Parkinson's disease GWAS	2021	807	690	Hispanic/Latin American	GWAS
Late-onset Alzheimer GWAS	2013	8,572	11,312	European	GWAS
Late-onset Alzheimer GWAS	2019	21,982	41,944	European	GWAS
Lewy body dementia GWAS	2021	2,981	4,391	European	GWAS
Parkinson disease GWAS	2019	56,306	426,424	European	GWAS
Parkinson disease GWAS	2023	1,200	2,445	African	GWAS
Parkinson disease progression GWAS	2019	4,093	N/A	European	GWAS
Parkinson disease progression GWAS	2020	2,848	N/A	European	GWAS

Abbreviations: GR@CE = Genome Research at Fundacio ACE; GWAS = genome-wide association study; N/A = not applicable.
Further details regarding the neurologic datasets captured by the Neurodegenerative Disease Knowledge Portal can be accessed online at ndkp.hugeamp.org/datasets.html.
[a] 25,696 individuals had a maternal family history of Alzheimer disease, and 14,338 individuals had a paternal family history of Alzheimer disease.

subsequent analyses, and perform a linear regression–based effect size scaling for all quantitative phenotypes.[18] Variant associations are then meta-analyzed, using the METAL algorithm that infers and accounts for sample overlap between datasets to calculate an integrated "bottom-line" association for each variant and each trait.[27] The bottom-line analysis can both identify novel associations that are not significant at the level of individual datasets but become significant when multiple studies are considered and identify artifactual associations that may be significant in one dataset but are not replicated in others using a fixed-effect method. Using these bottom-line associations, we run the Variant Effect Predictor[28] to annotate predicted variant impact and perform LD clumping using the PLINK method[29] to group variants into genetically linked sets. We use the MAGMA algorithm per gene,[30] to calculate gene-level association scores based on nearby common variant associations, and per trait, to generate lists of biological pathways whose constituent genes are enriched for genetic associations for that trait. We apply the LD score regression method (LDSC) in 2 calculations.[31,32] Cross-trait LDSC is used to calculate the genetic correlations between all traits while stratified LDSC provides a measure of the enrichment of genetic association signals for each trait within annotated genomic regions such as enhancers and promoters. Finally, we apply the Human Genetic Evidence (HuGE) Calculator across all associations to categorize the weight of evidence supporting the relevance of each gene to each trait.[33] These methods are documented in the "Help" pages of the NDKP and were also described previously in detail.[18]

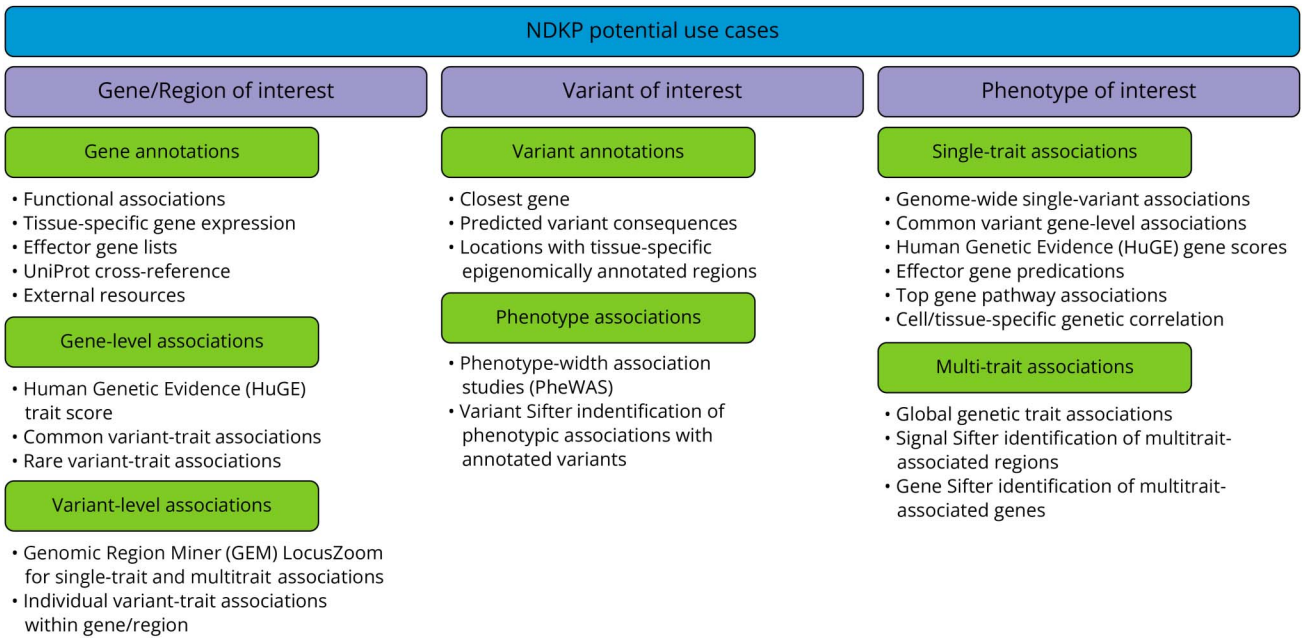
Application for the Study of Neurodegeneration

In addition to securely hosting large genomic datasets, one of the founding aims of the NDKP is to provide accessible workflows and tools to effectively use the datasets and assist in the facilitation of customized genomic analyses. To allow users to perform these aims, the portal offers 4 core page types, including regional pages, gene pages, variant pages, and phenotype pages, in addition to a variety of tools to allow for more structured analyses. Across these pages and tools, users are provided with summary results derived from the genomic datasets to explore genes, genomic regions, variants, or phenotypes of interest (Figure 3).

Exploring Genes/Regions of Interest

Commonly, researchers from disciplines outside the realm of computational or statistical genomics identify genes or regions of the genome of interest from experimental study, such as comparative functional genomic analyses with model organisms, protein-protein interaction analyses, or expression quantitative trait loci analyses.[34,35] After such studies, researchers may wish to further explore whether human genetic and genomic results support the hypotheses generated by experimentation. However, it has often been difficult for these research groups to gain access to the necessary large-scale genotyping or sequencing datasets to explore these results. Furthermore, even if data were freely available, these researchers may have lacked the expertise to efficiently or

Figure 3 Potential Uses of the Data and Tools Encompassed Within the Neurodegenerative Disease Knowledge Portal (NDKP)



The NDKP aims to provide accessible workflows and tools to use the datasets and assist in the facilitation of customized genomic analyses. The portal offers 4 core search pages and a variety of tools to provide summary results derived from the genomic datasets to explore genes, genomic regions, variants, or phenotypes of interest.

accurately pull the required summary-level results to substantiate their hypotheses. The NDKP has aimed to fill this gap, providing a variety of results that may be of interest both to the genetics community and to researchers outside the discipline to explore regions of the genome and specific genes that may represent new risk loci or therapeutic targets for specific neurodegenerative phenotypes (Figure 3).

After the search of a gene of interest, the NDKP returns a variety of gene-level and variant-level association summary results. At the gene level, the search returns both common variant and rare variant gene-wide trait associations. More specifically, these results represent phenotypes for which a genetic association exists with the genes when common or rare variants, respectively, are binned and the burden of variants within the gene are compared between a cohort of individuals with the phenotype and a control cohort that does not have the phenotype. The NDKP also returns HuGE Calculator trait scores for the gene, which represent the extent of human genetic evidence captured within the Knowledge Portals that supports gene-phenotype associations.[33] For example, the well-established ALS-associated gene, *SOD1*, has a calculated HuGE score of 350, representing a "compelling" level of evidence for involvement of the gene in ALS, whereas the gene *LDLR*, which is traditionally associated with familial hypercholesterolemia and has no known associations with ALS, has a calculated HuGE score of 1.33, representing "anecdotal" evidence.

In addition to gene-level summary results, the search of a gene in the NDKP will also return variant-level summaries, including a list of variants within the gene that have individual associations with any of the phenotypes captured across the various datasets. Similarly, the search of a region of interest will return individual variant-level trait associations that have been identified across the NDKP datasets within the given region. The search of a region of interest will also return the Genomic Region Miner (GEM) LocusZoom tool, which visualizes variant associations with single or multiple traits. Figure 4 displays the results of searching for the region surrounding a well-known Parkinson disease gene, *SNCA* (chr 4: 90,571,496-90,809,466). Using the GEM LocusZoom tool, not only can the variants with significant Parkinson disease associations be visualized, but also if other trait associations are suspected in the region, as is the case for Lewy body dementia in this region, additional phenotypes can be queried. A table of the variant-level data captured by the GEM LocusZoom tool is also provided by the NDKP.

In addition to the genetic association summary results computed and returned by the NDKP, a variety of gene annotations can be found from the search of a given gene or region. The search of a gene of interest returns functional associations of the gene, tissue-specific gene expression data, effector gene lists, UniProt cross-reference data, and external resource links as applicable. By contrast, the search of a region of interest returns a list of genes encompassed by the region.

Exploring Variants of Interest

Variants of interest, such as those identified through GWAS analysis or other association studies, can also be further explored using the NDKP. The search of a variant using the dbSNP identifier will return both variant annotations and

Figure 4 Genomic Region Miner (GEM) LocusZoom Visualization of Variant-Phenotype Associations Within the Region Surrounding SNCA (chr 4:90,571,496-90,809,466)

As part of the summary results returned when a region of interest is searched in the Neurodegenerative Disease Knowledge Portal (NDKP), the GEM LocusZoom tool provides a visualization of all variants within that region identified across the NDKP datasets and their individual associations with the most relevant phenotype. In the case of the region surrounding *SNCA*, Parkinson disease represents the most highly associated phenotype. However, the GEM LocusZoom tool also allows for customized visualization of variant associations with additional phenotypes, as is shown here for Lewy body dementia.

phenotype associations based on the datasets encompassed in the portal (Figure 3). More specifically, the variant search page will return information regarding the closest gene to the variant or the gene it resides within, as applicable, and any predicted variant consequences. The search page also returns results of a phenotype-wide association study, providing the statistical results that describe the level of associations of the variant with any given phenotype captured by the NDKP. For example, when a search of the NDKP is performed for the *APOE* e4 defining variant, rs429358, an unsurprising significant association is observed between the variant and an increased risk of late-onset Alzheimer disease (OR = 3.49, p = 4.94e-324); however, the variant is also found to be significantly associated with an increased risk of brain microbleeds (OR = 1.29, p = 7.48e-10). It is important to note that individual datasets can also be specifically queried for variants of interest, which can provide interesting sources of evidence for ancestry-specific analyses or variant curation exercises.[36]

Exploring Phenotypes of Interest

Unlike the abovementioned examples that are often driven by experimentally derived hypotheses, a researcher may also have a phenotype or disease of particular interest for which they want to develop novel human genomic-derived hypotheses. For these instances, the NDKP provides phenotype search page result summaries in addition to specific tools that allow for the exploration of genetic associations (Figure 3).

When only a single phenotype is of interest, the phenotype search page provides the greatest amount of information to the user, including both variant-level and gene-level result summaries. All datasets for which the phenotype of interest is captured are clearly outlined. At the variant level, the phenotype search page provides the top genome-wide single-variant associations, and at the gene level, associations based on the binning of common variants within each potential gene are provided. The search also provides top gene pathway associations, cell/tissue-specific genetic correlations, and effector gene predictions for the phenotype, as applicable.

Using ALS as a case study, the user will find 7 datasets that capture the ALS phenotype, each of which can be further explored. As anticipated, the top single-variant association signal for ALS is an intronic variant (rs2453555) within *C9orf72* (OR = 1.19, p = 1.78e-41), which tags a hexanucleotide repeat expansion known to be one of the most common genetic causes of ALS.[37-40] Similarly, *C9orf72* (p = 3.04e-20, variants = 24) is the gene with the second highest common variant gene-level association, after *MOB3B* (p = 6.53e-29, variants = 95), a gene located nearby *C9orf72*. The NDKP also indicates that ALS is significantly associated with the acanthocytosis pathway (p = 3.22e-7)—an example of a potential novel association that may prompt hypothesis generation—and ALS genetic associations are significantly enriched within regions annotated as enhancers in CNS tissues (p = 7.07e-5). In addition to the results captured by the phenotype search pages, the NDKP also assists with single-trait analysis through the use of the HuGE Calculator that computes HuGE scores for any given phenotype-gene combination, which are described further above.[33]

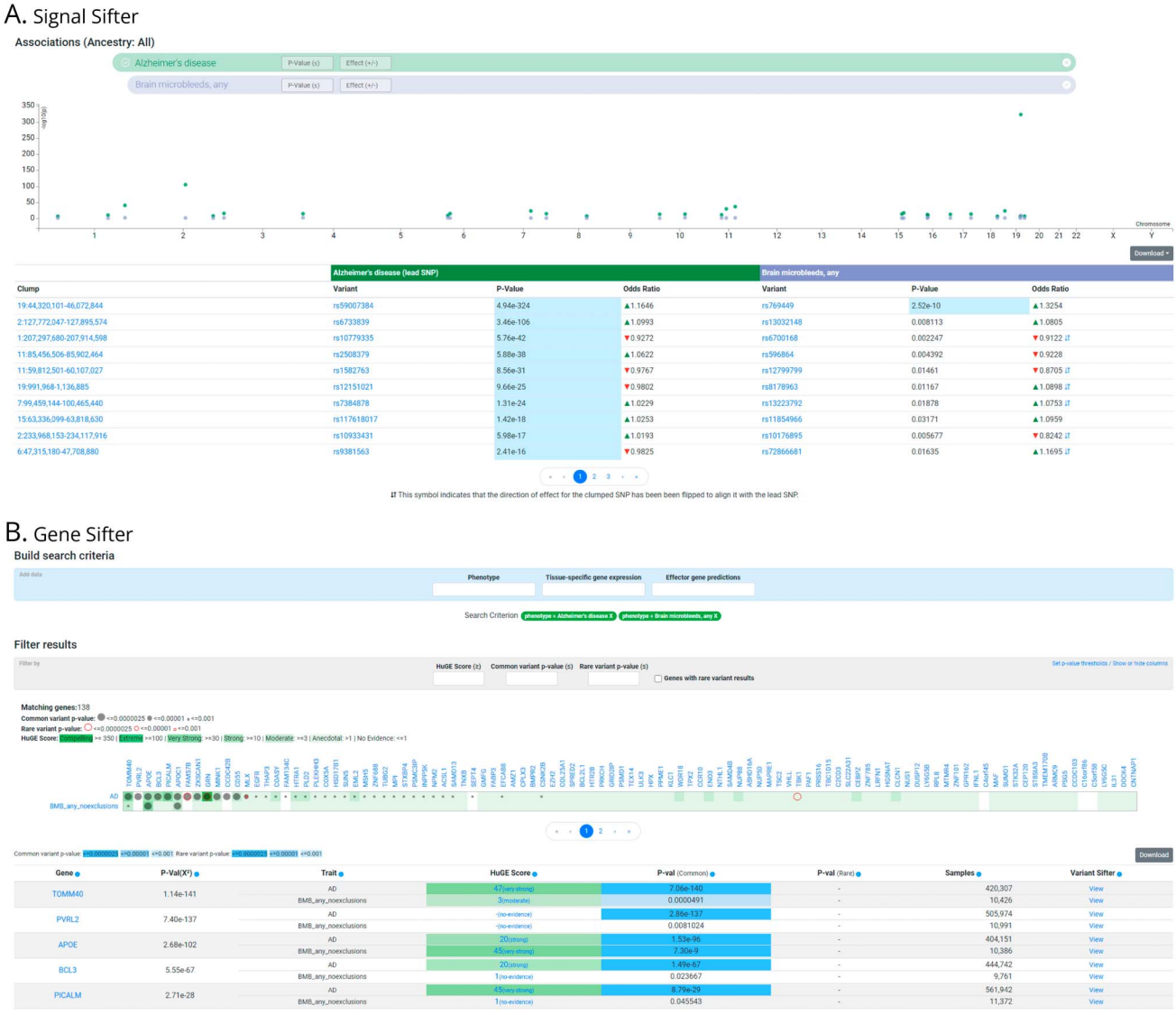
Of additional utility, the NDKP offers summary results and tools that allow for effective multitrait analysis. Directly within the phenotype search page, a list of genetically correlated traits for the phenotype of interest can be found. Using Alzheimer disease as a case study, it is unsurprising to find a significant genetic correlation with late-onset Alzheimer disease (r = 0.90, p = 1.22e-70); however, there is also a significant genetic correlation observed with Parkinson disease (r = 0.26, p = 7.80e-8).

The NDKP also hosts 3 tools that allow for more detailed multitrait analysis: (1) the Signal Sifter, (2) the Gene Sifter, and (3) the Variant Sifter. The Signal Sifter and Gene Sifter tools work in a similar manner, such that multiple traits can be queried and genetic associations relevant to 2 or more phenotypes will be returned, but the Signal Sifter returns regions with LD-clumped variants while the Gene Sifter returns genes. Often, the user will explore genetic correlations by beginning with multiple phenotypes that they know, or suspect, are clinically correlated. It is important to note that the integration of these tools directly within the framework of the NDKP affords researchers the ability to explore the genetic underpinnings of common comorbidities across the neurodegenerative disease spectrum.

Again, using Alzheimer disease as a primary phenotype, the user may wish to explore its genetic correlations with brain microbleeds based on observations of neurovascular damage in cases of neurodegenerative disease.[41-43] Indeed, on investigation of these 2 phenotypes with the NDKP, the Signal Sifter returns regions of LD-clumped variants significantly associated with increased risk of both traits, including the top associated region chr 19:45,387,459-45,428,235 (Alzheimer-associated variant rs11556505, p = 4.94e-324; brain microbleed–associated variant rs769449, p = 2.52e-10) (Figure 5A). Similarly, the Gene Sifter returns 138 genes with significant chi-square p values that represent a measure of overall association for the gene and both traits (Figure 5B). The top 3 of these associated genes are *TOMM40* ($p[X^2]$ = 1.14e-141), *PVRL2* ($p[X^2]$ = 7.40e-137), and *APOE* ($p[X^2]$ = 2.68e-102), expectedly, all of which are captured in the top region identified with the Signal Sifter and have been previously associated with the 2 phenotypes independently.[10,44-48]

The Variant Sifter is the Knowledge Portal's most recently developed tool and encompasses a wide range of capabilities, broadly allowing the user to explore variant-phenotype associations based on a range of filter options including focusing on credible sets and tissue-specific epigenomic annotations. Although there are many ways to use the tool, the user typically will begin with a phenotype and a region or gene of interest. The Variant Sifter returns a list of variants in the region that are associated with the phenotype that can then be

Figure 5 Multitrait Analysis Using Tools Integrated Into the Neurodegenerative Disease Knowledge Portal (NDKP), Which Demonstrated Genomic Associations With Alzheimer Disease and Brain Microbleeds



(A) Signal Sifter identified regions of LD-clumped variants significantly associated with risk of both traits. (B) Gene Sifter identified 138 genes with a significant chi-square *p* value, indicating overall associations between the genes and both traits.

filtered based on user-defined criteria. The filters allow for the identification of variants in credible sets; variants within tissue-specific regulatory region annotations of interest, integrated from the CMDGA; and variants linked to specific genes.

Recently, a novel ALS-associated gene, *KANK1*, was discovered using a rare variant association analysis approach, which identified not only an enrichment of rare variants in coding regions of the gene in individuals with ALS but also rare variants in noncoding enhancer and promoter regions.[7] The NDKP Variant Sifter can be used to determine whether any individual variants within the surrounding regulatory regions of *KANK1* demonstrate a significant association with ALS, which may be important for further functional analyses regarding this gene's association. After the search of the chr9: 370,291–846,105 region using the Variant Sifter tool regarding the ALS phenotype, the tool returns all variants reported within the NDKP in an association plot (Figure 6A). The variants can then be filtered based on a variety of annotations of interest to the researcher, such as identifying variants by location within regulatory regions annotated in broad tissue categories based on the epigenomic data derived from the CMDGA. In this case, we were interested in identifying variants within an enhancer regulatory element in the CNS linked to *KANK1*. We first filtered for variants located within enhancer regions and specified to only include those identified in tissues of the CNS (Figure 6B). The Variant Sifter then provides a filter to identify variants linked to genes, using which we specified to only include variants linked to *KANK1* (Figure 6C). Using this filtration strategy that leveraged the

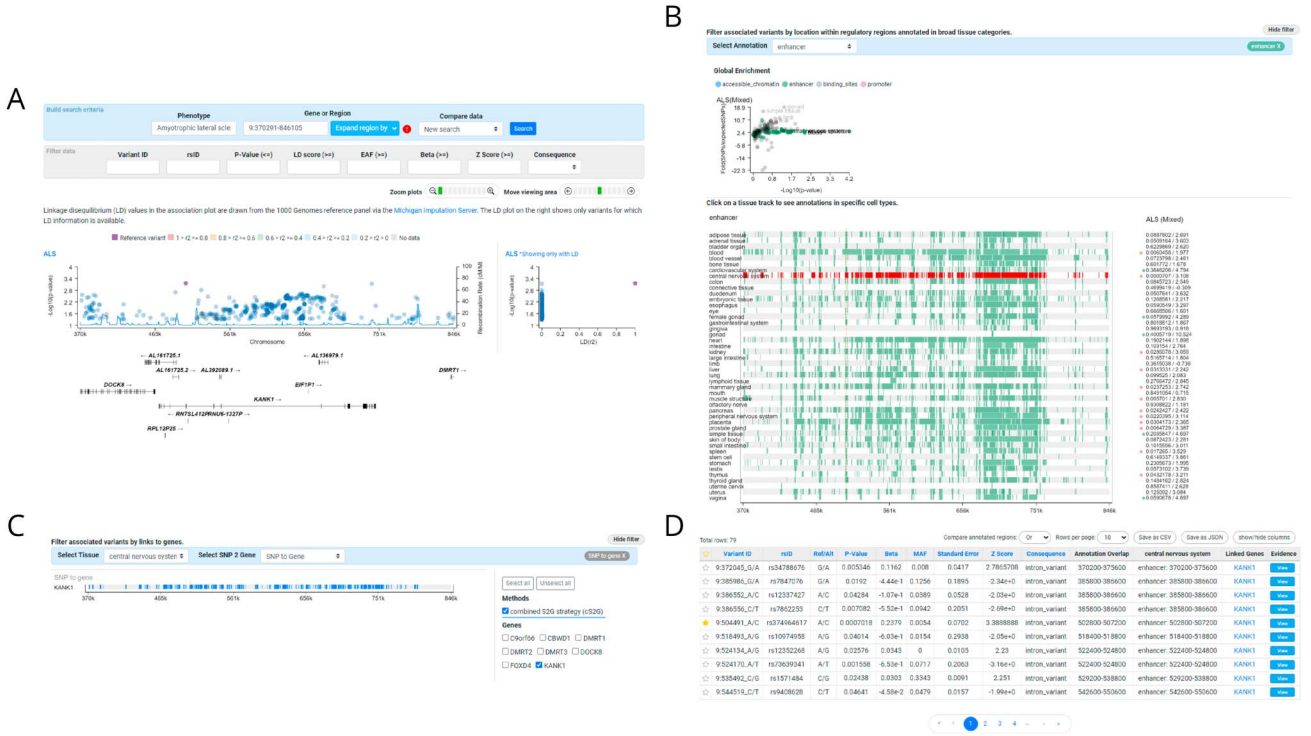
epigenomic data derived from the CMDGA, the Variant Sifter tool returned 79 variants, including one variant (chr9: 504,491:A>C) demonstrating an association with ALS based on the meta-analysis of NDKP data that is approaching significance ($\beta = 0.238$, $p = 7.01e\text{-}4$; Figure 6D).

Discussion

As researchers and consortia continue to expend immense effort and resources in producing large-scale genomic analyses, it is essential that the greatest potential for discovery is realized from these datasets. The NDKP offers a centralized knowledge base for researchers that can act as a secure, accessible, and innovative solution for data sharing, not only achieving aims of transparency when reporting novel results but also allowing for continued discovery in neurodegenerative disease research. In contrast to disease-agnostic resources that aggregate large-scale genomic datasets, such as Open Targets[49] or the GWAS Catalog,[50] the NDKP focuses the presented results on traits most relevant to neurodegenerative phenotypes and benefits from the careful curation provided by neurogenetic experts to ensure that all analyses of high impact are incorporated appropriately and displayed in ways most useful to the end user. Yet, unlike highly disease-specific "omic" resources, such as the Alzheimer's Disease Variant Portal[51] or Agora,[52] the NDKP still allows for the assessment of comorbidities across the neurodegenerative spectrum, which is particularly important based on the large amount of clinical overlap between these conditions. Furthermore, the various user interfaces and analytic tools are custom-designed for the purposes of the Knowledge Portals and enable consistent extraction of high-quality results at the source, for both genomics experts and those in other disciplines, while still protecting the integrity of the data.

In addition to its potential for discovery, the NDKP provides a centralized hub allowing the user to replicate or further investigate findings from their own independent datasets. The generation of "omics" datasets can be cost prohibitive, particularly considering the need for both discovery and replication subsets[53]; by offering a secondary dataset for replication of novel discoveries, researchers can maximize the statistical power harnessed from their in-house data. In addition, the breadth of data types and tools available through the portal offer the ability to further explore their findings beyond only replication of results. Our goal is to continue to add available datasets to the portal. Regular data releases are planned, at minimum on a yearly basis, including the addition of at least 9 new datasets spanning multiple neurodegenerative diseases and

Figure 6 Exploration and Filtration of Variant Associations With Amyotrophic Lateral Sclerosis (ALS) Within the Surrounding Region of *KANK1* (chr9:370,291-846105) Using the Variant Sifter Tool



(A) Association plot of all variants identified within the meta-analyzed datasets encompassed within the Neurodegenerative Disease Knowledge Portal (NDKP) within the surrounding region of *KANK1* in reference to their meta-analyzed associations with ALS. (B) Filtration of variants to include only those in enhancer regulatory element within the CNS based on epigenomics data encompassed within the NDKP from the Common Metabolic Diseases Genome Atlas (CMDGA). (C) Filtration of variants to include only those linked to *KANK1*. (D) All remaining variants after application of the annotation filters using the Variant Sifter tool. The star represents a variant of interest that has been manually selected based on its association with ALS that is approaching significance.

diverse ancestral populations. We aim to prioritize the integration of additional "omic" datatypes, such as single-cell, bulk RNA-seq, and proteomics analyses, in addition to incorporating deeply phenotyped clinical datasets as they become available. As we move toward achieving this goal, we also remain committed to the development of appropriate data mining methods and bioinformatics tools to appropriately use the data, which is particularly important for complex phenotypes such as neurodegenerative diseases.[54] Finally, we welcome new collaborations, including the opportunity to incorporate additional data, methods, and tools into the NDKP. Researchers are encouraged to contact the data intake team (amp-dcc-dat@broadinstitute.org) to discuss prospective collaborations and data deposition.

Although effort is being made to expand the portal, it is important to recognize that the NDKP currently has inherent limitations regarding the available data. Most notably, there is an overrepresentation of individuals of European ancestry, largely reflecting the lack of diversity observed across the field of genomics.[55] Furthermore, most currently available datasets represent GWAS summary statistics, which do not represent all information from the original genotyping microarray data. While offering potential for further discovery and replication of common variant signals, GWAS datasets typically do not capture rare genetic biomarkers for phenotypes of interest.

While we have provided a comprehensive overview of the vast amount of data included in the NDKP and their possible applications, there are unlimited potential use cases. Additional detailed potential workflows have been outlined by the Knowledge Portal developers, including using the NDKP to perform multitrait analysis, rare variant association gene-level analysis, and integrative analysis available within the "Workflow" subsection of the "Help" pages. The developers have also generated ample tutorials, webinars, and presentations to aid in NDKP use available within the "Videos, webinars, and presentations" subsection of the "Help" pages. Ultimately, our goal is for available data to be accessible and easy to use for both novel discovery and replication purposes, promoting open science and collaboration, and resulting in reproducible conclusions that will improve target discovery for neurodegenerative diseases.

Author Contributions

A.A. Dilliott: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M.C. Costanzo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Bandres-Ciga: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Blauwendraat: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. Casey: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. Q. Hoang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. H. Iwaki: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Jang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. J.J. Kim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H.L. Leonard: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K.S. Levine: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Makarious: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T.T. Nguyen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. G.A. Rouleau: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.B. Singleton: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Smadbeck: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. J. Solle: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Vitale: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Nalls: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. J. Flannick: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. N.P. Burtt: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. S.M.K. Farhan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

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serves on the scientific advisory board for Clover Therapeutics and is a scientific founder at Neuron23 Inc; he also owns stocks. Go to Neurology.org/NG for full disclosures.

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