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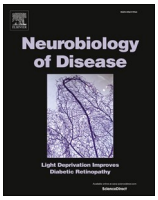

Multi-omic insights into Parkinson's Disease: From genetic associations to functional mechanisms

Brian M. Schilder [a,b,c,d,e,f,g,*], Elisa Navarro [a,b,c,d,e,h], Towfique Raj [a,b,c,d,e,**]

[a] Nash Family Department of Neuroscience & Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[b] Ronald M. Loeb Center for Alzheimer's disease, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[c] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[d] Icahn Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[e] Estelle and Daniel Maggin Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[f] Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, United Kingdom
[g] UK Dementia Research Institute at Imperial College London, London, United Kingdom
[h] Sección Departamental de Bioquímica y Biología Molecular, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

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ABSTRACT

Genome-Wide Association Studies (GWAS) have elucidated the genetic components of Parkinson's Disease (PD). However, because the vast majority of GWAS association signals fall within non-coding regions, translating these results into an interpretable, mechanistic understanding of the disease etiology remains a major challenge in the field. In this review, we provide an overview of the approaches to prioritize putative causal variants and genes as well as summarise the primary findings of previous studies. We then discuss recent efforts to integrate multi-omics data to identify likely pathogenic cell types and biological pathways implicated in PD pathogenesis. We have compiled full summary statistics of cell-type, tissue, and phentoype enrichment analyses from multiple studies of PD GWAS and provided them in a standardized format as a resource for the research community (https://github.com/RajLabMSSM/PD_omics_review). Finally, we discuss the experimental, computational, and conceptual advances that will be necessary to fully elucidate the effects of functional variants and genes on cellular dysregulation and disease risk.

1. Introduction

Parkinson's disease (PD) (Parkinson, 1817) is the second most common neurodegenerative disease globally (Kim et al., 2018) and is projected to double in prevalence between 2005 and 2030 (Dorsey et al., 2007). PD is characterized by both motor symptoms (e.g. bradykinesia, rigidity, tremor) and a diversity of non-motor symptoms (e.g. cognitive impairment, autonomic dysfunction, sleep cycle dysregulation), but there is substantial heterogeneity in the exact clinical presentation and age of onset, as well as phenotypic overlap with other PD-like disorders (Poewe et al., 2017). This phenotypic heterogeneity, which is potentially a reflection of heterogeneity at the molecular level, has further compounded the challenge of developing methodologies that can effectively identify, treat and prevent this disorder.

PD is characterized by two main pathological hallmarks: the loss of dopaminergic (DA) neurons in the substantia nigra (SN) pars compacta (Damier et al., 1999; Fearnley and Lees, 1991) and the accumulation of Lewy bodies, caused by the intracellular aggregation of α-synuclein (Braak et al., 2003; Braak and Del Tredici, 2017; Poewe et al., 2017). This leads to the dysfunction of basal ganglia circuitry and is thought to be the primary driver of classical motor symptoms (Kalia and Lang, 2015). The main pharmacological intervention is levodopa replacement but there is currently no cure for the disease. PD cases are typically categorized into two main forms: monogenic and idiopathic. The so-called monogenic cases (sometimes called Mendelian, familial, or genetic) only account for 5–10% of total cases (Bandres-Ciga et al., 2020a, 2020b; Lesage and Brice, 2009). The vast majority of PD cases are idiopathic (also called sporadic or sometimes "non-genetic"), which we now know has a substantial genetic component that comprises many common, small-effect variants across the genome. PD has been

* Correspondence to: B.M. Schilder, 86 Wood Ln, Sir Michael Uren Hub, 7th floor, UK Dementia Research Institute, Imperial College London, London W12 0BZ, United Kingdom.
** Correspondence to: T. Raj, 1425 Madison Avenue, Icahn 10-70E, Icahn School of Medicine at Mount Sinai, New York City, NY 10029, United States.
E-mail addresses: brian_schilder@alumni.brown.edu (B.M. Schilder), towfique.raj@mssm.edu (T. Raj).

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Table 1
Parkinson's Disease omics resources.

Resource	Phenotypes	Description	Data types	Levels	Last update	No request needed	API	URL	Reference
Alfradique-Dunham et al. (2021)	Parkinson's	Full genome-wide summary statistics from Alfradique-Dunham et al. (2021) PD motor subtypes GWAS.	GWAS	Variants	2021	Y	N	https://pdgenetics.org/resources	(Alfradique-Dunham et al. 2021)
AMP-PD	Parkinson's	Whole-genome sequencing (WGS), familial PD-associated mutation status, transcriptome and clinical evaluations in a cohort of PD and control participants. Some of the data is compiled from other databases (BioFIND, PDBP, PPMI) and harmonized to facilitate re-analysis.	WGS, bulkRNA-seq	Variants, Genes, Phenotypes	2021	N	Y	https://amp-pd.org	(Iwaki et al. 2020)
Blauwendraat et al. (2019)	Parkinson's	Full genome-wide summary statistics from Blauwendraat et al. (2019) PD onset GWAS, excluding 23andMe.	GWAS	Variants	2019	Y	N	https://pdgenetics.org/resources	(Blauwendraat et al. 2019)
FOUNDIN-PD	Parkinson's	Extensive multi-omics resource from PD patient-derived iPSCs.	Genotype, WGS, mitoDNA-seq DNA methylation, HiC, scATAC-seq, bulkRNA-seq, smallRNA-seq, scRNA-seq, Proteomics, Clinical, Imaging	Variants, Epigenomics, Genes, Cell-types, Tissues, Phenotypes	2021	Y	Y	https://www.foundinpd.org	(Bressan et al., 2021)
GP2	Parkinson's	The Global Parkinson's Genetics Program (GP2) is the first resource project of the Aligning Science Across Parkinson's (ASAP) initiative. It aims to collect multi-modal data from a diverse international cohort of PD patients, including genotyping in 150k+ individuals and WGS in 10k+ individuals.	Genotype, GWAS, WGS	Variants, Epigenomics, Genes, Cell-types, Tissues, Phenotypes	2021	N	Y	https://www.gp2.org	(The Global Parkinson's Genetics Program, 2021)
iPDGC Locus Browser	Parkinson's	Top summary statistics from three PD GWAS with variant annotation, causal gene(s) nomination, brain eQTL integration, statistical fine-mapping results, co-expression networks and burden analyses.	GWAS, QTL, bulkRNA-seq, scRNA-seq	Variants, Genes, Phenotypes	2021	Y	N	https://pdgenetics.shinyapps.io/GWASBrowser	(Grenn et al. 2020)
iPDGC MR Portal	Parkinson's	Two-sample Mendelian Randomisation (MR) comparing PD to 5,854 other GWAS traits provided by the International Parkinson Disease Genomics Consortium (IPDGC).	GWAS	Variants, Phenotypes	2019	Y	N	https://pdgenetics.shinyapps.io/MRportal	(Noyce et al. 2019)
MJFF	Parkinson's	A compilation of PD genomics datasets and tools funded by MIchael J. Fox Foundation (MJFF).	GWAS, WGS, bulkRNA-seq, Clinical, Imaging	Variants, Genes, Phenotypes	2021	N	N	https://www.michaeljfox.org/data-sets	(Padmanabhan et al. 2019)
Nalls et al. (2019)	Parkinson's	Full genome-wide summary statistics from Nalls et al. (2019) PD GWAS, excluding 23andMe.	GWAS	Variants	2019	Y	N	https://pdgenetics.org/resources	(Nalls et al. 2019)
PD Gene	Parkinson's	Search tool for Nalls et al. (2014) GWAS summary statistics.	GWAS	Variants, Genes	2017	Y	N	http://pdgene.org	(Nalls et al. 2014)
PPMI	Parkinson's	A compilation of PD genomics datasets and tools funded by MJFF via the Parkinson's Progression Markers Initiative (PPMI) initiative.	GWAS, WGS, bulkRNA-seq, Clinical, Imaging	Variants, Genes, Phenotypes	2019	Y	N	http://www.ppmi-info.org	(Aleksovski et al. 2018)
PDBP	Parkinsonianisms	Repository for biosamples and biomarkers data funded by National Institute of Neurological Disorders and Stroke (NINDS) via the Parkinson's Disease Biomarkers Program (PDBP).	GWAS, bulkRNA-seq, Clinical	Variant, Genes, Cell-types, Tissues, Phenotypes	2021	N	Y	https://pdbp-demo.cit.nih.gov	(Rosenthal et al. 2016)
echolocatoR Fine-mapping Portal	Multiple	Multi-tool fine-mapping results and locus visualizations across 11+ GWAS/QTL.	GWAS, QTL	Variants, Genes, Cell-types	2021	Y	Y	https://rajlab.shinyapps.io/Fine_Mapping_Shiny	(Schilder et al.)
EpiGraphDB	Multiple	Multi-modal epidemiological networks of linking data across phenotypes, literature terms, genes, tissues, drugs and more. ukbiobank-tools provides API access to certain aspects of the database (https://ukbiobank-tools.readthedocs.io/en/latest/index.html).	GWAS, Literature	Variants, Genes, Cell-types, Tissues, Phenotypes	2021	Y	Y	https://www.epigraphdb.org	(Liu et al. 2020)
EpiMap	Multiple	Expanded and standardised collection of all epigenomics data from ENCODE, the Roadmap Epigenomics Project, and the Genomics of Gene Regulation (GGR). Includes multi-modal networks integrating epigenomics and GWAS.	Epigenomics	Variants, Genes, Cell-types Tissues, Phenotypes	2021	Y	Y	http://compbio.mit.edu/epimap	(Boix et al. 2021)
eQTL Catalogue	Multiple	Uniformly reprocessed, tabix-indexed summary statistics and statistical fine-mapping results from 112 QTL datasets across 21 studies, including QTL for: gene expression, exon expression, transcript usage, and txrevise event usage.	QTL	Variants, Genes, Cell-types, Tissues	2021	Y	Y	https://www.ebi.ac.uk/eqtl	(Kerimov et al. 2020)
FUMA GWAS	Multiple	Web tool for automated GWAS annotation and cell-type/tissue enrichment.	GWAS	Variants, Genes, Cell-types, Tissues, Phenotypes	2021	Y	N	https://fuma.ctglab.nl	(Watanabe et al. 2017)
GenoML	Multiple	Toolkit to facilitate the creation of novel deep learning architectures for genomics data.	GWAS,QTLEpigeno	Variants, Genes, Cell-types, Phenotypes	2021	Y	Y	https://genoml.com	(Makarious et al., 2021)
Janggu	Multiple	Toolkit to facilitate the creation of novel deep learning architectures for genomics data.	GWAS,QTLEpigeno	VariantsGenes	2021	Y	Y	https://github.com/BIMSBbioinfo/janggu	(Kopp et al., 2020)
Kipoi	Multiple	Pre-trained deep learning models for genomics data.	GWAS,QTLEpigeno	VariantsGenes	2021	Y	Y	https://kipoi.org	(Avsec et al., 2019)
MDSGene	Multiple	Databases of variants, genes and symptoms associated with movement disorders in the literature.	Literature	Variants, Genes, Phenotypes	2020	Y	N	http://www.mdsgene.org	(Klein et al. 2018)
MungeSumstats	Multiple	Tool for automatic, robust, and scalable standardization of GWAS summary statistics. Provides API-access to MRC IEU Open GWAS	GWAS	Variants, Phenotypes	2021	Y	Y	https://github.com/neurogenomics/MungeSumstats	(Murphy and Skene, 2021)
OMIM	Multiple	Manually curated database of genes associated with various disease phenotypes.	Literature	Variants, Genes, Phenotypes	2021	Y	Y	https://omim.org/entry/168600	(Hamosh et al. 2005)
Open GWAS	Multiple	The MRC IEU Open GWAS Project is an online database of semi-standardised, full genome-wide summary statistics from 39k+ GWAS. All GWAS are provided in tabix-indexed VCF format for rapid querying.	GWAS	Variants, Phenotypes	2021	Y	Y	https://gwas.mrcieu.ac.uk	(Elsworth et al. 2020)
Open Targets	Multiple	Query engine to gather variant- and gene-level annotations, GWAS summary statistics, colocalization results, and fine-mapping results.	GWAS, QTL	Variants, Genes	2021	Y	Y	https://www.opentargets.org/genetics-portal	(Carvalho-Silva et al. 2019)
Simple ClinVar	Multiple	Variant annotations including clinical relevance, deleteriousness, and phenotype associations.	GWAS	Variants, Genes, Phenotypes	2021	Y	N	http://simple-clinvar.broadinstitute.org	(Pérez-Palma et al. 2019)
UK Biobank	Multiple	Repository genotyping, imaging, and whole-genome sequencing of deeply phenotyped individuals.	GWAS	Variants, Genes, Phenotypes	2021	Y	Y	http://www.nealelab.is/uk-biobank	(Bycroft et al. 2018)
UK Biobank Correlation	Multiple	Pairwise genetic correlations across all UK Biobank phenotypes.	Phenotype correlations	Phenotypes	2019	Y	N	https://ukbb-rg.hail.is	(Bycroft et al., 2018)
ONTIME	Multiple	Online Neurodegenerative Trait Integrative Multi-Omics Explorer (ONTIME).	GWASQTLProteomi	VariantsGenes	2020	Y	N	https://ontime.wustl.edu/	(Yang et al., 2021)
PheWeb	Multiple	A tool to build a website to browse hundreds or thousands of GWAS.	GWAS	VariantsPhenoty	2021	Y	Y	https://github.com/statgen/pheweb	(Gagliano Taliun et al., 2020)

Datasets, tools, and other resources relevant to Parkinson's Disease multi-omics research.

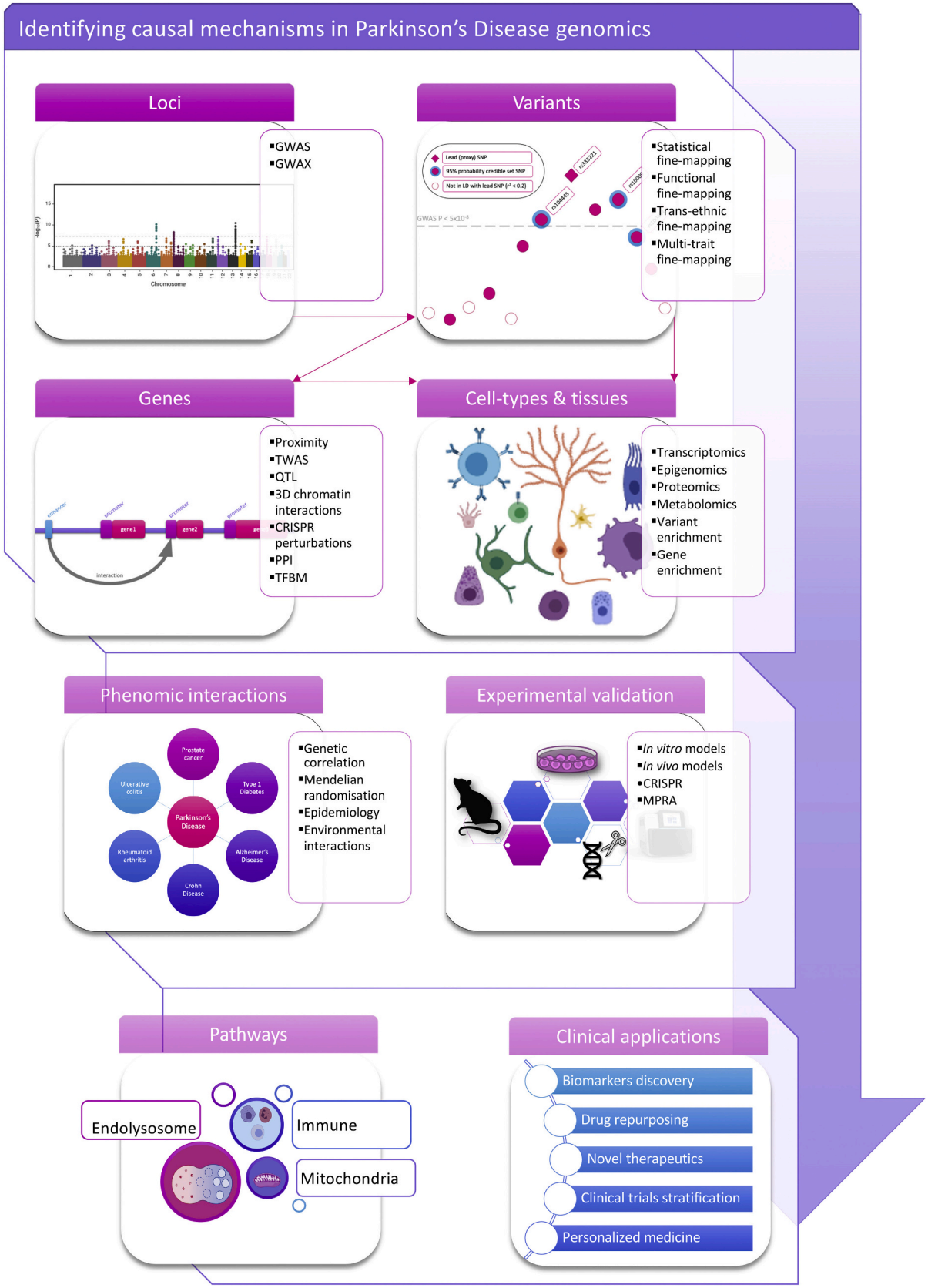

Fig. 1. Common workflows in the investigation of PD.
Generalized workflow of PD genomics research, from GWAS to validated functional mechanisms. A variation of GWAS is Genome-wide association Study by proXy (GWAX), in which relatives of disease-diagnosed individuals are used as genetic proxies for actual cases. We provide this as a summary of what has commonly been done to date, with the understanding that the development of novel, innovative approaches not described in this diagram will be vital to progressing neurodegenerative disease research.

estimated to be anywhere from 27-34% heritable based on twin studies (Goldman et al., 2019; Wirdefeldt et al., 2011), to 22–27% heritable based on genetic (SNP-based) studies (Blauwendraat et al., 2020; Chang et al., 2017; Keller et al., 2012). Despite large-scale multi-national efforts, presently known genetic factors can only explain 22–36% of PD risk heritability in populations of European descent (Nalls et al., 2019). Even the monogenic forms of PD do not have 100% penetrance and therefore are likely modified by genetic background as well as environmental interactions. In this review, we will focus primarily on the idiopathic form of PD.

A surge of advances in multi-omics technologies continue to accelerate our understanding of disease biology. In this review, our objective is not necessarily to enumerate all variants and genes that have been implicated in PD pathology (for these details, see: (Bandres-Ciga et al., 2020a, 2020b; Blauwendraat et al., 2020; Nalls et al., 2019; Redenšek et al., 2018)). Instead, we will highlight methods of investigation across multiple scales of biology (variants, genes, pathways, cell-types, tissues, phenotypes), direct readers to studies, tools, and datasets relevant to PD -omics (Table 1), bring attention to conceptual challenges in the field while suggesting some potential avenues of progress. We have also compiled standardized cell-type and tissue enrichment results (Table S1) as well as genetic correlations between PD and other phenotypes (Table S2) across multiple studies of PD genomics. Through this, we hope to promote a more cohesive understanding of the complex biology of PD in the service of ultimately improving the lives of those afflicted by this disease. (See Fig. 1.)

2. Multi-scale omics: from genome to phenome

Genome-wide association studies (GWAS) have been an invaluable tool to investigate the molecular etiology underlying many complex phenotypes, including PD (Blauwendraat et al., 2020; Chang et al., 2017; Nalls et al., 2014, 2019; Parkinson's Disease Genomics, 2017). To date, there have been over 24 GWAS conducted in PD (Bandres-Ciga et al., 2020a, 2020b; Redenšek et al., 2018) since 2009 (Simon-Sanchez et al., 2009), identifying 78 PD risk-associated loci (Nalls et al., 2019). Of the known PD risk-associated variants identified through GWAS, the vast majority fall within presumed non-protein-coding regions (Nalls et al., 2019), posing both additional challenges and opportunities when identifying the genes, pathways, and cell-types via which they exert their effects. Disentangling these systems is complicated by non-independence at multiple biological scales (Table S3A). In addition, one must ultimately consider the developmental, life and/or disease stage at which a genetic risk factor exerts its effects relative to when the patient is being treated (Faa et al., 2014; Kovacs et al., 2014). Underlying all of these goals is the need to first distinguish causal from non-causal risk-associated variants. Thus, the mechanisms underlying known genetic factors are still far from fully understood (Ohnmacht et al., 2020).

2.1. Prioritizing putative causal variants

Fine-mapping is a class of statistical tools that aims to identify the causal variants underlying a given phenotype (Benner et al., 2017; Hutchinson et al., 2020; Schaid et al., 2018). Applying fine-mapping to identify candidate causal variants within a given GWAS locus is essential as it cannot be assumed that the lead SNP (the one with the smallest *p*-value) is causal for the phenotype (e.g. PD) due to widespread linkage disequilibrium (LD) (Broekema et al., 2020; Pasaniuc and Price, 2017; Pritchard and Przeworski, 2001). This problem is further exacerbated by the fact that most GWAS are performed using low-coverage genotyping arrays, meaning the majority of SNP-level effects are imputed from haplotype or whole-genome sequencing reference panels (Shi et al. 2018). Depending on the method, fine-mapping requires either raw genomic sequences or GWAS summary statistics, and may utilize genome-wide functional annotations (e.g. to compute SNP-wise prior probabilities) (Farh et al., 2015; Kichaev et al., 2017; Weissbrod et al., 2020). Parsing out the causal PD risk-associated SNPs from non-causal correlates is an essential step that can dramatically alter the validity of many downstream analyses which rely upon the identification of the causal sequence motifs. Statistical fine-mapping (without functional annotation input) using FINEMAP (Benner et al., 2016) was recently performed on all loci from the latest PD GWAS summary statistics (Grenn et al., 2020). Additional efforts have been made to statistically fine-map GWAS across many different phenotypes, including PD, via the Open Targets Data Portal (Carvalho-Silva et al., 2019). In a study by our group (Schilder and Raj, 2021), we employed a multi-tool consensus fine-mapping approach (Schilder et al., 2021), which included functional fine-mapping of 74/78 known PD GWAS loci using PolyFun (Weissbrod et al., 2020) and cell-type-specific epigenomic variant-annotations, to reduce the average number of putative causal SNPs from 85 to 3 per locus. While the lead SNPs were indeed within the 95% probability union credible set (nominated by at least one tool) for 69/74 (93.2%) loci, they were in the consensus SNP set (nominated by at least two tools) in only 29/74 (39.2%) of loci. This emphasizes the need for robust fine-mapping to disambiguate causal variants from their close correlates. Two specific examples of consensus fine-mapped SNPs from this study include rs7294619 (LRRK2 locus), which was predicted to disrupt *LRRK2* expression via a *FCGR2A* TFBM in a microglia-specific enhancer, and rs4771268 (MBNL2 locus), which was predicted to disrupt an *MBNL2*-regulating enhancer in oligodendrocytes alone. Fine-mapping results and figures from all of these studies are freely available via their respective online data portals (Table 1).

In recent years, machine learning (ML) has been especially successful at computationally modeling the functional genome in a data-driven manner, thus improving the accuracy and precision of the functional impact of mutations (Avsec et al., 2019, 2021; Eraslan et al., 2019; Kelley et al., 2018; Zhou and Troyanskaya, 2015). Dey et al. (2020) have provided genome-wide predictions from multiple deep learning models (e.g. DeepSEA (Zhou and Troyanskaya, 2015), Basenji (Kelley et al., 2018), ExPecto (Zhou et al., 2018), and Enformer (Avsec et al., 2021)) for all possible genomic mutations through a process called *in silico* mutagenesis. These predictions are of particular relevance to PD (Schilder and Raj, 2021) as they were generated by models trained on blood- or brain-specific epigenomic/transcriptomic data. In an effort to facilitate research and minimize redundant efforts, we have compiled a table of existing resources relevant to PD (Table 1). We would like to note several particularly relevant and useful resources for making powerful ML tools accessible to non-experts, including GenoML (Makarious et al., 2021), Kipoi (Avsec et al., 2019), and Janggu (Kopp et al., 2020).

2.2. Prioritizing putative causal genes

There are several main approaches commonly used when inferring the genes that non-coding variants may regulate: 1) proximity (often based on transcription start site or gene body position), 2) quantitative trait loci (QTL) (Falconer, 1996; Kearsey, 1998), 3) Transcriptome-Wide Association Studies (TWAS) (Gamazon et al., 2015; Gusev et al., 2016), and 4) 3D chromatin interactions (Bhattacharyya et al., 2019; Fulco et al., 2019; Juric et al., 2019; Nasser et al., 2021; Sey et al., 2020). Many investigations of PD have used Multi-marker Analysis of GenoMic Annotation (MAGMA), which largely relies on a proximity-based strategy with some correction of LD effects (de Leeuw et al., 2015). However, disease-associated SNPs frequently regulate the gene (or genes) that are not the one closest to the lead (or even causal) SNP (Fulco et al., 2019; Garrido-Martín et al., 2021; Mumbach et al., 2017; Nasser et al., 2021). Thus proximity alone is not necessarily a reliable proxy for variant-gene interactions. Identifying causal genes in GWAS loci is especially challenging as these regions tend to be gene-dense. In the case of PD, there are 305 genes within the 78 known risk loci (±1 Mb from the lead SNPs) (Nalls et al., 2019),

One approach to prioritize putative causal genes is to incorporate information from expression, splicing, protein or other forms of molecular QTLs. Early attempts searched for overlap between PD-associated SNPs from several GWAS (Lill et al., 2012) and QTLs in GTEx (Coetzee et al., 2016; Pierce and Coetzee, 2017a). However, as described above, LD confounds the accurate identification of causal SNPs in both GWAS and QTL studies. To identify colocalization of GWAS and eQTL associations, Raj et al. (2014a) applied Regulatory Trait Concordance (RTC) scores (Nica et al., 2010) in monocytes datasets to identify shared eQTL and PD GWAS signals in seven PD GWAS loci (including *LRRK2*, *BST1*, and *SNCA*). Others have used Bayesian colocalization tests (e.g. with the tool *coloc*) (Giambartolomei et al., 2014) to assess whether the genetic signals underlying GWAS and QTL in a particular genomic region are shared, thereby mitigating the confounding effects of LD. This has been applied to PD in multiple studies using partially overlapping QTL reference datasets (Li et al., 2019; Schilder and Raj, 2021). This is a much more robust approach than simply checking whether a specific genome-wide significant GWAS SNP is also a significant QTL hit (confusingly, also often referred to as "colocalization" when the term "overlap" would be more appropriate). More recently, as part of the Myeloid Cell Neurodegenerative disease (MyND) project, Navarro et al. (2021) observed that in 17 PD susceptibility loci, the PD risk variants are likely to modify disease susceptibility, at least in part, by modulating gene expression and/or splicing in peripheral monocytes. Another study by our group used the Microglia Genomic Atlas (MiGA), de Paiva Lopes et al. (2020) to demonstrate that 18 PD GWAS loci colocalize with microglia eQTLs, including *P2RY12*. *P2RY12* is highly expressed in microglia in comparison to other brain and myeloid cell types and has been shown to play a role in microglia migration and activation. Despite the utility of mRNA-based QTLs, transcript levels do not always correlate with protein levels of the same gene. Thus, there is additional value in conducting protein QTL (pQTLs) studies. A recent study identified hundreds of pQTL loci in cerebrospinal fluid (CSF; $n = 971$ donors), blood plasma ($n = 636$ donors), and brain ($n = 458$ donors) (Yang et al., 2021a), a subset of which were strongly colocalized with PD GWAS loci. This provided novel evidence for peripheral biomarkers and putative drug targets in PD, including the protein IDUA which degrades glycosaminoglycans within lysosomes. However, it should be cautioned that currently available proteomic assays can be heavily biased towards capturing certain types of associations (Sun et al., 2018), and tend to be lower throughput (hundreds to thousands of genes) than mRNA-based assays (thousands to tens-of-thousands of genes).

Mendelian Randomization (MR) is a statistical methodology used to infer the causal relationships between multiple genotype-phenotype association datasets (Yang et al., 2021b). Nalls et al. (2019) applied MR to PD GWAS loci, expression QTLs and methylation QTLs from multiple cell types and tissues to narrow the potential candidates to 150 genes. They found that one of the putative causal genes was the one nearest to the putative causal SNP in 53/70 (76%) of PD GWAS loci. However, most loci contained multiple putative causal genes according to this approach. More extensive gene nomination was later performed using MR on fine-mapped GWAS loci and blood/brain eQTLs, in combination with a literature-based gene scoring strategy (Grenn et al., 2020).

Another approach to prioritize causal genes in GWAS loci is to directly test for association between a disease and gene expression. However, such a study design is currently not practical as it requires profiling gene expression across hundreds of thousands of individuals in cases and controls. An alternative approach is to perform TWAS, which leverages information from separate GWAS and eQTL datasets to impute (or predict) the gene expression of cases and controls, thus recovering disease-gene associations without directly profiling gene expression in every individual (Gamazon et al., 2015; Gusev et al., 2016). TWAS have been performed on a number of neurological disorders, incorporating a variety of source tissues and cell types (Gusev et al., 2018; Raj et al., 2018). With respect to PD, Li et al. (2019) performed TWAS using bulk transcriptomes across multiple tissues from GTEx (GTEx Consortium, 2015; Pers et al., 2015), as well as prefrontal cortex (Fromer et al., 2016), and immune cells (Fairfax et al., 2014; Heng et al., 2008; Raj et al., 2014a; Rotival et al., 2011) to nominate 66 PD-related genes, as well as specific transcripts. It was shown that transcript isoforms can have more tissue- and cell-type-specific effects via alternative splicing. Later, Kia et al. (2021) repeated a subset of these analyses with eQTL data from GTEx V7 and UK Brain Expression Consortium Braineac eQTL dataset ($n = 134$ individuals) (Ramasamy et al., 2014; Trabzuni et al., 2011, 2013), as well as novel Methylation-wide Association Study (MWAS) (Gusev et al., 2016) data from PD donors (Daniel and Lees, 1993). An extension of TWAS that incorporates epigenomic information to improve predictions (ETWAS) (Yao et al., 2021a) was recently applied to PD GWAS in combination with GTEx V8 brain tissue eQTLs to implicate an additional 18 genes in the disease, such as *LRRC37A2* and *ZSWIM7* (Yao et al., 2021b). Perplexingly, SN was not amongst the significantly enriched brain tissues ($p = 0.067$) in this study, though this could be related to insufficient sample sizes in GTEx. Furthermore, none of the above TWAS utilized the full, most recent PD GWAS (Nalls et al., 2019) which includes additional privacy-protected data from 23andMe. We also note that there are inherent limitations to these gene prioritization methods. TWAS (as well as colocalization and MR-based methods) are prone to gene co-regulation bias, where the total expression of the causal gene correlates with another gene, which can lead to a false-positive associations (see Wainberg et al. (2019) for further discussion). Gene expression-based methods more generally struggle to distinguish gene dysregulation that causes illness from that which is an unrelated consequence of (or an adaptive response to) disease risk genetics (Hu et al., 2018; Liu and Montgomery, 2020; Porcu et al., 2021) (see Table S3.A).

Lastly, 3D genomic information, usually in the form of chromatin interaction maps, can be utilized to infer SNP-gene relationships, using Chromosome Conformation Capture coupled with sequencing (HiC) maps (Lieberman-Aiden et al., 2009) (e.g. H-MAGMA) (Sey et al., 2020), HiChIP (Mumbach et al., 2016) and/or Proximity Ligation-Assisted ChIP-seq (PLAC-seq) (Fang et al., 2016; Park, 2009) (e.g. Model-based Analysis of PLAC-seq (MAPS) (Juric et al., 2019; Nott et al., 2019; Schilder and Raj, 2021) and FitHiChIP (Bhattacharyya et al., 2019; Corces et al., 2020)), and Activity-by-Contact (ABC) maps from CRISPRi-FlowFISH (Fulco et al., 2019; Nasser et al., 2021). The availability of large-scale, harmonized databases like EpiMap (Boix et al., 2021) will permit researchers to fully utilize these tools. This approach is promising due to its strong basis in mechanistic understanding of genome regulation and direct experimental measurement, but is currently limited by the fact that chromatin interaction maps differ across cell-types, which are difficult to disentangle from bulk data alone.

Nevertheless, even these more sophisticated methods can be subject to false positive associations and are highly dependent on the availability and selection of QTL/epigenomic datasets in relevant tissues and cell-types. Varying sample sizes can also falsely make more well-powered datasets (e.g. eQTLs in blood) appear to contain causal associations with disease GWAS (Grenn et al., 2020; Pierce and Coetzee, 2017b). Furthermore, most studies have only considered *cis*-QTLs due to the multiple testing burden intrinsic to *trans*-QTL studies, though some recent advances have been made to reduce this burden through tensor decomposition (Ramdhani et al., 2020). Therefore, care and expertise are required when attempting to integrate GWAS and QTL data for SNP or gene prioritization. The development of new technologies and the generation of new datasets that resolve chromatin interaction maps at single-cell resolution will be invaluable moving forward.

2.3. Identifying pathogenic cell-types and tissues

In addition to DA neurons, a wide variety of cell-types has been implicated in the genetic etiology of PD. Nalls et al. (2019) tested for enrichment of PD GWAS-inferred genes across 88 brain cell-types in a

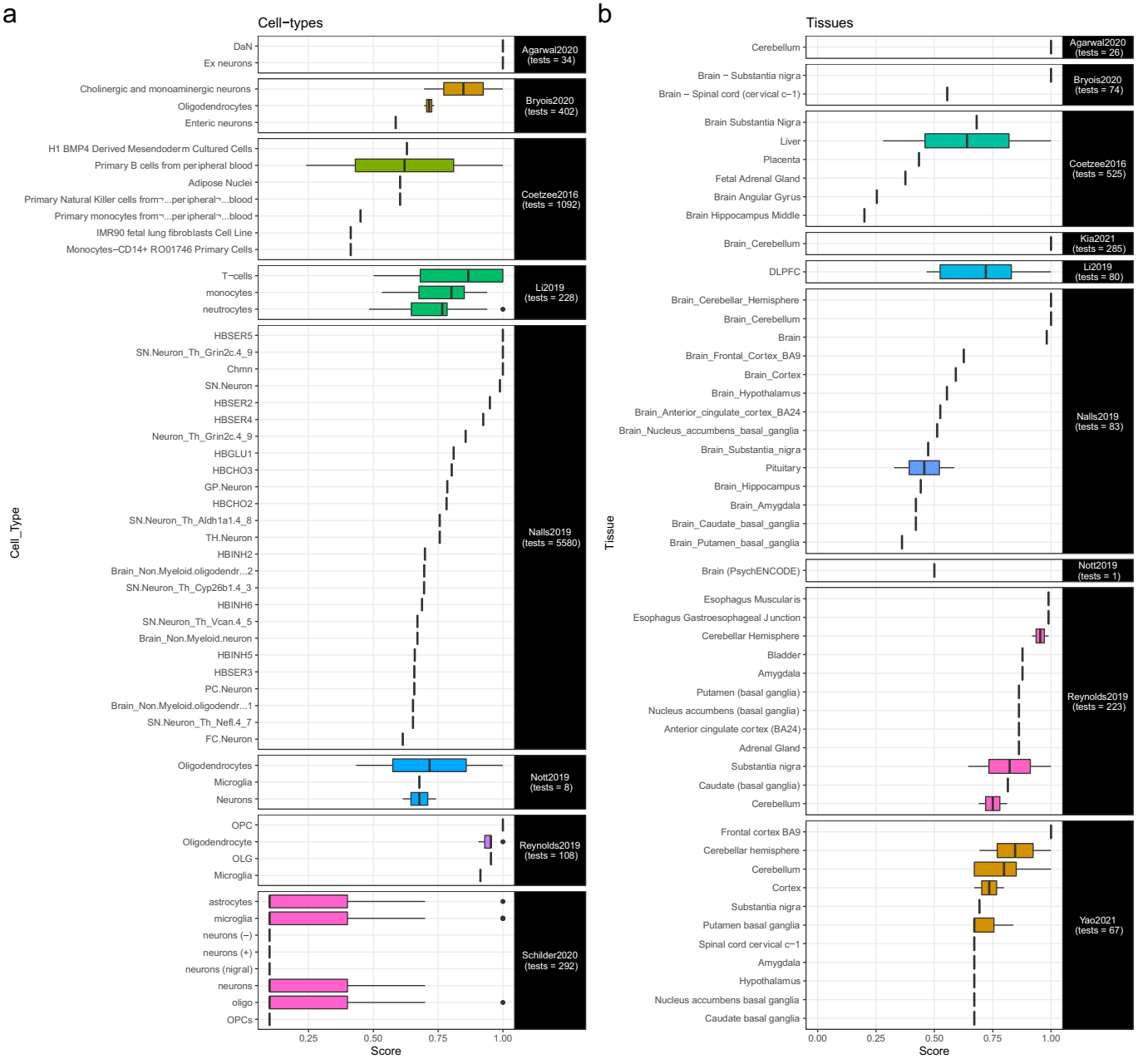

Fig. 2. Meta-analysis of cell-types and tissues enriched in PD GWAS.
Harmonized results of PD GWAS enrichment results at the level of (a) cell-type (a) and tissues (see Table S1 for full data). We derived "Scores" from -log10 normalised and rescaled false discovery rate (FDR) where available, or posterior probability (PP). Only up to the top 25 cell-types per study, and only the top 15 tissues per study, are shown to improve plot legibility.

mouse single-cell RNA-seq (scRNA-seq) reference. The strongest enrichment was in neurons of the SN, globus pallidus, thalamus, posterior cortex, frontal cortex, hippocampus, and entopeduncular nucleus. Similarly, others have also found enrichment for various neuronal subtypes including nigrostriatal DA neurons (using a human transcriptomic reference) (Agarwal et al., 2020) and their parent class monoaminergic neurons (using a mouse transcriptomic reference) (Bryois et al., 2020), cortical excitatory neurons, as well as cortical inhibitory neurons (Agarwal et al., 2020; Li et al., 2021). Other studies have implicated various glial cell-types, including oligodendrocytes (Agarwal et al., 2020; Nott et al., 2019), oligodendrocyte precursor cells (OPCs) of the SN (but not the cortex) (Agarwal et al., 2020), astrocytes (Kam et al., 2020), and microglia (Andersen et al., 2021; Badanjak et al., 2021; de Paiva Lopes et al., 2020; Ho, 2019; Kam et al., 2020). Genes that are differentially expressed across Braak stages in post-mortem PD brain samples (Dijkstra et al., 2015) were also enriched for transcriptional signatures of DA neurons and oligodendrocytes (Bryois et al., 2020). Interestingly, some evidence suggests that *LRRK2* is more highly expressed in nigral OPCs than any other cell-type in that region (Agarwal et al., 2020), though replication with more individuals is needed. One hypothesis regarding the role of microglia is that they serve to clear α-synuclein through phagocytosis (Ho, 2019; Poewe et al., 2017), though other studies could find no significant enrichment for microglia in PD GWAS (Agarwal et al., 2020; Reynolds et al., 2019). Additional candidate cell-types within the peripheral immune system have also been proposed, including lymphocytes (Coetzee et al., 2016), T-cells (Garretti et al., 2019), monocytes (Navarro et al., 2021; Raj et al., 2014a) and macrophages (Navarro et al., 2021). Some studies have even

implicated enteric neurons (Bryois et al., 2020), mesoderm, liver and fat cells (Coetzee et al., 2016). Lastly, some have found a lack of genome-wide PD heritability enrichment for any particular cell-type, suggesting the mechanism was at the level of cell-type-agnostic processes such as lysosomal function (Reynolds et al., 2019). This is despite the fact that they did indeed find cell-type-specific enrichment for schizophrenia heritability, and used a highly similar methodology to another study that found enrichment for several tissues and cell-types in PD heritability (Bryois et al., 2020). Similarly, others have found no genome-wide enrichment of cell-type-specific epigenomic signatures in PD GWAS after multiple testing corrections across multiple phenotypes (Nott et al., 2019).

We have compiled and harmonized cell-type/tissue enrichment results across multiple investigations of PD GWAS (Table S1) (Bryois et al., 2020; Corces et al., 2020; Kia et al., 2021; Li et al., 2019; Nalls et al., 2019; Reynolds et al., 2019; Schilder and Raj, 2021; Yao et al., 2021b), and visualized the heterogeneity of these findings (Fig. 2). The source of these seemingly inconsistent genetic enrichment results could be both biological and methodological in origin. In particular, differing genetic enrichment tool types, versions and parameters can capture different aspects of the PD etiology and thus have dramatic impacts on conclusions, e.g.; genome-wide LD SCore regression (LDSC) (Finucane et al., 2015), or gene-level enrichment using MAGMA and Expression Weighted Cell-type Enrichment (EWCE) (Bryois et al., 2020; Skene and Grant, 2016). We elaborate on these non-mutually exclusive possibilities in Table S3C-D. Another important distinction to make is between studies that use cell-type references derived from a small number of individuals or animals (e.g. (Agarwal et al., 2020; Corces et al., 2020; Nott et al., 2019; Reynolds et al., 2019; Schilder and Raj, 2021)) and those that use population-scale cell-type references (de Paiva Lopes et al., 2020; Navarro et al., 2021; Young et al., 2021).

Rather than testing for enrichment of particular cell-types genome-wide, a complementary approach is to systematically investigate locus-specific mechanisms. Similar to some prior studies (Nott et al., 2019;

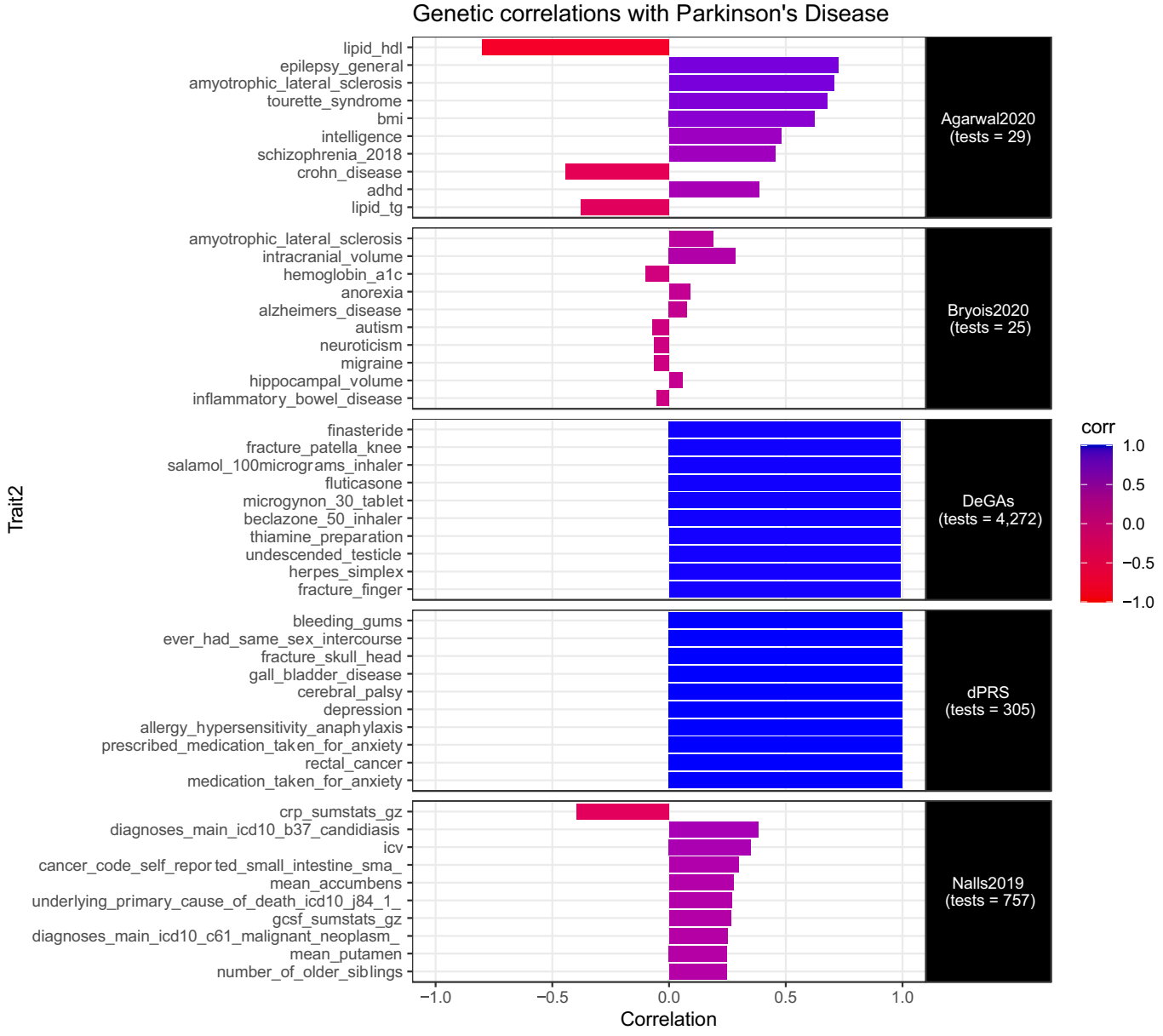

Fig. 3. Meta-analysis of genetic correlations between PD and other traits.
Pairwise genetic correlations between PD traits aggregate across multiple studies. Per study, only the top 10 traits with the greatest absolute genetic correlation values are shown to improve plot legibility. Note that differing methodologies were used in each study to compute trait-trait correlations.

Reynolds et al., 2019), Corces et al. (2020) found no genome-wide enrichment for any major brain cell-type or neuronal cell-subtype based on chromatin accessibility peaks in PD, despite finding enrichment for other brain-related phenotypes (e.g. schizophrenia). In contrast, when they systematically interrogated each PD GWAS locus using cell-type-specific epigenomics (scATAC-seq) and interactomics (HiChIP and PLAC-seq), they were able to identify putatively causal mechanisms. For example, within the ITIH1 PD locus they identified a fine-mapped SNP (rs18139313) whose PD-associated allele falls within a *KLF4* transcription factor binding motif (TFBM), and interacts with the transcription start site (TSS) of the gene *STAB1* exclusively in microglia. Prior to this, there was no known mechanism by which this locus influenced PD risk. Using a similar per-locus approach, Schilder and Raj (2021) found that fine-mapped consensus SNPs fell within a single cell-type (neurons, astrocytes, oligodendrocytes or microglia) in only 14/74 loci (19%), two cell-types in 12 loci (16%), three cell-types in 10 loci (14%), and all four cell-types in 9 loci (12%). Fine-mapped PD-associated SNPs most frequently fell within microglia peaks, followed by neurons (including nigral neurons) and then oligodendrocytes/oligodendrocyte precursor cells. Of course, the per-locus approach comes with its own set of drawbacks (e.g. availability of multi-omics data in the relevant cell-types) and should be considered complementary to genome-wide enrichment strategies.

Very recently, single-cell and single-nuclei datasets from PD patient samples have begun to emerge, as opposed to the majority of existing datasets which come from mice or humans without PD. Early results indicate that microglia, astrocytes and oligodendrocytes are differentially activated relative to patients with multiple systems atrophy (MSA) and/or controls (Pande et al., 2021; Teeple et al., 2021). Remarkably, these genes were enriched for PD GWAS genes. MSA is sometimes used as a comparator to determine whether the observed effects are specific to PD or more broadly indicative of neurodegenerative disease. However, comparing PD to MSA alone has limited utility as MSA shares some of the same underlying pathology (e.g. synucleinopathy) and is by no means representative of the full spectrum of neurodegenerative diseases. Therefore, a more systematic comparison across many different neurodegenerative diseases (with varying degrees of shared pathology) would be more informative. Single-nucleus datasets from non-PD post-mortem brain samples are also valuable resources to indirectly explore PD-related questions, including some done in SN (n = 5 individuals) (Agarwal et al., 2020), midbrain DA neurons (Kamath et al., 2021), frontal cortex (Langston et al., 2021b), developing human brain (Bocchi et al., 2021; Cao et al., 2020; Domcke et al., 2020). Bulk cell-type purified RNA-seq in peripheral monocytes (n = 230 individuals) (Navarro et al., 2021) and microglia (n = 55 PD individuals) (de Paiva Lopes et al., 2020) from PD patients has revealed increased expression of mitochondrial related pathways relative to age-matched controls. Currently there is a lack of population-scale datasets in SN or striatum that are sufficiently well-powered to reliably perform analyses such as QTL, much less in cohorts of PD patients. Existing post-mortem studies from SN all have 16 or fewer PD cases (Lesnick et al., 2007; Moran et al., 2006). These datasets allow for comparisons of cell-type-specific signatures, opening up new possibilities for more deeply understanding the cell-type-specific mechanisms underlying PD. Efforts to gather population-scale single-cell QTL datasets are currently underway (van der Wijst et al., 2020). Additionally, the reduced capacity for single-nucleus data (relative to single-cell data) to capture cell-subtype and disease state-associated transcriptional signatures must be taken into account (Thrupp et al. 2020; Skene and Grant, 2016).

2.4. Considering the phenome

PD in the absence of any other illness is exceedingly rare given the age demographic of patients and the ubiquity of pleiotropy (Li et al., 2017). Therefore, there is a strong impetus to conceptualize human health as a continuous multi-dimensional spectrum. Indeed, within-patient clinical presentations of PD can evolve over time depending on life stage, comorbidities, medications and environmental exposures. Thus, it can be useful to think of PD not as a singular diagnosis, but as a constellation of sub-traits (e.g. symptoms) that can each be linked to specific genetic and cellular mechanisms. Methods designed to explore phenome-wide interactions include epidemiological comorbidity observations, genetic correlation using heritability estimates, fine-mapped causal variant overlap, MR, dimensionality reduction (Tanigawa et al., 2019), and multi-trait Polygenic Risk Scores (PRS) (Aguirre et al., 2021). Indeed, a study of 17 autoimmune diseases GWAS revealed extensive genetic sharing (i.e. pleiotropy) between these conditions and PD, providing a causal mechanism underlying the longstanding observation of comorbidity between these conditions (Witoelar et al., 2017). The possibility of large-scale multi-phenotype studies has become increasingly feasible with the advent of databases such as the OpenGWAS (Elsworth et al., 2020) and the Global Biobank Engine (McInnes et al., 2019), as well GWAS summary statistics standardisation pipelines like MungeSumstats (Murphy et al., 2021).

In Table S2, we provide genetic correlations between PD and many other phenotypes compiled across multiple studies and databases (Agarwal et al., 2020; Aguirre et al., 2021; Bryois et al., 2020; Nalls et al., 2019; Tanigawa et al., 2019), allowing for the re-analysis of previously reported relationships and the discovery of novel ones. As illustrated in Fig. 3., there is substantial heterogeneity in the types of traits that correlate with PD. As might be expected, PD has shared genetic architecture with other neurodegenerative diseases (e.g. Amyotrophic Lateral Sclerosis (ALS), AD) and neurological disorders (e.g. epilepsy, depression, anxiety disorders). However, there are equally strong (or stronger) correlations with somewhat less intuitively related traits, such as cholesterol levels, which are nevertheless recapitulated in epidemiological studies (Huang et al., 2007; Scigliano et al., 2006) and could represent opportunities for biomarker discovery and drug repurposing. PD also has a complex relationship with risk for bone fractures (e.g. fracture_patella_knee, fracture_finger, fracture_skull_head) which may be the result of pleiotropic genetics affecting skeletal and nervous systems, pharmacological side effects, secondary consequences of having a motor disorder, or some combination of these factors (Torsney et al., 2014; Yao et al., 2021b).

2.5. Biological pathways

GWAS and multi-omics approaches have been invaluable for the discovery of causal variants, genes, and cell types underlying PD. However, merging these findings into a cohesive, mechanistic understanding of the pathways they are part of is especially challenging. Protein-Protein-Interaction (PPI) (Pintacuda et al., 2021) and multimodal (Bandres-Ciga et al., 2020a, 2020b; Boix et al., 2021; Greene et al., 2015; Kia et al., 2021; Liu et al., 2020; Wang et al., 2019; Wong et al., 2018) networks have often been used to link these components. However, these approaches often suffer from an over-saturation of interactions that obscure relevant signals, as well as limited actionability. Here, we highlight several pathways with some of the strongest evidence for their role in the pathogenesis of PD: endolysosomal/protein degradation, immune, and mitochondrial.

2.5.1. Endolysosomal pathway and protein degradation

Endolysosomal pathways encompass a number of processes essential for cell homeostasis. Lysosomes degrade structurally diverse substances, not only proteins but also nucleic acids, lipids, helped by the acidic environment inside these organelles mainly driven by the V-ATPase proton pump and the presence of a number of proteases which are active at acidic pH. Lysosomes receive cargo from autophagic and endocytic pathways, which deliver substrates from either intracellular or extracellular compartments, respectively. Both processes require the formation, transport and fusion of vesicles, with extensive crosstalk and shared mechanisms (Birgisdottir and Johansen, 2020). Of direct

relevance to PD, the intracellular homeostasis of α-synuclein is maintained by the actions of the ubiquitin–proteasome system and the Lysosomal Autophagy System (LAS).

The discovery of roles for *LRRK2* in vesicular trafficking and *GBA* in lysosomal function, in addition to the fact that a number of monogenic forms of PD affect autophagy genes, implicate this pathway in the pathogenesis of the disease. Moreover, several independent approaches have demonstrated that this pathway is also enriched for genetic risk in idiopathic forms of PD. Driven by the fact that *GBA* mutations can also cause Gaucher disease, a lysosomal storage disorder (LSD), Robak et al. showed an increased prevalence of damaging LSD-associated variants in PD participants relative to controls (n = 2,835 individuals) Robak et al. (2017). Applying PRS to 252 endosomal membrane trafficking pathway genes showed their cumulative contribution to PD (Bandres-Ciga et al., 2019). In a broader investigation of pathway enrichment in PD, the vesicle transport pathway was significantly associated with PD risk genetics (Bandres-Ciga et al., 2020a, 2020b). Others have used single-cell RNA-seq from cortical and SN samples in PD donors to reconstruct cell-cell interactions and implicate the proteasome, autophagy, endocytosis and vesicle-mediated pathway (Agarwal et al., 2020). Moreover, transcriptomics of human fresh microglia and monocytes from idiopathic cases of PD showed a downregulation of proteo-lysosomal genes (Navarro et al., 2021).

2.5.2. Mitochondria

Dysfunctional mitochondrial activity has a well-established role in the pathology of PD (Poewe et al., 2017). Evidence for this primarily comes from observations in environmentally induced mitochondrial blockades (Williams, 1984), and histopathological investigations of mitochondrial complex I disruption in postmortem brains of patients with idiopathic PD (Mizuno et al., 1989; Schapira et al., 1990). That said, mitochondrial dysfunction is also a major pathway altered in monogenic forms of PD, specifically those associated with *PRKN/PINK1* missense mutations (Padmanabhan et al., 2019; Pickrell and Youle, 2015). Yet the putative role of common PD-associated variants in mitochondrial pathways has been more difficult to define. Interestingly, researchers calculated a mitochondrial PRS and demonstrated that common variants within mitochondrial pathway genes are associated with PD disease status (Billingsley et al., 2019). In an independent line of evidence, PD susceptibility variants within mitochondrial pathway genes were identified using Whole-Genome Sequencing (WGS) and subsequently confirmed using functional validation experiments (Jansen et al., 2017). In a transcriptomic characterization of human myeloid cells in PD, we showed how there is a significant dysregulation in genes associated to oxidative phosphorylation, even though the directionality of the effect seems to be flipped in monocytes *vs* . microglia/macrophages (Navarro et al., 2021). Other authors have also shown mitochondrial alterations in human-derived cells (Annesley et al., 2016; Mortiboys et al., 2010; Teves et al., 2017). Thus, mitochondrial pathways play a role in PD etiology at multiple layers.

Finally, it is worth mentioning that the mitochondrial pathway is not independent of other pathways implicated in PD. For example, the autophago-lysosomal pathway is necessary to remove damaged mitochondria, and its dysfunction increases the accumulation of aberrant organelles which contributes to pathology. This can lead to deleterious feedback loops between lysosomes and mitochondria (Park et al., 2018).

2.5.3. Immune system

Beyond the neuronal component, immune cells have also been associated with the development of PD through the identification of several common genetic variants within genes related to immune response (e.g. *LRRK2*, *TNF*, *HLA-DRB5*) (Chu et al., 2012; Hamza et al., 2010; Paisán-Ruíz et al., 2004; Zimprich et al., 2004). Additional evidence suggests PD heritability enrichments for epigenomic marks (including DNase I hypersensitive sites, histone modifications, and TFBM) in both adaptive and innate immune cells (Gagliano et al., 2016). A number of PD-associated genes are preferentially expressed in microglia (Gosselin et al., 2017). Raj et al. (2014b) demonstrated that monocyte eQTLs are enriched for PD GWAS signal, suggesting a functional role of the innate immune system in the development of PD. Additionally, a TWAS of PD found 29 loci mediated through either mRNA expression or splicing in monocytes to be associated with PD, including both *LRRK2* and *SNCA* (Li et al., 2019). Studies performed in human-derived monocytes have shown increased reactivity, metabolic alterations and increased levels of *LRRK2* (Cook et al., 2017; Grozdanov et al., 2014, 2019; Schlachetzki et al., 2018; Smith et al., 2018). A population-based dataset of freshly isolated monocytes from idiopathic cases of PD showed profound dysfunction in the peripheral immune system, further solidifying the pivotal role of these cell-types (Navarro et al., 2021).

In addition to myeloid cells, recent findings have also implicated the adaptive immune system in causal PD pathology. In particular, there is evidence of T-cell infiltration in postmortem PD brains (Brochard et al., 2009) and α-synuclein driving cytotoxic responses in T-cells. A recent study suggests that CD8+ T-cell infiltration is an early pathogenic event that precedes α-synuclein aggregation and DA neuronal loss (Galiano-Landeira et al., 2020). More specifically, Gate and collaborators showed CD4+ T-cells are in the surroundings of Lewy bodies and DA neurons (Gate et al., 2021). Larger datasets of derived from PD patients are needed to further elucidate the role of T-cells and their subtypes (e.g. CD4+ *vs.* CD8+) in PD etiology.

The inflammatory component in PD has been corroborated through multiple observations in humans, including the presence of reactive microglia in post-mortem brains (Banati et al., 1998; Imamura et al., 2003; McGeer et al., 1988; Mirza et al., 2000), increased cytokine levels in plasma (Dobbs et al., 1999; Rentzos et al., 2007; Stypuła et al., 1996) and CSF (Mogi et al., 1994, 1995), as well as microgliosis investigated using Positron Emission Tomography (PET) imaging (Gerhard et al., 2006). All these findings support the hypothesis that microglia (resident immune cells in the central nervous system) as well as peripheral monocytes and macrophages play a causal role in the development of this disease (Kannarkat et al., 2013; Tansey and Romero-Ramos, 2018). Together, these studies are beginning to provide a mechanistic understanding of the frequently observed comorbidity between PD and immune disorders (Arai et al., 2006; Li et al., 2012; McGeer and McGeer, 2004; Phani et al., 2012; Witoelar et al., 2017).

3. Experimental validation

Although analysis of human samples is useful for hypothesis generation, validating causal relationships between proposed mechanisms and disease risk/progression requires a degree of experimental control that would be logistically infeasible (e.g. sample collection and processing) and/or unethical in human patients (e.g. untested drug screens or genetic perturbations). As PD susceptibility appears to be a human-specific trait (Garcia-Ruiz and Espay, 2017), animal models that can reliably recapitulate key features of PD are currently lacking (Potashkin et al., 2010). Thus, new experimental tools are needed to validate and further understand the functional consequences of PD-associated variants. Here we review some of the most prominent experimental *in vitro* methodologies and results that have been used to validate PD GWAS-nominated risk factors. For reviews of animal models in PD research, please see the following: (Jagmag et al., 2015). While there is a much more extensive literature on validation of rare PD risk factors (Poewe et al., 2017), we primarily focus on methods and results pertaining to common PD risk variants and the exciting opportunities that lay ahead in this area.

3.1. In vitro modeling

High-throughput technologies are emerging to validate disease-associated variants and understand their functional consequences.

Induced pluripotent stem cells (iPSCs) can be generated from patient tissue samples and thereafter differentiated into a variety of cell-types (Takahashi and Yamanaka, 2006), opening up a wide range of possibilities fo PD research (Coccia and Ahfeldt, 2021). One major advantage of patient-derived iPSCs over animal models is that they are able to capture the genome-wide complexity of human disease genetics, as opposed to one or several artificially-introduced genetic perturbations amidst a non-human genomic background. Thus, iPSC-derived DA neurons from PD patients can be compared to those of healthy, matched controls (Soldner et al., 2009). Taking this approach, several studies have shown that patient-derived DA-neurons recapitulate pathogenic events such as loss of dendritic arborization and autophagy defects (Sánchez-Danés et al., 2012), epigenomic dysregulation (Fernández-Santiago et al., 2015), microRNA and piRNA alterations (Schulze et al., 2018; Tolosa et al., 2018) and hypermethylation of regulatory regions (Fernández-Santiago et al., 2019). Another is to stratify iPSC-derived cells by PRS, as a way to move from genetic risk to phenotypic characterization.

However, increased genomic complexity and variation of models also mean that small, context-dependent effects are difficult to detect, especially when sample sizes are limited due to practical or budget constraints. A powerful complementary functional validation approach uses CRISPR-Cas9 (Adli, 2018; Cong et al., 2013) to induce targeted genetic editing of prioritized variants in isogenic human iPSC-derived cells, allowing researchers to directly observe the consequences of specific variants while keeping genetic background constant. Of especial help are new versions of CRISPR which use a dead-Cas9 and allow to either activate gene expression (CRISPRa) or repression (CRISPRi), rather than completely knocking out genes. Gene editing has been widely used to model rare monogenic PD mutations (Burbulla et al., 2017; Fong et al., 2013; Ryan et al., 2013; Soldner et al., 2011), but has far more rarely been applied to common PD variants. One of the earliest examples comes from Soldner et al. (2016), in which they targeted a common variant in a non-coding distal enhancer and demonstrated a significant effect on the expression of *SNCA*, one of the most consistent genetic risk genes in PD. Others have focused on common variants associated with *LRRK2* in iPSC-derived neurons (Marrone et al., 2018) and microglia (Langston et al., 2021a). We (de Paiva Lopes et al., 2020; Schilder and Raj, 2021) and others (Langston et al., 2021a) have demonstrated that microglia-specific regulatory regions that may modulate *LRRK2* expression, but Langston et al. (2021a) found no difference between protective and risk variants (for the lead GWAS SNP, rs76904798) using CRISPR-Cas9 editing in iPSC-derived microglia. However, it is plausible that the causal variant is one other than the lead SNP,such as rs7294619 which we nominated through consensus fine-mapping (Schilder and Raj, 2021).

Rather than focusing on one variant at a time, new technologies are being developed to perform combinatorial CRISPR-based genetic perturbation screens in iPSCs, permitting the exploration of both additive and interactive effects of multiple variants at once (Fernando et al., 2020). Even greater resolution can be achieved by combining these methods with single-cell RNA-seq, as in Perturb-seq (Dixit et al., 2016), allowing for the investigation of cell-specific effects of genetic modifications on gene expression. This approach has been applied to studies of transcriptional regulation unfolded protein response (Adamson et al., 2016), neuronal development (Alyagor et al., 2018) or autism risk genetics (Jin et al., 2020). In PD research, a knock-out CRISPR-Cas9 screen was developed to assess genetic regulators of the gene *PRKN* (Potting et al., 2018). Another example is PRISM (Perturbing Regulatory Interactions by Synthetic Modulators), a platform that edits random transcription factors (TFs) with CRISPR-Cas9 to assess transcriptional networks that protect against α-synuclein in yeast (Chen et al., 2017). Moving forward, these approaches are expanding to the use of CRISPRa (CRISPR activation), CRISPRi (CRISPR interference) and gene editing, and will help to disentangle the genetics of polygenic diseases such as PD. In this line, Tian and collaborators recently published genome-wide CRISPRi and CRISPRa screens in human-derived neurons, where they uncover molecular pathways related to lysosomal failure and oxidative stress, implicating the PD-related genes *FBXO7* and *PSAP* (Tian et al., 2021).

A complementary, unbiased approach for discovering and/or verifying disease-associated variants is the use of massively parallel reporter assays (MPRAs), which assess the functional impact of thousands of variants and sequences in parallel. This high-throughput technology has been used to study the "regulatory grammar" of genomic sequences and is extensively reviewed in the context of neuropsychiatric disorders elsewhere (Mulvey et al., 2021; Townsley et al., 2020). This approach permits comparisons of the activity in transfected *vs* . reference cells, allowing the identification of regulatory elements in a cell and context-specific manner. It has been applied to assess thousands of human polymorphisms with the identification of up to 842 variants which affect gene expression across different GWAS traits, including *STX4* regulation in PD (Tewhey et al., 2018).

Although iPSCs are an invaluable tool for studying disease mechanisms and expediting drug discovery, they have several key limitations at present. High variability (between cell lines and between laboratories), makes comparisons across research groups or studies extremely challenging. Therefore, improved experimental protocols, data harmonization, and *in silico* data integration will be pivotal moving forward. In addition, these experiments are expensive and labor intensive. Nor do they currently account for genetic and epigenetic changes acquired in culture that are missed by standard karyotyping screens (Hughes et al. 2007), the lack of maturation, or the fact that these cells are isolated in a dish as opposed to integrated into a living system. That said, organoids generated from stem cells may be better able to recapitulate certain aspects of human biology, such as the integration of multiple cell types in the same model, and self-organizing 3D structure. Of especial relevance, midbrain organoids may be able to better model the orchestrated behavior of multiple cell-types in PD pathogenesis (Galet et al., 2020; Kim et al., 2019; Smits et al., 2019). In addition, the iPSC Neurodegeneration Initiative (INDI) is planning to generate publicly accessible isogenic iPSC carrying PD-relevant mutations (Riley and Schekman, 2021), which will serve as an important resource for researchers and help to harmonize PD model results.

4. Future directions and conclusions

Various large-scale initiatives are currently underway to generate or add to multi-omics datasets for research into PD (Table 1). Some notable examples include the Parkinson's Progression Markers Initiative (PPMI) (Rosenthal et al., 2016), the Accelerating Medicine Partnership: Parkinson's Disease (AMP-PD) (Iwaki et al., 2020), the Foundational Data Initiative for Parkinson's Disease (FOUNDIN-PD) (Bressan et al., 2021), Aligning Science Across Parkinson (ASAP) (Schekman and Riley, 2019), and the Global Parkinson's Genetics Program (GP2) (The Global Parkinson's Genetics Program, 2021). The UK Biobank (UKB) is a more general resource containing genotyping data from 500,000 deeply phenotyped individuals (Bycroft et al., 2018), >200,000 of which now also have whole-genome sequencing data available. One of the main challenges moving forward is the lack of ethnic variation in previous PD genetic studies, as these were performed almost exclusively in individuals of European ancestry with limited translatability to other populations (Duncan et al., 2019). More recently, research initiatives have begun to address this by expanding PD genomics studies to more diverse populations (Loesch et al., 2021; The Global Parkinson's Genetics Program, 2021).

Similarly, more work is needed to conclusively resolve the causal cell-types underlying PD. Progress is being made by consortia such as the Human Cell Atlas (HCA) (Regev et al., 2017) and single-cell eQTLGen (van der Wijst et al., 2020). Furthermore, it should be noted that while identifying the cell-types that causally underlie a disease is undoubtedly an informative and worthwhile pursuit, these may not necessarily be the

ideal candidate cell-types to directly target with therapeutics. Additional factors that first need to be considered are the delivery method and the potential for off-target effects. To fully utilize such resources, we also need well-designed, programmatically-accessible, cloud-based architectures, improved data sharing standards and novel computational methods.

Lastly, we would like to emphasize that the approaches laid out here should be in no way construed as a comprehensive list of all the ways in which PD may be investigated. The various subfields of biomedicine are constantly evolving at a rapid pace, whilst producing data at a rate that lends itself to underutilization. Therefore, novel innovative experimental designs, computational tools, and conceptual frameworks in the years to come will be essential to tackle the formidable challenges that arise when dissecting the complexities of diseases such as PD.

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Data and code availability

All data and code used to produce the plots and meta-analyses described in this manuscript are publicly available via the dedicated GitHub repository:
https://github.com/RajLabMSSM/PD_omics_review

Declaration of Competing Interest

None.

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This work is dedicated to Robert Neil Cronin.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2021.105580.

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