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Identifying Genes in Parkinson's disease: State of the Art

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Abstract (max 100 words)

The movement disorder symptoms of Parkinson's disease (PD) was first described two centuries ago. Identification of mutations in genes such as *SNCA*, *LKRR2* and *GBA* in monogenic, familial forms of PD demonstrate that there is a genetic basis to the disease, yet most sporadic PD cases do not carry mutations in the those genes. Recent genome-wide association studies and next generation sequencing have identified multiple new genetic loci and variants associated with PD risk. These findings implicate new molecular mechanisms such as lysosomal function in PD pathogenesis, but also illustrate the genetic heterogeneity underlying PD and challenges that lie ahead.

Perspective

Parkinson's disease (PD) is a common neurodegenerative disorder which manifests as bradykinesia, movement rigidity and tremors in affected individuals. The understanding of the genetic basis of PD has been steadily increasing since the initial report of α -synuclein mutations two decades ago. Mutations implicated in familial PD fully account for monogenic inheritance in these families and point to potential functional mechanisms underlying PD (reviewed in ^{1,2}). However, most sporadic PD cannot be accounted for by known familial PD genes, with the late-onset nature of PD making further linkage studies challenging. Recent genome wide association studies (GWAS) and whole-genome sequencing (WES) have implicated a growing list of mutations and genes in PD, which are expected to provide new insights into potential pathways involved in PD pathogenicity.

The most recent GWAS and genome wide meta-analysis by Chang et al³ conducted across the largest cohort of PD patients and controls to date has identified 17 novel genome-wide significant risk loci, bringing the total number of PD-associated loci to 40^{4,5}. While this has improved confidence for PD risk prediction in pre-symptomatic individuals, the confidence level is still low and not suitable for clinical applications. Further genetic studies in larger patient cohorts is envisaged to uncover not just common variants with increasingly small effect sizes, but also increasingly rare variants that may have larger effect sizes that may in turn improve genetic risk prediction scores. Neuro-centric candidate genes at these 17 novel loci and pathway enrichment analysis confirmed the importance of lysosomal pathway regulation in PD, a pathway implicated in PD since *GBA* mutations were discovered in PD patients. Of note, Robak et al independently reported increased burden of non-synonymous and deleterious variants in lysosomal storage disorder genes in PD cases, even when the well-established *GBA* variants were disregarded⁶. The implication of lysosomal pathway genes in PD point towards lysosome involvement in α -synuclein degradation, supporting the use of current therapeutics which target lysosomal regulatory mechanisms to attenuate α -synuclein accumulation in PD patients.

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28 Since GWAS can only robustly assess common single nucleotide polymorphism, the discovery of
29 novel and rare PD variants requires genomic sequencing approaches such as WES. WES in Finnish⁷
30 and European⁸ population has identified a total of 33 novel candidate genes for early-onset PD. WES
31 by Siitonen et al in 185 Finnish PD patients and 440 controls⁷ uncovered three novel exome-wide
32 and statistically significant low penetrance PD candidate genes (*MPHOSPH10*, *SERPINA1*, *TAS2R19*).
33 Further confirmation in larger datasets is needed for these small effect size variants uncovered in
34 this low powered analysis. Another WES study by Jansen et al in 1148 European PD patients and 503
35 controls⁸ identified 27 high penetrance PD genes with rare recessive loss-of-function variants from
36 mostly single observations of homozygotes or compound heterozygotes, out of which 7 could be
37 replicated in an independent cohort. Potential functional role of variants were assessed via
38 mitochondrial morphology changes and α -synuclein-mediated toxicity after knockdown of selected
39 PD variant-harboursing genes, but exact functional implications in PD remain unclear. More genetic
40 evidence, such as replication in diverse populations, should be accrued before further effort is
41 placed into elucidating the precise PD-related functions of these candidate genes. While the
42 approach adopted by Jansen et al is feasible for preliminary functional validation of high penetrance
43 loss-of-function variants, alternative methods may be needed for low penetrance PD variants.

44

45 Studies conducting WES accompanied by linkage in families have continued to identify novel PD
46 candidate genes and mutations, such as *EIF4G1*⁹, *VPS35*¹⁰, *DNAJC13*¹¹ and more recently, *CHCHD*¹²
47 and *TMEM230*¹³. However, the implication of some of these genes in PD is still unclear and
48 sometimes contentious. For example, the implication of *TMEM230* in PD is currently being debated
49 with opposing findings from different groups^{14, 15}. Follow up studies in larger datasets after the initial
50 reports has refuted any major involvement of these genes in sporadic PD in both European and
51 Asian populations¹⁶. This example emphasised the need for replication and validation of newly
52 discovered genes and variants in large numbers of patients.

Overall, mutations and genes identified by WES in case-control studies and families appear to be extremely rare and account for a very small fraction of PD cases, thus highlighting the extreme genetic heterogeneity underlying PD. Furthermore, the identification of 22q11.2 deletions in sporadic PD cases¹⁷ and the report of early onset PD in a small fraction of deletion carriers¹⁸ add further to the phenotypic and genotypic complexity of the disease. Statistically, very large numbers of samples (n>10,000) will be needed to provide sufficient statistical power to confirm the involvement of each gene or variant in PD. Comprehensive network or pathway analyses will be needed to assess how seemingly diverse genes and mutations lead to a common disease outcome. It is also increasingly important to develop and validate *in vitro* and *in vivo* models of such variants identified by GWAS and exome or genome sequencing. Recent developments in derivation of midbrain organoids from human pluripotent stem cells¹⁹ and neuroepithelial stem cells²⁰ provide exciting prospects for modelling the effects of genetic variants *in vitro* as well as conducting compound screens for drug development.

All of the large genetic studies on PD so far were done in European populations. Examples of the PD G2019S risk variant in *LRRK2*²¹ which are rare or absent in the Asian population and the PD N370S/L444P risk variants in *GBA*²² which are enriched in Ashkenazi Jews has illustrated that disease risk variants may not be similarly implicated in PD across populations. As such, the validation of both common and rare risk variants across diverse populations is necessary. Variant discovery in non-European datasets are similarly important in unravelling the underlying genetic basis of PD across populations.

It is increasingly clear from the genetic findings of diverse PD risk factors among different populations as well as patient-specific mutations that PD is not a single disease with a single treatment approach. Instead, treatments should be tailored according to clinical and mutation/risk

variant profile and thus would require systematic precision medicine approach²³. There is also the dimension of pharmacogenetics to consider as drug metabolism in patients also impacts treatment strategy (reviewed in ²⁴).

It is important to note that the genetic findings mentioned thus far are germline variants that were detected in biological materials collected from non-invasive, non-pathogenic sites such as lymphocytes from peripheral blood. However, there is increasing awareness that somatic mutations that arise during development or accumulate with age^{25, 26} at the site of disease pathology^{27, 28} may also account for some sporadic cases of PD. These mutations are only detectable in post-mortem brain tissue and therefore are not useful for diagnostics or risk prediction, but could nevertheless point to potential novel pathways and “druggable” targets. Furthermore, current sequencing approaches to detect rare variants focuses on coding regions, and leaves out the detection of variants at non-coding regulatory regions. Future efforts should also be placed into deciphering the epigenetic landscape in PD^{29, 30} to enable a system-based approach to understand PD.

There are two major challenges in the quest to identify underlying genetic factors in PD to date, as alluded to above. First, large cohorts of PD patients and samples are required in future efforts to detect increasingly rare variants with potentially smaller effect sizes. Second, there is a lack of comprehensive patient clinical data to associate with genetic data. PD is extremely heterogeneous, and patient cohorts may encompass individuals with similar PD-associated symptoms but different underlying genetic basis, e.g. 22q11.2 deletions. Comprehensive clinical data will greatly aid to delineate patients for genetic analysis. Analysis of genetic association together with longitudinal patient clinical data is crucial for the dissection of differences in drug response and disease progression with respect to PD-associated variants.

In summary, the recent studies demonstrate an important step towards large PD patient collections for genetic studies. It is clear that genetic basis underlying PD is highly heterogeneous and potentially population-specific, thus there are limitations to the current approaches and a lot more remains to be discovered. The discovery of highly penetrant genetic variants will be increasingly important in genetic counselling of PD patients and family members as we accrue greater understanding of their mechanistic implications in PD. Potential PD treatment approaches explored currently, such as Ambroxol to reduce *GBA* variant-associated α -synuclein accumulation and small molecule inhibitors against *LRK2*, have been informed by genetic findings. Comprehensive analysis of PD genetic variants are expected to point us towards more drug targets for PD treatment and management. Thus, concerted efforts should be placed into the discovery of additional PD variants and replication of existing ones in large cohort sizes and across diverse populations with longitudinal follow-up, which is only possible through international collaborations and consortium work. Functional validation *in vitro* and *in vivo* will improve the capability to further mine the enormous amount of genomic data to correlate with phenotypic features that would define the future of genomic and precision medicine.

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