Pleiotropy and the Increasing Complexity of Parkinson's Disease Genetics

Parkinson's disease (PD) is a heterogeneous and complex genetic disorder.[1] More than 100 genes or genetic loci have been implicated, including alleles with variable penetrance that can manifest as either familial or sporadic forms. Most PD cases likely arise from the action of multiple risk genes, including both common and rare genetic variants, along with aging and possible environmental factors. Two recent studies from the *Annals of Neurology*,[2,3] Sun et al (August issue) and Dafsari et al (this issue), highlight the increasing complexity of PD genetics, establishing that the autophagy gene, *EPG5*—previously known to cause the rare recessive neurodevelopmental disorder, Vici syndrome[4,5]—also causes recessive PD/parkinsonism. This exemplifies pleiotropy, which occurs when a single gene can influence multiple traits. Interestingly, pleiotropy is not new to PD: before its discovery as a common PD genetic risk factor,[6] *GBA1* was long known to cause the lysosomal storage disorder, Gaucher disease.

The 2 new studies feature highly complementary study designs and their findings reinforce one another. Dafsari and colleagues pursued a gene-centric approach, comprehensively characterizing 211 proband cases with pathogenic *EPG5* variants from 147 families in Europe. This is the largest cohort of *EPG5*-related disorders assembled to date. On the other hand, Sun and colleagues examined several genetically heterogeneous Chinese PD cohorts, including both familial or sporadic PD cases. They pinpointed 7 cases of PD or atypical, juvenile-onset parkinsonism associated with compound heterozygous *EPG5* mutations. Together, the 2 studies reveal a remarkable genotype-phenotype relationship, whereby the specific clinical phenotype appears to relate in part to the severity of *EPG5* dysfunction, creating a continuum from (i) classical Vici syndrome (severe), to (ii) atypical parkinsonism (moderate), and (iii) typical PD (mild).

Complete or near-complete loss-of-function in *EPG5* causes Vici syndrome, a heterogeneous multisystem disorder, including agenesis of the corpus callosum, cataracts, hypopigmentation, cardiomyopathy, and immunodeficiency.[4] Dafsari and colleagues found that the majority of these cases were compound heterozygous (or homozygous) for truncating *EPG5* variants or had a truncating variant in combination with a missense variant. They further document an expanded clinical phenotype, including epilepsy, cognitive and motor delay, myopathy (with mitochondrial abnormalities on muscle biopsy), and a variety of movement disorders (eg, spasticity, parkinsonism, dystonia, and myoclonus). Whereas strong hypomorphic combinations of truncating alleles had a median survival of only 28 months, including many with prenatal or early infantile death, individuals with more modest *EPG5* loss-of-function due to homozygous or compound heterozygous missense variants, have substantially improved survival. In these latter cases, Dafsari et al describe a delayed presentation during adolescence with rapidly progressive atypical parkinsonism, along with dystonia and cognitive decline/dementia. Sun et al independently report 2 siblings having a similar clinical presentation from a family with presumed autosomal recessive juvenile-onset parkinsonism. Last, more mild *EPG5* partial loss-of-function appears to cause an attenuated clinical phenotype with adult-onset, apparently sporadic PD (age at onset = 20–51 years). The 5 cases described by Sun et al are consistent with typical PD, including asymmetric onset of parkinsonian signs, levodopa response, and non-motor symptoms (hyposmia, psychosis, and rapid eye movement sleep behavior disorder). A positive dopamine transporter scan (DaTSCAN) and anti-phospho-alpha-synuclein immuno-positive Lewy pathology in skin biopsies were also documented in selected cases.

EPG5 encodes a key regulator of lysosomal autophagy,[7] a cellular process that maintains protein homeostasis and organellar quality control. Consistent with this, Sun et al and Dafsari et al documented markers of defective autophagy in patient skin biopsies or derived fibroblasts. Both studies also examined mouse models harboring *Epg5* knockout or missense alleles, in which progressive autophagic failure is accompanied by substantia nigra dopaminergic neuronal loss and motor impairment. Importantly, many other genes that cause PD (*GBA1*, *LRRK2*, and *VPS35*) or atypical parkinsonism (*ATP13A2* and *VPS13C*) have been previously linked to lysosomal function and autophagy,[1] which is important for turnover of alpha-synuclein protein. In addition, several well-established causes of autosomal recessive juvenile-onset parkinsonism, including Parkin/*PARK2* and *PINK1*, are key regulators of mitophagy (mitochondrial autophagy). In the Dafsari et al study, patient-derived fibroblasts with *EPG5* mutations accumulated damaged mitochondria, likely due to defective PINK1-Parkin dependent mitophagy.

Whereas the Sun et al and Dafsari et al studies provide substantial evidence in support of the dose-dependent relationship between *EPG5* dysfunction and the resulting clinical phenotypes, overlap exists between the genotype–phenotype groups, making confirmatory studies important. Regardless, the findings are reminiscent of other pleomorphic risk loci for PD,[8] in which multiple alleles of varying severity and frequency affecting a single gene contribute to disease risk. For example, in the case of the *SNCA* gene, encoding alpha-synuclein protein, rare missense variants cause autosomal dominant Mendelian PD, with early-onset and more rapidly progressive disease, whereas common regulatory variants are associated with typical, late-onset sporadic PD.[1] In order to comprehensively understand the full spectrum of potential *EPG5* alleles contributing to PD, it will be important to interrogate much larger cohorts with greater ancestral diversity. Consistent with prior observations,[4] Dafsari and colleagues noted a number of PD cases among several families of Vici syndrome probands, suggesting the intriguing, albeit speculative possibility that heterozygous carriers of *EPG5* loss-of-function variants might harbor subclinical autophagic dysfunction that further declines with aging, leading to a modest, increased risk for later-onset, apparently sporadic PD. Indeed, a preliminary query of the Neurodegenerative Disease Knowledge Portal (including approximately 5,000 PD cases and 740,000 controls),[9,10] hints that deeper investigation is warranted, highlighting an approximately 3-fold increased PD risk among heterozygous carriers of rare *EPG5* truncating or missense variants (burden test p value $= 9.6 \times 10^{-4}$).

The discovery of *EPG5* adds to a growing number of pleiotropic genes linked to PD risk. Similar to *EPG5*, near complete loss-of-function in *GBA1* causes the lysosomal disorder, Gaucher, whereas partial loss-of-function increases risk for PD.[6] In addition, microdeletions at 22q11.2 cause PD, schizophrenia, or the neurodevelopmental disorder, DiGeorge syndrome.[11] Recently, *ITSN1* haploinsufficiency, which was previously linked to autism,[12] was shown to also increase PD risk by approximately 10-fold.[13,14] Interestingly, individuals with autism spectrum disorder may be at 3-fold increased risk to develop PD,[15,16] suggesting the possibility of additional shared heritability. Remarkably, each of these examples highlights genetic links between PD—a strongly age-influenced disorder with peak incidence in the 80s—to a broader phenotypic continuum that includes childhood neurodevelopmental disorders. Whether this intriguing pattern is unique to PD or may be generalizable to other neurodegenerative conditions remains to be determined. Thus far, these intriguing connections have been serendipitous discoveries, bridging disparate studies of exquisitely rare pediatric disorders, like Vici, and one of the most common movement disorders affecting older adults, PD. In the future, we might consider innovative, all-encompassing study designs to systematically dissect the potential impact of genetic variants across the life course.

Author contributions

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