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Abstracts

Articles appearing in the October 2020 issue

Genetic risk scores and hallucinations in patients with Parkinson disease

Objective We examine the hypothesized overlap of genetic architecture for Alzheimer disease (AD), schizophrenia (SZ), and Parkinson disease (PD) through the use of polygenic risk scores (PRSs) with the occurrence of hallucinations in PD.

Methods We used 2 population-based studies (ParkWest, Norway, and Parkinson's Environment and Gene, USA) providing us with 399 patients with PD with European ancestry and a PD diagnosis after age 55 years to assess the associations between 4 PRSs and hallucinations after 5 years of mean disease duration. Based on the existing genome-wide association study of other large consortia, 4 PRSs were created: one each using AD, SZ, and PD cohorts and another PRS for height, which served as a negative control.

Results A higher prevalence of hallucinations was observed with each SD increase of the AD-PRS (odds ratio [OR]: 1.37, 95% confidence interval [CI]: 1.03–1.83). This effect was mainly driven by *APOE* (OR: 1.92, 95% CI: 1.14–3.22). In addition, a suggestive decrease and increase, respectively, in hallucination prevalence were observed with the SZ-PRS and the PD-PRS (OR: 0.77, 95% CI: 0.59–1.01; and OR: 1.29, 95% CI: 0.95–1.76, respectively). No association was observed with the height PRS.

Conclusions These results suggest that mechanisms for hallucinations in PD may in part be driven by the same genetic architecture that leads to cognitive decline in AD, especially by *APOE*.

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Integrated sequencing and array comparative genomic hybridization in familial Parkinson disease

Objective To determine how single nucleotide variants (SNVs) and copy number variants (CNVs) contribute to molecular diagnosis in familial Parkinson disease (PD), we integrated exome sequencing (ES) and genome-wide array-based comparative genomic hybridization (aCGH) and further probed CNV structure to reveal mutational mechanisms.

Methods We performed ES on 110 subjects with PD and a positive family history; 99 subjects were also evaluated using genome-wide aCGH. We interrogated ES and aCGH data for pathogenic SNVs and CNVs at Mendelian PD gene loci. We confirmed SNVs via Sanger sequencing and further characterized CNVs with custom-designed high-density aCGH, droplet digital PCR, and breakpoint sequencing.

Results Using ES, we discovered individuals with known pathogenic SNVs in *GBA* (p.Glu365Lys, p.Thr408Met, p.Asn409Ser, and p.Leu483Pro) and *LRRK2* (p.Arg1441Gly and p.Gly2019Ser). Two subjects were each double heterozygotes for variants in GBA and LRRK2. Based on aCGH, we additionally discovered cases with an *SNCA* duplication and heterozygous intragenic *GBA* deletion. Five additional subjects harbored both SNVs (p.Asn52Metfs*29, p.Thr240Met, p.Pro437Leu, and p.Trp453*) and likely disrupting CNVs at the *PRKN* locus, consistent with compound heterozygosity. In nearly all cases, breakpoint sequencing revealed microhomology, a mutational signature consistent with CNV formation due to DNA replication errors.

Conclusions Integrated ES and aCGH yielded a genetic diagnosis in 19.3% of our familial PD cohort. Our analyses highlight potential mechanisms for *SNCA* and *PRKN* CNV formation, uncover multilocus pathogenic variation, and identify novel SNVs and CNVs for further investigation as potential PD risk alleles.

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