Integrative 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 the 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.Glu365Asp, 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.Trp112Ter, p.Arg1441Gly, and p.Gly2019Ser) 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 because of 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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Novel dominant MPAN family with a complex genetic architecture as a basis for phenotypic variability

**Objective** Our aim was to study a Hungarian family with autosomal dominantly inherited neurodegeneration with brain iron accumulation (NBIA) with markedly different intrafamilial expressivity.

**Methods** Targeted sequencing and multiplex ligation-dependent probe amplification (MLPA) of known NBIA-associated genes were performed in many affected and unaffected members of the family. In addition, a trio whole-genome sequencing was performed to find a potential explanation of phenotypic variability. Neuropathologic analysis was performed in a single affected family member.

**Results** The clinical phenotype was characterized by 3 different syndromes—1 with rapidly progressive dystonia parkinsonism with cognitive deterioration, 1 with mild parkinsonism associated with dementia, and 1 with predominantly psychiatric symptoms along with movement disorder. A heterozygous stop-gain variation in the C19orf12 gene segregated with the phenotype. Targeted sequencing of all known NBIA genes, and MLPA of PLA2G6 and PANK2 genes, as well as whole-genome sequencing in a trio from the family, revealed a unique constellation of oligogenic burden in 3 NBIA-associated genes (C19orf12 p.Trp112Ter, CP p.Val105PhefsTer5, and PLA2G6 dup(ex14)). Neuropathologic analysis of a single case (39-year-old man) showed a complex pattern of alpha synucleinopathy and tauopathy, both involving subcortical and cortical areas and the hippocampus.

**Conclusions** Our study expands the number of cases reported with autosomal dominant mitochondrial membrane protein-associated neurodegeneration and emphasizes the complexity of the genetic architecture, which might contribute to intrafamilial phenotypic variability.

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