WHAT'S HAPPENING IN

Neurology® Genetics

Neurology.org/NG

Abstracts

Papers appearing in the October 2020 issue

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 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.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 additionlly 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 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.

NPub.org/NG/9601a

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.

NPub.org/NG/9601b

Most-Read Articles

As of October 26, 2020

Mutation in *POLR3K* causes hypomyelinating leukodystrophy and abnormal ribosomal RNA regulation

I. Dorboz, H. Dumay-Odelot, K. Boussaid, et al. 2018;4:e289. doi.org/10.1212/NXG.0000000000000289

Copy number loss in *SFMBT1* is common among Finnish and Norwegian patients with iNPH

V. E. Korhonen, S. Helisalmi, A. Jokinen, et al. 2018;4:e291. doi.org/10.1212/NXG.0000000000000291

Variant repeats within the *DMPK* CTG expansion protect function in myotonic dystrophy type 1

J. N. Miller, E. van der Plas, M. Hamilton, et al. 2020;6:e504. doi.org/10.1212/NXG.0000000000000504

Cerebral arteriopathy associated with heterozygous variants in the casitas B-lineage lymphoma gene

Y. Hong, A. Keylock, B. Jensen, et al. 2020;6:e448. doi.org/10.1212/NXG.0000000000000448

Intragenic variants in the *SMN1* gene determine the clinical phenotype in 5q spinal muscular atrophy

R. de Holanda Mendonça, C. Matsui, G. J. Polido, et al. 2020;6:e505. doi.org/10.1212/NXG.0000000000000505

