NUBPL MUTATIONS LINK PARKINSON’S DISEASE AND OTHER MOVEMENT DISORDERS TO RECESSIVE COMPLEX I DEFICIENCY

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ABSTRACT

Complex I Deficiency (CID) in an autosomal recessive disorder caused by NUBPL or compound heterozygotes in mutations in one of 13 nuclear-encoded genes, which includes Complex I (CI) activity and assembly factors (PARKHUB1, Parkinson’s disease (PD)-related protein 1). In this study, we performed array comparative genomic hybridization (aCGH) on a cohort of 476 PD patients to identify copy number variants (CNVs) impacting nuclear genes potentially causative of PD. We also observed that, in a subset of CID patients with Complex I (CI) deficiency, had a CNV identical to that found in our PD patient on one allele, and a splicing mutation (c.815-51C>T) that disrupted a donor splice site (see Table, footnote d identified in exon sequencing (one patient). In a second family, we performed array comparative genomic hybridization (aCGH) on a PD cohort of 100 families, to identify copy number variants (CNVs) impacting nuclear genes potentially causative of PD. This genome-wide screen led to the identification of one patient with a large, complex chromosomal rearrangement that was an apparent loss of function mutation impacting CI assembly factor NUBPL, which further supports the role of this CI assembly factor in late-onset PD. We also observed three patients that are heterozygous for the splicing mutation (c.815-51C>T) in NUBPL (see Table, footnote d). We also observed at these patients that the additional gain on the other allele (c.815-51C>T). These observations support that a loss-of-function mutation in NUBPL is associated with complex I deficiency, and that NUBPL and other complex I subunits may be involved in the pathogenesis of PD and other movement disorders.

RESULTS

Discovery of NUBPL as a Candidate PD Gene

NUBPL Variants Link Recessive CI Deficiency to PD, ET, and RLS

HYPOTHESIS

NUBPL Variants: Autosomal Dominant/Recessive (AD) and Autosomal Recessive (AR) Movement Disorders

PD, ET, and RLS

ACKNOWLEDGEMENTS & REFERENCES

We are indebted to the PD patients participating in this study for their commitment to help move the research towards a cure. We are also grateful to the Complex I deficiency families for publicly sharing their medical odysseys (sponserly.org) and family histories, and their commitment to research to NUBPL for the benefits of neurodegenerative and metabolic disorders.

REFERENCES

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